

厚生労働科学研究費補助金 難治性疾患等政策研究事業
(免疫アレルギー疾患等政策研究事業(免疫アレルギー疾患政策研究分野))

小児期あるいは成人移行の若年性特発性関節炎(JIA)の
全国実態調査とその臨床的検討

平成28年度 総括研究報告書

研究代表者 森 雅 亮

平成29(2017)年3月

目 次

I 構成員名簿

II 総括研究報告・・・・・・・・・・・・・・・・・・・・・・・・

小児期あるいは成人移行の若年性特発性関節炎(JIA)の全国実態調査とその臨床的検討

研究代表者 東京医科歯科大学大学院医歯学総合研究科

生涯免疫難病学講座 教授 森 雅亮

III 研究成果の刊行に関する一覧表

IV 研究成果刊行物・別冊

小児期あるいは成人移行の若年性特発性関節炎(JIA)の全国実態調査とその臨床的検討

区 分	氏 名	所 属 等	職 名
研 究 代 表 者	森 雅亮	東京医科歯科大学大学院医歯学総合研究科生涯免疫難病学講座	教授
研 究 分 担 者	宮坂 信之	東京医科歯科大学大学院医歯学総合研究科膠原病・リウマチ内科	名誉教授/非常勤講師
	小池 隆夫	NTT東日本札幌病院/北海道大学内科リウマチ学	院長/名誉教授
	針谷 正祥	東京女子医科大学附属膠原病リウマチ痛風センター リウマチ性疾患薬剤疫学研究部門	特任教授
	上阪 等	東京医科歯科大学大学院医歯学総合研究科膠原病・リウマチ内科	教授
研 究 協 力 者	伊藤 保彦	日本医科大学大学院医学研究科小児・思春期医学	大学院教授
	岡本 奈美	大阪医科大学大学院医学研究科泌尿生殖・発達医学講座小児科/大阪医科大学付属病院難病総合センター	助教／副センター長
	小林 一郎	北海道大学大学院医学研究科医学専攻生殖・発達医学講座小児科学分野 /KKR札幌医療センター小児・アレルギーリウマチセンター	客員教授/センター長
	武井 修治	鹿児島大学医学部保健学科看護学専攻母性・小児看護学講座	教授
	富板 美奈子	千葉県こども病院アレルギー・膠原病科	部長
	秋岡 親司	京都府立医科大学大学院医学研究科小児科学/附属病院小児科	講師
	五十嵐 徹	日本医科大学大学院医学研究科小児・思春期医学	講師
	井上 祐三朗	東千葉メディカルセンター小児科	副部長
	岩田 直美	あいち小児保健医療総合センター感染症・予防診療科	医長
	梅林 宏明	宮城県立こども病院総合診療科	部長
	江川 祥子	北海道薬科大学薬学部基礎薬学系生命科学分野	教授
	大倉 有加	KKR札幌医療センター小児・アレルギーリウマチセンター	医長
	越智 史博	愛媛大学大学院医学系研究科分子・機能領域寄付講座小児科	講師
	金兼 弘和	東京医科歯科大学大学院医歯学総合研究科発生発達病態学分野（小児科）	准教授
	金城 紀子	琉球大学大学院医学研究科育成医学（小児科）	助教
	久保田 知洋	鹿児島大学病院小児科	医員
	小林 法元	信州大学医学部附属病院小児科	講師
	笹原 洋二	東北大学大学院医学系研究科小児病態学分野	准教授
	佐藤 智	埼玉県立小児医療センター感染免疫・アレルギー科	医長
	清水 正樹	金沢大学医薬保健研究域医学系小児科	助教
	謝花 幸祐	大阪医科大学大学院医学研究科泌尿生殖・発達医学講座小児科	臨床研修専任指導医
	竹崎 俊一郎	北海道大学病院小児科	医員
	田中 絵里子	東京医科歯科大学大学院医歯学総合研究科発生発達病態学分野（小児科）	助教
	中岸 保夫	兵庫県立こども病院リウマチ科	医長
	中野 直子	愛媛大学大学院医学系研究科分子・機能領域小児科学講座	助教
	西田 豊	群馬大学大学院医学系研究科小児科	大学院生
	西村 謙一	横浜市立大学大学院医学研究科発生成育小児医療学	助教
	西本 憲弘	大阪リウマチ・膠原病クリニック/ 東京医科大学医学総合研究所難病分子 制御学部門	院長／兼任教授
	野澤 智	横浜市立大学大学院医学研究科発生成育小児医療学	助教
	野中 由希子	鹿児島大学病院小児科	医員
	原 良紀	横浜市立大学大学院医学研究科発生成育小児医療学	助教
	松井 利浩	東京医科歯科大学大学院医歯学総合研究科生涯免疫難病学講座	准教授
	水田 麻雄	金沢大学医薬保健研究域医学系小児科	診療従事者
	八代 将登	岡山大学病院小児科	助教
	八角 高裕	京都大学大学院医学研究科発生発達医学講座発達小児科学	講師
	安村 純子	広島大学大学院医歯薬保健学研究科小児科学	クリニカルスタッフ
	山口 賢一	聖路加国際病院 Immuno－Rheumatology Center	医長
	山崎 和子	埼玉医科大学総合医療センター小児科	講師
	山崎 雄一	鹿児島大学病院小児科	助教
	脇口 宏之	山口大学大学院医学系研究科医学専攻小児科学講座	助教

厚生労働科学研究費補助金 難治性疾患等政策研究事業

(免疫アレルギー疾患等政策研究事業(免疫アレルギー疾患政策研究分野))

研究課題:小児期あるいは成人移行の若年性特発性関節炎(JIA)の全国実態調査と
その臨床的検討(課題番号:H28-免疫-一般-002)

研究代表者

森 雅亮 東京医科歯科大学大学院医歯学総合研究科生涯免疫難病学講座 寄附講座教授

研究分担者

宮坂 信之 東京医科歯科大学 名誉教授

東京医科歯科大学大学院医歯学総合研究科 膠原病・リウマチ内科 非常勤講師

小池 隆夫 NTT 東日本札幌病院 院長、北海道大学 名誉教授

針谷 正祥 東京女子医科大学附属膠原病リウマチ痛風センター
リウマチ性疾患薬剤疫学研究部門 特任教授

上阪 等 東京医科歯科大学大学院医歯学総合研究科 膠原病・リウマチ内科 教授

研究要旨

小児期医療の進歩により、これまで難治であった患者を救命もしくは寛解・治癒に導くことが可能になった。しかし、それに伴い原疾患もしくはその合併症、後遺症を抱えたまま成長し、思春期、成人期を迎える患者が増加しており、このような患者は young adults with special health care needs (以下、YASHCN) と呼ばれている。YASHCN は年齢を重ねるごとに成人の病態の比重が増していくことになるが、こうした患者に対して現状では小児期医療および成人期医療は適切な医療を提供できていないと言いき難い。若年性特発性関節炎(juvenile idiopathic arthritis、以下 JIA)においても同様であり、生物学的製剤をはじめとする治療の進歩により、小児期の関節破壊進行を抑え、思春期、成人期へと移行できる症例が増加している一方で、成人診療科への移行に際して小児科医師と成人診療科医師の連携は十分とは言えず、どの時点でのどのような引継ぎが妥当か等の議論も乏しい。

本研究の目的は、小児期のみならず成人移行を兼ねた JIA 全般の全国実態調査を行い、JIA の小児期および成人移行後の診療実態を明らかにすることであった。本研究における JIA 患者実数調査は、本研究班、日本リウマチ学会、日本小児リウマチ学会の連携のもとで行われた、本邦初の本格的な JIA 全国疫学調査であった。日本小児科学会専門医認定施設を対象にした**小児期 JIA 患者の全国実態調査**と日本リウマチ学会専門医を対象とした**成人移行 JIA 患者の全国実態調査**を施行し、現在の年齢が 16 歳未満あるいは 16 歳以上の JIA 症例の実数を全国的に把握し得た。2017 年 3 月末日の時点で、前者の回答率は **91.3% (519 施設中 474 施設から回答)** と極めて高い回答が全国規模で得られた。その結果、16 歳未満の JIA 患者は 1704 名、16 歳以上は 750 名であったことから、統計学的解析を行い全国で小児科専門施設がフォローしている JIA 患者は計約 2,700 名であることが判明した。一方、日本リウマチ学会専門医が所属している 27 都道府県 83 施設からも、16 歳未満の JIA 患者を 29 名、16 歳以上の JIA 患者を 164 名診療しているとの回答があった。小児科以外のリウマチ科や整形外科においても、少なからず小児期から移行期にかけての JIA 患者を診療している実態が初めて明らかにされた。

A. 研究目的

本研究の目的は、小児期のみならず成人移行を兼ねた若年性特発性関節炎 (juvenile idiopathic arthritis、以下 JIA) 全般の全国実態調査を行い、①JIA の小児期および成人移行後の診療実態を明らかにする、②JIA の病型毎の差異を明確にすることで、従来の JIA 分類基準の妥当性を検証する、③小児から成人移行までの JIA を長期に観察することにより、寛解あるいは機能障害に至る予後予測因子を検証する、④今後長期的に継続して観察評価できる長期データベース構築のための基礎データを収集し、診断までの過程、治療、投薬内容を検討する、の 4 点に焦点を当てて、多角的に小児 (JIA) と成人 (関節リウマチ: RA) との異同について検証することであり、本研究初年度の平成 28 年度は小児期のみならず成人移行を兼ねた JIA 全般の全国実態調査を行い、JIA の小児期および成人移行後の診療実態を明らかにすることとした。

B. 研究方法

日本小児科学会専門医認定施設を対象にした**小児期 JIA 患者の全国実態調査**と日本リウマチ学会専門医を対象とした**成人移行 JIA 患者の全国実態調査**を施行した (前者の回答率は **91.3%** と高い回答が全国規模で得られた) (資料 1、2)。

本研究では、その一次調査により JIA 患者を有すると回答した施設に対し、診断時の情報として「関節炎の有無及び罹患関節数」、「罹病期間」、「発熱・熱型」、「全身症状」、「皮膚症状の有無」、「付着部炎の有無」、「虹彩炎・ぶどう膜

炎の有無」、「リウマトイド因子」、「サイトカイン異常の有無」、「血管内皮障害の有無」に加えて、把握可能な情報 (薬物治療の内容、疾患活動性や身体機能、就労状況) に関する詳細な二次調査を実施する。この調査では、現状のみの把握でなく、JIA 診断時の情報も併せて収集する。日本小児科学会専門医認定施設を網羅した小児期 JIA 患者の全国実態調査は、研究代表者である森が担当し、日本リウマチ学会専門医全般を対象とした成人移行 JIA 患者の全国実態調査は、研究分担者である宮坂、小池、針谷、上阪の 4 名が担当した。

本研究では、①JIA の小児期および成人移行後の診療実態を明らかにする、②JIA の病型毎の差異を明確にすることで、従来の JIA 分類基準の妥当性を検証する、③小児から成人移行までの JIA を長期に観察することにより、寛解あるいは機能障害に至る予後予測因子を検証する、④今後長期的に継続して観察評価できる長期データベース構築のための基礎データを収集し、診断までの過程、治療、投薬内容を検討する、の 4 つの臨床上の問題点を解決することで、将来小児 (JIA) と成人 (関節リウマチ: RA) との異同について検証していく。

(倫理面への配慮)

本研究において研究対象となる患児ならびに保護者に対して研究参加に関する利益と不利益について口頭および文書にて説明し同意を得た上で、患者病歴について疫学的調査を行った。また患児と保護者より研究参加に関する同意が

なされなかった場合にも不利益が生じない旨、口頭および文書にて伝えた。本疫学研究は本学（東京医科歯科大学）の倫理審査にて承認を得られており、それを元にして参加施設のうち倫理委員会の承認を必要とした施設に関しては各施設で承認審査を受けていただいた。

2) 個人情報の保護に関する法律（平成15年5月法律第57号）第50条の規定に沿い、得られた患者の情報は外部に一切漏れないように厳重に管理し、研究結果の公表に際しては、個人の特定が不可能であるよう配慮した。

3) 本研究は動物実験を行う研究には該当しない。

C. 研究結果

本研究における JIA 患者実数調査は、本研究班研究、日本リウマチ学会、日本小児リウマチ学会の連携のもとで行われた、本邦初の本格的な JIA 全国疫学調査であった。日本小児科学会専門医認定施設を対象にした**小児期 JIA 患者の全国実態調査**と日本リウマチ学会専門医を対象とした**成人移行 JIA 患者の全国実態調査**を施行し、現在の年齢が 16 歳未満あるいは 16 歳以上の JIA 症例の実数を全国的に把握し得た。2017 年 3 月末日の時点で、最終的に前者の回答率は **91.3%（519 施設中 474 施設から回答）**と極めて高い回答が全国規模で得られた。その結果、16 歳未満の JIA 患者は 1,704 名、16 歳以上は 750 名であったことから、統計学的解析を行い全国で小児科専門施設がフォローしている JIA 患者は計約 2,700 名であることが判明し

た。一方、日本リウマチ学会専門医が所属している 27 都道府県 83 施設からも、16 歳未満の JIA 患者を 29 名、16 歳以上の JIA 患者を 164 名診療しているとの回答があった。小児科以外のリウマチ科や整形外科においても、少なからず小児期から移行期にかけての JIA 患者を診療している実態が初めて明らかにされた。

日本小児科学会専門医認定施設を網羅した小児期 JIA 患者の全国実態調査は、研究代表者である森が担当し、日本リウマチ学会専門医全般を対象とした成人移行 JIA 患者の全国実態調査は、研究分担者である宮坂、小池、針谷、上阪の 4 名にご協力を仰いだ。

D. 評価

1) 達成度について

本研究の最終目標は、小児期のみならず成人移行を兼ねた JIA 全般の全国実態調査を行い、①JIA の小児期および成人移行後の診療実態を明らかにする、②JIA の病型毎の差異を明確にすることで、従来の JIA 分類基準の妥当性を検証する、③小児から成人移行までの JIA を長期に観察することにより、寛解あるいは機能障害に至る予後予測因子を検証する、④今後長期的に継続して観察評価できる長期データベース構築のための基礎データを収集し、診断までの過程、治療、投薬内容を検討する、の 4 点に焦点を当てて、多角的に小児(JIA)と成人(関節リウマチ:RA)との異同について検証するこ

とであるが、初年度にあたる平成 28 年度は「①JIA の小児期および成人移行後の診療実態を明らかにする」ことに主眼をおいたが、概ね当初の研究目標は達成した。

2) 今後の展望について

本年度の研究は、「小児期のみならず成人移行を兼ねた JIA 全般の全国実態調査を行い、小児期および成人移行後の診療実態を明らかにする」ための全国疫学調査であった。

この調査において、JIA 患者を有すると回答した施設に対し、診断時の情報として「関節炎の有無及び罹患関節数」、「罹病期間」、「発熱・熱型」、「全身症状」、「皮膚症状の有無」、「付着部炎の有無」、「虹彩炎・ぶどう膜炎の有無」、「リウマトイド因子」、「サイトカイン異常の有無」、「血管内皮障害の有無」に加えて、把握可能な情報(薬物治療の内容、疾患活動性や身体機能、就労状況)に関しての詳細な二次調査を今後実施する予定である。この具体的な研究成果を駆使して、他の重要な課題(「JIA の病型毎の差異を明確にすることで、従来の JIA 分類基準の妥当性を検証する」「小児から成人移行までの JIA を長期に観察することにより、寛解あるいは機能障害に至る予後予測因子を検証する」「今後長期的に継続して観察評価できる長期データベース構築のための基礎データを収集し、診断までの過程、治療、投薬内容を検討する」の 3 点に実質的に取り組み、「多角的に JIA と RA との異同につ

いて検証する」という本研究の最終目標に向けて研究を進めていく。更に将来的には、JIA の移行期症例における就労や出産の正確な実態把握、長期予後の検討を行うことで、幼小児期に発症した JIA 患者自身およびその親に対し、その後の中長期的なビジョンを示す貴重な情報を整え、小児・移行期・成人にわたる一貫としたデータベースの構築を作成することも視野に入れていく。

E. 結論

本研究初年度の平成 28 年度は、小児期のみならず成人移行を兼ねた JIA 全般の全国実態調査を行い、JIA の小児期および成人移行後の診療実態を明らかにした。JIA 患者実数調査は、本研究班、日本リウマチ学会、日本小児リウマチ学会の連携のもとで行われた、本邦初の本格的な JIA 全国疫学調査であった。日本小児科学会専門医認定施設を対象にした小児期 JIA 患者の全国実態調査と日本リウマチ学会専門医を対象とした成人移行 JIA 患者の全国実態調査を施行し、現在の年齢が 16 歳未満あるいは 16 歳以上の JIA 症例の実数を全国的に把握し得た。統計学的解析より、全国で小児科専門施設がフォローしている JIA 患者は計約 2,700 名であることが判明した。また、小児科以外のリウマチ科や整形外科においても、少なからず小児期から移行期にかけての JIA 患者を診療している実態も明確になった。

F. 研究発表

1) 国内

<論文>

- ・ 森 雅亮. 全身性エリテマトーデス. VIII. リウマチ性疾患とその周辺疾患. 小児内科 47 (増刊) 856-862, 2016.
- ・ 森 雅亮. 若年性特発性関節炎. 小児慢性疾患の成人期移行の現状と問題点. 小児科臨床 69:661-667, 2016.
- ・ 森 雅亮. 若年性特発性関節炎 (JIA) 初期診療の手引き【第1回】定義・病態と診断. Salvus 4-5, 2016.
- ・ 森 雅亮. これって肝臓病? トランスアミナーゼと病態 自己免疫疾患. 小児内科 48:860-864, 2016.
- ・ 森 雅亮. 自己免疫疾患-Preclinical State から発症・早期診断まで- 小児リウマチ性疾患. 医学のあゆみ 258: 990-998, 2016
- ・ 森 雅亮. 慢性疾患児に一生を診る- 若年性特発性関節炎 (全身型). 小児内科 48: 1658-1661, 2016
- ・ 岡本奈美、岩田直美、梅林宏明、大倉有加、金城紀子、国島知子、久保田知洋、清水正樹、野澤 智、安村純子、森 雅亮、武井修治、横田俊平. 「若年性特発性関節炎初期診療の手引き」改定のためのアンケート調査結果の検討. 小児リウマチ 7:5-13, 2016.
- ・ 森 雅亮. 若年性特発性関節炎. リウマチ病学テキスト 改訂第2版. pp137-141. 日本リウマチ財団教育研修員会・日本リウマチ学会生涯教育委員会 編集. 診断と治療社. (東京).

2016. 1

- ・ 森 雅亮. 若年性特発性関節炎. 11. 免疫・膠原病. 小児科診療ガイドラインー最新の診療指針ー第3版. Pp534-540. 総合医学社 (東京). 2016. 3
- ・ 森 雅亮. 疾病別で学ぶ自己注射使用の現状と使いやすさの向上. 第13節 若年性特発性関節炎. 自己注射に対する医師・患者ニーズと製品開発への落とし込み. pp88-96. 技術情報協会 (東京). 2016. 3
- ・ 森 雅亮. 膠原病・リウマチ・アレルギー疾患を診療する. 若年性特発性関節炎 (JIA). Pp308-314. 膠原病・リウマチ・アレルギー 研修ノート (東京). 2016. 4.

<発表>

- ・ 森 雅亮. 小児におけるバイオ医薬品等の開発および早期実用化に向けた取り組み. 第60回日本リウマチ学会学術集会. 2016. 4. 横浜
- ・ 森 雅亮. 難治性移行期若年性特発性関節炎患者におけるセルトリズマブペゴルの使用経験. 第44回日本臨床免疫学会総会. 2016. 9. 東京
- ・ 森 雅亮. 『川崎病急性期治療の夜明け: インフリキシマブ療法』 既存治療で効果不十分な急性期川崎病に対するインフリキシマブの臨床試験の概要. <シンポジウム> 第36回日本川崎病学会・学術集会. 2016. 9. 横浜
- ・ 森 雅亮. ドラッグ・リポジショニングが変える膠原病リウマチ性疾患治療. 既存治療で効果不十分な腸管型・神経型・血管型ベ

ーチェック病および急性期川崎病に対して追加適応を取得したインフリキシマブ. <シンポジウム> 第31回日本臨床リウマチ学会. 2016. 9. 東京

- ・森 雅亮. JIA 研修会-エタネルセプト-. 第25回日本小児リウマチ学会総会・学術集会. 2016. 10. 千葉
- ・森 雅亮. 血漿交換療法を要する、免疫グロブリン大量点滴静注療法不応川崎病の冠動脈障害危険因子の検討. 第37回日本アフェレシス学会学術大会. 2016. 11. 東京
- ・森 雅亮. 小児用医薬品の開発開始時期を考える. 小児におけるバイオ医薬品等の開発. PMDA 小児ワークショップ. 2016. 11. 東京

2) 国外

<論文>

- ・Kanetaka T, Mori M, Nishimura K, Nozawa T, Kikuchi M, Sakurai N, Hara R, Yamazaki K, Yokota S.. Characteristics of FDG-PET findings in the diagnosis of systemic juvenile idiopathic arthritis. Mod Rheumatol 26:362-7, 2016.
- ・Yokoyama K, Mori M, Yoshida A. Mycophenolate mofetil therapy for two cases of antiphospholipid antibody-associated chorea. Mod Rheumatol. 2016 Feb 16:1-3. [Epub ahead of print]
- ・Nozawa T, Mori M, Nishimura K, Sakurai

N, Kikuchi M, Hara R, Yokota S. Usefulness of two interferon- γ release assays for rheumatic disease. Pediatr Int. 58:347-52, 2016

- ・Hisa K, Yanagimachi MD, Naruto T, Miyamae T, Kikuchi M, Hara R, Imagawa T, Yokota S, Mori M . PADI4 and the HLA-DRB1 shared epitope in juvenile idiopathic arthritis. PLoS One. 2017 Feb 9;12(2):e0171961.
- ・Tanaka Y, Takeuchi T, Miyasaka N, Sumida T, Mimori T, Koike T, Endo K, Mashino N, Yamamoto K. Efficacy and safety of rituximab in Japanese patients with systemic lupus erythematosus and lupus nephritis who are refractory to conventional therapy. Mod. Rheumatol. 26(1) : 80-86, 2016.
- ・Kojima M, Nakayama T, Kawahito Y, Kaneko Y, Kishimoto M, Hirata S, Seto Y, Endo H, Ito H, Kojima T, Nishida K, Matsushita I, Tsutani K, Igarashi A, Kamatani N, Hasegawa M, Miyasaka N, Yamanaka H. The process of collecting and evaluating evidences for the development of Guidelines for the management of rheumatoid arthritis, Japan College of Rheumatology 2014: Utilization of GRADE approach. Mod. Rheumatol. 26(2) : 175-179, 2016.

- Tanaka Y, Harigai M, Takeuchi T, Yamanaka H, Ishiguro N, Yamamoto K, Ishii Y, Nakajima H, Baker D, Miyasaka N, Koike T. Prevention of joint destruction in patients with high disease activity or high C-reactive protein levels: Post hoc analysis of the GO-FORTH study. *Mod. Rheumatol.* 26(3):323-330, 2016.
- Takeuchi T, Yamamoto K, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, Watanabe A, Origasa H, Kobayashi M, Shoji T, Togo O, Miyasaka N, Koike T. Post-hoc analysis showing better clinical response with the loading dose of certlizumab pegol in Japanese patients with active rheumatoid arthritis. *Mod. Rheumatol.* 26(4):473-480, 2016.
- Tanaka Y, Harigai M, Takeuchi T, Yamanaka H, Ishiguro N, Yamamoto K, Miyasaka N, Koike T, Baker D, Ishii Y, Yoshinari T; GO-FORTH study group. Clinical efficacy, radiographic progression, and safety through 156 weeks of therapy with subcutaneous golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis despite prior methotrexate therapy: final results of the randomized GO-FORTH trial. *Mod. Rheumatol.* 26(4):481-490, 2016.
- Sakai R, Hirano F, Kihara M, Yokoyama W, Yamazaki H, Harada S, Nanki T, Koike R, Miyasaka N, Harigai M. High prevalence of cardiovascular comorbidities in patients with rheumatoid arthritis from a population based cross-sectional study of a Japanese health insurance database. *Mod. Rheumatol.* 26(4):522-528, 2016.
- Kaneko Y, Atsumi T, Tanaka Y, Inoo M, Kobayashi-Haraoka H, Amano K, Miyata M, Murakawa Y, Yasuoka H, Hirata S, Nagasawa H, Tanaka E, Miyasaka N, Yamanaka H, Yamamoto K, Takeuchi T. Comparison of adding tocilizumab to methotrexate with switching to tocilizumab in patients with rheumatoid arthritis with inadequate response to methotrexate: 52-week results from a prospective, randomized, controlled study (SURPRISE study). *Ann. Rheum. Dis.* 75(11):1917-1923, 2016.
- Yoshihashi-Nakazato Y, Kawahata K, Kimura N, Miyasaka N, Kohsaka H. Interferon- γ , but not interleukin-4, suppresses experimental polymyositis. *Arthritis Rheumatol.* 68(6): 1505-1510, 2016.
- Tanaka Y, Yamanaka H, Ishiguro N, Miyasaka N, Kawana K, Hiramatsu K, Takeuchi T.

Adalimumab discontinuation in patients with early rheumatoid arthritis who were initially treated with methotrexate alone or in combination with adalimumab: 1 year outcomes of the HOPEFUL-2 study. RMD Open. 2016 Feb 18;2(1)

- Yamazaki H, Hirano F, Takeuchi T, Amano K, Kikuchi J, Kihara M, Yokoyama W, Sugihara T, Nagasaka K, Hagiwara H, Nonomura Y, Sakai R, Tanaka M, Koike R, Nanki T, Kohsaka H, Miyasaka N, Harigai M. Simplified disease activity index remission at month 6 is an independent predictor of functional and structural remissions at month 12 during abatacept treatment in patients with rheumatoid arthritis: A multi-center, prospective cohort study in Japan. Mod. Rheumatol. 15:1-8, 2016.
- Matsuo Y, Mizoguchi F, Saito T, Kawahata K, Ueha S, Matsushima K, Inagaki Y, Miyasaka N, Kohsaka H. Local fibroblast proliferation but not influx is responsible for synovial hyperplasia in a murine model of rheumatoid arthritis. Biochem. Biophys. Res. Commun. 470(3):504-509, 2016.
- Harigai M, Nanki T, Koike R, Tanaka M, Watanabe-Imai K, Komano Y, Sakai R, Yamazaki H, Koike T, Miyasaka N. Risk for

malignancy in rheumatoid arthritis patients treated with biological disease-modifying antirheumatic drugs compared to the general population: A nationwide cohort study in Japan. Mod. Rheumatol. 26(5): 642-650, 2016.

- Hirano F, Yokoyama W, Yamazaki H, Amano K, Hayashi T, Tamura N, Yasuda S, Dobashi H, Fujii T, Ito S, Kaneko Y, Matsui T, Okuda Y, Saito K, Suzuki F, Yoshimi R, Sakai R, Koike R, Kohsaka H, Miyasaka N, Harigai M; T2T Epidemiological Study Group. Achieving simplified disease activity index remission in patients with active rheumatoid arthritis is associated with subsequent good functional and structural outcomes in a real-world clinical setting under a treat-to-target strategy. Mod. Rheumatol. 21:1-9, 2016.
- Kojima M, Nakayama T, Otani T, Hasegawa M, Kawahito Y, Kaneko Y, Kishimoto M, Hirata S, Seto Y, Endo H, Ito H, Kojima T, Nishida K, Matsushita I, Tsutani K, Igarashi A, Kamatani N, Miyasaka N, Yamanaka H. Integrating patients' perceptions into clinical practice guidelines for the management of rheumatoid arthritis in Japan. Mod. Rheumatol. 2017 Jan 25:1-6 [Epub ahead of print]

- Harigai M, Ishiguro N, Inokuma S, Mimori T, Ryu J, Takei S, Takeuchi T, Tanaka Y, Takasaki Y, Yamanaka H, Watanabe M, Tamada H, Koike T. Postmarketing surveillance of the safety and effectiveness of abatacept in Japanese patients with rheumatoid arthritis. *Mod Rheumatol*. Jan 8: 1-8, 2016.
- Ikeda K, Narita A, Ogasawara M, Ohno S, Kawahito Y, Kawakami A, Ito H, Matsushita I, Suzuki T, Misaki K, Ogura T, Kamishima T, Seto Y, Nakahara R, Kaneko A, Nakamura T, Henmi M, Fukae J, Nishida K, Sumida T, Koike T. Consensus-based identification of factors related to false-positives in ultrasound scanning of synovitis and tenosynovitis. *Mod Rheumatol*. 26(1):9-14, 2016.
- Atsumi T, Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, Watanabe A, Origasa H, Yasuda S, Yamanishi Y, Kita Y, Matsubara T, Iwamoto M, Shoji T, Okada T, van der Heijde D, Miyasaka N, Koike T. The first double-blind, randomised, parallel-group certolizumab pegol study in methotrexate-naïve early rheumatoid arthritis patients with poor prognostic factors, C-OPERA, shows inhibition of radiographic progression. *Ann Rheum Dis*. 75(1):75-83, 2016.
- Utsunomiya M, Dobashi H, Odani T, Saito K, Yokogawa N, Nagasaka K, Takenaka K, Soejima M, Sugihara T, Hagiyaama H, Hirata S, Matsui K, Nonomura Y, Kondo M, Suzuki F, Tomita M, Kihara M, Yokoyama W, Hirano F, Yamazaki H, Sakai R, Nanki T, Koike R, Kohsaka H, Miyasaka N, Harigai M. Optimal regimens of sulfamethoxazole-trimethoprim for chemoprophylaxis of *Pneumocystis pneumonia* in patients with systemic rheumatic diseases: results from a non-blinded, randomized controlled trial. *Arthritis Res Ther*. 19(1):7, 2017.
- Mimori T, Harigai M, Atsumi T, Fujii T, Kuwana M, Matsuno H, Momohara S, Takei S, Tamura N, Takasaki Y, Ikeuchi S, Kushimoto S, Koike T. Safety and effectiveness of 24-week treatment with iguratimod, a new oral disease-modifying antirheumatic drug, for patients with rheumatoid arthritis: interim analysis of a post-marketing surveillance study of 2679 patients in Japan. *Mod Rheumatol*. doi: 10.1080/14397595.2016.1265695. [Epub ahead of print] PubMed PMID: 27919207. 2016.
- Ishiguro N, Atsumi T, Harigai M, Mimori T, Nishimoto N, Sumida T, Takeuchi T, Tanaka Y, Nakasone A, Takagi N, Yamanaka H. Effectiveness and safety of tocilizumab in achieving clinical and functional remission, and sustaining efficacy in biologics-naïve patients with rheumatoid arthritis: The FIRST Bio study. *Mod Rheumatol*. [Epub ahead of print] PubMed PMID:27414105, 2016.

<発表>

1. 学会発表

- ・ R. Sakai, S. Kasai, F. Hirano et al. Incidence rate and the risk of herpes zoster in patients with rheumatoid arthritis using Japanese health insurance database. Annual European Congress of Rheumatology (EULAR) 2016. London, England

・ 知的所有権の出願・取得状況（予定を含む）

1) 特許取得、2) 実用新案登録とも、
該当なし。

表1. 全国調査依頼文書と回答用紙

<p>日本小児科学会専門医研修施設 殿</p> <p>厚生労働科学研究費補助金（難治性疾患等政策研究事業） 「若年性特発性関節炎を主とした小児リウマチ性疾患の診断基準・重症度分類の標準化とエビデンスに基づいた診療ガイドラインの策定に関する研究」（森班 患者実数アンケート調査ご協力のお願い）</p> <p>拝啓</p> <p>時下、ますますご清栄のこととお慶び申し上げます。</p> <p>私どもは平成 27 年度より、上記研究班を立ち上げ、小児リウマチ性疾患の診断基準・重症度分類の標準化と診療ガイドラインの策定についての研究を遂行する事になりました。小児期発症リウマチ性疾患患者の現状を把握し、治療内容、合併症の内容、経過と予後を検討することにより、より良い小児リウマチ性疾患診療を提供することを目的としています。</p> <p>現在、それぞれの日本小児科学会専門医研修施設にて御診療して頂いております小児リウマチ性疾患患者の実数についてお伺いしたく存じます。つきましてはお忙しいと存じますが、添付の一次調査アンケートにご回答いただき、7 月 1 5 日までに往復葉書にてご回答いただければ幸いです。</p> <p>尚、一次調査にて小児リウマチ性疾患患者を御診療されている御施設には、後日二次調査のご協力もお願い申し上げます。</p> <p>お忙しいところを恐縮ですが、何とぞよろしくお願い申し上げます。</p> <p>末筆ながら、貴施設のますますのご発展を祈念いたします。</p> <p style="text-align: right;">敬具</p> <p>平成 28 年 5 月吉日</p> <p>「若年性特発性関節炎を主とした小児リウマチ性疾患の診断基準・重症度分類の標準化とエビデンスに基づいた診療ガイドラインの策定に関する研究」 研究代表者：森 雅亮（東京医科歯科大学 生涯免疫難病学講座教授） 〒113-8519 東京都文京区湯島 1-5-4 5 東京医科歯科大学 生涯免疫難病学講座</p>	<p>御施設名：_____</p> <p>記入者：_____</p> <p>連絡先 TEL または e-mail：_____</p> <p>平成 28 年 4 月 1 日の時点で貴院で経過観察されています小児期発症（16 歳未満で発症した患者）のリウマチ性疾患の患者数についてお答え下さい。</p> <p>1. 若年性特発性関節炎（JIA）の症例（あり・なし）</p> <p>①16 歳未満 約（ 名） ②16 歳以上 約（ 名）</p> <p>2. 小児期発症の全身性エリテマトーデス（SLE）の症例（あり・なし）</p> <p>①16 歳未満 約（ 名） ②16 歳以上 約（ 名）</p> <p>3. 若年性皮膚筋炎（JDM）の症例（あり・なし）</p> <p>①16 歳未満 約（ 名） ②16 歳以上 約（ 名）</p> <p>4. 小児期発症のシェーグレン症候群の症例（あり・なし）</p> <p>①16 歳未満 約（ 名） ②16 歳以上 約（ 名）</p> <p>5. 血管炎症候群（川崎病・シェーンラインヘノッフ症候群を除く）の症例（あり・なし）</p> <p>結節性多発動脈炎 ①16 歳未満 約（ 名） ②16 歳以上 約（ 名） 大動脈炎症候群 ①16 歳未満 約（ 名） ②16 歳以上 約（ 名） その他 ①16 歳未満 約（ 名） ②16 歳以上 約（ 名）</p> <p style="text-align: right;">ご協力どうもありがとうございました。</p>
---	---

表2. 全国調査結果と回収結果

回収率 91.32%

(474 施設/519 施設、症例有り 275・症例なし 199)

1. 若年性特発性関節炎 (JIA) の症例

①16 歳未満 1,704 名、 ②16 歳以上 750 名

2. 小児期発症の全身性エリテマトーデス(SLE) の症例

①16 歳未満 404 名、 ②16 歳以上 525 名

3. 若年性皮膚筋炎 (JDM) の症例

①16 歳未満 268 名、 ②16 歳以上 113 名

4. 小児期発症のシェーグレン症候群の症例

①16 歳未満 148 名、 ②16 歳以上 126 名

5. 血管炎症候群(川崎病・シェーンラインヘノッホ症候群を除く)の症例

結節性多発動脈炎 ①16 歳未満 14 名 ②16 歳以上 19 名

大動脈炎症候群 ①16 歳未満 70 名 ②16 歳以上 70 名

その他 ①16 歳未満 58 名 ②16 歳以上 40 名

表3. 都道府県別小児リウマチ・膠原病患者数

		若年性特発性関節炎		SLE		皮膚筋炎		シェーグレン症候群		結節性多発動脈炎		高安病		他の血管炎	
		16歳未満	16歳以上	16歳未満	16歳以上	16歳未満	16歳以上	16歳未満	16歳以上	16歳未満	16歳以上	16歳未満	16歳以上	16歳未満	16歳以上
北海道・東北	北海道	69	25	16	10	14	2	16	5	1	1	2	6	3	1
	青森	8	4	4	10	2	1	0	0	0	1	1	0	0	0
	岩手	3	4	1	2	0	2	1	0	0	0	0	0	0	0
	宮城	31	15	12	13	5	3	2	0	0	1	3	3	1	0
	秋田	14	13	8	6	3	0	1	2	0	0	3	0	1	1
	山形	6	8	1	1	1	0	1	0	0	0	1	1	0	0
	福島	17	6	5	11	3	2	0	0	0	0	0	0	2	0
関東	茨城	23	6	9	9	1	1	0	1	0	0	1	0	0	0
	栃木	46	13	8	5	3	0	0	2	0	3	1	1	1	0
	群馬	30	17	8	1	5	0	1	3	0	0	1	0	0	0
	埼玉	94	40	14	18	7	14	5	3	0	0	5	7	9	9
	千葉	82	28	15	19	6	4	13	6	2	0	2	1	0	1
	東京	194	103	58	80	33	9	25	29	0	1	10	6	10	6
	神奈川	120	100	17	88	18	28	9	12	1	1	6	17	7	1
中部	新潟	41	10	15	9	7	1	0	2	0	1	1	2	1	2
	富山	5	2	0	1	0	0	0	0	0	0	0	0	0	0
	石川	26	17	4	10	2	0	3	1	1	0	0	3	0	2
	福井	6	2	4	1	1	0	1	1	0	0	1	1	0	0
	山梨	4	1	7	0	0	0	0	0	0	0	0	0	0	0
	長野	12	11	6	9	3	1	0	1	0	0	0	0	0	0
	岐阜	17	6	1	7	4	1	1	0	0	0	1	0	0	0
	静岡	70	9	19	3	13	1	6	1	0	1	1	1	0	0
関西	愛知	125	45	22	33	26	13	10	10	2	0	4	3	2	1
	三重	17	5	4	5	5	0	0	4	0	0	0	0	0	0
	滋賀	21	6	7	5	1	2	4	2	0	0	1	0	0	0
	京都	104	45	6	11	7	2	4	3	0	5	2	5	2	0
	大阪	118	53	22	29	20	6	8	11	1	2	5	3	7	3
	兵庫	74	5	7	13	5	0	3	0	1	0	6	0	5	5
	奈良	10	1	7	0	4	0	4	0	0	0	0	0	0	0
中国・四国	和歌山	6	6	3	6	2	0	2	0	0	0	0	0	0	0
	鳥取	9	1	3	4	1	0	1	0	1	0	1	0	0	0
	島根	3	0	2	2	0	0	0	0	0	0	0	1	0	0
	岡山	27	10	11	9	5	3	5	1	0	0	1	2	0	1
	広島	44	13	13	2	9	4	1	2	0	0	0	1	0	0
	山口	19	6	2	3	4	0	2	2	0	0	0	1	0	1
	徳島	7	5	2	6	0	0	0	1	0	1	0	0	0	0
	香川	6	1	5	1	0	0	2	0	0	0	1	0	0	0
	愛媛	22	18	5	5	1	2	2	1	1	0	0	2	0	0
	高知	10	2	3	5	0	0	0	0	0	0	0	0	0	0
九州・沖縄	福岡	51	24	15	9	15	3	5	3	2	0	3	2	3	0
	佐賀	4	3	2	3	1	0	0	3	0	0	1	0	0	0
	長崎	12	2	7	1	2	0	3	1	0	0	1	0	1	0
	熊本	23	7	5	14	5	1	1	2	0	1	0	0	1	0
	大分	8	10	2	0	1	1	0	0	0	0	0	1	1	1
	宮崎	9	1	2	0	4	0	1	0	0	0	0	0	0	0
	鹿児島	28	25	8	19	13	2	2	6	1	0	3	0	0	3
	沖縄	23	10	7	23	5	4	2	5	0	0	0	0	0	1

表4. JIA分担班施設におけるJIA患者数

所属	JIA <16	JIA ≥16
北海道大学病院	10	7
KKR札幌医療センター	4	5
東北大学病院	1	0
宮城県立こども病院	29	15
群馬大学医学部附属病院	19	7
埼玉医科大学総合医療センター	2	0
埼玉県立小児医療センター	80	40
千葉大学医学部附属病院	5	6
千葉県こども病院	63	11
東京医科歯科大学医学部附属病院	24	27
日本医科大学付属病院	25	21
聖路加国際病院	31	15
公立大学法人 横浜市立大学附属病院	93	83
国立大学法人 信州大学医学部附属病院	12	8
金沢大学附属病院	20	15
あいち小児保健医療総合センター	103	37
京都府立医科大学附属病院	87	39
京都大学医学部附属病院	11	6
大阪医科大学附属病院	60	29
兵庫県立こども病院	50	2
岡山大学病院	13	6
広島大学病院	22	5
山口大学医学部附属病院	8	4
愛媛大学医学部附属病院	20	13
鹿児島大学医学部・歯学部附属病院	26	24
琉球大学医学部附属病院	23	10
本研究班全施設	841	435
全国	1694	743
%	49.6%	58.5%

研究成果の刊行に関する一覧表(平成28年度)

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年(西暦)
Kanetaka T, <u>Mori M</u> , Nishimura KI, Nozawa T, Kikuchi M, Sakurai N, Hara R, Yamazaki K, Yokota S.	Characteristics of FDG-PET findings in the diagnosis of systemic juvenile idiopathic arthritis.	Mod Rheumatol	29	1-6	[Epub ahead of print]
Hisa K, Yanagimachi MD, Naruto T, Miyamae T, Kikuchi M, Hara R, Imagawa T, Yokota S, <u>Mori M</u> .	PADI4 and the HLA-DRB1 shared epitope in juvenile idiopathic arthritis.	PLoS One.	12(2):e0171961.		2017
Mimori T, <u>Harigai M.</u> , Atsumi T, Fujii T, Kuwana M, Matsuno H, Momohara S, Takei S, Tamura N, Takasaki Y, Ikeuchi S, Kushimoto S, <u>Koike T</u> .	Safety and effectiveness of 24-week treatment with iguratimod, a new oral disease-modifying antirheumatic drug, for patients with rheumatoid arthritis: interim analysis of a post-marketing surveillance study of 2679 patients in Japan.	Mod Rheumatol	doi: 10.1080/14397595.2016.1265695. [Epub ahead of print] PubMed PMID: 27919207.	doi: 10.1080/14397595.2016.1265695. [Epub ahead of print] PubMed PMID: 27919207.	2016
Ishiguro N, Atsumi T, <u>Harigai M.</u> , Mimori T, Nishimoto N, Sumida T, Takeuchi T, Tanaka Y, Nakasone A, Takagi N, Yamanaka H.	Effectiveness and safety of tocilizumab in achieving clinical and functional remission, and sustaining efficacy in biologics-naïve patients with rheumatoid arthritis: The FIRST Bio study.	Mod Rheumatol.	[Epub ahead of print] PubMed PMID:27414105.	[Epub ahead of print] PubMed PMID:27414105.	2016
<u>Harigai M.</u> , Nanki T, Koike R, Tanaka M, Watanabe-Imai K, Komano Y, Sakai R, Yamazaki H, <u>Koike T</u> , <u>Miyasaka N</u> .	Risk for malignancy in rheumatoid arthritis patients treated with biological disease-modifying antirheumatic drugs compared to the general population: A nationwide cohort study in Japan.	Mod Rheumatol.	26(5)	642-50	2016
Takada H, Hosoya T, Kimura N, Kawahata K, <u>Kohsaka H</u> .	Successful use of rituximab in a patient with refractory thrombotic thrombocytopaenic purpura complicated by polymyositis.	Scand J Rheumatol			in press
Hasegawa H, Kawahata K, Mizoguchi F, Okiyama N, <u>Miyasaka N</u> , <u>Kohsaka H</u> .	Direct suppression of auto aggressive CD8+ T cells with CD80/86 blockade in CD8+ T cell-mediated polymyositis models of mice.	Clin Exp Rheumatol			in press
Matsumoto T, Saito T, <u>Kohsaka H</u> .	A case of chronic myelomonocytic leukemia complicated with spondyloarthritis.	Mod Rheumatol			in press
Hosoya T, Iwai H, Yamaguchi Y, Kawahata K, <u>Miyasaka N</u> , <u>Kohsaka H</u> .	Cell cycle regulation therapy combined with cytokine blockade enhances anti-arthritis effects without increase of immune suppression.	Ann Rheum Dis	75(1)	253-9	2016
Kamiya M, Shane PY, Soejima M, Tohda S, <u>Miyasaka N</u> , <u>Kohsaka H</u> .	IgG4-Related Sialoadenitis with a Skin Lesion and Multiple Mononeuropathies Suggesting Coexistent Cryoglobulinemic Vasculitis.	Int Med	55(10)	1355-61	2016
Ota M, Iwai H, Imai K, Kamiya M, Yoshihashi-Nakazato Y, <u>Miyasaka N</u> , <u>Kohsaka H</u> .	Acute tubulointerstitial nephritis associated with infliximab in a patient with Crohn’s disease.	Int Med	55(10)	1367-70	2016
Tomimitsu H, Ohta A, Nagai M, Nishina M, Ishihara S, <u>Kohsaka H</u> .	Epidemiologic analysis of the clinical features of Japanese patients with polymyositis and dermatomyositis.	Mod Rheumatol	26(3)	398-402	2016
Hirano F, Mizoguchi F, <u>Harigai M.</u> , <u>Miyasaka N</u> , <u>Kohsaka H</u> .	Tacrolimus was used successfully to induce remission in a patient with refractory eosinophilic granulomatosis with polyangiitis complicated by invasive aspergillosis and chronic hepatitis B.	Int J Rheum Dis			in press
Yoshihashi-Nakazato Y, Kawahata K, Kimura N, <u>Miyasaka N</u> , <u>Kohsaka H</u> .	Interferon-gamma but not interleukin-4 restrains experimental polymyositis.	Arthritis Rheumatol	68(6)	1505-10	2016
Matsuo Y, Mizoguchi F, Saito T, Kawahata K, Ueha S, Matsushima K, Yinagaki Y, <u>Miyasaka N</u> , <u>Kohsaka H</u> .	Local fibroblast proliferation but not influx is responsible for synovial hyperplasia in a murine model of rheumatoid arthritis.	Biochem Biophys Res Commun	470(3)	504-9	2016
Kusuda T, Hosoya T, Mori T, Ihara K, Nishida H, Chiga M, Sohara E, Rai T, Koike R, Uchida S, <u>Kohsaka H</u> .	Acquired Gitelman syndrome in an anti-SSA antibody positive patient with a SLC12A3 heterozygous mutation: A case report.	Int Med	55 (21)	3201-04	2016
Tagawa Y, Saito T, Takada K, Kawahata K, <u>Kohsaka H</u> .	Successful treatment of severe refractory lupus hepatitis with mycophenolate mofetil.	Lupus	25	543-46	2016
Ishiwata Y, Nagata M, Arai T, Makiishi M, Yoshikawa M, Takahashi H, <u>Kohsaka H</u> , Yasuhara M.	Effects of miconazole oral gel on blood concentrations of tacrolimus and cyclosporine: a retrospective observational study.	Ther Drug Monit	38 (6)	717-21	2016
Sasaki H, Yamazaki H, <u>Kohsaka H</u> .	A case of ANCA-associated Large Vessel Vasculitis with Multiple Saccular Aneurysms.	J Rheumatol	43 (1)	179	2016

