研究成果の刊行に関する一覧表（平成27年度）

研究分担者氏名：　深　江　　淳

書籍

	著者氏名	論文タイトル名	書籍全体の編集者名 書籍名	出版社名 出版地	出版年 ページ
1	深江　淳	関節リウマチ診療における超音波検査装置へのニーズ	骨・関節・軟骨治療のための新製品開発と臨床ニーズ	株）技術情報協会 東京	2015 173-177
2	深江　淳	治療効果判定における超音波の有用性	監修：川上　純 リウマチ診療のための関節エコー活用ガイド	診断と治療社 東京	2015 72-76
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研究成果の刊行に関する一覧表（平成27年度）

研究分担者氏名：　松　下　　功

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
1	Ito H, Kojima M, Nishida K, Matsushita I, Kojima T, Nakayama T, Endo H, Hirata S, Kaneko Y, Kawahito Y, Kishimoto M, Seto Y, Kamatani N, Tsutani K, Igarashi A, Hasegawa M, Miyasaka N, Yamanaka H.	Postoperative complications in patients with rheumatoid arthritis using a biological agent - A systematic review and meta-analysis.	Mod Rheumatol.	25(5)	672-8	2015
2	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.	Aug 12	1-5. [Epub ahead of print]	2015
3	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.	Oct 12	1-6. [Epub ahead of print]	2015
4	松下　功	今後の新薬・新たに期待される薬剤.	関節外科	34	108-14	2015
5	松下　功	学会を聞く　第29回日本整形外科学会基礎学術集会	整形外科	66	286-8	2015
6	元村　拓、松下　功、下条竜一、木村友厚	滑膜組織における病理学的所見と超音波パワードップラー信号.	臨床リウマチ	27	40-50	2015
7	元村　拓、松下　功、木村友厚	疾患活動性を厳密にコントロールした関節リウマチ患者に対する関節温存前足部形成術.	中部整形災害外科学会誌	58	311-2	2015
8	松下　功、元村 拓、今西理恵子、木村友厚	Short taper wedge 型ステムを用いたセメントレス人工股関節置換術の臨床成績とX線学的評価　－RAとOAの比較検討－.	日本人工関節学会誌	45	833-4	2015
9	今西理恵子、松下　功、元村 拓、木村友厚	JHEQを用いたTHA術後早期の臨床評価.	Hip Joint	41	159-62	2015
10	廣川達郎、元村拓、松下 功、木村友厚	両足関節破壊をきたした分類不能関節炎の1例.	整形外科	66	1373-6	2015
11	浦田隆司、長田龍介、頭川峰志、元村拓、松下　功、木村友厚	非定型大腿骨骨折に対して大腿骨内側顆からの有茎薄骨移植を行った1例.	整形外科	66	1177-80	2015
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	著者氏名	論文タイトル名	書籍全体の編集者名 書籍名	出版社名 出版地	出版年 ページ
1	松下　功	骨びらん・軟骨障害	川上　純 リウマチ診療のための関節エコー活用ガイド	診断と治療社 東京	2015 52-56
2	松下　功	運動器の外科的療法	日本リウマチ学会・日本リウマチ財団 リウマチ病学テキスト	診断と治療社 東京	2015 452-457
3	松下　功	骨破壊のメカニズム（関節リウマチ）	 骨・関節・軟骨治療のための新製品開発と臨床ニーズ	技術情報協会 東京	2015 41-44
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Original article

Biologic-free remission of established rheumatoid arthritis after discontinuation of abatacept: a prospective, multicentre, observational study in Japan

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Abstract

Objective. The aim of this study was to determine whether biologic-free remission of RA is possible with discontinuation of abatacept.

Methods. Japanese RA patients in 28-joint DAS with CRP (DAS28-CRP) remission (<2.3) after >2 years of abatacept treatment in a phase II study and its long-term extension entered this 52 week, multicentre, non-blinded, prospective, observational study. At enrolment, the patients were offered the option to continue abatacept or not. The primary endpoint was the proportion of patients who remained biologic-free at 52 weeks after discontinuation. Clinical, functional and structural outcomes were compared between those who continued and those who discontinued abatacept.

Results. Of 51 patients enrolled, 34 discontinued and 17 continued abatacept treatment. After 52 weeks, 22 of the 34 patients (64.7%) remained biologic-free. Compared with the continuation group, the discontinuation group had a similar remission rate (41.2% *vs* 64.7%, $P=0.144$) although they had a significantly higher mean DAS28-CRP score at week 52 (2.9 *vs* 2.0, $P=0.012$). The two groups were also similar with regard to mean HAQ Disability Index (HAQ-DI) score (0.6 for both, $P=0.920$), mean change in total Sharp score (ΔTSS; 0.80 *vs* 0.32, $P=0.374$) and proportion of patients in radiographic remission ($\Delta TSS \leqslant 0.5$) at the endpoint (64.3% *vs* 70.6%, $P=0.752$). Those attaining DAS28-CRP < 2.3 or < 2.7 without abatacept at the endpoint had significantly lower HAQ-DI score and/or CRP at enrolment. Non-serious adverse events occurred in three patients who continued or resumed abatacept.

Conclusion. Biologic-free remission of RA is possible in some patients after attaining clinical remission with abatacept. Lower baseline HAQ-DI or CRP may predict maintenance of remission or low disease activity after discontinuation of abatacept.

Trial registration: UMIN Clinical Trials Registry, http://www.umin.ac.jp/ctr/ (UMIN000004137).

Key words: rheumatoid arthritis, abatacept, biologic-free remission, observational study.

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Introduction

RA is a systemic inflammatory disease characterized by polyarthritis and progressive joint destruction. In RA, synovial monocyte-/macrophage-like cells and dendritic cells serve as antigen-presenting cells (APCs) due to their expression of antigen-MHC class II complexes and co-stimulatory molecules such as CD80 and CD86 [1]. Activated $CD4^+$ T cells expressing CD28 significantly infiltrate into the synovial membrane of affected joints and exacerbate synovitis and joint destruction by secreting inflammatory cytokines and activating synovial cells and osteoclasts [2–4]. The activation of $CD4^+$ T cells is therefore an important stage in the development of rheumatic synovitis, with the CD28-mediated co-stimulatory signal being required for full T cell activation and playing a major role in the immunopathological process of RA.

Abatacept is a genetically engineered humanized fusion protein consisting of the extracellular domain of human cytotoxic T lymphocyte-associated molecule 4 (CTLA-4) connected to a modified Fc region (hinge-CH2-CH3 domain) of human immunoglobulin G-1. Abatacept is a novel anti-rheumatic drug that acts by modulating the activation of naive T cells through the competitive binding of co-stimulation molecules expressed on APCs (CD80 and CD86) and blockade of $CD4^+$ T cell co-stimulation via CD28 [5].

Abatacept has been reported to control disease activity, prevent or delay joint destruction and improve quality of life [6–12]. Further, abatacept exhibits similar efficacy in Japanese MTX-intolerant patients with active RA, achieving clinical remission [28-joint DAS with CRP (DAS28-CRP) <2.6] in 24.6% of patients after 24 weeks [7]. Due to the high cost of biologic DMARDs and concerns regarding their long-term safety, the potential for biologic-free remission has been identified as an issue for further investigation [13, 14]. No previous studies have addressed this potential therapeutic application of abatacept despite evidence of its ability to suppress $CD4^+$ T cell activation in autoimmune diseases such as RA.

Thus we conducted the present study in Japanese RA patients who had completed a phase II study of abatacept [7] and its long-term extension in order to determine whether clinical remission attained with the drug was sustained following its discontinuation.

Methods

Before enrolment in this study, written informed consent was obtained from each participating patient according to the Declaration of Helsinki (updated 2008). Prior to the start of the study, the institutional review board of each centre reviewed and approved the study.

Study design and patients

In the previous phase II study [7], 194 Japanese RA patients received double-blind treatment with abatacept or placebo for 24 weeks in addition to prior MTX therapy and 174 of them entered its long-term extension and received open-label abatacept for a mean of 37.7 months (range 3.6–45.1). Those who had completed the phase II study [7] and its long-term extension were eligible for this multicentre, non-blinded, prospective, observational study if they were in clinical remission (DAS28-CRP < 2.3) and not receiving any other biologic therapy at enrolment. Inclusion criteria for the phase II study were age $\geqslant 20$ years; fulfilment of the 1987 ACR criteria for the diagnosis of RA with a functional status of class I, II or III; previous treatment with MTX at 6–8 mg/week for at least 12 weeks and one or more of the following: $\geqslant 10$ swollen joints (66-joint count), $\geqslant 12$ tender joints (68-joint count) or CRP $\geqslant 1.0$ mg/dl.

