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特集　リウマチ医に必要な呼吸器合併症の知識—診断と治療の実際

# ニューモシスチス肺炎の予防と治療の実際*

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**Key Words**：*Pneumocystis*, rheumatic disease, diagnosis, treatment

## はじめに

ニューモシスチス肺炎は，*Pneumocystis jirovecii*によりひき起こされる日和見感染症である．リウマチ性疾患では，原病に基づく免疫異常や免疫抑制薬使用に伴う獲得免疫の低下が存在しており[1)~3)]，時にニューモシスチス肺炎が併発する．最近，リウマチ性疾患の生存率が改善される一方で，感染症による死亡率が相対的に高くなり，死因の30～50％を占め，このなかにはニューモシスチス肺炎による死亡も含まれる．また，関節リウマチ(RA)の治療においてTNF阻害療法がきわめて高い疾患活動性制御・骨破壊抑制効果をもつことより脚光を浴びているが，一方では，免疫抑制作用が強力であるがゆえに生じる有害事象が認められ，そのなかにはニューモシスチス肺炎の発症が含まれる．したがって，リウマチ医にとって，ニューモシスチス肺炎は重要な呼吸器合併症であり，その診断・加療に関する知識が必要である．とくに，ニューモシスチス肺炎による致死率は早期診断に依存するとされ，いかに早期に診断して治療を開始するかが重要であるが，そのためには早期診断が不可欠である．本稿では，リウマチ性疾患に併発するニューモシスチス肺炎の早期診断・治療さらには一次予防基準に関して概説する．

## ニューモシスチス肺炎に関する概論

### 1．ニューモシスチスとは

ニューモシスチスは，Antonio Cariniiによりモルモットの肺で確認されたが，当時は新種の原虫と考えられ*Pneumocystis carinii*と名づけられた．1988年になり16Sリボゾームやミトコンドリア DNAの解析により真菌に分類されたが[4)]，その後の研究でニューモシスチス感染には，かなり厳格に宿主特異性があり，ヒトに感染するニューモシスチスは*Pneumocystis jirovecii*の一種類であることが解明された．したがって，現在では“カリニ肺炎”から“ニューモシスチス肺炎”へ改称された．細胞壁成分として他の真菌と同様にβ-D-glucanを豊富に含有し，血清β-D-glucanの上昇はニューモシスチス肺炎の活動期に高頻度でみられ，治療効果の評価にも有用である[5)6)]．一方，他の真菌と異なり細胞増殖に関してエルゴステロール合成が関与しないために，エルゴステロール合成系を標的とするアンホテリシンやアゾール系の抗真菌薬は無効である．したがって，β-D-glucanの上昇をカンジダやアスペルギルスなどの真菌症と決めうちして，これらの抗真菌剤でのみ加療を継続すると痛い目にあう．

* Treatment of *Pneumocystis* pneumonia in patients with rheumatic diseases.

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表1　ニューモシスチスDNA診断と臨床検査値

| | DNA診断 | | |
|---|---|---|---|
| | 陰性(n＝10) | 陽性(n＝19) | *P*-value |
| Age | 58.0±5.4 | 57.2±13.3 | NS |
| WBC(/mm³) | 13,933±1,726 | 6,882±836 | ＜0.01 |
| Lymphocytes(/mm³) | 710±157 | 280±50 | ＜0.05 |
| CRP(mg/dl) | 12.8±2.7 | 7.9±1.5 | NS |
| ESR(mm/hr) | 80.7±16 | 49.9±7.6 | NS |
| LDH(IU/l) | 597±195 | 768±172 | NS |
| IgG(mg/dl) | 1,189±175 | 842±72 | ＜0.05 |
| KL-6(U/ml) | 1,397±681 | 1,684±425 | NS |
| β-D-glucan(pg/ml) | 16.5±7.7 | 170±129 | ＜0.01 |

(文献[11]より引用改変)

### 2．ニューモシスチスの生態

2～3歳以上のヒト血清には，ほとんどニューモシスチスに対する抗体が検出されることより，ヒトに対しては，幼少時に不顕性感染すると考えられている[4]．感染経路に関しては，まだ不明な点が多いが，集団感染や家族内感染がみられることなどより経気道感染であることが類推されている．リウマチ性疾患の治療中に発症するニューモシスチス肺炎は，免疫力の低下に伴い潜在しているニューモシスチスが再活性化されるのではなく，新たな経気道感染において生じるとの見方が強い．

### 3．ニューモシスチス肺炎の病態

ニューモシスチス表面に存在するglycoprotein Aは，I型肺胞上皮より産生されるムチンと高い親和性をもち，肺胞壁に強固に固着した状態で増殖する．ニューモシスチス肺炎の進行性低酸素血症は，著しい肺胞―毛細血管における酸素化障害によりもたらされるが，ニューモシスチスの増殖による単なる物理的な肺胞上皮の被覆による酸素化障害が起こるのではなく，肺胞上皮に固着したニューモシスチスに対して，宿主の免疫応答による局所での炎症が惹起されることによりガス交換の障害が生じるとされる．後天性免疫不全症候群(AIDS)では，宿主の免疫が非常に低下しており，肺胞に多量のニューモシスチスを認めるものの，宿主免疫がひき起こす炎症が軽微で，低酸素血症も緩徐進行性である．一方，非AIDSのニューモシスチス肺炎では肺胞のニューモシスチス量は少ないものの急速進行性の場合が多く，致命率も高いことから，早期診断がより重要となる．

### 4．ニューモシスチス肺炎の臨床症状

一般的には，極初期の症状は非特異的な全身倦怠感などの全身症状であり，その後呼吸器症状に移行する．乾性咳嗽(1～2週)，歩行時などの息切れ，胸骨後部のtightness(咳，吸気において増強)などが呼吸器症状の初期症状として認められ，8～9割で発熱がみられるが必発ではない．これらの臨床症状の聴取はきわめて早期診断に重要である．低酸素血症は，胸写上の変化に先んじて認められることが多く，胸部単純撮影においてとくに異常を認めない進行性低酸素血症，安静時には認めないが歩行後に出現する強い息切れなどがみられた場合には，ニューモシスチス肺炎を強く疑って鑑別診断すべきである．また，通常初期に呼吸音異常はないとされるが，後期には30～40%でラ音が聴取される．

### 5．ニューモシスチス肺炎の臨床検査所見

われわれは，後述するPCR(polymerase chain reaction)法を用いたDNA診断を用いて特異度，感度が高いニューモシスチス肺炎の早期診断を日常的に施行してきた[7)～9)]．その結果より，患者背景と臨床検査成績につき検討したところ**表1**に示すような特徴がみられた．すなわち，白血球数が10,000以上の高値症例ではむしろ他の細菌感染症が疑われる一方，リンパ球に関してはニューモシスチス陽性群では有意差をもって低値を示した．血清IgGに関しては，ニューモシスチス陽性群ではその8割が1,000以下を示した．LDHやKL-6はニューモシスチス肺炎の活動性に相関することが知られるが[10)～12)]，皮膚筋炎をはじめとしてリウマチ性疾患では，原病に起因す

る間質性肺炎の存在がこれらの値を修飾するため，ニューモシスチス陽性・陰性者群間での差は検出されなかった．一方，ニューモシスチスの構成成分にはβ-D-glucanが豊富であることより，ニューモシスチス肺炎発症時に高値を示すことが知られ，血清β-D-glucanは本検討においても陽性群で異常高値を示した．また，血清β-D-glucan値は，ニューモシスチス肺炎の重症度・治療の効果を評価するのにきわめて有用である[5)6)]．したがって，低酸素血症や間質性肺炎とともにβ-D-glucanの上昇がみられた場合，他の深在性真菌症の除外は必要であるが，積極的にニューモシスチス肺炎を疑う根拠となる．ただし，ニューモシスチス肺炎の確定診断例においても，発症極早期にはβ-D-glucanは正常上限で数日後に高値となった症例も存在しており，このような症例を考慮の上臨床症状を重視し高解像度CT(HRCT)を施行するとともに，β-D-glucanを再検するべきであると考える．

### 6．ニューモシスチス肺炎の画像所見

放射線学的には，胸部単純撮影におき典型的には肺門部より生じる間質影を呈する．通常，蝶型に下肺から上肺野に広がる病変を認めるが，胸膜直下や肺門部近傍あるいは肺尖部は保たれることが多い．リウマチ性疾患による間質性肺炎は，背側下肺野より上向性に進行することが多い点で異なるが，絶対的な鑑別点ではなく，実際にはしばしば鑑別診断が難しい．Computed tomography(CT)においては，胸部単純撮影で異常が認められなくても，びまん性に肺胞のconsolidationや肺胞壁の肥厚像がみられるが，これらの所見の早期検出にはHRCTが有用であり，ニューモシスチス肺炎が疑われる症例では必ず施行することが推奨される．

