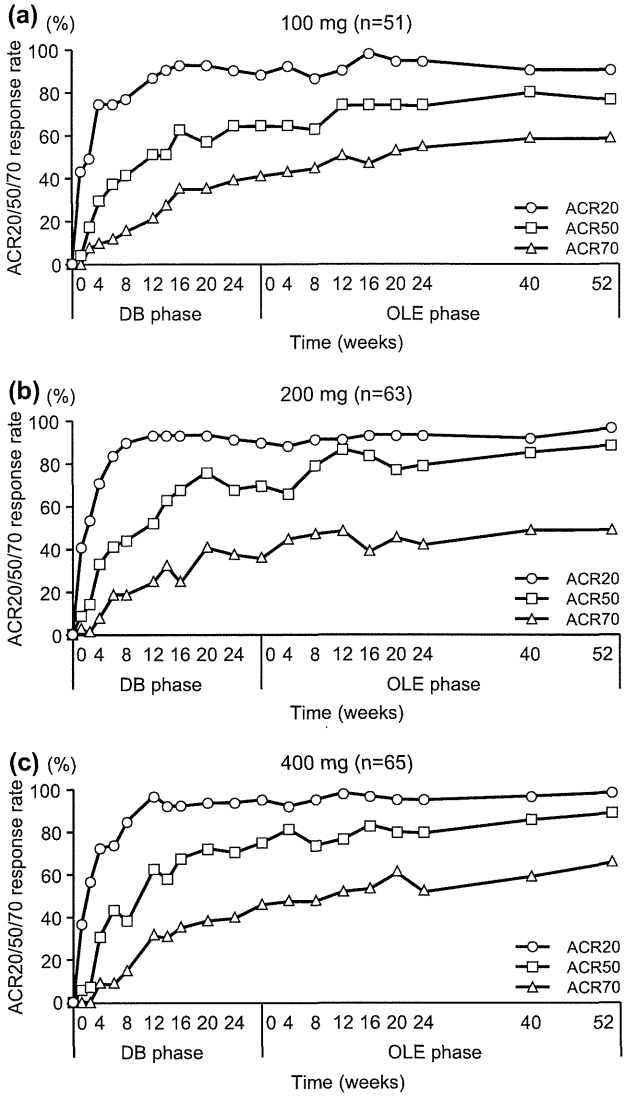

Figure 5. Post-hoc analysis of ACR20/ACR50/ACR70 response rates in patients from Groups II, III and IV excluding those who were in the placebo group during the DB phase (CZP-DB completers). The ACR20, ACR50 and ACR70 response rates of post-hoc analysis patients treated with (a) 100 mg ($n = 51$), (b) 200 mg ($n = 63$) or (c) 400 mg ($n = 65$) of CZP during the DB phase were plotted against time for the DB and the OLE phase of the study (LOCF imputation).

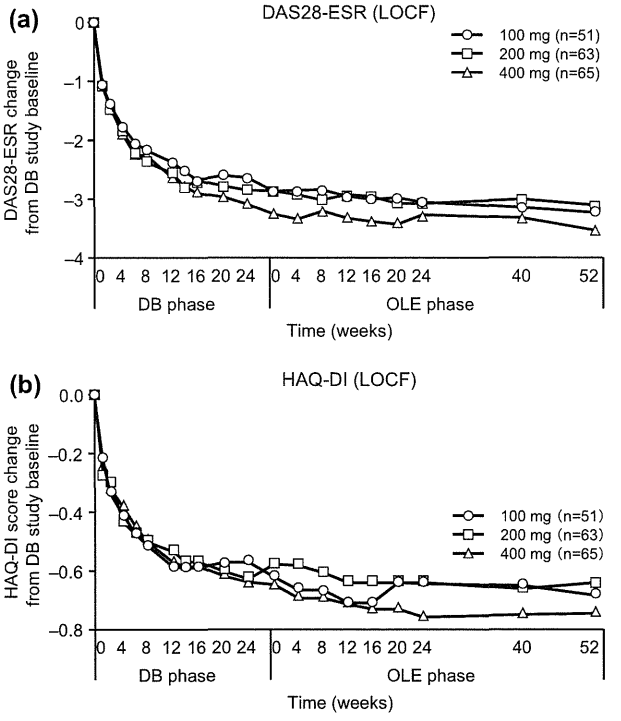

Figure 6. Post-hoc analysis of changes in (a) DAS28-ESR and (b) HAQ-DI scores from J-RAPID pre-study baseline in patients from Groups II, III and IV excluding those who were in the placebo group during the DB phase (CZP-DB completers). The changes of DAS28-ESR and HAQ-DI scores of post-hoc analysis patients treated with 100 mg ($n = 51$), 200 mg ($n = 63$) or 400 mg ($n = 65$) of CZP during the DB phase were plotted against time for the DB and the OLE phase of the study (LOCF imputation).

DB phase, respectively (Figure 7). The remission rates (DAS28-ESR < 2.6) were 31.4%, 25.4% and 38.5% at OLE entry, and 47.1%, 34.9% and 49.2% at week 52, in CZP-DB completers receiving 100, 200 and 400 mg CZP during the DB phase, respectively (Figure 7). Therefore, this post-hoc analysis demonstrates that the efficacy of CZP can be sustained in long-term CZP treatment, even when the analysis set is restricted to patients who have achieved an ACR20 clinical response after 12–14 weeks of CZP treatment.

Adverse events (AE)s reported during long-term CZP plus MTX treatment

During the 52 weeks of the OLE phase, 253 patients (88.8%) experienced AEs and 31 patients (10.9%) experienced serious AEs (Table 3). Among SAEs, two patients (0.7%) exhibited abnormal hepatic function, two patients (0.7%) developed bronchitis, three patients (1.1%) displayed RA exacerbations and two patients (0.7%) developed subarachnoid hemorrhage. Two patients (0.7%) developed a malignancy (breast cancer, colon cancer). The most common AEs were nasopharyngitis, pharyngitis and upper respiratory tract infections. Most AEs were mild to moderate (84.6%). The rate, severity and distribution of AEs were similar among all groups (Groups I–IV), suggesting that no obvious differences in AEs are observed based on the CZP treatment schedule. No tuberculosis infections or deaths were reported. No unanticipated AEs occurred in any of the groups. Thus, over 52 weeks of the OLE phase, CZP coadministered with MTX was well tolerated, with no new safety precautions when compared with the DB phase (Table 3).

Discussion

The 24-week treatment of CZP has been shown to be efficacious in improving RA disease activity [11–14]. This was also true in patients who showed an inadequate response to MTX. In the DB placebo-controlled J-RAPID study, the combination of CZP plus MTX for 24 weeks improved disease outcome in RA patients who showed an inadequate response to MTX [13]. Although several data on short-term CZP plus MTX treatment have been available [17–19], the clinical efficacy and safety of long-term CZP plus MTX treatment is unknown in Japanese RA patients. Thus, we conducted an OLE study of the J-RAPID study to evaluate the safety of combined long-term CZP plus MTX treatment and to investigate whether the clinical benefit obtained from the 24-week DB phase of the J-RAPID study could be sustained by extending the treatment for another 52 weeks. In addition, we used the OLE herein to assess the efficacy of two different maintenance dosing schedules, the standard dosing (CZP 200 mg Q2W) and an alternative regimen (CZP 400 mg Q4W), both with concomitant MTX.

Our data demonstrate that long-term CZP treatment sustains the clinical efficacy obtained in overall DB completers. This was

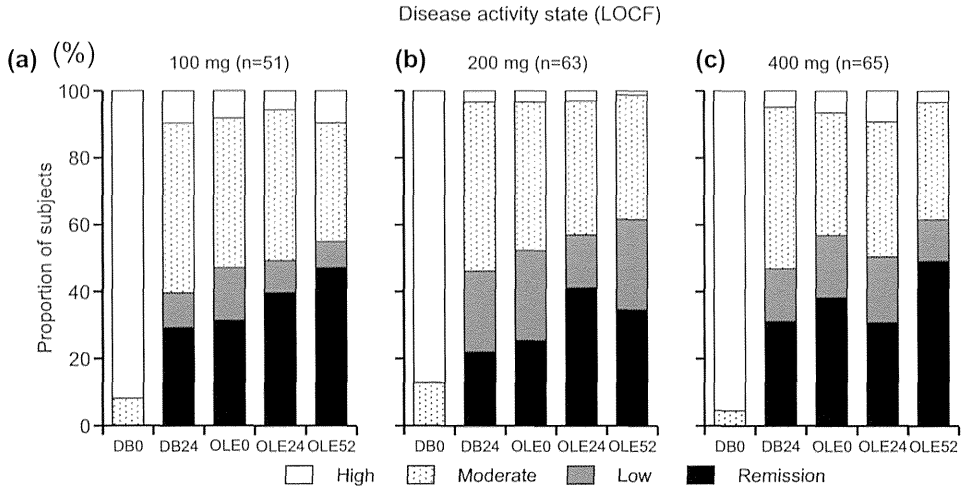

Figure 7. Post-hoc analysis of disease activity states in patients from Groups II, III and IV excluding those who were in the placebo group during the DB phase (CZP-DB completers). The proportions of patients with high (defined as DAS28-ESR > 5.1), moderate (> 3.2 and ≤ 5.1), low (≤ 3.2), or remission (< 2.6) disease activity states at DB week 0 (DB0), DB week 24 (DB24), OLE week 0 (OLE0), OLE week 24 (OLE24) and OLE week 52 (OLE52) among patients treated with (a) 100 mg ($n = 51$), (b) 200 mg ($n = 63$) and (c) 400 mg ($n = 65$) during the DB phase are shown (LOCF imputation).

true for ACR response rates, DAS28-ESR, SF-36 scores and the pain VAS. In addition, clinical remission was observed in 42.6% of patients with long-term treatment at 52 weeks of the OLE study. Functional remission was also observed in 77.5% at 52 weeks of the OLE. Moreover, an analysis of mTSS scores showed that radiographic non-progression (ΔmTSS ≤ 0.5) was achieved in 68.3% of the patients. In terms of the radiographic scores, as described in the Materials and Methods, all patients received CZP in this OLE, and the changes in mTSS scores were within the 52 weeks of the OLE. Therefore, there are no significant differences seen in radiographic progression between groups. On a separate note, the disconnect between the improvements in signs and symptoms and changes in radiographic manifestations of disease has been previously reported in patients treated with TNF antagonists [20].

Together, these results suggest that long-term CZP treatment is effective at controlling RA disease progression, even with the relatively low dose of concomitant MTX (6–8 mg/week). The low withdrawal rate (2.5%) of patients from the study due to lack of efficacy further supports this notion. This was true even for patients that were initially treated with the lower dose of CZP

Table 3. Treatment-emergent adverse events.

	Group I CZP 200 mg Q2W ($n = 81$)	Group II CZP 200 mg Q2W ($n = 19$)	Group III CZP 200 mg Q2W ($n = 93$)	Group IV CZP 400 mg Q4W ($n = 92$)	Total (Groups I + II+ III + IV) ($n = 285$)
Any adverse event, n (%)*	72 (88.9)	16 (84.2)	83 (89.2)	82 (89.1)	253 (88.8)
Intensity#, n (%)*					
Mild	36 (44.4)	6 (31.6)	39 (41.9)	41 (44.6)	122 (42.8)
Moderate	34 (42.0)	8 (42.1)	43 (46.2)	34 (37.0)	119 (41.8)
Severe	2 (2.5)	2 (10.5)	1 (1.1)	7 (7.6)	12 (4.2)
Treatment-related[a]	36 (44.4)	7 (36.8)	43 (46.2)	44 (47.8)	130 (45.6)
Death, n (%)*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Most common adverse events (≥ 5% in any group), n (%)*					
Nasopharyngitis	20 (24.7)	7 (36.8)	28 (30.1)	28 (30.4)	83 (29.1)
Pharyngitis	8 (9.9)	0 (0.0)	8 (8.6)	7 (7.6)	23 (8.1)
Upper respiratory tract infection	12 (14.8)	2 (10.5)	10 (10.8)	10 (10.9)	34 (11.9)
Contusion	7 (8.6)	0 (0.0)	7 (7.5)	2 (2.2)	16 (5.6)
RA	3 (3.7)	3 (15.8)	4 (4.3)	7 (7.6)	17 (6.0)
Eczema	5 (6.2)	2 (10.5)	7 (7.5)	5 (5.4)	19 (6.7)
Hypertension	4 (4.9)	1 (5.3)	6 (6.5)	6 (6.5)	17 (6.0)
Serious adverse events, n (%)*	9 (11.1)	3 (15.8)	7 (7.5)	12 (13.0)	31 (10.9)
Serious adverse events (≥ 0.5% in any group), n(%)					
Hepatic function abnormal	1 (1.2)	0 (0.0)	0 (0.0)	1 (1.1)	2 (0.7)
Bronchitis	1 (1.2)	1 (5.3)	0 (0.0)	0 (0.0)	2 (0.7)
RA	0 (0.0)	1 (5.3)	0 (0.0)	2 (2.2)	3 (1.1)
Subarachnoid hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)	2 (0.7)

*Number of patients (%).
[a]Treatment-emergent adverse events for which the relationship to the study drug cannot be ruled out.
#The severity of an adverse event was assessed according to the following three categories.
1) Mild: An event that caused discomfort, but did not interfere with daily activities.
2) Moderate: An event that was sufficiently discomforting to restrict or interfere with daily activities.
3) Severe: An event that prevented work or daily activities.