Procedures

At enrolment, patients were offered the option to continue or discontinue abatacept during the study. Those who discontinued abatacept treatment (discontinuation group) were periodically followed up for disease activity. Those who chose to continue abatacept (continuation group) were treated with the drug every 4 weeks at its approved dosage and received similar follow-up. Abatacept could be restarted at a fixed dose of 10 mg/kg in response to a sign of relapse (DAS28-CRP > 2.7 at two consecutive visits) or at the investigator's discretion. If restarted after an interval of $\leqslant 12$ weeks, administration was every 4 weeks, whereas if started after an interval of >12 weeks, the first two doses were administered every 2 weeks and subsequent doses every 4 weeks.

During the study, dose modifications of non-biologic DMARDs (e.g. MTX) and glucocorticoids were allowed at the investigator's discretion. Concomitant administration of NSAIDs was permitted, but that of biologic agents was not.

Efficacy outcomes

The primary outcome measure of this study was the proportion of patients who remained biologic-free at 52 weeks after discontinuation of abatacept. Secondary and tertiary outcomes were efficacy and safety, respectively.

RA disease activity was assessed in terms of DAS28-CRP and DAS28-ESR at weeks 0, 4, 12, 24, 36 and 52. If a patient resumed abatacept treatment, this assessment was made at the time of resumption as well as after 12 and 24 weeks.

In accordance with DAS28-CRP scores, disease activity was classified as remission (< 2.3), low ($\leqslant 2.3$ to < 2.7), moderate ($\leqslant 2.7$ to < 4.1) or high ($\geqslant 4.1$) [15]. The proportion of patients in each disease activity class at each specified time and the proportion of patients in DAS28-CRP remission (< 2.3) at week 52 were calculated.

Similarly, disease activity was classified by DAS28-ESR as remission (< 2.6), low (LDA; $\leqslant 2.6$ to < 3.2), medium (MDA; $\leqslant 3.2$ to < 5.1) or high (HAD; $\geqslant 5.1$) [15]. To assess disease impact on a patient's level of functional ability, the HAQ Disability Index (HAQ-DI) was determined at weeks 0, 4, 12, 24, 36 and 52.

Radiographic progression of joint destruction was assessed in terms of van der Heijde-modified total Sharp score (mTSS) [16, 17] at weeks 0 and 52 or at the time of withdrawal from the study, where possible. Changes from baseline in TSS (ΔTSS), joint erosion (ΔJE) score and joint space narrowing (ΔJSN) score at week 52 were determined. The proportion of patients with no (ΔTSS $\leqslant$ 0), little (ΔTSS $\leqslant$ 0.5; defined as radiographic remission) and rapid radiographic progression (RRP; ΔTSS $\geqslant$5) [18] was calculated.

Time to abatacept treatment resumption

The mean time to resumption of abatacept treatment was determined in the discontinuation group.

Safety

Patients remaining on abatacept were monitored for adverse events (AEs) throughout the study period. In the discontinuation group, AE monitoring was done only if and after abatacept was resumed following relapse. To investigate the relationship between the immunogenicity of abatacept and its tolerability, the anti-abatacept antibody titre in blood was measured at the time of discontinuation, time of resumption and 24 weeks after resumption of abatacept, if applicable.

Statistical analysis

Missing data were imputed by linear extrapolation (radiographic assessments) or last observation carried forward (LOCF) (other efficacy variables). Continuous metric data were summarized in terms of descriptive statistics and were expressed as the mean (S.D.). Data between the two groups were compared using Wilcoxon's rank sum test (demographic and baseline characteristics, DAS28, HAQ-DI, ΔTSS, ΔJE and ΔJSN) or Fisher's exact test (proportion of patients in DAS28-CRP remission at week 52 and the proportions of patients with ΔTSS $\leqslant$0, $\leqslant$0.5 and $\geqslant$5).

Results

Patient disposition and baseline characteristics

Fifty-one consenting patients were enrolled and chose to either discontinue (n = 34) or continue (n = 17) abatacept. Nine of the 34 patients from the discontinuation group restarted abatacept at the investigator's discretion (n = 8) or due to relapse (n = 1). Six patients from the discontinuation group (with an additional patient withdrawn after resumption) and two from the continuation group dropped out of the study, leaving a total of 28 and 15 patients, respectively. Nineteen patients from the discontinuation group remained biologic-free at week 52 (Fig. 1). The demographic and baseline characteristics of the 51 patients enrolled are summarized in Table 1. The two groups had comparable baseline characteristics, except for significantly shorter disease duration and significantly less joint damage in terms of JSN and TSS in those who discontinued abatacept at enrolment ($P < 0.05$ for all comparisons).

Efficacy outcomes

Of the 34 patients who discontinued abatacept at enrolment, 22 patients from an intention-to-treat (ITT) analysis (64.7%) remained biologic-free after 52 weeks. While the mean DAS28-CRP score remained constant in the continuation group, it gradually increased over time in the discontinuation group, leading to a significant difference between the groups at week 52 (2.9 *vs* 2.0, P = 0.012).

This was also true when the subgroup of discontinuing patients who remained in the study and never restarted

FIG. 1 Patient disposition

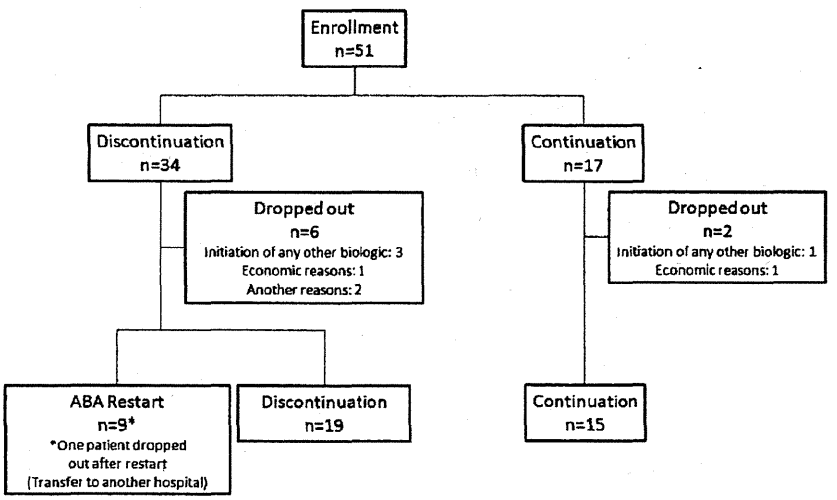


TABLE 1 Patient characteristics

	Discontinuation ($n = 34$)	Continuation ($n = 17$)	*P*-value
Age, mean (S.D.), years	56.9 (11.4)	60.9 (9.5)	0.195[a]
Male, *n* (%)	5 (14.7)	4 (23.5)	0.443[b]
Female, *n* (%)	29 (85.3)	13 (76.5)	
RA disease duration, mean (S.D.), years	9.6 (5.2)	15.3 (10.5)	0.018[a]
DAS28-CRP, mean (S.D.)	1.8 (0.4)	1.7 (0.5)	0.803[a]
Tender joint count (0–28), mean (S.D.)	0.3 (0.6)	0.1 (0.5)	0.788[a]
Swollen joint count (0–28), mean (S.D.)	0.5 (0.8)	0.6 (0.9)	0.429[a]
HAQ-DI, mean (S.D.)	0.5 (0.5)	0.5 (0.5)	0.356[a]
CRP, mean (S.D.), mg/dl	0.3 (0.5)	0.2 (0.2)	0.285[a]
ESR, mean (S.D.), mm/h	18.7 (9.5)	17.6 (8.5)	0.790[a]
DAS28-ESR, mean (S.D.)	2.4 (0.5)	2.3 (0.6)	0.705[a]
MMP-3, mean (S.D.), ng/ml	79.5 (63.3)[c]	75.3 (46.3)[d]	0.707[a]
RF, mean (S.D.), IU/ml	72.8 (128.5)[c]	50.7 (76.1)[e]	0.822[a]
RF positive, *n* (%)	14 (48.3)[c]	6 (60.0)[e]	0.394[b]
PGA (0–100 mm VAS), mean (S.D.)	12.7 (10.7)	17.4 (15.2)	0.363[a]
Erosion, mean (S.D.)	29.9 (37.9)[f]	62.0 (58.4)	0.015[a]
Joint space narrowing, mean (S.D.)	28.6 (27.2)[f]	55.5 (41.2)	0.020[a]
TSS (0–448), mean (S.D.)	58.5 (64.1)[f]	117.5 (97.7)	0.016[a]
Concomitant use of MTX, *n* (%)	19 (55.9)	12 (70.6)	1.000[a]
MTX dose, mean (S.D.), mg/week	6.7 (2.2)[g]	8.7 (2.3)[h]	0.211[a]
Concomitant use of PSL, *n* (%)	12 (35.3)	8 (47.1)	0.372[a]
PSL dose, mean (S.D.), mg/day	4.0 (2.8)[i]	3.9 (2.8)[j]	0.538[a]