## ニューモシスチス肺炎の早期診断のために

まず，ニューモシスチス肺炎を疑う根拠となるのは患者自覚症状であり，これを問診などにおいて大切にする必要がある．①乾性咳嗽，労作時息切れ，発熱，②進行性低酸素血症，③胸写・胸部CTにおいて間質性肺炎を呈した症例は強くニューモシスチス肺炎が疑われる．現時点ではニューモシスチスを*in vitro*で培養することは不可能であり，診断は患者呼吸器由来検体を鏡検してニューモシスチスの存在を確認することによる．しかしながら，初発症状は乾性咳嗽であり，しかもニューモシスチスが肺胞上皮に固着しているために，初期には良質の喀痰を採取できないことが多い．2％食塩水を吸入後に採取する誘発喀痰は，その点をある程度克服可能で，鏡検による診断では，50～90％の陽性率が得られる．したがって，検体採取は，まず非侵襲的に誘発喀痰を用いて検査し，これで診断がつかない場合に気管支鏡を用いて肺胞洗浄液を採取するように提唱されている[13)]．

当科では，乾性咳嗽，急速進行性低酸素血症，胸写・CTにおけるスリガラス陰影などを呈したニューモシスチス肺炎の疑診例に対して，積極的にPCR法を用いたDNA診断を施行し，ニューモシスチス肺炎の確定診断に非常に役立てている．方法は，2％食塩水10m*l*を超音波ネブライザーにおいて吸入した後，誘発喀痰よりDNAを調整しPCRを施行後，124bpの特異的バンドとして検出する[7)~9)14)15)]．図1にニューモシスチス肺炎を生じた患者誘発喀痰を用いてのDNA診断の結果を示す．

## リウマチ性疾患における ニューモシスチス肺炎の実際

われわれは1998年から約5年の間に，臨床的にニューモシスチス肺炎が強く疑われた59症例に誘発喀痰を用いたニューモシスチス特異的DNA診断を施行し，検出率，患者背景，臨床検査などにつき検討した．リウマチ性疾患患者59名中30名(全身性エリテマトーデス9名，多発性筋炎7名，悪性リウマチ4名，血管炎症候群3名，混合性結合組織病3名，RA3名，その他1名)においてニューモシスチスDNA陽性と診断された．本法による検出率は52％で鏡検診断の陽性率(4.5％)に比較して高い検出率を示した．ニューモシスチス肺炎と確定診断された19名の患者のうちステロイド単独で加療中での発症は全例PSL換算1 mg/kg/day以上のステロイド服用者であった．ステロイド内服量がそれ以下での発症例は全例ステロイドに加えて免疫抑制療

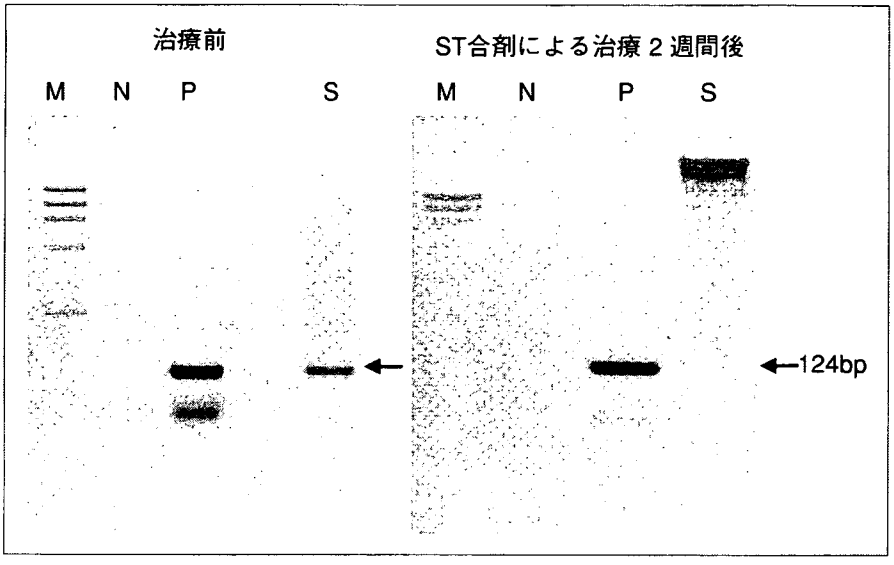


図1　*Pneumocystis*のPCRによるDNA診断
M：Marker 4(φ×174 Hae III digest)，N：negative control, P：positive control, S：sample

表2　ニューモシスチス肺炎の治療法

| |
|---|
| Trimethoprim/sulfamethoxazole(TMP/SMX；ST合剤) |
| Trimethoprim成分で15～20mg/kg/日を6～8時間に分割して経口 |
| 14日間(BW 50kgであればバクタ®9～12錠/日) |
| 経口投与できない場合，効果が期待できない場合静注 |
| (BW 50kgであればバクトラミン®3～4アンプル×3回/日) |
| Pentamidine |
| ST合剤がアレルギーなどで使用できないとき |
| 3～4 mg/kg/日を1回/日で14日間点滴静注 |
| 予防には300mgを注射用蒸溜水に溶解して吸入 |
| Prednisolone |
| 発症早期に中等度以上の重症例に上記治療と併用 |
| 80mg 5日間→40mg 5日間→20mg |

法中であった．なお，PCRによる微量の病原微生物のDNA診断においては，存在するDNAを高度に増幅するために，偽陽性がしばしば問題となるが，正常人およびびまん性閉塞性患者由来の誘発喀痰ではニューモシスチスDNAは検出されなかった．さらに，DNA診断において陽性と診断した症例は，ST合剤による治療開始後，ニューモシスチスDNAは臨床的改善とともに2週間前後で消失することを確認しており，本検討に用いたPCRの感度では疑陽性はないと考えられる．

一方，RAに対してTNF阻害療法施行中のニューモシスチス肺炎発症が散見され，その診断・治療法の確立が急務となっている．厚生労働省の指導の下，抗TNF-α抗体；インフリキシマブ市販後5,000例の全例調査が施行され最近その調査結果が報告された．ニューモシスチス肺炎の発症は22例(0.4%)で，当初懸念された結核の発症(14例；0.3%)を上回った．TNF-αはニューモシスチスの肺胞内でのクリアランスに関与し，その抗体による抑制はクリアランスの低下を招き，ニューモシスチス肺炎発症に密接に関与することが動物実験で明らかにされている[16][17]．

## リウマチ性疾患における ニューモシスチス肺炎の治療

ニューモシスチス肺炎の標準的治療法を表2に示した．基本的には80～90%以上の例でtrimethoprim/sulfamethoxazole(TMP/SMX；ST合剤)が奏効する．急性ではなく，経口薬使用可

能であるとき，$PaO_2$>70mmHgの第一選択薬は，ST合剤4Tを8時間ごとに経口で14日間，急性発症で経口薬が服用不可能，$PaO_2$<70mmHgの場合には，trimethoprim成分で15mg/kg/日を6～8時間ごとに分割して14日間静注する．あるいは第二選択としてペンタミジン4mg/kg/日静注14日間施行する．この際，ステロイド投与に関しては，ニューモシスチス肺炎の治療後には局所で過剰な炎症反応が生じるために，治療後3～4日はかえって低酸素血症が増悪することが知られる．この過剰反応を抑制する目的で，一般的に中等症以上のニューモシスチス肺炎の治療では，ST合剤の投与と同時にステロイドを2～4週間併用する．ST合剤投与15～30分前にプレドニン(80mg経口1日2回5日間，その後40mg24時間ごと5日間，その後20mg24時間ごと11日間)を投与する．

一般にST合剤，ペンタミジンが無効であることは少なく，治療経過中の増悪に関しては，サイトメガロウイルスを含む他の感染症の併発や薬剤に対するアレルギーなどを考えるべきである．加えて，肺胞—毛細血管の膜透過性が亢進して肺浮腫や成人呼吸窮迫症候群の病態に進展することもあり，輸液量を慎重に管理する必要がある．とくに，ST合剤を静脈注射する場合，溶解にかなりの容量の輸液が必要であり，輸液量過剰には注意を要する．治療に対する反応が明らかになるまでの平均期間は4～6日であり，治療反応性は発熱，呼吸回数，$PaO_2$，CRP，β-D-glucan値において確認しつつ，非AIDS患者での発症では2週間，AIDS患者での発症例では3週間服薬するのが標準的治療である．また，PCR法で陽性，気管支肺胞洗浄液での細胞診で陰性の場合に関して，最近のニューモシスチス肺炎に関するNew England Journal of Medicineでの総説では，このような場合には治療を開始することを推奨している[13]．また，ST合剤の血中半減期は11時間であるが末期腎機能障害時には20～60時間となる．腎障害がある時には，一回投与量を減量する必要がある(CCr>50～90：100%，10～50：50%，<10：推奨されない)．

