closely monitored, as limited sampling from renal biopsy may miss more serious renal histology.

Severe disease

This refers to patients with Class III or Class IV LN (alone or in combination with Class V membranous features), or Class V LN with heavy proteinuria. These patients present with active urinary sediment (in the case of Class III or IV LN), variable degree of proteinuria, with or without renal function impairment. Even if the serum creatinine is within the normal range, a decrease or deterioration in estimated glomerular filtration rate should alert the clinician to the possibility of severe nephritis. When there is practical difficulty in obtaining a renal biopsy, patients with microscopic haematuria and dysmorphic red cells, with or without red cell casts, an active lupus serology profile with high anti-dsDNA titres and evidence of complement activation such as low level of complement components, variable levels of proteinuria and renal function, should be considered to have severe nephritis and treated accordingly. In patients with renal biopsy prior to starting treatment, features indicating a need for more aggressive treatment include the presence of crescents, fibrinoid necrosis affecting the glomerular capillaries, and thrombotic microangiopathy. Reporting of renal biopsy findings according to the 2003 International Society of Nephrology / Renal Pathology Society (ISN/RPS) Classification of LN is standard practice.[69] Inter-observer variation remains a limitation of activity and chronicity indices,[70] and the inclusion of these indices in the renal biopsy report is variable but recommended. The severity of tubulo-interstitial fibrosis and tubular atrophy is a well-established prognostic indictor for renal survival.[71] Since the responsiveness to treatment and the tolerance to immunosuppressive medications vary between individuals, it is recommended that patients be monitored closely during the early phase of induction treatment, at a frequency of once weekly or every two weeks initially, before there is evidence of serological or clinical improvement.

For the treatment of Class III or Class IV LN, alone or in combination with Class V features, members of the ALNN agreed on the following:

1. It is important to expedite the investigative and diagnostic process to aim for starting treatment early, since delay of effective treatment implies continuous attrition of nephron mass, renal reserve, and a negative impact on renal survival.
2. Initial (induction) treatment should be combination immunosuppression comprising high-dose corticosteroids and an immunosuppressive agent. The latter can be intravenous pulse CYC, MMF, or oral CYC for a limited duration, and the choice takes into consideration cost, compliance, geographical access, and reimbursement policy. The duration of this 'induction' phase lasts four to six months. There was consensus that intravenous pulse corticosteroid treatment, at a dose of 250–1000 mg methylprednisolone daily for three days, should be administered to patients with crescentic involvement of 10% or more of the glomeruli on renal biopsy, or those with deteriorating renal function attributed to the nephritic process. There were diverse opinions on the use of pulse corticosteroid in patients with lesser degrees of disease severity. Following pulse corticosteroid therapy, oral prednisolone is commenced at a dose of 0.5–0.6 mg/kg daily, while the starting dose is 0.8–1.0 mg/kg daily when not preceded by intravenous pulses. The dose of oral corticosteroids is thereafter tapered to target a dose of prednisolone below 20 mg daily after 3 months, and below 10 mg daily at 6 months from baseline.
3. Combination immunosuppression with corticosteroids and MMF is considered a standard-of-care treatment option, in view of the published data demonstrating its efficacy and tolerability in the majority of Asian patients treated with this regimen.[31–33,35] However, it should be noted that patients with crescentic LN and rapidly deteriorating renal function were often excluded from prior clinical trials. Also, the results of a post-hoc analysis of pooled data suggest that while the short-term efficacy was similar between MMF or CYC based induction treatment in patients with Class III/IV LN and renal impairment, CYC induction may be associated with more sustained remission and more favorable long-term renal outcome.[72] It is therefore important to monitor the responsiveness when MMF is used to treat patients with very severe disease. In the same context, the recent finding that disease flares were more common in patients given MMF for less than 24 months after MMF induction compared with patients treated with MMF for longer durations also suggest that remission might be more sustained following CYC induction treatment.[35,44]
4. The recommended target dose for MMF during the induction phase is 1.5–2 g daily in Asian patients, and it is advisable not to reduce the daily dose of MMF to below 1.5 g within the first year, and not to go below 1 g daily within the second year. When MMF is used as induction treatment, caution should be exercised when its treatment duration is shorter than 24 months in view of the reported association with increased risk of relapse.[35]
5. Preliminary data suggest that dual immunosuppression with corticosteroids and tacrolimus or triple immunosuppression with corticosteroids, MMF at reduced dose, and tacrolimus may be effective treatments for Class III/IV nephritis or concomitant Class III/IV and Class V disease. Long-term data with these treatment regimens are awaited. The safety of calcineurin inhibitors during pregnancy is an added advantage.

For the treatment of Class V LN, members of the ALNN agreed on the following:

1. The threshold for immunosuppressive treatment is proteinuria ≥ 2 g/day in patients with normal renal function and inactive lupus serology, while a lower threshold may apply in patients with evidence of deterioration in proteinuria or renal function or active lupus serology.

2. Immunosuppressive treatment for pure Class V LN with heavy proteinuria should be a combination of corticosteroids and either CYC, AZA, MMF, or a calcineurin inhibitor. In view of individual variations in pharmacokinetics, blood level monitoring is important in patients treated with calcineurin inhibitors to ensure adequate drug exposure and to prevent drug-induced adverse effects such as nephrotoxicity.
3. Anticoagulation should be considered in patients with persistent heavy proteinuria, especially when additional prothrombotic risk factors are present concomitantly.
4. Control of hypertension and risk factors such as dyslipidaemia and diabetes mellitus is important to prevent accelerated vascular complications.

CONCLUSIONS AND AREAS FOR FURTHER INVESTIGATION

Progress in the management of LN over the past two decades has translated into improved renal and patient survival rates. With prompt diagnosis and treatment, the long-term outcome of Asian patients appears more favorable than patients of African or Hispanic descent. Different effective immunosuppressive treatment options are now available, which facilitates individualization of treatment to optimize the efficacy-vs-risk balance. Socio-economic factors remain obstacles in the access to optimal care. In addition to immunosuppression, the importance of adjunctive treatment such as blood pressure control, minimization of vascular risk factors, and reno-preservation cannot be over-emphasized.

The knowledge gaps include the optimal management of patients with crescentic LN or thrombotic microangiopathy, the role of mycophenolic acid blood level monitoring, the role of biologics, the optimal surveillance and management of infectious complications, and the management of patients who are intolerant to current treatments. The large number of LN patients and the growing number of investigators in Asia presents a valued opportunity for investigations into these unanswered questions.

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ORIGINAL ARTICLE

Tocilizumab is clinically, functionally, and radiographically effective and safe either with or without low-dose methotrexate in active rheumatoid arthritis patients with inadequate responses to DMARDs and/or TNF inhibitors: A single-center retrospective cohort study (KEIO-TCZ study) at week 52

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Abstract

Objectives. To explore the effectiveness and safety of tocilizumab (TCZ) with or without methotrexate (MTX) in active rheumatoid arthritis (RA) patients showing inadequate responses to DMARDs and/or TNF inhibitors in clinical practice.

Methods. We observed consecutive 115 RA patients initiating TCZ treatment in Keio University Hospital, dividing them into two groups with (TCZ + MTX group) or without MTX (TCZ group), and evaluated clinical, functional and structural outcomes besides safety at week 52.

Results. Overall mean age, RA duration, and DAS28-ESR were 55.4, 8.4 years, and 5.0, respectively. Proportions of the prior use of TNF inhibitors and concomitant MTX were 45.5% and 57.4%, respectively. Mean dose of concomitant MTX was 8.4 mg/week. Baseline characteristics were comparable between the groups. TCZ improved disease activity measured by DAS28-ESR to 2.1 at week 52 overall, without significant difference between the groups. Clinical (DAS28-ESR < 2.6), functional (HAQ-DI ≤ 0.5), and structural (ΔTSS ≤ 0.5) remission rates in the TCZ group and the TCZ + MTX group were 79.1%/63.8% ($P = 0.10$), 62.8%/54.4% ($P = 0.40$), and 70.0%/53.8% ($P = 0.61$), respectively. Retention rates were 81.0% in the TCZ + MTX group and 88.5% in the TCZ group ($P = 0.47$). The rate of serious adverse events was comparable between the groups.

Conclusions. TCZ was clinically, functionally, and radiographically effective and safe either with or without low-dose MTX.