Tanaka Y, Takeuchi T, <u>Miyasaka N</u> , Sumida T, Mimori T, <u>Koike T</u> , Endo K, Mashino N, Yamamoto K.	Efficacy and safety of rituximab in Japanese patients with systemic lupus erythematosus and lupus nephritis who are refractory to conventional therapy.	Mod. Rheumatol.	26(1)	80-86	2016
Atsumi T, Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, Watanabe A, Origasa H, Yasuda S, Yamanishi Y, Kita Y, Matsubara T, Iwamoto M, Shoji T, Okada T, van der Heijde D, <u>Miyasaka N</u> , <u>Koike T</u> .	The first double-blind, randomized, parallel-group certolizumab pegol sutudy in methotrexate-naïve early rheumatoid arthritis patients with poor prognostic factors, C-OPERA, shows inhibition of radiographic progression.	Ann. Rheum. Dis.	75(1)	75-83	2016
Kojima M, Nakayama T, Kawahito Y, Kaneko Y, Kishimoto M, Hirata S, Seto Y, Endo H, Ito H, Kojima T, Nishida K, Matsushita I, Tsutani K, Igarashi A, Kamatani N, Hasegawa M, <u>Miyasaka N</u> , Yamanaka H.	The process of collecting and evaluating evidences for the development of Guidelines for the management of rheumatoid arthritis, Japan College of Rheumatology 2014: Utilization of GRADE approach.	Mod. Rheumatol.	26(2)	175-179	2016
Tanaka Y, <u>Harigai M</u> , Takeuchi T, Yamanaka H, Ishiguro N, Yamamoto K, Ishii Y, Nakajima H, Baker D, <u>Miyasaka N</u> , <u>Koike T</u> .	Prevention of joint destruction in patients with high disease activity or high C-reactive protein levels: Post hoc analysis of the GO-FORTH study.	Mod. Rheumatol.	26(3)	323-330	2016
Takeuchi T, Yamamoto K, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, Watanabe A, Origasa H, Kobayashi M, Shoji T, Togo O, <u>Miyasaka N</u> , <u>Koike T</u> .	Post-hoc analysis showing better clinical response with the loading dose of certlizumab pegol in Japanese patients with active rheumatoid arthritis.	Mod.Rheumatol.	26(4)	473-480	2016
Tanaka Y, <u>Harigai M</u> , Takeuchi T, Yamanaka H, Ishiguro N, Yamamoto K, <u>Miyasaka N</u> , <u>Koike T</u> , Baker D, Ishii Y, Yoshinari T; GO-FORTH study group.	Clinical efficacy, radiographic progression, and safety through 156 weeks of therapy with subcutaneous golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis despite prior methotrexate therapy: final results of the randomized GO-FORTH trial.	Mod. Rheumamol.	26(4)	481-490	2016
Sakai R, Hirano F, Kihara M, Yokoyama W, Yamazaki H, Harada S, Nanki T, Koike R, Miyasaka N, <u>Harigai M</u> .	High prevalence of cardiovascular comorbidities in patients with rheumatoid arthritis from a population based cross-sectional study of a Japanese health insurance database.	Mod. Rheumatol.	26(4)	522-528	2016
Kaneko Y, Atsumi T, Tanaka Y, Inoo M, Kobayashi-Haraoka H, Amano K, Miyata M, Murakawa Y, Yasuoka H, Hirata S, Nagasawa H, Tanaka E, <u>Miyasaka N</u> , Yamanaka H, Yamamoto K, Takeuchi T.	Comparison of adding tocilizumab to methotrexate with switching to tocilizumab in patients with rheumatoid arthritis with inadequate response to methotrexate: 52-week results from a prospective, randomized, controlled study(SURPRISE study).	Ann. Rheum. Dis.	75(11)	1917-1923	2016
Matsuo Y, Mizoguchi F, Saito T, Kawahata K, Ueha S, Matsushima K, Inagaki Y, <u>Miyasaka N</u> , <u>Kohsaka H</u> .	Local fibroblast proliferation but not influx is responsible for synovial hyperplasia in a murine model of rheumatoid arthritis.	Biochem. Biophys. Res. Commun.	470(3)	504-509	2016
Yoshihashi-Nakazato Y, Kawahata K, Kimura N, <u>Miyasaka N</u> , <u>Kohsaka H</u> .	Interferon-γ, but not interleukin-4, suppresses experimental polymyositis.	Arthritis Rheumatol.	68(6)	1505-1510	2016
Tanaka Y, Yamanaka H, Ishiguro N, <u>Miyasaka N</u> , Kawana K, Hiramatsu K, Takeuchi T.	Adalimumab discontinuation in patients with early rheumatoid arthritis who were initially treated with methotrexate alone or in combination with adalimumab: 1 year outcomes of the HOPEFUL-2 study.	RMD Open.	2016 Feb 18;2(1)		
Yamazaki H, Hirano F, Takeuchi T, Amano K, Kikuchi J, Kihara M, Yokoyama W, Sugihara T, Nagasaka K, Hagiyaama H, Nonomura Y, Sakai R, Tanaka M, Koike R, Nanki T, <u>Kohsaka H</u> , <u>Miyasaka N</u> , <u>Harigai M</u> .	Simplified disease activity index remission at month 6 is an independent predictor of functional and structural remissions at month 12 during abatacept treatment in patients with rheumatoid arthritis: A multi-center, prospective cohort study in Japan.	Mod. Rheumatol.	15	1-8	2016
Hirano F, Yokoyama W, Yamazaki H, Amano K, Hayashi T, Tamura N, Yasuda S, Dobashi H, Fujii T, Ito S, Kaneko Y, Matsui T, Okuda Y, Saito K, Suzuki F, Yoshimi R, Sakai R, Koike R, <u>Kohsaka H</u> , <u>Miyasaka N</u> , <u>Harigai M</u> ; T2T Epidemiological Study Group.	Achieving simplified disease activity index remission in patients with active rheumatoid arthritis is associated with subsequent good functional and structural outcomes in a real-world clinical setting under a treat-to-target strategy.	Mod. Rheumatol.	21	1-9	2016

Atsumi T, Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, Watanabe A, Origasa H, Yasuda S, Yamanishi Y, Kita Y, Matsubara T, Iwamoto M, Shoji T, Okada T, van der Heijde D, <u>Miyasaka N</u> , Koike T.	The first double-blind, randomised, parallel-group certolizumab pegol study in methotrexate-naive early rheumatoid arthritis patients with poor prognostic factors, C-OPERA, shows inhibition of radiographic progression.	Ann Rheum Dis.	75(1)	75-83	2016
Tanaka Y, Takeuchi T, <u>Miyasaka N</u> , Sumida T, Mimori T, <u>Koike T</u> , Endo K, Mashino N, Yamamoto K.	Efficacy and safety of rituximab in Japanese patients with systemic lupus erythematosus and lupus nephritis who are refractory to conventional therapy.	Mod Rheumatol. .	26(1)	80-86	2016
Tsuru T, Tanaka Y, Kishimoto M, Saito K, Yoshizawa S, Takasaki Y, Miyamura T, Niuro H, Morimoto S, Yamamoto J, Lledo-Garcia R, Shao J, Tatematsu S, Togo O, <u>Koike T</u> .	Safety, pharmacokinetics, and pharmacodynamics of epratuzumab in Japanese patients with moderate-to-severe systemic lupus erythematosus: Results from a phase 1/2 randomized study.	Mod Rheumatol.	26(1).	87-93	2016
Ikeda K, Narita A, Ogasawara M, Ohno S, Kawahito Y, Kawakami A, Ito H, Matsushita I, Suzuki T, Misaki K, Ogura T, Kamishima T, Seto Y, Nakahara R, Kaneko A, Nakamura T, Henmi M, Fukae J, Nishida K, Sumida T, <u>Koike T</u>	.Consensus-based identification of factors related to false-positives in ultrasound scanning of synovitis and tenosynovitis.	Mod Rheumatol.	26(1)	9-14	2016
Utsunomiya M, Dobashi H, Odani T, Saito K, Yokogawa N, Nagasaka K, Takenaka K, Soejima M, Sugihara T, Hagiyaama H, Hirata S, Matsui K, Nonomura Y, Kondo M, Suzuki F, Tomita M, Kihara M, Yokoyama W, Hirano F, Yamazaki H, Sakai R, Nanki T, Koike R, <u>Kohsaka H</u> , <u>Miyasaka N</u> , <u>Harigai M</u> .	Optimal regimens of sulfamethoxazole-trimethoprim for chemoprophylaxis of Pneumocystis pneumonia in patients with systemic rheumatic diseases: results from a non-blinded, randomized controlled trial.	Arthritis Res Ther	19(1)	7	2017
<u>Koike T</u> , <u>Harigai M</u> , Ishiguro N, Inokuma S, Takei S, Takeuchi T, Yamanaka H, Takasaki Y, Mimori T, Hiramatsu K, Komatsu S, Tanaka Y.	Effect of Methotrexate Plus Adalimumab on the Achievement of Rheumatoid Arthritis Therapeutic Goals:Post Hoc Analysis of Japanese Patients (MELODY Study).	Rheumatol Ther	3(1)	129-141	2016
<u>Harigai M</u> , Ishiguro N, Inokuma S, Mimori T, Ryu J, Takei S, Takeuchi T, Tanaka Y, Takasaki Y, Yamanaka H, Watanabe M, Tamada H, <u>Koike T</u> .	Postmarketing surveillance of the safety and effectiveness of abatacept in Japanese patients with rheumatoid arthritis	Mod Rheumatol	26(4)	491-8	2016

RESEARCH ARTICLE

PADI4 and the HLA-DRB1 shared epitope in juvenile idiopathic arthritis

Kaori Hlisa^{1,2}, Masakatsu D. Yanagimachi^{1,3*}, Takuya Naruto¹, Takako Miyamae¹, Masako Kikuchi¹, Rhokl Hara¹, Tomoyuki Imagawa^{1,2}, Shumpei Yokota¹, Masaaki Mori^{1,4}

1 Department of pediatrics, Yokohama City Graduate School of Medicine, Yokohama, Japan, **2** Department of infectious disease and immunology, Kanagawa Children's Medical Center, Yokohama, Japan, **3** Department of Pediatrics, Tokyo Medical and Dental University, Tokyo, Japan, **4** Department of Lifetime Clinical Immunology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan

* myanagimachi.ped@tmd.ac.jp



Abstract

Objective

Both genetic and environmental factors are associated with susceptibility to juvenile idiopathic arthritis (JIA). Many studies have reported that both a 'shared epitope' (SE) encoded by several HLA-DRB1 alleles and the peptidyl arginine deiminase type 4 (PADI4) gene polymorphisms are associated with susceptibility to rheumatoid arthritis (RA). However, it is uncertain whether JIA and RA share the latter genetic risk factor. Therefore, here we investigated relationships between HLA-SE and PADI4 polymorphisms with clinical subtypes of JIA.

Methods

JIA patients (39 oligoarthritis, 48 RF-positive polyarthritis, 19 RF-negative polyarthritis and 82 systemic) and 188 healthy controls were genotyped for HLA-DRB1 by PCR-sequence-specific oligonucleotide probe methodology. Three PADI4 gene single nucleotide polymorphisms (SNPs), rs2240340, rs2240337 and rs1748033, were genotyped using TaqMan SNP Genotyping Assays.

Results

Frequencies of the HLA-SE were higher in RF-positive polyarticular JIA than in healthy controls. RF-positive polyarticular JIA was associated with HLA-SE (OR = 5.3, 95% CI = 2.5–11.9, $p < 0.001$). No associations were found between clinical subtypes of JIA and PADI4 allele frequency. Nonetheless, rs2240337 in the PADI4 gene was significantly associated with anti-cyclic citrullinated peptide antibody (ACPA)-positivity in JIA. The A allele at rs2240337 was a significant risk factor for ACPA positivity in JIA (OR = 5.6, 95% CI = 1.71–23.7 $p = 0.03$).

OPEN ACCESS

Citation: Hlisa K, Yanagimachi MD, Naruto T, Miyamae T, Kikuchi M, Hara R, et al. (2017) PADI4 and the HLA-DRB1 shared epitope in juvenile idiopathic arthritis. PLoS ONE 12(2): e0171961. doi:10.1371/journal.pone.0171961

Editor: Masataka Kuwana, JAPAN

Received: October 16, 2016

Accepted: January 27, 2017

Published: February 9, 2017

Copyright: © 2017 Hlisa et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This work was supported by a grant from Grand-in-Aid for Scientific Research from Japan Society for the Promotion of Science (No. 16790583). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: Apart from the submitted work, Masaaki Mori has received grants from Takeda Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co.,

Ltd., Mitsubishi Tanabe Pharma, AbbVie LLC, UCB Japan Co. Ltd., Astellas Pharma Inc., and Eisai Co., Ltd. Dr. Mori has also received lecture fees from MSD K.K and AbbVie LLC, and consulting fees from Daiichi Sankyo Co., Ltd. and Taisho Pharmaceutical Co., Ltd. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

Conclusion

PADI4 gene polymorphism is associated with ACPA-positivity in JIA. The association of HLA-SE with RF-positive polyarticular JIA as well as RA is confirmed in Japanese. Thus, HLA-SE and PADI4 status both influence JIA clinical manifestations.

Introduction

Juvenile idiopathic arthritis (JIA) is defined as a chronic arthritis developing in children <16 years of age and persisting for ≥6 weeks. According to the International League of Associations for Rheumatology (ILAR) classification criteria for JIA, it has 7 subtypes [1]. The 4 major subtypes are oligoarthritis, rheumatoid factor (RF)-positive polyarthritis, RF-negative polyarthritis and systemic arthritis. The major pathology of oligoarthritis and polyarthritis is articular inflammation and joint destruction. RF-positive polyarthritis is considered to be a counterpart of adult rheumatoid arthritis (RA) [2]. In contrast to the above forms of JIA, the major pathology of systemic JIA is systemic inflammation, which is considered similar to adult Still's disease [3,4].

In RA and JIA, both genetic and environmental factors are associated with disease susceptibility [5]. HLA class II gene polymorphisms are considered the most influential for RA susceptibility [6]. Many studies have reported the association of a 'shared epitope' (SE) encoded by several HLA-DRB1 alleles with RA susceptibility in adults [7]. Similarly, an association between HLA-SE and susceptibility to JIA has been reported in Caucasians [8]. We have previously reported that HLA-DRB1*04:05, a major SE-containing allele, is associated with polyarticular JIA also in the Japanese population [9].

More recently, a number of RA susceptibility genes outside of the HLA region have been identified by genome-wide association studies (GWAS) [10,11]. One of these, peptidyl arginine deiminase type 4 (PADI4) was first reported in Japanese RA patients [12,13], and subsequently confirmed in several Asian groups and subgroups of Europeans [14–17]. PADI4 is one member of PADI gene family. It codes for enzymes responsible for the posttranslational conversion of arginine residues into citrulline. It was indicated that an RA susceptibility haplotype in PADI4 was associated with increased stability of PADI4 mRNA [13]. And it could lead to accumulation of PADI4 protein, with subsequent increases in citrullinated proteins and enhanced production of autoantibodies against these citrullinated peptides [18].

PADI4 mRNA is detected in hematological cells and pathological synovial tissues [19,20]. And it was reported that PADI4 significantly overexpressed in the blood cells of RA patients [21]. Moreover, PADI4 have a nuclear localization signal, which affects the expression control of various genes [22]. PADI4 may have various role in the immune system and associated with development of autoimmune disease.

In each of the JIA subtypes, age of onset, clinical course and serological findings are different, which may be accounted for by different influences of the genetic background. However, it is uncertain whether JIA (particularly the RF-positive polyarthritic form) and RA share any genetic risk factors other than HLA-SE. There are no reports that PADI4 risk alleles are involved in JIA disease susceptibility. In the present study, which includes our previous cohort [9], we investigated relationships between HLA-SE and PADI4 polymorphisms, and clinical subtypes of JIA in the Japanese population.

Materials and methods

Study population

Patients were eligible if they met the ILAR classification criteria for JIA. A total of 188 JIA patients (39 oligoarthritis, 48 RF-positive polyarthritis, 19 RF-negative polyarthritis and 82 systemic), comprising 59 boys and 129 girls, was enrolled in this study and followed at the Yokohama City University Hospital between December 2006 and December 2009. This cohort included the 106 oligo- and poly-articular JIA patients who were described in our previous study [9]. Clinical data including age at onset, gender, RF and anti-cyclic citrullinated peptide antibody (ACPA) status were reviewed.

We conducted this study in accordance with the Declaration of Helsinki and with the approval of the Ethics Committee of the Yokohama City University School of Medicine. Written informed consent was obtained from each patient and/or their guardian. (Approval number: A090528002)

HLA genotyping

Genomic DNA was isolated from peripheral blood using the QIAamp DNA Mini kit (Qiagen K.K., Tokyo, Japan). JIA patients and healthy adult controls were genotyped for HLA-DRB1 using PCR sequence-specific oligonucleotide probes (SSOP) by the Luminex method with Genosearch HLA-A, -B and -DRB1 Ver. 2 (Medical & Biological Laboratories Co., Ltd. Nagoya, Japan), as described previously [9]. HLA-DRB1*01:01, *04:01, *04:04, *04:05, *04:10, *10:01, *14:02 and *14:06 were regarded as HLA-SE alleles [23].

PADI4 genotyping

Three single nucleotide polymorphisms (SNPs), rs2240340, rs2240337 and rs1748033 in the PADI4 gene were selected based on previous research [12,13]. Genotyping for these in 188 JIA patients and 188 healthy adult controls was performed using TaqMan SNP Genotyping Assays (AB assay ID: C_16176717_10 for rs2240340, C_3123009_1 for rs2240337 and C_7541083_1 for rs1748033). These SNPs were analyzed by real-time PCR using the AB7500 Real Time PCR system (Applied Biosystems, Foster City, CA, USA) under the conditions recommended by the manufacturer. Allele discrimination was accomplished using SDS software version 1.4 (Applied Biosystems).

Statistical analysis

The statistical significance of the differences in the frequencies of HLA-DRB1 alleles or PADI4 gene polymorphisms between JIA subtypes was evaluated by Fishers exact test. A corrected P-value (P_c) was calculated by multiplying the P-value by the number of HLA-DRB1 alleles tested at each locus. For the PADI4 gene polymorphisms, we examined 3 SNPs and used a total of 5 independent tests.

Results

Patients' characteristics

Characteristics of the patients studied are shown in Table 1. Patients comprised 39 children with oligoarthritis, 48 with RF-positive polyarthritis, 19 with RF-negative polyarthritis and 82 with systemic arthritis. The mean age at onset of oligoarthritis was 5.6 years, RF-positive polyarthritis was 8.2 years, RF-negative polyarthritis was 7.1 years and systemic arthritis 5.0 years.

Table 1. Clinical characteristics of JIA patients.

	Oligo articular JIA (n = 39)	RF positive, polyarticular JIA (n = 48)	RF negative, polyarticular JIA (n = 19)	Systemic JIA (n = 82)
Age at JIA onset (years, mean)	5.6	8.2	7.1	5
Gender (female, %)	35 (90%)	40 (83%)	10 (53%)	44 (53%)
ANA (>1:160, %)	16 (41%)	19 (40%)	3 (16%)	3/78 (4%)
RF (>14.0 IU ml ⁻¹ , %)	9 (23%)	48 (100%)	0 (0%)	-
Anti-CCP (>4.5 U ml ⁻¹ , %)	8 (21%)	40 (83%)	0 (0%)	0/43 (0%)

doi:10.1371/journal.pone.0171961.t001

HLA-DRB1 and JIA subtypes

188 healthy controls was genotyped for HLA-DRB1 to determine associations of HLA-DRB1 and HLA-SE with JIA subtype susceptibility. According to ILAR classification criteria for JIA, RF-positive oligoarticular JIA is classified as "undifferentiated". Thus, such cases were excluded from the oligoarthritis group in HLA association studies. RF-positive polyarticular JIA was significantly associated with HLA-DRB1*04:05 and HLA-SE (OR = 5.1, 95% CI = 2.5–11, $p < 0.001$; OR = 5.3, 95% CI = 2.5–11, $P < 0.001$, respectively) (Table 2). In contrast, frequencies of HLA-DRB1*04:05 and HLA-SE were not higher in the other types of JIA patients.

PADI4 polymorphisms and JIA subtypes

Frequencies of PADI4 gene polymorphisms studied in JIA patients and controls are shown in Table 3. There were no associations between clinical subtypes of JIA and PADI4 gene polymorphisms. Nonetheless, the PADI4 SNPs were significantly associated with ACPA positivity in JIA (Table 4). Because the ACPA status of all systemic JIA patients measured in this study was negative (0/43), systemic JIA was excluded from the data in Table 4. Hence, the A allele at rs2240337 is a significant risk factor for ACPA positivity in oligo- and poly-articular JIA (OR = 5.6, 95% CI = 1.7–24 $P = 0.03$). Finally, there were no associations between HLA-SE and PADI4 gene polymorphisms in oligo- and poly-articular JIA (Table 5).

Table 2. Association of HLA-DRB1 *04:05 and HLA-SE with susceptibility to JIA subtypes.

HLA-DRB1*0405	Genotype (*0405/any)	OR	95% CI	P-value	Pc
control (n = 188)	40 (21.3%)	-	-	-	-
Oligoarticular JIA (n = 30)	1 (3.3%)	0.1	0.01–0.82	0.02	NS
RF positive, polyarticular JIA (n = 48)	28 (58.3%)	5.1	2.50–10.7	<0.001	<0.001
RF negative, polyarticular (n = 19)	4 (21.1%)	1	0.30–4.42	0.98	NS
RF negative (oligo+poly) (n = 49)	5 (10.2%)	0.4	0.06–8.17	0.078	NS
Systemic JIA (n = 82)	21 (25.6%)	1.3	0.66–2.42	0.43	NS
HLA-SE	Genotype (SE/any)	OR	95% CI	P-value	Pc
control (n = 188)	68 (36.2%)	-	-	-	-
Oligoarticular JIA (n = 30)	6 (20.0%)	0.4	0.14–1.18	0.082	NS
RF positive polyarticular JIA (n = 48)	36 (75.0%)	5.3	2.47–11.9	<0.001	<0.001
RF negative, polyarticular (n = 19)	5 (26.3%)	0.6	0.17–1.96	0.39	NS
RF negative (oligo+poly) (n = 49)	15 (30.6%)	0.8	0.37–1.60	0.47	NS
Systemic JIA (n = 82)	33 (40.2%)	1.8	0.67–2.09	0.59	NS

SE, shared epitope; HLA-DRB1*04:05, 01:01, 04:01, 04:10, 10:01, 14:02, 14:06

doi:10.1371/journal.pone.0171961.t002

Table 3. Association between PADI4 gene polymorphisms and susceptibility to JIA subtypes.

rs2240340	G allele	A allele	MAF	OR	95% CI	P	Pc
Control (n = 188)	223	153	0.41	-	-	-	-
Oligoarticular JIA (n = 30)	37	23	0.38	0.9	0.49–1.64	0.73	NS
RF positive, polyarticular JIA (n = 48)	49	47	0.49	1.4	0.87–2.25	0.17	NS
RF negative, polyarticular (n = 19)	24	14	0.37	0.9	0.39–1.78	0.64	NS
RF negative, oligo+poly articular (n = 49)	61	37	0.38	0.9	0.54–1.43	0.6	NS
Systemic JIA (n = 82)	92	72	0.44	1.1	0.77–1.68	0.51	NS
rs2240337	G allele	A allele	MAF	OR	95% CI	P	Pc
Control (n = 188)	350	26	0.07	-	-	-	-
Oligoarticular JIA (n = 30)	57	3	0.05	0.7	0.13–2.43	0.45	NS
RF positive, polyarticular JIA (n = 48)	85	11	0.12	1.7	0.75–3.82	0.14	NS
RF negative, polyarticular (n = 19)	37	1	0.03	0.4	0.01–2.36	0.25	NS
RF negative, oligo+poly articular (n = 49)	94	4	0.04	0.6	0.14–1.71	0.21	NS
Systemic JIA (n = 82)	149	15	0.18	1.4	0.65–2.74	0.38	NS
rs1748033	G allele	A allele	MAF	OR	95% CI	P	Pc
Control (n = 188)	239	137	0.36	-	-	-	-
Oligoarticular JIA (n = 30)	42	18	0.30	0.7	0.39–1.39	0.33	NS
RF positive, polyarticular JIA (n = 48)	55	41	0.43	1.3	0.80–2.10	0.29	NS
RF negative, polyarticular (n = 19)	26	12	0.32	0.8	0.36–1.72	0.55	NS
RF negative, oligo+poly articular (n = 49)	68	30	0.31	0.8	0.46–1.27	0.28	NS
Systemic JIA (n = 82)	120	44	0.27	0.6	0.42–0.97	0.03	NS

doi:10.1371/journal.pone.0171961.t003

Table 4. Association between PADI4 gene polymorphisms and ACPA positivity in oligo- and poly- articular JIA patients (n = 106).

		Anti-CCP (-) (<4.5U ml ⁻¹) (n = 58)	Anti-CCP (+) (≥4.5U ml ⁻¹) (n = 48)	OR	95% CI	P	Pc
rs2240340	allele	75	46	2	1.1–3.6	0.018	NS
	recessive	26	11	2.7	1.1–7.1	0.024	NS
	dominant	49	35	2	0.70–6.0	0.158	NS
rs2240337	allele	112	80	5.6	1.7–24	0.002	0.03
	recessive	54	32	6.6	1.9–30	<0.001	<0.001
	dominant	-	-	-	-	-	-
rs1748033	allele	80	52	1.9	1.0–3.4	0.03	NS
	recessive	30	14	2.6	1.1–6.4	0.029	NS
	dominant	53	38	2.8	0.78–11	0.095	NS

Recessive: GG versus (GA/AA), dominant: (GG/GA) versus AA

doi:10.1371/journal.pone.0171961.t004

Table 5. Association between PADI4 gene polymorphisms and SE positivity in oligo- and poly- articular JIA (n = 106).

		GG	GA/AA	OR	95% CI	P-value
rs2240340	SE-	20	31	1.4	0.60–3.5	0.42
	SE+	17	38	-	-	-
rs2240337	SE-	42	9	1.2	0.39–3.5	0.81
	SE+	44	11	-	-	-
rs1748033	SE-	23	28	1.3	0.57–3.1	0.56
	SE+	21	34	-	-	-

doi:10.1371/journal.pone.0171961.t005

Discussion

Susceptibility to RA is influenced by both genetic and environmental factors such as smoking. Many studies have determined that the major RA disease susceptibility genes are the HLA class II alleles. The shared epitope (SE) hypothesis for risk of RA is well-established [7], indicating that multiple HLA-DRB1 alleles are the strongest known genetic risk factors for RA by virtue of encoding a shared amino acid sequence, known as a shared epitope, SE [6]. Several studies have also reported associations between the genetic background and JIA susceptibility [5], including associations with HLA alleles [24–29]. An association between HLA-SE and susceptibility to JIA has been confirmed in 204 RF- or ACPA-positive Caucasian JIA patients [8].

The contribution of HLA to RA susceptibility, however, accounts for only about 30% of incidence, implying that genes other than those in the HLA region are involved; some estimates suggest as many as 100. Other genes influencing RA susceptibility have now been identified, such as PADI4, PTPN22 and CTLA4. Numerous non-HLA JIA susceptibility genes have also been imputed using GWAS [11]. Variants at the PTPN22, STAT4, TNF- α , TNFAIP3, MIF, WISP3, SLC11A1 and IL2-R α loci have been reported as risk factors for JIA by several investigators [5], although it was also reported that several of these are not necessarily shared between different ethnic groups [10,30]. Thus, there are likely to be different genetic risk factors for JIA in different ethnic groups. Therefore, here we sought an influence of HLA-SE and PADI4 on JIA susceptibility in Japanese, because both HLA-SE and PADI4 were reported as significant genetic risk factors for RA independent of ethnicity [14,15,31].

We previously reported an association of HLA-A*02:06 with JIA accompanied by uveitis and of HLA-DRB1*04:05 with polyarticular JIA [9]. In the present study, we confirmed the association between HLA-SE and RF-positive polyarticular JIA in Japanese. However, we found that HLA-SE was not associated with oligoarticular or systemic JIA in our cohort. Recently, it was reported that five amino acids in three HLA molecules, including three amino acid positions (11, 71 and 74) in HLA-DRB1, were associated with RF-seropositive RA by the HLA-imputation method [32]. It should therefore be evaluated whether these HLA amino acids are also associated with JIA susceptibility in future.

In addition to RF, ACPA is the most specific serologic marker in adult RA with a specificity of 95% and a sensitivity of 80%, similar to RF [33,34]. Considering all JIA subtypes together, ACPA was detected in 1.8–28.6% of patients, a low frequency compared to RA. However, ACPA was present in 70–90% of RF-positive polyarticular JIA patients [35]. Bone destruction is more severe in these ACPA-positive patients [36]. These results suggest that ACPA-positive polyarticular JIA may be similar to RA with regard to pathogenetic processes.

PADI4, a member of the PADI family, was first reported to be associated with RA in a Japanese population [12,13]. It encodes a peptidyl arginine deiminase responsible for the post-translational conversion of arginine residues into citrulline. We investigated associations between PADI4 gene polymorphisms and ACPA positivity in JIA in our Japanese population. The stability of PADI4 mRNA differs according to these gene polymorphisms, which may represent the mechanism by which it influences the production of ACPA [13]. To the best of our knowledge, there are no reports that PADI4 risk alleles are involved in JIA disease susceptibility. It is likely that PADI4 is also a JIA susceptibility gene in ethnic groups other than Japanese, especially in ACPA-positive JIA. This hypothesis needs further exploration.

We found no association between HLA-SE and PADI4 in JIA patients, implying that HLA-SE and PADI4 are independent JIA susceptibility genes. However, an association between HLA-SE and citrullination in the pathogenesis of RA has been noted [37]. The electropositive P4 pocket of HLA-DRB1*04:01/04 can accommodate citrulline-containing epitopes, and the CD4⁺ T cell repertoire for citrullinated antigens is increased in RA patients

harboring HLA-DRB1*04:01/04. These potential pathogenetic mechanisms may also contribute to JIA. Further study is needed to determine whether this is the case.

In conclusion, we found an association of PADI4 gene polymorphisms with ACPA-positivity in JIA, as was already known for RA. We also confirmed the influence of HLA-SE on RF-positive polyarticular JIA in the Japanese population. Thus, JIA may be classified into clinical and genetic background-based subtypes using HLA-SE and PADI4 genotyping.

Acknowledgments

This work was supported by a grant from Grand-in-Aid for Scientific Research from Japan Society for the Promotion of Science (No. 16790583).

Author Contributions

Conceptualization: KH MDY MM.

Data curation: KH MDY.

Formal analysis: KH MDY.

Funding acquisition: SY MM.

Investigation: KH MDY TN TM MK RH TI SY MM.

Methodology: KH MDY MM.

Project administration: MDY SY MM.

Resources: KH MDY TN TM MK RH TI SY MM.

Supervision: SY MM.

Validation: KH MDY TN MM.

Visualization: KH MDY MM.

Writing – original draft: KH MDY MK MM.

Writing – review & editing: KH MDY MK SY MM.

References

1. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. (2004) International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 31: 390–392. PMID: 14760812
2. Lin YT, Wang CT, Gershwin ME, Chiang BL (2011) The pathogenesis of oligoarticular/polyarticular vs systemic juvenile idiopathic arthritis. *Autoimmun Rev* 10: 482–489. doi: 10.1016/j.autrev.2011.02.001 PMID: 21320644
3. Mellins ED, Macaubas C, Grom AA. (2011) Pathogenesis of systemic juvenile idiopathic arthritis: some answers, more questions. *Nat Rev Rheumatol* 7: 416–426. doi: 10.1038/nrrheum.2011.68 PMID: 21647204
4. Rossi-Semerano L, Kone-Paut I. (2012) Is Still's Disease an Autoinflammatory Syndrome? *Int J Inflamm* 2012: 480373. doi: 10.1155/2012/480373 PMID: 22611516
5. Angeles-Han S, Prahalad S. (2010) The genetics of juvenile idiopathic arthritis: what is new in 2010? *Curr Rheumatol Rep* 12: 87–93. doi: 10.1007/s11926-010-0087-0 PMID: 20425016
6. Plenge RM. (2009) Rheumatoid arthritis genetics: 2009 update. *Curr Rheumatol Rep* 11: 351–356. PMID: 19772830
7. Gregersen PK, Silver J, Winchester RJ. (1987) The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. *Arthritis Rheum* 30: 1205–1213. PMID: 2446635

8. Prahalad S, Thompson SD, Conneely KN, Jiang Y, Leong T, Prozonc J, et al. (2012) Hierarchy of risk of childhood-onset rheumatoid arthritis conferred by HLA-DRB1 alleles encoding the shared epitope. *Arthritis Rheum* 64: 925–930. doi: [10.1002/art.33376](https://doi.org/10.1002/art.33376) PMID: [21953520](https://pubmed.ncbi.nlm.nih.gov/21953520/)
9. Yanagimachi M, Miyamae T, Naruto T, Hara T, Kikuchi M, Hara R, et al. (2011) Association of HLA-A*02:06 and HLA-DRB1*04:05 with clinical subtypes of juvenile idiopathic arthritis. *J Hum Genet* 56: 196–199. doi: [10.1038/hg.2010.159](https://doi.org/10.1038/hg.2010.159) PMID: [21179106](https://pubmed.ncbi.nlm.nih.gov/21179106/)
10. Okada Y, Terao C, Ikari K, Kochi Y, Ohmura K, et al. (2012) Meta-analysis identifies nine new loci associated with rheumatoid arthritis in the Japanese population. *Nat Genet* 44: 511–516. doi: [10.1038/ng.2231](https://doi.org/10.1038/ng.2231) PMID: [22446963](https://pubmed.ncbi.nlm.nih.gov/22446963/)
11. Okada Y, Wu D, Trynka G, Raj T, Terao C, Suzuki A, et al. (2014) Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature* 506: 376–381. doi: [10.1038/nature12873](https://doi.org/10.1038/nature12873) PMID: [24390342](https://pubmed.ncbi.nlm.nih.gov/24390342/)
12. Ikari K, Kuwahara M, Nakamura T, Momohara S, Hara M, Yamanaka H, et al. (2005) Association between PADI4 and rheumatoid arthritis: a replication study. *Arthritis Rheum* 52: 3054–3057. doi: [10.1002/art.21309](https://doi.org/10.1002/art.21309) PMID: [16200584](https://pubmed.ncbi.nlm.nih.gov/16200584/)
13. Suzuki A, Yamada R, Chang X, Tokuhira S, Sawada T, Suzuki M, et al. (2003) Functional haplotypes of PADI4, encoding citrullinating enzyme peptidylarginine deiminase 4, are associated with rheumatoid arthritis. *Nat Genet* 34: 395–402. doi: [10.1038/ng1206](https://doi.org/10.1038/ng1206) PMID: [12833157](https://pubmed.ncbi.nlm.nih.gov/12833157/)
14. Kang CP, Lee HS, Ju H, Cho H, Kang C, Bae SC, et al. (2006) A functional haplotype of the PADI4 gene associated with increased rheumatoid arthritis susceptibility in Koreans. *Arthritis Rheum* 54: 90–96. doi: [10.1002/art.21536](https://doi.org/10.1002/art.21536) PMID: [16385500](https://pubmed.ncbi.nlm.nih.gov/16385500/)
15. Kochi Y, Suzuki A, Yamada R, Yamamoto K. (2010) Ethnogenetic heterogeneity of rheumatoid arthritis—implications for pathogenesis. *Nat Rev Rheumatol* 6: 290–295. doi: [10.1038/nrrheum.2010.23](https://doi.org/10.1038/nrrheum.2010.23) PMID: [20234359](https://pubmed.ncbi.nlm.nih.gov/20234359/)
16. Gandjbakhch F, Fajardy I, Ferre B, Dubucquoi S, Filpo RM, Roger N, et al. (2009) A functional haplotype of PADI4 gene in rheumatoid arthritis: positive correlation in a French population. *J Rheumatol* 36: 881–886. doi: [10.3899/jrheum.080398](https://doi.org/10.3899/jrheum.080398) PMID: [19332633](https://pubmed.ncbi.nlm.nih.gov/19332633/)
17. Cheng J, Zhang H, Zhuang C, Liu R. (2012) Peptidylarginine deiminase type 4 and methyl-CpG binding domain 4 polymorphisms in Chinese patients with rheumatoid arthritis. *J Rheumatol* 39: 1159–1165. doi: [10.3899/jrheum.120007](https://doi.org/10.3899/jrheum.120007) PMID: [22505706](https://pubmed.ncbi.nlm.nih.gov/22505706/)
18. Cha S, Choi CB, Han TJ, Kang CP, Kang C, Bae SC, et al. (2007) Association of anti-cyclic citrullinated peptide antibody levels with PADI4 haplotypes in early rheumatoid arthritis and with shared epitope alleles in very late rheumatoid arthritis. *Arthritis Rheum* 56: 1454–1463. doi: [10.1002/art.22570](https://doi.org/10.1002/art.22570) PMID: [17469103](https://pubmed.ncbi.nlm.nih.gov/17469103/)
19. Vossenaar ER, Zendman AJ, van Venrooij WJ, Pruijn GJ. (2003) PAD, a growing family of citrullinating enzymes: genes, features and involvement in disease. *Bioessays* 25: 1106–1118. doi: [10.1002/bies.10357](https://doi.org/10.1002/bies.10357) PMID: [14579251](https://pubmed.ncbi.nlm.nih.gov/14579251/)
20. Chang X, Yamada R, Suzuki A, Sawada T, Yoshino S, Tokuhira S, et al. (2005) Localization of peptidylarginine deiminase 4 (PADI4) and citrullinated protein in synovial tissue of rheumatoid arthritis. *Rheumatology (Oxford)* 44: 40–50.
21. Foulquier C, Sebbag M, Clavel C, Chapuy-Regaud S, Al Badine R, Mechin MC, et al. (2007) Peptidylarginine deiminase type 2 (PAD-2) and PAD-4 but not PAD-1, PAD-3, and PAD-6 are expressed in rheumatoid arthritis synovium in close association with tissue inflammation. *Arthritis Rheum* 56: 3541–3553. doi: [10.1002/art.22983](https://doi.org/10.1002/art.22983) PMID: [17968929](https://pubmed.ncbi.nlm.nih.gov/17968929/)
22. Nakashima K, Hagiwara T, Yamada M. (2002) Nuclear localization of peptidylarginine deiminase V and histone deimination in granulocytes. *J Biol Chem* 277: 49562–49568. doi: [10.1074/jbc.M208795200](https://doi.org/10.1074/jbc.M208795200) PMID: [12333868](https://pubmed.ncbi.nlm.nih.gov/12333868/)
23. Kochi Y, Yamada R, Kobayashi K, Takahashi A, Suzuki A, Sekine A, et al. (2004) Analysis of single-nucleotide polymorphisms in Japanese rheumatoid arthritis patients shows additional susceptibility markers besides the classic shared epitope susceptibility sequences. *Arthritis Rheum* 50: 63–71. doi: [10.1002/art.11366](https://doi.org/10.1002/art.11366) PMID: [14730600](https://pubmed.ncbi.nlm.nih.gov/14730600/)
24. Barron KS, Silverman ED, Gonzales JC, Owerbach D, Reveille JD. (1992) DNA analysis of HLA-DR, DQ, and DP alleles in children with polyarticular juvenile rheumatoid arthritis. *J Rheumatol* 19: 1611–1616. PMID: [1391203](https://pubmed.ncbi.nlm.nih.gov/1391203/)
25. Clemens LE, Albert E, Ansell BM. (1983) HLA studies in IgM rheumatoid-factor-positive arthritis of childhood. *Ann Rheum Dis* 42: 431–434. PMID: [6603824](https://pubmed.ncbi.nlm.nih.gov/6603824/)
26. Forre O, Dobloug JH, Hoyeraal HM, Thorsby E. (1983) HLA antigens in juvenile arthritis. Genetic basis for the different subtypes. *Arthritis Rheum* 26: 35–38. PMID: [6401993](https://pubmed.ncbi.nlm.nih.gov/6401993/)

27. Nepom BS, Nepom GT, Mickelson E, Schaller JG, Antonelli P, Hansen JA, et al. (1984) Specific HLA-DR4-associated histocompatibility molecules characterize patients with seropositive juvenile rheumatoid arthritis. *J Clin Invest* 74: 287–291. doi: [10.1172/JCI111413](https://doi.org/10.1172/JCI111413) PMID: [6610692](https://pubmed.ncbi.nlm.nih.gov/6610692/)
28. Thomson W, Barrett JH, Donn R, Pepper L, Kennedy LJ, Ollier WE, et al. (2002) Juvenile idiopathic arthritis classified by the ILAR criteria: HLA associations in UK patients. *Rheumatology (Oxford)* 41: 1183–1189.
29. Vehe RK, Begovich AB, Nepom BS. (1990) HLA susceptibility genes in rheumatoid factor positive juvenile rheumatoid arthritis. *J Rheumatol Suppl* 26: 11–15. PMID: [2082016](https://pubmed.ncbi.nlm.nih.gov/2082016/)
30. Ikari K, Momohara S, Inoue E, Tomatsu T, Hara M, Yamanaka H, et al. (2006) Haplotype analysis revealed no association between the PTPN22 gene and RA in a Japanese population. *Rheumatology (Oxford)* 45: 1345–1348.
31. Lee YH, Bae SC. (2016) Association between susceptibility to rheumatoid arthritis and PADI4 polymorphisms: a meta-analysis. *Clin Rheumatol* 35: 961–971. doi: [10.1007/s10067-015-3098-4](https://doi.org/10.1007/s10067-015-3098-4) PMID: [26474773](https://pubmed.ncbi.nlm.nih.gov/26474773/)
32. Raychaudhuri S, Sandor C, Stahl EA, Freudenberg J, Lee HS, Jia X, et al. (2012) Five amino acids in three HLA proteins explain most of the association between MHC and seropositive rheumatoid arthritis. *Nat Genet* 44: 291–296. doi: [10.1038/ng.1076](https://doi.org/10.1038/ng.1076) PMID: [22286218](https://pubmed.ncbi.nlm.nih.gov/22286218/)
33. Schellekens GA, de Jong BA, van den Hoogen FH, van de Putte LB, van Venrooij WJ. (1998) Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. *J Clin Invest* 101: 273–281. doi: [10.1172/JCI11316](https://doi.org/10.1172/JCI11316) PMID: [9421490](https://pubmed.ncbi.nlm.nih.gov/9421490/)
34. Schellekens GA, Visser H, de Jong BA, van den Hoogen FH, Hazes JM, Breedveld FC, et al. (2000) The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. *Arthritis Rheum* 43: 155–163. doi: [10.1002/1529-0131\(200001\)43:1<155::AID-ANR20>3.0.CO;2-3](https://doi.org/10.1002/1529-0131(200001)43:1<155::AID-ANR20>3.0.CO;2-3) PMID: [10643712](https://pubmed.ncbi.nlm.nih.gov/10643712/)
35. Syed RH, Gilliam BE, Moore TL. (2008) Rheumatoid factors and anticyclic citrullinated peptide antibodies in pediatric rheumatology. *Curr Rheumatol Rep* 10: 156–163. PMID: [18460272](https://pubmed.ncbi.nlm.nih.gov/18460272/)
36. Lipinska J, Brozik H, Stanczyk J, Smolewska E. (2012) Anticitrullinated protein antibodies and radiological progression in juvenile idiopathic arthritis. *J Rheumatol* 39: 1078–1087. doi: [10.3899/jrheum.110879](https://doi.org/10.3899/jrheum.110879) PMID: [22382337](https://pubmed.ncbi.nlm.nih.gov/22382337/)
37. Scally SW, Petersen J, Law SC, Dudek NL, Nel HJ, Loh KL, et al. (2013) A molecular basis for the association of the HLA-DRB1 locus, citrullination, and rheumatoid arthritis. *J Exp Med* 210: 2569–2582. doi: [10.1084/jem.20131241](https://doi.org/10.1084/jem.20131241) PMID: [24190431](https://pubmed.ncbi.nlm.nih.gov/24190431/)



ORIGINAL ARTICLE

Characteristics of FDG-PET findings in the diagnosis of systemic juvenile idiopathic arthritis

Taichi Kanetaka^{1,2}, Masaaki Mori³, Ken-ichi Nishimura², Tomo Nozawa², Masako Kikuchi², Nodoka Sakurai², Ryoki Hara², Kazuko Yamazaki², and Shumpei Yokota²

¹Department of Pediatrics, Yokosuka Kyosai Hospital, Yokosuka, Japan, ²Department of Pediatrics, Yokohama City University School of Medicine, Yokosuka, Japan, and ³Department of Pediatrics, Yokohama City University Medical Center, Yokosuka, Japan

Abstract

Objective: To examine and delineate inflammatory focus in patients with juvenile idiopathic arthritis (JIA), ¹⁸F-Fluoro-deoxy-glucose (FDG)-positron emission tomography (PET) (¹⁸F-FDG-PET) was applied to patients with JIA, and the images of these patients were compared.

Methods: Sixty-eight children (59 with systemic JIA (s-JIA) and 9 with polyarticular JIA) were included. The diagnosis of JIA was done to meet the International League of Associations for Rheumatology (ILAR) criteria. After 6-h fasting, whole-body positron emission tomography (PET) scans were acquired 60 min after intravenous injection of 3–5 MBq/kg ¹⁸F-FDG. The interpretation of ¹⁸F-FDG uptake was based on visual characteristics.

Results: Two types of PET images were outstanding in s-JIA; one was ¹⁸F-FDG uptake in red bone marrow, such as the spine, pelvis, and long bones as well as spleen (12 cases), and other type was the uptake in the major joints, such as hips, elbows, wrists, knees, and ankles (8 cases). The former findings were correlated with elevated levels of inflammatory markers, while the latter were with significantly increased levels of MMP-3 ($p < 0.05$).

Conclusion: There was a noticeable accumulation of ¹⁸F-FDG uptake in bone marrow of s-JIA patients which may indicate the inflammatory focus of this disease and play an important role in the pathogenic basis of arthritis and systemic inflammation of s-JIA.

Keywords:

Diagnosis, F-Fluoro-deoxy-glucose-positron emission tomography, Systemic juvenile idiopathic arthritis

History

Received 1 April 2015

Accepted 3 August 2015

Published online 28 September 2015

Introduction

Systemic juvenile idiopathic arthritis (s-JIA) is a systemic chronic inflammatory disease, the main symptoms of which are remittent fever, rheumatoid rash, and arthritis [1]. During the clinical course, about 7% of patients suffer from macrophage activation syndrome (MAS), which can be life-threatening. Some patients develop MAS as the first symptom of the disease [2,3]. In s-JIA, the whole range of symptoms is rarely observed at the onset, with remittent fever being an early symptom in most cases, while arthritis tends to appear later. Therefore, early diagnosis is required but no appropriate diagnostic marker has been established to date. However, it has been determined that heme oxygenase-1 (HO-1) and interleukin-18 (IL-18) are markedly increased at the active phase of s-JIA, unlike in polyarticular and oligoarticular juvenile idiopathic arthritis, and these two factors have been reported to be useful serological diagnostic markers [4,5]. In addition, matrix metalloproteinase 3 (MMP-3), which is produced by inflamed synovial cells and fibroblasts, is a useful activity marker for cartilage destruction. It has become possible to diagnose the disease and evaluate its activity relatively easily. Together with a marked elevation in inflammatory markers, such as C-reactive protein (CRP) and blood sedimentation rate, the diagnosis of s-JIA can become more accurate.

Although s-JIA is currently classified as one subtype of JIA, there is a school of thought considering the disease as an autoinflammatory syndrome [6]. Affected joints are markedly different from polyarticular and oligoarticular JIA, and the process of cartilage and bone destruction is also different, suggesting that s-JIA is a different disease. Marked osteoporosis and poor development of epiphyseal nuclei are observed in the systemic type, whereas narrowing of the joint space is characteristic of the articular type [7,8], suggesting different mechanisms responsible for disease onset of systemic versus articular type.

In the present study, the primary inflammatory lesion was investigated by ¹⁸F-FDG-PET (FDG-PET) in >400 cases with remittent fever. The FDG-PET findings were compared in 59 cases of s-JIA diagnosed based on serological evaluation and clinical course, so that characteristic FDG-PET findings for the disease could be determined. In cases that do not receive a firm diagnosis, these characteristic FDG-PET findings may be used as potent diagnostic tools.

Patients and methods

A total of 68 cases with JIA examined by FDG-PET between January 2002 and December 2011 at our hospital were retrospectively investigated. There were 59 cases of s-JIA (31 boys and 28 girls; average age, 9.1 ± 3.9 years) and nine polyarticular JIA (p-JIA) (5 boys and 4 girls; average age, 11.6 ± 5.2 years). Joints at the bilateral shoulders, elbows, hands, hips, knees, and ankles were evaluated. Articular symptoms of tenderness and swelling of each joint were recorded. White blood cell count (WBC), CRP,

Correspondence to: Masaaki Mori, Department of Pediatrics, Yokohama City University Medical Center, 4-57 Urafune-cho, Minami-ku, Yokohama 232-0024, Japan. E-mail: mmori@med.yokohama-cu.ac.jp

serum amyloid A (SAA), erythrocyte sedimentation rate (ESR), ferritin, and FDP-E were assessed as inflammatory markers, while MMP-3 was used as a marker of articular destruction; plasma G-CSF, IL-6, and IL-18 were measured at the same time.

For FDG-PET, ^{18}F -FDG was intravenously infused after 6 h of fasting, and images were scanned 1 h later. SUVmax ≥ 0.5 was considered positive for defining ^{18}F -FDG accumulation. Next, clinical symptoms and laboratory data at the time of FDG-PET and accumulation patterns of ^{18}F -FDG were compared among the 12 joints listed above. In addition, cases with characteristic ^{18}F -FDG accumulation findings were extracted and their images were examined.

This study was carried out as part of advanced medical research of the hospital (Registration No. 158-1) and all patients participated in the study only after they gave informed consent.

Results

^{18}F -FDG accumulation in children without inflammation

After exploration of a remittent fever, a case without inflammation is presented here, as an example (Figure 1). In children without inflammation, ^{18}F -FDG accumulates in the brain, heart, bladder, and joints during growth. This patient is an 8-year-old girl with low-grade fever of unknown origin and pain in the extremities. Her complaints were severe and her parents wanted to have her examined as extensively as possible. We undertook FDG-PET after obtaining informed consent from her and her parents. It was confirmed that she had no inflammation and she was diagnosed as suffering from fibromyalgia.

Characteristics of ^{18}F -FDG accumulation in cases with p-JIA

In 11 cases with p-JIA, ^{18}F -FDG accumulation showed a diffuse distribution pattern in inflamed joints. It was often observed that ^{18}F -FDG accumulated in almost all large joints as in (Figure 2a) and (Figure 2b) or in those joints with severe inflammation as

in (Figure 2c). There was no accumulation in the bone marrow and no significant difference in accumulation in the liver or spleen.