## ニューモシスチス肺炎の一次予防とその問題点

われわれは，上述した誘発喀痰を検体としたニューモシスチス肺炎の非侵襲的DNA診断を試み，検出率，特異性，迅速性における有用性を検討するとともにこれによりニューモシスチス肺炎を早期診断し得たリウマチ性疾患約30例の解析より，ニューモシスチス肺炎発症リスクを抽出し，当該症例へのST合剤あるいはペンタミジンによる一次予防を施行した[9)14)15)]．すなわち，一次予防指標として，①PSL換算≧1mg/kg使用，②PSL換算≧0.5mg/kgかつ免疫抑制薬併用，③リンパ球≦400/$mm^3$，④IgG≦700mg/dlのうち，①または②，かつ，③または④を満たす症例と定め，本基準に該当するリウマチ性疾患症例に対してST合剤1g連日あるいは2g隔日投与などの一次予防を施行し，ニューモシスチス肺炎の発症は1例のみであった(1例はペンタミジン吸入での一次予防者)．一方，一次予防基準に該当しない症例よりのニューモシスチス肺炎の発症が3例あったが，1例がレフルノミド，2例がTNF阻害療法中でありすべてRA患者での発症であった．RAでは使用されるステロイド服用量は少量であり，また生物学的製剤に関する項目を設けていないため，本基準には多くの症例が該当しなかった．今後，β-D-glucan高値，高齢者，既存肺疾患，血球減少，糖尿病合併などをも盛り込んだ他のリウマチ疾患と分別化したRA独自の一次予防基準設定が必要であり，そのためには発症頻度を考慮すると，単一期間での検討は困難であり全国的な症例の収集・解析を要すると思われる．なお，以前から葉酸代謝阻害作用をもつメトトレキサートとST合剤との併用は禁忌とされる趣きがあったが，そのようなエビデンスはなく，現在では血球減少，肝障害などのモニタリングを怠らない限り併用には支障ないとされる[13]．一方，実際にST合剤の予防投与を施行してみると，有害事象が22名(28%)/全患者数78名で認められ，ST合剤の市販後調査における頻度10%に比較してリウマチ性疾患では約3倍と明らかに高く，かなりの症例でペンタミジンの吸入に変更を余儀なくされた．すなわち，実

際にはST合剤を服用できない症例が多くなることが想定され，セカンドチョイスとなるペンタミジン吸入を施行することになるが，ペンタミジンの吸入による予防は絶対的なものではなく，肺尖部のニューモシスチス肺炎や肺外でのニューモシスチス発症が報告される．

## おわりに

リウマチ性疾患に併発するニューモシスチス肺炎に対して，一次予防が有効であることが明らかであり，実践が肝要である．一方，早期診断に欠かせないのが，自覚症状を見逃さないようにする患者教育であり，他覚所見を確実に鑑別する医師の注意深い問診・診察である．さらに，疑われたときに確定診断するには，今回呈示したような誘発喀痰を用いたPCR(polymerase chain reaction)によるDNA診断が感度，特異度，迅速性に優れる．当科では検体提出日に結果を得ることも可能であるが，一般臨床検査機関へ提出した際には，結果報告まで数日を要する．したがって，症状，画像所見やβ-D-glucanなどから強くニューモシスチスを疑った場合，ST合剤で治療開始して経過を慎重に追跡する場合もある．一次予防薬として使用されるST合剤はHIV感染症患者ではその予防基準が確立し，有効性も確認されている．しかしながら，ST合剤の有害事象はとくにRAをはじめとするリウマチ性疾患では有意に高く，インフリキシマブ投与全患者に予防投与するのは賢明ではない．今後，どのような症例でニューモシスチス肺炎は生じるのか，その危険因子を解析した上で適切な一次予防ガイドラインが制定される必要がある．

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ORIGINAL ARTICLE

# Comparison of trimethoprim–sulfamethoxazole and aerosolized pentamidine for primary prophylaxis of *Pneumocystis jiroveci* pneumonia in immunocompromised patients with connective tissue disease

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**Abstract** To evaluate the efficacy of primary prophylaxis for *Pneumocystis jiroveci* pneumonia (PCP) in patients with connective tissue disease (CTD) and immunosuppression, we compared trimethoprim–sulfamethoxazole (TMP-SMZ) with aerosolized pentamidine. Forty-eight CTD patients of Kitasato University Hospital whose CD4+ lymphocyte count in the peripheral blood was less than 300 $\mu l^{-1}$ were reviewed from 2002 to 2004. Twenty-seven patients received TMP–SMZ and none of them developed PCP. Among 18 patients receiving aerosolized pentamidine, three patients developed PCP. These data indicate that TMP–SMZ is better for prophylaxis than aerosolized pentamidine.

**Keywords** Trimethoprim–sulfamethoxazole · Pentamidine aerosol · *Pneumocystis jiroveci* pneumonia

## Introduction

*Pneumocystis jiroveci* pneumonia (PCP) occurs in patients with impaired cellular immunity, especially debilitated premature infants, patients with primary immunodeficiency, patients on immunosuppressive therapy, and most commonly patients with human immunodeficiency virus (HIV) infection [1, 2]. Considerable progress has been made in the treatment of connective tissue disease (CTD) through the use of potent immunosuppressive agents. However, we encounter PCP quite often in this field because of the marked immunosuppression caused by corticosteroids and other immunosuppressants [3]. In patients with CTD, PCP may have a higher mortality rate than it does in patients with HIV [4].

For primary prevention of PCP in HIV patients, oral trimethoprim–sulfamethoxazole (TMP–SMZ) and aerosolized pentamidine are commonly used [1]. In patients with AIDS, TMP–SMZ has been shown to be more effective than aerosolized pentamidine at conventional doses for the prevention of primary and recurrent PCP. Recent studies have also shown that TMP–SMZ the first choice for prophylaxis in HIV patients [1, 2]. In CTD patients, we also choose TMP–SMZ for primary prophylaxis when they develop immunodeficiency. However, especially in patients with systemic lupus erythematosus (SLE) adverse effects of TMP–SMZ such as allergic reactions and renal dysfunction are not uncommon [5, 6]. In such cases, we use aerosolized pentamidine as the first-line drug.

Although several studies have examined the efficacy of these two drugs, there have been no reports of a comparison between their prophylactic effect in CTD patients. In the present study we retrospectively compared TMP–SMZ with aerosolized pentamidine for the prevention of PCP.

## Materials and methods

### Patients

A total of 330 CTD patients were treated at our department from January 2002 to December 2004 and received more

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than 30 mg of predonisolone daily (including steroid pulse therapy) and/or immunosuppressant therapy. Among them, 45 patients had a peripheral blood CD4+ lymphocyte count of less than 300 $\mu l^{-1}$ and received prophylaxic PCP. The diagnosis of CTD was based on the criteria listed in several reports. The average age of the patients at the time hospitalization was 49.2 ± 17.5 years, and the male to female ratio was 16:29. Seventeen patients had vasculitis, 14 had SLE, seven had polymyositis/dermatomyocytis (PM/DM), three had adult Still's disease, and four had other diseases (cryoglobulinemic vasculitis). Immunosuppresants (cyclophosphamide, cyclosporine, methotrexate, azathioprine, and mizoribine) were administered to 25 patients and the mean total dose of steroids (prednisolone equivalent) was 18,118 mg (Table 1).

Occurrence of PCP was presumed when a patient developed respiratory distress and had an increased serum β-D-glucan level without any other fungal infection [7]. PC was detected in sputum or BALF by polymerase chain reaction (PCR) analysis.

**Table 1** Clinical profile of the two groups

| | | ST group | PI group |
|---|---|---|---|
| Number of patients | | 27 | 19 |
| Age at start of study (mean ± SD) | | 50.4 ± 17.1 years | 48.3 ± 17.8 years |
| Sex (female:male) | | 18:9 | 13:6 |
| CTD | | | |
| Vasculitis | 18 | 13 | 5 |
| SLE | 14 | 4 | 10 |
| PM/DM | 7 | 5 | 2 |
| Adult still | 3 | 2 | 1 |
| Others | 4 | 3 | 1 |
| Immunologic data | | | |
| CD4 ($\mu l^{-1}$) | | 174 | 160 |
| alb (g/dl) | | 3.5 ± 0.5 | 3.2 ± 0.5 |
| IgG (mg/dl) | | 949 ± 332 | 1083 ± 696 |
| Drugs | | | |
| PSL dose (mg) | | 11,098 | 27,562 |
| Immuno suppressants | | 16 (59.3%) | 9 (52.6%) |
| Complications | | | |
| IPF | | 13 (44.4%) | 4 (21.1%) |

ST group, patients receiving TMP–SXZ; PI group, patients receiving aerosolized pentamidine

CTD, Connective tissue disease; PM/DM, polymyositis/dermatomyositis; Adult Stll, adult Still's disease; others (cryoglobulinemic vasculitis); alb, serum albumin level; IgG, immunoglobulin G; PSL, predonisolne; IPF, interstitial pneumonitis

Methods

As prophylaxis for PCP, 1 tablet of TMP–SMZ was administered daily, which contained 400 mg of sulfamethoxazole and 80 mg of trimethoprim (Baktar®). Patients who could not take TMP–SMZ, such as those with renal dysfunction and/or allergies, were given aerosolized pentamidine at a dose of 300 mg every 4 weeks. Fifteen patients (33.3%) had interstitial lung disease (ILD). Results are expressed as the mean ± standard deviation. Difference between the two prophylaxis groups were assessed by using Fisher's exact test and $P < 0.05$ was considered significant (Table 2). The Mann–Whitney test was used for comparison of the CD4+ lymphocyte count between the two groups.

## Results

Forty-eight patients had a CD4+ lymphocyte count in the peripheral blood of less than 300 $\mu l^{-1}$ and received prophylaxis for PCP: 27 patients received TMP–SMZ and the other 18 patients were given aerosolized pentamidine.

Eighteen patients had vasculitis, including ANCA-associated vasculitis, Wegener's granulomatosis, and cryoglobulinemic vasculitis. The 14 patients with SLE tended to have lupus nephritis or drug allergies and consequently received aerosolized pentamidine. Seven patients had PM/DM and three patients had adult Still's disease.