Keywords

Joint destruction, Methotrexate, Remission, Rheumatoid arthritis, Tocilizumab

History

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Introduction

Tocilizumab (TCZ) is a humanized antihuman anti-interleukin-6 receptor (IL-6R) monoclonal antibody of the IgG1 subclass directed to the IL-6Rα chain, originally developed in Japan, and has been widely used for rheumatoid arthritis (RA) in a real-world setting since 2008 in Japan, 2009 in Europe, and 2010 in U.S.A. Nowadays, TCZ is approved as one of the first-line biologic agents for active RA patients with inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs) by Japanese, European, and US regulatory agencies. Recently, European League against Rheumatism (EULAR) announced 2013 update of the 2010 recommendations for the management of RA with synthetic and biological DMARDs, in which TCZ is essentially considered to be as efficacious and safe as abatacept or TNF inhibitors and should be used as a first-line biologic agent as well as these biologics for RA patients who are resistant or toxic to conventional DMARDs [1].

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Methotrexate (MTX) is an anchor drug for RA patients to have better clinical conditions as well as reduction of radiographic progression. American College of Rheumatology (ACR) and EULAR recommend MTX as first-line therapy for patients with active RA. So far a lot of studies have revealed that MTX and TNF inhibitors have synergistic benefits for active RA patients [2–4]. As to TCZ, however, there is little knowledge about additive effect of MTX. A phase II dose-ranging study in Europe, CHARISMA study, indicated that TCZ in combination with MTX was clinically superior to TCZ monotherapy or MTX monotherapy [5]. But the CHARISMA study had only a 16-week observation period and no data on radiographic outcomes. In turn, a randomized controlled trial, ACT-RAY study, showed that TCZ plus MTX therapy was significantly superior to TCZ monotherapy at week 52 in terms of DAS28-ESR remission rate and the proportion of patients with no progression in the Genant-modified Sharp score (GSS $< = 1.5$) although as for those outcomes at week 24 and the other outcomes at week 52 including the SDAI and CDAI remission rates, the change in Health Assessment Questionnaire-Disability Index (HAQ-DI), and the change in the total GSS, there was no significant difference between the both arms [6,7]. And a retrospective observational study in Japan, the REACTION study, also indicated that clinical

remission rate at week 52 was significantly higher for RA patients treated with TCZ plus MTX than those with TCZ without MTX [8]. Should TCZ be really used in combination with MTX? Hence, we conducted the single-centered KEIO-TCZ cohort study to retrospectively investigate the effectiveness and safety of TCZ with or without MTX in active RA patients with inadequate responses to DMARDs and/or TNF inhibitors in clinical practice.

Patients and methods

Patients

All the patients with RA included in our study fulfilled the 1987 classification criteria of the American College of Rheumatology [9]. After the approval of TCZ in April 2008 in Japan, all the patients who had been started on TCZ by March 2011 in Keio University Hospital, Tokyo, were consecutively enrolled into the KEIO-TCZ cohort and were followed up every 4 weeks at the time of the infusion. We had a total of 115 RA patients during the study period. Baseline demographics and characteristics were collected from the medical charts. At each visit, the following parameters were analyzed: tender joint count (TJC) 28, swollen joint count (SJC) 28, patient's global assessment of disease activity (Pt-GA), physician's global assessment of disease activity (Ph-GA), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), matrix metalloproteinase-3 (MMP-3), and HAQ-DI. Disease activity was assessed by the disease activity score 28 (DAS28)-ESR that was calculated according to the authorized formula [10].

The KEIO-TCZ cohort study was a single-center retrospective observational study using anonymized information. Our study was conducted in conformity with Declaration of Helsinki and approved by the Institutional Review Board in our institution. The patients' written informed consents were waived according to the guideline of Health, Labour and Welfare Ministry of Japan.

TCZ treatment

TCZ was infused every 4 weeks at a dose of 8 mg/kg in accordance with the drug labeling and the TCZ therapy guidelines of the Japan College of Rheumatology (JCR) [11]. In the JCR guidelines, TCZ is recommended for RA patients with inadequate response despite at least 3-month treatment with the standard dose of one or more DMARDs. Adjustment of concomitant MTX dose and DMARDs other than MTX was at the discretion of the attending physicians. Before initiating TCZ, patients received gradually increasing doses of MTX up to tolerable maximum doses and remained on stable doses of concomitant MTX during the study. In Japan, the maximum doses of MTX were approved up to 8 mg/week until February 2011, and then approved up to 16 mg/week by the regulatory agency.

Clinical, functional and structural effectiveness

Among a total of 115 patients, clinical effectiveness was evaluated for 101 patients who have the composite measures of DAS28-ESR at both baseline and the second or subsequent visits. Functional disability was assessed by means of HAQ-DI. Radiographs of hands and feet at both baseline and week 52 were available for 46 patients for assessing the radiographic damage. The images were scored by two independent, well-trained rheumatologists (KI and YK) according to the previously reported the van der Heijde's modified Sharp (vdH-Sharp) method. Estimated yearly progression was calculated as previously reported [12].

Clinical remission was defined as a DAS28-ESR of less than 2.6 or as a Clinical Disease Activity Index (CDAI) score of 2.8 or less, functional remission as HAQ-DI of 0.5 or less, and structural remission as a change in the total vdH-Sharp score (ΔTSS) of 0.5 or less from baseline to week 52.

Safety

Safety data from a total of 115 patients were assessed based on the adverse events reported by patients as well as on the findings of physical examinations and standard clinical laboratory tests recorded during the study period. Adverse events judged to be serious by the attending physicians were individually listed.

Statistical analyses

Demographic and baseline characteristics were summarized using mean (standard deviation), median (interquartile range), or n (%), as appropriate, for patient subgroups stratified by concomitant use of MTX at baseline. The baseline data were analyzed by the Mann–Whitney U-test or Student's t-test (for continuous variables) and Pearson's chi-square test or Fisher's exact test (for categorical variables) for the group that used concomitant MTX (TCZ + MTX group) versus the group that did not use concomitant MTX (TCZ group). The last observation carried forward method was used in each analysis, and radiographic data were extrapolated to 52 weeks.

Mean values of DAS28-ESR and HAQ-DI at weeks 0, 4, 12, 24, 52 and the last observation were analyzed using the Mann–Whitney U-test between the TCZ + MTX group and the TCZ group. And remission rates defined by DAS28-ESR and CDAI at week 52, and adverse event rates were also analyzed in the same way.

Kaplan–Meier analysis was used to estimate retention rates during the first 52 weeks, and the difference in retention curves was examined by means of a log-rank test. Reasons for discontinuation were categorized for all the patients who withdrew at any time.

All reported P values are two-sided and not adjusted for multiple testing. P values < 0.05 were considered significant. All statistical analyses were performed with JMP version 9.0.2 statistical software (SAS Institute Inc., Cary, NC, USA).

Results

Demographic and baseline characteristics of patients

Baseline characteristics of the 101 patients who have all the composite measures of DAS28-ESR at baseline and at the second or subsequent visits are shown in Table 1. Mean age of the patients was 55.4 ± 12.8 years, mean RA duration was 8.4 ± 7.8 years, and DAS28-ESR was 5.0 ± 1.3. Mean dose of concomitant MTX was 8.4 ± 3.4 mg/week. DMARDs other than MTX were used in 7 patients (bucillamine in 3 patients; salazosulfapyridine, 2; mizoribine, 1; and tacrolimus, 1) in the TCZ + MTX group and 10 (mizoribine, 3; tacrolimus, 3; actarit, 1; cyclosporine, 1; leflunomide, 1; and salazosulfapyridine, 1) in the TCZ group. There were no significant differences between the TCZ + MTX group and the TCZ group in the baseline data except for body weight (55.0 ± 10.9 vs. 50.5 ± 7.9, $P = 0.010$). Mean age of the TCZ + MTX group tended to be lower than that of the TCZ group (53.8 ± 13.2 years vs. 58.0 ± 12.2 years, $P = 0.077$) (Table 2). More patients in the TCZ + MTX group tended to have previously experienced treatment with anti-TNF biologics than those in the TCZ group (53.5% vs. 34.9%, $P = 0.072$).

Changes in DAS28-ESR and HAQ-DI during 52 weeks of TCZ treatment

As seen in Figure 1a, DAS28-ESR of the TCZ + MTX group and the TCZ group promptly showed a significant decrease from 5.1 ± 0.2 and 4.9 ± 0.1 at baseline to 3.3 ± 0.2 and 3.3 ± 0.1 at week 4; 2.4 ± 0.2 and 2.5 ± 0.1 at week 12; 2.2 ± 0.2, and 2.3 ± 0.1 at week 24; 2.1 ± 0.2 and 2.0 ± 0.1 at week 52. In the both groups, disease activity status was significantly improved as

Table 1. Overall baseline characteristics.