(100 mg) during the DB phase. Although the rate of LDA was approximately 7% lower in patients treated with 100 mg CZP during the DB phase compared with patients treated with 200 mg CZP at 52 weeks of the OLE phase, there were no overall significant differences in disease activity state regardless of the dose received during the DB phase (Figure 7).

This is the first study that demonstrates the benefits of continued long-term treatment of CZP administration in Japanese RA patients. Similar studies have been conducted internationally. In the RAPID1 trial, sustained benefit in clinical signs and symptoms and radiographic progression was observed after 2 years of continuous CZP treatment [15]. More recently, the 5-year OLE study from the RAPID1 trial showed continued efficacy up to 256 weeks with no new safety signals identified [21]. Our data presented here suggest that Japanese patients continue to receive relief from RA symptoms after long-term TNFα inhibition by CZP. Importantly, long-term CZP plus MTX treatment was well-tolerated as no unexpected new AEs were detected in patients compared with those observed in previous clinical studies involving short-term CZP plus MTX treatment.

CZP is a novel anti-TNFα monoclonal antibody consisting of a humanized Fab' fragment fused to a 40-kD PEG moiety [22,23]. One drawback of Fab' fragments is that the clearance of Fab' fragments is accelerated in the absence of the Fc region, leading to shorter *in vivo* half-lives compared with full antibodies. However, by attachment of the PEG moiety to the Fab' fragment, the plasma half-life of CZP was extended to about 2 weeks. Because of the extended half-life, a more spaced out CZP maintenance dosing schedule is possible. Our current study provides evidence that extending the interval to Q4W for CZP maintenance therapy is as effective as the Q2W regimen. No obvious differences in clinical efficacy and safety were observed between patients treated with CZP 200 mg Q2W and CZP 400 mg Q4W (Group III vs. Group IV). Thus, patients and physicians have the flexibility of choosing either of two maintenance dosing schedules based on their needs. For example, a Q4W dosing schedule might decrease the number of doctor visits and thus, might be an attractive option for some patients.

The design of the J-RAPID OLE study included patients that were previously on placebo during the DB phase of the J-RAPID study. To observe the effects of continuous CZP treatment through the DB and OLE phases of the study (80 weeks), an additional post-hoc analysis was performed on CZP-DB completers (Groups II–IV) who received CZP during the DB phase. Restricting our analysis to these patients clearly showed that long-term CZP plus MTX treatment sustained the clinical, radiographic and functional efficacy against disease. Thus, we conclude that long-term CZP plus MTX treatment for up to 80 weeks results in a sustained positive response.

Administration of MTX remains the cornerstone for treatment of RA [24,25]. However, some patients do not achieve the desired response when MTX is used as monotherapy [25]. Thus, it is important to identify drugs that can be used in conjunction with MTX to more effectively treat the symptoms of RA. The J-RAPID study demonstrated that CZP is clinically effective in combination with MTX for treatment of patients who failed to achieve a satisfactory response with MTX alone. Our current study is the first to investigate the clinical efficacy of CZP with MTX treatment over an ~80-week period (28 weeks during the DB phase + 52 weeks during the OLE phase) in Japanese RA patients. Our data demonstrate that long-term CZP plus MTX treatment sustains the beneficial effect of CZP plus MTX afforded after 24 weeks of therapy. Moreover, no new unexpected AEs were discovered during the OLE phase, suggesting that additional risks are not incurred by long-term treatment with CZP plus MTX. Based on results from clinical trials and from post market surveys, the AEs observed with long-term CZP treatment are comparable to those seen with other TNF inhibitors such as infliximab, etanercept, adalimumab and golimumab. As an added benefit, the local skin reaction to subcutaneous injection of CZP tends to be lower than other subcutaneously administered TNF inhibitors. Together, these data suggest that if the patient obtains a positive response to CZP treatment after 12–14 weeks, clinicians can expect sustained efficacy without additional risks by continuing onto long-term use of CZP plus MTX.

In summary, our data suggest that continuous long-term CZP treatment is a beneficial option in patients with active RA and an inadequate response to MTX, by providing long-term clinical, functional and radiographic disease control. This was true for both the Q2W and Q4W maintenance dosing schedules of CZP. Moreover, long-term treatment was well-tolerated with no new unexpected adverse events observed. One limitation of our study was that this was an OLE study and therefore not blinded. However, we believe that our data still suggest that long-term CZP treatment is beneficial for continued suppression of RA. Thus, we propose that patients with active RA and an inadequate response to MTX should undergo continuous combined long-term treatment with either a CZP 200 mg Q2W or CZP 400 mg Q4W schedule with MTX to achieve long-lasting suppression of RA symptoms.

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Conflict of interest

The competing interests of all authors are provided below.

- Y. Tanaka has received research funding from BMS, MSD, Chugai, Mitsubishi-Tanabe, Astellas, Abbvie and Daiichi-Sankyo and has served on speaker bureaus for UCB, Mitsubishi-Tanabe, Abbott, Abbvie, Eisai, Chugai, Janssen, Pfizer, Takeda, Astellas, Daiichi-Sankyo, GSK, AstraZeneca, Eli Lilly, Quintiles, MSD and Asahi Kasei.
- K. Yamamoto has served as a consultant for UCB, Pfizer, Abbott, BMS, Roche, Chugai, Mitsubishi-Tanabe and Eisai and has received research funding from UCB, Pfizer, Abbott, Santen, Mitsubishi-Tanabe and Eisai.
- T. Takeuchi has served as a consultant for AstraZeneca, Eli Lilly, Novartis, Mitsubishi-Tanabe and Asahi Kasei; has received research support from Abbott, Astellas, BMS, Chugai, Daiichi-Sankyo, Eisai, Janssen, Mitsubishi-Tanabe, Nippon Shinyaku, Otsuka, Pfizer, Sanofi-Aventis, Santen, Takeda and Teijin; and has served on speaker bureaus for Abbott, BMS, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer and Takeda.
- H. Yamanaka has served as a consultant for, and received research funding from, UCB, Abbott, Astellas, BMS, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer and Takeda.
- N. Ishiguro has received research funding from Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, BMS, Eisai, Janssen, Kaken and Pfizer and has served on speaker bureaus for Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, BMS, Eisai, Janssen, Kaken, Pfizer, Taisho-Toyama and Otsuka.
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- H. Origasa has served as a consultant for UCB and Astellas.
- T. Shoji is an employee of UCB.
- N. Miyasaka has received research support from Pfizer, Takeda, Mitsubishi-Tanabe, Chugai, Abbott, Eisai and Astellas.
- T. Koike has served on speaker bureaus for UCB, Pfizer, Chugai, Abbott, Mitsubishi-Tanabe, Takeda, Eisai, Santen, Astellas, Taisho-Toyama, BMS, Teijin and Daiichi-Sankyo.

References

1. Balanescu A, Wiland P. Maximizing early treatment with biologics in patients with rheumatoid arthritis: the ultimate breakthrough in joints preservation. Rheumatol Int. 2013;33(6):1379–86.
2. Sharma P, Pathak K. Are biological targets the final goal for rheumatoid arthritis therapy? Expert Opin Biol Ther. 2012;12(12):1611–22.
3. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med. 1999; 130(6):478–86.
4. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003;48(1):35–45.
5. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Furst D, Weisman MH, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. Arthritis Rheum. 2004;50(4):1051–65.
6. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum. 2002;46:1443–50.
7. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004;50(5):1400–11.
8. Tanaka Y. Recent progress in the treatment of rheumatoid arthritis. Clin Calcium 2012;22(2):169–78.
9. Nesbitt A, Fossati G, Bergin M, Stephens P, Stephens S, Foulkes R, et al. Mechanism of action of certolizumab pegol (CDP870): In vitro comparison with other anti-tumor necrosis factor alpha agents. Inflamm Bowel Dis. 2007;13(11):1323–32.
10. Horton S, Walsh C, Emery P. Certolizumab pegol for the treatment of rheumatoid arthritis. Expert Opin Biol Ther. 2012;12(2):235–49.
11. Keystone E, Heijde D, Mason D Jr, Landewé R, Vollenhoven RV, Combe B, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. 2008;58(11):3319–29.
12. Smolen J, Landewe RB, Mease P, Brzezicki J, Mason D, Luijtens K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID2 study. A randomised controlled trial. Ann Rheum Dis. 2009;68(6):797–804.
13. Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial. Mod Rheumatol. 2013; (epub ahead of print) doi:10.3109/14397595.2013.864224
14. Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, et al. Efficacy and safety of certolizumab pegol without methotrexate co-administration in Japanese patients with active rheumatoid arthritis: the HIKARI randomized, placebo-controlled trial. Mod Rheumatol. 2013; (epub ahead of print) doi:10.3109/14397595.2013.843764
15. Keystone EC, Combe B, Smolen J, Strand V, Goel N, van Vollenhoven R, et al. Sustained efficacy of certolizumab pegol added to methotrexate in the treatment of rheumatoid arthritis: 2-year results from the RAPID1 trial. Rheumatology (Oxford) 2012;51(9):1628–38.
16. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31(3):315–24.
17. Ramiro S, van Tubergen AM, Landewe RB. RAPID and FAST4WARD trials: Certolizumab pegol for rheumatoid arthritis. Expert Rev Clin Immunol. 2010;6(5):713–20.
18. Strand V, Mease P, Burmester GR, Nikaï E, Coteur G, van Vollenhoven R, et al. Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID1 randomized controlled trial. Arthritis Res Ther. 2009;11(6):R170.
19. Connock M, Tubeuf S, Malottki K, Uthman A, Round J, Bayliss S, et al. Certolizumab pegol (CIMZIA) for the treatment of rheumatoid arthritis. Health Technol Assess. 2010;14(Suppl 2):1–10.
20. Boers M for the COBRA Study Group. Demonstration of response in rheumatoid arthritis patients who are nonresponders according to the American College of Rheumatology 20% criteria: the paradox of beneficial treatment effects in nonresponders in the ATTRACT trial. Arthritis Rheum. 2001;44(11):2703–4.

21. Keystone E, Landewé R, van Vollenhoven R, Combe B, Strand V, Mease P, et al. Long-term safety and efficacy of certolizumab pegol in combination with methotrexate in the treatment of rheumatoid arthritis: 5-year results from the RAPID 1 trial and open-label extension. Ann Rheum Dis. 2013; (epub ahead of print).
22. Patel AM, Moreland LW. Certolizumab pegol: a new biologic targeting rheumatoid arthritis. Expert Rev Clin Immunol. 2010;6(6):855–66.
23. Kaushik VV, Moots RJ. CDP-870 (certolizumab) in rheumatoid arthritis. Expert Opin Biol Ther. 2005;5(4):601–6.
24. Shankar S, Handa R. Biological agents in rheumatoid arthritis. J Postgrad Med. 2004;50(4):293–9.
25. Benedek TG. Methotrexate: from its introduction to non-oncologic therapeutics to anti-TNF-alpha. Clin Exp Rheumatol. 2010;28 (5 Suppl 61):S3–8.

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ORIGINAL ARTICLE

Efficacy and safety of abatacept in routine care of patients with rheumatoid arthritis: Orencia® as Biological Intensive Treatment for RA (ORBIT) study

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Abstract

Objective. To investigate the efficacy and safety of abatacept for treating patients with rheumatoid arthritis (RA) in routine clinical practice.

Methods. We performed a retrospective study of 137 RA patients who were treated with abatacept for 24 weeks between October 2010 and June 2011 at four rheumatology centers in Japan. Outcomes were compared between biologic-naïve and biologic-experienced patients. Disease activity was assessed using the Simplified Disease Activity Index (SDAI) and the 28-joint Disease Activity Score based on the erythrocyte sedimentation rate (DAS28-ESR).