To compare the level of immune function, we assessed the peripheral blood CD4+ cell count in the group receiving TMP–SMZ (ST group) and that receiving pentamidine (PI group). We found that CD4+ cell counts were similar in both groups (Fig. 1). In addition, the serum levels of albumin and IgG, the immunosuppressant doses, and the total dose of steroids showed no significant differences between the two groups. These data indicate that there was no difference of underlying immunity between the ST group and the PI group.

Next, we compared the incidence of PCP between the ST and PI groups (Table 2). In the PI group, three out of 18

**Table 2** Comparison of TMP–SMZ and aerosolized pentamidine for primary prophylaxis of *Pneumocystis jiroveci* pneumonia (PCP)

| | ST group | PI group |
|---|---|---|
| PCP (+) | 0 (0%) | 4 (21%) |
| PCP (−) | 27 (100%) | 15 (79%) |

*P* value: $P = 0.0238$. Comparison of the incidence of *Pneumocystis jiroveci* pneumonia (PCP) between the ST group (TMP–SMZ) and the PI group (aerosolized pentamidine). In the PI group, 4 of 19 patients (21%) developed PCP and the primary prophylaxis rate was 79%. No patient developed PCP in the ST group and difference between the two groups was significant ($P = 0.023$, Fisher's exact test)

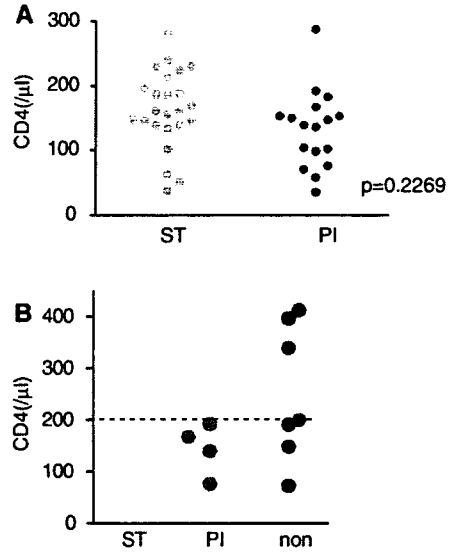


**Fig. 1** **a** Comparison of the CD4+ lymphocyte count in the ST and PI groups (ST vs. PI). Evaluation of CD4 counts to compared the base immunity between two groups. No significant difference was found. **b** Comparison of the CD4+ lymphocyte count in the patients with PCP (ST vs. PI: groups and PI group vs. no prophylaxis). We examined the CD4+ lymphocyte count at the onset of PCP. Among eight patients who did not receive prophylaxis for PCP, 5 had a CD4+ lymphocyte count of 200 $\mu l^{-1}$ or less and we confirmed that a low CD4+ lymphocyte count is one of the most important factors leading to PCP. Daily TMP–SMZ was useful for prophylaxis, while pentamidine in four cases

patients (17%) developed PCP and the effective prophylaxis rate was 83%. In contrast, no patient developed PCP in the ST group and the effective prophylaxis rate was 100%. TMP–SMZ was significantly more effective than aerosolized pentamidine as prophylaxis for PCP.

Details of the three patients who developed PCP during aerosolized pentamidine prophylaxis are shown in Table 3. To assess their immune function, we evaluated the CD4+ cell count, the albumin and IgG levels, and the existence of ILD compared with the patients who did not develop PCP in the PI group. No significant differences were found (Fig. 1a, b).

**Table 3** Clinical features of four patients who developed PCP during aerosolized pentamidine prophylaxis

| | Age | Diseases | Sex | CD4 | alb | IgG | ILD |
|---|---|---|---|---|---|---|---|
| 1. | 74 | Clioglobulinemia | M | 76 | 2.8 | 2,952 | – |
| 2. | 63 | MPA | M | 197 | 3.1 | 518 | + |
| 3. | 62 | STILL | F | 192 | 2.9 | 1,087 | – |
| 4. | 63 | MPA | F | 139 | 2.5 | 1,185 | + |

*MPA* Microscopic polyangiitis, *STLL* adult Still's disease, *M* male, *F* female, *CD4* CD4+ lymphocyte count in the peripheral blood at the onset of PCP, *Alb* serum albumin concentration, *IgG* serum immunoglobulin G concentration, *ILD* interstitial lung disease

Adverse reactions occurred in six patients receiving TMP–STZ, including hemolytic disorder in two, thrombocytopenia in one, leucopenia in one, skin rash in two, liver dysfunction in one, and renal dysfunction in one. All adverse reactions were mild and continuation of treatment was possible. None of the patients showed adverse reactions to aezolized pentamidine.

## Discussion

We evaluated the prophylactic effect of TMP–SMZ against PCP in patients whose CD4+ lymphocyte count was less than 300 $\mu l^{-1}$. Among CTD patients who were admitted to our rheumatology department from 2002 to 2004, 11 patients had PCP confirmed by positive PCR analysis of sputum or BALF. Review of the clinical records showed that eight out of 11 patients had not received any prophylaxis, while the other three patients all received aerosolized pentamidine as prophylaxis for PCP. Thus, no patient administered TMP–SMZ developed PCP in our department and this was the most useful prophylactic agent for patients with CTD. On the other hand, aerosolized pentamidine prophylaxis failed to prevent the occurrence of PCP in three cases.

Another group also reported on the use of TMP–SMX for PCP prophylaxis in patients older than 50 years receiving high-dose steroid or immunosuppressant therapy and none of them developed PCP during about 5 years.

We examined the CD4+ lymphocyte count in the 11 patients with PCP. Among the eight patients who did not receive any prophylaxis, five patients had a CD4+ lymphocyte count of 200 $\mu l^{-1}$ or less. Li et al. also reported that the CD4+ lymphocyte count was less than 250 $\mu l^{-1}$ in all 7 patients with CTD who developed. These data indicate that a decrease of the CD4+ lymphocyte count is one of the risk factors for PCP. Setting a higher limit for the CD4+ lymphocyte count and starting aerosolized pentamidine earlier might have reduced the PCP rate among the patients who could not use TMP–SMZ. It was previously reported that the serum IgG and albumin levels were low at the onset of PCP and that the serum IgG level was decreased significantly in CTD patients. However, these levels did not change in our patients at the onset of PCP.

In patients with HIV and a CD4+ lymphocyte count <200 $\mu l^{-1}$, TMP–SMZ once daily is more effective as primary and secondary prophylaxis against PCP than aeroslized pentamidine once a month. Other reports also indicate that aeroslized pentamidine therapy often fails as prophylaxis for PCP in patients with HIV. However adverse drug reactions are more frequent with TMP–SMZ. Aerosolized pentamidine has a low incidence of systemic adverse reactions because the drug is delivered directly to the lungs.

However, adverse reactions to TMP–SMZ were mild and recovered after temporary withdrawal of therapy, so its continuation was possible in our CTD patients.

This study has the limitations of being retrospective and not double blind. However, patients with immunosuppression need prophylaxis for PCP, so we could not design a double-blind study that included patients who did not take any prophylactic agent on ethical grounds.

In conclusion, immunosuppressive therapy is widely used these days and PCP is becoming a serious problem in CTD patients. We concluded that TMP–SMZ is superior for prophylaxis of PCP compared with aerosolized pentamidine and we recommend the use of TMP–SMZ for patients on strong immunosuppressive regimens.

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ORIGINAL ARTICLE

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# Efficacy and safety of iguratimod compared with placebo and salazosulfapyridine in active rheumatoid arthritis: a controlled, multicenter, double-blind, parallel-group study

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**Abstract** We conducted a 28-week, randomized, double-blind, parallel-group study of iguratimod in 376 Japanese patients with active rheumatoid arthritis to compare the efficacy and safety of the drug with those of placebo and salazosulfapyridine. In the American College of Rheumatology (ACR) 20 response rate, iguratimod was superior to placebo (53.8% versus 17.2%; Fisher's exact test, $P < 0.001$) and was not inferior to salazosulfapyridine (63.1% versus 57.7%, 95% confidence interval for the rate difference, −7.9% to 18.7%). Iguratimod began exhibiting its therapeutic effect within 8 weeks after the initiation of treatment and was effective even in patients who had a poor response to previous treatment with disease-modifying antirheumatic drugs. No statistically significant difference was noted in the incidence of adverse reactions between iguratimod and salazosulfapyridine. The study results suggest that iguratimod could become a new option for the treatment of rheumatoid arthritis.