$n = 101$	Mean ± SD	Median (IQR)
Age, years	55.4 ± 12.8	58.0 (47.0–64.0)
Women, %	93.1	
RA duration, years	8.4 ± 7.8	6.1 (2.2–13.0)
Steinbrocker		
Stage I/II/III/IV, %	19.8/36.6/7.9/35.7	
Class 1/2/3/4, %	13.9/69.3/16.8/0	
MTX use, %	57.4	
Overall MTX dose, mg/week	4.9 ± 4.9	6.0 (0.0–8.0)
MTX dose in its use subjects, mg/week	8.4 ± 3.4	8.0 (6.0–10.0)
Previous anti-TNF agent use, %	45.5	
Glucocorticoid use, %	43.0	
Overall PSL dose, mg/day	2.6 ± 3.7	0.0 (0.0–5.0)
PSL dose in its use subjects, mg/day	6.0 ± 3.4	5.0 (4.0–8.0)
Tender joint count (0–28)	5.4 ± 5.1	4.0 (2.0–7.0)
Swollen joint count (0–28)	6.3 ± 4.9	5.0 (3.0–8.0)
ESR, mm/h	50.7 ± 34.6	45.0 (20.0–70.0)
CRP, mg/dL	1.9 ± 2.2	1.2 (0.2–3.1)
Pt-GA, VAS (0–100), mm	48.4 ± 24.9	50.0 (30.0–66.5)
DAS28-ESR	5.0 ± 1.3	5.0 (4.0–6.1)
HAQ-DI	1.1 ± 0.8	1.1 (0.5–1.7)
MMP-3, ng/mL	227.2 ± 210.2	159.8 (72.2–289.8)
MMP-3 > 60, %	81.4	
RF, IU/mL	95.2 ± 122.7	51.5 (23–124.5)
RF positive (≧20), %	80.0	
Anti-CCP antibody, U/mL	63.6 ± 67.3	58.5 (9.1–100)
Anti-CCP antibody positive (≧4.5), %	81.0	

CCP, cyclic citrullinated protein/peptide; CRP, C-reactive protein; DAS, disease activity score; ESR, erythrocyte sedimentation rate; HAQ-DI, health assessment questionnaire disability index; MMP, matrix metalloproteinase; MTX, methotrexate; PSL, prednisolone; Pt-GA, patient's global assessment; RA, rheumatoid arthritis; RF rheumatoid factor; TNF, tumor necrosis factor; VAS, visual analogue scale.

early as at week 4 and changed from high or moderate disease activity at baseline to clinical remission or low disease activity during the treatment with TCZ. In the TCZ + MTX group and the TCZ group, clinical remission was obtained in 34.0% and 26.3% of the patients at week 4; 60.8% and 62.5% at week 12; 62.0% and 61.0% at week 24; 63.8% and 79.1% at week 52, respectively (Figure 1c). These findings indicated that the treatment with TCZ promptly improved RA disease activity and that clinical remission was achieved for most of the patients in the TCZ + MTX group and the TCZ group.

HAQ-DI in the TCZ + MTX group and the TCZ group also significantly decreased from 1.21 ± 0.11 and 1.06 ± 0.10 at baseline to 0.62 ± 0.11 and 0.53 ± 0.12 at week 52 (Figure 1b).

Clinical and functional remission rates

As shown in Figure 1c, rate of clinical remission at week 52 defined as a DAS28-ESR of less than 2.6 was comparable between the TCZ + MTX group and the TCZ group (63.8% vs. 79.1%, $P = 0.097$). Besides, in rate of clinical remission at week 52 defined as a CDAI score of 2.8 or less, which does not contain CRP, there was no significant difference between the TCZ + MTX group and the TCZ group (34.5% vs. 53.5%, $P = 0.056$) (Table 2). Functional remission (HAQ-DI ≦ 0.5) rate in the TCZ + MTX group and the TCZ group comparably increased from 24.1% and 28.2% at baseline to 62.2% and 68.4% at week 52, with no significant difference at week 52 between the groups ($P = 0.35$; Figure 1d).

Inhibition of radiographic damage by TCZ treatment

Radiographic damage was evaluated in 46 of the 101 patients. Most baseline parameters did not differ significantly between the patients who underwent radiographic evaluation ($n = 46$) and a total of 101 patients (data not shown).

There was no significant difference in structural remission (ΔTSS ≦ 0.5) rate between the TCZ + MTX group ($n = 26$) and the TCZ group ($n = 20$) (53.8% vs. 70.0%, $P = 0.61$; Figure 2a). In addition, when clinically relevant radiographic progression (CRRP) is defined as ΔTSS of > 3 [13], the proportion of RA patients with CRRP was 7.7% in the TCZ + MTX group and 5.0% in the TCZ group. ΔTSS at week 52 from baseline, which did not significantly differ between the two groups (1.1 ± 2.2 vs. 1.9 ± 3.9, $P = 0.55$; Figure 2b), was smaller than estimated yearly progression at baseline in both the TCZ + MTX group and the TCZ group (2.9 ± 3.2 vs. 6.5 ± 11.4).

Retention rate during 52 weeks of treatment with TCZ and causes of its discontinuation

The retention rate of treatment with TCZ in the TCZ + MTX group and the TCZ group was 98.4% and 94.2% at week 12; 92.1% and 92.3% at week 24; 81.0% and 88.5% at week 52, respectively. There was no significant difference in retention rate during 52 weeks between the two groups ($P = 0.47$). Twelve (19.1%) patients in the TCZ + MTX group and six patients (11.5%) in the TCZ group discontinued TCZ treatment because of lack of effectiveness (7/63, 11.1% vs. 1/52, 1.9%), adverse events (3/63, 4.8% vs. 3/52, 5.8%), and other reasons (2/63, 3.2% vs. 2/52, 3.8%). Most of the adverse events were infections such as Pneumocystis pneumonia, small intestine perforation, and phlegmon. The other adverse events were malignant lymphoma, pruritus with facial flush, and nausea. Miscellaneous reasons included transfer to other hospitals and difficulty in catheterization.

Discussion

Our study evaluated the effectiveness and safety of TCZ with or without concomitant low-dose (approximately 8 mg/week) MTX for patients with active RA in clinical practice, suggesting that TCZ with low-dose MTX combination and TCZ without MTX had no difference in clinical, structural, and functional effectiveness and safety for active RA patients.

Table 2. Comparison of the baseline data and the results of the three studies (KEIO-TCZ study, REACTION study, and ACT-RAY study).

	KEIO-TCZ study ($n = 101$)		REACTION study ($n = 232$)		ACT-RAY study ($n = 553$)	
	TCZ + MTX ($n = 58$)	TCZ ($n = 43$)	TCZ + MTX ($n = 127$)	TCZ ($n = 102$)	TCZ + MTX ($n = 277$)	TCZ ($n = 276$)
Age, years	53.8 ± 13.2	58.0 ± 12.2	62.8 ± 11.9	55.5 ± 14.0	53.0 ± 13.4	53.6 ± 11.9
Women, n (%)	53 (91.4)	41 (95.4)	104 (82.0)	89 (87.0)	227 (81.9)	217 (78.6)
RA duration, years	7.7 ± 7.1	9.4 ± 8.7	10.3 ± 8.5	15.0 ± 13.2	8.2 ± 8.0	8.3 ± 8.4
Steinbrocker						
Stage I/II/III/IV, %	22.4/32.8/10.3/34.5	16.3/41.9/4.7/37.2	ND	ND	II or more	II or more
Class 1/2/3/4, %	17.2/63.8/19.0/0.0	9.3/76.7/14.0/0.0	ND	ND	ND	ND
MTX dose, mg/week	8.4 ± 3.4	0	8.7 ± 3.1	0	16.1 ± 4.4	16.3 ± 4.2*
Other DMARD use, %	12.1	23.3	ND	ND	0	0
Previous anti-TNF agent use, %	53.5	34.9	72.0	51.0	0	0
Glucocorticoid use, %	43.1	44.2	75.0	76.0	50.5	50.7
Overall PSL dose, mg/day	2.5 ± 3.5	2.7 ± 3.9	5.3 ± 2.6	5.4 ± 3.8	6.8	6.7
PSL dose in its use subjects, mg/day	5.9 ± 3.1	5.8 ± 3.9	ND	ND	ND	ND
Tender joint count	5.9 ± 5.1	4.9 ± 5.0	6.7 ± 5.4	9.3 ± 7.3	25.8 ± 13.9	26.6 ± 15.2
Swollen joint count	6.4 ± 5.1	6.1 ± 4.6	7.1 ± 5.1	6.3 ± 8.0	14.4 ± 8.9	15.3 ± 10.2
ESR, mm/h	51.4 ± 32.9	49.8 ± 37.2	61.4 ± 28.5	64.1 ± 31.4	ND	ND
CRP, mg/dL	2.0 ± 2.3	1.7 ± 2.1	3.2 ± 2.8	3.1 ± 3.3	ND	ND
Pt-GA, VAS (0–100), mm	50.9 ± 24.0	45.0 ± 26.0	53.2 ± 23.8	60.5 ± 22.6	ND	ND
DAS28-ESR	5.1 ± 1.4	4.9 ± 1.1	5.5 ± 1.2	5.9 ± 1.3	6.33 ± 0.98	6.36 ± 1.00
HAQ-DI	1.2 ± 0.8	1.1 ± 0.7	1.4 ± 0.7	1.7 ± 0.8	1.46 ± 0.65	1.48 ± 0.60
Total Sharp Score	27.6 ± 38.2†	30.0 ± 34.7†	127 ± 93.8†	157 ± 109†	30.8 ± 32.2‡	37.2 ± 40.6‡
MMP-3, ng/mL	253.7 ± 216.5	192.7 ± 199.0	346.0 ± 434.5	319.0 ± 277.4	ND	ND
MMP-3 > 60, %	76.6	87.2	ND	ND	ND	ND
RF, IU/mL	91.0 ± 114.0	100.3 ± 134.2	ND	ND	ND	ND
RF positive, %	76.2	84.8	ND	ND	66.3	64.1
Anti-CCP antibody, U/mL	73.3 ± 80.9	51.7 ± 44.0	ND	ND	ND	ND
Anti-CCP antibody positive, %	81.2	80.8	ND	ND	81.9	76.6
DAS28-ESR remission rate at week 52, %	63.8	79.1	49.6	36.9	45.5	36.6
CDAI remission rate at week 52, %	34.5	53.5	ND	ND	22.7	15.9
Change in HAQ-DI	− 0.49 ± 0.644	− 0.47 ± 0.778	ND	ND	− 0.59 ± 0.713	− 0.67 ± 0.630