Results. The retention rate of abatacept at 24 weeks was 79.6%. SDAI (from 24.6 ± 12.5 to 12.9 ± 11.6) and DAS28-ESR (from 5.2 ± 1.4 to 3.9 ± 1.4) decreased significantly from baseline to Week 24 (both $P < 0.001$). Remission/low disease activity were achieved in 2.2%/11.2% (SDAI) and in 5.3%/2.3% (DAS28-ESR). The change in SDAI and the remission/low disease activity rates at Week 24 was greater in biologic-naïve patients than in biologic-experienced patients. Structural remission (van der Heijde-modified total Sharp score ≤ 0.5) was achieved by 63.4% of patients.

Conclusions. The present results confirm that abatacept is effective in routine clinical practice and support its use as the first-line biologic agent in patients.

Keywords

Abatacept, Joint destruction, Remission, Retrospective study, Rheumatoid arthritis

History

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Introduction

Activated T cells proliferate and stimulate the production of pro-inflammatory cytokines in patients with rheumatoid arthritis (RA) [1–4]. Existing biologic agents indicated for RA inhibit the activity of pro-inflammatory cytokines, especially tumor necrosis factor (TNF) and interleukin (IL)-6. Abatacept is a soluble recombinant fusion protein composed of the Fc domain of human IgG1 (hinge-CH2-CH3 region) fused to the extracellular domain of human cytotoxic T lymphocyte antigen-4 (CTLA4). Therefore, unlike other biologic agents, abatacept suppresses T-cell activation by preventing antigen-presenting cells located upstream of the initiation of inflammation from delivering the co-stimulatory signal to T cells [5,6]. This ultimately inhibits the production of downstream pro-inflammatory cytokines and mediators.

Abatacept suppressed RA activity, improved physical function, and suppressed joint destruction over an extended period of time in RA patients non-responsive to methotrexate (MTX) [7–12]. Abatacept was also effective in RA patients with inadequate responses to anti-TNF agents [13–16], and in patients with early RA [17–19]. In Japan, unlike in Europe and the United States, abatacept has also been administered to biologic-naïve patients since its approval in September 2010.

Although numerous premarketing phase (I–III) studies of abatacept have been performed in Japan, very few studies have been evaluated with its efficacy and safety for treating RA in the context of actual clinical practice. Therefore, we performed a retrospective analysis of the clinical, functional, and radiographic responses to abatacept, and its safety, over 24 weeks of treatment in all Japanese RA patients at Keio University, Saitama Medical University, Tokyo Women's Medical University, and the University of Occupational and Environmental Health who started their treatment with abatacept since its approval in September 2010. We also compared the clinical outcomes between patients who were naïve to biologic agents (biologic-naïve patients) and those who had previously received a biologic agent (biologic-experienced patients), and sought to identify possible predictors of response.

Methods

Patients

This was an open-label, non-randomized, observational and retrospective study involving all RA patients ($n = 137$) who fulfilled the classification criteria of the American College of Rheumatology

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[20,21] and who were treated with abatacept between October 2010 and June 2011 at one of the four major rheumatology centers in Japan: (1) the Institute of Rheumatology, Tokyo Women's Medical University ($n = 28$); (2) the Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Saitama Medical Center, Saitama Medical University, Saitama ($n = 17$); (3) the Department of Rheumatology and Clinical Immunology, School of Medicine, Keio University, Tokyo ($n = 47$); or (4) the First Department of Internal Medicine of the School of Medicine, University of Occupational and Environmental Health Japan, Kitakyushu ($n = 45$). Demographic data, including age, sex, disease duration, and concomitant therapy, were collected from medical charts in a retrospective manner. The study was approved by the ethics committees/institutional review boards at each institution, and informed consent for data collection was obtained from each patient before they started treatment with abatacept.

Abatacept treatment

Abatacept was administered in accordance with the Guidelines for the Use of Abatacept in Patients with Rheumatoid Arthritis of the Japan College of Rheumatology (available at: http://www.ryumachi-jp.com/info/guideline_ABT_100930.html). Patients received a fixed dose of abatacept of about 10 mg/kg body weight; patients weighing < 60 kg received 500 mg of abatacept, those weighing 60–100 kg received 750 mg, and those weighing > 100 kg received 1000 mg. Abatacept was administered in a 30-min intravenous infusion at Weeks 0, 2, and 4, and then every 4 weeks for up to 24 weeks. Concomitant use of MTX, disease-modifying anti-rheumatic drugs other than MTX, and/or oral steroids was at the discretion of the attending physician. All concomitant therapies were administered in accordance with Japanese Guidelines for the Treatment of Rheumatoid Arthritis (available at: http://www.ryumachi-jp.com/guideline.html).

Measurements

The following parameters were evaluated at baseline, and at 4, 8, 12, and 24 weeks of treatment with abatacept: 28-tender joint count (TJC), 28-swollen joint count (SJC), patient's global assessment of disease activity (PGA), evaluator's global assessment of disease activity (EGA), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), matrix metalloproteinase 3 (MMP-3), and rheumatoid factor (RF).

Clinical efficacy

Disease activity was assessed using the Simplified Disease Activity Index (SDAI) and the 28-joint Disease Activity Score (DAS28)-ESR, which were calculated as previously described [22]. The remission rate after 24 weeks of therapy was evaluated using the Boolean-based definition proposed by the American College of Rheumatology/European League Against Rheumatism in 2011 [23], in which patients needed to satisfy all of the following: TJC ≤ 1, SJC ≤ 1, CRP ≤ 1 mg/dL and PGA ≤ 1 (on a 0–10 scale).

SDAI scores ≤ 3.3, < 11.0, 11.0–26.0, and > 26.0 were classified as representing remission, low disease activity, moderate disease activity, and high disease activity, respectively.

DAS28-ESR scores < 2.6, < 3.2, 3.2–5.1, and > 5.1 were defined as representing remission, low disease activity, moderate disease activity, and high disease activity, respectively.

Disability was assessed by the Health Assessment Questionnaire Disability Index (HAQ-DI) using the original HAQ [24] or the Japanese version of the HAQ [25]. Functional remission was defined as a HAQ-DI score of ≤ 0.5, and an improvement was defined as a decrease in the HAQ-DI score of > 0.22.

Joint damage was assessed by the van der Heijde-modified total Sharp score (mTSS) [26]. Two expert readers independently scored articular damage and progression in a blinded fashion according to the mTSS scoring methods. Structural remission was defined as a ΔmTSS score of < 0.5.

The primary clinical efficacy endpoint was the decrease in SDAI from baseline to Week 24; secondary endpoints included the decrease in HAQ-DI scores from baseline to Week 24, and ΔmTSS.

Safety surveillance

All patients were assessed every month to evaluate adverse events (AEs); AEs were recorded at Weeks 0, 4, 8, 12, and 24.

Statistical analysis

Patient baseline characteristics are summarized as the mean and standard deviation (SD), with percentiles for the overall patient population. The improvements in SDAI and HAQ-DI scores from baseline to Week 24 were analyzed using the Friedman test. The improvement in ΔmTSS scores was analyzed using Wilcoxon's signed rank test. The chi-squared test was used to compare the remission rates and the proportions of patients with low disease activity between the composite indices (SDAI, Clinical Disease Activity Index (CDAI), or DAS28-ESR) and according to prior use of biologic agents. Multiple regression analysis was performed to determine factors associated with clinical remission (i.e., SDAI), functional remission (i.e., HAQ-DI), and structural remission (i.e., ΔmTSS) at Week 24. The last observation carried forward method was used to evaluate efficacy outcomes because data could not be obtained from patients who discontinued abatacept therapy before Week 24. All reported P values are two-sided, and were not adjusted for multiple testing. Values of $P < 0.05$ were considered statistically significant. All analyses were conducted using SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

We retrospectively analyzed data on 137 patients who were treated at the four centers. The mean age of the patients was 60.9 ± 13.4 years, and 81.0% (111/137) were female. The mean disease duration was 10.0 ± 9.1 years. Overall, 64 (46.7%) patients were biologic-naïve and 73 (53.3%) were biologic-experienced. Among biologic-experienced patients, abatacept was the second biologic agent in 33 (24.1%), the third in 28 (20.4%), and the fourth or fifth in 12 (8.8%). MTX was concomitantly administered in 101 (73.7%) patients, with a mean dose of 8.2 ± 2.6 mg/week. Glucocorticoids were used concomitantly in 54 (39.4%) patients, with a mean dose of 5.4 ± 3.4 mg/day (prednisolone equivalents) (Table 1).

Of the 137 patients included in this study, abatacept therapy was discontinued in 28 patients, resulting in a retention rate at Week 24 of 79.6% (Figure 1). Reasons for discontinuing abatacept were lack of efficacy (10.9%), AEs (3.6%), transfer to another hospital (2.9%), or another reason (2.9%).

Disease activity

Disease activity was assessed using the SDAI and DAS28-ESR. The mean $\pm$ SD SDAI score among all 137 patients decreased significantly from 24.6 ± 12.5 at baseline to 12.9 ± 11.6 at Week 24 ($P < 0.001$). There were also decreases from baseline to Week 24 for each component of the SDAI, as follows: SJC, from 6.2 to 2.5; TJC, from 6.5 to 2.8; PGA, from 55.0 to 39.3; and CRP, from 1.8 to 1.0. The changes in SJC and TJC from baseline to Week 24 were

Table 1. Patient characteristics.

Variable	Value
n	137
Age (years)	60.9 ± 13.4
Females, *n* (%)	111 (81.0)
Disease duration (years)	10.0 ± 9.1
Prior use of biologic agents, *n* (%)	73 (53.3)
RF positive, *n* (%)	94 (74.0)
MTX use, *n* (%)	101 (73.7)
MTX dose (mg/week)	8.2 ± 2.6
Oral steroid use, *n* (%)	54 (39.4)
Oral steroid dose (mg/day*)	5.3 ± 3.4
MMP-3 (ng/mL)	205.6 ± 171.9
SJC (possible range, 0–28)	6.2 ± 4.8
TJC (possible range, 0–28)	6.5 ± 5.6
ESR (mm/h)	47.8 ± 31.9
CRP (mg/dL)	1.8 ± 2.3
PGA, VAS 0–100 mm	55.0 ± 25.0
SDAI	24.6 ± 12.5
DAS28-ESR	5.2 ± 1.4
HAQ-DI	1.4 ± 0.8
mTSS	59.1 ± 72.9
Median (IQR)	33.2 (6.0–91.5)
Estimated yearly progression of mTSS (ΔmTSS)	34.2 ± 114.6
Median (IQR)	3.8 (1.7–12.7)

Values are means ± standard deviation, median (IQR), or *n* (%).

RA, rheumatoid arthritis; RF, rheumatoid factor; MTX, methotrexate; MMP-3, matrix metalloproteinase 3; SJC, swollen joint count; *TJC*, tender joint count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PGA, patient's global assessment of disease activity; VAS, visual analogue scale; SDAI, Simplified Disease Activity Index; DAS28, 28-joint Disease Activity Score; HAQ-DI, Health Assessment Questionnaire Disability Index; mTSS, van der Heijde-modified total Sharp score; IQR, interquartile range.

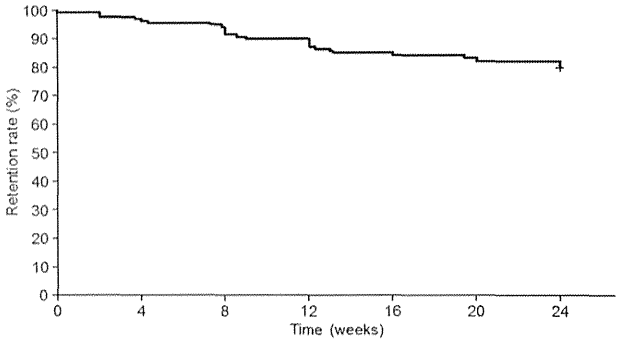


Figure 1. Retention rate at 24 weeks in all patients ($n = 137$).

statistically significant. On the basis of SDAI scores, 2.2%, 11.2%, 44.0%, and 42.5% of patients were classified as showing remission, low disease activity, moderate disease activity, and high disease activity, respectively, at baseline. The corresponding values at Week 24 were 16.1%, 57.7%, 31.4%, and 10.9% (Figure 2).

The mean ± SD DAS28-ESR score for all 137 patients decreased significantly from 5.2 ± 1.4 at baseline to 3.9 ± 1.4 at Week 24 ($P < 0.001$). On the basis of DAS28-ESR scores, 5.3%, 2.3%, 39.4%, and 53.0% of patients were classified as showing remission, low disease activity, moderate disease activity, and high disease activity, respectively, at baseline. The corresponding values at Week 24 were 16.3%, 34.1%, 43.7%, and 22.2% (Figure 2).