Relationship between arthritis and ^{18}F -FDG accumulation in cases with p-JIA

Relationships between SUVmax and other laboratory data such as CRP, ESR, WBC, and MMP-3 were examined, but no significant correlations were found (Figure 2).



Figure 1. FDG-PET findings in a healthy child. Despite no abnormal inflammation, accumulation in the brain, heart, bladder, and joints at the growth stage is observed.

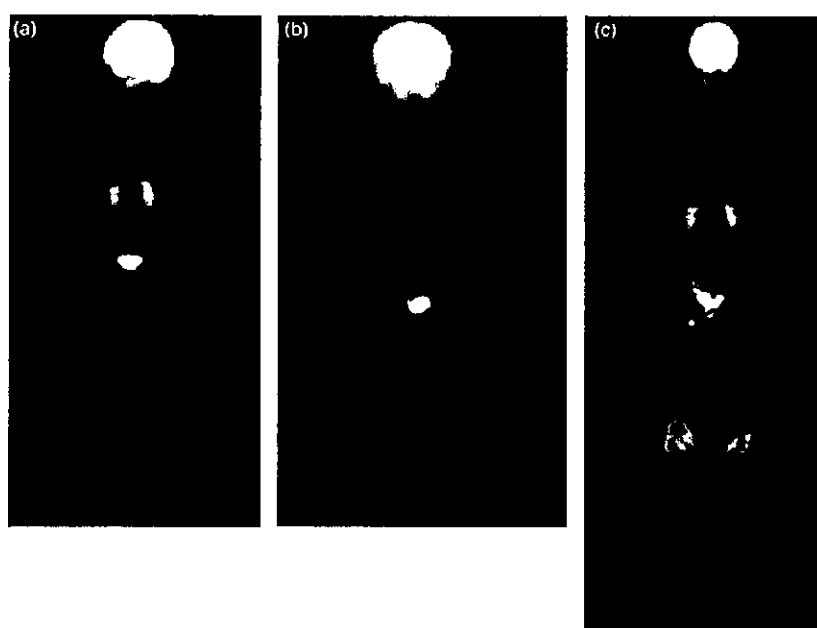


Figure 2. FDG accumulation in cases with p-JIA. (a) Accumulation is observed at the bilateral shoulders, elbows, wrists, and in the knees. In particular, marked accumulation was observed at the bilateral shoulders, the left elbow, and in the right knee. (b) Accumulation is observed at the bilateral shoulders, in the elbows, wrists, hips, knees, and ankles. (c) Marked accumulation is observed in the bilateral knees and the right wrist.

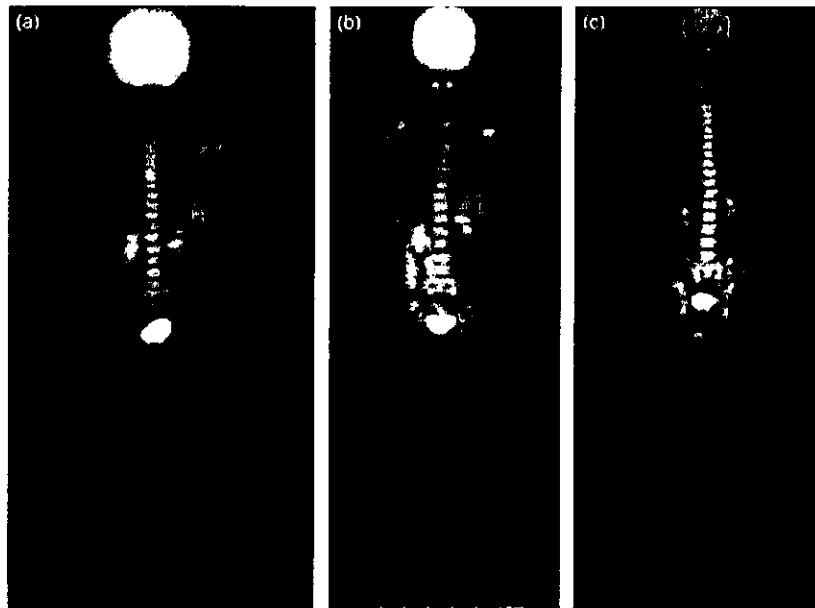


Figure 3. FDG accumulation in s-JIA (type I). (a) Accumulation is observed at the bilateral shoulders, in the vertebrae, pelvis, spleen, and bilateral knees. Accumulation is centered on the head of the humerus at the shoulder and the proximal tibial bone at the knee. (b) Accumulation is observed at the bilateral shoulders, in the vertebrae, pelvis, spleen, and bilateral knees. (c) Marked accumulation at the bilateral shoulders, in the vertebrae, pelvis, and spleen. Accumulation is also observed in the knee. At the shoulder and in the knee, accumulation is observed not in the joint but at the epiphysis (bone marrow tissue). In the pelvis, accumulation is marked at the ala of the ilium that contained red bone marrow.

Characteristics of ^{18}F -FDG accumulation in cases with s-JIA

There were two characteristic patterns in ^{18}F -FDG accumulation in the 59 cases with s-JIA. They were designated type I and type II as follows:

- (1) Characteristic accumulation was found in all vertebral bodies and pelvis and around large joints, such as shoulders and knees. The accumulation was not in the joint synovia but the bone itself or at the end of the long bones. It was considered that accumulation was not in the joints but in the bone marrow. In addition, compared with the liver, greater accumulation in the spleen was characteristic (Figure 3) (type I, 12 cases).
- (2) As in cases with p-JIA, diffuse accumulation in inflamed joints was recognized. There was no accumulation in the bone marrow and no significant difference between the liver and spleen (Figure 4) (type II, 8 cases).

Relationship between arthritis and ^{18}F -FDG accumulation in cases with s-JIA

Relationships between SUVmax and other laboratory data such as CRP, ESR, WBC, and MMP-3 were examined, but no significant correlations were found.

Comparison of different accumulation patterns in cases with s-JIA

Age, gender, duration from onset, treatment intervention, transition to MAS, reduction in the steroid dose 1 year later, cases treated with biological agents, and number of refractory cases were compared between type I and type II. With regard to laboratory data, WBC, CRP, SAA, ESR, ferritin, FDP-E, MMP-3, IL-6, IL-18, and G-CSF were compared (Tables 1 and 2, and Figure 5).

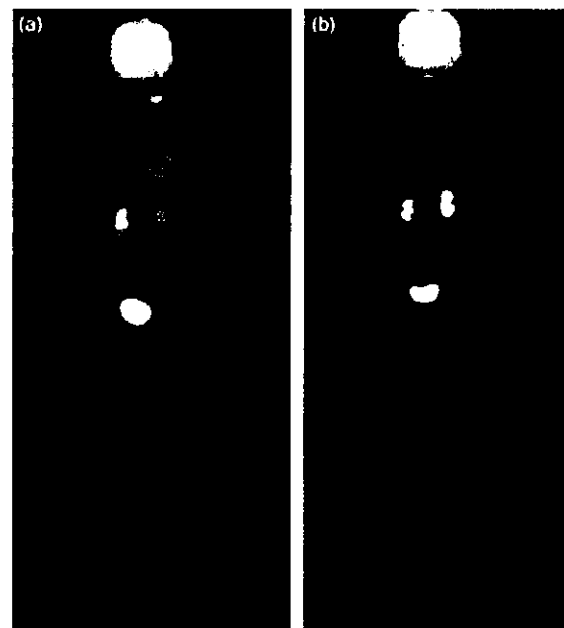


Figure 4. FDG accumulation in s-JIA (type II). (a) Accumulation is observed at the bilateral shoulders, in the elbows, hands, hips, knees, and ankles. In particular, it is marked in the hands, knees, and ankles. (b) Accumulation is observed at the bilateral shoulders, in the hands, knees, and ankles. It is marked in the knees and ankles.

Type I accumulation in FDG-PET was observed in boys, in particular, immediately after onset and before treatment; the risk of developing MAS seemed high. There was no significant difference in treatment resistance.

The test results (Figure 5) showed that inflammation markers such as WBC, CRP, SAA, ESR, ferritin, IL-6, IL-18, and G-CSF

were significantly higher in type I, whereas the synovitis marker MMP-3 was significantly higher in type II.

Discussion

FDG-PET results for the diagnosis of remittent fever and reference findings of JIA were collected for retrospective comparison over a 10-year period at our department. Of these, 68 cases with JIA were analyzed. In cases with p-JIA, ^{18}F -FDG accumulated in the joints with synovitis, as is seen in adult rheumatoid arthritis. These findings were almost identical to the physical, ultrasonographic, and magnetic resonance imaging (MRI) findings for arthritis. Although it was reported that SUVmax correlates with the severity

of arthritis, there was no such significant correlation in the present study. The degree of accumulation was influenced by the interval from radioisotope injection to scanning, a meal and exercise taken before the test, and age and body build of the subjects, and there was a large interindividual variation in measurements.

Characteristic images of ^{18}F -FDG accumulation in the red bone marrow tissue of the whole body were obtained in 12 cases, as shown in Figure 3. Among cases diagnosed with s-JIA, findings similar to those of p-JIA were sometimes obtained. Cases with accumulation in the bone marrow tissue had a shorter period from onset, had received less intensive treatment, and showed an increase in serological markers for systemic inflammatory status (WBC, CRP, SAA, ESR, ferritin, FDP-E, IL-6, IL-18, and G-CSF). Diagnosis of s-JIA at an early stage after onset is a critical issue for treatment selection; these findings will be useful for diagnosis in this regard.

For reference, in this study, FDG-PET images from 23 juvenile systemic lupus erythematosus patients, 20 juvenile dermatomyositis, 10 mixed connective tissue disease, 8 systemic sclerosis, and 10 Kawasaki disease patients were examined and no characteristic findings in these diseases were observed.

It has been demonstrated that imaging modalities are useful for the diagnosis and evaluation of arthritis in JIA, and recent advances in joint ultrasonography, in particular, for p-JIA, have been remarkable [9]. It is highly significant that this modality enables real-time evaluation of inflammation based on the presence of synovitis, retention of synovial fluid, stratification of synovial membrane, and increased blood flow by power Doppler imaging. Additionally, joint ultrasonography is useful for the evaluation of arthritis in cases with s-JIA, but differential diagnosis is very difficult when the patient presents with a remittent fever with unclear arthritis. However, an elevation in HO-1 [4] and IL-18 [5] is disease-specific and these can be useful serological markers for diagnosis. Therefore, it is expected that they will be widely used as serological markers.

FDG-PET showed characteristic findings in this study. In type I s-JIA, ^{18}F -FDG accumulation was observed in the bone marrow, in particular the red bone marrow, reflecting systemic inflammation; accumulation was also more marked in the spleen than in the liver. These findings are otherwise seen only in some diseases

Table 1. Comparison of type-I and type-II s-JIA (at scanning).

Background of s-JIA subtypes	s-JIA type I	s-JIA type II
Number of cases	12	8
Age (years) (range)	8.8 \pm 2.8 (3~14)	7.9 \pm 4.1 (3~18)
Boy:girl ratio	8:4	3:5
Duration from onset (months)	1.3 \pm 1.7 (0~10)	23.4 \pm 43 (0~66)
No treatment when PET taken	7 cases (58%)	1 case (13%)

Table 2. Comparison of type-I and type-II s-JIA (all clinical courses).

Course of s-JIA subtypes	s-JIA type I	s-JIA type II
Number of cases	12	8
Macrophage activation syndrome	3 cases (25%)	0 cases
Reduction rate of PSL dosage (after 1 year)	-63.1%	-54.9%
Treatment with biologics	11 cases (91.7%)	6 cases (85.7%)
Refractory cases	3 cases (1 articular 2 systemic course)	5 cases (all cases had articular courses)

Laboratory findings of s-JIA. Comparing Type I with Type II.

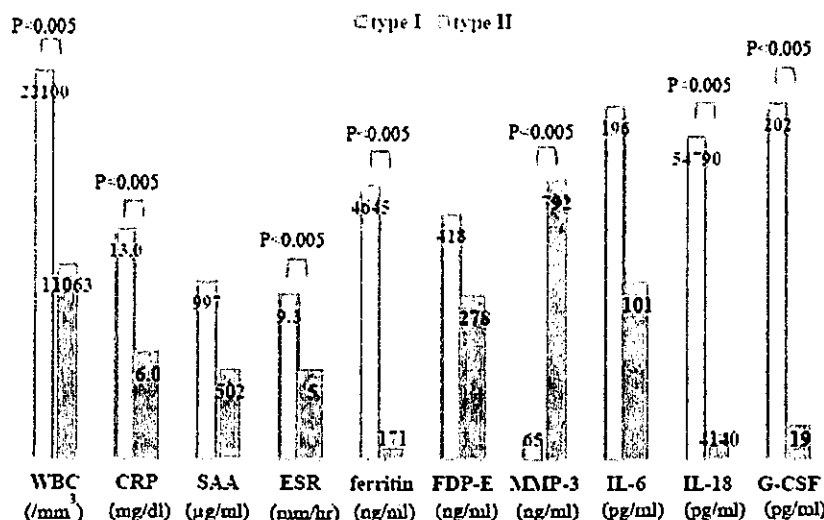


Figure 5. Laboratory findings of s-JIA: comparing type I with type II. Inflammation markers, such as WBC, CRP, SAA, ESR, ferritin, IL-6, IL-18, and G-CSF, were significantly higher in type I, whereas the synovitis marker MMP-3 was significantly higher in type II.

such as sepsis and are thus considered relatively specific for the diagnosis of s-JIA in combination with serological tests. FDG also accumulates in the bone marrow of patients with leukemia. Nevertheless, FDG-PET in s-JIA is different in that there is relatively homogeneous accumulation in the bone marrow, whereas in leukemia it has a speckled distribution.

It should be noted that adult-onset Still's disease, a disease similar to s-JIA, also exhibits characteristic accumulation of ^{18}F -FDG in the bone marrow, spleen, and lymph nodes, and FDG-PET is considered an effective modality for its diagnosis at the stage of exploration of remittent fever in adults [10]. In addition, FDG accumulation was observed in inflamed joints as a characteristic finding in type-II s-JIA, suggesting synovitis. Furthermore, there was no significant difference in the amount of FDG accumulation in the liver relative to the spleen, and there was no accumulation in the bone marrow. In type-II s-JIA, some cases manifest arthritis as the main symptom after a long clinical course, while others have a tendency to improve after anti-inflammatory treatment such as with steroids. The clinical course of type-I and type-II s-JIA is different, as reflected in differences at the sites of ^{18}F -FDG accumulation. In p-JIA, ^{18}F -FDG accumulated only at the joints with inflammation and there was no significant difference in the accumulation in the bone marrow and spleen. These findings are consistent with the FDG-PET findings observed in adult rheumatoid arthritis [11] and are interpreted as ^{18}F -FDG accumulation at the joint synovial membrane and synovial fluid in the joint capsule. s-JIA rarely develops a remittent fever, rash, and arthritis at the same time during disease progression. It starts with a remittent fever and rash, following which arthritis develops, and in the long-term eventually causes problems in daily life activities due to polyarthritis [2]. It is an inflammatory disease in which systemic inflammation precedes the appearance of arthritis that eventually becomes the main symptom.

Exploration by FDG-PET in this study showed two patterns of type-I and type-II s-JIA ^{18}F -FDG accumulation, with type-I revealing a pattern at the early stage after onset based on clinical findings and laboratory data, and showing inflammation localized to the bone marrow and spleen. In contrast, type II is an advanced inflammatory disease and progression to arthritis is expressed similarly to p-JIA and rheumatoid arthritis.

According to the national survey on exploration of "remittent fever," s-JIA is the most frequent outcome with a definite diagnosis [12]. In general, it takes a long time before a definite diagnosis can be made. In addition, 6.8 to 13% of cases develop MAS and their prognosis is often poor [13]. Therefore, early diagnosis is desirable for s-JIA to initiate appropriate mitigating treatment. Our results that FDG-PET showed a characteristic accumulation pattern for early systemic inflammation indicate that this imaging modality is useful for early diagnosis of s-JIA.

Accumulation of ^{18}F -FDG in the bone marrow suggests that these cells are proliferating, and differentiating [14]. G-CSF and GM-CSF administered to counter the adverse effects of chemotherapy is associated with accumulation of ^{18}F -FDG in the bone marrow and spleen [15]. In that study, plasma G-CSF levels were markedly increased at the time of FDG-PET in cases with s-JIA [15], most of whom also showed an increase in peripheral blood granulocytes. Therefore, it was suggested that excessive G-CSF was involved in the accumulation of ^{18}F -FDG in systemic inflammation at the early stage of s-JIA, and thus not only IL-6 but also G-CSF was potentially involved in disease pathogenesis [16].

Because HO-1 and IL-18 are increased in the serum [4,5] and amyloidosis is an important factor influencing the development of joint destruction, marked osteoporosis [6], and the prognosis of s-JIA, it is clear that this disease exhibits different characteristics relative to p-JIA. The systemic type has the characteristics of

an "autoinflammatory syndrome" as a systemic inflammatory disease lacking associations with external factors, and its tentative assignment into this disease category is currently under consideration [17,18].

Characteristics of FDG-PET findings were elucidated in the present study. After infectious disease and malignancy were ruled out based on a blood culture test and bone marrow testing, the findings of FDG accumulation in the bone marrow (red bone marrow) and spleen are consistent with the proposal that s-JIA should be classified as an "autoinflammatory disease." Investigations of larger numbers of similar cases to support the utility of FDG-PET for disease diagnosis is now required.

Conflict of interest

Masaaki Mori has received lecture fees from MSD, Sumitomo Dainippon Pharma, and Pfizer Japan Inc, and has served as a consultant adviser to Bristol-Myers Squibb and Astellas Pharm. Shumpei Yokota hold a patent for tocilizumab and receives royalties for Actemra. All other authors have declared no conflicts of interest.

References

1. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldberg J, He X. International league of associations for rheumatology classification of juvenile idiopathic arthritis: second revision. Edmonton. 2001. *J Rheumatol*. 2004;31:390-2.
2. Yokota S. Juvenile rheumatoid arthritis (in Japanese). *Nihon Rinsho*. 2005;63Suppl5:274-80.
3. Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet*. 2007;369:767-78.
4. Takahashi A, Mori M, Naruto T, Nakajima S, Miyamae T, Imagawa T, et al. The role of heme oxygenase-1 in systemic-onset juvenile idiopathic arthritis. *Mod Rheumatol*. 2009;19(3):302-8.
5. Maeno N, Takei S, Imanaka H, Yamamoto K, Kuriwaki K, Kawano Y, et al. Increased interleukin-18 expression in bone marrow of a patient with systemic juvenile idiopathic arthritis and unrecognized macrophage-activation syndrome. *Arthritis Rheum*. 2004;50(6):1935-58.
6. Ozawa R, Inaba Y, Mori M, Hara R, Kikuchi M, Higuchi R, et al. Definitive differences in laboratory and radiological characteristics between two subtypes of juvenile idiopathic arthritis: systemic arthritis and polyarthritis. *Mod Rheumatol*. 2012;22(4):558-64.
7. Reed MH, Wilmet DM. The radiology of juvenile rheumatoid arthritis. A review of the English language literature. *J Rheumatol*. 1991;Suppl31:2-22.
8. Inaba Y, Ozawa R, Imagawa T, Mori M, Hara R, Miyamae T, et al. Radiographic improvement of damaged large joints in children with systemic juvenile idiopathic arthritis following tocilizumab treatment. *Ann Rheum Dis*. 2011;70(9):1693-5.
9. Janow GL, Panghual V, Trinh A, Badger D, Levin TL, Howite NT. Detection of active disease in juvenile idiopathic arthritis: sensitivity and specificity of the physical examination vs. ultrasound. *J Rheumatol*. 2011;38(12):2671-4.
10. Yamashita H, Kubota K, Takahashi Y, Minumimoto R, Morooka M, Kaneko H, et al. Clinical value of ^{18}F -fluoro-deoxyglucose positron emission tomography/computed tomography in patients with adult-onset Still's disease: a seven-case series and review of the literature. *Mod Rheumatol*. 2014;24(4):645-50.
11. Beckers C, Ribbens C, André B, Marcelis S, Kaye O, Mathy L, et al. Assessment of disease activity in rheumatoid arthritis with ^{18}F -FDG PET. *J Nucl Med*. 2004;45(6):956-64.
12. Kasai K, Mori M, Hara R, Miyamae T, Imagawa T, Yokota S. National survey of childhood febrile illness cases with fever of unknown origin in Japan. *Pediatr Int*. 2011;53(4):421-5.
13. Minoia F, Davi S, Horne A, Demirkaya E, Bovis F, Li C, et al. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients. *Arthritis Rheumatol*. 2014;66(11):3160-9.
14. Morooka M, Kubota K, Murata Y, Shibuya H, Ito K, Mochizuki M, et al. ^{18}F -FDG-PET/CT findings of granulocyte colony stimulating

- factor (G-CSF)-producing lung tumors. *Ann Nucl Med.* 2008; 22(7):635-9.
15. Goshen E, Davidson T, Yeshurun M, Zwas ST. Combined increased and decreased skeletal uptake of F-18 FDG. *Clin Nucl Med.* 2006;31(9):520-2.
16. Yokota S, Miyamae T, Imagawa T, Iwata N, Katakura S, Mori M. Inflammatory cytokines and systemic-onset juvenile idiopathic arthritis. *Mod Rheumatol.* 2004;14(1):12-17.
17. Hinks A, Martin P, Thompson SD, Sudman M, Stock CJ, Thomson W, et al. Autoinflammatory gene polymorphisms and susceptibility to UK juvenile idiopathic arthritis. *Pediatr Rheumatol Online J.* 2013;11(1):14.
18. Lin YT, Wang CT, Gershwin ME, Chiang BL. The pathogenesis of oligoarticular/polyarticular vs. systemic juvenile idiopathic arthritis. *Autoimmun Rev.* 2011;10(8):482-9.

RESEARCH ARTICLE

Open Access



Optimal regimens of sulfamethoxazole-trimethoprim for chemoprophylaxis of *Pneumocystis* pneumonia in patients with systemic rheumatic diseases: results from a non-blinded, randomized controlled trial

Masako Utsunomiya^{1,2,3}, Hiroaki Dobashi⁴, Toshio Odani^{5,18}, Kazuyoshi Saito⁶, Naoto Yokogawa⁷, Kenji Nagasaka^{1,2,8}, Kenchi Takenaka^{2,8}, Makoto Soejima^{8,19}, Takahiko Sugihara⁹, Hiroyuki Hagiyama¹⁰, Shinya Hirata¹¹, Kazuo Matsui^{12,20}, Yoshinori Nonomura¹³, Masahiro Kondo¹⁴, Fumihito Suzuki^{15,21}, Makoto Tomita¹⁶, Mari Kihara^{1,2}, Waka Yokoyama^{1,2}, Fumio Hirano^{1,2}, Hayato Yamazaki^{1,2}, Ryoko Sakai^{1,2,17}, Toshihiro Nanki^{1,2,22}, Ryuji Koike^{1,2}, Hitoshi Kohsaka², Nobuyuki Miyasaka² and Masayoshi Harigai^{1,2,17*}

Abstract

Background: Sulfamethoxazole-trimethoprim (SMX/TMP) is a standard drug for the prophylaxis of *Pneumocystis* pneumonia (PJP) in immunosuppressed patients with systemic rheumatic diseases, but is sometimes discontinued due to adverse events (AEs). The objective of this non-blinded, randomized, 52-week non-inferiority trial was to quest an effective chemoprophylaxis regimen for PJP with a low drug discontinuation rate. Results at week 24 were reported.

Methods: Adult patients with systemic rheumatic diseases who started prednisolone ≥ 0.6 mg/kg/day were randomized into three dosage groups: a single-strength group (SS, SMX/TMP of 400/80 mg daily), half-strength group (HS, 200/40 mg daily), and escalation group (ES, started with 40/8 mg daily, increasing incrementally to 200/40 mg daily). The primary endpoint was non-incidence rates (non-IR) of PJP at week 24.

Results: Of 183 patients randomly allocated at a 1:1:1 ratio into the three groups, 58 patients in SS, 59 in HS, and 55 in ES started SMX/TMP. A total of 172 patients were included in the analysis. No cases of PJP were reported up to week 24. Estimated non-IR of PJP in patients who received daily SMX/TMP of 200/40 mg, either starting at this dose or increasing incrementally, was 96.8–100% using the exact confidence interval as a post-hoc analysis. The overall discontinuation rate was significantly lower with HS compared to SS ($p = 0.007$). The discontinuation rates due to AEs were significantly lower with HS ($p = 0.006$) and ES ($p = 0.004$) compared to SS. The IR of AEs requiring reduction in the dose of SMX/TMP ($p = 0.009$) and AEs of special interest ($p = 0.003$) were different among the three groups with significantly higher IR in SS compared to HS and ES.

(Continued on next page)

* Correspondence: harigai.masayoshi@twmu.ac.jp

¹Department of Pharmacovigilance, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU), 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan

²Department of Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU), 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan

Full list of author information is available at the end of the article



© The Author(s). 2017 **Open Access** This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated.

(Continued from previous page)

Conclusions: Although there were no PJP cases, the combined group of HS and ES had an excellent estimated non-IR of PJP and both were superior in safety to SS. From the perspective of feasibility and drug discontinuation rates, the daily half-strength regimen was suggested to be optimal for prophylaxis of PJP in patients with systemic rheumatic diseases.

Trial registration: The University Hospital Medical Information Network Clinical Trials Registry number is UMIN000007727, registered 10 April 2012.

Keywords: *Pneumocystis pneumonia*, Sulfamethoxazole-trimethoprim, Prophylaxis, Efficacy, Safety, Drug discontinuation rate, Rheumatic disease, Randomized controlled trial

Background

Pneumocystis pneumonia (PJP; also known as PCP) is a potentially life-threatening opportunistic infection caused by *Pneumocystis jirovecii* [1, 2]. It has a predilection for immunocompromised patients. In the absence of chemical prophylaxis, the incidence of PJP is more than 50% in human immunodeficiency virus (HIV)-positive patients [3], 22–45% in patients with hematological malignancy [4, 5], and 5–10% in post-organ transplantation patients [4, 6–8]. In rheumatic diseases, the overall incidence is around 2% [9, 10]; however, the risk is increased by the use of moderate to high doses of corticosteroids and concomitant immunosuppressive drugs and by demographic characteristics and comorbidities of patients [11–14].

It is also known that morbidity differs according to underlying rheumatic diseases: 8–12% in granulomatosis with polyangiitis, 6.5% in polyarteritis nodosa, 2.7% in polymyositis/dermatomyositis, 2% in systemic lupus erythematosus, and 0.1–0.3% in rheumatoid arthritis [15]. From the results of post-marketing surveillance programs for tumor necrosis factor inhibitors in patients with rheumatoid arthritis in Japan, the incidence rates of PJP were higher compared to those in the USA [16–18]. In patients who started corticosteroids, conventional immunosuppressants or biologics for active rheumatic diseases, PJP is reported to be the second most frequent pulmonary infection after bacterial pneumonia [19]. It is also reported that when HIV-negative patients develop PJP, the onset is more abrupt and mortality is higher compared to that in HIV-positive patients [1, 20, 21].

The most common and effective prophylactic method against PJP is the oral administration of low-dose sulfamethoxazole-trimethoprim (SMX/TMP) [22, 23]. SMX-TMP consists of two components, SMX and TMP, both of which inhibit different enzymes in the folate synthetic pathway of *Pneumocystis* [24]. In HIV-positive patients the prevention rate has been reported to be 89–100% [25–28] if taken properly. Despite the high efficacy of SMX/TMP, clinicians often have to stop or reduce the dose of the

drug due to adverse events (AEs) such as gastrointestinal symptoms, rash, increased serum creatinine, renal tubular acidosis, elevation of liver enzymes, hypoglycemia, hyperkalemia, and hyponatremia [29–31]. As a second line drug, pentamidine isethionate, dapsone, or atovaquone is sometimes used, but these drugs are inferior to SMX/TMP in prophylactic effect [22, 32]. Because patients with rheumatic diseases are frequently in need of long-term or sometimes lifelong immunosuppressive therapy, it would be very helpful to have an effective chemoprophylaxis regimen with a high drug retention rate.

Takenaka et al. [33] conducted a retrospective study to compare the effectiveness and safety of the conventional regimen (one daily single-strength tablet of SMX/TMP, 400 mg/80 mg) and the dose escalation regimen (started with the 10% dose of one single-strength tablet and increased the dose by 10% per week). They reported that there was no significant difference in the prophylactic effect on PJP; however, the drug retention rate of the dose escalation regimen group was better than that of the conventional regimen group. There is also a systematic literature review and meta-analysis involving 1245 non-HIV adults and children with hematologic malignancies, bone marrow transplants, or organ transplants. No differences in the efficacy between one daily double-strength (DS) tablet and one DS tablet thrice a week were reported [28]. Despite these efforts, the optimal dose and regimen for prophylaxis of PJP in HIV-negative patients is yet to be determined.

We hypothesized that SMX/TMP of 200 mg/40 mg with dose escalation had a better drug retention rate and consequently a better prevention rate than SMX/TMP of daily 400 mg/80 mg. Considering a cumbersome prescription of the drug with dose escalation, we also set up an arm of SMX/TMP of 200 mg/40 mg without dose escalation. We conducted an open, randomized controlled trial (RCT) for 52 weeks involving 183 patients with systemic rheumatic diseases starting prednisolone ≥ 0.6 mg/kg/day to compare the efficacy, safety, and treatment discontinuation rates of the three regimens. Here, we

report the results of the interim analysis of this study up to week 24.

Methods

Patients

This study was implemented in five university hospitals and 10 referral hospitals in Japan. Patients were eligible for enrollment if they fulfilled all the following criteria: (1) being 20 years of age or older; (2) being admitted to one of the participating institutions for treatment of new-onset or relapsed systemic rheumatic diseases in the period from 30 March 2012 to 28 February 2015; (3) giving written informed consent; (4) starting 0.6 mg/kg/day or more of oral prednisolone or equivalent doses of corticosteroids regardless of concomitant immunosuppressive drugs; (5) having not used SMX/TMP, pentamidine isethionate, or dapsone previously; and (6) having serum creatinine within the upper limit of the normal range of the institution. Major exclusion criteria were: (1) withdrawing consent; (2) having contraindications to SMX/TMP; (3) using biologic agents; (4) having a history of PJP; (5) having uncontrollable complications; (6) having body weight below 40 kg; (7) being pregnant or a nursing woman; (8) planning to be pregnant within 24 weeks; and/or (9) being unable to start SMX/TMP within 10 days of starting prednisolone.

Study design

This study is a multicenter, open RCT. We performed computer-based, central, dynamic allocation by using block randomization. When attending physicians registered patients to the website, they were automatically randomly allocated by computer into the single-strength dosage group (SS), the half-strength dosage group (HS), or the escalation dosage group (ES), at the ratio of 1:1:1. All patients were prescribed SMX/TMP in granule form. Patients in SS started SMX/TMP at the dose of a single-strength tablet (400 mg/80 mg) and continued the same dose for 24 weeks. Patients in HS started SMX/TMP at the half-dose of a single-strength tablet (200 mg/40 mg) and continued the same dose for 24 weeks. Patients in ES started SMX/TMP at 10% of the dose of a single-strength tablet (40 mg/8 mg), and the dose was increased by 10% weekly up to the half-dose of a single-strength tablet (200 mg/40 mg) and was continued up to week 24. If SMX/TMP was discontinued before week 24 due to any reason, onward prophylaxis was at the discretion of attending physicians.

After week 24, the use of SMX/TMP including doses and intervals, and treatment duration were determined by the attending physician. The observation period was up to week 52 irrespective of continuation/discontinuation of SMX/TMP unless a patient met the exclusion

criteria. With regard to the protocol, as described in "Statistical analyses", we increased the number of cases because the number of participants meeting the exclusion criteria was greater than expected. There was no change in eligibility criteria during the trial. This study was approved by the ethics committee of the Tokyo Medical and Dental University Hospital (TMDU) (#2349) and those of the participating institutions (Additional file 1: Table S1). This study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000007727).

Endpoints and objectives

The primary endpoint was the non-incidence rate of PJP (i.e., prevention rate) at week 24. Secondary endpoints were the following: PJP non-incidence rate at week 52, treatment discontinuation rate, and AEs. The primary objective of this study was to show non-inferiority of ES to SS in terms of non-incidence rates of PJP at week 24. No patients developed PJP by week 24; thus, we estimated the non-incidence rates of PJP using the exact confidence interval [33] as a post-hoc analysis. The secondary objectives were to compare PJP non-incidence rates between HS and SS, and drug retention rates and safety among the three groups.

If cases of PJP, suspected PJP, or serious AEs were reported, a clinical event review committee would be convened according to the study protocol. It comprised three physicians and included experts in pulmonary medicine, infectious diseases, and rheumatology. Validation of PJP as an endpoint was planned to be performed by the clinical event review committee.

Statistical analyses

The full analysis set (FAS) of patients in this study were those who were enrolled in this study, met the inclusion criteria, did not meet the exclusion criteria, received at least one dose of SMX/TMP as a study drug, and had at least one follow-up visit after starting the drug. We used the FAS of the patients to analyze efficacy, safety, and treatment discontinuation rates. An intention-to-treat analysis was used for assessment of efficacy.

With respect to sample size, we assumed the PJP non-incidence rate in SS to be 93% and that in ES to be 98%, assuming that a lower discontinuation rate in the latter would result in better efficacy [23, 33]. We set a non-inferiority limit of 5%, one-sided α of 0.05, and β of 0.20. Assuming a percentage of patients who were randomized but did not meet the aforementioned criteria of FAS (i.e., FAS exclusion) as 5%, we calculated the sample size to be 55 for each group and a total of 165 patients. However, at one year after the start of the enrollment, the percentage for FAS exclusion was found to be more than 5%. We recalculated the sample

size assuming the percentage to be 10%, and enrolled 58 patients in each group, giving a total of 174 patients.

For statistical analysis we used SPSS (ver.20). Data in accordance with the normal distribution were assessed by the mean value \pm standard deviation, and data that did not conform to the normal distribution were assessed by the median and interquartile range. With regard to primary outcome, we interpreted that non-inferiority will be proved if the lower limit of the 95% confidence interval of the difference between SS and ES was greater than -5%. For secondary outcomes, we used Kaplan-Meier methods and the log-rank test to analyze non-incidence rates and treatment discontinuation rates, and Fisher's exact test with adjusted residuals to analyze the incidence of AEs. If a patient stopped taking SMX/TMP and restarted the drug within one week, we deemed the treatment as being continued. The protocol of this trial will be provided on request.

Results

Randomization and follow-up

The patient disposition is shown in Fig. 1. One-hundred and eighty-three patients were randomized into SS ($n = 62$), HS ($n = 61$), or ES ($n = 60$). Four patients in SS, two in HS, and five in ES were found to be ineligible after randomization and were excluded: 58 patients in SS, 59 in HS, and 55 in ES started treatment with SMX/TMP and met the definition of the FAS. Two patients in SS, two in HS, and three in ES discontinued

the study because of transfer to another hospital or death. There were 24 patients in SS, 11 in HS, and 14 in ES who stopped or reduced the dosages of SMX/TMP due to AEs, prescription errors, or at the discretion of the attending physician (Fig. 1). All patients except those who died or were transferred to other hospitals were followed for 24 weeks.

Baseline characteristics of the patients

Baseline characteristics of the FAS of the patients are shown in Table 1. The average age was around 60 years in each group. The proportion of the patients with underlying polymyositis or dermatomyositis in HS and of patients with vasculitis syndrome in SS was slightly higher. Median duration of underlying disease was 2–4 months. The proportion of the patients with interstitial lung disease as a comorbidity was almost the same across all groups, except for other lung diseases in SS and diabetes mellitus in ES, which were slightly higher than in the others.

Corticosteroids were used before enrollment by 13.3–15.5% of patients and the dose of prednisolone was 0.94–0.97 mg/kg/day when starting SMX/TMP across all three groups. Prednisolone dose at week 24 was around 10 mg/day in each group. The proportions of patients who used methylprednisolone pulse therapy between weeks 0 and 12 and those of patients who used immunosuppressive drugs between weeks 0–12 and weeks 12–24 were slightly different among the three groups.

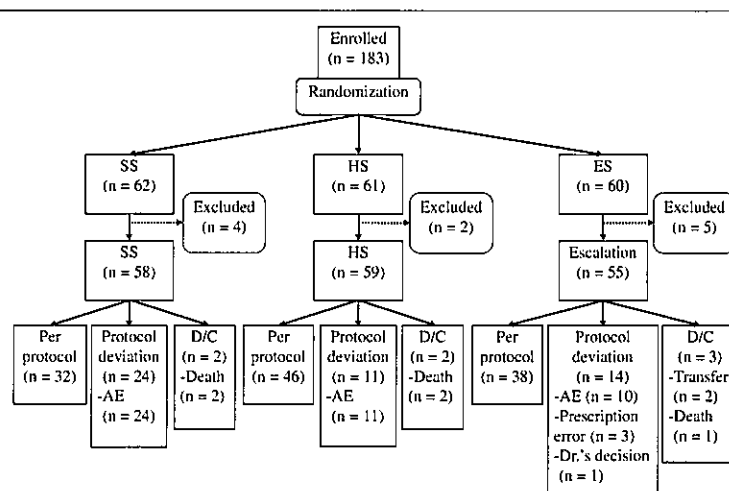


Fig. 1 Randomization and follow-up. There were 183 patients randomized into the single-strength sulfamethoxazole-trimethoprim (SMX/TMP) dosage group (SS) ($n = 62$), half-strength dosage group (HS) ($n = 61$), and the escalation dosage group (ES) ($n = 60$). There were 4 patients in SS, 2 in HS, and 5 in ES who were found to be ineligible after randomization and were excluded. There were 58 patients in SS, 59 in HS, and 55 in ES who started treatment with SMX/TMP and met the definition of the full analysis set (FAS). Of these, in SS, HS, and ES, respectively, 2, 2, and 3 patients discontinued this study because of transfer to another hospital or death, and 24, 11, and 14 patients stopped or reduced SMX/TMP because of adverse events (AE), prescription error, or on the decision of the attending physician. D/C discontinued

Table 1 Patient characteristics

	SS (n = 58)	HS (n = 59)	ES (n = 55)
Age, years	58.5 ± 15.0	58.1 ± 15.9	60.1 ± 14.4
Female, %	63.8	64.4	70.9
Body weight, kg	55.9 ± 11.8	56.8 ± 10.9	54.5 ± 9.9
Diagnosis			
RA, %	8.6	6.8	7.3
SLE, %	10.3	11.9	10.9
PM/DM, %	19.0	37.3	29.1
Vasculitis syndrome, %	44.8	25.4	30.9
Others ^a , %	17.2	18.6	21.8
Disease duration, months (IQR)	2 (1–5)	3 (2–7)	4 (2–9)
Comorbidities, %	72.4	79.7	78.2
ILD, %	38.0	44.1	43.6
Other lung comorbidities ^b , %	12.1	8.5	5.5
Hypertension, %	13.8	18.6	14.5
Diabetes, %	6.9	5.1	14.5
CVD ^c , %	3.4	5.1	5.5
CKD, %	1.7	0	0
Malignancies, %	6.9	11.9	9.1
Others, %	41.4	42.3	36.4
Baseline laboratory data			
WBC, /μL (NR, 3300–8600)	10401 ± 5359	9901 ± 4767	9743 ± 5177
Lymphocyte, /μL	1766 ± 1106	1933 ± 1244	1656 ± 877
IgG, mg/dL (NR, 861–1747)	1676 ± 677	1668 ± 679	2006 ± 1945
Treatment before enrollment ^d			
CS, %	15.5	13.3	14.5
Dosage of CS ^e , mg/day (IQR)	13.8 (5–15)	8.8 (5–10.6)	6.8 (5–8.125)
IS ^f , %	1.7	3.2	7.3
Biologics, %	1.7	0	0
Dosage of concomitant CS			
At baseline, mg/kg/day (IQR)	0.97 (0.89–1.01)	0.97 (0.81–1.02)	0.94 (0.75–1.05)
At week 24, mg/day (IQR)	12.5 (10–14.25)	11 (9–15)	10 (9–12.5)
Other immunosuppressive treatment between weeks 0 and 12			
IV pulsed mPSL, %	20.6	32.2	20
IS, %	70.6	67.8	81.8
Biologics, %	1.7	3.4	1.8
Other immunosuppressive treatment between weeks 12 and 24			
IV pulsed mPSL, %	1.7	3.4	0
IS, %	65.5	72.9	78.2
Biologics, %	1.7	1.7	3.6

Values that conform to the normal distribution are expressed as the mean ± SD. Values that do not conform to the normal distribution are expressed as the median (interquartile range). ^aOthers include systemic sclerosis, mixed connective tissue diseases, Sjogren's syndrome, adult-onset Still's disease, relapsing polychondritis, IgG4-related disease, and antiphospholipid syndrome. ^bOther lung comorbidities include chronic obstructive lung disease, bronchiectasis, bronchial asthma, pulmonary hypertension, and old tuberculosis. ^cCardiovascular diseases include cerebral infarction, cerebral hemorrhage, myocardial infarction, and angina pectoris. ^dTreatment between 84 days and 1 day before starting or intensifying immunosuppressive treatment. ^ePrednisolone equivalent dose. ^fImmunosuppressive drugs include azathioprine, cyclophosphamide, cyclosporine, methotrexate, mizoribine, and mycophenolate mofetil, and tacrolimus. SS the single-strength dosage group, HS the half-strength dosage group, ES the escalation dosage group, RA rheumatoid arthritis, SLE systemic lupus erythematosus, PM polymyositis, DM dermatomyositis, IQR interquartile range, ILD interstitial lung disease, CVD cardiovascular disease, CKD chronic kidney disease, WBC white blood cell, NR normal range, CS corticosteroids, mPSL methylprednisolone, IS immunosuppressive drugs, IV intravenous

Efficacy and drug discontinuation rate

Although the primary objective of this study was to compare the non-incidence rates of PJP at week 24 in SS and ES, no cases of PJP were reported up to week 24 in any group. As a post-hoc analysis, we estimated the non-incidence rates of PJP using the exact confidence interval [34]. The estimated non-incidence rates in SS, HS, and ES were 93.8–100%, 93.9–100%, and 93.5–100%, respectively. Because the patients in HS and ES received doses of SMX/TMP at 200 mg/40 mg daily over 24 weeks and 19 weeks, respectively, we combined these two groups and the estimated non-incidence rate of PJP was 96.8–100% ($n = 114$). Estimation using the rule of three essentially produced the same results [35, 36].

Figure 2a shows the cumulative discontinuation rates due to any reason, using Kaplan-Meier curves. A significant difference was observed between SS and HS ($p = 0.007$). The cumulative discontinuation rate in ES was lower than in SS; however, the difference was not statistically significant after Bonferroni correction. Figure 2b shows the cumulative discontinuation rates due to AEs. A significant difference was observed between SS and ES ($p = 0.004$), and SS and HS ($p = 0.006$).

Safety

AEs and the breakdown of different AEs are shown in Table 2. There was no significant difference in the incidence

rates of all AEs and serious AEs. The proportion of the patients with AEs who required reduction in the dose of SMX/TMP ($p = 0.009$) and of patients with AEs of special interest ($p = 0.003$) were significantly different across the three groups, and were higher in SS than in the other two groups. The AEs of special interest, thrombocytopenia and hyponatremia, were observed numerically more frequently in SS. We did not determine the statistical significance of differences in the numbers of each AE of special interest because of the relatively small number of cases.

Discussion

In this study, we compared the non-incidence rates, discontinuation rates, and safety among SS, HS, and ES, in order to determine the optimal dose and regimen of SMX/TMP as prophylaxis for PJP during the treatment of systemic rheumatic diseases with prednisolone ≥ 0.6 mg/kg/day. Because no patients developed PJP by week 24 in this clinical trial, it was not possible to show the non-inferiority of ES to SS. Regarding secondary endpoints, the discontinuation rate was significantly lower in HS compared to SS, and it was lower in ES compared to SS, although the difference was not statistically significant after adjusting for multiple testing in the latter comparison. The discontinuation rates due to AEs were significantly lower in HS and ES than in SS. The incidence of AEs that required reduction in the dose of

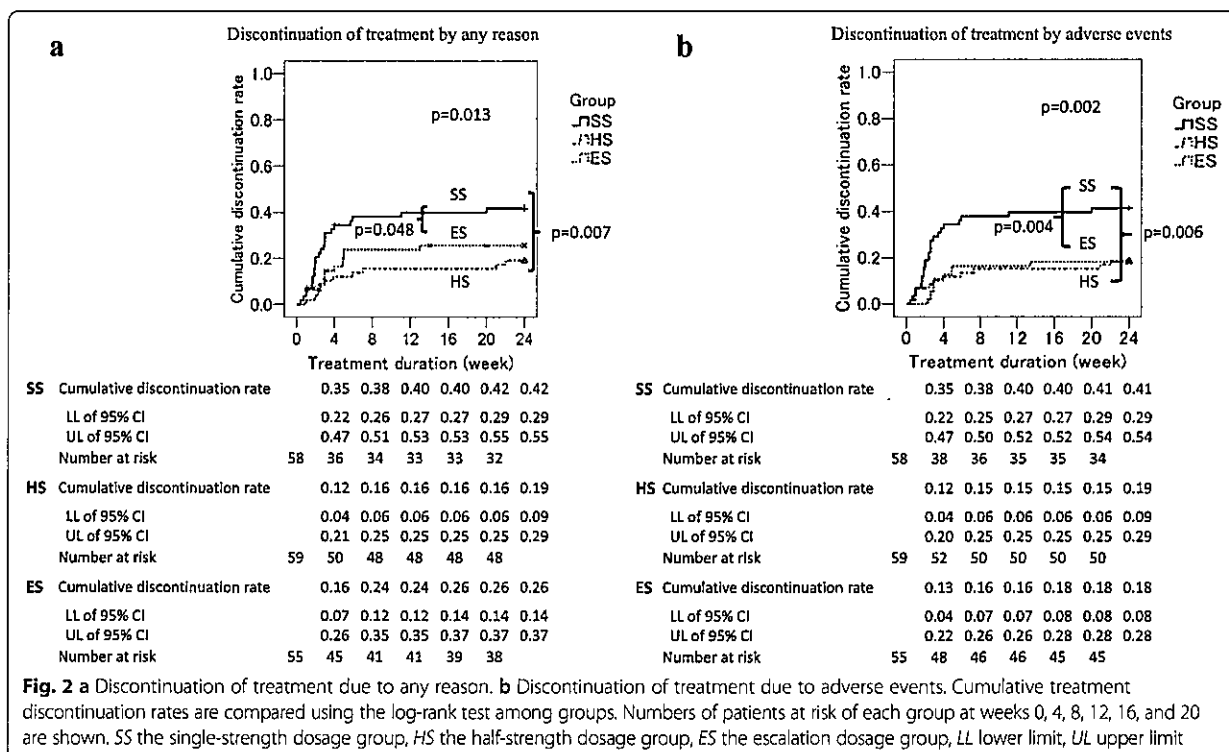


Table 2 Adverse events

	SS (n = 58)	HS (n = 59)	ES (n = 55)	P value
AE, n (%) (95% CI)	32 (55.2) (41.5–68.3)	24 (40.7) (28.1–54.3)	26 (47.3) (33.7–61.2)	0.300
Serious AE ^a , n (%) (95% CI)	9 (15.5) (7.3–27.4)	11 (18.6) (9.7–30.9)	6 (10.9) (4.1–22.2)	0.534
AE required dose reduction of SMX/TMP, n (%), (95% CI)	11 (19.0) (9.9–31.4)	2 (3.4)* (0.4–11.7)	3 (5.5)* (1.1–15.1)	0.009
AE required discontinuation of SMX/TMP, n (%), (95% CI)	12 (20.7) (11.2–33.4)	5 (8.5) (2.8–18.7)	5 (9.1) (3.0–20.0)	0.110
AE leading to death, n (%), (95% CI)	1 (1.7) (0–9.2)	3 (5.1) (1.1–14.1)	1 (1.8) (0–9.7)	0.622
AE of special interest, n (%), (95% CI)	26 (44.8) (31.7–58.5)	12 (20.3)* (11.0–32.8)	10 (18.2)* (9.1–30.9)	0.003
Fever, n (%)	2 (3.4)	0 (0.0)	0 (0.0)	ND
Rash, n (%)	5 (8.6)	2 (3.4)	1 (1.8)	ND
Appetite loss, n (%)	1 (1.7)	0 (0.0)	1 (1.8)	ND
Anemia, n (%)	1 (1.7)	1 (1.7)	0 (0.0)	ND
Leukocytopenia, n (%)	1 (1.7)	1 (1.7)	0 (0.0)	ND
Thrombocytopenia, n (%)	9 (15.5)	4 (6.8)	5 (9.1)	ND
Elevated LFT, n (%)	7 (12.1)	6 (10.2)	4 (7.3)	ND
Elevated serum creatinine, n (%)	3 (5.2)	1 (1.7)	1 (1.8)	ND
Hyponatremia, n (%)	5 (8.6)	1 (1.7)	0 (0.0)	ND
Hyperpotassemia, n (%)	3 (5.2)	3 (5.1)	1 (1.8)	ND

^aSerious adverse events (AE): sepsis, organizing pneumonia, severe liver failure, flare of rheumatic disease, rash that required hospitalization, thrombocytopenia that required hospitalization, mental disorder that required hospitalization, and death. SS the single-strength dosage group, HS the half-strength dosage group, ES the escalation dosage group, AE adverse events, SMX/TMP sulfamethoxazole-trimethoprim, LFT liver function test, ND not done. * $p < 0.05$ by adjusted residuals vs. SS

SMX/TMP and AEs of special interest were significantly different among the three groups, and both of these AEs were observed more frequently in SS than in the other two groups, with statistical significance.