PGA: patient's global assessment of disease activity; VAS: visual analogue scale; RF: rheumatoid factor; TSS: total Sharp score; PSL: prednisolone. [a]Wilcoxon's rank sum test; [b]Fisher's exact test; [c]$n = 29$; [d]$n = 14$; [e]$n = 10$; [f]$n = 28$; [g]$n = 17$; [h]$n = 12$; [i]$n = 9$; [j]$n = 8$.

abatacept ($n = 19$) were compared with the continuing patients remaining in the study ($n = 15$; 2.8 *vs* 2.1, $P = 0.036$).

Fig. 2 shows the proportion of patients in each RA disease activity class at specified times. In the discontinuation group there was a tendency towards a decrease in the proportion of patients in DAS28-CRP remission and an increase in the proportion of those with HDA as follow-up progressed. At week 52 (LOCF), the proportion of patients in remission was 41.2% in the discontinuation group compared with 64.7% in the continuation group ($P = 0.144$). Sixteen of the 17 continuing patients (94.1%) experienced no disease flare (DAS28-CRP < 2.7), while 20 of the 34 discontinuing patients (58.8%) were in remission or maintained LDA. Compared with the 14 patients who failed to do so, these 20 patients had significantly lower baseline HAQ-DI scores and CRP ($P = 0.036$ and $P = 0.048$, respectively). Of the 19 patients who went without abatacept for 52 weeks, 7 were in remission at the endpoint and 12 were not. These two subgroups had comparable baseline characteristics, except that more patients in remission than not in remission at the endpoint were in functional remission (HAQ-DI $\leqslant 0.5$) at enrolment (100% *vs* 41.7%, $P = 0.016$). The mean time-averaged DAS28-CRP (TA-DAS28-CRP) [19, 20] was 1.9 (S.D. 0.4) for those who maintained LDA compared with 3.0 (S.D. 0.7) for those who failed to do so ($P < 0.0001$).

In contrast to consistently low (<2.6) scores in the continuation group, the mean DAS28-ESR score in the discontinuation group increased slightly, from 2.4 at baseline to 2.7 at week 4, 3.1 at week 12, 3.3 at week 24, 3.5 at week 36 and 3.6 at week 52. According to the endpoint DAS28-ESR scores, 24.2% of the discontinuing *vs* 47.1% of the continuing patients were in remission, 30.3% *vs* 35.3% had LDA, 27.3% *vs* 17.6% had MDA and 18.2% *vs* 0% had HDA. The mean HAQ-DI scores for the two groups followed similar time courses and were 0.6 for both groups at week 52 ($P = 0.920$; Fig. 3).

The TSS at weeks 0 and 52 was similar in the discontinuation and continuation groups, but the baseline TSS was higher for the continuation group (Fig. 4A). Mean ΔTSS (0.80 *vs* 0.32, $P = 0.374$) and ΔJE (−0.02 *vs* 0.32, $P = 0.466$) were similar for the two groups, while mean ΔJSN was significantly greater in the discontinuation group (0.82 *vs* 0, $P = 0.035$; Fig. 4B). After correction by linear extrapolation, the proportion of patients in radiographic remission (ΔTSS $\leqslant 0.5$) was 64.3% in the discontinuation group compared with 70.6% in the continuation group ($P = 0.752$; Fig. 4C). No radiographic progression was seen in 42.9% and 47.1% of patients, while RRP was seen in 14.3% and 0% of patients in the discontinuation and continuation groups, respectively (Fig. 4C). The four patients who showed RRP after discontinuation had significantly higher CRP at enrolment in this study and lower RF in the previous phase III study compared with the 24 patients who did not show RRP in this group ($P = 0.034$ and $P = 0.020$, respectively).

FIG. 2 Proportion of disease activity

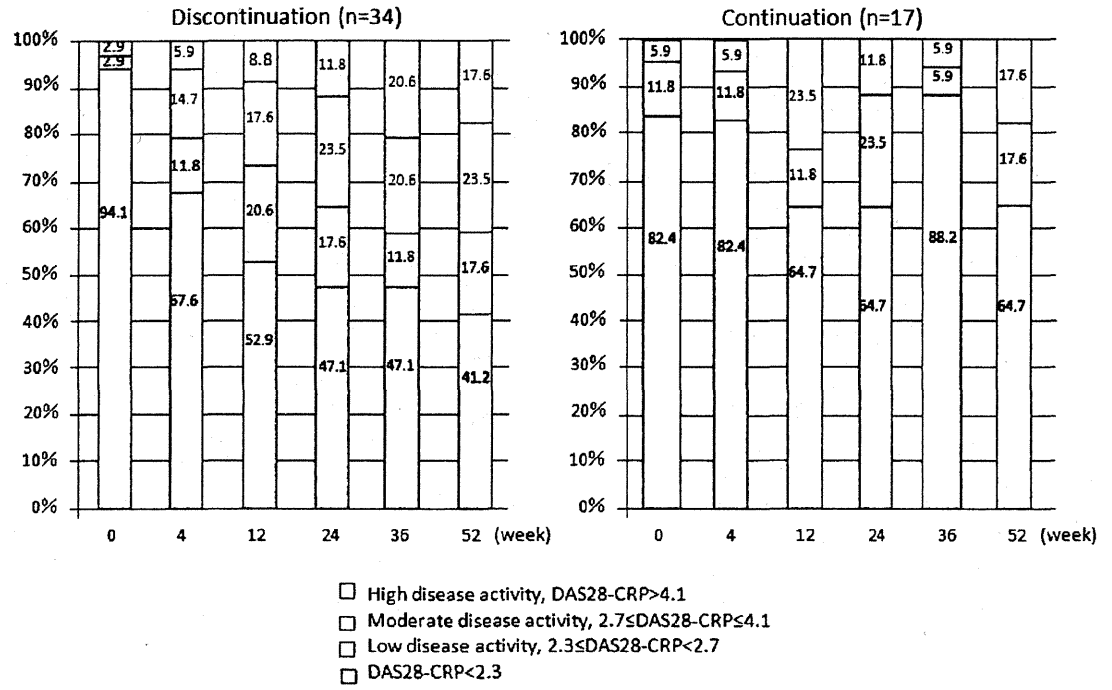
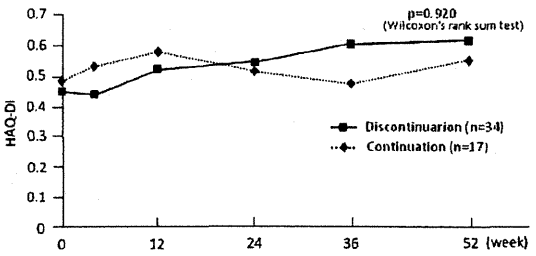


FIG. 3 Transition diagram of HAQ-DI



DI: Disability Index.

In the discontinuation group, 10 of the 14 patients in DAS28-CRP remission at week 52 were evaluable for ΔTSS, of whom 7 (70%) were in radiographic remission. In the continuation group, all 11 patients in DAS28-CRP remission at week 52 were evaluable for ΔTSS and 7 (63.6%) were in radiographic remission.