On the basis of these SDAI and DAS28-ESR scores at Week 24, the percentage of patients with low disease activity was significantly higher ($P < 0.001$) based on SDAI scores (57.7%) than on DAS28-ESR scores (34.1%), suggesting that more patients achieved low disease activity on the SDAI than on the DAS28-ESR scores.

Multiple regression analysis of SDAI scores showed that no previous use of a biologic agent (correlation coefficient = 0.211, $P = 0.002$), glucocorticoid use (correlation coefficient = 0.160, $P = 0.020$), and baseline SDAI score (correlation coefficient = 0.564, $P < 0.001$) were significantly associated with SDAI after 24 weeks of treatment (Table 2). When we evaluated disease activity according to history of using biologic agents, we found that the SDAI score decreased significantly from baseline to Week 24 in biologic-naïve patients (from 24.1 to 9.7; $P < 0.001$; $n = 64$) and in biologic-experienced patients (from 25.0 to 15.8; $P < 0.001$; $n = 73$); the magnitude of improvement was therefore greater in biologic-naïve patients. The remission rate and the percentage of patients with low disease activity at Week 24 were both higher in biologic-naïve patients (26.6% and 43.8%, respectively) than

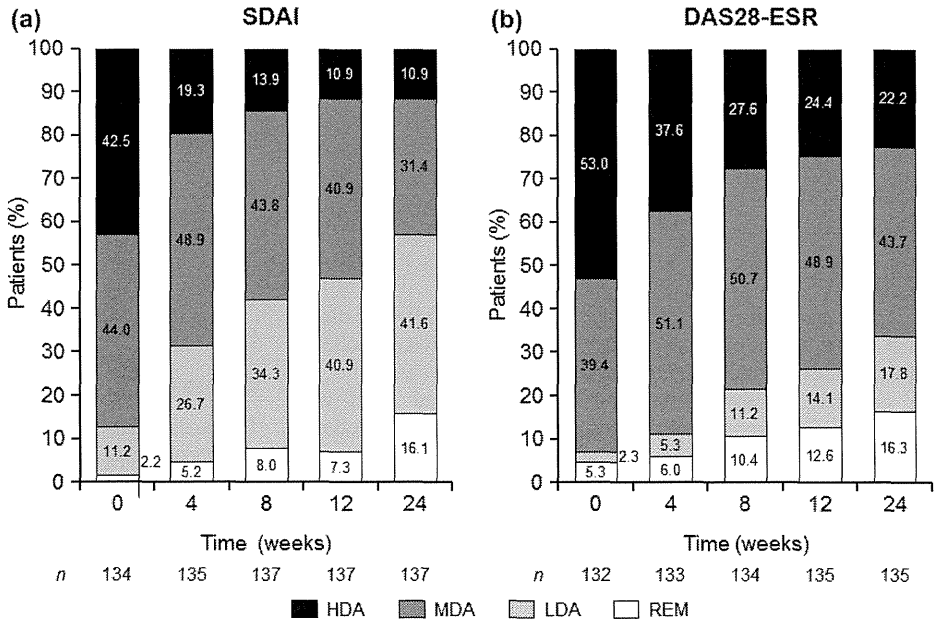


Figure 2. Classification of disease activity according to (a) the Simplified Disease Activity Index (*SDAI*) and (b) 28-joint Disease Activity Score based on the erythrocyte sedimentation rate (*DAS28-ESR*). REM, remission; LDA, low disease activity; MDA, moderate disease activity; HDA, high disease activity.

Table 2. Multiple regression analyses of SDAI and HAQ-DI scores at Week 24 ($n = 137$).

Variable	SDAI correlation coefficient	P	HAQ-DI correlation coefficient	P
Disease duration	0.006	0.926	**0.119**	**0.033**
Sex	−0.009	0.899	−0.057	0.293
Age	0.038	0.594	0.044	0.442
No prior history of using a biologic agent	**0.211**	**0.002**	**0.158**	**0.004**
Concomitant use of MTX	0.062	0.378	−0.039	0.469
Oral steroid use	**0.160**	**0.020**	0.044	0.423
CRP at baseline	0.023	0.752	−0.037	0.500
RF at baseline	0.090	0.187	0.017	0.751
MMP-3 at baseline	−0.067	0.335	0.035	0.511
SDAI at baseline	**0.564**	**<0.001**	0.041	0.480
HAQ-DI at baseline	0.047	0.524	**0.734**	**<0.001**

Values in bold are statistically significant at $P < 0.05$, and are therefore independently associated with the dependent variable.

SDAI, Simplified Disease Activity Index; HAQ-DI, Health Assessment Questionnaire Disability Index; MTX, methotrexate; CRP, C-reactive protein; RF, rheumatoid factor; MMP-3, matrix metalloproteinase 3.

in biologic-experienced patients (6.8% and 39.7%, respectively) (Figure 3).

HAQ-DI

HAQ-DI scores in all 137 patients decreased significantly from 1.4 ± 0.8 at baseline to 1.1 ± 0.8 at Week 24 ($P < 0.001$). The functional remission rate (i.e., HAQ ≤ 0.5) increased from 17.5% at baseline to 34.3% at Week 24. Multiple regression analysis of HAQ-DI scores revealed that disease duration (correlation coefficient = 0.119, $P = 0.033$), no previous use of a biologic agent (correlation coefficient = 0.158, $P = 0.004$), and baseline HAQ-DI score (correlation coefficient = 0.734, $P < 0.001$) were significantly associated with the HAQ-DI score after 24 weeks of treatment with abatacept (Table 2). Among biologic-experienced patients ($n = 73$), the HAQ-DI score decreased from 1.4 at baseline to 1.3 at Week 24, which was not statistically significant. However, among biologic-naïve patients ($n = 64$), the HAQ-DI score decreased significantly from 1.3 at baseline to 0.9 at Week 24 ($P = 0.001$). At Week 24, the percentages of patients with an HAQ-DI score of ≤ 0.5 or of > 0.5 to ≤ 1.0 were 23.3% and 12.3%, respectively, among biologic-experienced patients, compared with 48.4% and 17.2%, respectively, among biologic-naïve patients. These results indicate that the functional remission rate was higher in biologic-naïve patients than in biologic-experienced patients.

Radiographic outcomes

In this retrospective multicenter study, the timing of radiography of the hands and feet was at the discretion of the attending physician. For this reason, bone destruction was only evaluable in 101/137 patients. The median ΔmTSS decreased significantly from 6.0 at baseline to 0.0 at Week 24 ($P < 0.001$) (Figure 4). As shown in Figure 4, structural remission, defined as ΔmTSS ≤ 0.5, was achieved in 63.4% of patients at Week 24. Rapid radiographic progression, which was defined as an increase in ΔmTSS ≥ 5 in 1 year, occurred in only 4.0% (4/101) of patients. The probability plots in biologic-naïve and biologic-experienced patients are shown in Figure 4c. The ΔmTSS score of ≤ 0.5 was achieved in 66.0% of biologic-naïve patients and in 60.4% of biologic-experienced patients, which was not statistically significant.

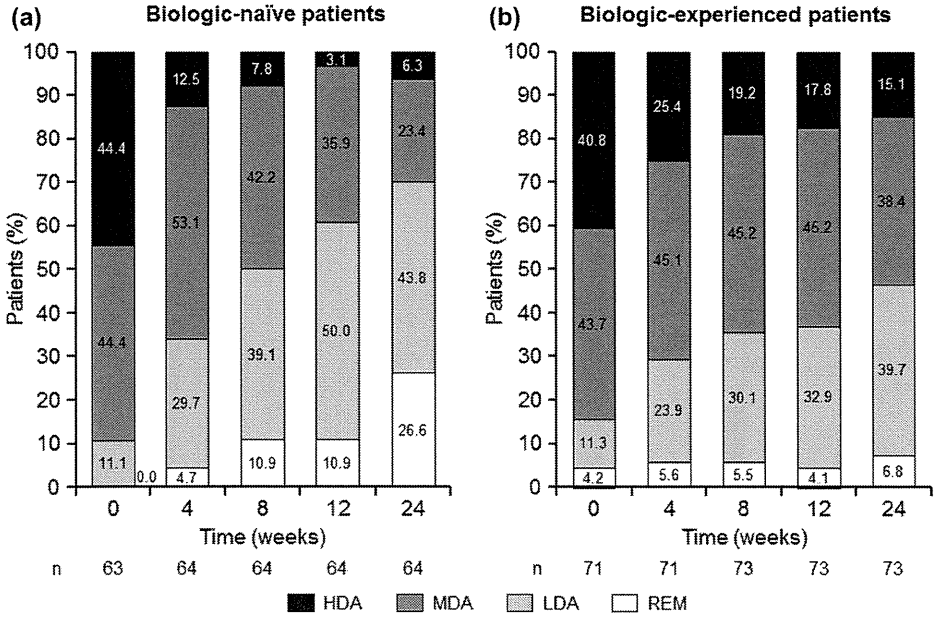


Figure 3. Classification of disease activity according to the Simplified Disease Activity Index (SDAI) in (a) biologic-naïve and (b) biologic-experienced patients. REM, remission; LDA, low disease activity; MDA, moderate disease activity; HDA, high disease activity.

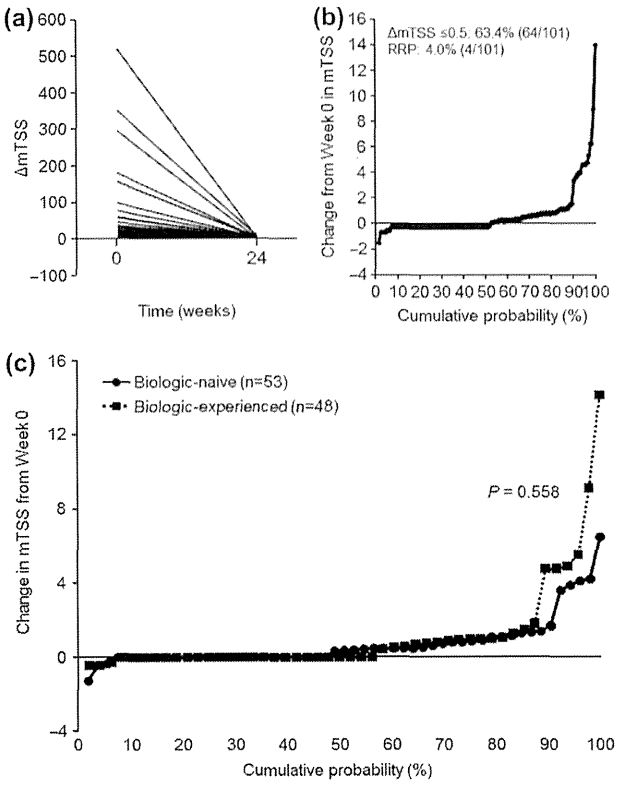


Figure 4. (a) Estimated yearly progression in van der Heijde-modified total Sharp score (mTSS) in individual patients. mTSS was evaluated in 101 patients with radiographs of the hands and feet at Weeks 0 and 24. (b) Cumulative probability plot for the change in van der Heijde-modified total Sharp score (mTSS) from Week 0 to Week 24 in 101 patients with radiographs of the hands and feet at Weeks 0 and 24. (c) Cumulative probability plot for the change in mTSS from Week 0 to Week 24 in biologic-naïve ($n = 53$) and biologic-experienced ($n = 48$) patients. RRP, rapid radiographic progression.

Boolean definition

The remission rate at Week 24 was compared between biologic-naïve patients and biologic-experienced patients according to the DAS28-ESR, SDAI scores, and Boolean definitions. The remission rates determined using the DAS28-ESR scores and Boolean definitions were not significantly different between the two groups of patients. However, the remission rate determined using the SDAI scores was significantly greater in biologic-naïve patients than in biologic-experienced patients (26.6% vs. 6.8%; $P = 0.001$; Figure 5). Similarly, the proportions of patients with low disease activity at Week 24 were not statistically significantly different between the two groups of patients based on the DAS28-ESR score and Boolean definitions. The proportion of patients with low disease activity assessed using the SDAI scores was significantly greater in biologic-naïve patients than in biologic-experienced patients (70.3% vs. 46.6%; $P = 0.006$; Figure 5).

In an analysis of all 137 patients, the percentages of patients who satisfied the individual Boolean criteria of SJC28 ≤ 1, TJC28 ≤ 1, CRP ≤ 1 mg/dl, PGA ≤ 1, and EGA ≤ 1 were 54.0%, 54.7%, 70.8%, 17.5%, and 38.0%, respectively. The percentages of patients who achieved each of these criteria, except for TJC28 ≤ 1, were significantly higher in biologic-naïve patients than in biologic-experienced patients (Figure 5).