**Key words** Controlled study · Iguratimod · Rheumatoid arthritis · Salazosulfapyridine

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## Introduction

Disease-modifying antirheumatic drugs (DMARDs) can control the activity of rheumatoid arthritis but have several disadvantages such as inter-patient differences in drug response, slow action, the escape phenomenon, and frequent adverse reactions. Although the treatment of rheumatoid arthritis has made progress (e.g., the recent approval of anticytokine therapy), currently available antirheumatic drugs are not effective in all patients. More effective antirheumatic drugs have been awaited to increase options for the treatment of rheumatoid arthritis. Iguratimod (*N*-[7-[(Methanesulfonyl)amino]-4-oxo-6-phenoxy-4*H*-1-benzopyran-3-yl]formamide) is a novel immunomodulator. The drug suppresses inflammatory cytokine production in cultured human synovial cells and human THP-1 cells.[1–3] It also reduces immunoglobulin (Ig) production by acting directly on B lymphocytes in both mice and humans despite no notable action on B-lymphocyte proliferation.[4] Iguratimod has anti-inflammatory effects and improves abnormal immunological findings in animal models with arthritis or autoimmune disease.[5,6] Inflammatory cytokines are known to be involved in synovitis associated with rheumatoid arthritis. Recent studies suggest the efficacy of anti-CD20 antibody in rheumatoid arthritis.[7,8] Because iguratimod acts on both inflammatory cytokines and B lymphocytes, it is a hopeful novel DMARD. We compared the efficacy and safety of iguratimod with those of placebo and salazosulfapyridine, a strong DMARD, in Japanese patients with active rheumatoid arthritis.

## Patients and methods

The study was conducted at 81 medical institutions in Japan between October 1999 and April 2002 in compliance with the Declaration of Helsinki (amended by the World Medical Association General Assembly in the Republic of South Africa in 1996). The study drugs were provided by the study sponsors (Toyama Chemical and Eisai, Tokyo, Japan). An independent efficacy and safety evaluation committee was organized to discuss study protocol amendments and premature termination of the study. The study protocol was reviewed and approved by the Institutional Review Board of each participating medical institution. Written informed consent was obtained from all patients before they participated in the study.

### Patients

We screened 376 Japanese patients with active rheumatoid arthritis who were 20 years old or older, who met the American College of Rheumatology (ACR) revised criteria for the classification of rheumatoid arthritis,[9] who had suffered from active rheumatoid arthritis for 6 months or longer, and who had never received iguratimod or salazosulfapyridine therapy. Sex and the inpatient/outpatient status were not specified. The patients also fulfilled the following three criteria: (1) six or more tender joints; (2) three or more swollen joints; and (3) either a blood C-reactive protein concentration of at least 1.0 mg/dl, or a Westergren erythrocyte sedimentation rate of at least 30 mm/h. A 4-week washout period was established for DMARDs and immunosuppressive drugs before the initiation of study treatment. The concomitant use of corticosteroids was permitted during the study treatment only when corticosteroids were used at a prednisolone-equivalent dose of 5 mg/day or lower without changes in their dosing regimen at least 4 weeks before the initiation of study treatment.

### Study design

The study was conducted in a multicenter, randomized, double-blind, parallel-group manner. The patients were randomly assigned to iguratimod, salazosulfapyridine, or placebo at a ratio of 2:2:1. The study drugs were iguratimod 25-mg tablets, salazosulfapyridine 500-mg tablets, and their placebo tablets. All these drugs were administered orally twice daily (morning and evening) for 28 weeks in a double-dummy manner. The daily dose of iguratimod was 25 mg for the first 4 weeks and 50 mg for the subsequent 24 weeks. The daily dose of salazosulfapyridine was 1000 mg throughout the treatment period.

### Efficacy and safety evaluations

After the initiation of study treatment, the improvement in rheumatoid arthritis was evaluated every 4 weeks with the following modified ACR core set measures[10]: tender joint count in 48 joints, swollen joint count in 46 joints, patient's assessment of pain with the visual analogue scale, patient's global assessment of disease activity with the scale, physician's global assessment of disease activity with the scale, the modified Health Assessment Questionnaire score,[11] and either blood C-reactive protein concentration or erythrocyte sedimentation rate. Blood concentrations of rheumatoid factor, IgG, IgM, and IgA were measured at baseline and weeks 16 and 28. Efficacy evaluation used the ACR 20 response rate.[10] The primary variable was the ACR 20 response rate at the completion of study treatment (hereinafter referred to as the ACR 20 response rate unless otherwise specified). Other variables were used to evaluate drug efficacy and safety. For the patients whose plain posteroanterior radiographs of the hands at baseline and at the completion of at least 24-week study treatment were available, three blinded radiographic reviewers (a radiologist, a rheumatologist in orthopedics, and a rheumatologist in internal medicine) scored radiographic changes with the modified Sharp method by Fries and colleagues.[12,13] The mean radiographic scores were used to assess the progression of articular destruction. The safety variable was the incidence of adverse events, particularly adverse events of which relationship with the study drug could not be ruled out (i.e., adverse reactions).

### Statistical analysis

A two-staged closed testing procedure was used to test the superiority of iguratimod to placebo and, after the superiority was shown, to test the noninferiority of iguratimod to salazosulfapyridine within a margin of 10%. The 10% margin was selected as a commonly used margin in noninferiority tests. For the superiority analysis population, the following patients were excluded from patients randomized: patients who stopped visiting the medical institution after the initial visit and had no available efficacy data; patients who received no study drug; patients who violated Good Clinical Practice; patients who did not meet all the inclusion criteria; and patients who met any of the exclusion criteria for efficacy considerations. For the noninferiority analysis population, the following patients were excluded from the superiority analysis population: patients whose duration of study treatment was less than 16 weeks (less than 8 weeks in the case of premature study discontinuation owing to aggravated symptoms/signs or lack of efficacy) and patients whose treatment compliance was less than 70% of the study drug. We used different populations for superiority analysis and noninferiority analysis because intention to treat population type for superiority analysis and per protocol population type for noninferiority analysis were usually employed to lead to more conservative results in the superiority and noninferiority analyses. Nonetheless, we performed the noninferiority analysis in the population which satisfied the eligibility criteria for the superiority analysis to examine the sensitivity and the robustness of the result.

In the superiority and noninferiority evaluations, baseline patient characteristics were compared between the three treatment groups at a significance level of 15% (two-sided) with a parametric or nonparametric method according to data types. When an intergroup difference in the characteristics was detected, the influence of the difference was assessed with statistical adjustment. In the superiority evaluation, Fisher's exact test at a significance level of 2.5% (one-sided) was performed to compare the ACR 20 response rates between the treatment groups; 95% confidence interval (CI) was calculated for differences in the rate. The noninferiority (within a margin of 10%) was evaluated at 95% CI for differences in the ACR 20 response rate at approximate normal distribution. Other variables were compared between the treatment groups at a significance level of 5% (two-sided) with one-sample Wilcoxon test, *U*-test, *t*-test, or Fisher's exact test.

In the safety evaluation, the following patients were excluded from the safety analysis population (patients randomized): patients who stopped visiting the medical institution after the initial visit and had no available safety data; patients who received no study drug; patients who violated Good Clinical Practice; and patients whose duration of study treatment was less than 8 weeks without any adverse reactions or abnormal laboratory data. The incidence of adverse events was calculated by dividing the number of patients with adverse events by the number of patients included in the safety analysis. The incidence of adverse reactions was calculated in the same manner. The incidence of premature study discontinuation was calculated by dividing the number of patients withdrawn from the study by the number of patients randomized. All three incidences were assessed at a significance level of 5% (two-sided) with Fisher's exact test.

## Results

### Baseline patient characteristics

A total of 376 patients were randomly assigned to the iguratimod group ($n$ = 147), the salazosulfapyridine group ($n$ = 156), or the placebo group ($n$ = 73). The eligibility of all the patients was evaluated with the eligibility criteria (Table 1). The superiority analysis population consisted of 132 patients of the iguratimod group and 64 of the placebo group. The noninferiority analysis population consisted of 103 patients of the iguratimod group and 104 of the salazosulfa-

**Table 1.** Decision of evaluable/unevaluable patients

| Eligibility criteria | Number of patients | | | Included/Excluded[a] | | | |
|---|---|---|---|---|---|---|---|
| | Iguratimod | SASP | Placebo | FAS | Superiority | Noninferiority | Safety |
| Informed consent | | | | | | | |
| Failure to obtain re-confirmation of study consent although an occasion was available | 1 | 0 | 0 | × | × | × | × |
| GCP noncompliance | | | | | | | |
| Noncompliance with GCP at medical institution | 1 | 2 | 1 | × | × | × | × |
| Inclusion criteria | | | | | | | |
| Not satisfied with required level of rheumatic activity | 4 | 7 | 4 | ○ | × | × | ○ |
| Exclusion criteria | | | | | | | |
| Experienced Iguratimod or SASP therapy | 2 | 1 | 3 | ○ | × | × | ○ |
| Treatment | | | | | | | |
| Surgical operation during study period | 0 | 1 | 0 | ○ | × | × | ○ |
| Start corticosteroid therapy or change doses | 1 | 4 | 1 | ○ | × | × | ○ |
| Corticosteroid intravenous or intramuscular dosing | 1 | 0 | 0 | ○ | × | × | ○ |
| Arthrocentesis/drainage or corticosteroid intra-articular injection | 2 | 0 | 0 | ○ | × | × | ○ |
| Insufficient drug compliance (less than 70% compliance) | 0 | 5 | 0 | ○ | ○ | × | ○ |
| No drug compliance (0% compliance) | 1 | 0 | 0 | × | × | × | × |
| Lack of data | | | | | | | |
| Lack of efficacy data (data available only before or after study initiation) | 4 | 1 | 0 | × | × | × | ○ |
| Lack of efficacy data (data available only before 2 weeks or more from study initiation) | 1 | 0 | 1 | ○ | × | × | ○ |
| Lack of safety data (data available only at study initiation) | 4 | 1 | 0 | ○ | ○ | ○ | × |
| Early discontinuation | | | | | | | |
| Discontinued before 8 weeks (occurrence of ADR/abnormal laboratory parameter) | 14 | 27 | 7 | ○ | ○ | × | ○ |
| Discontinued before 8 weeks (no ADR/abnormal laboratory parameter) | 15 | 9 | 5 | ○ | ○ | × | × |
| Discontinued before 16 weeks (8weeks if "worsened/insufficient effect") | 7 | 9 | 3 | ○ | ○ | × | ○ |
| Unblinded | 1 | 0 | 0 | × | × | × | ○ |