Resumption of abatacept treatment

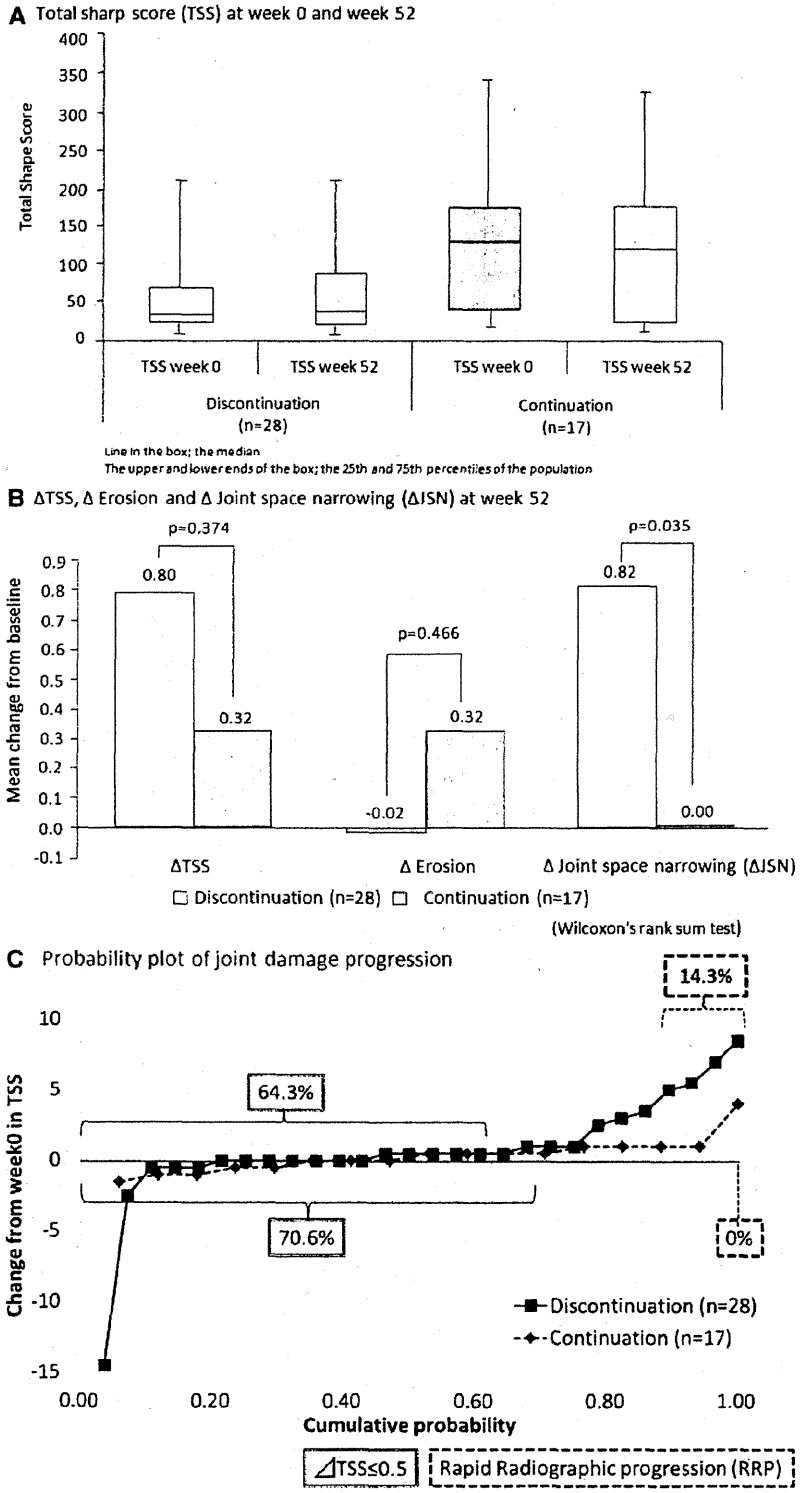
Nine patients resumed abatacept treatment after a mean interval of 149.6 days (S.D. 34.5). After resumption, the mean DAS28-CRP score steadily decreased, from 5.0 (S.D. 1.1) to 3.7 (S.D. 1.6) at 12 weeks and to 3.7 (S.D. 1.7) at 24 weeks, as was observed in the previous phase II/III study [from 4.8 (S.D. 0.8) at baseline to 3.0 (S.D. 0.9) at week 12 and to 2.8 (S.D. 0.9) at week 24; not significant by Wilcoxon's rank sum test].

In the previous study, time to remission in those who resumed ($n = 9$) and did not resume ($n = 25$) abatacept was similar ($P = 0.643$; log rank test); clinical remission was achieved in 2 of 9 (22.2%) *vs* 13 of 25 (52.0%) patients at week 24 and in 88.9% *vs* 96.0% of patients at the endpoint, respectively. The two populations also had comparable demographic and baseline characteristics.

Safety

Non-serious AEs occurred in one patient who resumed abatacept (acute upper respiratory tract infection) and two patients who continued the drug (acute bronchitis in one and low back pain, cystitis, constipation, common cold and left scapulohumeral periarthritis in the second). No serious AEs were reported. Anti-abatacept antibody titre was measured in 26 of the 34 patients upon discontinuation of abatacept, as well as in 7 of 9 and 6 of 9 patients immediately and at 24 weeks after resumption. Positive titres were recorded in four patients (15.4%) upon discontinuation, in two patients (28.6%) immediately after resumption and in no patients at 24 weeks after resumption. Two of the four patients with positive titres upon discontinuation restarted abatacept. Both patients had positive titres again upon resumption, but not after 24 weeks. None of the patients with positive anti-abatacept antibody titre developed AEs or responded poorly to abatacept.

FIG. 4 Total Sharp score



Discussion

Accumulating evidence suggests that $CD4^+$ T cells play a key role in RA-associated inflammation [21–23], although the extent to which they contribute to this disease is not fully understood. Abatacept, which blocks a T cell co-stimulation pathway, has been shown to have favourable efficacy and tolerability profiles in Japanese and non-Japanese MTX-intolerant, TNFinhibitor-intolerant or MTX-naive [early (<2 years)] RA patients [7–12].

The ACR and European League Against Rheumatism treatment recommendations propose that remission or LDA should be the primary target for treatment of RA [24]. Combined therapy with currently available biologic and non-biologic DMARDs can help attain current treatment targets in the majority of RA patients. Nonetheless, the high costs of biologic agents have encouraged ongoing efforts to reduce the economic burden upon patients, including trials to discontinue biologic therapy in patients in sustained clinical remission. While existing data support the potential for biologic-free remission following intensive treatment with TNFinhibitors [25–28], definitive evidence for this potential following discontinuation of abatacept is limited. One study suggested that there was no further radiographic or MRI progression of joint destruction after discontinuation of abatacept in patients with undifferentiated inflammatory arthritis or very early RA [29]. Here we determined the potential of abatacept in promoting biologic-free remission in RA patients already in clinical remission.

At week 52, 64.7% of the patients who discontinued abatacept in an ITT population remained biologic-free (primary endpoint). In a drug-free follow-up of 102 RA patients (mean disease duration 5.9 years) who attained LDA with infliximab [25], 55% of the patients maintained LDA and 39 of the 83 patients (47%) who had achieved remission (DAS28 < 2.6) at enrolment remained in remission for 1 year. In a similar study for adalimumab [28], 14 of 22 patients (64%) maintained LDA (DAS28-CRP < 2.7) without the drug for 1 year. On comparison with these TNF inhibitors, abatacept seems to have a similar potential in the induction of biologic-free remission.

After discontinuation of abatacept, the mean DAS28-CRP score gradually increased and reached a level significantly higher than in the continuation group at week 52. This was also true when the mean endpoint DAS28-CRP score was compared between the 19 patients who went without abatacept and the 15 patients who continued the drug for 52 weeks. In the discontinuation group, the number of patients in DAS28-CRP remission decreased and the number of patients with HDA increased. HAQ-DI and CRP are two baseline parameters that were significantly different between those with ($n = 20$) and without ($n = 14$) LDA at week 52. In addition, HAQ-DI is the only baseline parameter that was significantly different between those in remission ($n = 7$) and those not in remission ($n = 12$) without abatacept at week 52. These findings suggest that the HAQ-DI or CRP immediately before discontinuation of abatacept may predict the probability of subsequent maintenance of remission or LDA. According to TA-DAS28-CRP data, those with LDA at the endpoint maintained LDA throughout the period of follow-up. Comparison between the discontinuation and continuation groups showed similar proportions of patients in clinical remission at week 52 and similar changes in the HAQ-DI over time, indicating that the effects of abatacept on clinical and functional outcomes are durable even after discontinuation.

In RA, joint destruction progresses over time, causing significant disability, which imposes an enormous social burden. Although the recently introduced biologic agents, including abatacept, can prevent or delay joint destruction in a proportion of patients, it is not known if they prevent disease relapse following discontinuation. In the present study, radiographic assessment of joint destruction showed no significant difference between those who discontinued and those who continued abatacept with regard to mean ΔTSS or the percentage of patients with ΔTSS $\leqslant 0$, $\leqslant 0.5$ or $\geqslant 5$. These data confirm that abatacept exerts a sustainable effect in preventing or delaying joint damage and thus keeps patients in radiographic remission even after discontinuation. These radiographic benefits of abatacept appear to be comparable to those of infliximab and adalimumab (in early RA), as evidenced by 67% [25] and 81% [27] of patients with LDA remaining in radiographic remission after discontinuation of those drugs.