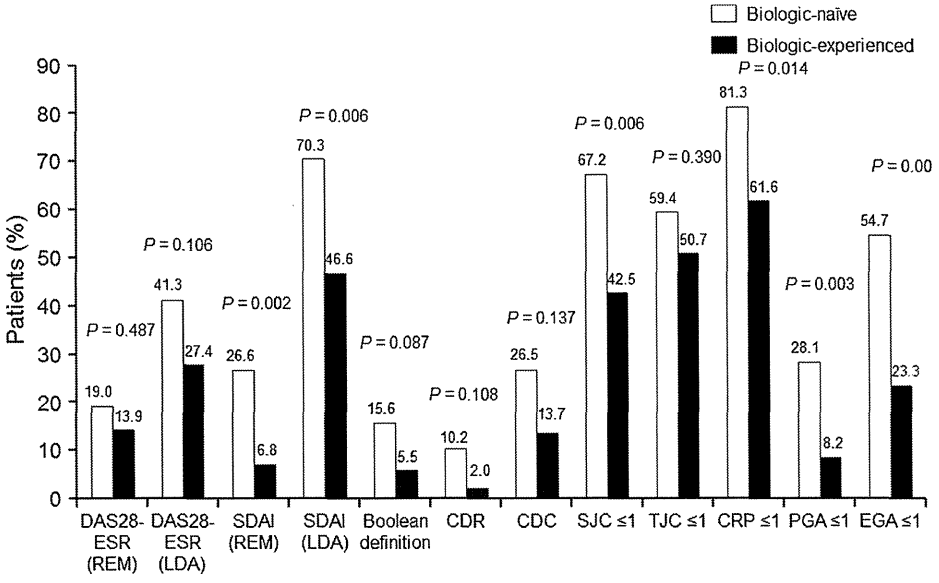
Of the 100 patients in whom both HAQ and ΔmTSS scores were evaluable, 6.0% (6/100) achieved comprehensive disease remission, which was defined as SDAI ≤ 3.3, HAQ ≤ 0.5, ΔmTSS ≤ 0.5, while 20.0% (20/100) of patients achieved comprehensive disease control, which was defined as SDAI ≤ 11.0, HAQ ≤ 0.5, and ΔmTSS ≤ 0.5.

Laboratory data

MMP-3 was measured in 92.0% (126/137) of patients, and decreased significantly during the observation period from 203.7 ± 171.3 ng/mL at Week 0, to 162.6 ± 150.5 ng/mL at Week 4, to 137.8 ± 146.1 ng/mL at Week 8, to 141.2 ± 228.0 ng/mL at Week 12, and to 131.5 ± 224.1 ng/mL at Week 24 in the total cohort.

MMP-3 was regularly measured in 98.4% (63/64) of biologic-naïve patients and in 86.3% (63/73) of biologic-experienced patients. The MMP-3 levels in biologic-naïve and biologic-experienced patients were 198.1 ± 169.5 ng/mL and 209.3 ± 174.2 ng/mL, respectively, at baseline and decreased to 97.8 ± 122.6 ng/mL and 165.2 ± 289.7 ng/mL, respectively, at Week 24. The decreases from baseline to Week 24 were statistically significant in both groups (both $P < 0.001$) (Figure 6a). However, the MMP-3 levels were significantly higher in biologic-experienced patients than in biologic-naïve patients at baseline and at Week 24 ($P = 0.002$).

Figure 5. Comparison of efficacy rates between biologic-naïve ($n = 64$) and biologic-experienced ($n = 73$) patients with the last observation carried forward. *DAS28-ESR*, 28-joint Disease Activity Score based on the erythrocyte sedimentation rate; REM, remission; LDA, low disease activity; SDAI, Simplified Disease Activity Index; SJC, swollen joint count; TJC, tender joint count; CDR, comprehensive disease remission; CDC, comprehensive disease control; CRP, C-reactive protein; PGA, patient's global assessment of disease activity; EGA, evaluator's global assessment of disease activity.



RF (IgM) was assessed in 92.7% (127/137) of all patients. The proportion of RF-positive patients did not change significantly from baseline to Week 24 ($P = 0.576$), with values of 74.0% at Week 0, 74.0% at Week 4, 73.2% at Week 8, 72.4% at Week 12, and 70.1% at Week 24. In the stratified analysis, 79.3% of biologic-naïve and 69.6% of biologic-experienced patients were RF positive (cutoff, 15 IU/mL). Although the proportion of RF-positive patients tended to decrease in the biologic-naïve group, reaching 70.7% at Week 24, the difference between baseline and Week 24 was not significant in this group ($P = 0.391$, Figure 6b). No change in the proportion of RF-positive patients was found in the biologic-experienced group at Week 24 (69.6%; $P = 1.000$, Figure 6b). The RF titers in biologic-naïve and biologic-experienced patients decreased from 129.8 ± 276.5 ng/mL and 209.1 ± 532.9 ng/mL, respectively, at baseline, to 99.8 ± 190.8 ng/mL and 202.2 ± 513.8 ng/mL, respectively, at Week 24. The reductions in RF titers were statistically significant in both groups (both $P < 0.001$).

Safety

Overall, 14.6% (20/137) of patients experienced AEs during the treatment period, which included 17.8% (13/73) of biologic-experienced patients and 10.9% (7/64) of biologic-naïve patients. One patient died because of interstitial lung disease. Although the event was causally related to abatacept therapy, the patient was over 70 years old and had RA for more than 20 years. He was a biologic-experienced patient with Stage IV and Class II disease, and had a history of obstructive lung disease and spinal canal stenosis. After 30 days of abatacept treatment, the patient experienced acute exacerbation of interstitial lung disease and died. In addition to abatacept, the patient was being treated with leflunomide. Abatacept was discontinued by 3.6% (5/137) of patients because of AEs, which included ulcer (plantar ulcer) and pneumonia (right middle lobe) in one patient each (biologic-experienced patients), and liver damage/kidney damage, stomatitis, and upper respiratory inflammation in one patient each (biologic-naïve patients). Other AEs included upper respiratory infection, liver damage, interstitial pneumonia, stomatitis, liver damage, anemia, acute upper respiratory inflammation, diarrhea, headache, psoriasis, Pneumocystis pneumonia, vasculitis angiitis exacerbation, skin ulcer, hair loss, compression fracture (12th thoracic vertebrae), and secretory otitis media. Abatacept was continued until Week 24 in all of these patients.

Discussion

The efficacy and safety of abatacept for treating RA have been investigated in numerous large-scale clinical studies in the United States and Europe [9,11,13,14,16,17,27]. The present study evaluated the efficacy and safety of abatacept over a period of 24 weeks in all RA patients treated with abatacept at four major rheumatology centers in Japan. We, for the first time, also analyzed the factors associated with the response to abatacept in patients treated in actual clinical practice settings. Notably, almost half of the patients included in this study were biologic-naïve. This analysis revealed that no history of using a biologic agent, concomitant use of glucocorticoids, and baseline SDAI score were significantly associated with the SDAI score after 24 weeks of treatment with abatacept. Multivariate analysis revealed that disease duration, no history of using biologic agents, and baseline HAQ-DI were significantly associated with HAQ-DI scores, as a measure of functional remission.

As abatacept selectively inhibits co-stimulation of activated T cells [5,6], it is likely to exert potent effects in early RA [19], a disease phase that is associated with increased T-cell activity [28,29]. Good efficacy of abatacept in patients with early RA was reported in the Abatacept trial to Gauge Remission and joint damage progression in methotrexate-naive patients with Early Erosive rheumatoid arthritis study [17]. Notably, the present study showed that the improvements in SDAI and HAQ-DI scores after 24 weeks of abatacept therapy were greater in biologic-naïve patients than in biologic-experienced patients, supporting the use of abatacept as a first-line biologic agent.

RA activity is often assessed using composite indices, including DAS28, SDAI, and CDAI. In the present study, the remission rates and the percentages of patients with low disease activity after 24 weeks of abatacept therapy, based on these indices, were compared. Interestingly, the percentage of patients with low disease activity tended to be higher when the disease activity was assessed using the SDAI scores than when it was assessed using the DAS28-ESR scores. Comparison of the remission rates and the percentages of patients achieving low disease activity according to previous use

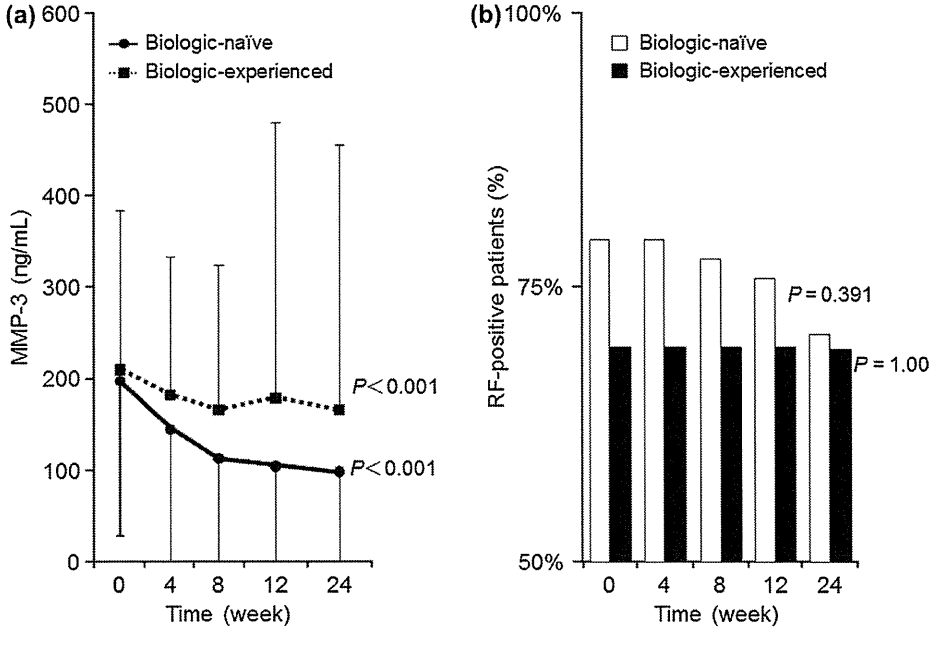


Figure 6. (a) Time course of changes in serum matrix metalloproteinase 3 levels in biologic-naïve ($n = 63$) and biologic-experienced ($n = 63$) patients. (b) Proportions of biologic-naïve ($n = 63$) and biologic-experienced ($n = 63$) patients who were positive for rheumatoid factor at each visit. MMP-3, matrix metalloproteinase 3; RF, rheumatoid factor.

of a biologic agent revealed statistically significant differences between biologic-naïve and biologic-experienced patients when assessing the disease activity using the SDAI scores, but not when assessing the disease activity using the other indices. Therefore, the response to abatacept seems to be more pronounced when disease activity was evaluated using the SDAI. A possible cause for this is that the SDAI places more emphasis on subjective symptoms than the DAS28. In fact, as shown in Figure 5, the SJC, PGA, and EGA components of the SDAI showed marked differences in the percentages of patients with values ≤ 1 between biologic-naïve and biologic-experienced patients, which likely contributed to the significant differences in SDAI scores between these two groups.

In this study, no previous use of a biologic agent, glucocorticoid use, and baseline SDAI score were significantly associated with the SDAI score at Week 24. The use and efficacy of MTX were also reported to predict SDAI score in earlier studies of infliximab (a TNF inhibitor) [30] and tocilizumab (an interleukin-6 receptor inhibitor) [31], but not in the present study using abatacept. Because the ACR/EULAR recommend the use of MTX as the first treatment of RA [32,33], MTX should be used if possible. However, abatacept appears to be as effective as MTX in patients who cannot use MTX. We also found that the use of glucocorticoids was a predictor of the SDAI score at Week 24. Although it is possible that the use of a steroid with a potent anti-inflammatory effect enhanced the effects of abatacept, there is almost no evidence that steroids prevent bone destruction. Therefore, the use of steroids should be minimized.

The present study also showed that abatacept significantly decreased the RF titer in biologic-naïve and biologic-experienced patients. In addition, the proportion of RF-positive biologic-naïve patients also tended to decrease over time, although the reduction was not statistically significant. It was reported that, unlike TNF inhibitors, abatacept has strong therapeutic effects in RF-positive patients [34]. Because similar findings were reported for rituximab [35,36], it seems likely that this may be a characteristic of drugs targeting T cells or B cells. However, although abatacept significantly improved the RF titer, this improvement was not predictive of the changes in SDAI or HAQ-DI scores. In previous reports, improved disease activity was maintained in patients treated with abatacept for 2 years [37–39]. Therefore, one reason for the failure of detecting it as a predictor may be that the data analyzed in the present report are the results up to Week 24.