There were no cases of PJP in this study. It is conceivable that high awareness of PJP prophylaxis in the participating facilities influenced the non-incidence rate. In the 49 patients who could not continue the allocated treatment with SMX/TMP, only 6 patients through weeks 0–12, and 10 patients through weeks 12–24, did not have PJP prophylaxis at all, and the others had some form of chemoprophylaxis such as reduced dosage of SMX/TMP, aerosolized pentamidine isethionate, or atovaquone. The incidence rates of PJP in patients with rheumatic diseases who did not receive chemoprophylaxis is reported to be 7.5–9.0% [23, 28, 37]. These data may explain why there were no cases of PJP in this clinical trial, at least up to week 24.

We estimated the non-incidence rate of PJP in the combined HS and ES group ($n = 114$) as 96.8–100% by the exact confidence interval. The patients in HS and ES received doses of SMX/TMP at 200 mg/40 mg daily for at least 19 weeks, and the estimated non-incidence

rates of PJP were quite similar. Taking these figures into account, it is plausible that a non-incidence rate of PJP in 114 patients receiving SMX/TMP at a dosage of 200 mg/40 mg daily could be as high as that of the combined group, suggesting a clinically meaningful prophylactic effect of this regimen on PJP.

The treatment discontinuation rate due to any reason was significantly lower in HS compared to SS. The treatment discontinuation rates due to AEs were significantly lower in HS and ES compared to SS. The incidence rates of AEs that required discontinuation of SMX/TMP were lower in HS (8.5%) and ES (9.1%) compared to SS (20.7%), although there was no statistically significant difference. These figures were consistent with the previously reported SMX/TMP discontinuation rates of 8.5–17.9% in patients with rheumatic diseases [33, 37]. AEs that required a reduction in the dose of SMX/TMP were significantly more frequent in SS compared to the other groups. These data indicate that SMX/TMP of 200 mg/40 mg daily, starting either at this dose or with a dose-escalation regimen, is superior in its safety and drug retention rate compared to SMX/TMP of 400 mg/80 mg daily. Considering that three patients in ES

discontinued the allocated treatment of SMX/TMP by prescription errors, the cumbersome regimen of ES appeared to be less feasible than the simple regimen of HS in clinical practice.

This study has some limitations. First, there was the possibility of bias from the participating institutions. All institutions were specialized in rheumatic diseases, had a high awareness of PJP prophylaxis, and carried out PJP preventive measures more properly than expected when the allocated treatment of SMX/TMP was discontinued.

Second, because this was non-blinded study, there might be a detection bias. Doctors could have an expectation that there might be more AEs in SS due to the higher dosage. In ES, the necessity of increasing the dosage might affect the incidence of AEs, considering more opportunities to check the condition of the patient compared to a fixed-dose regimen.

Third, the study period for this interim analysis was only 24 weeks. In the report of 116 HIV-negative patients, the median duration from the initiation of corticosteroids to PJP onset has been reported to be 12 weeks [20], and 25% of them developed PJP after 8 weeks or less of corticosteroid treatment. Taking these data into account, a 24-week observation period for this analysis would be appropriate. To overcome this limitation, we are continuing this clinical trial up to week 52.

The fourth point is the exclusion criteria of this study. Patients with decreased renal function or low body weight may be in need of PJP prophylaxis in a clinical setting. Because HS was superior to SS in safety, chemoprophylaxis with SMX/TMP of 200 mg/40 mg daily may be applicable to these patients.

Fifth, the variability of the quality of reporting of AEs and serious AEs should be taken into consideration. To increase the reliability of the reports, each report was checked and the research headquarters directed enquiries to the attending physician as needed. Finally, this trial is focused on primary prophylaxis of PJP, and there is no evidence on the use of SMX/TMP of 200 mg/40 mg daily as secondary prophylaxis (i.e., prophylaxis after the first event of PJP) at this time.

Conclusions

This study is the first multicenter RCT comparing the efficacy, safety, and discontinuation rate of PJP prophylaxis using different dosing regimens of SMX/TMP in systemic rheumatic diseases. Although there were no cases of PJP in any group, it is estimated that daily or incremental administration of 200 mg/40 mg of SMX/TMP had a clinically meaningful prophylactic effect on PJP, had a significantly lower discontinuation rate due to AEs than the daily single-strength tablet dose of 400 mg/80 mg, and was shown to be superior in safety. From the perspective of efficacy, safety, and feasibility,

these data suggest that daily SMX/TMP at 200 mg/40 mg was the optimal regimen for chemoprophylaxis of PJP in patients with systemic rheumatic diseases. Further research is required to ascertain data on the efficacy and safety of PJP prophylaxis using 200 mg/40 mg daily of SMX/TMP in a clinical setting.

Additional file

Additional file 1: List of ethics committees that approved this study. (DOCX 13 kb)

Abbreviations

AE: adverse event; CKD: chronic kidney disease; CS: corticosteroids; CVD: cardiovascular disease; D/C: discontinued; DM: dermatomyositis; DS: the double-strength dosage group; ES: the escalation group; FAS: full analysis set; HIV: human immunodeficiency virus; HS: the half-strength group; ILD: interstitial lung disease; IQR: interquartile range; IS: immunosuppressive drugs; IV: intravenous; LFT: liver function test; mPSL: methylprednisolone; ND: not done; PJP: *Pneumocystis pneumonia*; PM: polymyositis; RA: rheumatoid arthritis; RCT: randomized controlled trial; SLE: systemic lupus erythematosus; SMX/TMP: sulfamethoxazole-trimethoprim; SS: the single-strength dosage group; TMDU: Tokyo Medical and Dental University Hospital; WBC: white blood cell

Acknowledgements

We thank the site investigators of this study who contributed in recruiting patients and collecting clinical data: Yasushi Nawata (Center of Rheumatology, Saiseikai Narashino Hospital), Michi Tsutsumino (Department of Pharmacovigilance, Tokyo Medical and Dental University), Tsuyoshi Takeda (Third Department of Internal Medicine, Obihiro-Kosei General Hospital), Hiroto Nakano and Kenichiro Tokunaga (Kameda Medical Center), Yoshiko Murakawa (Department of Rheumatology, Faculty of Medicine, Shimane University), Kayoko Kaneko and Fumiaki Kondo (Department of Rheumatology, Soka Municipal Hospital). We also thank Ms. Marie Kokido for her contribution at the secretariat of this study. We sincerely thank all the rheumatologists and medical staff who took care of the patients enrolled in this study.

Funding

This work was supported by unrestricted research grants to the Department of Pharmacovigilance, Tokyo Medical and Dental University and to the Division of Epidemiology and Pharmacoepidemiology, Institute of Rheumatology, Tokyo Women's Medical University.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to future analysis plans.

Authors' contributions

MU collected and handled the data, conducted statistical analyses and drafted the manuscript. HD, TO, KS, NY, KN, KT, MS, TS, HH, SH, KM, YN, MKondo, FS, MKihara, YW, FH, HY, and RS are site investigators of the study group and substantially contributed to recruiting participants and collection of data. MT participated in the statistical analysis plan and interpretation of the data. TN, RK, HK, and NM participated in interpretation of the data. MH conceived the study, planned statistical analyses, and contributed to drafting the manuscript. All authors contributed to the discussion, critically reviewed the manuscript, and have given final approval for publication.

Competing interests

Tokyo Medical and Dental University (TMDU) received unrestricted research grants for Department of Pharmacovigilance from Abbvie Japan Co., Ltd., Astellas Pharma Inc., Bristol-Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Mitsubishi Tanabe Pharma Co., Ono Pharmaceuticals, Pfizer Japan Inc., Sanofi-Aventis K.K., Santen Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and UCB Japan, with which TMDU paid the salary of KN, RS, HY, and MH. KS received manuscript fee from Bristol-Myers Squibb K.K. MKondo received research funding from Chugai Pharmaceutical Co., Eisai Co., Ltd., and Mitsubishi Tanabe Pharma Co. TN received research funding

from Chugai Pharmaceutical Co. HK received lecture fee and research funding from Chugai Pharmaceutical Co. and Mitsubishi Tanabe Pharma Co. MU, HD, TO, NY, KT, MS, TS, HH, SH, KM, YN, FS, MT, MKihara, WY, FH, HY, RK, and NM have nothing to declare.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The protocol was approved by the Institutional Review Board of Tokyo Medical and Dental University (#2349) and by the respective boards of other participating institutions. Written informed consent was obtained from each patient. The study was performed in compliance with the ethical guidelines for epidemiological research in Japan and the Helsinki Declaration (revised in 2008).

Author details

¹Department of Pharmacovigilance, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU), 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan. ²Department of Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU), 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan. ³Department of Rheumatology, Musashino Red Cross Hospital, 1-26-1 Kyonanchō, Musashino, Tokyo 180-0023, Japan. ⁴Department of Internal Medicine, Division of Hematology, Rheumatology and Respiratory Medicine, Faculty of Medicine, Kagawa University, 1750-1 Ikenobe, Miki-cho, Kida-gun, Kagawa 761-0793, Japan. ⁵Third Department of Internal Medicine, Obihiro-Kosei General Hospital, West-6, South-8, Obihiro, Hokkaido 080-0016, Japan. ⁶First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahata-nishi-ku, Kitakyushu, Fukuoka 807-8555, Japan. ⁷Department of Rheumatic Diseases, Tokyo Metropolitan Tama Medical Center, 2-8-29 Musashidai, Fuchu, Tokyo 183-8524, Japan. ⁸Department of Rheumatology, Ome Municipal General Hospital, 4-16-5 Higashi-Ome, Ome, Tokyo 198-0042, Japan. ⁹Department of Medicine and Rheumatology, Tokyo Metropolitan Geriatric Hospital, 35-2 Sakaecho, Itabashi-ku, Tokyo 173-0015, Japan. ¹⁰Department of Rheumatology, Yokohama City Minato Red Cross Hospital, 3-12-1, Shinyamashita, Naka-ku, Yokohama, Kanagawa 231-8682, Japan. ¹¹Department of Hematology, Rheumatology, and Infectious Disease, Kumamoto University Graduate School of Medicine, 1-1-1 Honjo, Kumamoto, Kumamoto 860-8556, Japan. ¹²Department of Rheumatology, Kameda Medical Center, 929 Higashi-cho, Kamogawa, Chiba 296-8602, Japan. ¹³Department of Rheumatology, Tokyo Kyosai Hospital, 2-3-8 Nakameguro, Meguro-ku, Tokyo 153-8934, Japan. ¹⁴Department of Rheumatology, Faculty of Medicine, Shimane University, 89-1 Enya-cho, Izumo, Shimane 693-8501, Japan. ¹⁵Department of Rheumatology, Soka Municipal Hospital, 2-21-1 Soka, Soka, Saitama 340-0043, Japan. ¹⁶Clinical Research Center, Medical Hospital of Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo, Tokyo 113-8549, Japan. ¹⁷Division of Epidemiology and Pharmacoepidemiology of Rheumatic Diseases, Institute of Rheumatology, Tokyo Women's Medical University, 10-22 Kawada-cho, Shinjuku-ku, Tokyo 162-0054, Japan. ¹⁸Department of Internal Medicine, Hokusei Hospital, 5-1-1 Seiryu, Chitose, Hokkaido 066-0081, Japan. ¹⁹Department of Rheumatology, Soka Municipal Hospital, 2-21-1 Soka, Soka, Saitama 340-8560, Japan. ²⁰Department of Internal Medicine, Takikawa Municipal Hospital, 2-2-34 Oh-machi, Takikawa, Hokkaido 073-0022, Japan. ²¹Department of Rheumatology, JA Toride Medical Center, 2-1-1 Hongo, Toride, Ibaraki 302-0022, Japan. ²²Division of Rheumatology, Department of Internal Medicine, Toho University School of Medicine, 6-11-1 Omori-nishi, Ota-ku, Tokyo 143-8541, Japan.

Received: 26 August 2016 Accepted: 8 December 2016

Published online: 18 January 2017

References

- Thomas CFJ, Limper AH. Pneumocystis pneumonia. *N Engl J Med*. 2004;350:2487–98.
- Thomas CFJ, Limper AH. Current insights into the biology and pathogenesis of *Pneumocystis pneumonia*. *Nat Rev Microbiol*. 2007;5:298–308.
- Centers for Disease Control. Recommendations for prophylaxis against *Pneumocystis carinii* pneumonia for adults and adolescents infected with human immunodeficiency virus. *MMWR Recomm Rep*. 1992;41:1–11.
- Sepkowitz KA, Brown AE, Armstrong D. *Pneumocystis carinii* pneumonia without acquired immunodeficiency syndrome. More patients, same risk. *Arch Intern Med*. 1995;155:1125–8.
- Hughes WT, Feldman S, Aur RJA, Verzosa MS, Hustu HQ, Simone JV. Intensity of immunosuppressive therapy and the incidence of *pneumocystis carinii* pneumonitis. *Cancer*. 1975;36:2004–9.
- Hardy AM, Wajszczyk CP, Suffredini AF, Hakala TR, Ho M. *Pneumocystis carinii* pneumonia in renal-transplant recipients treated with cyclosporine and steroids. *J Infect Dis*. 1984;149:143–7.
- Hofflin JM, Potasman I, Baldwin JC, Oyer PE, Stinson EB, Remington JS. Infectious complications in heart transplant recipients receiving cyclosporine and corticosteroids. *Ann Intern Med*. 1987;106:209–16.
- Meyers JD, Flournoy N, Thomas ED. Nonbacterial pneumonia after allogeneic marrow transplantation: a review of ten years' experience. *Rev Infect Dis*. 1982;4:1119–32.
- Godeau B, Coutant-Perronne V, Le Thi HD, Guillemin L, Magadur G, De Bandt M, et al. *Pneumocystis carinii* pneumonia in the course of connective tissue disease: report of 34 cases. *J Rheumatol*. 1994;21:246–51.
- Sepkowitz KA. Opportunistic infections in patients with and patients without acquired immunodeficiency syndrome. *Clin Infect Dis*. 2002;34:1098–107.
- Komano Y, Harigai M, Koike R, Sugiyama H, Ogawa J, Saito K, et al. *Pneumocystis jirovecii* pneumonia in patients with rheumatoid arthritis treated with infliximab: A retrospective review and case-control study of 21 patients. *Arthritis Care Res*. 2009;61:305–12.
- Watanabe K, Sakai R, Koike R, Sakai F, Sugiyama H, Tanaka M, et al. Clinical characteristics and risk factors for *Pneumocystis jirovecii* pneumonia in patients with rheumatoid arthritis receiving adalimumab: a retrospective review and case-control study of 17 patients. *Mod Rheumatol*. 2013;23:1085–93.
- Tanaka M, Sakai R, Koike R, Komano Y, Nanki T, Sakai F, et al. *Pneumocystis jirovecii* pneumonia associated with etanercept treatment in patients with rheumatoid arthritis: a retrospective review of 15 cases and analysis of risk factors. *Mod Rheumatol*. 2012;22:849–58.
- Tanaka M, Sakai R, Koike R, Harigai M. *Pneumocystis jirovecii* pneumonia in Japanese patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors: a pooled analysis of 3 agents. *J Rheumatol*. 2015;42:1726–8.
- Roux A, Gonzalez F, Roux M, Mehrad M, Menotti J, Zahar JR, et al. Update on pulmonary *Pneumocystis jirovecii* infection in non-HIV patients. *Med Mal Infect*. 2014;44:185–98.
- Khanna D, McMahon M, Furst DE. Safety of tumour necrosis factor- α antagonists. *Drug Saf*. 2004;27:307–24.
- Harigai M, Koike R, Miyasaka N. *Pneumocystis pneumonia* under Anti-Tumor Necrosis Factor Therapy (PAT) Study Group. *Pneumocystis pneumonia associated with infliximab in Japan*. *N Engl J Med*. 2007;357:1874–6.
- Takeuchi T, Tatsuki Y, Nogami Y, Ishiguro N, Tanaka Y, Yamanaka H, et al. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. *Ann Rheum Dis*. 2008;67:189–94.
- Yamazaki H, Sakai R, Koike R, Miyazaki Y, Tanaka M, Watanabe K, et al. Assessment of risks of pulmonary infection during 12 months following immunosuppressive treatment for active connective tissue diseases: a large-scale prospective cohort study. *J Rheumatol*. 2015;42:614–22.
- Yale SH, Limper AH. *Pneumocystis carinii* pneumonia in patients without acquired immunodeficiency syndrome: associated illness and prior corticosteroid therapy. *Mayo Clin Proc*. 1996;71:5–13.
- Kovacs JA, Hiemenz JW, Macher AM, Stover D, Murray HW, Shelhamer J, et al. *Pneumocystis carinii* pneumonia: a comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. *Ann Intern Med*. 1984;100:663–71.
- Ioannidis JP, Cappelleri JC, Skolnik PR, Lau J, Sacks HS. A meta-analysis of the relative efficacy and toxicity of *Pneumocystis carinii* prophylactic regimens. *Arch Intern Med*. 1996;156:177–88.
- Ogawa J, Harigai M, Nagasaka K, Nakamura T, Miyasaka N. Prediction of and prophylaxis against *Pneumocystis pneumonia* in patients with connective tissue diseases undergoing medium- or high-dose corticosteroid therapy. *Mod Rheumatol*. 2005;15:91–6.
- Kovacs JA. *Pneumocystis pneumonia*. In: Goldman L, Schafer AI, editors. *Goldman-Cecil Medicine*. Philadelphia: Elsevier; 2016. p. 2091–2099.e3.
- Hardy WD, Feinberg J, Finkelstein DM, Power ME, He W, Kaczka C, et al. A controlled trial of trimethoprim-sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of *Pneumocystis carinii* pneumonia

- in patients with the acquired immunodeficiency syndrome. *AIDS Clinical Trials Group Protocol 021*. *N Engl J Med*. 1992;327:1842–8.
26. Schneider MM, Nielsen TL, Nelsing S, Hoepelman AI, Eeftink Schattenkerk JK, van der Graaf Y, et al. Efficacy and toxicity of two doses of trimethoprim-sulfamethoxazole as primary prophylaxis against *Pneumocystis carinii* pneumonia in patients with human immunodeficiency virus. *Dutch AIDS Treatment Group*. *J Infect Dis*. 1995;171:1632–6.
 27. Fischl MA, Dickinson GM, La Voie L. Safety and efficacy of sulfamethoxazole and trimethoprim chemoprophylaxis for *Pneumocystis carinii* pneumonia in AIDS. *JAMA*. 1988;259:1185–9.
 28. Green H, Paul M, Vidal L, Leibovici L. Prophylaxis of *Pneumocystis* pneumonia in immunocompromised non-HIV-infected patients: systematic review and meta-analysis of randomized controlled trials. *Mayo Clin Proc*. 2007;82:1052–9.
 29. Smilack JD. Trimethoprim-sulfamethoxazole. *Mayo Clin Proc*. 1999;74:730–4.
 30. Howe RA, Spencer RC. Cotrimoxazole. Rationale for re-examining its indications for use. *Drug Saf*. 1996;14:213–8.
 31. Jick H, Derby LE. A large population-based follow-up study of trimethoprim-sulfamethoxazole, trimethoprim, and cephalexin for uncommon serious drug toxicity. *Pharmacotherapy*. 1995;15:428–32.
 32. Kimura M, Tanaka S, Ishikawa A, Endo H, Hirohata S, Kondo H. Comparison of trimethoprim-sulfamethoxazole and aerosolized pentamidine for primary prophylaxis of *Pneumocystis jirovecii* pneumonia in immunocompromised patients with connective tissue disease. *Rheumatol Int*. 2008;28:673–6.
 33. Takenaka K, Komiya Y, Ota M, Yamazaki H, Nagasaka K. A dose-escalation regimen of trimethoprim-sulfamethoxazole is tolerable for prophylaxis against *Pneumocystis jirovecii* pneumonia in rheumatic diseases. *Mod Rheumatol*. 2013;23:752–8.
 34. Clopper C, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*. 1934;26:404–13.
 35. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. *JAMA*. 1983;249:1743–5.
 36. Eypasch E, Lefering R, Kum CK, Troidl H. Probability of adverse events that have not yet occurred: a statistical reminder. *BMJ*. 1995;311:619–20.
 37. Vananuvat P, Suwannalai P, Sungkanuparph S, Limsuwan T, Ngamjanyaporn P, Janwityanujit S. Primary prophylaxis for *Pneumocystis jirovecii* pneumonia in patients with connective tissue diseases. *Semin Arthritis Rheum*. 2011;41:497–502.

Submit your next manuscript to BioMed Central and we will help you at every step:

- We accept pre-submission inquiries
- Our selector tool helps you to find the most relevant journal
- We provide round the clock customer support
- Convenient online submission
- Thorough peer review
- Inclusion in PubMed and all major indexing services
- Maximum visibility for your research

Submit your manuscript at
www.biomedcentral.com/submit



ORIGINAL ARTICLE

Achieving simplified disease activity index remission in patients with active rheumatoid arthritis is associated with subsequent good functional and structural outcomes in a real-world clinical setting under a treat-to-target strategy

Fumio Hirano^{a,b}, Waka Yokoyama^{a,b}, Hayato Yamazaki^{a,b}, Koichi Amano^c, Atsushi Kawakami^d, Taichi Hayashi^e, Naoto Tamura^f, Shinsuke Yasuda^g, Hiroaki Dobashi^h, Takao Fujii^{i,j}, Satoshi Ito^j, Yuko Kaneko^k, Toshihiro Matsui^l, Yasuaki Okuda^m, Kazuyoshi Saitoⁿ, Fumihito Suzuki^o, Ryusuke Yoshimi^p, Ryoko Sakai^{a,b,j}, Ryuji Koike^{a,b}, Hitoshi Kohsaka^b, Nobuyuki Miyasaka^b, Masayoshi Harigai^{a,b,j} and the T2T Epidemiological Study Group

^aDepartment of Pharmacovigilance; ^bDepartment of Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU), Bunkyo, Japan; ^cDepartment of Rheumatology and Clinical Immunology, Saitama Medical Center, Saitama Medical University, Saitama, Japan; ^dUnit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; ^eDepartment of Rheumatology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan; ^fDepartment of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Bunkyo, Japan; ^gDivision of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, Sapporo, Japan; ^hDepartment of Internal Medicine, Division of Hematology, Rheumatology and Respiratory Medicine, Faculty of Medicine, Kagawa University, Takamatsu, Japan; ⁱDepartment of the Control for Rheumatic Diseases, Graduate School of Medicine, Kyoto University, Kyoto, Japan; ^jDepartment of Rheumatology, Niigata Rheumatic Center, Shibata, Japan; ^kDivision of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Minato, Japan; ^lDepartment of Rheumatology, Sagami National Hospital, National Hospital Organization, Sagami, Japan; ^mDepartment of Internal Medicine, Center for Rheumatic Diseases, Dohgo Spa Hospital, Matsuyama, Japan; ⁿThe First Department of Internal Medicine, University of Occupational and Environmental Health, School of Medicine, Kitakyushu, Japan; ^oDepartment of Rheumatology, Soka Municipal Hospital, Saitama, Japan; ^pDepartment of Hematology and Clinical Immunology, Yokohama City University School of Medicine, Yokohama, Japan

ABSTRACT

Objective: To verify predictive validity of simplified disease activity index (SDAI) remission for subsequent functional and structural outcomes in real-world clinical settings under a treat-to-target strategy (T2T).

Methods: In this multicenter, prospective cohort study, T2T was implemented in rheumatoid arthritis (RA) patients with moderate-to-high disease activity. SDAI or clinical disease activity index (CDAI) was assessed every 12 weeks, and treatment was adjusted to achieve clinical remission or low disease activity (LDA). Multivariate logistic regression models were used to examine the associations of SDAI remission (≤ 3.3) at week 24 with the health assessment questionnaire-disability index (HAQ-DI) ≤ 0.5 or with the delta van der Heijde-modified total Sharp score (Δ vdH-mTSS) $<$ smallest detectable change (SDC) at week 72.

Results: Of 318 patients enrolled, 271 completed the follow-up for 72 weeks and were subjects of the analyses. Factors [odds ratio (95% confidence interval)] significantly associated with the HAQ-DI ≤ 0.5 were SDAI remission at week 24 [2.99 (1.42–6.28), $p = 0.004$], baseline HAQ-DI [0.28 (0.18–0.45), $p = 1.3 \times 10^{-7}$], and baseline vdH-mTSS [0.986 (0.976–0.996), $p = 0.009$]. A factor associated with Δ vdH-mTSS $<$ SDC was SDAI remission at week 24 [3.53 (1.62–7.71), $p = 0.002$].

Conclusion: Predictive validity of SDAI remission for good outcomes was verified in a T2T-implementing cohort in the current clinical settings.

ARTICLE HISTORY

Received 25 August 2016
Accepted 24 November 2016



KEYWORDS

Health assessment questionnaire; Modified Sharp score; Rheumatoid arthritis; Simplified disease activity index; Treat-to-target


Introduction

The goal in treating patients with rheumatoid arthritis (RA) is to abrogate inflammation and prevent consequent joint destruction and functional disability. Concurrently, with the advent of new therapeutic agents for this purpose, much progress was made in terms of treatment strategy.

Publication of treat-to-target (T2T) recommendations formulated by an international task force was a landmark step in this endeavor [1]. It advocates that the strategy targeting clinical remission with periodical measurement of disease activity and adjusting therapy optimizes pertinent outcomes in RA.

CONTACT Masayoshi Harigai  harigai.masayoshi@twmu.ac.jp  Division of Epidemiology and Pharmacoepidemiology in Rheumatic Diseases, Institute of Rheumatology, Tokyo Women's Medical University, 10-22 Kawada-cho, Shinjuku-ku, Tokyo 1620054, Japan

^jPresent address of authors Masayoshi Harigai and Ryoko Sakai *Division of Epidemiology and Pharmacoepidemiology in Rheumatic Diseases, Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan* Takao Fujii *Department of Rheumatology and Clinical Immunology, Wakayama Medical University, Wakayama, Japan*

 Supplemental data for this article can be accessed [here](#).

© 2016 Japan College of Rheumatology

Several composite measures of disease activity are suggested for remission criteria in the T2T recommendations [2]. Amongst these measures, simplified disease activity index (SDAI) remission [3,4] was proposed as a provisional index-based definition of remission for clinical trials by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) on the basis of its face and predictive validity, stringency and the need to incorporate patient-reported outcomes [5]. The ACR recommends SDAI for the use in clinical practice as well [6]. Predictive validity of SDAI remission for good outcomes was shown mainly using data of patients who received methotrexate (MTX) monotherapy in clinical trials [5]. To set SDAI remission as a target of treatment in a real-world clinical setting, association of SDAI remission with later functional and structural good outcomes has to be validated using data of cohort studies enrolling patients with RA treated with a wide range of medications.

Cohort studies showing statistically robust results about the predictive validity of SDAI are quite limited. Ruysen-Witrand et al. [7] showed association of SDAI remission with a later good structural outcome in patients with early RA, but not with a later good functional outcome. Subjects of the analysis were retrospectively selected from an early arthritis cohort and some of the patients were not treated with disease-modifying antirheumatic drugs (DMARDs). In addition, the cohort did not reflect the current clinical setting in terms of treatment options and strategy because the cohort recruited patients far before the T2T recommendations and no specific treatment strategy was implemented. The results of other cohort studies were difficult to interpret because they did not adjust for potential confounders [8–10].

To generalize predictability of achieving SDAI remission for later good functional and structural outcomes in the current rheumatology practice where the T2T strategy has been widely accepted and implemented with various non-biological or biological DMARDs, we conducted a prospective cohort study implementing the T2T strategy on RA patients with moderate-to-high disease activity. We examined the association of achieving SDAI remission at week 24 after intensification of treatment with good functional and structural outcomes at week 72, and evaluated adherence to the T2T strategy in terms of adjusting treatment according to disease activity at week 12.

Patients and methods

Study design and ethics

This study was a multicenter, prospective cohort study, and its protocol was approved by the Institutional Review Board of Tokyo Medical and Dental University (#23-10) and by the respective boards of other participating institutions. Written informed consent was obtained from each patient. The study was performed in compliance with the ethical guidelines for epidemiological research in Japan and the Helsinki Declaration (revised in 2008).

Patients

Patients with active RA fulfilling the inclusion criteria were enrolled in the cohort at the time of treatment adaptation, either by starting, adding, or changing conventional synthetic DMARDs (csDMARDs), or by starting biological DMARDs (bDMARDs). The inclusion criteria were as follows: (1) 20 years of age or older, (2) met the 2010 ACR/EULAR classification criteria for RA [11], (3) had moderate-to-high disease activity according to SDAI [3] or clinical disease activity index (CDAI) [12] (SDAI >11 or CDAI >10), (4) had two or more swollen joint counts and two or more tender joint counts, (5) had no history of bDMARD use, and (6) could provide written informed consent to participate in this study. Patients who started, added, or changed any DMARDs within two weeks before enrolment were also eligible if they met criteria 1–6. We used either SDAI or CDAI for the enrolment because some institutions could not test C-reactive protein (CRP) on the same day of patients' visit.

Exclusion criteria were patients who were considered inappropriate for study enrolment by the attending physician, were pregnant or breastfeeding, or were thought to be unable to be followed up for 72 weeks.

Data collection

We collected demographic data and clinical data at baseline including height, body weight, comorbidities, medical history, smoking history, history of joint replacement or other joint surgery related to RA, treatment history of RA before enrolment, Steinbrocker stage and class [13], disease duration of RA, extra-articular manifestations, disease activity and laboratory data. Data related to disease activity were: swollen joint count in 46 joints and tender joint count in 48 joints, which included the 28 joints used for SDAI plus bilateral temporomandibular, sternoclavicular, ankle, tarsal, and metatarsophalangeal joints, with hip joints only for tender joint count; patient's and physician's global assessment of disease; and patient's global assessment of fatigue (visual analog scale of 10 cm). Collected laboratory data were rheumatoid factor, anti-cyclic citrullinated peptide (CCP) antibody, matrix metalloproteinase 3 (MMP-3), erythrocyte sedimentation rate (ESR), CRP, complete blood counts, transaminases, and serum creatinine levels. At follow-up visits, disease activity and laboratory data except for rheumatoid factor and anti-CCP antibody were collected every 12 weeks. Radiographs of hands and feet were taken at baseline and every 24 weeks. Structural outcomes were assessed using van der Heijde-modified total Sharp score (vdH-mTSS) [14]. Functional disability was measured every 12 weeks using the Health Assessment Questionnaire-Disability Index (HAQ-DI) [15]. HAQ remission (HAQ-DI ≤0.5) at week 72 was defined as a good functional outcome.

Treatment was adjusted according to SDAI or CDAI assessed every 12 weeks with remission (SDAI ≤3.3 or CDAI ≤2.8) or low disease activity (LDA) (SDAI ≤11 or CDAI ≤10) as the treatment target. We used either SDAI or CDAI for adjusting treatment because some institutions

could not obtain CRP on the same day of patients' visit. No medication sequence was specified in the protocol for treating RA. Therefore, the choice of medication was at physicians' discretion.

For each period of 12 weeks, site investigators were requested to clarify whether remission was achieved and maintained during the period. Site investigators were also requested to clarify whether the treatment was adjusted or not when remission was not achieved or maintained. If the treatment was not adjusted, they were asked to choose the reason from the following or to specify other reasons: (1) an attending physician predicted to achieve remission by continuing current therapy; (2) an attending physician permitted LDA as the treatment goal; (3) an attending physician had no better treatment option than current treatment; (4) financial reason of the patient; and (5) the patient disagreed with treatment intensification. We categorized 3–5 into "T2T not followed". If an attending physician reported that they adjusted treatment in a patient, but did not start, add or increase the dose of DMARDs within four weeks after the date of assessment, the patient was excluded from this group and included in the group of "T2T not followed". Similarly, if an attending physician reported that remission was achieved or they permitted LDA but did not achieve remission or LDA, respectively, either by SDAI or CDAI, the patient was included in the group of "T2T not followed".

Assessment of structural outcomes

Radiographs of hands and feet were scored in a chronological order by two readers who were blinded to the clinical information. Missing data were imputed by interpolation or extrapolation with available radiographs. When such radiographs were not available, missing data were subjects for multiple imputation [16] (detailed in the statistical analysis section). Changes in vdH-mTSS scores from baseline (Δ vdH-mTSS) were calculated for each patient. Smallest detectable change (SDC) [17] was calculated from the difference between the two readers' Δ vdH-mTSS. The Δ vdH-mTSS < SDC at week 72 was defined as a good structural outcome.

Statistical analysis

We chose to examine predictive validity of SDAI remission at week 24 for later good functional and structural outcomes because the EULAR recommends that the treatment target should be attained within six months [18]. We also assumed that disease activity status at week 24 is a result of adjusting treatment at week 12 by the T2T strategy as well as responses to treatment intensification at enrolment. We analyzed data using R version 3.0.3 software (R Development Core Team 2014, Vienna, Austria) with the Amelia II, Zelig, and mitool packages [19–21]. To deal with missing data, we applied the multiple imputation method [16,19], and generated five imputed data sets because five data sets are

adequate unless the missing rate is unusually high [22] (see supplementary material).

Multivariate logistic regression models were used to correct for confounding factors. For selection of potential confounding factors, we first performed univariate logistic regression analyses with the good functional outcome or the good structural outcome as a dependent variable. Second, we selected candidate covariates for multivariate analyses based on statistical significance in the univariate analyses (Supplementary Tables 1 and 2) and clinical significance, and determined several candidate sets of covariates. Third, the candidate sets of covariates were used for multivariate logistic regression analyses with stepwise selection in the five imputed data sets. We determined a final set of covariates which were selected commonly across the five imputed data sets. Fourth, we applied multivariate logistic regression analyses to the five imputed data sets with the forced-entry method using these final sets of covariates and determined their association with the good functional outcome or the good structural outcome. Finally, combined regression coefficients were obtained for each outcome by averaging the results of the analyses in the five imputed data sets as we applied the multiple imputation method. Statistical significance levels were adjusted for multiple testing using false discovery rate and the Benjamini-Hochberg (BH) method [23].

Results

Patient disposition

Of total 318 enrolled patients, 14 were excluded: eligibility criteria not met, 6; consent withdrawn, 1; and physician's decision, 7. In 33 of these 304 patients, follow-up was discontinued before week 72: lost to follow-up, 17; referred to other clinic, 7; consent withdrawn, 3; physician's decision, 3; death, 2; and moved, 1. The data from the remaining 271 patients (i.e. per protocol set) were used in this study.

Patient characteristics

Table 1 summarizes the characteristics of the 271 patients at baseline. Mean age was 61 years old, and 77% of the patients were women. Median disease duration of RA was 11 months. Forty-six percent of the patients were naive to DMARDs, and 66% of the patients were naive to MTX. All patients were naive to bDMARDs as per the eligible criteria.

Change in treatment over time

In this study, treatment was intensified by starting, adding, or changing DMARDs at enrolment. Newly started DMARDs at enrolment were as follows: MTX in 153 patients (56%), other csDMARDs in 26 patients (10%) (salsalazopyridine in 10 patients, bucillamine in 10 patients, tacrolimus in 2 patients, and 1 patient for each of the following: auranofin, iguratimod, salsalazopyridine plus bucillamin, and bucillamine plus tacrolimus), bDMARDs in

Table 1. Patients' characteristics at baseline ($n = 271$).

Characteristics	Percentage, mean, or median
Age, mean (SD) (years)	61 (14)
Female (%)	77
Disease duration, median (IQR) (months)	11 (3–72)
Ever smoker (%)	31
Extra-articular manifestation (%)	12
History of joint replacement related to RA (%)	5
Number of csDMARDs used before enrolment (%)	
0	46
1	31
2	13
3 or more	11
Naive to MTX (%)	66
Rheumatoid factor, positive (%)	76
Anti-CCP antibody, positive ($n = 253$) (%)	78
MMP-3/UNL, median (IQR)* ($n = 264$)	1.7 (0.9–3.6)
HAQ-DI score, median (IQR)	1.0 (0.5–1.8)
vdH-mTSS, median (IQR) ($n = 267$)	5.5 (1.0–17.5)
SDAI, median (IQR)	24.1 (17.7–33.9)

The percentage, mean, and median were calculated for 271 patients unless the number is specified otherwise.

*Serum levels of MMP-3 were shown as the ratio to the upper normal limit (UNL) because the UNLs are different between male and female.

SD = standard deviation; IQR = interquartile range; RA = rheumatoid arthritis; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; MTX = methotrexate; CCP = cyclic citrullinated peptide; MMP-3 = matrix metalloproteinase-3; UNL = upper normal limit; HAQ-DI = Health Assessment Questionnaire-Disability Index; vdH-mTSS = van der Heijde-modified total Sharp score; SDAI = simplified disease activity index.

94 patients (35%) (infliximab in 29 patients, etanercept in 13 patients, adalimumab in 6 patients, golimumab in 10 patients, tocilizumab in 25 patients, and abatacept in 11 patients) including 2 patients in whom MTX and a bDMARD were simultaneously started.

Changes in treatment during the study period in 271 patients are depicted in Figure 1. As a result of the intensification at enrolment, 226 patients (83%) were treated with MTX with or without any other csDMARDs or bDMARDs, and 94 (35%) were treated with bDMARDs with or without any csDMARDs. The number of patients treated with MTX decreased through the study period, whereas the number of the patients treated with a bDMARD increased. Three to five percent of the patients at each time point were seen without any DMARDs.

Corticosteroid was used in 79 patients (29%) during two weeks before the enrolment, in 95 patients (35%) after the enrolment and in 81 patients (30%) at week 72. The mean prednisolone-equivalent dosages amongst corticosteroid users were 5.6 mg/d at week 0 and 3.9 mg/d at week 72.

Detailed information of treatment regarding DMARDs and corticosteroid by remission status at week 24 is shown in Table 2. Use of these drugs was similar between the two groups except csDMARDs other than MTX (3% for

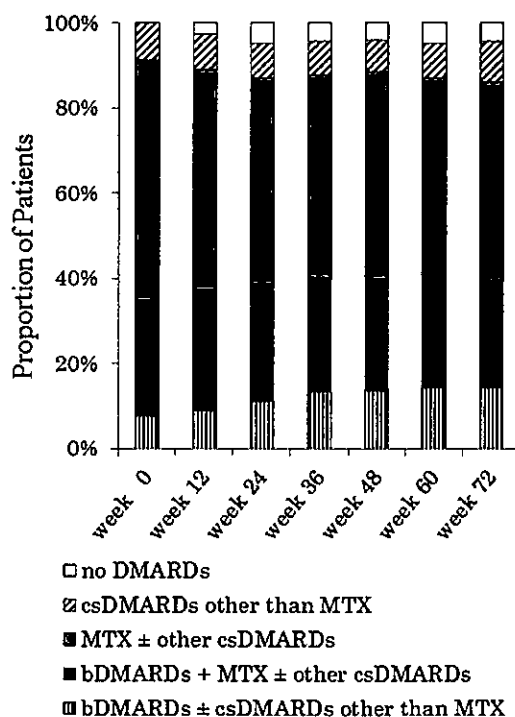


Figure 1. Changes in treatment over time. The Y-axis shows proportions of the patients of each treatment group. For week 0, treatment after intensification for enrolment is shown. For week 12 through week 60, treatment at the beginning of each 12-week period is shown. For week 72, treatment at the last day of follow-up is shown. DMARDs = disease-modifying antirheumatic drugs; csDMARDs = conventional synthetic DMARDs; MTX = methotrexate; bDMARDs = biological DMARDs.

remission group vs. 12% for non-remission group) and corticosteroids (27% for remission group vs. 41% for non-remission group).

Clinical, functional, and structural outcomes

Figure 2(A) shows the change in SDAI over time. At week 24, 34% of the patients achieved SDAI remission, and the proportion increased to 51% at week 72. Figure 2(B) shows the changes in HAQ-DI over time. At enrolment, 28% of the patients were in the range of HAQ remission (HAQ-DI ≤ 0.5). At week 24 and 72, 54 and 62% were in HAQ remission, respectively. Figure 3 is a cumulative probability plot of Δ vdH-mTSS (average of the two raters' score) at week 72 in 264 cases in whom vdH-mTSS were assessable both at weeks 0 and 72. In 21 of the 264 cases, Δ vdH-mTSS was interpolated or extrapolated using available radiographs. The

SDC was 2.98 and Δ vdH-mTSS at week 72 was <2.98 in 78% of the patients assessed.

Multivariate logistic regression models and factors associated with good functional and structural outcomes

Variables included in the final model for HAQ-DI ≤ 0.5 at week 72 were SDAI ≤ 3.3 at week 24, age in years, history of joint replacement related to RA, baseline HAQ-DI, and baseline vdH-mTSS. Those for Δ vdH-mTSS at week 72 $<$ SDC were SDAI ≤ 3.3 at week 24, baseline vdH-mTSS, \log_2 (MMP-3/upper normal limit (UNL) of MMP-3 in corresponding sex) at week 24 and number of csDMARDs used before enrolment. SDAI remission at week 24, HAQ-DI at baseline, and vdH-mTSS at baseline were significant predictors of HAQ remission at week 72 after adjusting for multiple test (Table 3). SDAI remission was also a significant

Table 2. Disease-modifying antirheumatic drugs and corticosteroid use by remission status at week 24.

	remission at week 24 (n = 93)	non-remission at week 24 (n = 168)
DMARDs		
no DMARDs	1 (1%)	6 (4%)
csDMARDs other than MTX	3 (3%)	19 (12%)
MTX \pm other csDMARDs	47 (51%)	75 (45%)
bDMARDs + MTX \pm other csDMARDs	33 (35%)	50 (30%)
bDMARDs \pm csDMARDs other than MTX	9 (10%)	18 (11%)
Corticosteroid		
Corticosteroid user	25 (27%)	72 (41%)
Mean prednisolone-equivalent dosage (mg/d)	3.9	5.5

Data are presented as the number and percentage of the patients in different categories of DMARDs treatment at week 24. The number and percentage of corticosteroid users and mean prednisolone-equivalent dosage amongst the corticosteroid users at week 24 are also presented. Ten patients whose disease activity were not assessable because of missing component variables at week 24 are excluded.

DMARDs = disease-modifying antirheumatic drugs; csDMARDs = conventional synthetic DMARDs; MTX = methotrexate; bDMARDs = biological DMARDs.

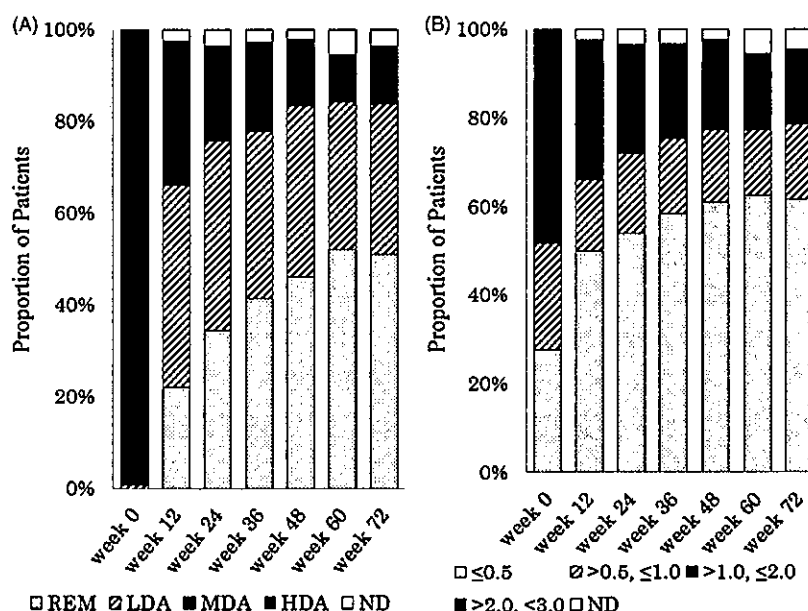


Figure 2. Change in outcomes over the period of 72 weeks. (A) Change in SDAI over time. The Y-axis shows proportions of the patients in different disease activity status using SDAI at each visit. At enrolment, two cases were LDA by SDAI, but were MDA by CDAI, meeting the inclusion criteria. (B) Change in HAQ-DI over time. The Y-axis shows proportions of the patients in different ranges of HAQ-DI score at each visit. SDAI = simplified disease activity index; CDAI = clinical disease activity index; REM = remission; LDA = low disease activity; MDA = moderate disease activity; HDA = high disease activity; ND = not determined; HAQ-DI = Health Assessment Questionnaire-Disability Index.

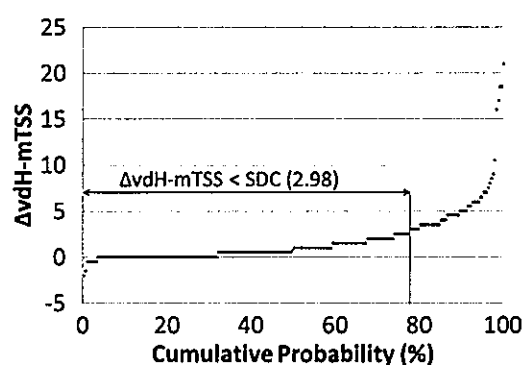


Figure 3. Cumulative probability plot of Δ vdH-mTSS at week 72 in 264 patients. vdH-mTSS = van der Heijde-modified total Sharp score; SDC = smallest detectable change.

Table 3. Multivariate logistic regression analysis with HAQ remission (HAQ-DI ≤ 0.5) at week 72 as a dependent variable.

Variables	Odds ratio (95% CI)	p value
(Intercept)	35.7 (7.62–167.3)	5.9×10^{-6}
SDAI ≤ 3.3 at week 24	2.99 (1.42–6.28)	0.004*
Age (year)	0.98 (0.95–1.00)	0.06
History of joint replacement related to RA	0.14 (0.02–1.01)	0.05
Baseline HAQ-DI	0.28 (0.18–0.45)	1.3×10^{-7} *
Baseline vdH-mTSS	0.986 (0.976–0.996)	0.009*

Predictors of HAQ remission (HAQ-DI ≤ 0.5) at week 72 were determined using multivariate logistic regression model with the forced entry method in the five imputed data sets, and the regression coefficients of each variable were averaged and converted to odds ratio.

*Significant after adjusting for multiple tests using false discovery rate and BH method [23].

HAQ-DI = Health Assessment Questionnaire-Disability Index; CI = confidence interval; SDAI = simplified disease activity index; RA = rheumatoid arthritis; vdH-mTSS = van der Heijde-modified total Sharp score.

Table 4. Multivariate logistic regression analysis with Δ vdH-mTSS at week 72 < SDC as a dependent variable.

Variables	Odds ratio (95% CI)	p value
(Intercept)	3.21 (2.10–4.93)	9.8×10^{-8}
SDAI ≤ 3.3 at week 24	3.53 (1.62–7.71)	0.002*
Baseline vdH-mTSS	0.994 (0.986–1.001)	0.11
$\log_2(\text{MMP-3/UNL})^\dagger$ at week 24	0.76 (0.59–0.97)	0.03
Number of csDMARDs used before enrolment	0.81 (0.64–1.02)	0.07

Predictors of Δ vdH-mTSS at week 72 < SDC at week 72 were determined using multivariate logistic regression model with the forced entry method in the five imputed data sets, and the regression coefficients of each variable were averaged and converted to odds ratio.

*Significant after adjusting for multiple tests using false discovery rate and BH method [23]. † Serum levels of matrix metalloproteinase-3 (MMP-3) were used as a variable after it was converted to the logarithmic of the ratio to the UNL with base 2 [$\log_2(\text{MMP-3/UNL})$] because the ULs were different between male and female. vdH-mTSS = van der Heijde-modified total Sharp score; SDC = smallest detectable change; CI = confidence interval; SDAI = simplified disease activity index; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs.

predictor of Δ vdH-mTSS at week 72 < SDC after adjusting for multiple test (Table 4).

Adherence to T2T strategy at week 12

As the protocol of this study requested the site investigators to follow a T2T strategy, we analyzed adherence to the strategy at week 12. At week 12, both SDAI and CDAI were not assessable in seven patients because one or more of the component variables were missing. These patients were excluded from this adherence analysis. In the remaining 264 patients, 60 patients achieved SDAI or CDAI remission. In 73 patients, remission was not achieved and treatment was adjusted. In four patients, attending physicians reported that

the patients achieved remission but did not actually achieve remission. In 33 patients, an attending physician reported that they adjusted treatment but did not intensify treatment within four weeks after the date of assessment.