As a proportion of RA patients have to suspend their biologic therapy for economic or other reasons, we also assessed the efficacy and safety of re-treatment with abatacept after relapse. Re-treatment with abatacept was effective in controlling disease activity but may be less effective than the initial treatment with abatacept, which was evaluated in the previous phase II study [7].

Abatacept was well tolerated after resumption and during extended use, with only non-serious AEs being reported in three patients. Regarding the immunogenicity of abatacept, two of the limited number of patients assessed were positive for anti-abatacept antibody at the resumption of treatment but were negative after 24 weeks. The disappearance of anti-abatacept antibody after resumption of abatacept treatment may reflect the immunomodulatory effect of the drug.

The present study has several limitations. First, this was an exploratory study about the possibility of biologic-free remission after attaining clinical remission with abatacept. This study had no hypothesis to be tested because no data were available about this possibility with any other biologic DMARDs when we planned this study. Second, this was a small, non-randomized, observational study. Only Japanese RA patients who had completed a phase II study of abatacept [7] and its long-term extension and were in DAS28-CRP remission (<2.3) were enrolled, and for ethical reasons they were offered the option to continue abatacept or not at enrolment. As an expected consequence, the two groups were not well matched at baseline; those who chose to discontinue the drug were at an earlier stage of RA and had less progressive joint damage. Therefore data comparing the two groups

should be interpreted cautiously. Third, we imputed missing data for non-radiographic efficacy variables using LOCF, a less favoured method than multiple imputation. This might introduce uncertainly about the reliability of the disease activity data and compromise their interpretation. Despite these limitations, the results are informative, as they indicate that the clinical remission achieved after abatacept treatment is potentially maintained following discontinuation of the drug in some of the patients, particularly in those who have also achieved a low HAQ-DI score and/or low CRP after the treatment. Given that the decision to continue or discontinue abatacept after attaining clinical remission was made by individual patients and their physicians, this finding will also be helpful for implementing the treat-to-target principle in RA practice.

Rheumatology key messages

- The effects of abatacept on clinical, functional and structural outcomes in RA continue after its discontinuation.
- Biologic-free remission of RA can be maintained after attaining sustained clinical remission with abatacept.
- Lower HAQ DI or CRP may predict maintenance of RA remission or low disease activity after discontinuation of abatacept.

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Assessment of Risks of Pulmonary Infection During 12 Months Following Immunosuppressive Treatment for Active Connective Tissue Diseases: A Large-scale Prospective Cohort Study

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ABSTRACT. ***Objective.*** Pulmonary infections (PI) are leading causes of death in patients with connective tissue diseases (CTD). The PREVENT study (Pulmonary infections in patients REceiving immunosuppressiVE treatmeNT for CTD) assessed risk of PI in patients with active CTD in the contemporary era of advanced immunosuppressive therapy.

Methods. In patients who started corticosteroids (n = 763), conventional immunosuppressants or biologics for active CTD were enrolled. Clinical and laboratory data, usage of drugs, and occurrence of PI were collected for 12 months. Baseline risk factors were investigated using Cox regression analysis. A nested case-control (NCC) study was performed with 1:2 matched case-control pairs to assess the risk for each drug category.

Results. During the observation period, 32 patients died (4.2%) and 66 patients were lost to followup (8.6%). Patients with PI (n = 61, 8%) had a significantly worse accumulated survival rate than patients without ($p < 0.01$). Cox hazard regression analysis using baseline data showed that these factors were significantly associated with PI: age ≥ 65 years (HR 3.87, 95% CI 2.22–6.74), ≥ 20 pack-years of smoking (2.63, 1.37–5.04), higher serum creatinine level (1.21, 1.05–1.41 per 1.0 mg/dl increase), and maximum prednisolone (PSL) dose during the first 2 weeks of treatment (2.81, 1.35–5.86 per 1.0 mg/kg/day increase). Logistic regression analysis by an NCC study revealed that maximum PSL dose within 14 days before PI (OR 4.82, 95% CI 1.36–17.01 per 1.0 mg/dl increase; 2.57, 1.28–5.16 if ≥ 0.5 mg/kg/day) was significantly associated with the events, while other immunosuppressants were not.

Conclusion. Physicians should be aware of the higher risks for corticosteroids of PI than other immunosuppressants and assess these risk factors before immunosuppressive treatment, to prevent PI. (First Release Feb 1 2015; J Rheumatol 2015;42:614–22; doi:10.3899/jrheum.140778)

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Treatment of connective tissue diseases (CTD) has advanced with the introduction of molecular-targeted therapies, such as biologics and new classes of immunosuppressants[1,2,3,4]. Corticosteroids, still indispensable for the treatment of CTD, as well as most of the new treatments have the potential to increase susceptibility to infection, and risk of infection should be compared across these medications within a single cohort. Among all infections, pulmonary infections (PI) are the most common and one of the leading causes of death in patients with CTD[5,6,7,8,9]; therefore prevention of PI is crucial for physicians treating these diseases.

To our knowledge, no authors have previously assessed specific risk factors for PI in patients with CTD, except for some reports from the rheumatoid arthritis (RA) population[10,11,12]. Assessment of risks of infection in patients with CTD is quite complicated and difficult to study because of the relatively low prevalence of the diseases and changes in immunosuppressive treatments over time. Only a few studies conducted in a population of single CTD cohorts have tried to resolve this clinical question[9,13,14,15]. However, many of the previous studies were retrospective in nature and did not include an adequate number of patients or infectious events for multivariate analyses. Results from single CTD cohorts cannot be generalized or applied to patients who receive similar immunosuppressive treatment for different CTD. It is also important to enroll patients with active-phase CTD when the immunosuppressive treatment starts or intensifies, and when the patients will be expected to be at the highest risk of PI. To overcome these restrictions, we conducted a large-scale, multicenter, prospective observational study (Pulmonary infections in patients REceiving immunosuppressiVE treatmeNT for CTD; PREVENT) and recruited patients with a variety of active CTD to identify risk factors for PI common to these patients.

In our study, we investigated incidence and characteristics of PI and risk factors for these life-threatening complications in patients receiving immunosuppressive treatments for active CTD, to establish milestone evidence and to ensure the safety of patients with CTD.

MATERIALS AND METHODS

Patients. Patients were eligible for enrollment in our study if they were admitted to participating hospitals for treatment of new-onset or relapsed CTD and if their attending physicians started 1 or a combination of the following 4 immunosuppressive treatments: (1) prednisolone (PSL) or other corticosteroids, (2) methylprednisolone (mPSL) pulse therapy, (3) conventional immunosuppressants, or (4) biologics. Patients who were receiving or had received immunosuppressive treatments were also eligible if they started any of the 4 treatments or increased the dose of corticosteroids or conventional immunosuppressants. Types of CTD and immunosuppressive treatments eligible for enrollment are summarized in Supplementary Table 1 (available online at jrheum.org). Ten university hospitals and 5 referring hospitals in Japan participated in our study and patients were enrolled from June 2008 to December 2010. This study was approved by the ethics committee of the Tokyo Medical and Dental University Hospital (TMDU) and those of the participating institutions. Written informed consent was obtained from each patient.

Data collection. We collected a predefined case report form at baseline, Month 6, and Month 12 after enrollment. We also collected demographic data and clinical data for CTD at baseline, data for candidate risk factors for PI at baseline and Month 6, and types and doses of administered medication and clinical course of CTD throughout the observation period. Candidate risk factors for PI were selected based on previous reports[16,17,18,19,20,21,22] conducted in both general populations and patients with CTD[10,11], and are summarized in Table 1. When patients developed PI, clinical, laboratory, and imaging data were collected to validate diagnoses of PI by the event-monitoring committee. All data were

Table 1. Baseline characteristics of patients from the PREVENT cohort[a]. Values are mean ± SD or % unless otherwise specified.