In this study, the clinical response was accompanied by reduced joint destruction. It should be noted that the reduction in joint destruction in patients treated with abatacept in the present study was comparable with that achieved by other TNF inhibitors in Japanese trials [40–44]. We suspect that abatacept controlled T-cell activation and inhibited the osteoclastogenic activity of RANKL in T cells, or had direct effects on osteoclasts [45]. Further experimental studies are needed to evaluate the joint protective effects of abatacept.

AEs occurred in about 15% of patients, but were slightly more common in biologic-experienced than in biologic-naïve patients. Nevertheless, only five patients discontinued because of AEs during the 24-week treatment period, supporting the tolerability of abatacept in patients with or without a history of using biologic agents.

Some limitations of this study warrant mention. First, this study was conducted as a retrospective observational study without a formal control group. Second, 28 patients discontinued abatacept before the 24-week evaluations, which meant that their baseline data were carried forward in the analyses. Finally, this study was conducted in four specialist centers in Japan; therefore, the patient population and the magnitude of improvements may not reflect those observed in general practice.

In conclusion, the present study evaluated the efficacy and safety of abatacept for treating RA in actual clinical practice. Over 24 weeks of treatment, 16.1%, 63.4%, and 34.3% of patients achieved clinical remission, structural remission, and functional remission, respectively. Moreover, comprehensive disease control was achieved by 20.0% of patients. It is notable that the response to abatacept was generally much better in biologic-naïve patients than in biologic-experienced patients. Furthermore, the incidence of AEs was low in patients with or without history of using biologic agents. As abatacept targets activated T cells, the results of the present study support the use of abatacept as the first-line biologic agent.

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Conflict of interest

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References

1. Bankhurst AD, Husby G, Williams RC Jr. Predominance of T cells in the lymphocytic infiltrates of synovial tissues in rheumatoid arthritis. Arthritis Rheum. 1976;19(3):555–62.
2. Cush JJ, Lipsky PE. Phenotypic analysis of synovial tissue and peripheral blood lymphocytes isolated from patients with rheumatoid arthritis. Arthritis Rheum. 1988;31(10):1230–8.
3. Fox RI, Fong S, Sabharwal N, Carstens SA, Kung PC, Vaughan JH. Synovial fluid lymphocytes differ from peripheral blood lymphocytes in patients with rheumatoid arthritis. J Immunol. 1982;128(1): 351–4.
4. Van Boxel JA, Paget SA. Predominantly T-cell infiltrate in rheumatoid synovial membranes. N Engl J Med. 1975;293(11):517–20. doi:10.1056/nejm197509112931101.
5. Kremer JM. Cytotoxic T-lymphocyte antigen 4-immunoglobulin in rheumatoid arthritis. Rheum Dis Clin North Am. 2004;30(2):381–91, viii. doi:10.1016/j.rdc.2004.02.002.
6. Korhonen R, Moilanen E. Abatacept, a novel CD80/86-CD28 T cell co-stimulation modulator, in the treatment of rheumatoid arthritis. Basic Clin Pharmacol Toxicol. 2009;104(4):276–84. doi:10.1111/j.1742-7843.2009.00375.x.
7. Guyot P, Taylor PC, Christensen R, Pericleous L, Drost P, Eijgelshoven I, et al. Indirect treatment comparison of abatacept with methotrexate versus other biologic agents for active rheumatoid

arthritis despite methotrexate therapy in the United kingdom. J Rheumatol. 2012;39(6):1198–206. doi:10.3899/jrheum.111345.
8. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2006;144(12):865–76.
9. Kremer JM, Russell AS, Emery P, Abud-Mendoza C, Szechinski J, Westhovens R, et al. Long-term safety, efficacy and inhibition of radiographic progression with abatacept treatment in patients with rheumatoid arthritis and an inadequate response to methotrexate: 3-year results from the AIM trial. Ann Rheum Dis. 2011;70(10):1826–30. doi:10.1136/ard.2010.139345.
10. Li T, Gignac M, Wells G, Shen S, Westhovens R. Decreased external home help use with improved clinical status in rheumatoid arthritis: an exploratory analysis of the Abatacept in Inadequate responders to Methotrexate (AIM) trial. Clin Ther. 2008;30(4):734–48.
11. Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis. 2008;67(8):1096–103. doi:10.1136/ard.2007.080002.
12. Takeuchi T, Matsubara T, Nitobe T, Suematsu E, Ohta S, Honjo S, et al. Phase II dose-response study of abatacept in Japanese patients with active rheumatoid arthritis with an inadequate response to methotrexate. Mod Rheumatol. 2013;23(2):226–35. doi:10.1007/s10165-012-0668-z.
13. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med. 2005;353(11):1114–23. doi:10.1056/NEJMoa050524.
14. Genovese MC, Schiff M, Luggen M, Becker JC, Aranda R, Teng J, et al. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. Ann Rheum Dis. 2008;67(4):547–54. doi:10.1136/ard.2007.074773.
15. Genovese MC, Schiff M, Luggen M, Le Bars M, Aranda R, Elegbe A, Dougados M. Longterm safety and efficacy of abatacept through 5 years of treatment in patients with rheumatoid arthritis and an inadequate response to tumor necrosis factor inhibitor therapy. J Rheumatol. 2012;39(8):1546–54. doi:10.3899/jrheum.111531.
16. Schiff M, Pritchard C, Huffstutter JE, Rodriguez-Valverde V, Durez P, Zhou X, et al. The 6-month safety and efficacy of abatacept in patients with rheumatoid arthritis who underwent a washout after anti-tumour necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial. Ann Rheum Dis. 2009;68(11):1708–14. doi:10.1136/ard.2008.099218.
17. Westhovens R, Robles M, Ximenes AC, Nayiager S, Wollenhaupt J, Durez P, et al. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis. 2009;68(12):1870–7. doi:10.1136/ard.2008.101121.
18. Yazici Y, Moniz Reed D, Klem C, Rosenblatt L, Wu G, Kremer JM. Greater remission rates in patients with early versus long-standing disease in biologic-naive rheumatoid arthritis patients treated with abatacept: a post hoc analysis of randomized clinical trial data. Clin Exp Rheumatol. 2011;29(3):494–9.
19. Emery P, Durez P, Dougados M, Legerton CW, Becker JC, Vratsanos G, et al. Impact of T-cell costimulation modulation in patients with undifferentiated inflammatory arthritis or very early rheumatoid arthritis: a clinical and imaging study of abatacept (the ADJUST trial). Ann Rheum Dis. 2010;69(3):510–6. doi:10.1136/ard.2009.119016.
20. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31(3):315–24.
21. Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis Rheum. 1992;35(5):498–502.
22. Anderson J, Caplan L, Yazdany J, Robbins ML, Neogi T, Michaud K, et al. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. Arthritis Care Res (Hoboken). 2012;64(5):640–7. doi:10.1002/acr.21649.
23. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum. 2011;63(3):573–86. doi:10.1002/art.30129.
24. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23(2):137–45.
25. Matsuda Y, Singh G, Yamanaka H, Tanaka E, Urano W, Taniguchi A, et al. Validation of a Japanese version of the Stanford Health Assessment Questionnaire in 3,763 patients with rheumatoid arthritis. Arthritis Rheum. 2003;49(6):784–8. doi:10.1002/art.11465.
26. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol. 2000;27(1):261–3.
27. Weinblatt M, Combe B, Covucci A, Aranda R, Becker JC, Keystone E. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study. Arthritis Rheum. 2006;54(9):2807–16. doi:10.1002/art.22070.
28. Cascao R, Moura RA, Perpetuo I, Canhao H, Vieira-Sousa E, Mourao AF, et al. Identification of a cytokine network sustaining neutrophil and Th17 activation in untreated early rheumatoid arthritis. Arthritis Res Ther. 2010;12(5):R196. doi:10.1186/ar3168.
29. Rasmussen TK, Andersen T, Hvid M, Hetland ML, Horslev-Petersen K, Stengaard-Pedersen K, et al. Increased interleukin 21 (IL-21) and IL-23 are associated with increased disease activity and with radiographic status in patients with early rheumatoid arthritis. J Rheumatol. 2010;37(10):2014–20. doi:10.3899/jrheum.100259.
30. Tanaka Y, Takeuchi T, Inoue E, Saito K, Sekiguchi N, Sato E, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan: one-year clinical outcomes (RECONFIRM-2). Mod Rheumatol. 2008;18(2):146–52. doi:10.1007/s10165-008-0026-3.
31. Takeuchi T, Tanaka Y, Amano K, Hoshi D, Nawata M, Nagasawa H, et al. Clinical, radiographic and functional effectiveness of tocilizumab for rheumatoid arthritis patients–REACTION 52-week study. Rheumatology (Oxford). 2011;50(10):1908–15. doi:10.1093/rheumatology/ker221.
32. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. 2013. doi:10.1136/annrheumdis-2013-204573.
33. Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis. 2010;69(6):964–75. doi:10.1136/ard.2009.126532.
34. Gottenberg JE, Ravaud P, Cantagrel A, Combe B, Flipo RM, Schaeverbeke T, et al. Positivity for anti-cyclic citrullinated peptide is associated with a better response to abatacept: data from the 'Orencia and Rheumatoid Arthritis' registry. Ann Rheum Dis. 2012;71(11):1815–9. doi:10.1136/annrheumdis-2011-201109.
35. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006;54(9):2793–806. doi:10.1002/art.22025.
36. Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, et al.; DANCER Study Group. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum. 2006;54(5):1390–400. doi:10.1002/art.21778.
37. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Results of a two-year followup study of patients with rheumatoid arthritis who received a combination of abatacept and methotrexate. Arthritis Rheum. 2008;58(4):953–63. doi:10.1002/art.23397.
38. Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S, et al. Clinical response and tolerability to abatacept in

patients with rheumatoid arthritis previously treated with infliximab or abatacept: open-label extension of the ATTEST Study. Ann Rheum Dis. 2011;70(11):2003–7. doi:10.1136/annrheumdis-2011-200316.
39. Bathon J, Robles M, Ximenes AC, Nayiager S, Wollenhaupt J, Durez P, et al. Sustained disease remission and inhibition of radiographic progression in methotrexate-naive patients with rheumatoid arthritis and poor prognostic factors treated with abatacept: 2-year outcomes. Ann Rheum Dis. 2011;70(11):1949–56. doi:10.1136/ard.2010.145268.
40. Takeuchi T, Tanaka Y, Kaneko Y, Tanaka E, Hirata S, Kurasawa T, et al. Effectiveness and safety of adalimumab in Japanese patients with rheumatoid arthritis: retrospective analyses of data collected during the first year of adalimumab treatment in routine clinical practice (HARMONY study). Mod Rheumatol. 2012;22(3):327–38. doi:10.1007/s10165-011-0516-6.
41. Takeuchi T, Yamanaka H, Inoue E, Nagasawa H, Nawata M, Ikari K, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan: one-year outcome of joint destruction (RECONFIRM-2J). Mod Rheumatol. 2008;18(5):447–54. doi:10.1007/s10165-008-0077-5.
42. Tanaka Y, Yamanaka H, Saito K, Iwata S, Miyagawa I, Seto Y, et al. Structural damages disturb functional improvement in patients with rheumatoid arthritis treated with etanercept. Mod Rheumatol. 2012;22(2):186–94. doi:10.1007/s10165-0110510-z.
43. Yamanaka H, Tanaka Y, Inoue E, Hoshi D, Momohara S, Hanami K, et al. Efficacy and tolerability of tocilizumab in rheumatoid arthritis patients seen in daily clinical practice in Japan: results from a retrospective study (REACTION study). Mod Rheumatol. 2011;21(2):122–33. doi:10.1007/s10165-010-0366-7.
44. Yamanaka H, Tanaka Y, Sekiguchi N, Inoue E, Saito K, Kameda H, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan (RECONFIRM). Mod Rheumatol. 2007;17(1):28–32. doi:10.1007/s10165-006-0532-0.
45. Axmann R, Herman S, Zaiss M, Franz S, Polzer K, Zwerina J, et al. CTLA-4 directly inhibits osteoclast formation. Ann Rheum Dis. 2008;67(11):1603–9. doi:10.1136/ard.2007.080713.

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Original article

Recovery of clinical but not radiographic outcomes by the delayed addition of adalimumab to methotrexate-treated Japanese patients with early rheumatoid arthritis: 52-week results of the HOPEFUL-1 trial

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Abstract

Objective. The aim of this study was to compare efficacy outcomes of initial treatment with adalimumab + MTX *vs* adalimumab addition following 26 weeks of MTX monotherapy in Japanese early RA patients naive to MTX with high disease activity.