In the remaining 94 patients, remission was not achieved, but treatment was not adjusted. The attending physicians specified the following reasons according to the study protocol: (1) an attending physician predicted to achieve remission by continuing current therapy in 50 patients; (2) an attending physician permitted LDA as the treatment goal and achieved LDA at week 12 in 14 patients; (3) an attending physician had no better treatment option than current treatment in two patients; (4) financial reason of the patient in three patients; (5) the patient disagreed with treatment intensification in four patients; and (6) other reasons in 18

patients. In three patients, an attending physician reported that they permitted LDA, but patients did not achieve LDA at week 12. Overall, 67 patients were deemed as "T2T not followed" according to the definition described in the methods section, and 197 (75%) of the 264 patients followed the strategy at week 12.

Discussion

This study showed that 34 and 51% of the patients with active RA achieved SDAI ≤ 3.3 at weeks 24 and 72, respectively, in a T2T-implementing cohort and that achieving SDAI ≤ 3.3 at week 24 was an independent predictor of good functional and structural outcomes at week 72. These results verified the predictive validity of SDAI remission for later good functional and structural outcomes in the real-world clinical setting and strengthen the evidence that SDAI is recommended as a disease activity measure for clinical practice under the T2T strategy.

Relationship between disease activity status by SDAI and consequent functional and structural outcomes has been investigated in several cohort studies [7–10], which provided moderate to weak evidence at best as follows. First, Ruysen-Witrand et al. [7] compared the performance of SDAI remission to that of SDAI LDA using a multivariate linear mixed model and revealed significantly different effects on a structural outcome between the two, but not on a functional outcome. The other studies simply compared outcomes of patients with different disease activity or calculated likelihood ratios for good outcomes without adjusting for potential confounders [8–10]. Second, these cohort studies started data collection far before the publication of T2T recommendations and did not implement the T2T strategy. As such, they did not necessarily reflect current clinical practice under the T2T advocacy. Third, in the report from Ruysen-Witrand et al., subjects of the analysis were not limited to patients with active RA who received treatment with DMARDs. In this study, we enrolled RA patients with moderate-to-high disease activity and treated them with the T2T strategy because we considered it is pertinent to examine predictive validity of achieving SDAI remission under the current rheumatology practice rather than simply being in the status of SDAI remission.

In the logistic regression model with structural outcome as a dependent variable, $\log_2(\text{MMP-3/UNL})$ at week 24 was selected as a covariate based on the results of univariate analyses and clinical significance. Although MMP-3 was not a significant predictor in the model after adjusting for multiple test, the association between MMP-3 and structural damage is plausible because MMP-3 is an enzyme involved in joint destruction and its serum level has been reported to associate with a structural outcome [24].

The T2T recommendations state that low-disease activity may be an acceptable alternative therapeutic goal, but remission should be a clear target [1]. Although we did not intend to compare remission to LDA as a treatment target in this study, remission may be a superior target, as the point estimates of the odds ratios of SDAI remission were

better than those of SDAI LDA (SDAI ≤ 11) for both outcomes [odds ratio (95% CI) for the good structural outcome, 2.35 (1.16–4.78); for the good functional outcome, 2.19 (1.08–4.46)] (Supplementary Tables 3 and 4). These data are concordant with the fact that clinical remission has been shown to convey better outcomes than other disease activity states, even LDA [7,25–29]. The superiority of SDAI remission to SDAI LDA should be further consolidated with additional evidence because the trials from which the T2T recommendations stemmed [30,31] mostly employed LDA as a treatment target, and few of them showed significantly better functional and structural outcomes in a targeted treatment group compared to a conventional treatment group.

This study has two methodological strengths. First, we adjusted for potential confounders associated with good functional and structural outcomes using the multivariate analysis. Amongst the above-mentioned cohort studies [7–10] where predictability of SDAI remission for good outcomes were analyzed, only Ruysen-Witrand et al. [7] adjusted for potential confounders. Second, we used multivariate logistic regression analysis with the multiple imputation method [16]. The rate of missing information in our cohort was not high since missing rates of the variables were 7% at most. However, with the multiple imputation method, we were able to make the most of the collected data for the multivariate analysis and could reflect the real-world practice on our study.

There are some limitations in this study. First is the institutional bias. We recruited patients with moderate-to-high disease activity from university hospitals and tertiary care centers in their geographical areas. Baseline data in Table 1 shows that 77% of the patients were women with mean age of 61 years and median disease duration of 11 months. All were naive to bDMARDs, and 66% were naive to MTX. These data indicate that the enrolled patients appeared to possess characteristics of active patients with recent-onset RA seen in usual clinical setting. Second is the lack of a specific medication sequence in our protocol to adjust the treatment. We intentionally did not specify treatment because we wanted to show the utility of the SDAI remission in clinical practice where various combinations and sequences of DMARDs are used. Third, this study did not compare patients who adhered to T2T with patients who did not. Instead, we focused on the achieved status of disease activity at week 24 as a candidate predictor of good outcomes further down the road. As the T2T strategy was widely accepted in clinical practice of rheumatology in Japan when this study was implemented, it was against ethical obligation to designate a non-T2T group. We believe our study had an appropriate study design to see whether achieved status of remission predicted subsequent good outcomes in a T2T-implementing cohort.

In conclusion, this study showed that achieving SDAI remission in RA patients with moderate-to-high disease activity 24 weeks after treatment intensification was an independent predictive factor of subsequent good functional and structural outcomes. This study is the first to show the significant association between achieving SDAI remission and both functional and structural outcomes in a T2T-

implementing cohort of adult RA patients with moderate-to-high disease activity.

Acknowledgments

We thank the site investigators of the T2T Epidemiological Study Group who contributed in recruiting patients and collecting clinical data: Takahiko Sugihara (Department of Medicine and Rheumatology, Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan), Yoshinori Nonomura (Department of Rheumatology, Tokyo Kyosai Hospital, Tokyo, Japan), Masayuki Inoo (Department of Rheumatology, Utazu-Hama Clinic, Kagawa, Japan), Makoto Soejima (Ome Municipal General Hospital, Ome, Japan), Hiroyuki Hagiyama (Department of Rheumatology, Yokohama City Minato Red Cross Hospital, Yokohama, Japan), Toshihiko Hidaka (Institute of Rheumatology, Zenjinkai Shimin-no-Mori Hospital, Miyazaki, Japan), Mitsuhiro Iwahashi (Higashihiroshima Memorial Hospital, Hiroshima, Japan), Shinya Hirata (Department of Hematology, Rheumatology, and Infectious Disease, Kumamoto University Graduate School of Medicine, Kumamoto, Japan), and Shuji Ohta (Oasis Clinic, Hitachi, Japan). We also thank Ms. Marie Kokido for her contribution at the secretariat of this study. We sincerely thank all the rheumatologists and medical staff who took care of the patients enrolled in this study.

Conflict of interest

Fumio Hirano and Waka Yokoyama have nothing to declare. Tokyo Medical and Dental University (TMDU) received unrestricted research grants for Department of Pharmacovigilance from Abbvie Japan Co., Ltd., Astellas Pharma Inc., Bristol-Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Mitsubishi Tanabe Pharma Co., Ono Pharmaceuticals, Pfizer Japan Inc., Sanofi-Aventis K.K., Santen Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and UCB Japan, with which TMDU paid the salary of Hayato Yamazaki. Koichi Amano received grants from Astellas Pharma Inc., Chugai Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc. and received consultant fees from Abbvie Japan Co., Ltd., Astellas Pharma Inc., Bristol-Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., and Pfizer Japan Inc. Atsushi Kawakami received grants from AbbVie GK, Eisai Co., Mitsubishi Tanabe Pharma Co., Takeda Pharmaceutical Company, Astellas Pharma Inc., ONO Pharmaceutical Co., Kissei Pharmaceutical Co., Boehringer Ingelheim Japan, AstraZeneca Co., Otsuka Pharmaceutical Co., Chugai Pharmaceutical Co., Santen Pharmaceutical Co., Daiichi Sankyo Co. and MSD Co., a consultant fee from Astellas Pharma Inc., and speaker's fees from AbbVie GK, Takeda Pharmaceutical Company, ONO Pharmaceutical Co., Astellas Pharma Inc., Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., MSD Co., Takeda Pharmaceutical Company and Pfizer Japan. Taichi Hayashi has nothing to declare. Naoto Tamura received grants from Astellas Pharma Inc., Ayumi Pharmaceutical Co., Chugai Pharmaceutical Co., Mitsubishi Tanabe Pharma Co., Takeda Pharmaceutical Co., Ltd. Shinsuke Yasuda received a grant from Bristol-Myers Squibb K.K. Hiroaki Dobashi has nothing to declare. Takao Fujii belongs to the department that is financially supported by four pharmaceutical companies (Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd., Bristol-Myers K.K., and Eisai Co., Ltd.). Takao Fujii also received honoraria (lecture fee) from Bristol-Myers K.K., Ono Pharmaceutical Co., Ltd. and Pfizer Japan Inc., and grant/research funding from AbbVie GK, Pfizer Japan Inc., Astellas Pharma Inc., Takeda Pharmaceutical Co., Santen Pharmaceutical Co., Ltd., Daiichi-Sankyo Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., and UCB Japan Co., Ltd. Satoshi Ito received honoraria from AbbVie GK, Bristol-Myers Squibb K.K., Eisai Co., Ltd., Mitsubishi Tanabe Pharma Co., Ltd., Chugai Pharmaceutical Co. Ltd., Janssen Pharmaceutical K.K. Yuko Kaneko has received lecture fees from AbbVie GK, Eisai Co., Ltd., Chugai Pharmaceutical Co., Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma Co., Bristol-Myers K.K., Astellas Pharma Inc., Pfizer,

Janssen, Santen Pharmaceutical Co., Ltd., Kyowa Hakko Kirin, and UCB Japan. Toshihiro Matsui and Yasuaki Okuda and Kazuyoshi Saito have nothing to declare. Fumihito Suzuki received an honorarium from Santen Pharmaceutical Co. Ltd. Ryusuke Yoshimi has received a Bristol-Myers K.K. RA Clinical Investigation Grant. TMDU received unrestricted research grants for Department of Pharmacovigilance from Abbvie Japan Co., Ltd., Astellas Pharma Inc., Bristol-Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Mitsubishi Tanabe Pharma Co., Ono Pharmaceuticals, Pfizer Japan Inc., Sanofi-Aventis K.K., Santen Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and UCB Japan, with which TMDU paid the salary of Ryoko Sakai. Ryoko Sakai has received a research grant from Bristol-Myers Squibb K.K. Ryuji Koike has nothing to declare. Hitoshi Kohsaka received research grants/support from Ajinomoto Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., Japan Science and Technology Agency, Chugai Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Teijin Pharma Ltd., Santen Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., AbbVie Inc., Astellas Pharma Inc., Japan Blood Products Organization, Bristol-Myers Squibb, Eisai Co., Ltd., Pfizer Inc., Actelion Pharmaceuticals Japan Ltd., Daiichi Sankyo Co., Ltd., and received honoraria (lecture fee) from Ono Pharmaceuticals Co., Ltd., Chugai Pharmaceutical Co., Ltd., and Mitsubishi Tanabe Pharma Co. Nobuyuki Miyasaka has nothing to declare. TMDU received unrestricted research grants for Department of Pharmacovigilance from Abbvie Japan Co., Ltd., Astellas Pharma Inc., Bristol-Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Mitsubishi Tanabe Pharma Co., Ono Pharmaceuticals, Pfizer Japan Inc., Sanofi-Aventis K.K., Santen Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and UCB Japan, with which TMDU paid the salary of Masayoshi Harigai.

This work was supported by a grant-in-aid from the Ministry of Health, Labour and Welfare, Japan, for the Study Group on the Standardization of Clinical Practice of Rheumatoid Arthritis in Japan, the Ministry of Health, Labour and Welfare of Japan (H23-meneki-shitei-016 and H26-meneki-shitei-021 to N.M. and M.H.).

References

- Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis*. 2010;69:631–7.
- Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis*. 2016;75:3–15.
- Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology (Oxford)*. 2003;42:244–57.
- Aletaha D, Ward MM, Machold KP, Nell VP, Stamm T, Smolen JS. Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. *Arthritis Rheum*. 2005;52:2625–36.
- Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American college of rheumatology/European league against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis*. 2011;70:404–13.
- Anderson J, Caplan L, Yazdany J, Robbins ML, Neogi T, Michaud K, et al. Rheumatoid arthritis disease activity measures: American college of rheumatology recommendations for use in clinical practice. *Arthritis Care Res (Hoboken)*. 2012;64:640–7.
- Ruyssen-Witrand A, Guernec G, Nigon D, Tobon G, Jamard B, Rat AC, et al. Aiming for SDAI remission versus low disease activity at 1 year after inclusion in ESPOIR cohort is associated with better 3-year structural outcomes. *Ann Rheum Dis*. 2015;74:1676–83.

8. Svensson B, Andersson ML, Bala SV, Forslind K, Hafstrom I. Long-term sustained remission in a cohort study of patients with rheumatoid arthritis: choice of remission criteria. *BMJ Open*. 2013;3:e003554.
9. Sakellariou G, Scire CA, Verstappen SM, Montecucco C, Caporali R. In patients with early rheumatoid arthritis, the new ACR/EULAR definition of remission identifies patients with persistent absence of functional disability and suppression of ultrasonographic synovitis. *Ann Rheum Dis*. 2013;72:245–9.
10. Lillegraven S, Prince FH, Shadick NA, Bykerk VP, Lu B, Frits ML, et al. Remission and radiographic outcome in rheumatoid arthritis: application of the 2011 ACR/EULAR remission criteria in an observational cohort. *Ann Rheum Dis*. 2012;71:681–6.
11. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 rheumatoid arthritis classification criteria: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis*. 2010;69:1580–8.
12. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, Smolen JS. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res Ther*. 2005;7:R796–806.
13. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. *J Am Med Assoc*. 1994;271:659–62.
14. van der Heijde DM, van Leeuwen MA, van Riel PL, van de Putte LB. Radiographic progression on radiographs of hands and feet during the first 3 years of rheumatoid arthritis measured according to Sharp's method (van der Heijde modification). *J Rheumatol*. 1995;22:1792–6.
15. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum*. 1980;23:137–45.
16. Rubin DB. Introduction. Multiple imputation for nonresponse in surveys. New Jersey: John Wiley & Sons; 2004: 1–26.
17. Bruynesteyn K, Boers M, Kostense P, van der Linden S, van der Heijde D. Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. *Ann Rheum Dis*. 2005;64:179–82.
18. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis*. 2014;73:492–509.
19. Honaker J, King G, Blackwell M. Amelia II: a program for missing data. *J Stat Soft*. 2011;45:1–47.
20. Imai K, King G, Zelig LO. Everyone's Statistical Software. Available from: <http://gking.harvard.edu/zelig/> [last accessed 16 Jan 2016].
21. Imai K, King G, Lau O. Toward a common framework for statistical analysis and development. *J Comp Graph Stat*. 2008;17:892–913.
22. Schafer JL. Multiple imputation: a primer. *Stat Methods Med Res*. 1999;8:3–15.
23. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B (Methodol)*. 1995;57:289–300.
24. Yamanaka H, Matsuda Y, Tanaka M, Sendo W, Nakajima H, Taniguchi A, Kamatani N. Serum matrix metalloproteinase 3 as a predictor of the degree of joint destruction during the six months after measurement, in patients with early rheumatoid arthritis. *Arthritis Rheum*. 2000;43:852–8.
25. Radner H, Smolen JS, Aletaha D. Remission in rheumatoid arthritis: benefit over low disease activity in patient-reported outcomes and costs. *Arthritis Res Ther*. 2014;16:R56.
26. Aletaha D, Funovits J, Smolen JS. The importance of reporting disease activity states in rheumatoid arthritis clinical trials. *Arthritis Rheum*. 2008;58:2622–31.
27. Smolen JS, Han C, van der Heijde DM, Emery P, Bathon JM, Keystone E, et al. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. *Ann Rheum Dis*. 2009;68:823–7.
28. Kavanaugh A, Fleischmann RM, Emery P, Kupper H, Redden L, Guertel B, et al. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. *Ann Rheum Dis*. 2013;72:64–71.
29. Emery P, Genovese MC, van Vollenhoven R, Sharp JT, Patra K, Sasso EH. Less radiographic progression with adalimumab plus methotrexate versus methotrexate monotherapy across the spectrum of clinical response in early rheumatoid arthritis. *J Rheumatol*. 2009;36:1429–41.
30. Schoels M, Knevel R, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas DT, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. *Ann Rheum Dis*. 2010;69:638–43.
31. Stoffer MA, Schoels MM, Smolen JS, Aletaha D, Breedveld FC, Burmester G, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update. *Ann Rheum Dis*. 2016;75:16–22.

ORIGINAL ARTICLE

Simplified Disease Activity Index remission at month 6 is an independent predictor of functional and structural remissions at month 12 during abatacept treatment in patients with rheumatoid arthritis: A multi-center, prospective cohort study in Japan

Hayato Yamazaki^{a,b}, Fumio Hirano^{a,b}, Tsutomu Takeuchi^c, Koichi Amano^d, Jun Kikuchi^c, Mari Kihara^{a,b}, Waka Yokoyama^b, Takahiko Sugihara^e, Kenji Nagasaka^f, Hiroyuki Hagiya^g, Yoshinori Nonomura^h, Ryoko Sakai^{a,b}, Michi Tanaka^{a,b}, Ryuji Koike^{a,b}, Toshihiro Nanki^{a,b}, Hitoshi Kohsaka^b, Nobuyuki Miyasaka^b and Masayoshi Harigai^{a,b}

^aDepartment of Pharmacovigilance and ^bDepartment of Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU), Tokyo, Japan, ^cDivision of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, ^dDepartment of Rheumatology/Clinical Immunology, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan, ^eTokyo Metropolitan Geriatric Hospital, Tokyo, Japan, ^fOme Municipal General Hospital, Tokyo, Japan, ^gYokohama City Minato Red Cross Hospital, Yokohama, Japan, and ^hTokyo Kyosai Hospital, Tokyo, Japan

ABSTRACT

Objective: To evaluate association of clinical remission at month 6 with functional and structural remissions at month 12 during abatacept treatment in patients with rheumatoid arthritis (RA).

Methods: This 12-month prospective, multicenter cohort study enrolled 168 patients with RA who started abatacept. Outcomes were assessed using composite measures, quality of life indices, and the van der Heijde-modified total Sharp score (mTSS). The logistic regression analysis was applied to identify factors associated with outcomes and their odds ratios (OR) with 95% confidence interval (95% CI).

Results: At month 6 and 12, 21.4% and 26.2% of the patients achieved Simplified Disease Activity Index (SDAI) remission (SDAI <3.3), and 40.6% and 41.7% achieved Health Assessment Questionnaire-Disability Index (HAQ-DI <0.5) remission. Among 129 patients whose mTSS progression was evaluated at month 12, 83 (64.3%) achieved structural remission (Δ mTSS ≤ 0.5 for 12 months). SDAI remission at month 6 was identified as a significant predictor of both functional (OR, 3.732; 95% CI, 1.328–10.489) and structural remissions (OR, 4.301; 95% CI, 1.298–14.243) at month 12 after adjusting for covariates.

Conclusions: Aiming for SDAI remission at month 6 is an appropriate strategy to obtain good functional and structural outcomes at month 12.

ARTICLE HISTORY

Received 4 August 2016
Accepted 4 November 2016

KEYWORDS

Abatacept; Outcome assessment; Remission; Rheumatoid arthritis

Introduction

The treatment of rheumatoid arthritis (RA) has significantly advanced with the introduction of biologic disease-modifying antirheumatic drugs (biologic DMARDs). Currently, five tumor necrosis factor (TNF) inhibitors, tocilizumab, and abatacept are widely used in Japan, and the numbers of patients treated with these agents are increasing. Abatacept, a new class of biologic DMARDs that inhibits T-cell activation by selective modulation of the interaction between CD80/86 and CD28, was approved in Japan in 2010. The result of post-marketing surveillance program revealed safety and effectiveness of abatacept for six months in clinical settings in Japan [1]. In recent meta-analyses, the efficacy of abatacept has been shown to be comparable to that of other classes of biologic DMARDs with relatively better safety profile [2,3].

Recommendations for RA treatment indicate the importance of periodic assessment of disease activity by using composite measures, including joint assessments [4]. Among currently available composite measures for RA, the Simplified Disease Activity Index (SDAI) is used for the provisional definition of remission because of its better association with subsequent good functional and structural outcomes than other candidate criteria. However, long-term benefits of achieving SDAI remission and risks for patients who were administered individual biological DMARDs in a clinical setting remain to be demonstrated. Therefore, we implemented a 12-month multi-center, prospective cohort study to investigate clinical, functional, and structural outcomes and safety in Japanese patients with RA treated with abatacept, and analyzed the association of clinical remission at month 6 with functional and structural remissions at month 12. This study identified patients with RA who were

most likely to obtain therapeutic benefits from treatment with abatacept in clinical practice. Our results indicated that SDAI remission at month 6 was an appropriate short-term treatment goal in patients with RA who were administered abatacept.

Materials and methods

Patients

Patients with active RA who newly started abatacept despite more than three months of treatment with DMARDs were enrolled. All patients had to satisfy the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA [5] and provide written informed consent. Seven institutions participated in this study, including three university hospitals and four referral hospitals in Japan. Enrollment in this study started from June 2010 to December 2012. This study was in accordance with the Helsinki Declaration (revised in 2008) and approved by the ethics committees of the Tokyo Medical and Dental University Hospital (#836) and the other participating institutions. A written informed consent was obtained from each patient. This study was registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000005144).

Treatment with abatacept

All patients were administered fixed doses of abatacept intravenously, based on a Japanese medical package insert; patients weighing <60 kg, 60–100 kg, and >100 kg were administered 500 mg, 750 mg, and 1000 mg of abatacept, respectively, at weeks 0, 2, 4, and then every four weeks for up to week 52. Concomitant use of methotrexate (MTX), DMARDs other than MTX, oral corticosteroids, and non-steroidal anti-inflammatory drugs (NSAIDs) was allowed at the discretion of the site investigators.

Data collection

We used a predefined case report form at baseline and six months and 12 months after enrollment. We collected demographic data at baseline and clinical data at baseline and after patients started abatacept. Disease activity was evaluated with SDAI, Clinical Disease Activity Index (CDAI), Disease Activity Score 28-erythrocyte sedimentation rate (DAS28-ESR), and DAS28-C-reactive protein (DAS28-CRP) [6]. American College of Rheumatology response rate was not collected because we considered that remission defined by composite indices including SDAI/CDAI was more stringent and suitable for our purpose [7]. Health-related quality of life was assessed with the Health Assessment Questionnaire-Disability Index (HAQ-DI) and EuroQol 5 Dimension (EQ-5D). Structural damage was measured with the van der Heijde modified total Sharp score (mTSS) [8]. SDAI, CDAI, DAS28-ESR, and

DAS28-CRP were collected at baseline and month 1, 3, 6, 9, and 12, and HAQ-DI and EQ-5D were collected at baseline and every three months. Radiographs of the hands and feet were collected at baseline and month 6 and 12 to define the yearly change of mTSS measured at month 12 (Δ mTSS). Radiographs of the hands and feet were scored in a chronological order by two independent raters. Linear extrapolation was used for patients without mTSS measured at month 12 if they had mTSS measured both at baseline and at month 6. Observation ceased when patients discontinued abatacept, died, or were lost to follow up. In cases where observation ceased by month 12, all outcome data were obtained on the day of the last visit. All serious adverse events (SAEs) were reported at the time of onset. Our definition of a SAE was based on the report by the International Conference on Harmonization [9].

Statistical analysis

Patient demographics, SDAI, CDAI, DAS28-ESR, DAS28-CRP, HAQ-DI, EQ-5D, and mTSS were summarized using descriptive statistics. Results were expressed as mean \pm standard deviation (SD) or medians and ranges based on the data distribution or number (%). The chi-square test for categorical variables, and Student's *t*-test or Mann-Whitney test for continuous variables were used for comparisons of two groups depending on the data distribution. The last-observation-carried-forward (LOCF) method was used for patients who discontinued observation by month 12 to replace missing data. Disease activity was categorized into remission (SDAI ≤ 3.3 , CDAI ≤ 2.8 , DAS28-ESR ≤ 2.6 , and DAS28-CRP ≤ 2.6), low disease activity ($3.3 < \text{SDAI} \leq 11$, $2.8 < \text{CDAI} \leq 10$, $2.6 < \text{DAS28-ESR} \leq 3.2$, and $2.6 < \text{DAS28-CRP} \leq 3.2$), moderate disease activity ($11 < \text{SDAI} \leq 26$, $10 < \text{CDAI} \leq 22$, $3.2 < \text{DAS28-ESR} \leq 5.1$, and $3.2 < \text{DAS28-CRP} \leq 5.1$), and high disease activity (SDAI > 26 , CDAI > 22 , DAS28-ESR > 5.1 , and DAS28-CRP > 5.1) based on the original definition [6]. The Kaplan-Meier method was used to assess the retention rate of abatacept. We identified the independent predictors for achieving SDAI remission (SDAI ≤ 3.3) at month 6 and HAQ (HAQ-DI ≤ 0.5) and structural remissions (Δ mTSS $\leq 0.5/\text{year}$) at month 12. First, we compared patients who succeeded and did not succeed to achieve each outcome by using univariate analyses. Second, we performed multivariate logistic regression analysis with forced entry method to determine the predictors for achieving each outcome. Variables included in the multivariate analysis were selected based on the results of the univariate analyses. Achievement of clinical remission with each composite index at month 6 was included as an independent variable in the multivariate analysis for HAQ and structural remissions at month 12. Collinearity and medical significance of the variables were also considered for the selection of independent variables. All *p* values were two-tailed, and *p* < 0.05 was considered statistically

Table 1. Baseline patient characteristics.

Variables	Total (n = 168)
Age, years	65.3 ± 11.2
Female (%)	84.5
Disease duration, years*	7.21 [0.3, 59.3]
Disease duration, <3 years (%)	51 (30.4)
Body mass index	21.7 ± 4.0
Ever smoker (%)	26.8
RF positive (%)	76.6 (n = 167)
Anti-CCP antibody positive (%)	87.2 (n = 156)
Comorbidity	64.3
Interstitial pneumonia (%)	18.5
COPD (%)	3.0
Previous pulmonary tuberculosis (%)	5.4
Diabetes mellitus (%)	10.7
Chronic kidney disease (%)	4.8
Prior use of biologics (%)	48.8
MTX use (%)	56.0
MTX dose, mg/week	8.2 ± 3.5 (n = 96)
Conventional DMARDs use excluding MTX†	25.6
Corticosteroid use (%)	51.2
Corticosteroid dose, mg/day‡	4.9 ± 2.9 (n = 88)
SJC, 0–28*	5.0 [0, 26]
TJC, 0–28*	4.0 [0, 26]
PtGA, VAS 0–100 mm	52.3 ± 25.7
PhGA, VAS 0–100 mm	47.1 ± 20.6
ESR, mm/h*	47.5 [2, 139]
CRP, mg/dl*	0.9 [0.00, 10.3]
MMP-3, ng/ml*	151.0 [26, 1357]
SDAI	24.1 ± 12.6
CDAI	22.4 ± 19.0
DAS28-ESR	5.14 ± 1.28
DAS28-CRP	4.35 ± 1.16
HAQ-DI*	1.3 [0.0, 3.0] (n = 167)
mTSS*	24.0 [0, 331.5] (n = 161)
mTSS yearly progression*	3.0 [0, 54.0] (n = 161)

CCP: cyclic citrullinated peptide; CDAI: Clinical Disease Activity Index; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; DAS: disease activity score; DMARDs: disease-modifying antirheumatic drugs; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire Disability Index; MMP-3: matrix metalloproteinase 3; mTSS: modified Sharp–van der Heijde total score; MTX: methotrexate; PhGA: physicians' global assessment of disease activity; PtGA: patients' global assessment of disease activity; RF: rheumatoid factor; SDAI: Simplified Disease Activity Index; SJC: swollen joint count; TJC: tender joint count.

Values are presented as mean ± standard deviation (SD) unless otherwise indicated.

*Median [minimum, maximum].

†Bucillamine (17 patients were given), tacrolimus (14), salazosulfapyridine (11), mizoribine (4), leflunomide (3), cyclosporin (1), and azathioprine (1).

‡Oral prednisolone-equivalent dose.

significant. These statistical analyses were conducted by using SPSS (version 20.0, SPSS Inc., Chicago, IL).

Results

Demographic and clinical characteristics of patients at baseline

A total of 168 patients were enrolled in this study. The baseline data of these patients are shown in Table 1. The mean ± SD age was 65.3 ± 11.2 years, and the percentage of patients >65 years was 52.4%. The disease duration was relatively long with a median [minimum, maximum] of 7.21 [0.3, 59.3] years, and 64.3% of the patients had comorbidities. The concomitant use of MTX and corticosteroids was 56.0% and 51.2% with mean doses of 8.2 ± 3.5 mg/week and 4.9 ± 2.9 mg/day of prednisolone-equivalent dose,

respectively. Most of the patients had moderate or high disease activity. The median [minimum, maximum] mTSS was 24.0 [0, 331.5], reflecting long-standing disease and high disease activity of this patient population.

Patient disposition

All patients received abatacept as scheduled and included in the analysis. The number of patients who discontinued abatacept for any reasons during the observation period was 52 (31.0%). The lack of effectiveness was the most common reason for abatacept discontinuation and reported in 34 patients (20.2%). The second most common reason of discontinuation was adverse events, which occurred in nine patients (5.4%) (Supplementary Table 1).

Among the 168 patients enrolled, two were excluded from the analysis of change of disease activity due to the lack of data after baseline. All disease activity indices decreased by three months after baseline and reached a plateau (Figure 1a,b). The percentage of the patients who achieved remission by SDAI, CDAI, DAS28-ESR, and DAS28-CRP at month 6 was 21.4%, 20.8%, 19.0%, and 47.0%, respectively. The percentage of patients who were categorized in remission or low disease activity was almost stable at month 6 and 12 (Figure 1c). As the remission rates using DAS28-CRP were higher than DAS28-ESR, we examined the correlations between DAS28-CRP and DAS28-ESR at month 6 and 12. The slopes and intercept of the regression lines were 1.009 and 0.847 at month 6 and 0.972 and 0.914 at month 12, respectively, which were similar to those of 1.01 and 0.59 reported previously from a large cohort of Japanese patients with RA [10]. The patients who achieved HAQ remission (HAQ-DI ≤ 0.5) and showed clinically important improvement in HAQ (ΔHAQ-DI ≤ -0.22) were stable with 38.1–42.3% and 46.4–53.0% at each visit after month 3, respectively (Figure 1d). The mean ± SD (number of the patients with available data) of EQ5D index at baseline and month 3, 6, 9, and 12 was 0.609 ± 0.159 (164), 0.661 ± 0.169 (153), 0.679 ± 0.195 (138), 0.686 ± 0.198 (123), and 0.684 ± 0.210 (109), respectively. The mean ± SD increase of EQ5D index from baseline to month 6 and 12 was 0.070 ± 0.180 and 0.075 ± 0.196, respectively.

Structural changes over time

A total of 129 patients were evaluated for mTSS progression at month 12. Among the patients, 100 underwent hand and feet radiographs at both baseline and month 12, whereas linear extrapolation method was applied to the other 29 patients to calculate for mTSS at month 12 using mTSS at baseline and month 6. The mean ΔmTSS at month 12 from baseline was 2.12 ± 10.46, and 83 patients (64.3% of the assessed patients) achieved structural remission (ΔmTSS ≤ 0.5). A total of nine patients (7.0%) showed rapid mTSS increase (ΔmTSS ≥ 5/year). One patient who obtained mTSS at month 12 using the linear extrapolation method showed pronounced ΔmTSS of 114/year. The mean ΔmTSS at

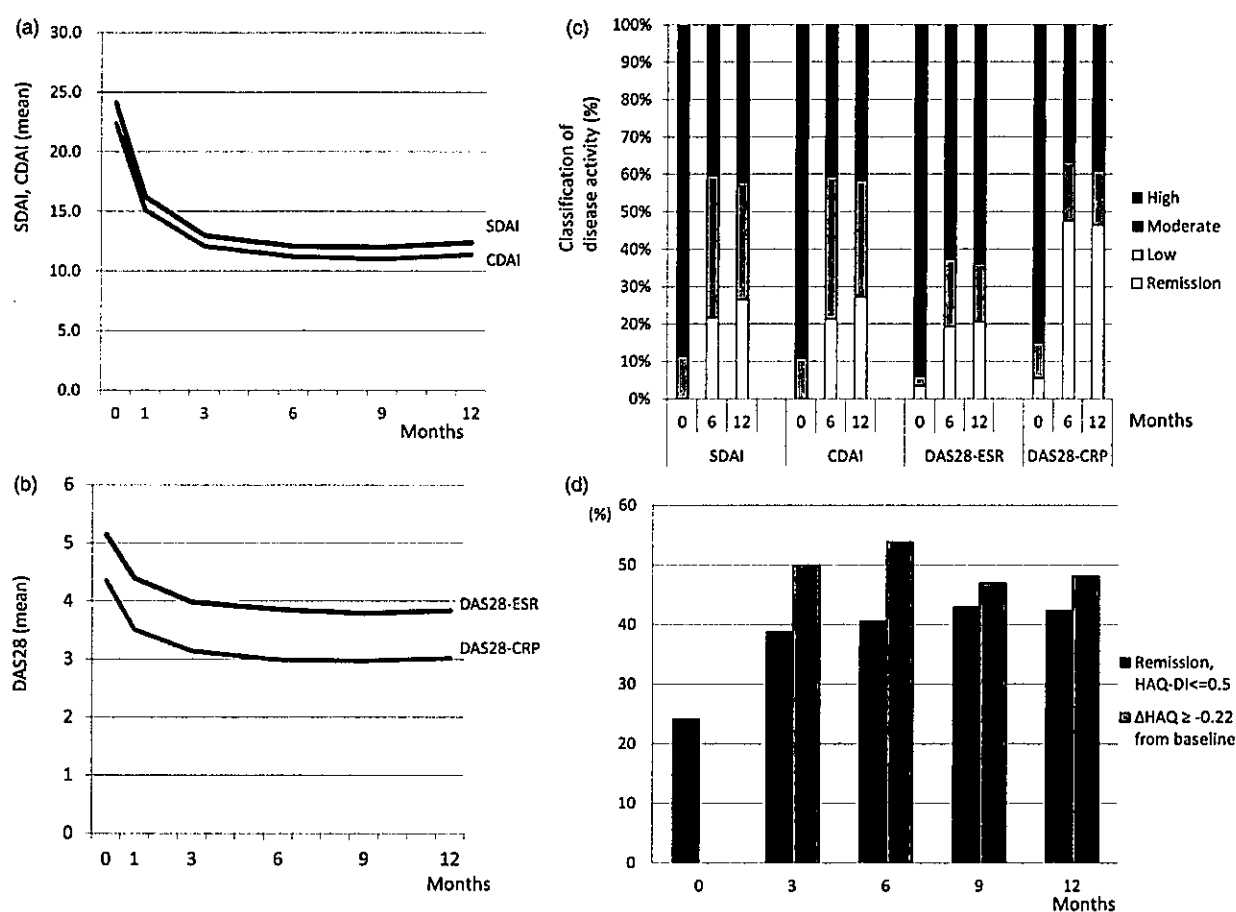


Figure 1. Changes of disease activity and physical function over time after commencement of abatacept. (a) A time course of mean SDAI and CDAI. (b) A time course of mean DAS28-ESR and DAS28-CRP. (c) Proportions of patients categorized as each disease activity by SDAI, CDAI, DAS28-ESR, and DAS28-CRP, at baseline, six months, and 12 months. (d) Proportion of patients with HAQ-DI ≤ 0.5 and Δ HAQ-DI ≥ -0.22 at baseline and each visit. Among all patients enrolled ($n = 168$), 166 were assessed with SDAI, CDAI, DAS28-CRP, DAS28-ESR, and HAQ-DI by using the last-observation-carried-forward method. Values shown in (a) and (b) illustrate the mean of each score. CDAI: clinical disease activity score; DAS28-CRP: disease activity score 28-C-reactive protein; DAS28-ESR: disease activity score 28-erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire Disability Index; SDAI: simplified disease activity index.

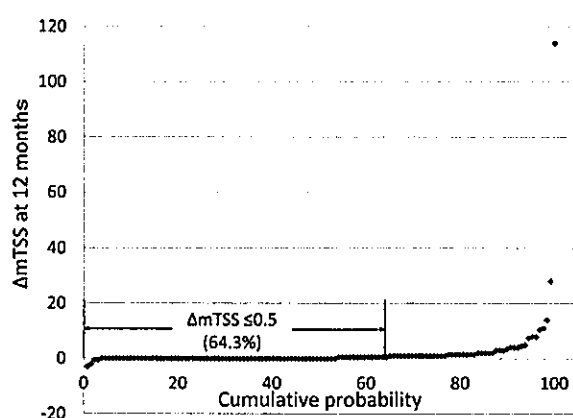


Figure 2. Cumulative probability of a change in mTSS at month 12. The mTSS progression of 129 patients was evaluated at month 12. Among them, 83 patients (64.3%) achieved structural remission (Δ mTSS ≤ 0.5).

month 12 excluding this case was 1.25 ± 3.32 , which suggested that one outlier considerably increased the mean Δ mTSS at month 12. The cumulative probability of Δ mTSS at month 12 is shown in Figure 2.

Factors associated with SDAI remission

We investigated the variables associated with SDAI remission at month 6. We compared patient baseline characteristics ($n = 166$) who did and did not achieve SDAI remission at month 6 using the univariate analyses, and identified that age, disease duration, prior use of biologics, patients' global assessment of the disease activity, physicians' global assessment, SDAI, CDAI, DAS28-ESR, DAS28-CRP, HAQ-DI, and mTSS were significantly different between the groups (data not shown). The concomitant MTX use was not significantly different between the groups. Among them, we selected age, sex, disease duration, prior use of biologics, and SDAI as covariates of the multivariate logistic regression analysis with forced entry method to calculate their odds ratios (OR) and 95% confidence intervals (95% CI). Age (per decade) (OR, 0.670; 95% CI, 0.472–0.951; $p = 0.025$), disease duration (years) (OR, 0.946; 95% CI, 0.898–0.997; $p = 0.039$), prior use of biologics (OR, 0.394; 95% CI, 0.169–0.917; $p = 0.031$), and SDAI at baseline (OR, 0.958; 95% CI, 0.922–0.996; $p = 0.030$) were significantly associated with achieving SDAI remission at month 6.

Table 2. Factors associated with HAQ remission at month 12.

	HAQ remission at month 12	
	OR (95% CI)	p value
Age, decades	1.386 (0.929–2.068)	0.110
Female (%)	1.297 (0.424–3.969)	0.649
Disease duration, years	0.963 (0.910–1.018)	0.181
Prior use of biologics, yes	0.323 (0.140–0.745)	0.008
Comorbidity, yes	0.604 (0.248–1.470)	0.267
SDAI at baseline	1.016 (0.977–1.057)	0.427
SDAI remission at month 6	3.732 (1.328–10.489)	0.012
HAQ-DI at baseline	0.148 (0.070–0.311)	<0.001
mTSS at baseline	1.003 (0.992–1.013)	0.634

CI: confidence interval; HAQ-DI: Health Assessment Questionnaire Disability Index; mTSS: modified Sharp–van der Heijde total score; OR: odds ratio; SDAI: Simplified Disease Activity Index.

Factors associated with HAQ remission

We next investigated the association of HAQ remission at month 12 and clinical response at month 6. We compared patients ($n=166$) who did and did not achieve HAQ remission at month 12 using the univariate analyses and found that disease duration, prior use of biologics, comorbidity, SDAI, CDAI, DAS28-ESR, DAS28-CRP, HAQ-DI, and mTSS at baseline and SDAI, CDAI, DAS28-ESR, and DAS28-CRP at month 6 were significantly different between the two groups (data not shown). We applied logistic regression analysis with forced entry method to identify significant predictors for achieving HAQ remission at month 12. For each model, age, sex, disease duration, prior use of biologics, comorbidity, HAQ-DI, and mTSS at baseline and one of the three disease activity indices (SDAI, DAS28-ESR, and DAS28-CRP) at both baseline and month 6 were included as covariates. CDAI at baseline and month 6 was not used as a covariate because SDAI and CDAI were found to have an extremely strong correlation, with a correlation coefficient of 0.987 and 0.992 at baseline and month 6, respectively. We found that prior use of biologics (OR, 0.323; 95% CI, 0.140–0.745), SDAI remission at month 6 (OR, 3.732; 95% CI, 1.328–10.489), and HAQ-DI at baseline (OR, 0.148; 95% CI, 0.070–0.311) were significantly associated with HAQ remission at month 12 (Table 2). When DAS28-ESR or DAS28-CRP was used in this model instead of SDAI, remission at month 6 was not identified as a significant predictor (data not shown).

Prognostic factors for structural changes

We finally investigated factors associated with achieving structural remission by the same procedure of analyzing predictors of HAQ remission. The univariate analyses revealed that age, disease duration ≤ 3 years, DAS28-CRP, SDAI, and mTSS at baseline and DAS28-CRP and SDAI at month 6 were significantly different between patients who did and did not achieve structural remission at month 12 (data not shown). The multivariate logistic regression analysis with forced entry method was applied to identify predictors of structural remission at month 12 using age, sex, disease duration ≤ 3 years, mTSS at baseline, and one of the three disease activity indices (SDAI, DAS28-ESR, and DAS28-CRP)

Table 3. Factors associated with structural remission at month 12.

	Δ mTSS ≤ 0.5 at month 12	
	OR (95% CI)	p value
Age, decades	0.696 (0.464–1.042)	0.079
Sex	0.601 (0.173–2.086)	0.423
Disease duration ≤ 3 years	3.225 (1.099–9.460)	0.033
SDAI at baseline	0.951 (0.918–0.986)	0.007
SDAI remission at month 6	4.301 (1.298–14.243)	0.017
mTSS at baseline	0.997 (0.989–1.005)	0.443

CI: confidence interval; mTSS: modified Sharp–van der Heijde total score; OR: odds ratio; SDAI: Simplified Disease Activity Index.

at both baseline and month 6. The results of the analyses showed that disease duration (≤ 3 years) (OR, 3.225; 95% CI, 1.099–9.460), SDAI at baseline (OR, 0.951; 95% CI, 0.918–0.986), and SDAI remission at month 6 (OR, 4.301; 95% CI, 1.298–14.243) were significantly associated with achieving structural remission at month 12 (Table 3). SDAI remission at month 6 was still identified as a significant predictor in this analysis, but not DAS28-ESR or DAS28-CRP (data not shown). Consequently, SDAI remission at month 6 was the best predictor not only for achieving HAQ remission, but also of achieving structural remission at month 12 in our cohort among all clinical activity indices analyzed.

Serious adverse events

A total of 17 SAEs were reported in 14 cases (8.3%) during the observation period (Supplementary Table 2). Of these, three events were considered to be related to the treatment with abatacept, causal relationship with the treatment could not be denied in eight events, and six events were unrelated to the treatment with abatacept according to the site investigators. The outcomes of all SAEs were reported as improved or recovered. Serious infections were reported in six patients: three cases of acute pyelonephritis, and one case each for skin abscess, *Pneumocystis jirovecii* pneumonia, and shingles. The incidence of serious infections was 4.29 (95% CI, 0.86–7.71) per 100 patient years (PY).

Discussions

We implemented a prospective cohort study to evaluate the association of clinical remission at month 6 with functional and structural remissions at month 12 in 168 Japanese patients with RA who were administered abatacept in the clinical setting. During 12 months of the observation period, SDAI and HAQ remissions were achieved in 21.4% and 40.6% at month 6 and 26.2% and 41.7% at month 12, respectively. Of 129 patients who were evaluated with mTSS at month 12, 64.3% achieved structural remission at month 12. The multiple logistic regression analysis showed that age, disease duration, prior use of biologics, and SDAI at baseline were significantly associated with SDAI remission at month 6. Clinical remission at month 6 with SDAI, but not with other indices, was significantly associated with both HAQ and structural remissions at month 12 after adjusting for covariates.

Although many studies regarding effectiveness and safety of abatacept for treating RA have been reported [11–14], studies seeking for predictors of treatment outcomes with abatacept are limited [15–21], particularly in the Asian population. Results of our study have identified predictors of all clinical, functional, and structural remissions of treatment with abatacept in Japanese patients with RA. For the assessment of clinical remission predictors, we used SDAI remission at month 6 as an objective variable of the multivariate analysis because it is used in the provisional definition of remission of RA proposed by ACR/EULAR [8] and because clinical response of treatment with abatacept plateaued after six months in previous studies [11–14]. Our results are in line with previous reports that identified age, prior use of biologics, and baseline disease activity as predictors of good clinical response in patients with RA treated with abatacept [16–19]. Seropositivity was not associated with clinical, functional, or structural remission in this study.

As structural damages account for a substantial proportion of functional impairment [22], prevention or minimization of the progression of structural damages is one of the most relevant goal in treatment of RA. Indeed, the provisional definition of RA remission based on ACR/EULAR [8], defined as SDAI ≤ 3.3 , is aimed to prevent progression of radiographic damage and decline of functional capacity. In our study, SDAI remission at month 6 was an independent predictor of HAQ and structural remissions at month 12, but DAS28-ESR or DAS28-CRP remission at month 6 was not an independent predictor. Among eight patients who achieved DAS28-ESR remission without achieving SDAI remission at month 6, four patients (50.0%) achieved HAQ remission at month 12 and only two patients (28.6%) out of seven patients who were evaluated mTSS achieved mTSS remission at month 12, respectively. In contrast, eight patients (66.7%) and 11 patients (91.7%) out of 12 patients who achieved SDAI remission without achieving DAS28-ESR remission at month 6 achieved HAQ remission and mTSS remission at month 12, respectively. These data suggest that SDAI remission at month 6 would be an appropriate short-term treatment goal to prevent the progression of structural damages as well as functional impairment in the next six months in patients with RA treated with abatacept. Results from a post hoc analysis of the abatacept study to gauge remission and joint damage progression in MTX-naïve patients with early erosive RA (AGREE) are in line with our data. In AGREE, patients receiving abatacept plus MTX who achieved remission or LDA according to composite indices at month 3 achieved greater improvements in HAQ-DI scores at month 12 versus patients with MDA or HAD. At every time point, mean HAQ-DI scores were numerically lower for patients in SDAI and CDAI remissions versus DAS28 remission [23].

In our study, functional impairment was evaluated not only by using HAQ-DI, but also by using EQ-5D. The mean of EQ5D index increased from 0.609 at baseline to 0.679 and 0.684 at month 6 and 12, respectively. Of 124 patients who had EQ-5D score <0.7 at baseline, 45 (36.3%) and 27 (21.8%) had EQ-5D scores >0.7 and >0.8 , respectively, at

month 6. As Tanaka et al. [24] reported that both mean expected annual out-of-pocket direct medical and nonmedical cost per patient with RA decreased with increased EQ-5D score, one could expect that nonmedical cost of these patients decreases after the successful treatment with abatacept.

Although treatment with abatacept increased the risk for serious infections in clinical trials [25,26], the risk might be modest compared with that of other biologic DMARDs [2]. The incidence rate of serious infection in this study [4.29 (95% CI, 0.86–7.71)/100 PY] was similar to that of Japanese patients with RA who were administered TNF inhibitors in 2008 or later in a prospective cohort study [3.33 (95% CI, 1.65–6.08)/100 PY] [27]. Considering older age (mean age \pm SD, 65.3 ± 11.2 years vs. 57.9 ± 14.8 years) and higher percentage of comorbidity (64.3% vs. 33.0%), which are the two major risk factors for infection in patients with RA [28,29], in the patients in this study compared with that of Sakai et al. [27], the use of abatacept was at least similar and may be associated with lower risk for serious infection in patients with RA than the TNF inhibitor use. Further studies are needed to compare the safety of abatacept with other biologic DMARDs in a clinical setting.

Our study has several limitations. First, we have to consider possible selection bias in our study. All patients were enrolled from university hospitals or referral hospitals that are dedicated to the treatment of RA. The effectiveness and safety data of this study may have been affected by unmeasured selection bias. Second, as many as 34% of patients discontinued abatacept during the 12-month observation period. As lack of effectiveness was the main reason for discontinuation, the majority of patients who prematurely dropped out of the study did not achieve good clinical response on their last observation day. The high percentage of patients who discontinued abatacept because of lack of effectiveness may be related to the relatively high percentage of patients (i.e. 48.8% of all patients) with prior use of biologics in our cohort. The LOCF method was applied to replace the missing data of our cohort, but the relatively high proportion of patients who discontinued abatacept might decrease the reliability of our results to some extent. Third, the number of patients included in our study may not be large enough to identify all relevant factors associated with clinical, structural, and functional remissions by using multiple logistic regression analyses. Finally, we could not show the effectiveness and safety of subcutaneous administered abatacept because all patients were administered intravenous abatacept. However, the results of our study would be applicable to patients who were administered subcutaneous abatacept because a non-inferiority study comparing subcutaneous and intravenous abatacept has shown the comparable efficacy and safety of these drugs [30].

In conclusion, our prospective cohort study has demonstrated that SDAI remission at month 6 in patients with RA who were administered abatacept was an independent predictor for achieving functional and structural remissions at month 12. SDAI remission at month 6 should be a short-term treatment goal to obtain greater therapeutic benefits with abatacept in patients with RA.