Variable	Infection Group, n = 61	Noninfection group, n = 702	p	Adjusted HR (95% CI)
Age, yrs	65.8 ± 13.1	52.1 ± 18.1	0.03	1.05 (1.03–1.07)
Age ≥ 65 yrs old	63.9	29.2	< 0.01	4.01 (2.37–6.80)
Female sex	62.3	75.1	0.03	0.69 (0.41–1.16)
Body weight, kg	52.6 ± 9.8	54.0 ±10.9	0.63	0.99 (0.96–1.02)
Disease duration, mos	42.2 ± 75.8	57.8 ± 90.1, n = 701	0.09	0.98 (0.99–1.01)
Incident use of immunosuppressive therapy	65.6	50.3	0.02	1.83 (1.08–3.10)
Ever smoker	45.9	33.5, n = 701	0.06	1.59 (0.85–2.97)
≥ 20 pack-yrs of smoking[b]	41.0	17.5, n = 695	< 0.01	2.42 (1.28–4.56)
Concurrent nonserious infection	4.9	3.1	0.45	1.14 (0.36–3.68)
Resolved serious infection within 6 mos	4.9	1.3	0.03	2.76 (0.86–8.86)
Performance status ≥ 3[c]	24.6	11.8	< 0.01	1.83 (1.01–3.32)
Dysphagia	4.9	2.3	0.24	2.56 (0.80–8.20)
Heart failure	6.6	3.3	0.18	2.04 (0.74–5.66)
Diabetes mellitus	26.2	14.4	0.01	1.19 (0.66–2.14)
Previous pulmonary tuberculosis[d]	14.8	5.3	< 0.01	1.72 (0.83–3.56)
Any pulmonary comorbidity	59.0	36.0	< 0.01	1.49 (0.87–2.53)
Interstitial pneumonia	42.6	25.7	< 0.01	1.34 (0.80–2.25)
COPD	8.2	2.1	< 0.01	2.25 (0.85–5.93)
Serum creatinine, mg/dl	1.08 ± 1.35	0.74 ± 0.67, n = 701	0.01	1.24 (1.07–1.44)
Serum albumin, mg/dl	3.15 ± 0.65, n = 60	3.33 ± 0.68, n = 694	0.03	0.83 (0.56–1.24)
Pneumococcal vaccine[e]	6.6	7.5	0.77	0.14 (0.17–0.29)
Influenza vaccine[f]	26.2	22.9	0.56	1.09 (0.62–1.93)
Medication during the first 14 days of immunosuppressive treatment				
Maximum PSL dose[g], mg/kg/day	0.83 ± 0.34	0.68 ± 0.41	0.02	4.06 (2.03–8.14)
Use of ≥ 0.5 mg/kg/day of PSL, yes[h]	85.2	65.3	< 0.01	3.69 (1.82–7.50)
Use of mPSL pulse therapy, yes[h]	26.2	17.1	0.07	2.00 (1.13–3.55)
Use of conventional immunosuppressants[i], yes[h]	29.5	43.7	0.03	0.60 (0.34–1.04)
Use of biologics[i], yes[h]	11.5	18.7	0.16	0.48 (0.22–1.06)
Diagnosis				
SLE	18.0	28.9	0.07	1.71 (1.03–2.85)[j]
RA	18.0	27.1		
Vasculitis	31.1	14.7		
PM/DM	19.7	14.7		
AOSD	4.9	5.7		
MCTD	3.3	2.8		
SSc	3.3	2.1		
Behçet's disease	0.0	1.6		
SS	1.6	1.1		

[a] Patients who developed (infection group) and did not develop PI (noninfection group) were compared. The Mann-Whitney U test was used for continuous measures, and the chi-square test for categorical measures to calculate p values between the infection group and the noninfection group. Corrections for multiple comparisons were not applied and p values were provided to show magnitude of difference between the 2 groups. The age- and sex-adjusted HR for development of PI was calculated for each variable using Cox proportional hazard regression analysis. [b] Pack-years of smoking: packs smoked per day × yrs as a smoker. [c] Performance status was evaluated using the Eastern Cooperative Oncology Group performance status. [d] Previous pulmonary tuberculosis includes suspected case. [e] Patients who were given pneumococcal vaccine before enrollment and during the observation period were included in calculation of percentages. Patients who were given pneumococcal vaccine after development of PI were excluded from the calculation. [f] Patients who were given influenza vaccine within 6 months before enrollment and during the observation period were included in calculation of percentages. Patients who were given influenza vaccine after development of PI were excluded. [g] Maximum PSL dose during the first 14 days of immunosuppressive therapy. The dose of corticosteroids other than PSL was substituted for the equivalent dose of PSL for analysis[23]. [h] Use of > 0.5 mg/kg/day of PSL, mPSL pulse therapy, conventional immunosuppressants, and biologics during the first 14 days of immunosuppressive therapy were included. [i] Included immunosuppressants and biologics are shown in Supplementary Table 1 (available online at jrheum.org). [j] HR of vasculitis and PM/DM versus other CTD was calculated. PREVENT: Pulmonary infections in patients REceiving immunosuppressiVE treatmeNT for CTD; COPD: chronic obstructive pulmonary disease; PSL: prednisolone; mPSL: methylprednisolone; Ig: immunoglobulin; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; PM: polymyositis; DM: dermatomyositis; AOSD: adult-onset Still's disease; MCTD: mixed connective tissue diseases; SSc: systemic sclerosis; SS: Sjögren syndrome; PI: pulmonary infections; CTD: connective tissue diseases.

submitted by the site investigators to the PREVENT Data Center at the Department of Pharmacovigilance of TMDU. Two authors (HY and RS) visited 4 institutions for source data validation after all data were collected. These institutions contributed 55.5% of the total enrollment of our study. Minor errors were found in 2.0% of the data collected; all data were corrected before finalizing the database and performing analyses.

Definition of PI. PI of interest were defined at the beginning of our study to include bacterial, atypical, *Pneumocystis jirovecii*, cytomegalovirus, and

mycotic pneumonias; pulmonary tuberculosis (TB), pleuritis, lung abscess, and other clinically important PI reported by site investigators. The validity of the diagnosis for PI was assessed by the event-monitoring committee consisting of 2 rheumatologists (RK and MH), a pulmonologist (YM), and an infection specialist (RK). The event-monitoring committee scrutinized all data of PI cases reported, and patients were accepted as having PI only when the committee confirmed the diagnosis of site investigators. The diagnosis of PI was made by the presence of new infiltrates, consolidation, ground-glass opacity, or effusion seen using chest radiography or computed tomography, along with suggestive clinical features and laboratory findings. The results of bacterial cultures of blood or sputum were also used for the diagnosis of PI, if detected.

Statistical analysis. The primary objective of our study was to identify risk factors using multivariate analyses for the development of PI in patients with CTD given immunosuppressive treatment. We expected to identify 5 or 6 significant risk factors, requiring at least 50 cases with PI to perform multivariate analyses with appropriate statistical power. Based on our unpublished data, we assumed that 7% of the enrolled patients would develop PI and that 5% of the patients would be lost to followup by Month 12. The targeted number of patients enrolled was therefore set at 750.

The start of the observation period was the date when 1 of the 4 categories of immunosuppressive treatments began (Supplementary Table 1, available online at jrheum.org). Observation ended either 12 months later, or on the day a patient died or was lost to followup, whichever came first. We identified independent risk factors for the development of PI, first by comparing baseline characteristics of the patients with and without PI using univariate analyses. Second, we performed multivariate Cox regression analyses to identify risk factors among baseline data for the development of PI. Third, because drugs and doses of immunosuppressive treatments substantially changed over time, we then used a nested case-control (NCC) study to assess the risk of each category of medication for the development of PI more precisely.

The chi-square test for categorical variables and the Student t test or Mann-Whitney U test for continuous variables were used for comparisons between groups. Missing categorical variables constituted only 0.08% of all categorical variables. Missing continuous variable values, 1.4% of all continuous variables, were substituted with the mean value of the corresponding variables. Variables included in the Cox regression model were chosen based on the results of the age- and sex-adjusted HR and 95% CI of each variable for the development of PI. Collinearity and medical significance of the variables were also considered for selection.

In the NCC study, we used a risk-set sampling design to select control patients. For each patient who developed PI (the case group), 2 age-matched (± 1 yr), sex-matched, and disease classification–matched patients who had not developed PI during the same length of observation periods were randomly selected as the control group. For this matching, CTD listed in Supplementary Table 1 (available online at jrheum.org) were classified into articular RA (i.e., RA treated for active arthritis with no active extraarticular involvement) or others (i.e., other CTD or RA treated for extraarticular involvement) because patients with articular RA used fewer corticosteroids and more biologics compared to others (mean ± SD PSL dose: 0.07 ± 0.08 vs 0.84 ± 0.31 mg/kg/day, use of biologics: 82.5% vs. 3.2%, observed during the first 14 days of immunosuppressive therapy). The observation period for the NCC study of a matched pair was defined using the length from the start of immunosuppressive treatment to onset of a PI. We assessed the risk of medications that were administered during the 14 days at the end of the observation period for the NCC study using univariate and multivariate logistic regression analyses. SPSS was used (version 18.0, SPSS Inc.). All p values were 2-tailed and $p < 0.05$ was considered statistically significant.