Methods. Patients completing the 26-week, randomized, placebo-controlled trial of adalimumab + MTX were eligible to receive 26 weeks of open-label adalimumab + MTX. Patients were assessed for mean change from baseline in the 28-joint DAS with ESR (DAS28-ESR) and modified total Sharp score (mTSS), and for the proportions of patients achieving clinical, functional or radiographic remission.

Results. Of 333 patients assessed, 278 (137 from the initial adalimumab + MTX and 141 from the initial placebo + MTX groups) completed the 52-week study. Significant differences in clinical and functional parameters observed during the 26-week blinded period were not apparent following the addition of open-label adalimumab to MTX. Open-label adalimumab + MTX slowed radiographic progression through week 52 in both groups, but patients who received adalimumab + MTX throughout the study exhibited less radiographic progression than those who received placebo + MTX during the first 26 weeks (mean ΔmTSS at week 52 = 2.56 *vs* 3.30, $P < 0.001$).

Conclusion. Delayed addition of adalimumab in Japanese MTX-naive early RA patients did not impact clinical and functional outcomes at week 52 compared with the earlier addition of adalimumab. However, the accrual of significant structural damage during blinded placebo + MTX therapy contributed to the persistence of differences between the treatment strategies, suggesting that Japanese patients at risk for aggressive disease should benefit from the early inclusion of adalimumab + MTX combination therapy.

Trial registration. ClinicalTrials.gov (http://clinicaltrials.gov/), NCT00870467.

Key words: adalimumab, rheumatoid arthritis, Japanese patients, MTX naive, safety.

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CLINICAL SCIENCE

Introduction

RA is a debilitating disease associated with inflammation of the synovial tissue in affected joints. Progression of the disease, if not abated, may lead to the erosive loss of bone and cartilage in affected joints and subsequent physical disability. The early inclusion of effective therapies aimed at tight control of disease activity minimizes the risk of irreversible erosive damage [1–4].

International recommendations suggest treatment initiation with MTX administered as monotherapy, which, in the event of an inadequate response, can then be supplemented with or switched to additional synthetic DMARDs or a biologic agent [5, 6]. Patients at risk for aggressive disease (e.g. those with autoantibody positivity, early erosive damage, etc.) may benefit from the early inclusion of a biologic agent, such as a TNF inhibitor, as a biologic combination with MTX suppresses inflammation and halts erosive damage more effectively than the addition of synthetic DMARDs [1, 7]. In fact, high disease activity along with the presence of risk factors may warrant the immediate inclusion of a TNF antagonist in the treatment regimen [5], given the relatively narrow window during which aggressive disease may be halted. Western trials of biologic agents have compared initial combination therapy *vs* initial MTX monotherapy in such patient populations [8–11], however, studies in Eastern populations are lacking, where environmental, genetic and medical and/or disease management differences may impact drug effectiveness and tolerability.

The combination of adalimumab, a fully human monoclonal antibody against TNF-α, with MTX has been shown in global clinical trials to significantly reduce disease activity, improve physical function and prevent structural damage more effectively than MTX monotherapy in MTX-naive patients with early RA and high disease activity [8, 12]. The HOPEFUL-1 trial (adalimumab, a human anti-TNF monoclonal antibody, outcome study for the persistent efficacy under allocation to treatment strategies in early RA) was conducted to assess the effect of adalimumab in combination with MTX *vs* MTX alone as a first-line therapy in Japanese patients not previously treated with MTX who had high disease activity and risk factors for aggressive disease. The trial consisted of a 26-week randomized controlled period (adalimumab + MTX *vs* placebo + MTX) followed by a 26-week open-label (OL) period (OL adalimumab + MTX). Adalimumab in combination with MTX was superior to placebo + MTX during the 26-week blinded period [13]; the current post hoc analysis assessed whether there was continued separation between the treatment strategies through week 52 (i.e. 26 weeks after all patients began receiving combination therapy).

Methods

Patients

Adult patients ⩾20 years of age with active RA, as defined by the 1987 revised ACR criteria [14], of <2 years duration and not previously treated with MTX were eligible for enrolment in this study. In addition, patients were required to have at least 10 tender joints (of 68 assessed), 8 swollen joints (of 66 assessed), CRP ⩾1.5 mg/dl or ESR ⩾28 mm/hour and at least one joint erosion (JE) or RF positivity. Exclusion criteria included prior exposure to more than two DMARDs, previous treatment with CYC, ciclosporin, AZA, tacrolimus or biologic DMARDs, and patients with a chronic infection, interstitial pneumonia or a history of tuberculosis or malignancy. The study was conducted with the approval of the study site ethical review boards and in accordance with the ethical principles of the Declaration of Helsinki; all patients provided written informed consent.

Study design

This phase 3 trial (clinicaltrials.gov identifier NCT00870467 [13]) was conducted at 94 centres in Japan from 11 April 2009 through 1 August 2011 and consisted of two periods. During the first period (blinded period), patients were randomized 1:1 to receive 40 mg adalimumab every other week + weekly MTX (initiated at 6 mg/week) or placebo every other week + weekly MTX for the first 26 weeks. The dose of MTX could be increased to 8 mg/week at week 8 if a ⩾20% improvement in the tender or swollen joint count from baseline was not achieved or at the discretion of the investigator, except in the case of a safety concern. Reduction of MTX to 4 mg/week was also permitted and at the discretion of the investigator. For ethical reasons, patients were eligible to be rescued with OL adalimumab + MTX if they experienced a ⩾20% increase from baseline in tender and swollen joint counts at week 12, 16 or 20 (rescue period). Patients completing 26 weeks of study drug, either during the blinded or rescue period, were eligible to receive OL adalimumab + MTX for an additional 26 weeks (OL period).

The primary endpoint of the study was the change in modified total Sharp score (mTSS) from baseline to week 26. Details of the scoring of radiographs as well as the results of the primary endpoint have been described [13]. Briefly, 22 and 20 bilateral joints of the hands, wrists and feet were scored for JE and joint space narrowing, respectively, the sum representing the mTSS [15]. Radiographs were read by two independent radiologists blinded to time, treatment and sequence at baseline, rescue (if necessary), week 26, and week 52, or at early termination. Clinical assessments included the 28-joint DAS with ESR (DAS28-ESR), the simplified disease activity index (SDAI) and the clinical disease activity index (CDAI). These assessments are composite measures of disease activity and may include tender and swollen joint counts, acute phase reactants (CRP or ESR), patient's global health on a visual analogue scale (VAS), patient's global assessment on a VAS and/or physician's global assessment on a VAS. Physical function was assessed through the disability index of the HAQ (HAQ-DI). Effectiveness measures for this post hoc analysis included the change from baseline to week 52 in DAS28-ESR and mTSS, the proportions of patients in DAS28-ESR

remission (<2.6), with low disease activity (⩾2.6 to <3.2), with moderate disease activity (⩾3.2 to ⩽5.1) or with high disease activity (>5.1), the proportions of patients achieving various definitions of clinical remission [SDAI ⩽3.3, CDAI ⩽2.8, Boolean (TJC ⩽1, SJC ⩽1, CRP ⩽1 and patient's global assessment ⩽10 on a 100-mm VAS)] and functional (HAQ-DI <0.5) remission, the proportions of patients without radiographic progression (defined as ΔmTSS ⩽0.5) from baseline to week 52, as well as the proportions of patients experiencing clinically relevant radiographic progression (ΔmTSS >3).

Safety

Adverse events (AEs) and clinical laboratory parameters were assessed throughout exposure to adalimumab + MTX. AEs of interest were summarized on the basis of initial treatment assignment (adalimumab + MTX or placebo + MTX) as both the number of events and events per 100 patient-years (E/100 PY). AEs were coded using Standardized MedDRA Queries (SMQs) version 13.1. Treatment-emergent AEs were defined as any event with an onset date on or after the first dose of adalimumab + MTX and up to 70 days after the last dose.

Statistical analyses

This post hoc analysis included data from the per protocol set (PPS), which excluded all patients with a major protocol violation. All analyses are based on the initial treatment assignment (adalimumab + MTX or placebo + MTX) and included patients entering into the OL period following completion of the blinded or rescue period. Fisher's exact test and Wilcoxon rank sum test were used for discrete and continuous variables, respectively. Last observation carried forward (LOCF) was used to impute missing data. LOCF was used for the analysis of radiographic progression to avoid the overestimation of mTSS in the control group. The last value during the blinded period was carried forward for those patients who entered into the rescue period but did not enter into the OL period. The safety analysis set included all patients receiving at least one dose of adalimumab + MTX.

Results

Patients

Of the 333 patients initially randomized, 155 and 151 completed 26 weeks of therapy from the initial adalimumab + MTX and placebo + MTX groups, respectively (Fig. 1). Of these, 10 patients from the adalimumab + MTX group and 24 patients from the placebo + MTX group completed the 26-week study following receipt of OL adalimumab + MTX rescue therapy. A total of 152 patients from the initial adalimumab + MTX and 150 patients from the initial placebo + MTX group entered into the OL period, with 137 and 141, respectively, completing the 52-week study. Withdrawal of consent appeared to be the primary reason for discontinuation in the OL period.

Baseline demographics and disease characteristics were well matched between treatment groups (Table 1). Patients tended to have aggressive RA, evidenced by the presence of multiple risk factors for rapid disease progression (e.g. anti-CCP positivity, RF positivity, early erosive damage and elevated CRP). Consistent with aggressive RA, baseline disease activity (mean DAS28 = 6.6) and functional disability were high (mean HAQ-DI = 1.2).

Clinical, functional and radiographic outcomes

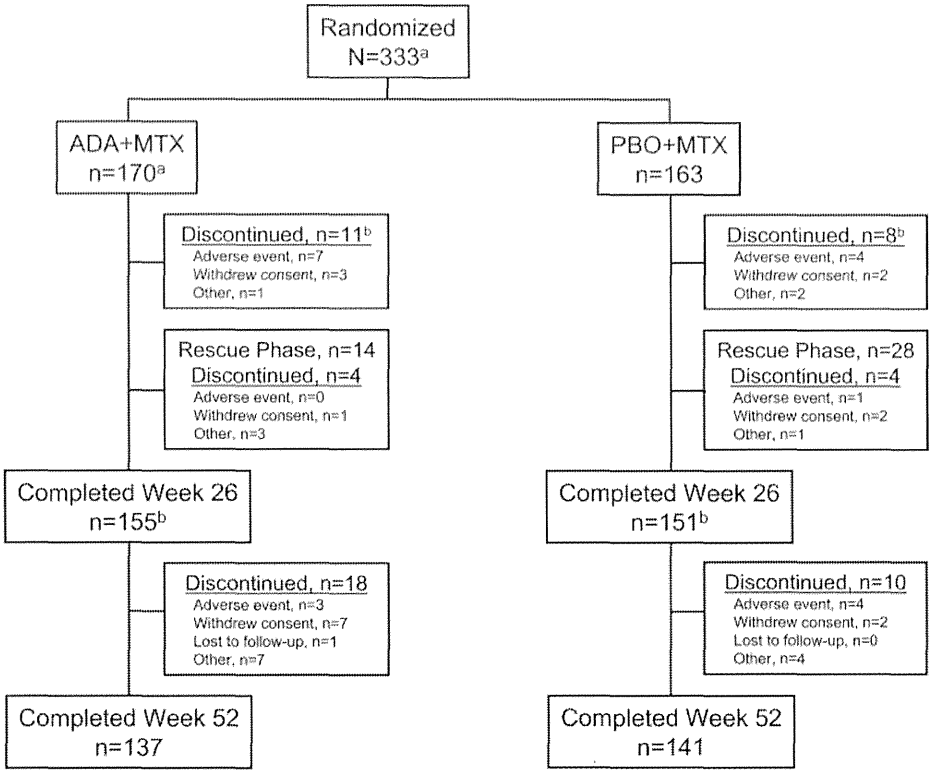
Treatment with adalimumab + MTX during the blinded period led to significant reductions in disease activity *vs* placebo + MTX (Fig. 2A) [13]. Patients who continued adalimumab + MTX throughout the study demonstrated a steady decline in mean DAS28-ESR levels through week 30, which then stabilized through week 52. The switch in placebo + MTX patients to OL adalimumab + MTX at week 26 resulted in an abrupt decline in mean DAS28-ESR levels. As a result, the differences in mean DAS28-ESR values observed during the first 26 weeks subsided within 8 weeks of adding OL adalimumab to the initial placebo + MTX population (Fig. 2A). Additionally, 26 weeks of OL adalimumab + MTX therapy in the initial placebo + MTX group led to a shift in the distribution of patients in the varying levels of disease activity (remission, low, moderate or high disease activity) such that the balance at week 52 was comparable with those who received adalimumab + MTX throughout the study (Fig. 2B). Furthermore, differences that were apparent between treatment groups at week 26 in the proportions of patients achieving additional composite measures of clinical or functional remission were less striking following an additional 26 weeks of OL adalimumab + MTX treatment (Fig. 2B and C).