Mean ± SD unless otherwise indicated. CCP, cyclic citrullinated protein/peptide; CRP, C-reactive protein; DAS, disease activity score; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ-DI, health assessment questionnaire disability index; MMP, matrix metalloproteinase; MTX, methotrexate; ND, no data; PSL, prednisolone; Pt-GA, patient's global assessment; RA, rheumatoid arthritis; RF, rheumatoid factor; TCZ, tocilizumab; TNF, tumor necrosis factor; VAS, visual analogue scale.

*The patients in the TCZ monotherapy arm of the ACT-RAY study had received MTX for more than 6 weeks until tocilizumab was initiated.

†The van der Heijde's modification of Sharp's method (maximum score, 448) was used.

‡The Genant's modification of Sharp's method (maximum score, 290) was used.

Insofar as reported, there are only two randomized controlled trials (CHARISMA [5] and ACT-RAY [6,7]) and mainly two retrospective observational studies (REACTION [8,14] and Nakashima et al. [15]) that compared TCZ with or without MTX. While the CHARISMA, ACT-RAY, and REACTION studies suggested that TCZ with MTX combination therapy may be clinically superior to TCZ without MTX, our study, along with that of Nakashima et al., showed that TCZ treatment without MTX has no difference in usefulness as compared to TCZ with MTX combination therapy. This discrepancy between the previously reported studies and our study might be due to the number of cases and the difference in the baseline characteristics since the present study included patients with milder disease activity. Therefore, we should note that our result must be interpreted with caution; nevertheless, we believe that it is an important finding that TCZ without MTX might not be inferior to TCZ with MTX. In comparison with the REACTION study, which is a multicentred (Tokyo Women's Medical University, Saitama Medical University, and University of Occupational and Environmental Health) retrospective cohort study of TCZ for Japanese RA patients, our study has younger overall mean age, shorter overall mean duration of RA, milder disease activity, and milder structural damage at baseline. The proportion of the patients who used TCZ as the first biologics was 54.5% in our study, which is higher than that in the REACTION study (37.2%). Clinical and functional remission rates at week 52 in our study were higher than those in the REACTION study. And retention rates at week 52 of the REACTION study and our study were 71.1% and 84.3%, respectively. This discrepancy in the effectiveness and safety between the REACTION study and our study might be due to their baseline differences mentioned above (Table 2).

The overall radiographic remission rate at week 52 was 60.9%, which was comparable with that in the REACTION study (62.8%). Our study also showed that the proportion of RA patients with CRRP was comparable with or without concomitant MTX (7.7% vs. 5.0%). Similarly, the REACTION study demonstrated that progression of joint destruction was comparable with or without concomitant MTX.

When our study is compared with the ACT-RAY study, some background data such as mean age (around 54 years), duration of RA (around 8 years), and the proportion of GC use (around 45%) were similar in the two studies. However, patients in our study had milder mean DAS28-ESR (5.0 vs. 6.3) and HAQ-DI (1.1 vs. 1.5), used previous anti-TNF agents more often (around 40% vs. 0%), and used lower mean dose of the concomitant MTX (8.4 mg/week vs. 16 mg/week) than those in the ACT-RAY study. In terms of clinical effectiveness at week 52 in the ACT-RAY study, TCZ in combination with MTX had significantly higher DAS28-ESR remission rate than TCZ monotherapy (45.5% vs. 36.6%), but there

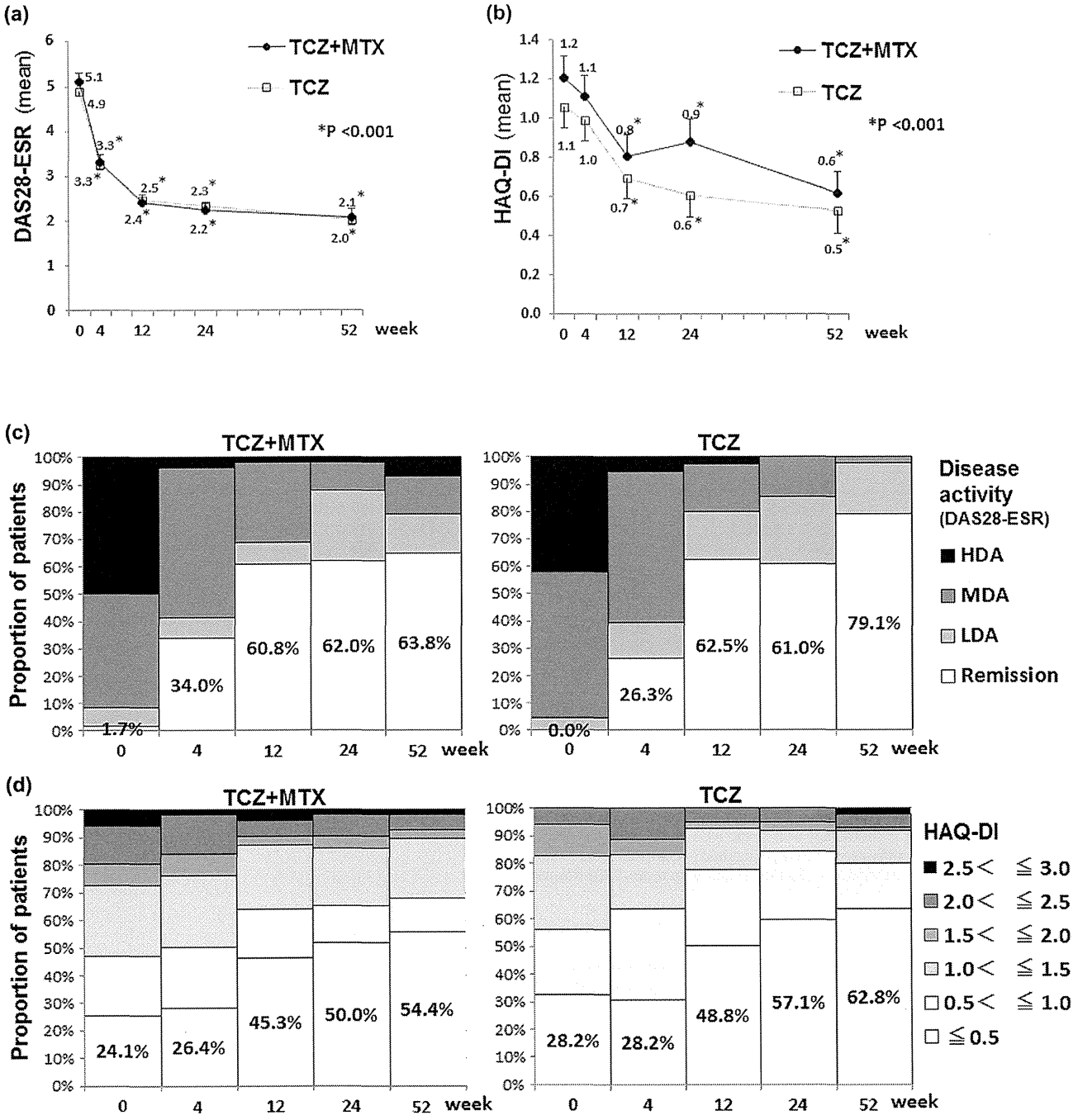

Figure 1. Changes in (a) DAS28-ESR and (b) HAQ-DI scores over 52 weeks of TCZ treatment with MTX (TCZ + MTX) or without MTX (TCZ). Values at each time point were compared with baseline. Categorical distribution of (c) disease activity status and (d) disability status over 52 weeks. HDA, high disease activity (DAS28-ESR > 5.1); MDA, moderate disease activity (3.2 ≦ DAS28-ESR ≦ 5.1); LDA, low disease activity (DAS28-ESR < 3.2); Remission (DAS28-ESR < 2.6).