RESULTS

Patient disposition. Among 774 enrolled patients, 11 were excluded and baseline data were acquired from 763 (Figure

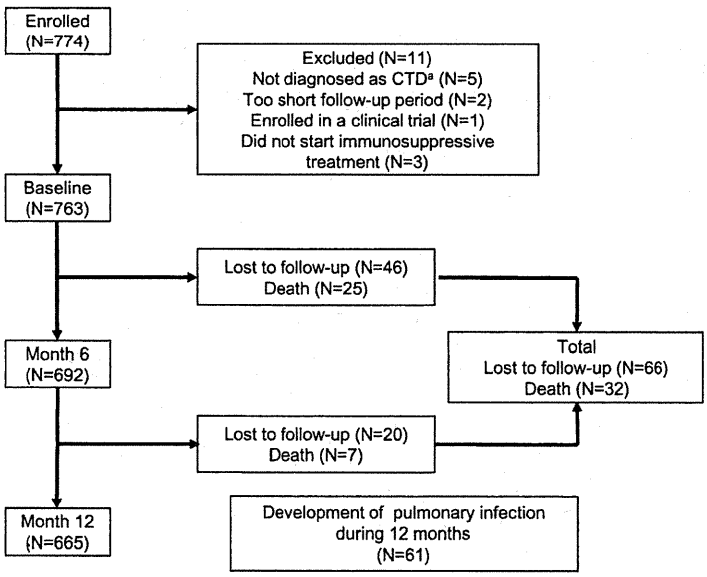

Figure 1. Patient disposition of the PREVENT cohort. Of the 774 patients who were registered in the PREVENT for CTD cohort, baseline data were acquired for 763 patients. Sixty-six patients were lost to followup and 32 patients died by Month 12; the remaining 665 patients completed 12 months of observation. Sixty-one patients developed pulmonary infection confirmed by the event-monitoring committee. [a]CTD denotes connective tissue disease. PREVENT: Pulmonary infections in patients REceiving immunosuppressiVE treatmeNT for CTD.

1). Sixty-six patients were lost during the followup and 32 patients died by Month 12. The mean ± SD and median observation periods of all patients were 334 ± 86 and 365 days; for those lost to followup, 136 ± 105 and 124 days; and for those who died were 114 ± 87 and 97 days. PI were reported by site investigators in 81 patients. Among these, the event-monitoring committee confirmed 61 infections after thorough reviews of the data.

Baseline characteristics of the patients. Baseline characteristics of patients who developed PI (infection group, n = 61) and those who did not (noninfection group, n = 702) are summarized in Table 1. The infection group was older and had fewer women, higher rates of incident use of immunosuppressive treatment, more patients with ≥ 20 pack-years of smoking, more resolved serious infections within the 6 months prior to enrollment, and poorer Eastern Cooperative Oncology Group performance status (ECOG PS ≥ 3) than the noninfection group. Also observed in the infection group was higher prevalence of diabetes mellitus, previous pulmonary TB, interstitial pneumonia, and chronic obstructive pulmonary disease. Diagnoses of vasculitis and polymyositis/dermatomyositis were associated with the infection group. The infection group had higher mean serum creatinine and lower serum albumin levels, while other laboratory data did not differ significantly (Supplementary Table 2, available online at jrheum.org). The infection group was given a higher maximum PSL dose and used fewer conventional immunosuppressants during the first 14 days of their immunosuppressive treatment. The use of each conventional immunosuppressant and biologic during the first 14 days and for the whole observation period is shown in Supplementary Table 3 (available online at jrheum.org). P values were not corrected for multiple comparisons.

Development and prognosis of PI. Development of PI was more conspicuous within 3 months after the initiation of the immunosuppressive treatment. Thirty-three patients (54.1%) developed PI by Month 3 (Supplementary Figure 1, available online at jrheum.org). Percentages of each PI are summarized in Table 2. Twenty-five patients developed bacterial pneumonia and 20 developed *P. jirovecii* pneumonia (PCP), which accounted for 41.0% and 32.8% of total PI, respectively. Of the 20 patients who developed PCP, only 3 had prophylaxis for PCP with monthly aerosolized pentamidine. Opportunistic infections, including PCP, mycotic pneumonia, cytomegalovirus pneumonia, and pulmonary TB were reported in 34 of the 763 patients (4.5%). Three patients who developed pulmonary TB did not show evidence of previous pulmonary TB on chest radiographs at baseline and did not receive chemoprophylaxis, while 105 patients who received chemoprophylaxis did not develop pulmonary TB.

Table 2. Types of pulmonary infections (PI)*.

Types of PI	n (%)
Bacterial pneumonia	25 (41.0)
Pneumocystis pneumonia	20 (32.8)
Mycotic pneumonia	5 (8.2)
Cytomegalovirus pneumonia	3 (4.9)
Pulmonary tuberculosis	3 (4.9)
Mixed infection, bacterial and mycosis	3 (4.9)
Pyothorax	2 (3.3)
Total	61 (100)

* Of the 81 reported PI cases reviewed by the event-monitoring committee, 61 patients were confirmed to have PI.

Table 3. Causes of death*.

Causes of Death	n (%)
Exacerbation of interstitial pneumonia	14 (43.8)
Sepsis	3 (9.4)
Malignancy	3 (9.4)
Pneumonia	3 (9.4)
Acute heart failure	3 (9.4)
Pulmonary hemorrhage	2 (6.3)
Acute liver failure	2 (6.3)
Perforation of gastric ulcer	1 (3.1)
Unknown	1 (3.1)
Total	32 (100)

* Thirty-two patients died during the observation period. Causes of death were confirmed by case report forms, additional information provided by each participating hospital, and discharge summaries.

Vital prognosis. Thirty-two patients died during the observation period; the causes of their deaths are summarized in Table 3. Causes of death were confirmed using case report forms, additional information provided by site investigators, and discharge summaries. Among the 32 patients who died, 8 patients developed PI and 3 died of pneumonia. Among the remaining 5 other patients who developed PI, 4 patients died of exacerbation of interstitial pneumonia and 1 patient died of sepsis. All of these 5 patients died subsequently to PI during the same admission, except for 1 patient who died of exacerbation of interstitial pneumonia. In the noninfection group, 24 patients died. Exacerbation of interstitial pneumonia was the most frequently reported cause of death (n = 10) in the noninfection group. Age-adjusted and sex-adjusted HR of PI for death using Cox regression analysis was significantly elevated (HR 5.25, 95% CI 2.23–12.35).

Independent risk factors for PI. We constructed Cox regression models to identify risk factors for PI. We initially calculated the age-adjusted and sex-adjusted HR for each variable for the development of PI (Table 1). Lower ends of 95% CI of HR were higher than 1.0 for age ≥ 65 years, incident use of immunosuppressive therapy, ≥ 20 pack-years of smoking, ECOG PS ≥ 3, serum creatinine levels, maximum PSL dose, use of PSL > 0.5 mg/kg/day, and use of mPSL pulse therapy during the first 14 days of immuno-

suppressive treatment. We subsequently included these variables and sex in the final Cox regression model (Table 4). Age ≥ 65 years (HR 3.87, 95% CI 2.22–6.74), ≥ 20 pack-years of smoking (2.63, 1.37–5.04), serum creatinine (1.21, 1.05–1.41, per 1.0 mg/dl increase), and maximum PSL dose during the first 14 days of the immunosuppressive treatment (2.81, 1.35–5.86, per 1.0 mg/kg/day increase) were significantly associated with PI. Other statistical models that included use of conventional immunosuppressants and biologics during the first 14 days of immunosuppressive treatment or CTD diagnosis showed essentially the same results (data not shown).