Acknowledgments

The authors sincerely thank Ms. Marie Yajima (Tokyo Medical and Dental University) for helping us in maintaining the database of this study. The authors also thank the patients and their health care providers who participated in this study.

Conflict of interest

Tokyo Medical and Dental University (TMDU) has received unrestricted research grants for Department of Lifetime Clinical Immunology from Chugai Pharmaceutical Co., Ltd., Ono Pharmaceuticals, Mitsubishi Tanabe Pharma Co., UCB Japan, CSL Behring, Towa Pharmaceutical Co., Ltd., Abbvie Japan Co., Ltd., Japan Blood Products Organization, Ayumi Pharmaceutical Co., and Nippon Kayaku Co., Ltd. with which TMDU currently pays the salary of *FH*. *FH* also has received a speaking fees from Astellas Pharma Inc. *TT* has received grants, consulting fees and/or speaking fees from Abbvie Japan Co., Ltd., Asahi Kasei Medical K.K., Astra Zeneca K.K., Astellas Pharma Inc., AYUMI Pharmaceutical Corporation, Bristol Myers Squibb K.K., Celtrion, Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Eli Lilly Japan K.K., Merck Serono Co., Ltd., Mitsubishi Tanabe Pharma Co., Nipponkayaku Co. Ltd., Novartis Pharma K.K., Janssen Pharmaceutical K.K., Pfizer Japan Inc., Taisho Toyama Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Teijin Pharma Ltd. *AK* has received grants and/or speaking fees from Abbvie Japan Co., Ltd., Astellas Pharma Inc., Bristol Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc. *TS* has received grants and/or speaking fees from Abbvie Japan Co., Ltd., Asahi Kasei Medical K.K., Astellas Pharma Inc., AYUMI Pharmaceutical Corporation, Bristol Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., Janssen Pharmaceutical K.K., Pfizer Japan Inc., Takeda Pharmaceutical Co., Ltd., Teijin Pharma Ltd. *RS* has received a grant from Bristol Myers Squibb K.K. *TN* has received grants, consulting fees and/or speaking fees from Bristol Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., and Eli Lilly Japan K.K. *MH* received unrestricted research grants for Department of Pharmacovigilance at TMDU from Abbvie Japan Co., Ltd., Astellas Pharma Inc., Bristol Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Mitsubishi Tanabe Pharma Co., Ono Pharmaceuticals, Pfizer Japan Inc., Sanofi-Aventis KK., Santen Pharmaceutical Co., Ltd., Sekisui Medical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Teijin Pharma Ltd., and UCB Japan with which TMDU paid salary for *HY*, *RS*, *TN*, and *MH*. *HK* received grants from AbbVie Japan Co., Ltd., Astellas Pharma Inc., Ayumi Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Japan Blood Products Organization, Mitsubishi Tanabe Pharma Co., Ono Pharmaceuticals, Pfizer Japan Inc., Takeda Pharmaceutical Co., Ltd., and Teijin Pharma Ltd. *KA*, *JK*, *MK*, *WY*, *KN*, *HH*, *YN*, *MT*, *RK*, and *NM* have nothing to declare.

Funding

This work was supported by Ministry of Health Labour and Welfare KAKENHI Grant Number H22-Menneki-Ippan-001 and unrestricted research grants for Department of Pharmacovigilance, Tokyo Medical and Dental University.

References

- Harigai M, Ishiguro N, Inokuma S, Mimori T, Ryu J, Takei S, et al. Postmarketing surveillance of the safety and effectiveness of abatacept in Japanese patients with rheumatoid arthritis. *Mod Rheumatol*. 2016;26:491–8.
- Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, et al. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. *CMAJ*. 2009;181:787–96.
- Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev*. 2011;2:CD008794.
- Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis*. 2010;69:631–7.
- Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62:2569–81.
- Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol*. 2005;23Suppl.39:S100–S8.
- Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis*. 2011;70:404–13.
- van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol*. 2000;27:261–3.
- ICH Steering Committee. Clinical safety data management: definitions and standards for expedited reporting [Internet]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf [accessed 3 Jun 2016].
- Inoue E, Yamanaka H, Hara M, Tomatsu T, Kamatani N. Comparison of Disease Activity Score (DAS)28-erythrocyte sedimentation rate and DAS28-C-reactive protein threshold values. *Ann Rheum Dis*. 2007;66:407–9.
- Maxwell LJ, Singh JA. Abatacept for rheumatoid arthritis: a Cochrane systematic review. *J Rheumatol*. 2010;37:234–45.
- Bathon J, Robles M, Ximenes AC, Nayiager S, Wollenhaupt J, Durez P, et al. Sustained disease remission and inhibition of radiographic progression in methotrexate-naïve patients with rheumatoid arthritis and poor prognostic factors treated with abatacept: 2-year outcomes. *Ann Rheum Dis*. 2011;70:1949–56.
- Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med*. 2006;144:865–76.
- Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med*. 2005;353:1114–23.
- Daïen CI, Morel J. Predictive factors of response to biological disease modifying antirheumatic drugs: towards personalized medicine. *Mediat Inflamm*. 2014;2014:386148.
- Leffers HC, Ostergaard M, Glinborg B, Krogh NS, Foged H, Tarp U, et al. Efficacy of abatacept and tocilizumab in patients with rheumatoid arthritis treated in clinical practice: results from the nationwide Danish DANBIO registry. *Ann Rheum Dis*. 2011;70:1216–22.
- Gottenberg JE, Ravaud P, Cantagrel A, Combe B, Flipo RM, Schaevebeke T, et al. Positivity for anti-cyclic citrullinated peptide is associated with a better response to abatacept: data from the 'Orencia and Rheumatoid Arthritis' registry. *Ann Rheum Dis*. 2012;71:1815–19.
- Takahashi N, Kojima T, Kaneko A, Kida D, Hirano Y, Fujibayashi T, et al. Use of a 12-week observational period for predicting low disease activity at 52 weeks in RA patients treated with abatacept: a retrospective observational study based on data from a Japanese multicentre registry study. *Rheumatology (Oxford)*. 2015;54:854–9.
- Tanaka Y, Kubo S, Yamanaka H, Amano K, Hirata S, Tanaka E, et al. Efficacy and safety of abatacept in routine care of patients with rheumatoid arthritis: Orencia® as Biological Intensive

- Treatment for RA (ORBIT) study. *Mod Rheumatol*. 2014;24:754–62.
20. Maneiro RJ, Salgado E, Carmona L, Gomez-Reino JJ. Rheumatoid factor as predictor of response to abatacept, rituximab and tocilizumab in rheumatoid arthritis: systematic review and meta-analysis. *Semin Arthritis Rheum*. 2013;43:9–17.
 21. Scarsi M, Ziglioli T, Airo P. Baseline numbers of circulating CD28-negative T cells may predict clinical response to abatacept in patients with rheumatoid arthritis. *J Rheumatol*. 2011;38:2105–11.
 22. Scott DL, Smith C, Kingsley G. Joint damage and disability in rheumatoid arthritis: an updated systematic review. *Clin Exp Rheumatol*. 2003;21:S20–S7.
 23. Smolen JS, Wollenhaupt J, Gomez-Reino JJ, Grassi W, Gaillez C, Poncet C, et al. Attainment and characteristics of clinical remission according to the new ACR-EULAR criteria in abatacept-treated patients with early rheumatoid arthritis: new analyses from the Abatacept study to Gauge Remission and joint damage progression in methotrexate (MTX)-naïve patients with Early Erosive rheumatoid arthritis (AGREE). *Arthritis Res Ther*. 2015;17:157.
 24. Tanaka E, Hoshi D, Igarashi A, Inoue E, Shidara K, Sugimoto N, et al. Analysis of direct medical and nonmedical costs for care of rheumatoid arthritis patients using the large cohort database, IORRA. *Mod Rheumatol*. 2013;23:742–51.
 25. Weinblatt M, Combe B, Covucci A, Aranda R, Becker JC, Keystone E. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study. *Arthritis Rheum*. 2006;54:2807–16.
 26. Weinblatt M, Schiff M, Goldman A, Kremer J, Luggen M, Li T, et al. Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. *Ann Rheum Dis*. 2007;66:228–34.
 27. Sakai R, Cho SK, Nanki T, Koike R, Watanabe K, Yamazaki H, et al. The risk of serious infection in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors decreased over time: a report from the registry of Japanese rheumatoid arthritis patients on biologics for long-term safety (REAL) database. *Rheumatol Int*. 2014;34:1729–36.
 28. Sakai R, Komano Y, Tanaka M, Nanki T, Koike R, Nagasawa H, et al. Time-dependent increased risk for serious infection from continuous use of tumor necrosis factor antagonists over three years in patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2012;64:1125–34.
 29. Schneeweiss S, Setoguchi S, Weinblatt ME, Katz JN, Avorn J, Sax PE, et al. Anti-tumor necrosis factor alpha therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. *Arthritis Rheum*. 2007;56:1754–64.
 30. Genovese MC, Covarrubias A, Leon G, Mysler E, Keiserman M, Valente R, et al. Subcutaneous abatacept versus intravenous abatacept: a phase IIIb noninferiority study in patients with an inadequate response to methotrexate. *Arthritis Rheum*. 2011;63:2854–64.

ORIGINAL ARTICLE

Postmarketing surveillance of the safety and effectiveness of abatacept in Japanese patients with rheumatoid arthritis

Masayoshi Harigai¹, Naoki Ishiguro², Shigeko Inokuma³, Tsuneyo Mimori⁴, Junnosuke Ryu⁵, Syuji Takei⁶, Tsutomu Takeuchi⁷, Yoshiya Tanaka⁸, Yoshinari Takasaki⁹, Hisashi Yamanaka¹⁰, Masahiko Watanabe¹¹, Hiroshi Tamada¹¹, and Takao Koike^{12,13}

¹Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan, ²Graduate School & Faculty of Medicine, Nagoya University, Nagoya, Japan, ³Chiba Central Medical Center, Chiba, Japan, ⁴Kyoto University Graduate School of Medicine, Kyoto, Japan, ⁵Nihon University School of Medicine, Tokyo, Japan, ⁶Faculty of Medicine, School of Health Sciences, Kagoshima University, Kagoshima, Japan, ⁷Keio University School of Medicine, Tokyo, Japan, ⁸University of Occupational and Environmental Health, Fukuoka, Japan, ⁹Juntendo University School of Medicine, Tokyo, Japan, ¹⁰Tokyo Women's Medical University, Tokyo, Japan, ¹¹Bristol-Myers K.K., Tokyo, Japan, ¹²NTT Sapporo Medical Center Minami, Sapporo, Japan, and ¹³Hokkaido University Graduate School of Medicine, Sapporo, Japan

Abstract

Objective: To perform a postmarketing surveillance study evaluating the safety and effectiveness of abatacept in Japanese patients with rheumatoid arthritis (RA).

Methods: Safety and effectiveness data were collected for all RA patients (at 772 sites) treated with intravenous abatacept between September 2010 and June 2011. Patients were treated by the approved dosing regimen according to the package insert. Treatment effectiveness was evaluated at baseline and at weeks 4, 12, and 24 using Disease Activity Score 28 (DAS28) according to erythrocyte sedimentation rate or serum C-reactive protein concentrations.

Results: Overall, 3882 and 3016 abatacept-naïve RA patients were included in safety and effectiveness analyses, respectively. Adverse drug reactions (ADRs) were reported for 15.66% of patients and serious ADRs were detected for 2.52% of patients. The incidence of serious infections was 1.03% and these were mainly attributed to different types of bacterial pneumonia. Disease activity improved significantly over 6 months. Separate multivariate analysis identified predictors of severe ADR, and severe infections and factors predictive of clinically meaningful DAS28 improvement after 6 months of treatment with abatacept.

Conclusions: Abatacept was efficacious and well tolerated in a clinical setting. No new safety concerns were detected.

Keywords

Abatacept, Japan, PMS, Rheumatoid arthritis, Safety

History

Received 7 September 2015

Accepted 13 November 2015

Published online 6 January 2016

Introduction

Rheumatoid arthritis (RA) is a persistent and erosive arthritis with systemic inflammation that affects the synovial membrane of the joints, causing erosion of cartilage and bone. Chronic inflammation can lead to joint deformity, disability, and poor quality of life [1,2]. A recently published study based on data from a Japanese claims database reported that the estimated prevalence of RA in Japan is ~0.6–1.0% (about 1.24 million individuals ranging from 16 to 75 years of age) [3].

According to the updated recommendations of the American College of Rheumatology (ACR) [4] and the recommendations of

the European League against Rheumatism (EULAR) [5], the treatment goal for RA is to achieve low disease activity or remission using a treat-to-target approach to prevent joint damage and deformity and preserve physical function and quality of life. In the Japanese guidelines [6], biologics are recommended when and if there is lack of response to initial treatment with disease-modifying anti-rheumatic drugs (DMARDs) over 3 months. Among biologic agents for the treatment of RA, tumor necrosis factor (TNF) inhibitors are the most widely used in Japan to reduce inflammation and prevent joint destruction. However, ~30% of patients treated with a TNF inhibitor failed to achieve improvement in ACR20 [7–9], and patients may also develop resistance to anti-TNF agents [10]. Therefore, other biologic agents such as abatacept that function via different mechanisms have been developed as alternatives to anti-TNF therapies.

Joint degradation in RA is caused by an inflammatory cascade triggered by T-cell activation [11]. Abatacept is a genetically engineered fusion protein that selectively inhibits T-cell activation by binding to CD80/86 and modulating its interaction with CD28. The safety and efficacy of abatacept in patients with RA who responded poorly to other biologics or DMARDs, such as TNF antagonists and methotrexate (MTX), have been shown in several

Correspondence to: Hiroshi Tamada, Bristol-Myers K.K., 6-5-1 Nishi-shinjuku, Shinjuku-ku, Tokyo 163-1328, Japan. Tel: +81 67057000. Fax: +81 367057982. E-mail: hiroshi.tamada@bms.com
This is an open-access article distributed under the terms of the CC-BY-NC-ND 3.0 License which permits users to download and share the article for non-commercial purposes, so long as the article is reproduced in the whole without changes, and provided the original source is credited. This article was originally published with an error in Figure 1. This version has been corrected. Please see Corrigendum (<http://dx.doi.org/10.3109/14397595.2015.1173986>).

randomized, controlled clinical trials (RCTs) [12–14]. Execution of all-cases (a mandatory registry) postmarketing surveillance (PMS) was required as a condition of regulatory approval for all patients in Japan undergoing treatment with intravenous (IV) abatacept [15]. This surveillance was undertaken by Bristol-Myers K.K., under the guidance of the Japan College of Rheumatology (JCR), to evaluate the real-world safety and effectiveness of abatacept in Japanese patients with RA.

Materials and methods

Study design and patients

In this all-cases PMS, patients treated with IV abatacept at 772 sites were registered between September 2010 and June 2011. Data on the safety and effectiveness of registered patients were prospectively collected during a 24-week treatment period and a 4-week follow-up period. All patients with RA who received commercial IV abatacept in Japan after the drug was approved were registered for inclusion. With a sample of 3000 patients, the probability of detecting an unknown rare adverse event (occurring at a frequency of 1 per 1000 patients) is 95%. Assuming a dropout rate of 25%, the target number of patients was determined to be 4000.

Abatacept was administered as an IV infusion (following the initial dose, it was given at week 2 and week 4, and then every 4 weeks thereafter). The recommended abatacept dose [15] was based on the patient's body weight and was increased in 250 mg increments as follows: weight <60 kg, 500 mg; 60–100 kg, 750 mg; and >100 kg, 1000 mg in accordance with the indications listed in its package insert and the guidelines of the JCR for the appropriate use of abatacept.

Data collected included age, sex, body weight, disease duration, Steinbrocker stage and class, past medical history, comorbidities, prior use of biologics, concomitant use of MTX and other DMARDs, and concomitant use of glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), or other medications. This PMS was conducted in accordance with Good Postmarketing Surveillance Practices and the ethical principles stated in the Declaration of Helsinki. Data collection was performed using both an electronic data capture system and report forms, depending on the preference of the researchers at each site. The ethics review board of each participating site approved the study.

Endpoints and assessments

Data on all adverse events (AEs, defined as any undesirable experience observed during the use of abatacept in a patient), serious AEs, adverse drug reactions (ADRs, defined as any noxious and unintended responses for which a causal relationship with the use of the drug could not be ruled out), and serious ADRs (defined as any ADR causing death, that was life-threatening, or caused hospitalization or prolongation of hospitalization, disability, or permanent injury) that occurred during the observation period (24-week treatment period and 4-week follow-up period) were prospectively monitored and collected. ADRs were reported in terms of system organ class using MedDRA version 15.0 (Maintenance and Support Services Organization, McLean, VA).

Disease activities were evaluated using Disease Activity Score 28 (DAS28), which takes into account the numbers of tender joints and swollen joints, general health status (patients' visual analog scale [mm], 0–100), and erythrocyte sedimentation rate (ESR, mm/h) or serum C-reactive protein concentration (CRP, mg/dL) [16], before and at weeks 4, 12, and 24 of abatacept treatment. Both DAS28-ESR and -CRP were divided into four categories using the same cut-off values (2.6, 3.2, and 5.1) as follows: remission (DAS28 <2.6), low disease activity (DAS28 \geq 2.6 and

<3.2), moderate disease activity (DAS28 \geq 3.2 and \leq 5.1), and high disease activity (DAS28 >5.1). Patients were categorized according to improvement in DAS28 as EULAR good, moderate, and nonresponders. A good response was defined as an improvement in DAS28 from baseline of <−1.2 and a DAS28 of \leq 3.2 during follow-up. Patients with score improvements of \geq −0.6, as well as those with improvements <−0.6 and \geq −1.2 plus a DAS28 of >5.1 during follow-up were defined as nonresponders. Moderate responders were those with DAS28 improvements from baseline of <−1.2 and a DAS28 >3.2 during follow-up and those with score improvements <−0.6 and \geq −1.2 plus a DAS28 of \leq 5.1 during follow-up [16].

Statistical analysis

Data from all patients who received at least one dose of abatacept were included in the safety evaluation. The incidence rate of ADRs was determined using descriptive statistics. The cumulative rates of AEs, ADRs, and drug-retention rates of abatacept were determined by the Kaplan–Meier analysis. Variables for multivariate analysis were selected based on the results of univariate analysis and degree of medical significance. Effectiveness was evaluated in all patients for whom DAS28 scores were available before and after abatacept treatment, and the last-observation-carried-forward (LOCF) method was used to impute data for withdrawals. The abatacept retention rate by the Kaplan–Meier analysis and paired *t*-tests were used to compare DAS28 scores change from baseline and week 24. Statistical significance was defined as *p* = 0.05 (two-tailed test). The *p* values reported in this manuscript are nominal without adjusting for multiplicity. Data and statistical analyses were conducted using SAS V.9.2 (SAS Institute Inc., Cary, NC).

Results

Patient disposition and baseline characteristics

In total, 3985 patients were treated with abatacept, 103 of whom had been administered abatacept in phase II and III clinical trials conducted for the new drug application. These 103 patients (i.e. abatacept non-naïve patients), did not meet the objective of this PMS to evaluate abatacept performance in a real clinical setting and were excluded; therefore, the number of patients in the safety analysis was 3882. For the effectiveness evaluation, a further 866 patients were excluded from the 3882 because their DAS data before abatacept treatment were not available. Table 1 summarizes the baseline characteristics of patients. The majority of patients were women (82.3%) with a mean age (\pm SD) of 61.4 \pm 12.6 years. The median disease duration was 8.2 years (IQR 3.3–15.3), and 69.5% of patients had comorbidities. Additionally, 69.6% of patients had been exposed previously to biologics other than abatacept (mainly anti-TNF agents), and 66.3% and 81.2% were being treated concomitantly with MTX or other DMARDs, respectively.

Overall safety and ADRs of interest

A total of 3882 patients with an observation period of 1886.2 patient-years were included in the safety analysis. Serious ADRs and all ADRs were reported by 2.52% and 15.66% of patients, respectively (Supplementary Table 1). The majority of the serious ADRs (1.03%) were categorized as infections and infestations. Commonly reported categories of all ADRs included infections and infestations (5.87%); skin and subcutaneous tissue disorders (2.19%); respiratory, thoracic, and mediastinal disorders (2.16%); gastrointestinal disorders (1.96%); and hepatobiliary disorders (1.06%).

Table 1. Patient demographic and clinical baseline characteristics.

Variables	Safety analysis set (<i>n</i> = 3882)	Effectiveness analysis set (<i>n</i> = 3016)
Sex (females, %)	82.3	82.4
Age [mean \pm SD, years (≥ 65 years)]	61.4 \pm 12.6 (44.1)	61.1 \pm 12.8 (43.4)
Body weight (mean \pm SD, kg)	53.5 \pm 10.5	53.6 \pm 10.4
Disease duration (median and IQR, years)	8.2 (3.3–15.3)	8.3 (3.4–15.5)
Steinbrocker stage I/II/III/IV (%)	10.8/26.0/31.5/31.6	11.2/26.5/31.3/31.0
Steinbrocker class 1/2/3/4 (%)	11.5/63.4/23.5/1.7	11.6/63.7/23.1/1.6
Past medical history (%)	29.1	29.4
Allergy history (%)	19.5	20.2
Smoking history (years)	12.7	12.8
Comorbidities (%)	69.5	69.3
History of surgery for RA (%)	23.6	23.1
Prior use of biologics (%)	69.6	70.2
Concomitant MTX use [% (mean \pm SD, mg/week)]	66.3 (7.1 \pm 2.7)	66.7 (7.1 \pm 2.6)
Concomitant DMARD use (%)	81.2	81.0
Concomitant oral glucocorticoid use [% (mean \pm SD, PSL equivalent dose, mg/day)]	63.1 (5.0 \pm 3.0)	63.0 (5.0 \pm 3.0)
Concomitant NSAID use (%)	69.8	69.3
Other concomitant medication use (%)	85.0	85.8
Baseline DAS28-ESR (mean \pm SD)	–	5.07 \pm 1.30
Baseline DAS28-CRP (mean \pm SD)	–	4.47 \pm 1.23

IQR = interquartile range; PSL = prednisolone; SD = standard deviation.

Table 2. Incidence rates of the most commonly reported adverse drug reactions ($\geq 0.5\%$).

ADRs	PMS (<i>n</i> = 3882)*	
	ADRs† (%)	Serious ADRs (%)
Upper respiratory tract inflammation	1.21	0.03
Herpes zoster	1.00	0.08
Bronchitis	0.90	0.03
Stomatitis	0.88	0
Nasopharyngitis	0.80	0
Abnormal hepatic function tests	0.75	0.05
Pyrexia	0.62	0
Rash	0.59	0

*1886.20 person-year.

†All ADR events including serious ADRs.

Table 2 shows the incidence rates of the most commonly reported ADRs in this PMS. Upper respiratory tract inflammation was the most common ADR (1.21%), followed by herpes zoster, bronchitis, stomatitis, nasopharyngitis, abnormal hepatic function tests, pyrexia, and rash, all with incidences ranging from 0.59% to 1.00%. The incidence of serious ADRs was 0.03% for upper respiratory inflammation and bronchitis, 0.05% for abnormal hepatic function tests, and 0.08% for herpes zoster.

A list of ADRs of interest is presented in Table 3. Pneumonia of different types was reported in 28 patients (0.72%), with mean treatment duration of 95.8 days. One and four patients developed tuberculosis (TB; 0.03%) and Pneumocystis pneumonia (0.10%), respectively. Twelve cases of interstitial pneumonia were reported, with an incidence rate of 0.31%. There were six cases of malignancy (0.15%), including two cases of lymphoma and one case each of gastric cancer, malignant lung neoplasm, colorectal cancer, and borderline ovarian cancer. Eight deaths (0.21%) occurred during the PMS, four of which were attributed to interstitial pneumonia and one case each to bronchopulmonary aspergillosis, mycosis/acute disseminated encephalomyelitis, Pneumocystis pneumonia, or pulmonary tuberculosis/tuberculous peritonitis. Kaplan–Meier analysis was used to assess the cumulative occurrence rates of AEs and ADRs (Supplementary

Figure 1). Occurrences of both AEs and ADRs increased at a constant rate until Day 197, with a slightly pronounced increase on Days 14 and 29.

Risk factors for ADRs

Multivariate logistic regression analysis revealed risk factors for all ADRs and serious ADRs (Figure 1a and b). Factors that significantly increased the risk for serious ADRs were Steinbrocker class 3 or 4 (odds ratio [OR] 1.63; 95% class interval [CI] 1.04–2.55; $p = 0.034$), comorbidity of hepatobiliary disorders (OR 1.99; 95% CI 1.12–3.55; $p = 0.020$), renal comorbidity (OR 2.06; 95% CI 1.03–4.10; $p = 0.041$), comorbidity or history of respiratory disease (OR 1.79; 95% CI 1.14–2.80; $p = 0.011$), peripheral lymphocyte count $<1000/\text{mm}^3$ (OR 1.76; 95% CI 1.11–2.78; $p = 0.016$), and concomitant glucocorticoid use (>5 mg/day of prednisolone) (OR 1.63; 95% CI 1.01–2.62; $p = 0.046$).

Multivariate logistic regression analysis also revealed significant risk factors for infections as follows: age ≥ 65 years, comorbidity of hepatobiliary disorders, comorbidity or history of respiratory disease, allergy history, prior use of biologics, and concomitant glucocorticoid use (>5 mg/day of prednisolone) (Figure 1c), and for serious infections: body weight <40 kg, comorbidity or history of respiratory disease, and concomitant glucocorticoid use (>5 mg/day of prednisolone) (Figure 1d).

Effectiveness

Figure 2 shows the change in DAS28 based on ESR (Figure 2a) and CRP (Figure 2c) from baseline to week 24. Mean \pm SD DAS28-ESR and -CRP at baseline were 5.07 \pm 1.30 and 4.47 \pm 1.23, respectively, and 3.93 \pm 1.40 and 3.25 \pm 1.33 at week 24, respectively. The changes from baseline in DAS28-ESR and -CRP at week 4 were -0.63 ± 1.03 and -0.73 ± 1.03 , respectively, and -1.14 ± 1.39 and -1.21 ± 1.34 at week 24, respectively. DAS28-ESR and -CRP at week 24 were significantly lower than at baseline ($p < 0.001$, paired t -tests) (Figure 2b and d). The DAS28 decreased progressively and significantly throughout the observation period in both DAS28-ESR and -CRP; however, the trend was more marked with DAS28-CRP.

Table 3. Summary and incidences rates of adverse drug reactions of interest.

Adverse drug reactions	n	Incidence rates (%)	Sex (males/females, n)	Age (years)		Duration of Onset (days)		Cause of incident
				Mean	Min–Max	Mean	Min–Max	
Deaths	8	0.21	3/5	73.5	61–86	97.4	30–176	(1) Interstitial pneumonia (n=4) (2) Bronchopulmonary aspergillosis (3) Mycosis/acute disseminated encephalomyelitis (4) Pneumocystis pneumonia (5) Pulmonary tuberculosis/tuberculous peritonitis
Pneumonia	28	0.72	7/21	66.2	25–79	95.8	6–178	(1) Pneumonia (n=18) (2) Bacterial pneumonia (n=5) (3) Bronchopneumonia (n=3) (4) Pneumococcal pneumonia (n=2)
Tuberculosis	1	0.03	0/1	86.0	–	176.0	–	Concurrent pulmonary tuberculosis and tuberculous peritonitis
Pneumocystis pneumonia	4	0.10	1/3	62.3	60–67	64.5	28–124	
Interstitial pneumonia	12	0.31	4/8	73.3	62–82	101.5	22–183	
Malignancies	6	0.15	1/5	75.2	62–83	98.3	59–127	(1) Lymphoma (n=2) (2) Gastric cancer (3) Malignant lung neoplasm (4) Colorectal cancer (5) Borderline ovarian cancer

Supplementary Figure 2a and b illustrates the proportion of patients in each DAS28 category from baseline to week 24. An increasing trend was observed in the proportion of patients with remission (<2.6) and low disease activity (≥ 2.6 and <3.2) by both DAS28-ESR and DAS28-CRP toward the end of the 24-week treatment period.

Supplementary Figure 2c and d shows the overall EULAR responses at weeks 4, 12, and 24. An increasing trend was observed in the proportion of patients that showed good responses by both DAS28-ESR (from 8.7% at week 4 to 24.3% at week 24) and DAS28-CRP (from 11.1% at week 4 to 27.5% at week 24) or moderate responses by both DAS28-ESR (from 33.9% at week 4 to 38.3% at week 24) and DAS28-CRP (33.3% at week 4 to 36.0% at week 24) toward the end of the 24-week treatment period. The overall Kaplan–Meier-estimated drug retention rate of abatacept decreased slowly and progressively from baseline until the end of the observation period (Day 169), but remained high at 78.9% (data not shown).

Separate multivariate analyses for patients with high or moderate disease activity at baseline were performed to detect factors predictive of a clinically meaningful DAS28 improvement after 6 months of treatment with abatacept. Of 773 patients with high disease activity, DAS28-CRP decreased from <-1.2 at baseline (clinically meaningful difference) in 526 patients. Multivariate analysis revealed that Steinbrocker class 1 and 2 ($p=0.029$), concomitant MTX use ($p=0.003$), and positive serology (ACPA or RF) ($p=0.026$) were significantly associated with a decrease in DAS28-CRP (DAS28-CRP of <-1.2) during abatacept treatment (Figure 3a). Prior use of two or more biologics was associated with not achieving DAS28-CRP <-1.2 . Of the 1394 patients with moderate disease activity, 648 achieved a change in DAS28-CRP of <-1.2 from baseline. On logistic regression analysis, Steinbrocker class 1 or 2 ($p<0.001$), biologic-naïve ($p<0.001$), and positive serology (RF or ACPA) ($p=0.002$) were highly significantly associated with DAS28-CRP <-1.2 during abatacept treatment. Concomitant MTX use was not selected as a variable for the final model (Figure 3b).

Discussion

In this PMS, we evaluated the safety and effectiveness of abatacept in a clinical practice setting in Japanese patients with RA.

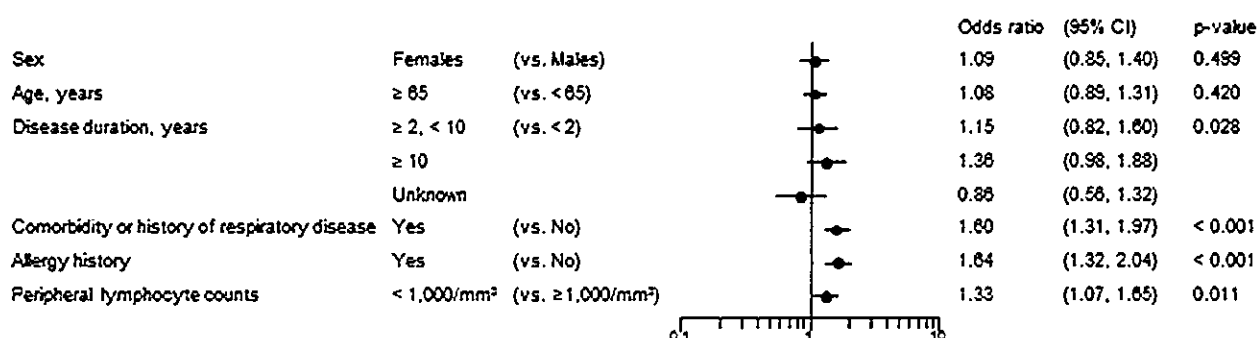
Abatacept was well tolerated, and no new safety concerns were detected. During the observation period, the indexes of disease activity of RA decreased significantly. Risk factors for ADRs and infections, as well as predictors of clinically meaningful improvement in DAS28 (DAS28-CRP change from baseline <-1.2) after 6 months of abatacept treatment, were identified.

In this PMS, serious ADRs and ADRs were reported by 2.52% and 15.66% of patients, respectively. The incidence rate of serious infections was not high (1.03%), in particular to various types of bacterial pneumonia, which were also the most common serious ADRs reported in PMS of etanercept [17] and adalimumab [18] in Japan. The most common ADR was upper respiratory tract inflammation (1.21%), followed by herpes zoster, bronchitis, stomatitis, nasopharyngitis, abnormal hepatic function tests, pyrexia and rash, all with very low incidences (0.59–1.00%). Furthermore, there were no particular periods of increased overall AE/ADR incidence rates during the treatment course as observed in the Kaplan–Meier analyses. In comparison with the ADRs reported at approval, the ADRs observed at the time of this PMS did not raise any new safety concerns.

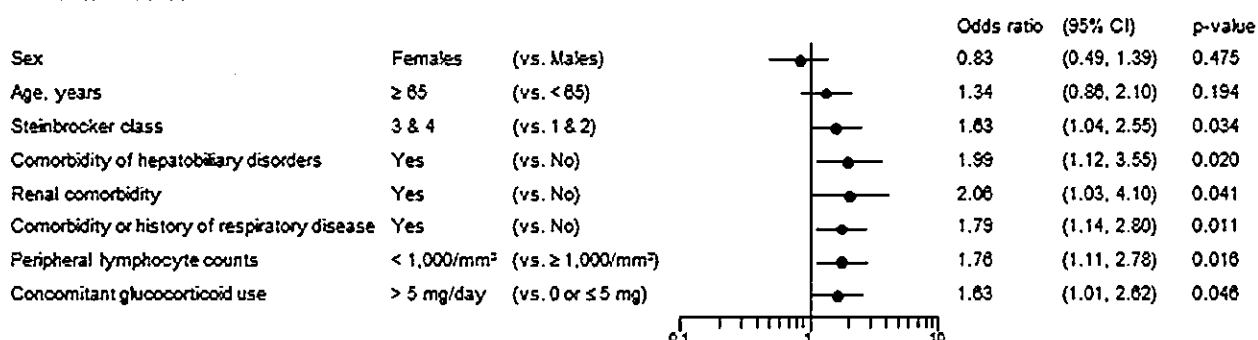
Notably, there was only one case of TB reported in this study. This finding is also in line with a previous epidemiological assessment by Simon et al. [19]. Patients to be treated with any of the biologics approved in Japan are required to go through TB screening. Therefore, the low incidence rate of TB found in this PMS suggests that this screening practice was successful for the diagnosis of pre-existing or concurrent pulmonary infections, such as TB, when identifying patients that can benefit from abatacept treatment. However, other PMS studies of biologics in Japan, such as infliximab [20], etanercept [17], and adalimumab [18], found higher incidences of TB. It has been reported that the mechanism of action of TNF inhibitors can activate latent TB infections [21–26]. These findings strongly suggest that TNF is more important for maintaining a latent TB lesion than the interaction with CD28-CD80/86. Additionally, physicians, under the auspices of the JCR, are being educated to screen for TB more thoroughly than before. As a result, patients with higher TB risk were excluded from treatment with abatacept.

Based on logistic regression analysis, we identified several risk factors that were significantly associated with infections and serious infections. Age ≥ 65 years, comorbidity of hepatobiliary

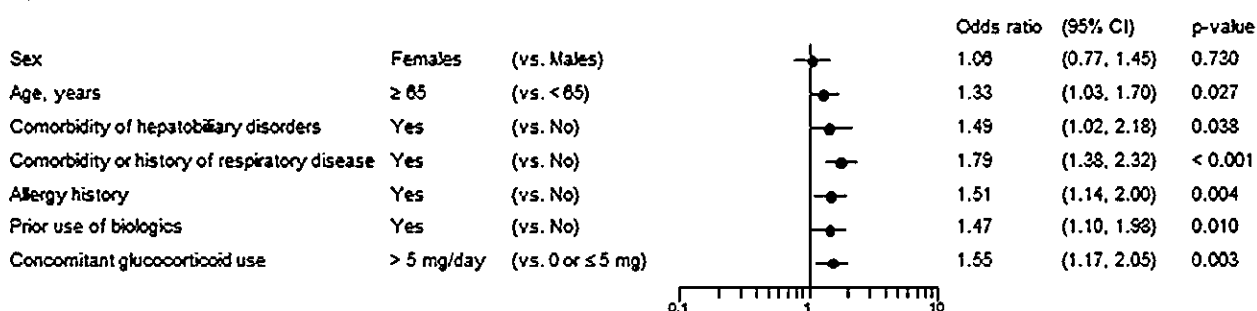
(a) ADRs



(b) Serious ADRs



(c) Infections



(d) Serious infections

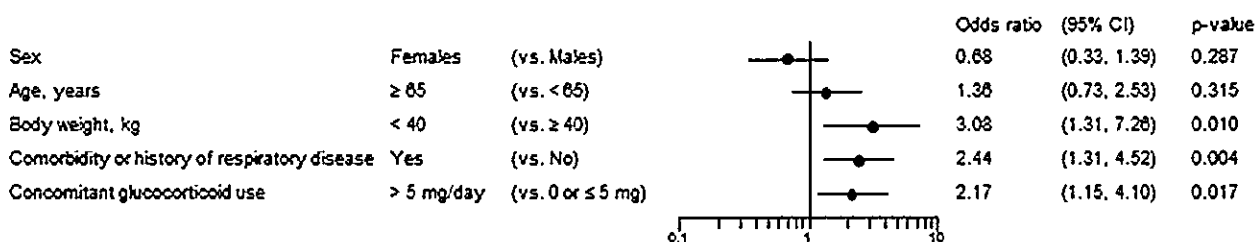


Figure 1. Multivariate logistic regression analysis revealed risk factors for all (a) ADRs, (b) serious ADRs, (c) infections, and (d) serious infections. Candidate variables for multivariate analysis were selected among many others based on their degree of clinical significance and the results of the univariate analysis. Variable selection for the final model of the multivariate logistic regression analysis was performed by stepwise methods.

disorders, comorbidity or history of respiratory disease, allergy history, prior use of biologics, and concomitant glucocorticoid use (>5 mg/day of prednisolone) were associated with a significant increase in the risk for infections. Body weight <40 kg, comorbidity or history of respiratory disease, and concomitant glucocorticoid (>5 mg/day of prednisolone) use were associated with serious infections. Interestingly, in a recent interim analysis of a PMS evaluating the safety of tocilizumab for the treatment

of RA, logistic regression analysis indicated that respiratory comorbidities or medical history of respiratory disorders, prednisolone dose >5 mg, and age ≥65 years were significant risk factors for the development of serious infections [27]. Similarly, a recently published PMS report evaluating the safety and effectiveness of adalimumab in Japanese patients with RA identified the concomitant use of glucocorticoids at a prednisolone-equivalent dose >5 mg/day, age, and pulmonary disease

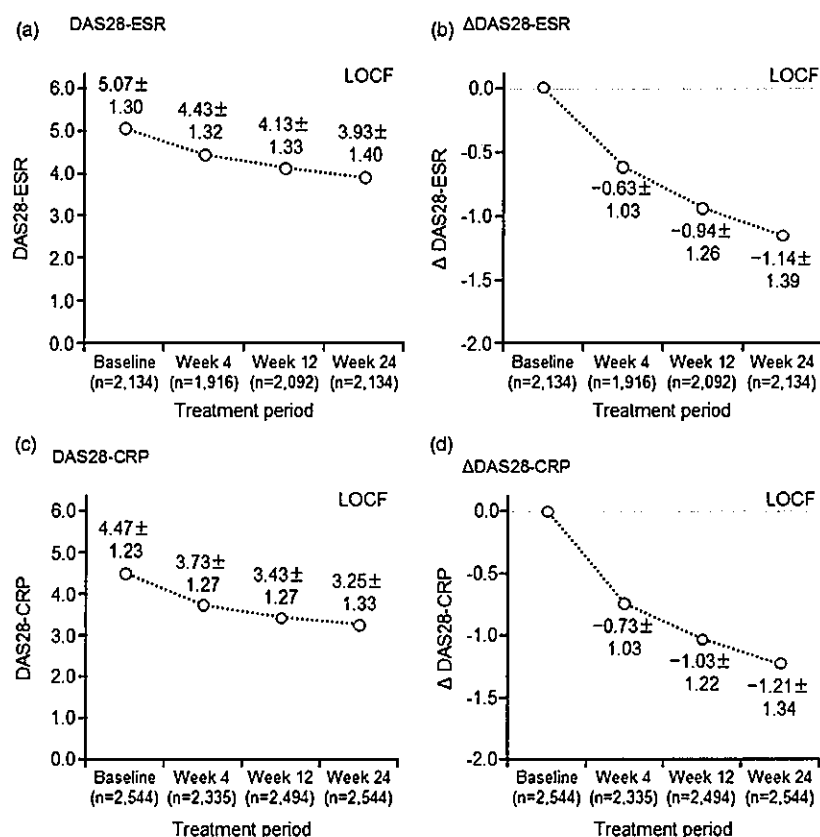
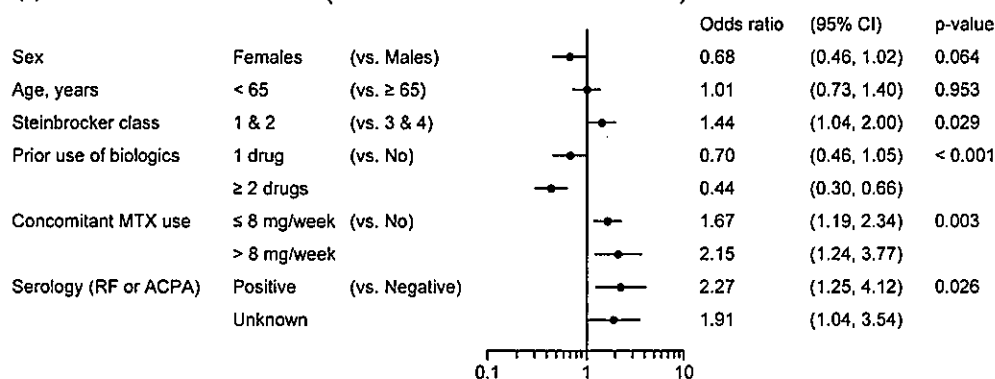


Figure 2. Change in disease activity over time in patients treated with abatacept. The last-observation-carried-forward (LOCF) imputation method was used. (a) DAS28 based on erythrocyte sedimentation rate (DAS28-ESR). (b) DAS28-ESR changes. (c) DAS28 based on C-reactive protein (DAS28-CRP). (d) DAS28-CRP changes.

(a) ΔDAS28-CRP < -1.2 (Baseline DAS28-CRP > 5.1)



(b) ΔDAS28-CRP < -1.2 (Baseline DAS28-CRP ≥ 3.2 and ≤ 5.1)

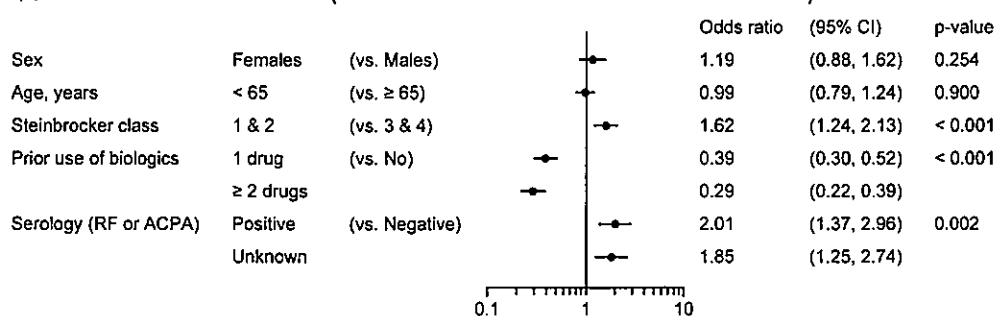


Figure 3. Multivariate logistic regression analysis revealed factors associated with improved DAS (DAS28-CRP51.2) in patients with (a) baseline DAS28-CRP45.1, and (b) baseline DAS28-CRP3.2 and 5.1. Candidate variables for multivariate analysis were selected among many others based on their degree of clinical significance and the results of the univariate analysis. Variable selection for the final model of the multivariate logistic regression analysis was performed by stepwise methods.

history or comorbidity as risk factors for infections, serious infections, and serious respiratory infections [28]. In the same report, co-existing diabetes mellitus and concomitant MTX at a dose of >8 mg/week were also found to increase the risk of infections and serious infections [28]. Conversely, these factors were not found to increase the risk of infections or serious infections among patients treated with abatacept in this study. These data indicated that respiratory comorbidity and taking prednisolone >5 mg/day are common risk factors for serious infection when receiving these biologics, whereas each biologic has its own risk factors. Patients should be evaluated carefully prior to abatacept treatment for the identified risk factors to evaluate benefit–risk balance.

The drug retention rate of abatacept treatment was $\sim 80\%$ in this PMS [29]. As the patients in the study cohort had a mean age of 61 years and long disease duration, RA was generally established and accompanied by comorbidities. Additionally, 70% of patients had a history of use of biologics, and these patients are usually difficult to treat; nonetheless, the majority of patients in this PMS experienced significant improvement in DAS28-ESR and -CRP by the end of the 6 months treatment. The effectiveness data were similar to findings in a recently published retrospective study by Tanaka et al. [30] of Japanese patients with RA treated with abatacept for 24 weeks. They reported that DAS28-ESR significantly decreased from baseline to week 24 (from 5.2 ± 1.4 to 3.9 ± 1.4) [30]. Similar findings were reported by Nüßlein et al. [31,32] in European and Canadian populations.

Multivariate logistic regression analysis indicated that Steinbrocker class 1 or 2, concomitant MTX use and positive serology (RF or ACPA) in patients with high disease activity, and Steinbrocker class 1 and 2 and positive serology (RF or ACPA) in patients with moderate disease activity were the factors significantly associated with an improvement of DAS28-CRP < -1.2 . Fewer biological treatment failures reported previously were also predictive of better response to treatment with abatacept. These findings are in line with a recent observational registry on abatacept treatment, which suggested that patients with seropositive RA status may have better responses to abatacept, independent from disease activity [29,33].

This PMS had several limitations, including a short observation period, absence of comparators, and lack of functional and structural endpoints. However, the results of this 6-month PMS demonstrate the only real-world, prospective, powered-for-safety study of abatacept in patients with RA. Abatacept was well tolerated in clinical practice, and no new safety concerns were detected. This study also demonstrated that less exposure to biologics and positive serology were associated with a good clinical outcome. The findings of this PMS should be helpful in considering the appropriate use of abatacept in Japanese patients with RA.

Acknowledgments

The authors thank all the medical institutions and physicians who participated in this surveillance for their cooperation, and Keyra Martinez Dunn, MD, for providing medical writing assistance, which was funded by Bristol-Myers K.K.

Conflict of interest

The competing interests of all authors are provided below:

M.H., N.I., S.I., T.M., J.R., S.T., T.T., Y.T., Y.T., H.Y., and T.K. are members of the Postmarketing Surveillance (PMS) Committee of the Japan College of Rheumatology. It is the belief of the authors that this does not constitute a conflict of interest.

The doctors participated in review and analysis of the PMS data in their capacity as committee members. The financial relationships of the authors with manufacturers of biological products used in the management of RA are listed. M.H. has received grants/research support from AbbVie, Astellas, Bristol-Myers K.K., Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Santen, Takeda, UCB, and Pfizer; has served as a consultant for AbbVie, Bristol-Myers K.K., Chugai, and Janssen; and has served on speakers bureaus for AbbVie, Astellas, Bristol-Myers K.K., Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Santen, Takeda, UCB, and Pfizer. N.I. has received grants/research support from Astellas and Bristol-Myers K.K.; has served as a consultant for AbbVie, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Pfizer, and Takeda; and has served on speakers bureaus for AbbVie, Astellas, Bristol-Myers K.K., Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Pfizer, and Takeda. S.I. has served on speakers bureaus for Asahi Kasei Pharma, Astellas, AbbVie, Bristol-Myers K.K., Chugai, Eisai, GlaxoSmithKline, Mitsubishi-Tanabe, Pfizer, Takeda, Santen, Teijin, Taisho-Toyama, Taiho, Daiichi-Sankyo, and Kyorin. T.M. has received grants/research support from Asahi Kasei Pharma, Astellas, Bristol-Myers K.K., Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Nippon Kayaku, Santen, and Takeda; and has served on speakers' bureaus for Asahi Kasei Pharma, Astellas, Bristol-Myers K.K., Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Santen, and Taisho Toyama. J.R. has reports no conflicts of interest. S.T. has received grants/research support from Chugai, Eisai, Takeda, and Bristol-Myers K.K.; and has served on speakers bureaus for Chugai, Eisai, Takeda, AbbVie, Astellas, Teijin, Novartis, Pfizer, and Asahi Kasei Pharma. T.T. has received grants/research support from Abbott, AbbVie, Asahi Kasei Pharma, Astellas, Bristol-Myers K.K., Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Pfizer, Sanofi-Aventis, Santen, Taisho-Toyama, Takeda, and Teijin; has served as a consultant for Asahi Kasei Pharma, AbbVie, Daiichi-Sankyo, AstraZeneca, Eli Lilly, Novartis, and Mitsubishi-Tanabe; and has served on speakers bureaus for Abbott, Astellas, Bristol-Myers K.K., Chugai, Daiichi-Sankyo, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer, and Takeda. Y. Tanaka has received grants/research support from Bristol-Myers K.K., MSD, Chugai, Mitsubishi-Tanabe, Astellas, AbbVie, Eisai, and Janssen; has served as a consultant for Mitsubishi-Tanabe, AbbVie, Eisai, Chugai, Janssen, Santen, Pfizer, Astellas, Daiichi-Sankyo, GlaxoSmithKline, AstraZeneca, Otsuka, Actelion, Eli Lilly, Nippon Kayaku, UCB, Quintiles Transnational, Ono, and Novartis; and has served on speakers bureaus for Mitsubishi-Tanabe, AbbVie, Eisai, Chugai, Janssen, Santen, Pfizer, Astellas, Daiichi-Sankyo, GlaxoSmithKline, AstraZeneca, Otsuka, Actelion, Eli Lilly, Nippon Kayaku, UCB, and Quintiles Transnational. Y. Takasaki has received grants/research support from Santen Pharmaceutical Co., Ltd., Daiichi Sankyo Company, Limited, Mitsubishi Tanabe Pharma Corporation, Bristol-Myers K.K., AstraZeneca plc, Astellas Pharma Inc., MSD K.K., Chugai Pharmaceutical Co., Ltd., Asahi Kasei Pharma Corporation, Eisai Co., Ltd., and Janssen Pharmaceutical K.K. H.Y. has received grants/research support from Abbott, AbbVie, Astellas, AstraZeneca, Bristol-Myers K.K., Chugai, Eisai, Mitsubishi-Tanabe, Pfizer, UCB, and Takeda; has served as a consultant for Abbott, AbbVie, Astellas, AstraZeneca, Bristol-Myers K.K., Chugai, Eisai, Mitsubishi-Tanabe, Pfizer, UCB, and Takeda; and has served on speakers bureaus for Abbott, AbbVie, Astellas, Chugai, Eisai, Mitsubishi-Tanabe, Pfizer, UCB, and Takeda. M.W. was an employee of Bristol-Myers K.K. during the work. H.T. is an employee of Bristol-Myers K.K. T.K. has served on speakers' bureaus for Chugai, Mitsubishi-Tanabe, Pfizer, Astellas, Bristol-Myers K.K., UCB, Takeda, Taisho-Toyama, Eisai, AbbVie, Teijin, and Santen.