was no significant difference in SDAI and CDAI remission rates between the two arms. And in regard to structural effectiveness at week 52 in the ACT-RAY study, TCZ in combination with MTX had significantly lower radiographic progression rate than TCZ monotherapy (7.2% vs. 13.9%) when radiographic progression is defined as the GSS > 1.5 (small detectable change), but there was no significant difference in the change in total GSS [7]. As for functional effectiveness, there was no difference in the change in HAQ-DI over 52 weeks between the two groups in the ACT-RAY study as well as in our study (Table 2) [7]. The distinct difference in background characteristics including RA severity, bio-naiveté, and MTX dose between the two studies might bring these different clinical and structural results, but the ACT-RAY study had results similar to our study in terms of the fact that there was no significant difference in SDAI and CDAI remission rates and the changes in total radiographic scores and HAQ-DI over 52 weeks.

Superior clinical and structural effectiveness of TNF inhibitor combination therapy with MTX over TNF inhibitor monotherapy has been demonstrated by many studies in and outside Japan [2,16–19]. While the studies outside Japan had patients with concomitant relatively high-dose MTX, the Japanese studies, such as the JESMR study and the HARMONY study, including patients

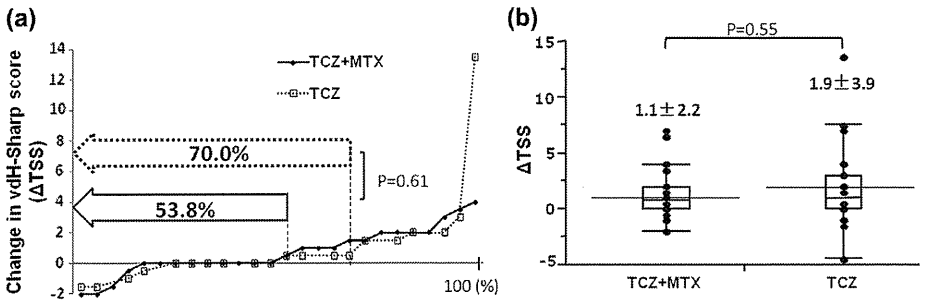

Figure 2. Effects of TCZ on radiographic damage with or without MTX. (a) Change in the total vdH-Sharp score (ΔTSS) represented by cumulative probability plot and structural remission rate over 52 weeks. (b) The mean and median change in the total ΔTSS at week 52 from baseline. Values are mean ± SD. Each box represents the 25th and 75 percentiles. Lines crossing the boxes represent the means. Lines inside the boxes represent the medians. Lines outside the boxes represent the inner fences (1.5 times the interquartile range below the lower quartile and above the upper quartile).

with relatively low-dose (7–8 mg/week) MTX, showed additive benefits of concomitant low-dose MTX use to TNF inhibitors in active RA patients with inadequate responses to DMARDs. As for TCZ, however, it had been little known whether concomitant low-dose MTX has additive benefits to TCZ treatment for RA.

Why is there a difference in the role of concomitant low-dose MTX between TNF inhibitors and TCZ? Nishina et al. reported that MTX (8.7 ± 2.3 mg/week) has an effect on decreasing not plasma TNF-α but plasma IL-6 in the treatment of RA and that the level of IL-6 rather than TNF-α after the use of MTX is important for the radiographic progression [20]. Moreover, RA disease activity is correlated with the serum level of IL-6 but not with the other cytokines including TNF-α [21]. Therefore, we think that TCZ may make a greater contribution to IL-6 inhibition than MTX because TCZ directly inhibits IL-6 signaling pathway so that the role of MTX may be little during the treatment of TCZ. Safety outcomes were similar in the TCZ + MTX group and the TCZ group. Although retention rates at week 52 and adverse events in the two groups were comparable, significantly more cases with lack of effectiveness were seen in TCZ + MTX than in the TCZ group (7 cases vs. 1 case). It may be partly due to the fact that more patients in the TCZ + MTX group tended to experience previous anti-TNF agents than those in the TCZ group (53.5% vs. 34.9%). Multivariate logistic regression analysis in the final report of the post-marketing surveillance of TCZ in Japan demonstrated that RA patients without a history of past anti-TNF inhibitors use had a significantly higher DAS28-ESR remission rate than those with [22].

In conclusion, the KEIO-TCZ cohort study revealed that TCZ was clinically, functionally, and radiographically effective and safe either with or without low-dose MTX for active RA patients who inadequately respond to DMARDs and/or TNF inhibitors in daily clinical setting. Although further prospective randomized studies are required, these real-world findings suggest that TCZ without MTX might be a useful therapeutic option for RA patients with a contraindication or intolerance to MTX.

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Conflict of interest

Kameda H has received lecture fees from Mitsubishi-Tanabe Pharma, Centocor, Pfizer Japan, Takeda Pharmaceutical Co Ltd, Abbott, Eisai Pharma, and Chugai Pharma. Takeuchi T has received lecture fees from Abbott Japan Co, Abbvie GK, Asahi Kasei Pharma Corp, Astellas Pharma Inc, Astra-Zeneca KK, Bristol-Myers KK, Chugai Pharmaceutical Co, Ltd., Daiichi-Sankyo Co, Eisai Co, Eli-Lilly Japan KK, Janssen Pharmaceutical KK, Mitsubishi Tanabe Pharma Co, Novartis Pharma KK, Pfizer Japan Inc, Sanofi-aventis KK, Santen Pharmaceutical Co, Ltd., Taisho Toyama Pharmaceutical Co, Ltd., Takeda Pharmaceutical Co, Ltd., and Teijin Pharma Ltd. The other authors declare no conflict of interest.

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Discordance in Global Assessments Between Patient and Estimator in Patients with Newly Diagnosed Rheumatoid Arthritis: Associations with Progressive Joint Destruction and Functional Impairment

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Discordance in Global Assessments Between Patient and Estimator in Patients with Newly Diagnosed Rheumatoid Arthritis: Associations with Progressive Joint Destruction and Functional Impairment

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ABSTRACT. ***Objective.*** Factors relevant to the discordance between the patient global assessment (PGA) and estimator global assessment (EGA) in patients newly diagnosed with rheumatoid arthritis (RA) were examined.

Methods. Seventy-five consecutive newly diagnosed patients with RA were prospectively enrolled. We used 3 models in which discordance between PGA and EGA at 12 months was set at 5 mm, 10 mm, or 20 mm. We adopted 10 mm as representative and examined time course changes in clinical variables over 12 months.

Results. No significant difference was found between the concordance and the higher PGA groups regarding baseline characteristics and treatment. At 12 months, EGA, swollen joint count, and inflammatory marker values were not different, but pain visual analog scale and tender joint count were significantly higher in the higher PGA group, and the Health Assessment Questionnaire improved less. In the 10 mm and 20 mm models, the structural remission rate was significantly lower in the higher PGA group and the rapid radiological progression rate significantly higher. The discrepancy was already significant at 3 months.

Conclusion. In newly diagnosed RA, PGA at 12 months may be more sensitive for indicating progressive joint destruction and functional impairment when compared with EGA, and there is a discrepancy directed toward a worse assessment by patients. (First Release May 1 2014; J Rheumatol 2014;41:1061–6; doi:10.3899/jrheum.131468)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
PATIENT GLOBAL ASSESSMENT
ESTIMATOR GLOBAL ASSESSMENT
DISCORDANCE

The management of rheumatoid arthritis (RA) involves multiple processes, including discussion and agreement between patients and their physicians. A patient's condition is generally expressed using patient's global assessment (PGA) and the physician's evaluation by estimator global assessment (EGA). The PGA does not necessarily agree with the EGA[1,2,3,4]. The discrepancy between PGA and EGA has been reported to be 24–76%, varying according to the definition of the discrepancy and often directed toward a better assessment by physicians than by patients. Nicolau, *et al*[1] reported that patients with a greater PGA discrepancy presented with higher pain scores and tender joint count (TJC). Barton, *et al*[2] reported that depressive symptoms are associated with greater PGA discordance. Studenic, *et al*[3] described the pain score as the most significant determinant of greater PGA discordance, and Khan, *et al*[4] reported that pain is the most important determinant of the PGA. Although these reports suggest that pain is the most influential factor for elevated PGA, the results were derived from cohorts including patients with long disease duration. Joint tenderness is an important feature of disease activity, but pain is also caused by established joint damage without active inflammation, which physicians may not be willing to take into account in disease activity.