In this table, ○ and × indicate how to handle each patient according to the criteria but do not necessarily reflect the final decision on the eligibility of each patient.
SASP, salazosulfapyridine; FAS, full analysis set; GCP, good clinical practice; ADR, adverse drug reaction
[a]○: Included; ×: Excluded

**Table 2.** Demographic and other baseline characteristics of the study population

| | Superiority analysis population | | Noninferiority analysis population | |
|---|---|---|---|---|
| | Iguratimod ($n$ = 132) | Placebo ($n$ = 64) | Iguratimod ($n$ = 103) | SASP ($n$ = 104) |
| Female (%) | 81.1 | 84.4 | 79.6 | 84.6 |
| Age (years)[a] | 57.5 ± 10.8 | 57.0 ± 10.8 | 57.1 ± 10.4 | 58.2 ± 11.2 |
| <65 (years, %) | 74.2 | 76.6 | 74.8 | 70.2 |
| ≥65 | 25.8 | 23.4 | 25.2 | 29.8 |
| Weight (kg)[a] | 53.2 ± 9.0 | 53.0 ± 9.0 | 53.2 ± 9.1 | 54.3 ± 10.0 |
| <40 (kg, %) | 4.5 | 4.7 | 2.9 | 4.8 |
| ≥40 | 94.7 | 93.8 | 96.1 | 94.2 |
| Unknown | 0.8 | 1.6 | 1.0 | 1.0 |
| Stage I (%) | 3.8 | 10.9 | 2.9 | 7.7 |
| Stage II (%) | 27.3 | 28.1 | 26.2 | 22.1 |
| Stage III (%) | 33.3 | 25.0 | 33.0 | 41.3 |
| Stage IV (%) | 35.6 | 35.9 | 37.9 | 28.8 |
| Class 1 (%) | 9.1 | 12.5 | 8.7 | 14.4 |
| Class 2 (%) | 73.5 | 65.6 | 73.8 | 65.4 |
| Class 3 (%) | 16.7 | 18.8 | 17.5 | 18.3 |
| Class 4 (%) | 0.8 | 3.1 | 0.0 | 1.9 |
| Positive rheumatoid factor (%) | 86.4 | 85.9 | 86.4 | 86.5 |
| Duration of disease (months)[b] | 110.5 | 84.5 | 96.0 | 84.5 |
| <2 (years, %) | 11.4 | 15.6 | 11.7 | 16.3 |
| 2–5 | 16.7 | 21.9 | 18.4 | 22.1 |
| 5–10 | 27.3 | 23.4 | 27.2 | 30.8 |
| ≥10 | 44.7 | 39.1 | 42.7 | 30.8 |
| Previous DMARD therapy (%) | 71.2 | 73.4 | 66.0 | 69.2 |
| Concomitant corticosteroid therapy (%) | 61.4 | 54.7 | 58.3 | 60.6 |

SASP, salazosulfapyridine; DMARD, disease-modifying antirheumatic drug
[a]Mean ± standard deviation
[b]Median

pyridine group. In both populations analyzed, no statistically significant difference in eligibility or ineligibility between the groups was noted (Fisher's exact test, $P = 0.650$ for the superiority analysis population and $P = 0.539$ for the noninferiority analysis population). Baseline patient characteristics of the iguratimod group in the superiority analysis population were similar to those in the noninferiority analysis population (Table 2). No statistically significant difference was found between the two populations in the characteristics shown in Table 2 ($P \leq 0.15$). In other characteristics, an unbalanced distribution was detected for body weight at the initiation of study treatment, the inpatient/outpatient status, and complications in the noninferiority analysis population. Each characteristic was analyzed by adjusting the ACR 20 response rate, and the lower limit of 95% CI for the rate difference was found to exceed −10% for all the characteristics. Accordingly, the results of the noninferiority analysis did not change. No unbalanced distribution was noted in the superiority analysis population. The characteristics of the safety analysis population did not differ from those of the efficacy analysis population.

## Superiority and noninferiority evaluations

In the superiority analysis population, the ACR 20 response rate was significantly higher for the iguratimod group than for the placebo group (53.8% versus 17.2%; Fisher's exact test, $P < 0.001$; Table 3). This shows the superiority of iguratimod to placebo. In the noninferiority analysis population, the ACR 20 response rate was 63.1% for the iguratimod group and 57.7% for the salazosulfapyridine group; the 95% CI for the rate difference ranged from −7.9% to 18.7%. This indicates that the efficacy of iguratimod is not lower than that of salazosulfapyridine by more than 10%. To examine the sensitivity and the robustness of this result, we performed the noninferiority analysis in the population that satisfied the eligibility criteria for the superiority analysis. The ACR 20 response rate was 53.8% (71/132; 95% CI, 44.9% to 62.5%) for the iguratimod group and 48.2% (68/141; 95% CI, 39.7% to 56.8%) for the salazosulfapyridine group. The 95% CI for the rate difference was −6.3% to 17.4%. With these results, the noninferiority of iguratimod to salazosulfapyridine was considered to be robust. The ACR 50 response rate was 33.0% (34/103) for the iguratimod group (95% CI, 24.1% to 43.0%) and 33.7% (35/104) for the salazosulfapyridine group (95% CI, 24.7% to 43.6%).

## Changes from baseline in outcomes

ACR core set data at the completion of study treatment were significantly better than those at baseline in both the iguratimod and salazosulfapyridine groups (Table 4).

**Table 3.** ACR 20 response rate for superiority and noninferiority analysis populations

| Analysis population | *n* | Responder | Nonresponder | ACR 20 response rate (%) | | *P* value[a] | Difference in the rate (%) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | 95% CI |
| Superiority | | | | | | | | |
| Iguratimod | 132 | 71 | 61 | 53.8 | 44.9–62.5 | <0.001 | 36.6 | 24.0–49.2 |
| Placebo | 64 | 11 | 53 | 17.2 | 8.9–28.7 | | | |
| Noninferiority | | | | | | | | |
| Iguratimod | 103 | 65 | 38 | 63.1 | 53.0–72.4 | 0.257 | 5.4 | −7.9–18.7 |
| SASP | 104 | 60 | 44 | 57.7 | 47.6–67.3 | | | |

Superiority, superiority analysis population; Noninferiority, noninferiority analysis population; SASP, salazosulfapyridine; CI, confidence interval
[a] Fisher's exact test (one-sided)

**Table 4.** Changes from baseline in outcome parameter data at the completion of study treatment (last-observation-carry-forward method)

| | | Iguratimod | | Placebo | |
|---|---|---|---|---|---|
| | | Baseline | Change | Baseline | Change |
| **a. Superiority analysis population** | | | | | |
| Tender joint count | *n* | 132 | 131 | 64 | 63 |
| | Mean ± SD | 13.4 ± 8.0 | −7.1 ± 7.9* | 13.6 ± 7.8 | −3.6 ± 8.3* |
| Swollen joint count | *n* | 132 | 131 | 64 | 63 |
| | Mean ± SD | 10.5 ± 6.9 | −5.0 ± 6.2* | 10.2 ± 5.5 | −3.1 ± 5.7* |
| Patient's assessment of pain (VAS, mm) | *n* | 130 | 129 | 64 | 63 |
| | Mean ± SD | 58.5 ± 23.3 | −17.9 ± 30.0* | 60.7 ± 22.5 | −1.7 ± 27.4 |
| Patient's global assessment of disease activity (VAS, mm) | *n* | 131 | 130 | 64 | 63 |
| | Mean ± SD | 59.6 ± 23.8 | −17.1 ± 31.4* | 65.5 ± 20.5 | −5.7 ± 28.6 |
| Physician's global assessment of disease activity (VAS, mm) | *n* | 132 | 131 | 64 | 63 |
| | Mean ± SD | 56.6 ± 18.0 | −18.9 ± 21.4* | 59.1 ± 18.5 | −6.9 ± 20.5* |
| MHAQ score | *n* | 131 | 130 | 64 | 63 |
| | Mean ± SD | 0.9 ± 0.5 | −0.2 ± 0.4* | 1.0 ± 0.5 | 0.1 ± 0.5 |
| ESR (mm/hour) | *n* | 128 | 123 | 60 | 59 |
| | Mean ± SD | 62.2 ± 25.7 | −13.1 ± 23.6* | 64.1 ± 28.1 | 6.2 ± 21.6* |
| CRP (mg/dl) | *n* | 131 | 127 | 64 | 62 |
| | Mean ± SD | 3.5 ± 3.1 | −0.7 ± 3.8* | 3.9 ± 3.0 | 0.3 ± 2.2 |
| **b. Noninferiority analysis population** | | | | | |
| Tender joint count | *n* | 103 | 103 | 104 | 104 |
| | Mean ± SD | 13.0 ± 7.3 | −7.8 ± 7.5* | 12.7 ± 7.0 | −7.1 ± 6.9* |
| Swollen joint count | *n* | 103 | 103 | 104 | 104 |
| | Mean ± SD | 10.6 ± 7.0 | −5.5 ± 6.0* | 9.3 ± 5.1 | −4.5 ± 4.6* |
| Patient's assessment of pain (VAS, mm) | *n* | 102 | 102 | 104 | 102 |
| | Mean ± SD | 57.0 ± 23.7 | −22.0 ± 27.7* | 56.0 ± 23.5 | −21.0 ± 28.3* |
| Patient's global assessment of disease activity (VAS, mm) | *n* | 103 | 103 | 104 | 102 |
| | Mean ± SD | 58.1 ± 24.0 | −21.3 ± 30.2* | 58.9 ± 22.4 | −21.8 ± 26.7* |
| Physician's global assessment of disease activity (VAS, mm) | *n* | 103 | 103 | 104 | 104 |
| | Mean ± SD | 55.0 ± 17.8 | −23.4 ± 20.9* | 58.4 ± 16.3 | −29.0 ± 20.8* |
| MHAQ score | *n* | 103 | 103 | 104 | 104 |
| | Mean ± SD | 0.8 ± 0.5 | −0.3 ± 0.4* | 0.9 ± 0.6 | −0.3 ± 0.5* |
| ESR (mm/hour) | *n* | 100 | 97 | 103 | 100 |
| | Mean ± SD | 64.0 ± 25.8 | −16.2 ± 23.4* | 61.2 ± 28.4 | −17.1 ± 24.4* |
| CRP (mg/dl) | *n* | 103 | 103 | 103 | 103 |
| | Mean ± SD | 3.6 ± 3.0 | −1.2 ± 3.2* | 3.2 ± 2.4 | −0.9 ± 2.1* |