Following 26 weeks of blinded therapy, the mean change from baseline in mTSS was 1.79 and 2.93 for the adalimumab + MTX and placebo + MTX groups, respectively. The addition of OL adalimumab + MTX slowed further radiographic progression in both groups through week 52, resulting in mean changes from baseline in mTSS of 2.56 and 3.30, respectively. Still, the significant differences that were apparent in mean ΔmTSS between the initial treatment groups at week 26 persisted through week 52 ($P < 0.001$; Fig. 3A). Moreover, significantly more adalimumab + MTX-initiated patients were without radiographic progression through 52 weeks of treatment than patients who initially received placebo + MTX (65.9% *vs* 42.9%, $P < 0.001$; Fig. 3B), and significantly fewer exhibited clinically relevant radiographic progression through week 52 (16.5% *vs* 36.0%, $P < 0.001$; Fig. 3C).

Safety

A total of 325 patients received at least one dose of adalimumab + MTX, representing 232.5 PY of exposure (153.6 PY in the initial adalimumab + MTX group and 78.9 PY in the initial placebo + MTX group). The majority of patients experienced at least one AE during exposure to adalimumab + MTX, although relatively few (~22%) were considered to be at least possibly related to the study drug; additionally, AEs described as serious or severe were rare (~2%; Table 2). Throughout the study

FIG. 1 Patient disposition through week 52



[a]PPS. One patient randomized to ADA + MTX received two doses of study drug at baseline and was excluded from this analysis. [b]Three patients in the ADA + MTX group and one in the PBO + MTX group discontinued from the study at week 26. ADA: adalimumab; PBO: placebo.

there were 305 infectious AEs reported, the most common being nasopharyngitis occurring in 29.8% of patients. Almost half of patients who experienced infectious AEs were assessed as probably or possibly related to adalimumab. A total of eight patients experienced nine serious infections during the course of the study. Serious infections included five cases of pneumonia reported in four patients, two cases of gastroenteritis, and one case each of bronchopneumonia and enteritis infectious. Five serious infections (3.3 E/100 PY) occurred in patients who received adalimumab + MTX throughout the study and four serious infections (5.1 E/100 PY) occurred in patients who received OL adalimumab + MTX only during the OL period. Hepatic and haematological events were relatively mild in severity and rare in frequency. Some elevations in liver function test levels were observed >2.5 times the upper limit of normal. Increased alanine aminotransferase was observed in 8.6% of patients, abnormal hepatic function in 7.4% and increased aspartate aminotransferase in 6.7%. A 55-year-old female who received initial adalimumab + MTX developed lupus-like syndrome and discontinued therapy at day 182 (week 26). There were no malignancies, tuberculosis, demyelinating disease or deaths during exposure to adalimumab + MTX.

Discussion

Patients with aggressive forms of RA, as indicated by the presence of high disease activity and poor prognostic factors (e.g. autoantibody positivity, early erosive damage, etc.) are at risk for the rapid accumulation of irreversible damage and subsequent physical disability. Hence early intervention with effective therapy capable of suppressing inflammation and preventing disease progression is the cornerstone of disease management [16]. MTX is considered to be an anchor drug for the treatment of RA and international organizations recommend an initial trial of MTX for a duration of 3–6 months prior to treatment escalation to a biologic DMARD (e.g. TNF inhibitor) [5, 6]. For patients at greatest risk for disease progression, delaying the addition of a TNF inhibitor by 2 years can impact long-term outcomes [17]. Whether an MTX trial of more limited duration (e.g. 3–6 months) is associated with suboptimal outcomes remains unclear.

The HOPEFUL-1 trial was designed to evaluate the 52-week clinical, functional and radiographic effectiveness of initial treatment with adalimumab + MTX *vs* adalimumab addition following up to 26 weeks of treatment with placebo + MTX in Japanese patients with early, aggressive

TABLE 1 Baseline demographics and disease characteristics

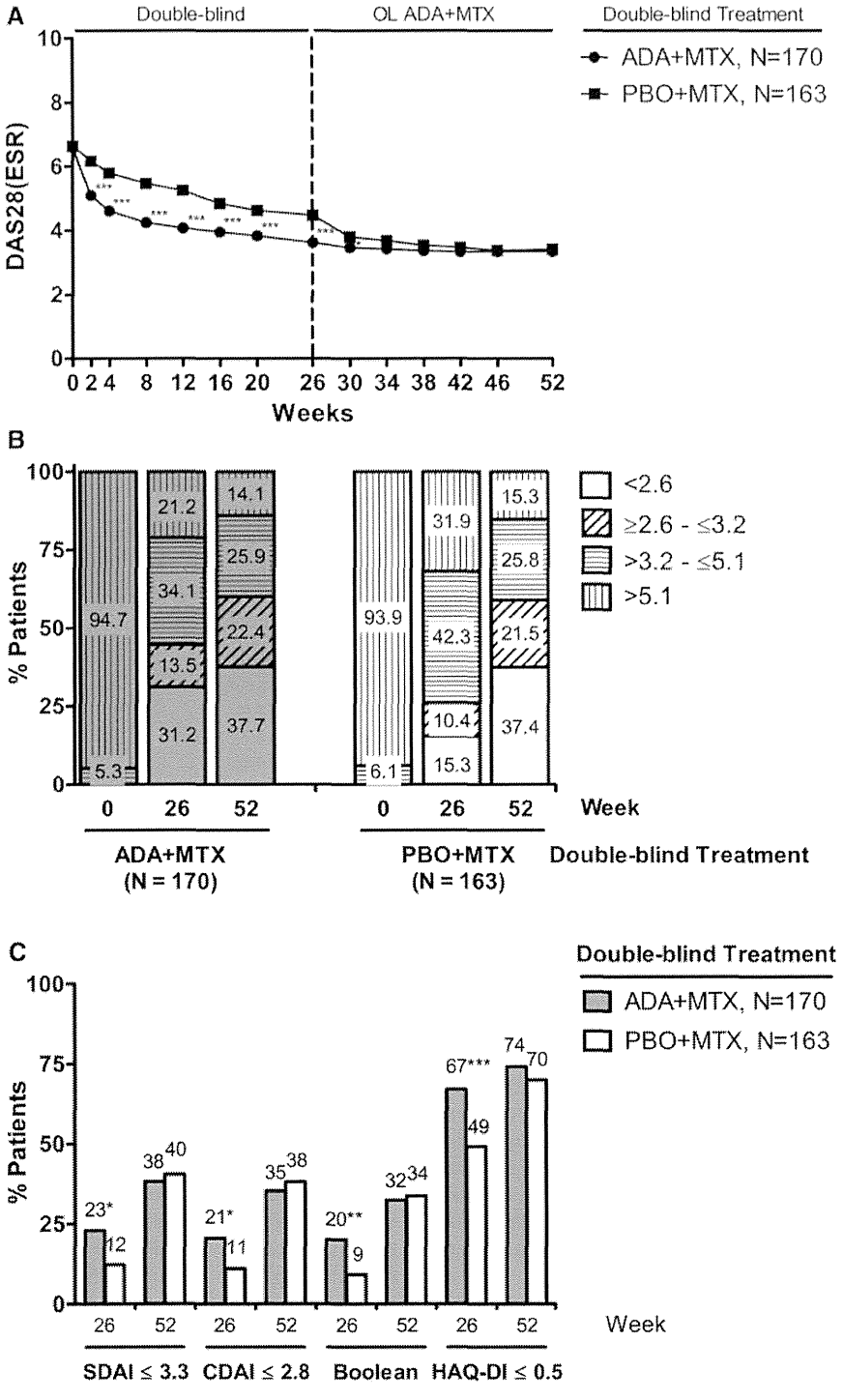
Parameter[a]	Adalimumab + MTX (*n* = 170)	Placebo + MTX (*n* = 163)
Age, years	54.0 (13.2)	54.0 (13.2)
Female, *n* (%)	143 (84.1)	128 (78.5)
RA duration, years	0.3 (0.4)	0.3 (0.4)
Weight, kg	54.4 (9.7)	56.1 (12.3)
Previous DMARD use, *n* (%)	74 (43.5)	87 (53.4)
1 DMARD	57 (33.5)	69 (42.3)
2 DMARDs	17 (10.0)	18 (11.0)
Baseline corticosteroid use, *n* (%)	58 (34.1)	49 (30.1)
RF positive, *n* (%)	145 (85.3)	136 (83.4)
Mean titre (S.D.), IU/ml	154.6 (202.9)	163.7 (362.8)
Anti-CCP positive, *n* (%)	144 (84.7)	136 (83.4)
Mean titre (S.D.), U/ml	388.3 (695.7)	241.3 (367.2)
ESR, mm/h	59.8 (30.2)	61.8 (29.0)
CRP, mg/dl	2.9 (3.0)	3.1 (3.3)
Swollen joint count		
0–28	11.6 (4.7)	11.8 (5.3)
0–66	16.5 (6.2)	17.3 (7.7)
Tender joint count		
0–28	13.2 (5.9)	13.2 (6.1)
0–66	20.7 (9.3)	21.1 (10.2)
mTSS	13.7 (22.3)	13.6 (17.4)
Erosion score	7.5 (11.7)	7.3 (9.2)
Joint space narrowing score	6.2 (11.4)	6.2 (9.4)
DAS28-ESR	6.6 (0.9)	6.6 (1.0)
HAQ-DI score	1.1 (0.7)	1.3 (0.7)
SDAI score	40.7 (12.0)	41.4 (13.8)
CDAI score	37.8 (10.9)	38.3(12.4)
Physician's global assessment of disease activity, mm	65.9 (18.4)	66.2 (18.8)
Patient's global assessment of disease activity, mm	64.3 (24.8)	66.4 (23.7)

[a]All values are given as mean (S.D.), unless otherwise indicated.

RA not previously treated with MTX. Significant differences between treatment groups were noted for a panel of clinical, functional and radiographic endpoints following 26 weeks of blinded therapy [13]. Differences between treatment groups in clinical and functional parameters disappeared rapidly following the addition of OL adalimumab + MTX at week 26, with comparable levels of disease activity observed within 8 weeks of OL adalimumab addition. Despite slowed radiographic progression upon OL adalimumab + MTX treatment, significant structural damage accumulated in many patients exposed to 26 weeks of placebo + MTX [13], resulting in more severe progression in the initial placebo + MTX group that could not be completely reversed upon switching to adalimumab + MTX.

During the blinded period (the first 26 weeks) of this study, inflammation persisted to a greater extent in those who received placebo + MTX *vs* adalimumab + MTX [13]. The addition of adalimumab + MTX led to a rapid suppression of inflammation, irrespective of whether treatment was initiated with combination therapy or whether a 26-week trial of placebo + MTX was administered. Over the short term, the persistence of elevated disease activity experienced by those in the placebo + MTX group did not appear to translate into a functional difference, as the proportions of patients achieving a state of normal function at week 52 were not different between the two treatment strategies. However, other measures of mental/physical ability and productivity were not assessed in the current analysis, and the possibility remains that long-term advantages to the early adoption of adalimumab + MTX exist in this capacity. In contrast, quantitative differences in the accumulation of structural damage persisted through 52 weeks, despite all patients receiving OL adalimumab + MTX after week 26. This observation underscores the irreversible nature of erosive bone and cartilage loss present in RA patients. Unique to this trial was the prevalence of significant damage accumulation over a relatively short timeframe [13], a phenomenon not seen in recent clinical trials of MTX-naive populations [12, 18], and rather more consistent with observations from the PREMIER trial [8]. Typically, mean ΔmTSS values are driven by relatively few patients who accumulate significant damage over time, with the remainder of the population experiencing little, if any, damage. Although this was true for HOPEFUL-1, more than one third of patients in the initial placebo + MTX group experienced clinically relevant progression through week 52. Identifying those patients most at risk for damage accumulation continues to be challenging, as

FIG. 2 Clinical and functional responses following up to 52 weeks of treatment with adalimumab (ADA) + MTX



(**A**) Mean DAS28-ESR values by visit. (**B**) The percentages of patients in remission (DAS28-ESR <2.6), low disease activity (DAS28-ESR ⩾2.6 to ⩽3.2), moderate disease activity (DAS28-ESR >3.2 to ⩽5.1) or high disease activity (DAS28-ESR >5.1) at the indicated time points. (**C**) The percentages of patients satisfying the indicated definitions of clinical (SDAI, CDAI, Boolean) or functional (HAQ-DI) remission at weeks 26 and 52. ***$P < 0.001$, **$P < 0.01$ and *$P < 0.05$.