Therefore, we focused on newly diagnosed patients with little joint destruction and examined factors relevant to discordance between the PGA and EGA 12 months after diagnosis.

MATERIALS AND METHODS

Patients. This study was conducted with part of the SAKURA cohort of consecutive patients who were newly diagnosed with RA at Keio

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University Hospital and had never been treated with either disease-modifying antirheumatic drugs or steroids and prospectively observed since September 2007. The diagnosis of RA was made based on the 1987 American College of Rheumatology (ACR) RA criteria[5] or 1994 Japanese College of Rheumatology (JCR) early RA criteria[6]. Our study was approved by the ethics committee, and all patients provided written consent.

Laboratory data included C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Patient pain, PGA, and EGA were measured on a visual analog scale (VAS) ranging from 0 to 100 mm. The questions for the PGA, EGA, and pain were, "How do you estimate your disease activity today?", "How do you estimate the patient's disease activity today?", and "How severe is your pain today?," respectively. A Health Assessment Questionnaire (HAQ) was filled out by each patient. EGA and joint assessment were recorded by 1 of any 5 rheumatologists, all of whom had more than 10 years of experience. Hands and feet radiographs were taken at the time of diagnosis and 12 months later. The radiographs were blinded and read independently by 2 readers (YK and MK) according to van der Heijde/modified total Sharp score (mTSS); the mean values were used in the analysis. The ∅mTSS value was the progression over a year by subtracting the mTSS at baseline from the mTSS at 12 months. Structural remission (sREM) and radiological rapid progression (RRP) were defined as ∅TSS ≤ 0.5/year and ≥ 5/year, respectively.

Analysis of factors relevant to discrepancies between PGA and EGA 12 months after diagnosis. In previous reports, the definition of discordance between the PGA and EGA was 5 to 30 mm[2,3,4,5]. We used 3 models in which the discordance at 12 months was set at 5 mm, 10 mm, or 20 mm. Each model divided the patients into 3 groups: higher PGA, concordance, and higher EGA.

Time course changes in clinical variables. We examined changes in PGA, EGA, pain VAS, 28-joint Disease Activity Score (DAS28), TJC, swollen joint count (SJC), CRP, and HAQ over 12 months and compared them between groups.

Statistical analysis. The means of continuous variables were compared by Student's t test, and proportions were compared by chi-square test. The level of concordance between PGA and EGA was analyzed using Lin's concordance correlation coefficient. The comparisons of time series data were analyzed by 2-way repeated measures of ANOVA using the posthoc Tukey method. All statistical analyses were performed using SPSS version 20.0.

RESULTS

Patients. A total of 75 consecutive patients were newly diagnosed as having RA in the SAKURA cohort between September 2007 and August 2009 and included in this study. Forty-two patients (56%) fulfilled 1987 ACR classification criteria, and 68 patients (91%) fulfilled 2010 ACR/European League Against Rheumatism (EULAR) criteria[7]. Eighty-six percent were female. At the time of diagnosis, the patients had a mean age of 60.9 years, and the mean duration from symptom onset to the time of diagnosis was 9.1 months. Seventy-nine percent were positive for anticyclic citrullinated peptide antibodies, and a mean DAS28 was 4.5.

Comparison of variables between the concordance group and higher PGA group. When the discordance was defined as 5 mm, 10 mm, or 20 mm, the higher PGA group comprised 38 (51%), 34 (45%), and 24 (32%) patients, the concordance group 29 (39%), 38 (51%), and 48 (64%) patients, and the higher EGA group 8 (10%), 3 (4%), and 3 (4%) patients, respectively. The higher EGA group did not have enough patients to analyze; therefore, we compared the higher PGA group and concordance group.

No significant differences were found between the concordance group and the higher PGA group regarding baseline characteristics and treatment at 12 months (Table 1). The EGA, SJC, CRP, and ESR did not differ between the groups in any model at 12 months. However, in all 3 models at 12 months, the pain and TJC were significantly higher in the higher PGA group than in the concordance group, and HAQ improved less. In the 10 mm and 20 mm model, radiological progression as a proportion of sREM and RRP was significantly worse in the higher PGA group and the RRP higher. In addition, in the 20 mm model, SJC was even higher in the higher PGA group.

Probability plot of yearly radiographic progression with 10 mm discordance. Because a radiological progression and the lesser improvement in HAQ were picked up by defining discordance as 10 and 20 mm, we adopted 10 mm as representative. The probability plot of ΔTSS for 10 mm is shown in Figure 1.

Time course changes in the level of concordance between EGA and PGA and disease activity-related variables. The changes in PGA and EGA over 12 months are presented in Appendix 1. The levels of concordance shown by Lin's concordance correlation coefficient were 0.55, 0.36, 0.37, 0.36, and 0.37 at baseline, 3, 6, 9, and 12 months, respectively. Time course changes in disease activity variables were examined at a discordance of 10 mm (Figure 2). In the concordance group, EGA and PGA decreased in parallel, as well as TJC, SJC, CRP, and HAQ. In the higher PGA group, the PGA did not change over 12 months, but the EGA decreased. The discrepancy between the PGA and EGA was significant at 3 months.

DISCUSSION

Our study shows that about half of newly diagnosed patients with RA exhibit discordance between PGA and EGA 12 months after diagnosis, and the PGA at 12 months might be more sensitive for detecting progressive joint destruction and less improvement of functional impairment when compared with EGA, and there is a discrepancy toward a worse assessment by patients.

There is a growing interest in the use of patient-reported outcomes in RA[8,9]. However, disagreement exists between patients and their physicians, often with PGA showing worse than EGA[1,2,3,4]. We examined patients' clinical characteristics using 3 different definitions and found that, even when defining discordance as 5 mm, a worse PGA reflected more TJC and worse pain. When the discordance was defined as 10 mm, the difference in sREM and RRP rates became significant. These results show that, while we could describe 5 mm as discordance between patients and their physicians, the appropriate definition of discordance

Table 1. Baseline and 12-month characteristics of concordance and higher PGA groups in the 3 models. Data are expressed as mean (SD) unless otherwise indicated. The numbers for current treatments include combination therapy use.