VAS, visual analogue scale; MHAQ, modified Health Assessment Questionnaire; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SASP, salazosulfapyridine
*$P \leq 0.05$ (intra-group paired *t* test or one-sample Wilcoxon test)

## Immunological tests

Figure 1a illustrates the time courses of mean blood concentrations of rheumatoid factor, IgG, IgM, and IgA in the superiority analysis population. All these concentrations were increased in the placebo group but were reduced in the iguratimod group with a statistically significant difference between the groups (repeated measures analysis of variance, $P \leq 0.001$). In the noninferiority analysis population, changes from baseline in these concentrations in the iguratimod group were compared with those in the salazosulfapyridine group. The mean change from baseline in

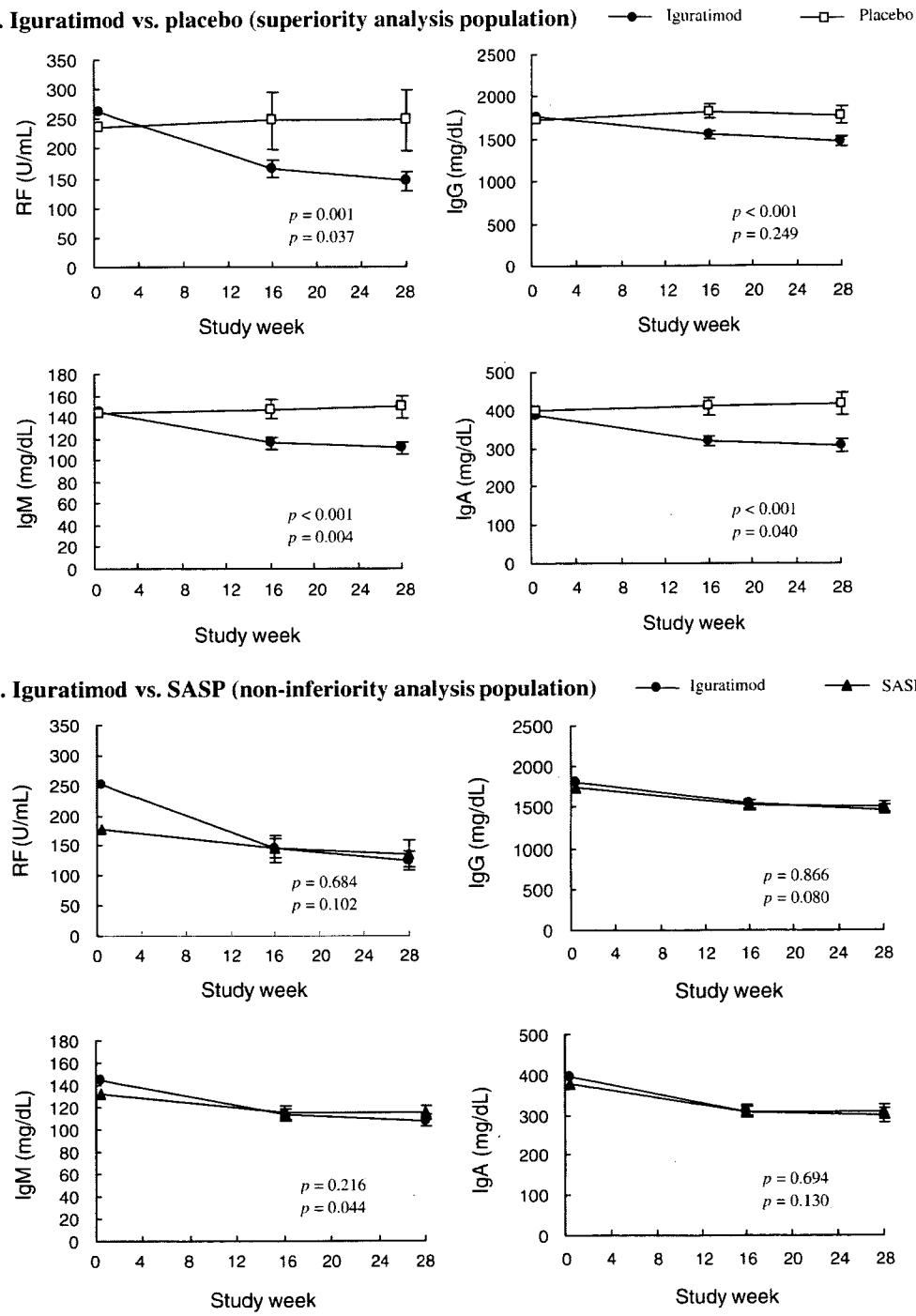


**Fig. 1a,b.** Time courses of immunological test values in superiority and noninferiority analysis populations. **a** Iguratimod vs. placebo (superiority analysis population). **b** Iguratimod vs. SASP (noninferiority analysis population). Adjusted means ±95% confidence intervals of immunological test data are shown. In all the panels, upper *P* values are for the main effect of individual drugs in a repeated-measures analysis of variance, and lower *P* values are for the interaction between the treatment groups and measurement points in the analysis. SASP, salazosulfapyridine; RF, rheumatoid factor; IgG, immunoglobulin G; IgM, immunoglobulin M; IgA, immunoglobulin A

blood IgM concentrations in the iguratimod group was significantly greater than that in the salazosulfapyridine group (*U*-test, $P = 0.020$). No statistically significant difference was noted in three other concentrations between the groups (*U*-test, $P = 0.206$ to 0.438). These results agree with the time courses of these concentrations (Fig. 1b).

## Onset of therapeutic effects

The ACR 20 response rate was 41.7% for the iguratimod group at week 8 and 68.6% for the iguratimod group at week 28 (Table 5).

## Subgroup analysis

For patients who received at least one DMARD within 6 months before the initiation of study treatment but had a poor response to the drug(s), the ACR 20 response rate was 61.3% (38/62) for the iguratimod group (95% CI, 48.1% to 73.4%) and 53.1% (34/64) for the salazosulfapyridine group (95% CI, 40.2% to 65.7%). No statistically significant difference was noted in the rate between the groups (Fisher's exact test, $P = 0.228$). For patients who received methotrexate within 6 months before the initiation of study treatment but had a poor response to the drug, the ACR 20 response rate was 56.3% (9/16) for the iguratimod group (95% CI,

**Table 5.** Time course of ACR 20 response rate in noninferiority analysis population

| | Study week | | | | | | |
|---|---|---|---|---|---|---|---|
| | 4 | 8 | 12 | 16 | 20 | 24 | 28 |
| Iguratimod | | | | | | | |
| Responder/*n* | 14/103 | 43/103 | 52/98 | 56/98 | 59/97 | 52/89 | 59/86 |
| Response rate (%) | 13.6 | 41.7 | 53.1 | 57.1 | 60.8 | 58.4 | 68.6 |
| SASP | | | | | | | |
| Responder/*n* | 17/104 | 31/104 | 48/98 | 52/98 | 56/93 | 54/87 | 57/87 |
| Response rate (%) | 16.3 | 29.8 | 49.0 | 53.1 | 60.2 | 62.1 | 65.5 |

SASP, salazosulfapyridine

29.9% to 80.2%) and 42.1% (8/19) for the salazosulfapyridine group (95% CI, 20.3% to 66.5%). No statistically significant difference was noted between the groups (Fisher's exact test, $P = 0.311$).