NCC study to identify the risk of medication on the development of PI. Because 45.9% of the PI developed at or after Month 4 of the observation period (Supplementary Figure 1) and immunosuppressive treatments changed substantially during the observation period in each patient, prediction of PI using baseline medications may not be sufficient. To overcome this, we implemented an NCC study to cautiously and precisely evaluate the association of treatment with PI. Among 61 patients in the infection group, 1 patient failed to match with appropriate control patients. The remaining 60 patients (case group) were successfully matched with 120 patients from the noninfection group (control group). Baseline characteristics and diagnosis of CTD were not significantly different between the groups. We compared medications used during the 14 days at the end of the observation period for the NCC study of each matched pair and found that the maximum PSL dose of the case group was significantly higher than that of the control group (0.55 ± 0.30 vs 0.44 ± 0.28 mg/kg/day, p = 0.02), and the use of PSL > 0.5 mg/kg/day was more prevalent in the case group (53.3% vs 34.2%, p = 0.01; Supplementary Table 4, available online at jrheum.org). Multivariate logistic regression analysis revealed that both maximum PSL doses as a continuous variable (Model 1, OR 4.82, 95% CI 1.36–17.01, per 1.0 mg/kg/day increase) and a categorical variable (Model 2, 2.57, 1.28–5.16, ≥ 0.5 mg/kg/day) were significant risk factors for the development of PI (Table 5) after adjusting for the covariates of ≥ 20 pack-years of smoking, serum creatinine, and performance status ≥ 3. However, the use of mPSL pulse therapy, conventional immunosuppressants, and biologics was not significantly associated with PI.

DISCUSSION

To our knowledge, ours is the first large-scale, multicenter prospective cohort study that investigated PI in patients with CTD receiving immunosuppressive treatment. Here, we report incidence and types of PI, their implications for vital prognosis, and risk factors for developing PI among patients with CTD receiving immunosuppressive treatments.

The association of baseline characteristics with PI in patients with CTD described in our study is consistent with the results of previous studies conducted in general populations. Because immune function becomes impaired with aging, older age has been identified as a risk for serious infections[16,17,18,19]. Smoking is also a known risk factor for community-acquired pneumonia[16,17,18,19,20]. Reduced ciliary and respiratory epithelial functions, as well as defects in humoral and cellular immunity caused by smoking, have been suggested to explain the vulnerability of smokers for PI[21,25,26]. Renal impairment is associated with reduced function of both innate and adaptive immune systems[27]. James, *et al*[22] reported an association of reduced glomerular filtration rates and increased risk of hospitalization and death from pneumonia, which is consistent with our results.

The most important information gained from our study is that the maximum dose of PSL clearly increased risk for PI, but the use of conventional immunosuppressants did not. We analyzed the risk of categories of medications for PI using 2 statistical methods, Cox regression analysis using baseline data in all patients and logistic regression analysis in the NCC study, and obtained the same results. For proper

Table 4. Multivariate analysis of independent risk factors for pulmonary infections (PI) in the PREVENT cohort[a].

Variable	HR	95% CI	p
Age ≥ 65 yrs, vs < 65	3.87	2.22–6.74	< 0.001[c]
Incident use of immunosuppressive therapy	1.42	0.82–2.44	0.210
≥ 20 pack-yrs of smoking, vs < 20	2.63	1.37–5.04	0.004[c]
Serum creatinine, mg/dl	1.21	1.05–1.41	0.011[c]
Performance status ≥ 3, vs ≤ 2	1.79	0.97–3.25	0.061
Maximum PSL dose, mg/kg/day[b]	2.81	1.35–5.86	0.006[c]

[a] The HR for development of PI of each variable was calculated using the Cox proportional hazard regression model after adjusting for sex. [b] Maximum PSL dose during the first 14 days of immunosuppressive therapy. The dose of corticosteroids other than PSL was substituted for the equivalent dose of PSL for analysis[23]. [c] These p values were statistically significant after corrections for multiple comparisons using false discovery rate and Benjamini-Hochberg procedure[24]. PREVENT: Pulmonary infections in patients REceiving immunosuppressiVE treatmeNT for CTD; PSL: prednisolone; CTD: connective tissue diseases.

Table 5. Association between immunosuppressive medications and PI in the NCC study[a].

Model	OR	95% CI	p
Model 1			
Maximum PSL dose, mg/kg/day[b]	4.82	1.36–17.01	0.015
Use of mPSL pulse therapy, yes[c]	0.26	0.04–1.57	0.144
Use of immunosuppressant[d], yes[c]	1.53	0.78–3.00	0.220
Use of biologics[e], yes[c]	1.80	0.63–5.12	0.270
Model 2			
Maximum PSL dose, yes, ≥ 0.5 mg/kg/day[b]	2.57	1.28–5.16	0.008[f]
Use of mPSL pulse therapy, yes[c]	0.37	0.07–2.01	0.246
Use of immunosuppressant[d], yes[c]	1.54	0.78–3.05	0.210
Use of biologics[e], yes[c]	1.75	0.63–4.90	0.284

[a] The OR for development of PI of each variable was calculated using the logistic regression model. Maximum PSL dose was included as a continuous variable in Model 1 and as a categorical variable in Model 2. Both models were adjusted for ≥ 20 pack-years of smoking, serum creatinine, and performance status ≥ 3. [b] Maximum PSL dose was counted during 14 days at the end of the observation period for the NCC study of each matched pair. The dose of corticosteroids other than PSL was substituted for the equivalent dose of PSL for analysis[23]. [c] mPSL pulse therapy, immunosuppressant, and biologics were counted if they were used at least 1 day during the 14 days at the end of the observation period for the NCC study of each matched pair. [d] Including methotrexate, leflunomide, cyclophosphamide, tacrolimus, cyclosporine, azathioprine, mycophenolate mofetil, and mizoribine. [e] Including infliximab, etanercept, adalimumab, tocilizumab, abatacept, and rituximab. [f] p value was statistically significant after corrections for multiple comparisons using false discovery rate and Benjamini-Hochberg procedure[24]. PI: pulmonary infections; NCC: nested case-control; PSL: prednisolone; mPSL: methylprednisolone.

evaluation of the infection risk of each medication category, the NCC design appears to be more appropriate to our cohort because using the risk set sampling model enables direct comparison of medication use during the observation period between the 2 groups. The use of mPSL pulse therapy, conventional immunosuppressants, and biologics was not associated with an increased risk for PI; this contradicts the results from previous reports[28,29,30,31]. The use of conventional immunosuppressants has been assumed to increase the risk for infections in some studies[32,33]. However, there are no high-quality epidemiological data that reveal an increased risk of infection from conventional immunosuppressants in a population exposed to high doses of PSL. It is plausible that the risk of conventional immunosuppressants for PI was masked in our patient population because 65.5% of our patients received PSL ≥ 0.5 mg/kg/day at baseline and the maximum PSL dose had a high HR of 2.81. The negative result of the risk of biologics for PI may derive from treatment regimen characteristics of our cohort in which a low percentage of patients (17.7%) were exposed to biologics.

The occurrence of opportunistic infections was 4.5% in our cohort. As many as 20 patients (2.6%) developed PCP, the incidence of which in Japan has been shown to be significantly higher than in Western countries[12,34,35,36]. It has also been suggested that the prior experience of a hospital in treating patients with PCP is associated with a higher likelihood of diagnosis of PCP[36]. All participating hospitals in our cohort were referral centers with vast experience in diagnosing and treating PCP; this may be associated with the higher incidence rate of PCP in our study compared to previous reports. Although 489 patients (64.1%) received prophylaxis for PCP at some point from baseline to Month 6, none of the 20 patients at the time who developed PCP had received prophylaxis with trimethoprim-sulfamethoxazole, which is quite effective against PCP[37,38]. Three patients who received monthly administration of aerosolized pentamidine developed PCP, which suggested a limited prophylactic effect of the drug against PCP[39,40]. The unadjusted incidence rate of pulmonary TB in our cohort was 450/100,000 patient-year, which is apparently higher than that of the general Japanese population (14/100,000 patient-yr) in 2010. All 3 patients who developed pulmonary TB had not received prophylactic medication against TB. The high incidence of PCP and TB warns us to implement prophylaxis more stringently against these opportunistic infections.

In the recommendations on the management of medium- to high-dose glucocorticoid therapy in CTD by the European League Against Rheumatism[41], evidence about risk management of infection was limited to those obtained from RA cohorts[42,43,44,45], which suggests the lack of high-quality evidence in patient populations of other CTD. Previous studies assessing risk factors for infections in patients with CTD have deficiencies in design and methods[13,14,15]. For proper identification of risk factors for PI common to patients with various CTD receiving immunosuppressive treatment, an ideal study design should meet the conditions of large sample sizes, prospective study design, and appropriate observation period to include the