This PMS was sponsored by Bristol-Myers K.K.

References

1. Silman AJ, Hochberg MC. Epidemiology of the rheumatic diseases. 2nd ed. New York: Oxford University Press; 2001.
2. Pollard L, Choy EH, Scott DL. The consequences of rheumatoid arthritis: quality of life measures in the individual patient. *Clin Exp Rheumatol*. 2005;23:S43–52.
3. Yamanaka H, Sugiyama N, Inoue E, Taniguchi A, Momohara S. Estimates of the prevalence of and current treatment practices for rheumatoid arthritis in Japan using reimbursement data from health insurance societies and the IORRA cohort (I). *Mod Rheumatol*. 2014;24:33–40.
4. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. Update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res*. 2012;64:625–39.
5. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis*. 2014;73:492–509.
6. Japan College of Rheumatology: Guideline for the use of abatacept in rheumatoid arthritis (revised August 23, 2014). Available from: http://www.ryumachi-jp.com/info/guideline_abatacept.html [Japanese] [last accessed 16 February 2015].
7. Lipsky PE, Heijde DM van der, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-tumor necrosis factor trial in rheumatoid arthritis with Concomitant Therapy Study Group. *N Engl J Med*. 2000;343:1594–602.
8. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med*. 1999;340:253–9.
9. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum*. 2003;48:35–45.
10. Finckh A, Simard JF, Gabay C, Guerne PA. Evidence for differential acquired drug resistance to anti-TNF agents in rheumatoid arthritis. *Ann Rheum Dis*. 2008;67:746–52.
11. Schiff M. Abatacept treatment for rheumatoid arthritis. *Rheumatology* 2011;50:437–9.
12. Kremer JM, Dougados M, Emery P, Durez P, Sibilia J, Shergy W, et al. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial. *Arthritis Rheum*. 2005;52:2263–71.
13. Schiff M, Keiserman M, Coddling C, Songcharoen S, Berman A, Niyiager S, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis*. 2008;67:1096–103.
14. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med*. 2006;144:865–76.
15. Takeuchi T, Kameda H. The Japanese experience with biologic therapies for rheumatoid arthritis. *Nat Rev Rheumatol*. 2010;6:644–52.
16. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum*. 1995;38:44–8.
17. Koike T, Harigai M, Inokuma S, Inoue K, Ishiguro N, Ryu J, et al. Postmarketing surveillance of the safety and effectiveness of etanercept in Japan. *J Rheumatol*. 2009;36:898–906.
18. Koike T, Harigai M, Ishiguro N, Inokuma S, Takei S, Takeuchi T, et al. Safety and effectiveness of adalimumab in Japanese rheumatoid arthritis patients: postmarketing surveillance report of the first 3000 patients. *Mod Rheumatol*. 2012;22:498–508.
19. Simon TA, Askling J, Lacaille D, Franklin J, Wolfe F, Covucci A, et al. Infections requiring hospitalization in the abatacept clinical development program: an epidemiological assessment. *Arthritis Res Ther*. 2010;12:R67.
20. Takeuchi T, Tatsuki Y, Nogami Y, Ishiguro N, Tanaka Y, Yamanaka H, et al. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. *Ann Rheum Dis*. 2008;67:189–94.
21. He D, Bai F, Zhang S, Jiang T, Shen J, Zhu Q, et al. High incidence of tuberculosis infection in rheumatic diseases and impact for chemoprophylactic prevention of tuberculosis activation during biologics therapy. *Clin Vaccine Immunol*. 2013;20:842–7.
22. Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Coster L, et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. *Arthritis Rheum*. 2005;52:1986–92.
23. Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum*. 2003;48:2122–7.
24. Solovic I, Sester M, Gomez-Reino JJ, Rieder HL, Ehlers S, Milburn HJ, et al. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. *Eur Respir J*. 2010;36:1185–206.
25. Wallis RS, Broder M, Wong J, Beenhouwer D. Granulomatous infections due to tumor necrosis factor blockade: correction. *Clin Infect Dis*. 2004;39:1254–5.
26. Wolfe F, Michaud K, Anderson J, Urbansky K. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. *Arthritis Rheum*. 2004;50:372–9.
27. Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, et al. Postmarketing surveillance of tocilizumab for rheumatoid arthritis in Japan: interim analysis of 3881 patients. *Ann Rheum Dis*. 2011;70:2148–51.
28. Koike T, Harigai M, Ishiguro N, Inokuma S, Takei S, Takeuchi T, et al. Safety and effectiveness of adalimumab in Japanese rheumatoid arthritis patients: postmarketing surveillance report of 7740 patients. *Mod Rheumatol*. 2014;24:390–8.
29. Nüßlein HG, Alten R, Galeazzi M, Lorenz H-M, Nurmohamed MT, Bensen WG, et al. Prognostic factors for abatacept retention in patients who received at least one prior biologic agent: an interim analysis from the observational, prospective ACTION study. *BMC Musculoskelet Disord*. 2015;16:176.
30. Tanaka Y, Kubo S, Yamanaka H, Amano K, Hirata S, Tanaka E, et al. Efficacy and safety of abatacept in routine care of patients with rheumatoid arthritis: Oencia[®] as Biological Intensive Treatment for RA (ORBIT) study. *Mod Rheumatol*. 2014;24:754–72.
31. Nüßlein HG, Alten R, Galeazzi M, Lorenz HM, Boumpas D, Nurmohamed MT, et al. Real-world effectiveness of abatacept for rheumatoid arthritis treatment in European and Canadian populations: a 6-month interim analysis of the 2-year, observational, prospective ACTION study. *BMC Musculoskelet Disord*. 2014;15:14.
32. Finckh A, Neto D, Iannone F, Loza E, Lie E, van Riel P, et al. The impact of patient heterogeneity and socioeconomic factors on abatacept retention in rheumatoid arthritis across nine European countries. *RMD Open* 2015;1:e000040.
33. Gottenberg JE, Ravaut P, Cantagrel A, Combe B, Flipo RM, Schaefferbeke T, et al. Positivity for anti-cyclic citrullinated peptide is associated with a better response to abatacept: data from the 'Oencia and Rheumatoid Arthritis' registry. *Ann Rheum Dis*. 2012;71:1815–19.

ORIGINAL ARTICLE

Consensus-based identification of factors related to false-positives in ultrasound scanning of synovitis and tenosynovitis

Kei Ikeda^{1*}, Akihiro Narita^{2*}, Michihiro Ogasawara^{3*}, Shigeru Ohno^{4*}, Yutaka Kawahito^{5*}, Atsushi Kawakami^{6*}, Hiromu Ito^{7*}, Isao Matsushita^{8*}, Takeshi Suzuki^{9*}, Kenta Misaki¹⁰, Takehisa Ogura¹¹, Tamotsu Kamishima^{12*}, Yohei Seto^{13*}, Ryuichi Nakahara¹⁴, Atsushi Kaneko^{15*}, Takayuki Nakamura¹, Mihoko Henmi^{2*}, Jun Fukae^{2*}, Keiichi Nishida^{14*}, Takayuki Sumida^{16*}, and Takao Koike^{17*}

¹Department of Allergy and Clinical Immunology, Chiba University Hospital, Chiba, Japan, ²Hokkaido Medical Center for Rheumatic Diseases, Sapporo, Japan, ³Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine, Tokyo, Japan, ⁴Center for Rheumatic Diseases, Yokohama City University Medical Center, Yokohama, Japan, ⁵Department of Inflammation and Immunology, Kyoto Prefectural University of Medicine, Kyoto, Japan, ⁶Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, ⁷Department of Orthopaedic Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan, ⁸Department of Orthopaedic Surgery, University of Toyama, Toyama, Japan, ⁹Division of Allergy and Rheumatology, Japanese Red Cross Medical Center, Tokyo, Japan, ¹⁰Department of Endocrinology and Rheumatology, Kurashiki Central Hospital, Kurashiki, Okayama, Japan, ¹¹Division of Rheumatology, Toho University Ohashi Medical Center, Tokyo, Japan, ¹²Faculty of Health Sciences, Hokkaido University, Sapporo, Japan, ¹³Department of Rheumatology, Tokyo Women's Medical University Yachiyo Medical Center, Yachiyo, Chiba, Japan, ¹⁴Department of Human Morphology, Science of Functional Recovery and Reconstruction, Okayama University Graduate School of Medicine, Okayama, Japan, ¹⁵Department of Orthopaedic Surgery and Rheumatology, Nagoya Medical Center, National Hospital Organization, Nagoya, Japan, ¹⁶Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, and ¹⁷NTT Sapporo Medical Center, Sapporo, Japan

Abstract

Introduction: We aimed to identify causes of false-positives in ultrasound scanning of synovial/tenosynovial/bursal inflammation and provide corresponding imaging examples.

Methods: We first performed systematic literature review to identify previously reported causes of false-positives. We next determined causes of false-positives and corresponding example images for educational material through Delphi exercises and discussion by 15 experts who were an instructor and/or a lecturer in the 2013 advanced course for musculoskeletal ultrasound organized by Japan College of Rheumatology Committee for the Standardization of Musculoskeletal Ultrasonography.

Results: Systematic literature review identified 11 articles relevant to sonographic false-positives of synovial/tenosynovial inflammation. Based on these studies, 21 candidate causes of false-positives were identified in the consensus meeting. Of these items, 11 achieved a predefined consensus ($\geq 80\%$) in Delphi exercise and were classified as follows: (I) Gray-scale assessment [(A) non-specific synovial findings and (B) normal anatomical structures which can mimic synovial lesions due to either their low echogenicity or anisotropy]; (II) Doppler assessment [(A) Intra-articular normal vessels and (B) reverberation)]. Twenty-four corresponding examples with 49 still and 23 video images also achieved consensus.

Conclusions: Our study provides a set of representative images that can help sonographers to understand false-positives in ultrasound scanning of synovitis and tenosynovitis.

Keywords

False-positive, Pitfall, Synovitis, Tenosynovitis, Ultrasound

History

Received 1 June 2015

Accepted 28 August 2015

Published online 19 October 2015

Introduction

Musculoskeletal ultrasonography visualizes inflammation in the synovial tissues as synovial hypertrophy with or without Doppler signals inside or as synovial fluid [1]. A number of studies have shown that ultrasound detects synovial inflammation more

sensitively than does clinical joint examination [2–5] and ultrasound-detected synovitis correlates well with magnetic resonance imaging (MRI) [4,6–8] and histopathological findings [9,10]. As synovial inflammation is the most characteristic pathophysiology of rheumatoid arthritis (RA), sonographic assessment of synovial inflammation has been shown to improve the accuracy of diagnosis [11–16], optimize the assessment of disease activity [15,17–22], predict relapse after discontinuation of biological treatment [23], and also improve the physicians' joint examination skill [24] in the management of RA. Therefore, a rapidly increasing number of rheumatologists now use ultrasound for the assessment of synovial inflammation in daily practice, training, and education [25].

*Members of the Japan College of Rheumatology Committee for the Standardization of Musculoskeletal Ultrasonography (JCR-CoSMUS). Correspondence to: Kei Ikeda, Department of Allergy and Clinical Immunology, Chiba University Hospital, 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba 260-8670, Japan. Tel: +81 432262198. Fax: +81 432262199. E-mail: K.Ikeda@faculty.chiba-u.jp

One of the advantages of ultrasound over other imaging modalities is its flexibility. In order to visualize highly polymorphic synovial lesions in various joints in patients under various conditions, the transducer of ultrasound can be placed at any joints, from various angles, using a variety of dynamic procedures (e.g. joint movement and applying pressure). The downside, however, is that this flexibility allows for variable imaging planes under variable conditions, which can result in variable interpretation of the same joint lesion, necessitating the standardization of the image acquisition and interpretation.

Japan College of Rheumatology Committee for the Standardization of Musculoskeletal Ultrasonography (JCR-CoSMUS) has previously shown that the sonographic assessment of milder synovial inflammation is less reproducible than that of more severe synovial inflammation even among experts with training and experience [26]. These data indicate that the assessment of mild or equivocal images is frequently affected by artifacts and within-normal/non-specific findings and may explain the limited specificity of low-grade sonographic findings for synovitis reported in recent studies [27–29]. Because joints with mild or equivocal inflammation are the ones where imaging plays a significant role in the management of rheumatic conditions, these sonographic false-positives need to be characterized for sonographers to discriminate between normal and arthritic joints and maximize the utility of ultrasound. However, no studies have systematically identified the causes of false-positives in imaging synovial inflammation with ultrasound.

The present study was undertaken by JCR-CoSMUS, aiming to identify causes of false-positives in ultrasound scanning of synovial/tenosynovial/bursal inflammation and provide a set of example images which represent the false-positives. For this purpose, we performed systematic literature review and built consensus through Delphi exercises and discussion.

Methods

Systematic literature review

We searched for original articles in English concerning humans, published between January 1985 and December 2013, and relevant to the false-positives in the sonographic evaluation of synovial inflammation using PUBMED and EMBASE databases. We first used the term, (synovitis OR tenosynovitis OR bursitis) AND (sonography OR ultrasound) AND (pitfall OR false positive), which identified a limited number of articles. Therefore, we next used the broader term, (synovitis OR tenosynovitis OR bursitis) AND (sonography OR ultrasound). Titles, abstracts, and full reports of articles identified were systematically screened for inclusion by two authors (Ikeda and Nakamura). We only included articles with data which identify the factor related to false-positives. Data were extracted from the selected articles using a standardized spreadsheet with particular attention paid to the following: (1) Who were the study subjects (e.g. healthy volunteers)? (2) Which joints were assessed? (3) What was the gold standard or comparator?

Consensus meeting and Delphi process

The consensus meeting was held during the JCR advanced course on musculoskeletal ultrasound in Tokyo in September 2013. Fifteen experts in musculoskeletal ultrasound (Ikeda, Narita, Ogasawara, Ohno, Kawahito, Kawakami, Ito, Matsushita, Suzuki, Misaki, Ogura, Kamishima, Seto, Nakahara, Kaneko), who were an instructor and/or a lecturer in the JCR advanced course, participated the consensus meeting and the Delphi processes. In the meeting, candidate factors, which possibly cause false-positives in the sonographic evaluation of synovial inflammation, were identified based on the preliminary results of

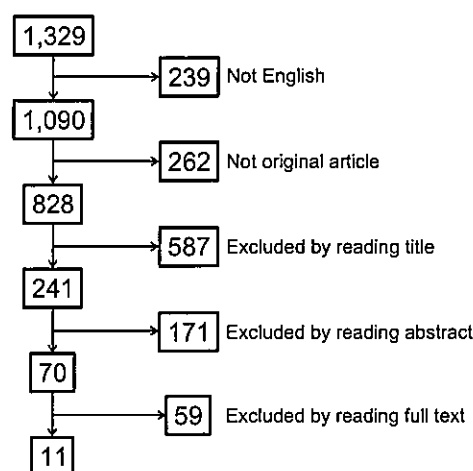


Figure 1. Flow chart of article selection. Shown in the box is the number of articles. The chart starts with the search results in the PUBMED and EMBASE databases from January 1985 to December 2013 using the terms (synovitis OR tenosynovitis OR bursitis) AND (sonography OR ultrasound) filtered for human research.

systematic literature review and also on their knowledge and experience. The first Delphi process was undertaken to determine the final items from these candidates. The participants were asked in questionnaire whether these factors should be presented as pitfalls in educational materials and asked to rate their level of agreement or disagreement with each candidate. The second Delphi process asked the participants whether the sample ultrasound images were appropriate. Each Delphi process took one round, in which participants were asked to answer according to a 1–5 Likert scale (1 = strongly disagree; 5 = strongly agree) and were also asked for the reason when the answer was not 5. Space for additional free comments was also provided. We predefined that group consensus was achieved when 80% or larger proportion of participants scored an item as 4 or 5.

Ultrasound images

Representative ultrasound images, which illustrate the identified causes of false-positives, were collected. All images were obtained from asymptomatic joints in healthy subjects using a HI VISION Avius with a linear array multi-frequency transducer (5–18 MHz for GS) (Hitachi Medical Corporation, Tokyo, Japan). Power Doppler images were obtained with a pulse repetition frequency of 800 Hz and a color gain of 40 dB.

Results

Systematic literature review

The first search identified a total of 17 articles, of which 11 were original articles in English. Six of these 11 articles were relevant to the topic. The second search identified a total of 1329 articles, of which 828 were original articles in English (Figure 1). Screening process, however, identified only 11 articles that are relevant to sonographic false-positives of synovial/tenosynovial inflammation and none for bursitis [30–40].

As shown in Table 1, three articles studied only patients with pain or arthritic conditions, three only healthy volunteers, four both patients and healthy volunteers, and one healthy volunteer and a cadaveric specimen. Patients studied were mostly those with RA. The earliest four studies performed ultrasound on large joints in patients and compared the findings with other imaging techniques such as computed tomography (CT), MRI, and arthroscopy. More recent studies focused on smaller joints in

Table 1. Causes of false positives identified in the systematic literature review.

Year	Author	Study subjects	Joints assessed	Comparator	Cause of false-positive
1989	Egund	Children with painful hips	Hip	CT	Obliquity of the scanning plane
2003	Soini	RA patients and healthy volunteers	Hip	MRI	Thickening of capsule
2003	Fiocco	RA and PsA patients	Knee	Arthroscopy	Blooming artifact after contrast-enhancement
2004	Karim	RA patients	Knee	Arthroscopy	Small amount of synovial fluid
2004	Terslev	Healthy volunteers ($n = 27$)	IP, PIP, MCP, and first CMC joints	None	Normal blood vessels
2007	Ellegaard	Healthy volunteers ($n = 24$)	DIP, IP, PIP, MCP joints	None	Thickening of synovium or collateral ligaments
2007	Robertson	Healthy volunteers ($n = 50$) and a cadaveric specimen ($n = 1$)	Extensor tendon sheaths of wrist	None	Anisotropy of retinaculum
2009	Luukkainen	Healthy volunteers ($n = 50$)	MTP and talocrural joints	None	Small amount of synovial fluid
2011	Millot	RA patients ($n = 127$) and age/sex-matched healthy volunteers ($n = 127$)	Second to fifth MCP and MTP joints	None	Low grade synovial thickening
2013	Magni-Manzoni	JIA patients ($n = 39$) and healthy children ($n = 39$)	IP, PIP, MCP, wrist, elbow, knee, ankle, MTP, and foot IP joints	None	Low grade joint effusion and low grade synovial hyperplasia, particularly in knee and MTP joints
2013	Sant'Ana Petterle	RA patients ($n = 50$) and healthy volunteers ($n = 50$)	Ankle and MTP joints	None	Low grade synovial thickening, particularly in first MTP and talonavicular joints

CT, computed tomography; RA, rheumatoid arthritis; JIA, juvenile idiopathic arthritis; MRI, magnetic resonance image; PsA, psoriatic arthritis; IP, interphalangeal; PIP, proximal interphalangeal; MCP, metacarpophalangeal; CMC, carpometacarpal; DIP, distal interphalangeal; MTP, metatarsophalangeal.

healthy subjects and reported non-specific findings and technical pitfalls. Most of the studies reported false-positives in the gray-scale evaluation of intra-articular synovitis, whereas one study reported that in the gray-scale evaluation of tenosynovitis and two studies reported those in the Doppler assessment of intra-articular synovitis. These results indicate that both non-specific findings and technical/interpretational pitfalls can cause false-positives in gray-scale and Doppler assessment of intra- and extra-articular synovial inflammation.

Consensus-based identification of causes of false-positives

Given the preliminary results of systematic literature review, a wide variety of candidate causes of false-positives were proposed and discussed in the consensus meeting. Twenty-one candidates were identified, which included 15 items for gray-scale assessment and six for Doppler assessment (Table 2).

In the Delphi process, predefined consensus ($\geq 80\%$) was achieved in 11 of 21 items (Table 2). For all of the 10 items which did not achieve consensus, the major reason for disagreement was that the item is too rudimentary and hardly causes false-positives in practice.

The 11 items, which achieved consensus, are listed in Table 3. These items are classified as factors related to false-positives in gray-scale assessment and those in Doppler assessment. Gray-scale items are further classified as non-specific synovial findings and normal anatomical structures, which can mimic synovial lesions due to either their low echogenicity or anisotropy. "Reverberation/mirror image artefact" was rephrased as "Reverberation" because a couple of participants pointed out that the major explanation for this artifact which appears below strong Doppler signal is reverberation instead of mirror image and all participants agreed with this correction.

Representative ultrasound images

We next collected ultrasound images which represent 11 identified factors related to false-positives. Twenty-seven examples with a

Table 2. Rating and agreement in expert panel on candidate causes of false-positives which should be presented as pitfalls in educational materials.

Items	Rating (1–5)	
	Mean	% Agreement (≥ 4)
Gray-scale assessment		
Non-specific thickening of synovial membrane*	4.60	93.3
Non-specific fluid collection*	4.79	93.3
Hyaline cartilage	3.79	66.7
Muscle	4.47	93.3
Intra-capsular connective tissues*	4.33	80.0
Fibrocartilage	4.53	93.3
Ligament*	4.73	93.3
Pulley	4.40	93.3
Retinaculum*	4.73	93.3
Tendon	4.87	100.0
Acoustic shadow	3.20	33.3
Inappropriately short distance from transducer	3.80	53.3
Inappropriate focus placement	3.67	66.7
Inappropriately low gain setting	3.80	66.7
Inappropriate frequency setting	3.80	66.7
Doppler assessment		
Extra-articular normal vessels*	4.27	73.3
Intra-articular normal vessels*	4.60	86.7
Motion artifact	3.60	60.0
Blooming artifact	4.27	73.3
Reverberation/mirror image artifact	4.53	93.3
Inappropriately high Doppler gain setting	3.53	60.0

*Candidate causes identified by systematic literature review. Other candidates were identified by discussion.

total of 55 still images and 26 video clips were obtained. In the second Delphi process, two examples did not reach predefined consensus agreement and three examples were excluded (Table 4). Representative example images are shown in Figures 2 and 3. All examples and video images are available as the Supplementary material.

Table 3. Systematic classification of factors which cause false-positives in sonographic evaluation of synovial inflammation.

(I) Gray-scale assessment
(A) Non-specific synovial findings
(1) Non-specific thickening of synovial membrane
(2) Non-specific fluid collection
(B) Normal anatomical structures which can mimic synovial lesions due to either their low echogenicity or anisotropy
(1) Intra-capsular connective tissues
(2) Fibrocartilage
(3) Ligament
(4) Pulley
(5) Retinaculum
(6) Tendon
(7) Muscle
(II) Doppler assessment
(A) Intra-articular normal vessels
(B) Reverberation

Discussion

In this study, we identified factors related to false-positives in ultrasound scanning of synovitis and tenosynovitis by systematic literature review, consensus exercise, and discussion. Furthermore, we provide a set of example images, which represent the identified false-positives. These images can be a unique educational material for increasing the awareness of false-positives in ultrasound scanning of synovitis and tenosynovitis.

The results of systematic literature review indicate that both non-specific findings and technical pitfalls can cause false-positives in gray-scale and Doppler assessment of intra- and extra-articular synovial inflammation (Table 1). However, JCR-CoSMUS members and experts in this field considered that these research-based false-positives identified in the literature did not cover all pitfalls we encounter in daily ultrasound examination. In fact, 5 of 11 items in the final list were ones which had not been reported in original articles in the literature but were considered important by the panel.

In the evaluation of synovitis, synovial fluid and hypertrophy are defined as “*abnormal* hypoechoic or anechoic-intraarticular material that is displaceable and compressible, but does not exhibit Doppler signal” and “*abnormal* hypoechoic intraarticular tissue that is nondisplaceable and poorly compressible and which may exhibit Doppler signal”, respectively [1]. Similar definitions also apply to tenosynovitis [13,21,23,41–43]. Therefore, *normal* amount of synovial fluid and *non-specific* hypoechoic thickening of synovium/tenosynovium detected in the majority of non-arthritis joints in healthy subjects should not be considered as pathologic or clinically significant. In fact, 6 of 11 causes of false-positives identified in the literature refer to non-specific synovial fluid or thickening (Table 1) [33,35,37–40]. In addition, although not included in our systematic literature review, Hiraga et al. recently demonstrated that non-arthritis metatarsophalangeal (MTP) joints usually exhibit intraarticular low-echoic area on ultrasound in the dorsal aspect [44]. Ten Cate also demonstrated that a small anechoic area is frequently observed at the distal portion of second metacarpophalangeal (MCP) joints in non-arthritis subjects [45]. Whether these non-specific synovial fluid and thickening should be rated as grade 0 or grade ≥ 1 in semiquantitative scoring system is an important matter of debate. Grading any detectable synovial fluid and thickening allows for more sensitive and consistent assessment, while assessment which only grades pathologic ones is more specific to rheumatic conditions.

Other articles had reported a technical pitfall (i.e. anisotropy) [30,36] and misinterpretation of non-synovial structure [31,35,36] that cause false-positives. These data demonstrate that any anatomical structures and any technical artifacts that exhibit hypoechogenicity in the vicinity of synovial tissues can cause

Table 4. Rating and agreement on candidate examples with still- and video-images which represent causes of false-positives in sonographic evaluation of synovial inflammation.

Causes of false-positives	Example Number number of video clips		Rating (1–5)	
			Mean % Agreement (≥ 4)	
<i>I-A-1</i>				
Non-specific thickening of synovial membrane	1	0	4.91	100
	2	0	4.91	100
	3	1	4.73	100
	4	1	4.64	91.7
<i>I-A-2</i>				
Non-specific fluid collection	1	0	4.55	83.3
	2	1	4.73	100
<i>I-B-1</i>				
Intra-capsular connective tissues	1	1	4.64	100
	2	1	3.73	58.3*
<i>I-B-2</i>				
Fibrocartilage	1	1	4.73	91.7
	2	1	4.82	100
<i>I-B-3</i>				
Ligament	1	1	4.64	100
	2	1	4.55	91.7
<i>I-B-4</i>				
Pulley	1	1	4.73	100
<i>I-B-5</i>				
Retinaculum	1	2	4.91	100
	2	1	4.73	91.7
	3	1	4.55	83.3
<i>I-B-6</i>				
Tendon	1	2	4.73	100
	2	1	4.82	100
	3	1	4.73	91.7†
	4	1	4.27	75.0†
<i>I-B-7</i>				
Muscle	1	1	5.00	100
	2	1	4.73	91.7
	3	1	4.82	100
<i>II-A</i>				
Intra-articular normal vessels	1	1	5.00	100
	2	1	4.82	100
<i>II-B</i>				
Reverberation	1	1	4.55	91.7
	2	1	4.55	91.7

*Excluded from the final examples because % agreement did not reach the predefined value.

†Excluded altogether because % agreement for the transverse view did not reach the predefined value.

false-positives in the gray-scale evaluation of synovitis/tenosynovitis. Therefore, we comprehensively included such structures, artifacts, and inappropriate machine settings as candidate pitfalls in the first Delphi process (Table 1). However, hyaline cartilage, acoustic shadow, and all inappropriate machine settings were considered too rudimentary by a significant proportion of expert panel and did not reach consensus (Table 1), while some members thought they are still important for the beginners. We all agreed that all sonographers should have good knowledge on anatomical structures of and around the joint not to confound normal low-echoic structure with gray-scale synovitis and should also find an imaging plane that demonstrates as little anisotropy as possible.

For Doppler assessment, two previous reports on false-positives were identified [7,32]. We excluded the blooming artifact after contrast-enhancement [32] from the first Delphi process since we do not use contrast-enhancement in daily practice. In addition to the intra-articular normal vessels reported by Terslev et al. [7], we included extra-articular normal vessels, three types of Doppler artifacts, and inappropriately high Doppler gain setting as candidate pitfalls in the first Delphi process, in which consensus

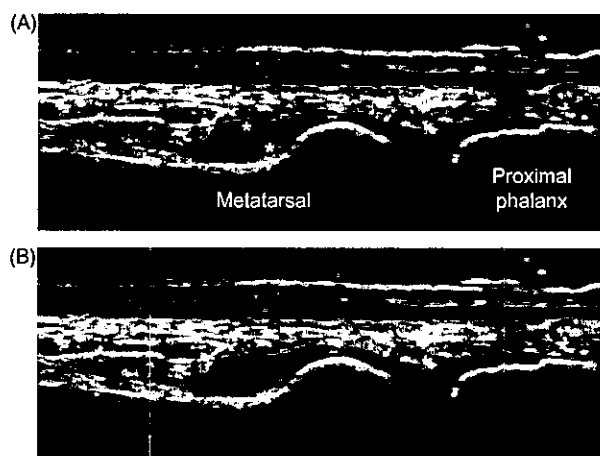


Figure 2. Representative images of non-specific thickening of synovial membrane. Dorsal aspect of metatarsophalangeal joint in the right first toe, longitudinal view. (A) gray-scale image and (B) power Doppler image. Asterisks indicate non-specific thickening of synovial membrane.

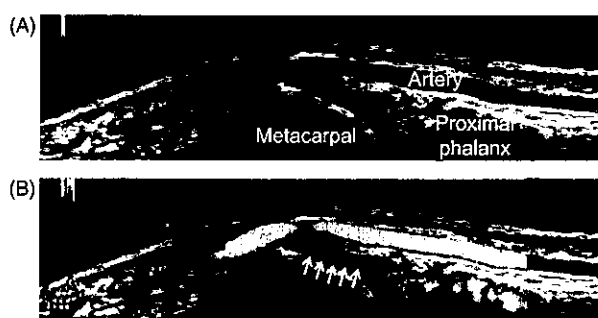


Figure 3. Representative images of reverberation mimicking synovial Doppler signals. Dorsal aspect of the left first metacarpophalangeal joint, longitudinal view. (A) gray-scale image and (B) power Doppler image. Arrows indicate reverberation on the hyaline cartilage due to superficial artery (see also Video 22).

was only achieved on two items (Table 1). Given that Doppler assessment influences the sonographic evaluation of overall activity of synovitis more significantly than does gray-scale assessment [26], at least these two pitfalls should be well known to sonographers who scan joints for this purpose.

False-positive due to intra-articular normal vessels can be avoided to some extent by knowing where in the joint normal vessels are usually identified and by not considering Doppler signals outside synovial hypertrophy as pathological blood flow due to synovitis/tenosynovitis. As advanced technology constantly increases sensitivity to detect very slow blood flow in normal joints, whether very mild Doppler signals inside synovial hypertrophy should be considered as pathological has become an important issue of debate. False-positive due to reverberation can be avoided by (1) scanning with a region of interest for the Doppler mode covering the superficial area not to overlook blood vessels, (2) scanning with multiple imaging planes to distinguish whether the Doppler signals are only present or increased below the blood vessels (Supplementary Figure and Videos 22 and 23), and (3) finding an optimal imaging plane on which blood vessels are not present above the structure if possible.

Although we provide representative still and video images that illustrate major factors related to false-positives in the sonographic evaluation of synovial inflammation, these images and videos do not cover all pitfalls that are characteristic or specific to each joint region. However, the structured list of factors related to false-positives

determined by consensus in our study (Table 3) can be utilized as framework to further identify and classify joint-specific pitfalls.

In conclusion, our study provides a set of representative images that can help sonographers to understand possible false-positives in the evaluation of synovial/tenosynovial inflammation and also provides framework to develop joint-region-specific pitfall atlases. Increased awareness of false-positive pitfalls by our study would improve the specificity of ultrasound-detected inflammation in synovial tissues and further maximize the benefits of musculoskeletal ultrasound in the management of rheumatic conditions.

Acknowledgments

We thank Mr. Gentetsu Hirayama and the Japan College of Rheumatology office for their contribution to the data management.

Conflict of interest

This work was supported in part by a Health Labour Sciences Research Grant on Allergic Disease and Immunology from the Ministry of Health, Labor and Welfare of Japan.

References

- Wakefield RJ, Balint PV, Szkudlarek M, Filippucci E, Backhaus M, D'Agostino MA, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol*. 2005;32:2485–7.
- Wakefield RJ, Green MJ, Marzo-Ortega H, Conaghan PG, Gibbon WW, McGonagle D, et al. Should oligoarthritis be reclassified? Ultrasound reveals a high prevalence of subclinical disease. *Ann Rheum Dis*. 2004;63:382–5.
- Naredo E, Bonilla G, Gamero F, Uson J, Carmona L, Laffon A. Assessment of inflammatory activity in rheumatoid arthritis: a comparative study of clinical evaluation with grey scale and power Doppler ultrasonography. *Ann Rheum Dis*. 2005;64:375–81.
- Ogishima H, Tsuboi H, Umeda N, Horikoshi M, Kondo Y, Sugihara M, et al. Analysis of subclinical synovitis detected by ultrasonography and low-field magnetic resonance imaging in patients with rheumatoid arthritis. *Mod Rheumatol*. 2014;24:60–8.
- Yoshimi R, Hama M, Takase K, Ihata A, Kishimoto D, Terauchi K, et al. Ultrasonography is a potent tool for the prediction of progressive joint destruction during clinical remission of rheumatoid arthritis. *Mod Rheumatol*. 2013;23:456–65.
- Horikoshi M, Suzuki T, Sugihara M, Kondo Y, Tsuboi H, Uehara T, et al. Comparison of low-field dedicated extremity magnetic resonance imaging with articular ultrasonography in patients with rheumatoid arthritis. *Mod Rheumatol*. 2010;20:556–60.
- Terslev L, Torp-Pedersen S, Savnik A, von der Recke P, Qvistgaard E, Danneskiold-Samsøe B, et al. Doppler ultrasound and magnetic resonance imaging of synovial inflammation of the hand in rheumatoid arthritis: a comparative study. *Arthritis Rheum*. 2003;48:2434–41.
- Kawashiri SY, Suzuki T, Nakashima Y, Horai Y, Okada A, Nishino A, et al. Synovial inflammation assessed by ultrasonography correlates with MRI-proven osteitis in patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2014;53:1452–6.
- Takase K, Ohno S, Takeno M, Hama M, Kirino Y, Ihata A, et al. Simultaneous evaluation of long-lasting knee synovitis in patients undergoing arthroplasty by power Doppler ultrasonography and contrast-enhanced MRI in comparison with histopathology. *Clin Exp Rheumatol*. 2012;30:85–92.
- Walter M, Harms H, Krenn V, Radke S, Faehndrich TP, Gohlke F. Correlation of power Doppler sonography with vascularity of the synovial tissue of the knee joint in patients with osteoarthritis and rheumatoid arthritis. *Arthritis Rheum*. 2001;44:331–8.
- Freeston JE, Wakefield RJ, Conaghan PG, Hensor EM, Stewart SP, Emery P. A diagnostic algorithm for persistence of very early inflammatory arthritis: the utility of power Doppler ultrasound when added to conventional assessment tools. *Ann Rheum Dis*. 2010;69:417–19.
- Filer A, de Pablo P, Allen G, Nightingale P, Jordan A, Jobanputra P, et al. Utility of ultrasound joint counts in the prediction of

- rheumatoid arthritis in patients with very early synovitis. *Ann Rheum Dis.* 2011;70:500–7.
13. Nakagomi D, Ikeda K, Okubo A, Iwamoto T, Sanayama Y, Takahashi K, et al. Ultrasound can improve the accuracy of the 2010 American College of Rheumatology/European League against rheumatism classification criteria for rheumatoid arthritis to predict the requirement for methotrexate treatment. *Arthritis Rheum.* 2013;65:890–8.
 14. Kawashiri SY, Suzuki T, Okada A, Yamasaki S, Tamai M, Nakamura H, et al. Musculoskeletal ultrasonography assists the diagnostic performance of the 2010 classification criteria for rheumatoid arthritis. *Mod Rheumatol.* 2013;23:36–43.
 15. Colebatch AN, Edwards CJ, Ostergaard M, van der Heijde D, Balint PV, D'Agostino MA, et al. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. *Ann Rheum Dis.* 2013;72:804–14.
 16. Fukae J, Shimizu M, Kon Y, Tanimura K, Matsushashi M, Kamishima T, et al. Screening for rheumatoid arthritis with finger joint power Doppler ultrasonography: quantification of conventional power Doppler ultrasonographic scoring. *Mod Rheumatol.* 2009;19:502–6.
 17. Naredo E, Collado P, Cruz A, Palop MJ, Cabero F, Richi P, et al. Longitudinal power Doppler ultrasonographic assessment of joint inflammatory activity in early rheumatoid arthritis: predictive value in disease activity and radiologic progression. *Arthritis Rheum.* 2007;57:116–24.
 18. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. *Arthritis Rheum.* 2008;58:2958–67.
 19. Naredo E, Moller I, Cruz A, Carmona L, Garrido J. Power Doppler ultrasonographic monitoring of response to anti-tumor necrosis factor therapy in patients with rheumatoid arthritis. *Arthritis Rheum.* 2008;58:2248–56.
 20. Fukae J, Isobe M, Kitano A, Henmi M, Sakamoto F, Narita A, et al. Radiographic prognosis of finger joint damage predicted by early alteration in synovial vascularity in patients with rheumatoid arthritis: Potential utility of power doppler sonography in clinical practice. *Arthritis Care Res (Hoboken).* 2011;63:1247–53.
 21. Ikeda K, Nakagomi D, Sanayama Y, Yamagata M, Okubo A, Iwamoto T, et al. Correlation of radiographic progression with the cumulative activity of synovitis estimated by power Doppler ultrasound in rheumatoid arthritis: difference between patients treated with methotrexate and those treated with biological agents. *J Rheumatol.* 2013;40:1967–76.
 22. Kirino Y, Hama M, Takase-Minegishi K, Kunishita Y, Kishimoto D, Yoshimi R, et al. Predicting joint destruction in rheumatoid arthritis with power Doppler, anti-citrullinated peptide antibody, and joint swelling. *Mod Rheumatol.* 2015;1–7.
 23. Iwamoto T, Ikeda K, Hosokawa J, Yamagata M, Tanaka S, Norimoto A, et al. Prediction of relapse after discontinuation of biologic agents by ultrasonographic assessment in patients with rheumatoid arthritis in clinical remission. *Arthritis Care Res (Hoboken).* 2014;66:1576–81.
 24. Ogasawara M, Murayama G, Yamada Y, Nemoto T, Kageyama M, Toyama S, et al. Autofeedback from ultrasound images provides rapid improvement in palpation skills for identifying joint swelling in rheumatoid arthritis. *J Rheumatol.* 2012;39:1207–14.
 25. Hama M, Takase K, Ihata A, Ohno S, Ueda A, Takeno M, et al. Challenges to expanding the clinical application of musculoskeletal ultrasonography (MSUS) among rheumatologists: from a second survey in Japan. *Mod Rheumatol.* 2012;22:202–8.
 26. Ikeda K, Seto Y, Narita A, Kawakami A, Kawahito Y, Ito H, et al. Ultrasound assessment of synovial pathologic features in rheumatoid arthritis using comprehensive multiplane images of the second metacarpophalangeal joint: identification of the components that are reliable and influential on the global assessment of the whole joint. *Arthritis Rheumatol.* 2014;66:523–32.
 27. Gartner M, Mandl P, Radner H, Supp G, Machold KP, Aletaha D, et al. Sonographic joint assessment in rheumatoid arthritis: associations with clinical joint assessment during a state of remission. *Arthritis Rheum.* 2013;65:2005–14.
 28. Yoshimi R, Hama M, Minegishi K, Kishimoto D, Watanabe T, Kamiyama R, et al. Ultrasonography predicts achievement of Boolean remission after DAS28-based clinical remission of rheumatoid arthritis. *Mod Rheumatol.* 2014;24:590–8.
 29. Ikeda K, Koike T, Wakefield R, Emery P. Is the glass half full or half empty? Comment on the article by Gartner et al. *Arthritis Rheumatol.* 2014;66:1055–6.
 30. Egund N, Wingstrand H. Pitfalls in ultrasonography of hip joint synovitis in the child. *Acta Radiol.* 1989;30:375–9.
 31. Soini I, Kotaniemi A, Kautiainen H, Kauppi M. US assessment of hip joint synovitis in rheumatic diseases. A comparison with MR imaging. *Acta Radiol.* 2003;44:72–8.
 32. Fiocco U, Ferro F, Cozzi L, Vezzu M, Sfriso P, Checchetto C, et al. Contrast medium in power Doppler ultrasound for assessment of synovial vascularity: comparison with arthroscopy. *J Rheumatol.* 2003;30:2170–6.
 33. Karim Z, Wakefield RJ, Quinn M, Conaghan PG, Brown AK, Veale DJ, et al. Validation and reproducibility of ultrasonography in the detection of synovitis in the knee: a comparison with arthroscopy and clinical examination. *Arthritis Rheum.* 2004;50:387–94.
 34. Terslev L, Torp-Pedersen S, Qvistgaard E, von der Recke P, Bliddal H. Doppler ultrasound findings in healthy wrists and finger joints. *Ann Rheum Dis.* 2004;63:644–8.
 35. Ellegaard K, Torp-Pedersen S, Holm CC, Danneskiold-Samsøe B, Bliddal H. Ultrasound in finger joints: findings in normal subjects and pitfalls in the diagnosis of synovial disease. *Ultraschall Med.* 2007;28:401–8.
 36. Robertson BL, Jamadar DA, Jacobson JA, Kalume-Brigido M, Caoili EM, Margalit Z, et al. Extensor retinaculum of the wrist: sonographic characterization and pseudotenosynovitis appearance. *Am J Roentgenol.* 2007;188:198–202.
 37. Luukkainen R, Ekman P, Luukkainen P, Koski JM. Ultrasonographic findings in metatarsophalangeal and talocrural joints in healthy persons. *Clin Rheumatol.* 2009;28:311–13.
 38. Millot F, Clavel G, Etchepare F, Gandjbakhch F, Grados F, Saraux A, et al. Musculoskeletal ultrasonography in healthy subjects and ultrasound criteria for early arthritis (the ESPOIR cohort). *J Rheumatol.* 2011;38:613–20.
 39. Magni-Manzoni S, Scire CA, Ravelli A, Klersy C, Rossi S, Muratore V, et al. Ultrasound-detected synovial abnormalities are frequent in clinically inactive juvenile idiopathic arthritis, but do not predict a flare of synovitis. *Ann Rheum Dis.* 2013;72:223–8.
 40. Sant'Ana Petterle G, Natour J, Rodrigues da Luz K, Soares Machado F, dos Santos MF, da Rocha Correa Fernandes A, et al. Usefulness of US to show subclinical joint abnormalities in asymptomatic feet of RA patients compared to healthy controls. *Clin Exp Rheumatol.* 2013;31:904–12.
 41. Bruyn GA, Hanova P, Iagnocco A, d'Agostino MA, Moller I, Terslev L, et al. Ultrasound definition of tendon damage in patients with rheumatoid arthritis. Results of a OMERACT consensus-based ultrasound score focussing on the diagnostic reliability. *Ann Rheum Dis.* 2014;73:1929–34.
 42. Naredo E, D'Agostino MA, Wakefield RJ, Moller I, Balint PV, Filippucci E, et al. Reliability of a consensus-based ultrasound score for tenosynovitis in rheumatoid arthritis. *Ann Rheum Dis.* 2013;72:1328–34.
 43. Naredo E, Rodriguez M, Campos C, Rodriguez-Heredia JM, Medina JA, Giner E, et al. Validity, reproducibility, and responsiveness of a twelve-joint simplified power doppler ultrasonographic assessment of joint inflammation in rheumatoid arthritis. *Arthritis Rheum.* 2008;59:515–22.
 44. Hiraga M, Ikeda K, Shigeta K, Sato A, Yoshitama T, Hara R, et al. Sonographic measurements of low-echoic synovial area in the dorsal aspect of metatarsophalangeal joints in healthy subjects. *Mod Rheumatol.* 2015;25:386–92.
 45. Ten Cate DF, Luime JJ, Hazes JM, Kleinrensink GJ, Jacobs JW. Is the frequent sonographic anechoic area distally in metacarpophalangeal joints a sign of arthritis? *Ultrasound Med Biol.* 2014;40:2537–41.



EXTENDED REPORT

The first double-blind, randomised, parallel-group certolizumab pegol study in methotrexate-naïve early rheumatoid arthritis patients with poor prognostic factors, C-OPERA, shows inhibition of radiographic progression

Tatsuya Atsumi,¹ Kazuhiko Yamamoto,² Tsutomu Takeuchi,³ Hisashi Yamanaka,⁴ Naoki Ishiguro,⁵ Yoshiya Tanaka,⁶ Katsumi Eguchi,⁷ Akira Watanabe,⁸ Hideki Origasa,⁹ Shinsuke Yasuda,¹ Yuji Yamanishi,¹⁰ Yasuhiko Kita,¹¹ Tsukasa Matsubara,¹² Masahiro Iwamoto,¹³ Toshiharu Shoji,¹⁴ Toshiyuki Okada,¹⁵ Désirée van der Heijde,¹⁶ Nobuyuki Miyasaka,¹⁷ Takao Koike^{1,18}

Handling editor Tore K Kvien

For numbered affiliations see end of article.

Correspondence to Professor Tatsuya Atsumi, Division of Rheumatology, Endocrinology and Nephrology, Graduate School of Medicine, Hokkaido University, North 15, West 7, Kita-ku, Sapporo, Hokkaido 060-8638, Japan; at3tat@med.hokudai.ac.jp

Received 26 February 2015
Revised 3 June 2015
Accepted 6 June 2015
Published Online First
2 July 2015



Open Access
Scan to access more
free content



To cite: Atsumi T, Yamamoto K, Takeuchi T, et al. *Ann Rheum Dis* 2016;75:75–83.

ABSTRACT

Objectives To evaluate efficacy and safety of combination therapy using certolizumab pegol (CZP) and methotrexate (MTX) as first-line treatment for MTX-naïve, early rheumatoid arthritis (RA) with poor prognostic factors, compared with MTX alone.

Methods MTX-naïve, early RA patients with ≤ 12 months persistent disease, high anti-cyclic citrullinated peptide, and either rheumatoid factor positive and/or presence of bone erosions were enrolled in this multicentre, double-blind, randomised placebo (PBO)-controlled study. Patients were randomised 1:1 to CZP+MTX or PBO+MTX for 52 weeks. Primary endpoint was inhibition of radiographic progression (change from baseline in modified Total Sharp Score (mTSS CFB)) at week 52. Secondary endpoints were mTSS CFB at week 24, and clinical remission rates at weeks 24 and 52.

Results 316 patients randomised to CZP+MTX (n=159) or PBO+MTX (n=157) had comparable baseline characteristics reflecting features of early RA (mean disease duration: 4.0 vs 4.3 months; Disease Activity Score 28-joint assessment (DAS28)) (erythrocyte sedimentation rate (ESR)): 5.4 vs 5.5; mTSS: 5.2 vs 6.0). CZP+MTX group showed significantly greater inhibition of radiographic progression relative to PBO+MTX at week 52 (mTSS CFB=0.36 vs 1.58; $p<0.001$) and week 24 (mTSS CFB=0.26 vs 0.86; $p=0.003$). Clinical remission rates (Simple Disease Activity Index, Boolean and DAS28 (ESR)) of the CZP+MTX group were significantly higher compared with those of the PBO+MTX group, at weeks 24 and 52. Safety results in both groups were similar, with no new safety signals observed with addition of CZP to MTX.

Conclusions In MTX-naïve early RA patients with poor prognostic factors, CZP+MTX significantly inhibited structural damage and reduced RA signs and symptoms, demonstrating the efficacy of CZP in these patients.