Discordance Model	5 mm			10 mm			20 mm		
	Concordance, n = 29	PGA Higher, n = 38	p	Concordance, n = 38	PGA Higher, n = 34	p	Concordance, n = 48	PGA Higher, n = 24	p
At baseline									
Age, yrs	62.5 (13.3)	57.1 (14.5)	0.12	62.6 (12.5)	57.2 (15.1)	0.10	61.9 (13.6)	56.4 (14.3)	0.13
Duration, mos	9.4 (14.5)	10.2 (20.6)	0.85	9.9 (22.2)	7.7 (9.9)	0.38	9.5 (20.0)	9.5 (11.3)	1.00
Smoking, n (%)	5 (24)	14 (37)	0.38	9 (24)	10 (35)	0.57	14 (29)	7 (29)	1.00
SE, n (%)	19 (66)	24 (63)	0.90	24 (63)	22 (65)	0.93	32 (67)	14 (58)	0.64
Anti-CCP, n (%)	18 (64)	21 (55)	0.40	25 (66)	18 (52)	0.16	30 (61)	13 (56)	0.61
DAS28	4.3 (1.2)	4.6 (1.1)	0.32	4.4 (1.1)	4.7 (1.1)	0.23	4.4 (1.2)	4.6 (1.0)	0.64
SDAI	15.3 (10.1)	16.9 (10.6)	0.54	16.2 (10.3)	17.2 (10.9)	0.68	17.0 (11.4)	16.0 (8.9)	0.66
CDAI	13.3 (8.7)	15.0 (9.2)	0.45	14.4 (9.3)	15.2 (9.5)	0.73	15.1 (10.0)	14.2 (7.8)	0.67
SJC	3.2 (2.8)	3.8 (3.7)	0.43	4.0 (3.5)	3.8 (3.7)	0.9	4.1 (3.9)	3.5 (3.0)	0.50
TJC	2.6 (2.9)	3.1 (3.4)	0.56	3.2 (3.2)	3.2 (3.5)	1.0	3.3 (3.7)	2.9 (3.1)	0.58
PGA, mm	42.6 (33.4)	42.9 (24.2)	0.97	40.7 (31.4)	43.6 (23.4)	0.67	42.4 (30.4)	41.5 (22.0)	0.89
Pain VAS, mm	42.8 (33.3)	43.7 (24.5)	0.90	41.3 (31.9)	44.7 (24.5)	0.61	44.0 (30.0)	40.8 (25.6)	0.65
EGA, mm	32.4 (24.1)	37.9 (21.3)	0.33	32.4 (23.7)	38.2 (20.8)	0.27	34.5 (24.4)	36.3 (18.0)	0.73
CRP, mg/dl	2.0 (2.9)	1.9 (2.1)	0.90	1.8 (2.6)	2.1 (2.2)	0.63	2.0 (2.7)	1.8 (2.0)	0.78
ESR, mm/h	56.7 (36.4)	60.6 (34.0)	0.65	51.4 (34.5)	61.5 (33.7)	0.11	54.2 (34.3)	64.3 (34.8)	0.25
HAQ	0.63 (0.75)	0.84 (0.70)	0.23	0.66 (0.75)	0.84 (0.63)	0.29	0.77 (0.80)	0.69 (0.49)	0.60
TSS	6.6 (7.0)	9.6 (20.5)	0.36	6.3 (7.0)	9.9 (21.4)	0.34	5.4 (6.5)	13.2 (24.9)	0.15
At 12 mos									
DAS28	2.3 (0.8)	3.0 (1.1)	*< 0.01*	2.3 (0.79)	3.1 (1.1)	*< 0.01*	2.3 (0.8)	3.3 (1.0)	*< 0.01*
SDAI	2.8 (5.1)	7.1 (5.1)	*< 0.01*	3.0 (4.6)	7.5 (5.2)	*< 0.01*	3.3 (4.5)	3.3 (4.5)	*< 0.01*
CDAI	2.7 (5.0)	6.8 (5.0)	*< 0.01*	2.85 (4.5)	7.3 (5.1)	*< 0.01*	3.1 (4.4)	8.5 (4.9)	*< 0.01*
SJC	0.8 (2.0)	1.3 (1.8)	0.30	0.8 (1.8)	1.3 (1.9)	0.16	0.7 (1.6)	1.8 (2.0)	*0.04*
TJC	0.2 (0.6)	1.0 (1.8)	*0.01*	0.3 (0.8)	1.0 (1.8)	*0.04*	0.3 (0.8)	1.3 (2.0)	*0.04*
PGA, mm	8.7 (17.0)	37.1 (21.0)	*< 0.01*	8.8 (15.2)	40.1 (20.2)	*< 0.01*	12.1 (16.5)	46.6 (18.9)	*< 0.01*
Pain VAS, mm	8.7 (16.3)	30.0 (23.2)	*< 0.01*	8.5 (14.5)	32.2 (23.6)	*< 0.01*	11.0 (17.1)	37.0 (22.3)	*< 0.01*
EGA, mm	8.2 (17.3)	8.3 (10.0)	0.98	8.7 (15.8)	8.8 (10.4)	0.98	8.7 (15.2)	8.8 (9.0)	0.96
CRP, mg/dl	0.1 (0.2)	0.3 (0.3)	0.06	0.2 (0.2)	0.3 (0.3)	0.16	0.2 (0.2)	0.3 (0.4)	0.23
ESR, mm/h	21.6 (18.7)	24.7 (22.2)	0.54	20.7 (17.5)	26.1 (22.9)	0.28	21.2 (18.7)	27.3 (23.0)	0.27
HAQ	0.26 (0.56)	0.58 (0.46)	*0.01*	0.25 (0.50)	0.61 (0.46)	*< 0.01*	0.29 (0.50)	0.67 (0.45)	*< 0.01*
∅TSS, n (%)	2.4 (6.7)	5.1 (9.2)	0.17	2.4 (6.3)	7.9 (12.8)	0.05	2.6 (6.0)	8.2 (14.8)	0.09
≤ 0.5 (sREM)	17 (59)	15 (39)		24 (63)	12 (35)		29 (60)	7 (29)	
0.5 to 5	7 (25)	10 (27)	0.22	8 (21)	9 (27)	*0.04*	10 (21)	7 (29)	*0.03*
≥ 5 (RRP)	5 (17)	13 (34)		6 (16)	13 (38)		9 (19)	10 (42)	
Current tx, n (%)									
MTX	17 (59)	24 (63)	0.90	24 (63)	21 (62)	0.90	31 (65)	14 (58)	0.80
Steroid	2 (7)	3 (8)	0.88	3 (8)	3 (9)	0.89	3 (6)	3 (13)	0.65
Biologic	5 (17)	10 (26)	0.56	6 (16)	9 (26)	0.41	10 (21)	5 (21)	1.00
Others	14 (48)	16 (42)	0.80	17 (45)	15 (44)	0.96	20 (42)	12 (50)	0.68

P values in italics are considered significant. SE: shared epitope; anti-CCP: anticyclic citrullinated peptide antibody; DAS28: 28-joint Disease Activity Score; SDAI: Simplified Disease Activity Score; CDAI: Clinical Disease Activity Score; TJC: tender joint count; SJC: swollen joint count; PGA: patient global assessment; VAS: visual analog scale; EGA: evaluator global assessment; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MMP: matrix metalloproteinase; HAQ: Health Assessment Questionnaire; TSS: van der Heijde/modified total Sharp score; sREM: structural remission (∅TSS ≤ 0.5/yr); RRP: rapid radiographic progression (∅TSS ≥ 5/yr); tx: treatment; MTX: methotrexate.

may be 10 mm, which allowed us to detect differences in the progression of structural damage.

Several reports showed that pain is the most influential factor for elevated PGA[1,2,3,4], and our results are compatible with those studies. Although PGA has been shown to be influenced by noninflammatory factors[10,11], our study shows that PGA at 12 months may be more sensitive than the EGA for indicating progressive joint destruction and functional disorder. Studenic, *et al*[3] reported that in patients with average pain a concordance between EGA and PGA is attained at 10 swollen joints, suggesting that physicians weigh SJC heavily. However, 10 swollen joints appears quite many, and some studies have reported that synovitis can be detected by sensitive modalities in joints without swelling[12]. We consider that EGA need to be more reflective of pain in newly diagnosed patients.

When we looked at the time course changes, the discordance was already significant at 3 months and increased at 6 months. This result is presumably due to decreases in SJC leading physicians toward an improved rating, but it is not

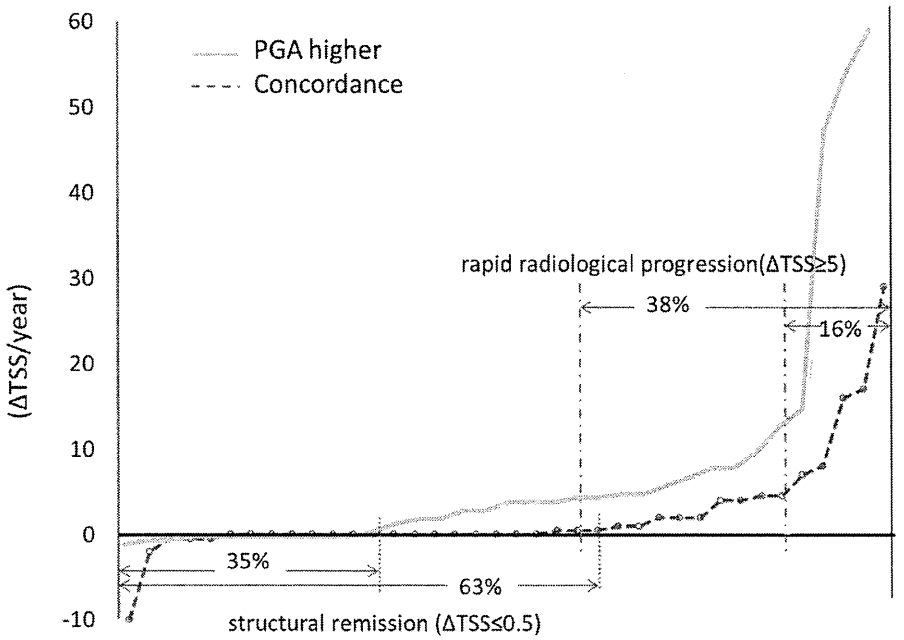

Figure 1. Radiological changes in patients at 12 months expressed by a probability plot with 10 mm discordance. The concordance group is indicated by solid lines, the higher PGA group by dotted lines. The PGA higher group showed worse progression than concordance group. The sREM rate was significantly lower in the higher PGA group and the RRP higher (35 vs 63%, 38 vs 16, respectively). TSS: modified total Sharp score; PGA: patient's global assessment; sREM: structural remission; RRP: rapid radiological progression.

necessarily the same for the perception of patients with persistent pain. Based on our results indicating that a higher level of pain or a modest increase in SJC can be associated with radiological progression, physicians should be more aware of the importance of pain and small changes in SJC in newly diagnosed patients.