### Premature study discontinuation

The incidence of premature study discontinuation was 37.4% (55/147) for the iguratimod group, 41.0% (64/156) for the salazosulfapyridine group, and 45.2% (33/73) for the placebo group. No statistically significant difference was noted in the incidence between the iguratimod group and the salazosulfapyridine group (Fisher's exact test, $P = 0.557$) as well as between the iguratimod group and the placebo group (Fisher's exact test, $P = 0.307$).

Among the patients who were withdrawn from the study, the incidence of premature study discontinuation owing to adverse reactions was 32.7% (18/55) for the iguratimod group, 42.2% (27/64) for the salazosulfapyridine group, and 9.1% (3/33) for the placebo. No statistically significant difference was found in the incidence between the iguratimod group and the salazosulfapyridine group (Fisher's exact test, $P = 0.345$). The incidence was significantly higher for the iguratimod group than for the placebo group (Fisher's exact test, $P = 0.019$). The incidence of premature study discontinuation owing to lack of efficacy was 27.3% (15/55) for the iguratimod group, 23.4% (15/64) for the salazosulfapyridine group, and 57.6% (19/33) for the placebo group. No statistically significant difference was found in the incidence between the iguratimod group and the salazosulfapyridine group (Fisher's exact test, $P = 0.676$). The incidence was significantly lower for the iguratimod group than that for the placebo group (Fisher's exact test, $P = 0.007$).

### Progression of articular destruction

The mean total Sharp score, which is the sum of erosion score and joint space narrowing score, at baseline was 31.9 for the iguratimod group ($n = 79$), 29.0 for the salazosulfapyridine group ($n = 76$), and 33.5 for the placebo group ($n = 33$). The mean increase from baseline in the total Sharp score at the completion of study treatment was 1.2 for the iguratimod group, 0.5 for the salazosulfapyridine group, and 2.7 for the placebo group. No statistically significant difference was noted in the increase between the iguratimod group and the salazosulfapyridine group ($U$-test, $P = 0.122$) as well as between the iguratimod group and the placebo group ($U$-test, $P = 0.584$).

### Safety evaluation

None of the patients died during the study. In the iguratimod group, serious adverse events occurred in nine patients. In seven of the nine patients, the events were regarded as adverse reactions: abnormal changes in laboratory data, such as increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT), in three patients (one with abnormal hematological data and one with jaundice); gastric ulcer in one; melena in one; interstitial pneumonia in one; and fever in one. In the salazosulfapyridine group, serious adverse events occurred in nine patients. In three of the nine patients, the events were regarded as adverse reactions: fever, vomiting, rash, leucopenia, and increased AST and ALT in one patient; fever and rash in one; and leucopenia and neutropenia in one. No unknown serious adverse events that could not be anticipated during the study and of which a relationship with the study drug could not be ruled out were reported from any treatment group.

The incidence of adverse events was 94.6% (123/130) for the iguratimod group, 91.0% (132/145) for the salazosulfapyridine group, and 85.1% (57/67) for the placebo group. A statistically significant difference was noted between the iguratimod group and the placebo group (Fisher's exact test, $P = 0.032$), but not between the iguratimod group and the salazosulfapyridine group (Fisher's exact test, $P = 0.353$). The incidence of adverse reactions was 50.0% (65/130) for the iguratimod group, 48.3% (70/145) for the salazosulfapyridine group, and 31.3% (21/67) for the placebo group. A statistically significant difference was noted between the iguratimod group and the placebo group (Fisher's exact test, $P = 0.015$), but not between the iguratimod group and the salazosulfapyridine group (Fisher's exact test, $P = 0.810$).

The incidence of increased AST or ALT was 21.5% (28/130) for the iguratimod group, 12.4% (18/145) for the salazosulfapyridine group, and 3.0% (2/67) for the placebo group. The incidence of increased AST or ALT regarded as an adverse reaction was 17.7% (23/130) for the iguratimod group, 9.7% (14/145) for the salazosulfapyridine group, and 3.0% (2/67) for the placebo group. The incidence of blood AST or ALT concentration of 100 IU or higher was

10.0% (13/130) for the iguratimod group, 2.8% (4/145) for the salazosulfapyridine group, and 0.0% (0/67) for the placebo group. The incidence of the elevated concentration regarded as an adverse reaction was 7.7% (10/130) for the iguratimod group and 2.1% (3/145) for the salazosulfapyridine group. The increased AST or ALT was resolved in all of the patients except one who could not be followed up because of no visit to the medical institution. In the iguratimod group, 14 patients who continued the study treatment regardless of increased AST or ALT recovered with no remedy. In 21 of 25 patients who continued the study treatment regardless of increased AST or ALT, the subsequent laboratory test revealed that a blood AST or ALT concentration returned to the reference range.

The incidence of gastrointestinal disorder was 37.7% (49/130) for the iguratimod group, 25.5% (37/145) for the salazosulfapyridine group, and 17.9% (12/67) for the placebo group. The incidence of the disorder regarded as an adverse reaction was 19.2% (25/130) for the iguratimod group, 9.0% (13/145) for the salazosulfapyridine group, and 9.0% (6/67) for the placebo group. In the iguratimod group, the most common gastrointestinal adverse reaction was upper abdominal pain (6.9%, 9/130), followed by stomatitis (4.6%, 6/130). As a serious adverse reaction, peptic ulcer was reported in two patients. The incidence of abnormal changes in hematological data was 33.8% (44/130) for the iguratimod group, 35.2% (51/145) for the salazosulfapyridine group, and 26.9% (18/67) for the placebo group. The incidence of the changes regarded as an adverse reaction was 12.3% (16/130) for the iguratimod group, 11.0% (16/145) for the salazosulfapyridine group, and 1.5% (1/67) for the placebo group. In the iguratimod group, all the abnormal changes in laboratory data were resolved, except the changes that began before the initiation of study treatment or were associated with rheumatoid arthritis. The incidence of dermatological disorder was 13.8% (18/130) for the iguratimod group, 30.3% (44/145) for the salazosulfapyridine group, and 9.0% (6/67) for the placebo group. The incidence of the disorder regarded as an adverse reaction was 3.8% (5/130) for the iguratimod group, 17.2% (25/145) for the salazosulfapyridine group, and 4.5% (3/67) for the placebo group.

## Discussion

Our clinical study of iguratimod used salazosulfapyridine, which is a widely used DMARD with well-established effectiveness, as an active control because methotrexate was not approved for the treatment of rheumatoid arthritis in Japan at the planning of the study. In baseline patient characteristics, the percentages of patients for each stage, class, and duration category of rheumatoid arthritis in our study were similar to those in two previous Japanese clinical studies of salazosulfapyridine.[14,15] This suggests no major differences in study populations between our study of iguratimod and the studies of salazosulfapyridine. We used placebo as an index of internal validity. Because some researchers reported that the ACR 20 response rate for the placebo group was 11.3% (9/80) and 28.6% (26/91),[16,17] our placebo group (ACR 20 response rate, 17.2%) seems to have served as an appropriate index of internal validity.

The superiority of iguratimod to placebo in efficacy was demonstrated in not only the superiority analysis population but also the full analysis set (139 patients of the iguratimod group and 72 patients of the placebo group) that included patients who were excluded from the superiority analysis population because of either violation of inclusion criteria or fulfillment of any exclusion criteria for efficacy considerations.

Our study demonstrated that the efficacy of iguratimod was not lower than salazosulfapyridine by more than 10%. ACR 20 core set data improved in both the iguratimod group and the salazosulfapyridine group, and the mean change from baseline in modified Health Assessment Questionnaire scores for the iguratimod group was similar to that for the salazosulfapyridine group. These results suggest that iguratimod is expected to improve the quality of life in patients with rheumatoid arthritis. For immunological tests (measurement of blood concentrations of rheumatoid factor, IgG, IgM, and IgA), the improvement in immunological data in the iguratimod group was significantly greater than that in the placebo group. Our study definitely demonstrated that iguratimod improved immunological data including blood IgM concentrations. This improvement seems to result from the immunomodulating effect of iguratimod on B lymphocytes.

Changes from baseline in the ACR 20 response rate determined every 4 weeks and the rate of 17.2% for the placebo group suggest that iguratimod began exhibiting its therapeutic effect within 8 weeks after the initiation of treatment. Because the rate was 61.3% for patients who had a poor response to previous DMARD therapy in the iguratimod group, iguratimod could be effective in such patients.

The assessment of progression of articular destruction revealed no statistically significant difference in efficacy between the iguratimod group and the salazosulfapyridine group or between the iguratimod group and the placebo group. This result can be explained by three characteristics of the study. First, the number of evaluable patients was insufficient for the assessment because the primary objective of the study was not to assess the progression of articular destruction. Second, the study period (6 months) was short for the assessment. Finally, most of the patients in the study had advanced rheumatoid arthritis with articular destruction. Some researchers have reported that the progression of articular destruction is best assessed in patients with early rheumatoid arthritis in which bone erosion is not involved.[18,19] In future studies, patients with early rheumatoid arthritis should be selected as the patient population to assess inhibitory effects of iguratimod on articular destruction.

No statistically significant difference was noted in the incidence of adverse events or reactions between the iguratimod group and the salazosulfapyridine group. Adverse event profiles, however, differed between the two groups.