Trial registration number (NCT01451203).

INTRODUCTION

The emergence of biological agents targeting inflammatory cytokines such as tumour necrosis

factor (TNF), which play key roles in the pathogenesis of rheumatoid arthritis (RA), has been of great importance. The effectiveness of these agents at inhibiting joint damage progression, in addition to providing symptom relief, has brought a paradigm shift to RA treatment.¹ Since joint damage progression is rarely reversible,^{2–3} earlier treatment with effective drugs would be relevant in clinical practice.

Treatment guidelines and recommendations published by the European League Against Rheumatism (EULAR), the American College of Rheumatology (ACR) and the Japan College of Rheumatology recommend that all patients with RA should be treated with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) from the point of diagnosis.^{4–6} Methotrexate (MTX), either as monotherapy or in combination with other csDMARDs, should be given first-line unless contraindicated. For patients at risk of rapid disease progression, addition of a biologic can be considered if treatment targets are not achieved using csDMARDs alone. Earlier recognition of RA has become possible for many patients by application of the 2010 ACR/EULAR classification criteria.^{7–8} Ultimately, early diagnosis and intervention with effective therapeutics maximises the chance of preventing joint damage progression in order to maintain quality of life.⁹

Certolizumab pegol (CZP) is a humanised anti-TNF antibody fragment conjugated to polyethylene glycol, approved for treatment of inflammatory diseases, including RA. Efficacy and safety of CZP in established RA has been demonstrated in several studies^{10–13} but is previously unreported in MTX-naïve early RA.

Herein, we conducted the Certolizumab-Optimal Prevention of joint damage for Early RA (C-OPERA) study, designed to include MTX-naïve, early RA patients with poor prognostic factors. The study was double-blind (DB) for 1 year, with either CZP or placebo (PBO) administered concomitantly with MTX. Following this, the trial was open label

for another year, whereby completers of the DB period were maintained on MTX monotherapy after discontinuing CZP. This report comprises results from the 1-year DB period.

METHODS

Patients

Eligible patients were 20–64 years old with RA fulfilling the 2010 ACR/EULAR classification criteria. Patients had ≤ 12 months of persistent arthritic symptoms, at least moderate disease activity (Disease Activity Score 28-joint assessment (DAS28) with erythrocyte sedimentation rate (ESR) ≥ 3.2) and were MTX-naïve. In addition, patients had poor prognostic factors: high anti-cyclic citrullinated peptide (anti-CCP) antibody ($\geq 3 \times$ upper limit of normal (ULN)) and either positive rheumatoid factor (RF) and/or presence of bone erosions (based on radiographs of hands/feet, assessed by the investigator at each study site). Patients with high risk of infection (current use of antibiotics, history of serious/chronic infection treated by antibiotics within 6 months) or history of/active tuberculosis or malignancy, and patients previously exposed to MTX, leflunomide or biological DMARDs were excluded.

Study design

C-OPERA, a phase III multicentre study (NCT01451203), was DB and PBO-controlled to week 52, with a subsequent 52-week follow-up period when patients received MTX monotherapy. Patients were randomised 1:1 to either CZP+MTX or PBO+MTX (MTX monotherapy) via an interactive web-response system. Drug administration was performed by dedicated non-

blinded persons due to distinguishability of CZP from PBO; however, these personnel were not permitted to engage in other study activities to maintain blinding. All investigators and healthcare professionals involved in safety/efficacy assessments were blind to study medications. Study drugs were subcutaneously administered as a loading dose of CZP 400 mg or PBO at weeks 0, 2 and 4, followed by CZP 200 mg or PBO every two weeks from week 6 to week 50. Oral MTX (8 mg/week) was initiated simultaneously. MTX dose was increased to 12 mg/week at week 4, 16 mg/week at week 8 and maintained at 16 mg/week thereafter. As per protocol, dose escalation of MTX could be postponed only for safety concerns or due to adverse events (AEs), in which case the dose was maintained at the highest tolerable dose. Patients who did not achieve an improvement of symptoms at or after week 24, that is, if moderate or higher disease activity (DAS28 (ESR) ≥ 3.2) persisted ≥ 4 weeks, in either treatment arm, were eligible to receive rescue treatment with open-label CZP after discontinuing DB period. Co-administration of any DMARD except MTX was prohibited during the study.

The study was conducted from October 2011 to August 2013 at 73 sites in Japan after approval by the Institutional Review Board designated by each site, in compliance with ethical principles of the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent.

Efficacy assessments

The primary efficacy endpoint was inhibition of joint damage progression, assessed as change from baseline (CFB) in van der

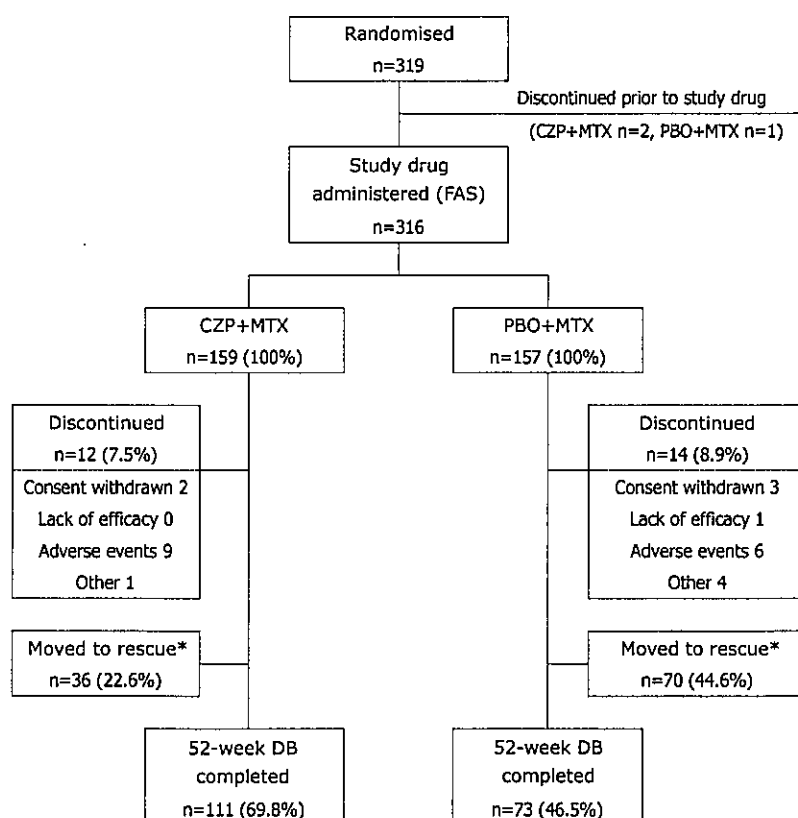


Figure 1 Patient disposition. *Patients who did not achieve an improvement of RA symptoms (defined as the persistence of DAS28[ESR] ≥ 3.2 for 4 weeks or longer) after Week 24 were eligible to withdraw from DB and move to rescue treatment with open label CZP. CZP, certolizumab pegol; DAS28, Disease Activity Score 28-joint assessment; DB, double blind; ESR, erythrocyte sedimentation rate; FAS, full analysis set; MTX, methotrexate; PBO, placebo; RA, rheumatoid arthritis.

Heijde modified Total Sharp Score (mTSS) at week 52. The same measure at week 24 was a secondary efficacy endpoint. mTSS was evaluated by two independent readers in accordance with previously reported methods.^{14 15} In addition to mTSS CFB, non-progression (defined: mTSS CFB ≤ 0.5) and the rapid radiographic progression rate (RRP; defined: yearly progression (YP) > 5)^{16 17} were analysed. Other secondary efficacy endpoints included clinical remission rates, assessed by ACR/EULAR criteria (Simple Disease Activity Index (SDAI)-based and Boolean-based) and DAS28 (ESR) at weeks 24 and 52.

Signs and symptoms were assessed by clinical remission rates (SDAI, Boolean and DAS28 (ESR)), functional remission rates (Health Assessment Questionnaire Disability Index (HAQ-DI)) and ACR20/50/70 responses, evaluated at each time point.

Safety assessments

All undesirable events during the DB period were recorded as AEs or serious AEs. Safety was evaluated by laboratory tests (haematological, blood chemistry, urinalysis), chest radiographs and ECGs.

Statistical analyses

Sample size was based on expected difference in mTSS CFB at week 52 between CZP and PBO groups of 2.57 ± 6.75 . Verification of superiority of CZP+MTX over MTX monotherapy for primary endpoint would then have 90% power at a two-sided significance level of 5% with 146 patients per group (thus the planned number was 150 patients).

Primary analyses used the full analysis set, defined as patients who received ≥ 1 dose of study drug and provided any efficacy data thereafter. For the imputation of missing data, linear extrapolation was used for mTSS and last observation carried forward used for other efficacy variables. Non-responder imputation was added as a sensitivity analysis for clinical remission analyses. For the primary endpoint, an analysis of covariance (ANCOVA) model was used for mTSS CFB by converting measured values to rank scores and using treatment group as a factor and baseline rank score as a covariate. Fisher's exact test was used for analyses of non-progression, RRP in mTSS, clinical remission and ACR20/50/70 response.

RESULTS

Patient baseline demographics/characteristics

Of 319 patients randomised, 316 (159, CZP+MTX; 157, PBO+MTX) received study drug. Of these, 111 patients (69.8%) in the CZP+MTX group and 73 patients (46.5%) in the PBO+MTX group completed the 52-week DB period (figure 1). Fewer PBO+MTX patients completed DB period than CZP+MTX patients, mainly due to the increased number of discontinuations (figure 1).

Treatment groups were generally balanced with respect to demographic and baseline characteristics (table 1). Overall, patients' mean age was 49 years (range 21–64 years). Mean RA duration (time from onset of persistent arthritic symptoms) was approximately 4 months in both groups. All patients had high titre (≥ 3 times ULN) anti-CCP antibody; approximately 95% were RF positive. Bone erosion was confirmed in 50% of patients. Mean \pm SD DAS28 (ESR) was 5.4 ± 1.1 for CZP+MTX and 5.5 ± 1.2 for PBO+MTX. Mean (median) mTSS in CZP+MTX and PBO+MTX groups was 5.2 (1.5) and 6.0 (1.5), and no radiographic damage (mTSS ≤ 0.5) was observed in 35.2% and 35.7% of patients, respectively. There was no difference between groups in mean baseline body weight (57.4 ± 11.3 in CZP+MTX, 57.4 ± 10.6 in PBO+MTX; kg, mean \pm SD) or

average weekly MTX dose throughout the study period (11.6 ± 3.0 in CZP+MTX, 11.6 ± 2.7 in PBO+MTX; mg/week).

Inhibition of joint damage progression

For the primary endpoint, mTSS CFB (mean \pm SD) at week 52 was 0.36 ± 2.70 with CZP+MTX and 1.58 ± 4.86 with PBO+MTX, statistically significant by ANCOVA on the ranks ($p < 0.001$). At week 24, smaller mTSS CFB was observed with CZP+MTX compared with PBO+MTX (0.26 ± 1.55 vs 0.86 ± 2.37 ; $p = 0.003$) (figure 2A).

The percentage of patients with non-progression (mTSS CFB ≤ 0.5) at week 52 was higher with CZP+MTX than with PBO+MTX (82.9% vs 70.7%; $p = 0.011$ by Fisher's exact test).

Table 1 Demographics and baseline characteristics (FAS population)

Parameter	CZP+MTX n=159	PBO+MTX n=157
Age (years)	49.4 \pm 10.6	49.0 \pm 10.3
Female, n (%)	129 (81.1)	127 (80.9)
Weight (kg)	57.4 \pm 11.3	57.4 \pm 10.6
BMI (kg/m ²)	22.4 \pm 3.9	22.5 \pm 3.7
RA duration (months)*	4.0 \pm 2.9	4.3 \pm 2.8
<3 months, n (%)	60 (37.7)	57 (36.3)
3–<6 months, n (%)	60 (37.7)	56 (35.7)
6–12 months, n (%)	39 (24.5)	44 (28.0)
Previous DMARDs use, n (%)	31 (19.5)	29 (18.5)
Steroid use at baseline, n (%)	26 (16.4)	31 (19.7)
Anti-CCP antibody positive, n (%)	159 (100.0)	157 (100.0)
High titre (≥ 3 times of ULN), n (%)	159 (100.0)	157 (100.0)
Titre (U/mL)†	176.7 \pm 107.5	185.2 \pm 107.7
RF positive, n (%)	153 (96.2)	146 (93.0)
High titre (≥ 3 times of ULN), n (%)	119 (74.8)	117 (74.5)
Titre (U/mL)†	182.5 \pm 177.4	167.3 \pm 166.5
Bone erosion (judged by physician), n (%)	79 (49.7)	80 (51.0)
TJC (28 joints)	8.4 \pm 6.1	8.9 \pm 6.5
SJC (28 joints)	8.3 \pm 5.3	8.4 \pm 5.3
PtGADA (mm)	50.4 \pm 22.4	52.9 \pm 22.7
PhGADA (mm)	56.7 \pm 20.5	58.4 \pm 21.4
ESR (mm/h)	38.4 \pm 25.3	43.7 \pm 28.2
CRP (mg/dL)	1.3 \pm 1.8	1.5 \pm 1.9
MMP-3 (ng/mL)‡	130.4 \pm 135.4	185.4 \pm 214.9
DAS28 (ESR)	5.4 \pm 1.1	5.5 \pm 1.2
SDAI	28.7 \pm 12.5	30.0 \pm 13.6
HAQ-DI score	1.0 \pm 0.6	1.1 \pm 0.7
mTSS	5.2 \pm 8.8	6.0 \pm 15.3
Negative (≤ 0.5), n (%)	56 (35.2)	56 (35.7)
Erosion score	2.2 \pm 4.4	2.8 \pm 7.9
Negative (≤ 0.5), n (%)	82 (51.6)	80 (51.0)
Joint space narrowing score	2.9 \pm 5.8	3.2 \pm 8.6
Negative (≤ 0.5), n (%)	87 (54.7)	82 (52.2)
Average weekly MTX dose (mg/week)	11.6 (3.0)	11.6 (2.7)

Values are mean \pm SD unless otherwise indicated.

*Time from onset of persistent arthritic symptoms.

†Data exceeding measurement upper limit (≥ 300 U/mL) are regarded as 300 U/mL.

‡Normal range: 36.9–121 (male), 17.3–59.7 (female) ng/mL.

BMI, body mass index; CCP, cyclic citrullinated peptide; CRP, C reactive protein; CZP, certolizumab pegol; DAS28 (ESR), Disease Activity Score 28-joint assessment; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire Disability Index; MMP-3, matrix metalloproteinase-3; mTSS, modified Total Sharp Score; MTX, methotrexate; PBO, placebo; PhGADA, physician global assessment of disease activity; PtGADA, patient's global assessment of disease activity; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, Simple Disease Activity Index; SJC, swollen joint count; TJC, tender joint count; ULN, upper limit of normal.

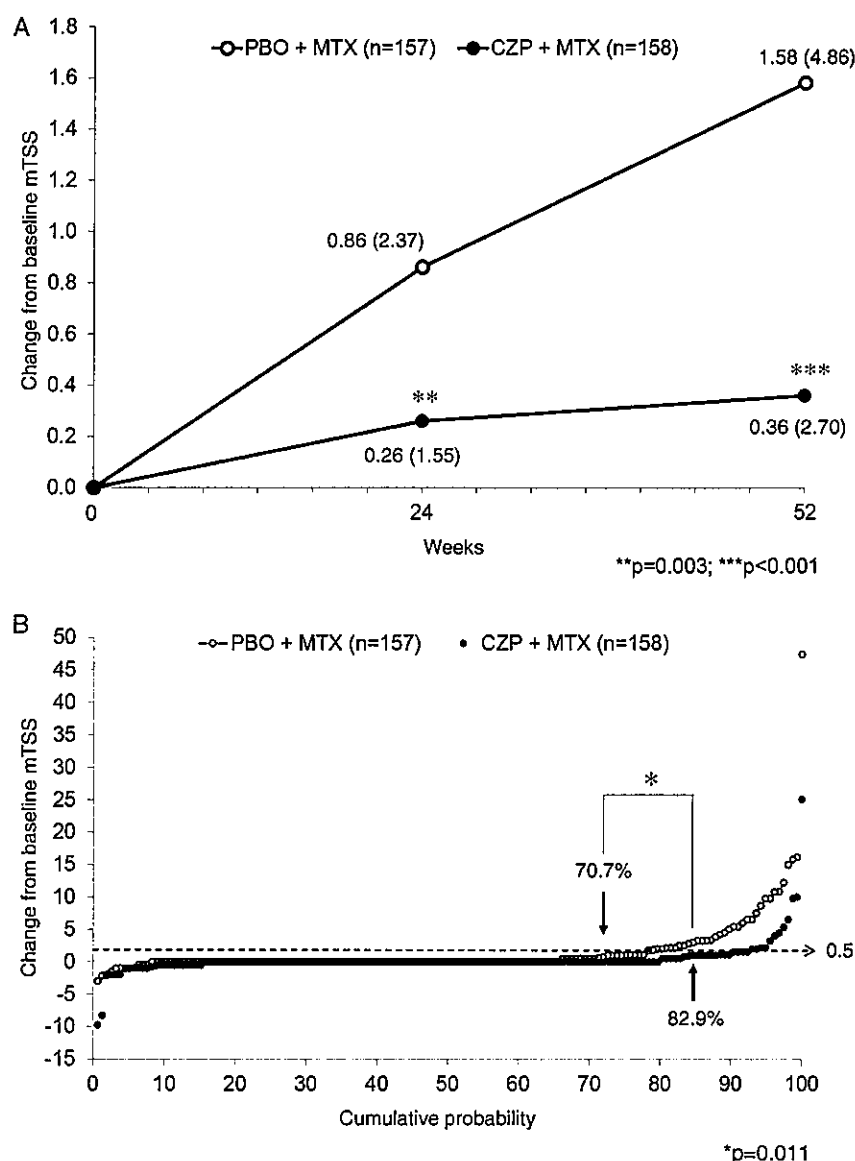


Figure 2 (A) Change from baseline in modified Total Sharp Score (mTSS CFB) at weeks 24 and 52. For calculation of p values, an ANCOVA model was used for mTSS CFB by converting measured values to rank scores and using treatment group as a factor and baseline rank score as a covariate. Values in the figure indicate mean (SD) at each time point and treatment group. (B) Cumulative probability plot of mTSS CFB at week 52. Percentages in the figure indicate non-progression (mTSS CFB ≤ 0.5) rates of each treatment group. P value is calculated by Fisher's exact test. The mTSS data used in (A) and (B) are all imputed using linear extrapolation (LINEAR) for FAS. The number of patients in the CZP+MTX group is 158 despite the FAS reported as 159 because one patient in the group had no mTSS data after treatment. CZP, certolizumab pegol; MTX, methotrexate; mTSS, modified total Sharp score; PBO, placebo.

Individual patient data are presented in the cumulative probability plot of mTSS CFB at week 52 (figure 2B). In addition, 3.2% of patients with CZP+MTX exhibited RRP (defined as YP > 5), compared with 10.8% with PBO+MTX (p=0.008).

Clinical responses

Higher ACR/EULAR remission rates were observed with CZP +MTX compared with PBO+MTX (SDAI remission at week 24: 48.4% vs 29.3%, p<0.001; at week 52: 57.9% vs 33.8%, p<0.001, respectively, and Boolean remission at week 24: 36.5% vs 22.3%, p=0.007; at week 52: 45.3% vs 28.0%, p=0.002, respectively). Similarly, DAS28 (ESR) remission rates at week 24 were approximately 20% higher with CZP+MTX than PBO +MTX (52.8% vs 30.6%; p<0.001); this difference was maintained until week 52 (57.2% vs 36.9%; p<0.001) (figure 3A).

ACR responses were higher at all time points with CZP +MTX compared with PBO+MTX, and a significant difference between the two arms was observed from week 1 in ACR20 and ACR50, and week 2 in ACR70 (figure 3B–D). ACR responses at week 52 in CZP+MTX vs PBO+MTX groups were 78.6% vs 68.8% (p=0.055 by Fisher's exact test) in ACR20, 73.0% vs 51.6% (p<0.001) in ACR50 and 57.2% vs 34.4% (p<0.001) in ACR70, respectively. A similar time course for HAQ-DI remission rates is shown in figure 3E.

Subgroup analyses for joint damage

Subgroup analyses of mTSS CFB at week 52, stratified by baseline parameters including anti-CCP antibody, RF, C-reactive protein (CRP), matrix metalloproteinase (MMP)-3, HAQ-DI, DAS28 (ESR), mTSS and average concomitant MTX dose are

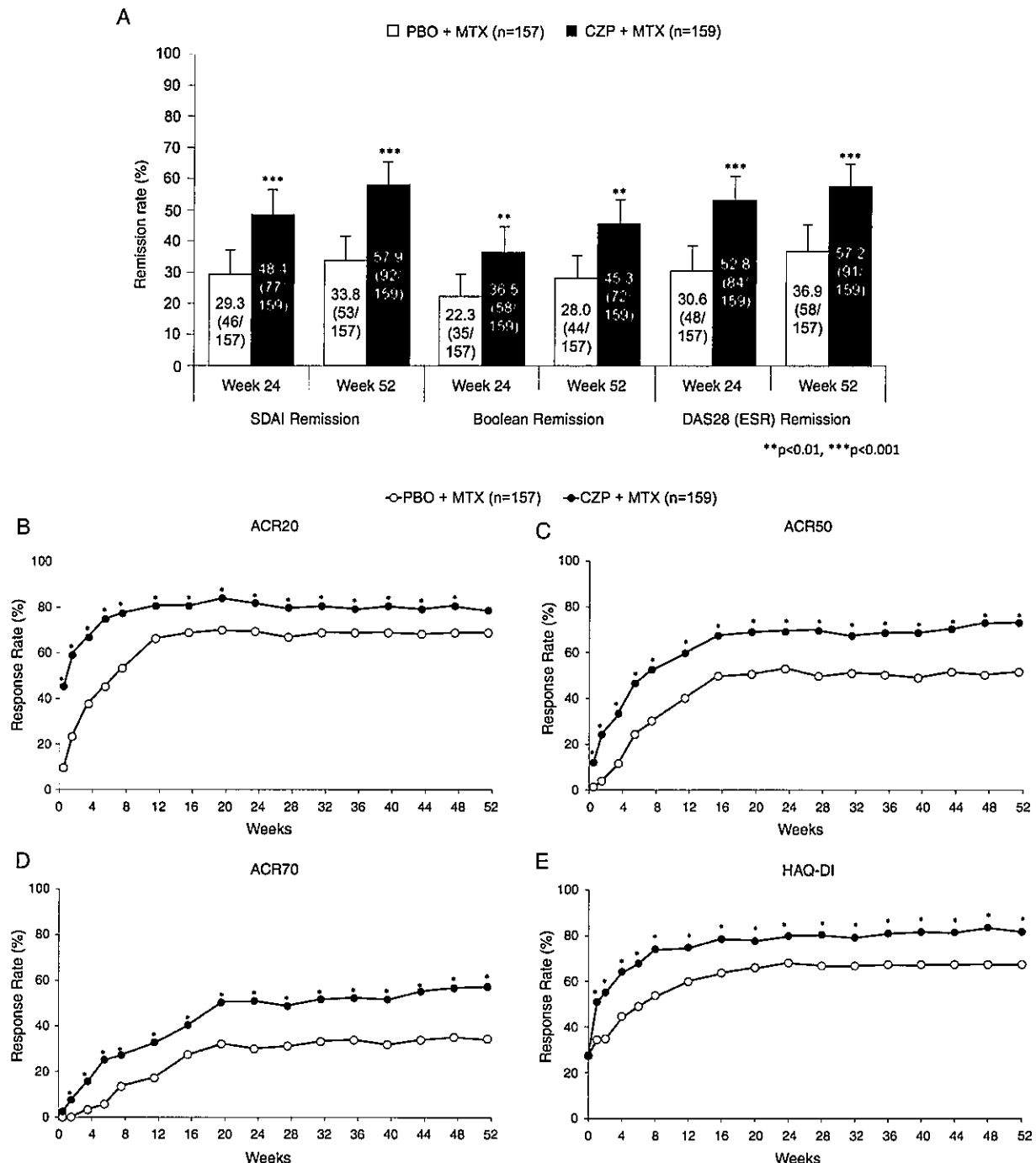


Figure 3 (A) Clinical remission rates at weeks 24 and 52 by Simple Disease Activity Index (SDAI), Boolean and Disease Activity Score 28-joint assessment (DAS28) (erythrocyte sedimentation rate (ESR)) criteria analysed using full analysis set (FAS), last observation carried forward (LOCF) data set. Error bars indicate 95% confidence interval of each remission rate. P values are calculated by Fisher's exact test. (B-E) Time course of American College of Rheumatology (ACR) response rates of (B) ACR20, (C) ACR50, (D) ACR70 and (E) Health Assessment Questionnaire Disability Index (HAQ-DI) remission rates. *p<0.05 between the groups at each particular time point, calculated by Fisher's exact test. CZP, certolizumab pegol; MTX, methotrexate; PBO, placebo.

shown in table 2. A comparison of mTSS CFB between treatment groups consistently showed less progression with CZP + MTX compared with PBO + MTX in all categories of these parameters, except for patients with baseline DAS28 (ESR) <3.2 (a small number of patients, n=8). Meanwhile, intra-parameter comparison of mTSS CFB revealed a trend of greater

mTSS CFB with higher titres of anti-CCP and RF, higher serum CRP and MMP-3, and higher HAQ-DI, DAS28 (ESR) and mTSS at baseline, which was greater in the PBO + MTX group relative to CZP + MTX. In contrast, with regard to concomitant MTX dose, the expected dose-dependent inhibitory effect was not found in either group.

Table 2 Subgroup analysis of mTSS CFB at week 52 by baseline parameters and concomitant MTX dose (FAS, LINEAR)

Parameter at baseline	Subgroup	n	CZP+MTX	n	PBO+MTX
			mTSS CFB mean±SD		mTSS CFB mean±SD
Anti-CCP antibody (U/mL)	<100	51	-0.03±0.69	51	1.34±3.11
	100–<300	57	0.11±1.99	56	1.52±3.79
	≥300	50	1.05±4.21	50	1.91±7.01
RF (U/mL)	<20	6	-0.26±0.45	11	2.20±5.14
	20–<60	33	0.06±1.09	29	0.82±3.07
	≥60	119	0.48±3.06	117	1.72±5.20
CRP (mg/dL)	≤0.5	75	0.13±0.74	69	0.39±2.12
	>0.5–≤1.0	22	0.00±0.52	27	1.85±3.23
	>1.0	61	0.78±4.25	61	2.82±6.97
MMP-3 (ng/mL)	<50	36	0.09±0.50	33	0.01±0.42
	50–<100	59	0.31±0.97	50	1.44±3.17
	≥100	63	0.57±4.17	74	2.38±6.47
HAQ-DI	≤0.5	43	0.27±1.61	43	0.52±2.71
	>0.5–≤1.0	44	0.10±0.98	41	1.60±4.09
	>1.0	71	0.58±3.76	73	2.21±6.04
DAS28 (ESR)	<3.2	5	0.10±0.22	3	0.00±0.00
	3.2–5.1	60	0.20±0.83	54	0.71±3.14
	>5.1	93	0.49±3.46	100	2.10±5.59
mTSS	≤0.5	55	0.20±0.64	56	0.42±0.99
	>0.5	103	0.45±3.32	101	2.23±5.93
Concomitant MTX—average dose (mg/week)	0–8	18	0.07±0.88	21	0.61±2.37
	8–≤12	64	0.38±4.01	59	1.40±2.98
	>12–16	76	0.42±1.27	77	1.99±6.31

CCP, cyclic citrullinated peptide; CFB, change from baseline; CRP, C reactive protein; CZP, certolizumab pegol; DAS28, Disease Activity Score 28-joint assessment; ESR, erythrocyte sedimentation rate; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire Disability Index; LINEAR, linear extrapolation; MMP-3, matrix metalloproteinase-3; mTSS, modified Total Sharp Score; MTX, methotrexate; PBO, placebo; RF, rheumatoid factor.

Safety

Study drug exposure during treatment period was greater in the CZP+MTX group (136.2 patient-years) compared with the PBO+MTX group (116.0 patient-years), as more PBO+MTX-treated patients withdrew (mainly due to lack of efficacy). Overall, 153 patients (96.2%) in the CZP+MTX group and 148 patients (94.3%) in the PBO+MTX group reported any AEs. Serious AEs were reported by 13 patients (8.2%) in the CZP+MTX group and 14 patients (8.9%) in the PBO+MTX group. No clinically relevant difference between groups was observed in overall incidence of AEs and serious AEs (table 3).

Overall incidence of infections and infestations was higher with CZP+MTX (61.0%) compared with PBO+MTX (55.4%), with no difference in the rate of serious infections (3.1% in CZP+MTX vs 4.5% in PBO+MTX). Similar incidences were observed for pneumonia (10 events reported in seven patients [4.4%] for CZP+MTX vs 10 events in eight patients [5.1%] for PBO+MTX), including three cases of *Pneumocystis jiroveci* pneumonia in each group.

There was no difference in the severity pattern of pneumonia events between CZP+MTX (four serious events) and PBO+MTX (six serious events). There was an apparent correlation between MTX dose and the occurrence of pneumonia since only one patient in each group experienced an event of bacterial pneumonia while receiving low MTX dose (0–8 mg/week) versus five and four patients in the CZP+MTX and PBO+MTX groups, respectively, who experienced ≥1 pneumonia event with high MTX dose (>12–16 mg/week).

The incidence of hepatic events was high (mostly abnormal hepatic function) although it was similar between groups

Table 3 Summary of treatment-emergent adverse events

Parameter	CZP+MTX n=159 PY=136.2 n (%)	PBO+MTX n=157 PY=116.0 n (%)
AE summary		
Any AEs	153 (96.2) 542.0*	148 (94.3) 548.2*
Serious AEs	13 (8.2) 11.0*	14 (8.9) 12.9*
Deaths	0	0
AEs of interest		
Infections and infestations	97 (61.0)	87 (55.4)
Serious infection	5 (3.1)	7 (4.5)
<i>Pneumocystis jiroveci</i> pneumonia	3 (1.9)	2 (1.3)
Bronchitis	1 (0.6)	0
Meningitis fungal	1 (0.6)	0
Pneumonia bacterial	1 (0.6)	2 (1.3)
Pneumonia	0	1 (0.6)
Pneumonia mycoplasmal	0	1 (0.6)
Pylonephritis acute	0	1 (0.6)
Pneumonia	7 (4.4)	8 (5.1)
Pneumonia bacterial	4 (2.5)	2 (1.3)
<i>Pneumocystis jiroveci</i> pneumonia	3 (1.9)	3 (1.9)
Bronchopneumonia	1 (0.6)	0
Pneumonia	0	2 (1.3)
Pneumonia mycoplasmal	0	1 (0.6)
Tuberculosis	0	0
Interstitial lung disease	5 (3.1)	1 (0.6)
Malignancies†	1 (0.6)	0
Hepatic disorders‡	68 (42.8)	70 (44.6)
Hematopoietic cytopenias§	12 (7.5)	13 (8.3)
Nausea/vomiting/decreased appetite	39 (24.5)	32 (20.4)
Stomatitis	19 (11.9)	26 (16.6)
Injection site reaction	5 (3.1)	2 (1.3)

*Event rate: per 100 patients-years.

†Cervix carcinoma.

‡Including following preferred terms: alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, hepatic function abnormal, hepatic enzyme increased, hepatic steatosis, hyperbilirubinaemia, liver disorder, liver function test abnormal.

§Including following preferred terms: granulocytopenia, leucopenia, lymphopenia, lymphocyte count decreased, white blood cell count decreased.

AE, adverse event; CZP, certolizumab pegol; MTX, methotrexate; PBO, placebo; PY, total summation of individual patient-years.

(hepatic disorders: 42.8% with CZP+MTX, 44.6% with PBO+MTX; 'investigations' system organ class in hepatic disorders: 6.9% with CZP+MTX; 8.9% with PBO+MTX), indicating that there was no increased risk with the addition of CZP. No patients were withdrawn from the study due to hepatic events, and almost all events were resolved by temporarily discontinuing or reducing MTX dose. No cases of tuberculosis, demyelinating disorders, lupus-like syndrome, serious allergic reactions or serious haematological disorders were reported.

DISCUSSION

Compared with similar studies of anti-TNF agents in MTX-naïve early RA patients, C-OPERA is characterised by two unique features. First, as far as we know, this is the first randomised controlled trial (RCT) to employ the 2010 ACR/EULAR classification criteria as the main inclusion criteria. Thus, patients enrolled in C-OPERA had very early stages of disease, strictly defined as the time from initiation of persistent arthritic

symptoms identified by medical interview (RA duration ≤ 12 months). Approximately 35% of patients had no joint damage (mTSS ≤ 0.5) in baseline radiographs, and mean baseline mTSS of 5.6 units (5.2–6.0) was the lowest among similar RCTs of biologics (approximately 10–20 units).^{18–22} Second, we intentionally enrolled only patients with high anti-CCP antibody titres, which is highly specific for RA,^{23–24} compensating for a relatively low specificity of classification criteria. Since positive anti-CCP antibody predicts poor prognosis and rapid progression,^{25–29} these patients are more likely to require and benefit from aggressive treatment during early disease.

Regarding radiographic joint damage, a statistically significant inhibitory effect was consistently confirmed in patients receiving CZP by analyses of mTSS CFB, non-progression rate, YP and RRP rate. In addition, an absolutely small mean YP (0.37) and high non-progression rate (82.9%) at week 52 in patients with CZP indicate that concomitant use of CZP with MTX brings proven benefits for inhibition of joint damage progression.

Overall, clinical remission rates were relatively high in patients receiving MTX monotherapy (SDAI: 33.8%; Boolean: 28.0%; DAS28 (ESR): 36.9% at week 52; figure 3A) compared with similar RCTs of biologics,^{18–22} but were higher in the group receiving CZP (SDAI: 57.9%; Boolean: 45.3%; DAS28 (ESR): 57.2%). Moreover, patients receiving CZP had better ACR responses and HAQ-DI remission rates as early as week 1.

By protocol, MTX dose was increased to 16 mg/week at week 8, unless there were safety concerns. Consequently, average MTX dose throughout the 52 weeks was approximately 12 mg/week, relatively low compared with reports from similar early RA studies, mainly conducted in the USA or the EU (15–17 mg/week).^{18–22} However, considering the difference in average patient body weight between C-OPERA (57 kg) and the above studies (74–79 kg), actual MTX dose per body weight was similar. Moreover, it has been reported that concentrations of MTX polyglutamates, a potential marker for MTX use, in red blood cells are relatively higher in the Japanese study compared with the US study, suggesting a lower dose of MTX may be sufficient in Japanese patients.³⁰ This is the first Japanese study to mandate use of maximum MTX dose (16 mg/week) by protocol, which may explain better MTX monotherapy results relative to those in previous Japanese studies.

Results of subgroup analyses stratified by MTX dose for mTSS CFB at week 52 (table 2) failed to prove the dose-dependent effect of MTX on joint damage inhibition, regardless of concomitant CZP. This was despite higher DAS28 (ESR) remission rates at week 52 with high-dose MTX (>12 –16 mg/week) (42.9%) compared with lower doses (8 – ≤ 12 mg/week) (30.5%) in patients on MTX monotherapy. Alternatively, the DAS28 (ESR) remission rates in patients with concomitant CZP were not different between high-dose and low-dose MTX groups (59.2% and 56.9%, respectively). It should be noted that MTX dose was not randomly selected, but only adjusted if there were issues of tolerability. There were some variations in baseline characteristics among the subgroups that could have affected the outcomes.

The Combination Therapy with Adalimumab in Subjects with Early Rheumatoid Arthritis (CONCERTO) study³¹ of adalimumab in early RA demonstrated a statistically significant trend of improved efficacy with increasing concomitant MTX dose, from 2.5 to 20 mg/week. However, clinical, functional and radiographic assessments at week 26 were similar between groups receiving 10 and 20 mg/week of concomitant MTX. This is consistent with our current findings from C-OPERA in terms of the lack of clear association between MTX dose and efficacy on joint damage inhibition, suggesting that higher doses of MTX

may not always be necessary when administered with concomitant anti-TNF agents. However, this is far from conclusive, requires further investigation and may be limited to effects on joint damage progression.

The number of AEs per 100 patient-years was approximately 1.3–1.5 times higher in C-OPERA than the Japan RA Prevention of Structural Damage (J-RAPID) study.¹² J-RAPID was similar to C-OPERA; it was conducted in Japanese patients with RA (although these patients had established RA and previous inadequate response to MTX), but average weekly MTX dose was lower (J-RAPID: 6–8 mg/week; C-OPERA: 12 mg/week). In the system, organ classes ‘infections and infestations’, ‘gastrointestinal disorders’ and ‘hepatobiliary disorders’ AEs were more frequently observed in C-OPERA than J-RAPID; these AEs were increased in both PBO and CZP arms, and there was no meaningful difference between the groups. This suggests that the increased frequency of these AEs in C-OPERA may have been associated with the higher MTX dose. Moreover, as all patients were MTX-naïve at study entry, their tolerance to MTX treatment could not be anticipated. Of note, hepatic events, including abnormal investigations, were resolved by temporarily discontinuing or reducing MTX dose and no additional safety risk was identified with CZP, based on the lack of a clinically significant difference between the two treatment groups in terms of the incidence or pattern of AEs.

Study limitations included not assessing the effect of CZP monotherapy, which is of interest in early RA treatment. As the current RA treatment recommendations suggest that MTX and/or conventional synthetic DMARDs should be used for initial treatment,^{5–32} a CZP monotherapy arm was not included in this study.

These efficacy and safety findings from C-OPERA in MTX-naïve early RA suggest that CZP could be used as possible first-line treatment concomitantly with MTX in patients with poor prognostic factors, as typified by high-titre anti-CCP antibody. Patients with higher disease activity, functional disability or bone erosion in the early stages of RA will have a higher chance of preventing joint damage and disease progression.

Author affiliations

¹Hokkaido University Graduate School of Medicine, Sapporo, Japan

²The University of Tokyo, Tokyo, Japan

³Keio University School of Medicine, Tokyo, Japan

⁴Tokyo Women's Medical University, Tokyo, Japan

⁵Faculty of Medicine, Nagoya University Graduate School, Nagoya, Japan

⁶University of Occupational and Environmental Health, Kitakyushu, Japan

⁷Sasebo Chuo Hospital, Nagasaki, Japan

⁸Tohoku University, Sendai, Japan

⁹University of Toyama School of Medicine, Toyama, Japan

¹⁰Hiroshima Rheumatology Clinic, Hiroshima, Japan

¹¹Yokohama Rosai Hospital, Yokohama, Japan

¹²Matsubara Mayflower Hospital, Kato, Japan

¹³Jichi Medical University, Tochigi, Japan

¹⁴UCB Pharma, Tokyo, Japan

¹⁵Astellas Pharma Inc., Tokyo, Japan

¹⁶Department of Rheumatology, Leiden University Medical Centre, Leiden, The Netherlands

¹⁷Tokyo Medical and Dental University, Tokyo, Japan

¹⁸NTT Sapporo Medical Centre, Sapporo, Japan

Correction notice This article has been corrected since it was published Online First. Figure 3E has been corrected.

Acknowledgements The authors would like to acknowledge all the patients, investigators and support staff who participated in the study. The authors also acknowledge Costello Medical Consulting, Cambridge, UK, for writing assistance, which was funded by UCB Pharma, and 'Matladi N. Ndlovu, PhD, UCB Pharma, Brussels, Belgium and Tomoko Suzuki, UCB Pharma, Tokyo, Japan, for publication coordination.

Contributors All the authors made substantial contributions to evaluation of the study results and to develop and review the manuscript.

Funding This study was sponsored by Otsuka Pharmaceutical Co. (Tokyo, Japan), Astellas Pharma (Tokyo, Japan) and UCB Pharma (Tokyo, Japan). UCB Pharma sponsored the study and the development of the manuscript. In addition to content approval by the authors, UCB signed off on the manuscript following a full review to ensure that the publication did not contain any information that has the potential to damage the intellectual property of UCB.

Competing interests TA has taken part in speakers' bureaus for Astellas, Bristol-Myers, Chugai and Mitsubishi-Tanabe; KY has received consultancy fees from Abbott, BMS, Chugai, Eisai, Mitsubishi-Tanabe, Pfizer, Roche and UCB Pharma, and has received research grants from Abbott, Eisai, Mitsubishi-Tanabe, Pfizer, Santen and UCB Pharma; TT has received consultancy fees from AstraZeneca, Asahi Kasei, Eli Lilly, Mitsubishi-Tanabe and Novartis, research grants from Abbott, Astellas, BMS, Chugai, Daiichi-Sankyo, Eisai, Janssen, Mitsubishi-Tanabe, Nippon Shinyaku, Otsuka, Pfizer, Sanofi-Aventis, Santen, Takeda and Teijin, and has taken part in speakers' bureaus for Abbott, BMS, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer and Takeda and UCB Pharma; HY has received consultancy fees from Abbott, Astellas, BMS, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer, Takeda and UCB Pharma; NI has received research grants from Abbott, Astellas, BMS, Takeda, Chugai, Eisai, Janssen, Kaken Mitsubishi-Tanabe and Pfizer, and has taken part in speakers' bureaus for Abbott, Astellas, BMS, Chugai, Eisai, Janssen, Kaken, Mitsubishi-Tanabe, Otsuka, Pfizer, Taisho-Toyama and Takeda; YT has received research grants from Astellas, AbbVie, BMS, Chugai, Daiichi-Sankyo, Mitsubishi-Tanabe, MSD, has received consultancy fees from Abbott, AbbVie, Asahi Kasei, Astellas, AstraZeneca, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, GSK, Janssen, Mitsubishi-Tanabe, MSD, Pfizer, Quintiles, Takeda and UCB Pharma, and has taken part in speakers' bureaus for Abbott, AbbVie, Asahi Kasei, Astellas, AstraZeneca, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, GSK, Janssen, Mitsubishi-Tanabe, MSD, Pfizer, Quintiles, Takeda and UCB Pharma; KE has received consultancy fees from UCB Pharma; AW has received research grants from Daiichi-Sankyo, Daiinippon-Sumitomo, Kyorin, Meiji Seika, Shionogi, Taiho, Taisho and Toyama Chemical, and has taken part in speakers' bureaus for Daiichi-Sankyo, Daiinippon-Sumitomo, GSK, Mitsubishi-Tanabe, MSD, Pfizer, Shionogi and Taisho-Toyama; HO has received consultancy fees from Astellas and UCB Pharma; SY has received research grant from BMS and taken part in speakers' bureaus for AbbVie, Astellas, Chugai, Eisai, Pfizer, Mitsubishi-Tanabe and Takeda; YY has no competing interests to disclose; YK has received speakers' bureau from Astellas, Chugai, and Ono; TM has received speaker honoraria from Pfizer Japan, Janssen Pharmaceutical Co. and Astellas Pharma; and research grants from Quintiles Transnational Japan K.K., Janssen Pharmaceutical Co., Takeda Chemical Industries, Daiichi Sankyo Co., Astellas Pharma, Eli Lilly Japan K.K., MSD Co., Nippon Kayaku Co., Parexel International Corp., Pfizer Japan and Bristol-Myers Squibb; MI has received payment for lectures from Astellas, Chugai, Ono and Tanabe-Mitsubishi, has received research grants from Pfizer and a royalty fee from Chugai; TS is an employee of UCB Pharma; TO is an employee of Astellas; DvdH has received consultancy fees from AbbVie, Amgen, AstraZeneca, Augurex, BMS, Celgene, Centocor, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GSK, Janssen Biologics, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB Pharma and Vertex; and is the Director of Imaging Rheumatology bv; NM has received research grants from Abbott, Astellas, Chugai, Eisai, Mitsubishi-Tanabe, Pfizer and Takeda; TK has received consultancy fees from AbbVie, Astellas, BMS, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Pfizer, Santen, Taisho-Toyama, Takeda, Teijin and UCB Pharma, and has taken part in speakers' bureaus for Abbott, Astellas, BMS, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Pfizer, Santen, Taisho-Toyama, Takeda, Teijin and UCB Pharma.

Patient consent Obtained.

Ethics approval This study was conducted after approval by the Institutional Review Board designated by each study site, in compliance with the ethical principles described in the Declaration of Helsinki and Good Clinical Practice.

Provenance and peer review Not commissioned; externally peer reviewed.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

REFERENCES

- Nam JL, Winthrop KL, van Vollenhoven RF, et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. *Ann Rheum Dis* 2010;69:976–86.
- van der Heijde DM. Radiographic imaging: the 'gold standard' for assessment of disease progression in rheumatoid arthritis. *Rheumatology (Oxford)* 2000;39 (Suppl 1):9–16.

- Quinn MA, Emery P. Window of opportunity in early rheumatoid arthritis: possibility of altering the disease process with early intervention. *Clin Exp Rheumatol* 2003;21 (5 Suppl 31):S154–7.
- Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014;73:492–509.
- Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res* 2012;64:625–39.
- Koike R, Takeuchi T, Eguchi K, et al. Update on the Japanese guidelines for the use of infliximab and etanercept in rheumatoid arthritis. *Mod Rheumatol* 2007;17:451–8.
- Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010;62:2569–81.
- Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010;69:1580–8.
- Nell VP, Machold KP, Eberl G, et al. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. *Rheumatology (Oxford)* 2004;43:906–14.
- Smolen J, Landewe RB, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Ann Rheum Dis* 2009;68:797–804.
- Keystone E, Heijde D, Mason D Jr, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 2008;58:3319–29.
- Yamamoto K, Takeuchi T, Yamanaka H, et al. Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial. *Mod Rheumatol* 2014;24:715–24.
- Yamamoto K, Takeuchi T, Yamanaka H, et al. Efficacy and safety of certolizumab pegol without methotrexate co-administration in Japanese patients with active rheumatoid arthritis: the HIKARI randomized, placebo-controlled trial. *Mod Rheumatol* 2014;24:552–60.
- van der Heijde DM, van Riel PL, Nuvér-Zwart IH, et al. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. *Lancet* 1989;1:1036–8.
- van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol* 2000;27:261–3.
- Tanaka Y, Takeuchi T, Mimori T, et al. Discontinuation of infliximab after attaining low disease activity in patients with rheumatoid arthritis: RRR (remission induction by Remicade in RA) study. *Ann Rheum Dis* 2010;69:1286–91.
- Takeuchi T, Tanaka Y, Amano K, et al. Clinical, radiographic and functional effectiveness of tocilizumab for rheumatoid arthritis patients—REACTION 52-week study. *Rheumatology (Oxford)* 2011;50:1908–15.
- St Clair EW, van der Heijde DM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004;50:3432–43.
- Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000;343:1586–93.
- Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006;54:26–37.
- Kavanaugh A, Fleischmann RM, Emery P, et al. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. *Ann Rheum Dis* 2013;72:64–71.
- Takeuchi T, Yamanaka H, Ishiguro N, et al. Adalimumab, a human anti-TNF monoclonal antibody, outcome study for the prevention of joint damage in Japanese patients with early rheumatoid arthritis: the HOPEFUL 1 study. *Ann Rheum Dis* 2014;73:536–43.
- Nishimura K, Sugiyama D, Kogata Y, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Ann Intern Med* 2007;146:797–808.
- van Gaalen FA, Linn-Rasker SP, van Venrooij WJ, et al. Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. *Arthritis Rheum* 2004;50:709–15.
- Syversen SW, Gaarder PI, Goll GL, et al. High anti-cyclic citrullinated peptide levels and an algorithm of four variables predict radiographic progression in patients with

- rheumatoid arthritis: results from a 10-year longitudinal study. *Ann Rheum Dis* 2008;67:212–17.
- 26 van der Helm-van Mil AH, Verpoort KN, Breedveld FC, *et al*. Antibodies to citrullinated proteins and differences in clinical progression of rheumatoid arthritis. *Arthritis Res Ther* 2005;7:R949–58.
 - 27 Berglin E, Johansson T, Sundin U, *et al*. Radiological outcome in rheumatoid arthritis is predicted by presence of antibodies against cyclic citrullinated peptide before and at disease onset, and by IgA-RF at disease onset. *Ann Rheum Dis* 2006;65:453–8.
 - 28 Meyer O, Labarre C, Dougados M, *et al*. Anticitrullinated protein/peptide antibody assays in early rheumatoid arthritis for predicting five year radiographic damage. *Ann Rheum Dis* 2003;62:120–6.
 - 29 Vencovsky J, Machacek S, Sedova L, *et al*. Autoantibodies can be prognostic markers of an erosive disease in early rheumatoid arthritis. *Ann Rheum Dis* 2003;62:427–30.
 - 30 Takahashi C, Kaneko Y, Okano H. Methotrexate polyglutamates in erythrocytes correlates with clinical response in Japanese patients with rheumatoid arthritis. *Ann Rheum Dis* 2014;73(Suppl 2):213–19.
 - 31 Burmester GR, Kivitz AJ, Kupper H, *et al*. Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial. *Ann Rheum Dis* 2015;74:1037–44.
 - 32 Smolen JS, Landewe R, Breedveld FC, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010;69:964–75.