Our study has some limitations. It was conducted in a single Japanese center. Because pain is expressed differently among different cultural backgrounds[13], future investigations are encouraged. As a result of the small sample size, very few patients were in the higher EGA group, which forced us to exclude those patients from the analysis. Patients with higher EGA may have different features[4] and need to be investigated. Some characteristics associated with poor prognosis were inclined to be higher in the higher PGA group, including HAQ and mTSS. Although these differences were not statistically significant, it might be partly due to the relatively small number of patients in each group. Moreover, over 12 months, more patients in the higher PGA group started to use biological agents. Hence, the differences in the worse outcomes in HAQ and mTSS may in addition to discordance between PGA and EGA reflect some underlying propensity for worse prognosis. Nonetheless, our findings point to focusing closer attention on the patient's disease experience. We did not examine a Routine Assessment of Patient Index Data 3 (RAPID3) score composed of major patient-reported outcomes: multidimensional HAQ, pain, and patient global estimate. However, our results warrant further research on the importance of patient-reported outcomes. Our patients were diagnosed based on 1987 ACR criteria or 1994 JCR early RA criteria because the SAKURA study was started before 2010 ACR/EULAR classification criteria were announced. However, because more than 90% of our patients fulfilled the new criteria, our results have enough generalizability.

In newly diagnosed patients with RA, PGA at 12 months may be more sensitive for indicating progressive joint destruction and less improvement of functional impairment when compared with EGA, and there is a discrepancy toward a worse assessment by patients.

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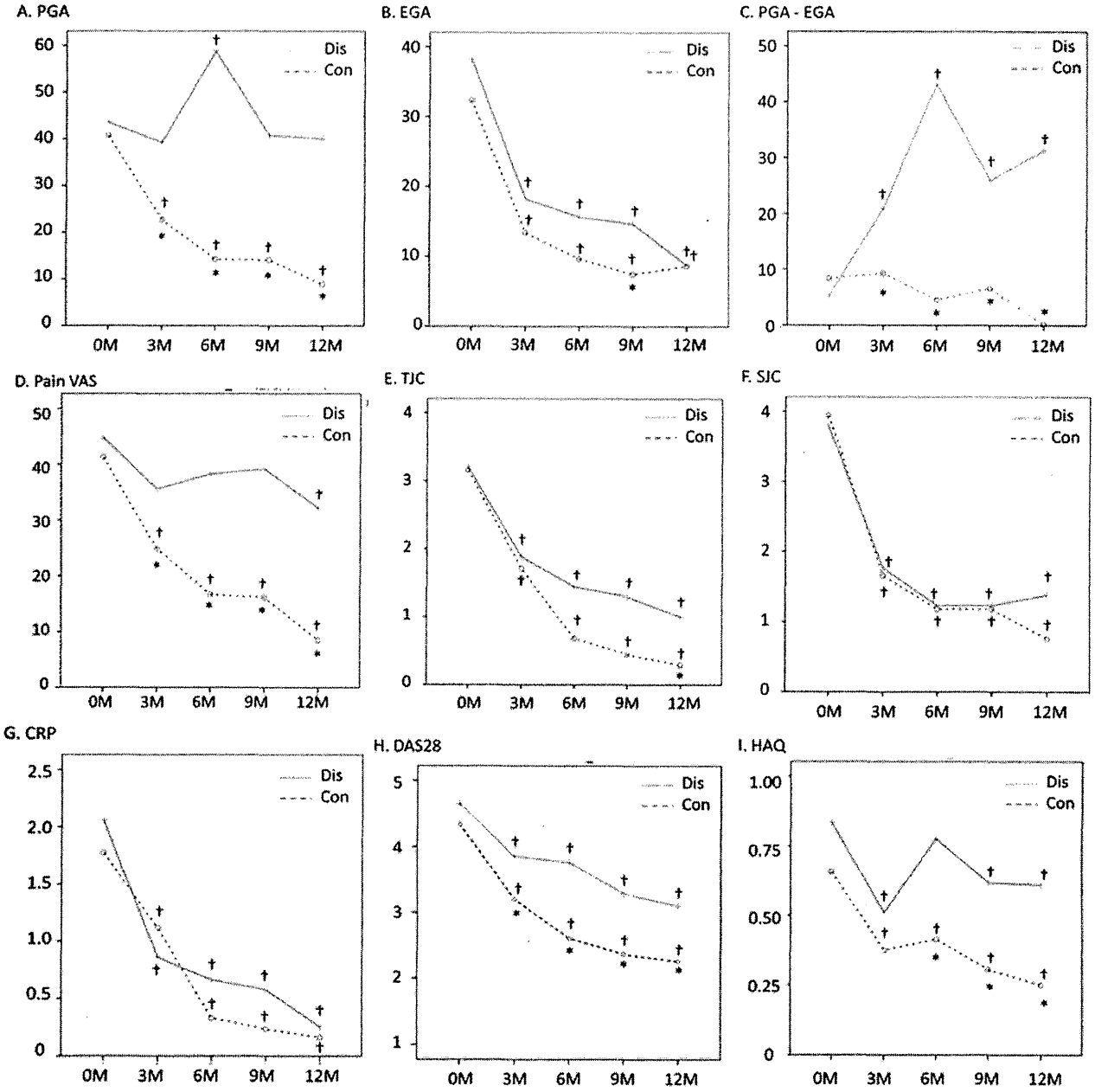

Figure 2. Changes in variables pertinent to disease activity over 12 months. A. Patient's global assessment (PGA). B. Evaluator global assessment (EGA). C. PGA-EGA. D. Pain visual analog scale (VAS). E. Tender joint count (TJC). F. Swollen joint count (SJC). G. C-reactive protein (CRP). H. 28-joint Disease Activity Score (DAS28). I. Health Assessment Questionnaire (HAQ). A discordance between the PGA and the EGA at 12 months was defined as 10 mm. The concordance group is indicated by solid lines, the higher PGA group by dotted lines. * $p < 0.05$ compared to the corresponding time point; † $p < 0.05$ compared to basal values.

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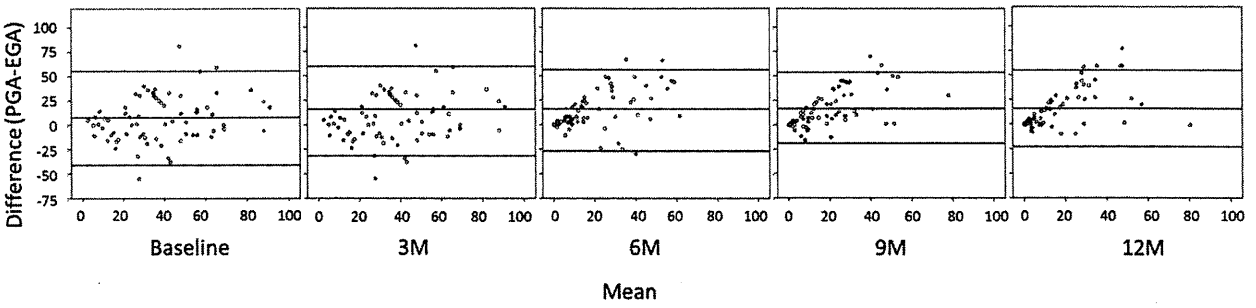
APPENDIX 1. The changes in PGA and EGA over 12 months were analyzed using Bland-Altman plots. The difference between PGA and EGA was assigned as the vertical value, and the mean of the PGA and EGA as the horizontal value, and t. Of 3 horizontal lines, the center one presented the mean value of the difference between the two, the upper was the mean plus 2 SD, and the lower the mean minus 2 SD. PGA: patient's global assessment; EGA: evaluator global assessment.



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ORIGINAL ARTICLE

Phase III, multicenter, open-label, long-term study of the safety of abatacept in Japanese patients with rheumatoid arthritis and an inadequate response to conventional or biologic disease-modifying antirheumatic drugs

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Abstract

Objectives. To examine the long-term safety of intravenous (IV) abatacept treatment in Japanese patients with rheumatoid arthritis (RA) and an inadequate response to methotrexate (MTX) or other conventional or biologic disease-modifying antirheumatic drugs.

Methods. This Phase III, open-label, long-term study (NCT00484289) comprised Japanese patients with RA who had completed abatacept Phase I or Phase II studies, and new patients intolerant to MTX. Patients from Phase I and Phase II studies received a weight-tiered dosing equivalent of 10 mg/kg abatacept, with MTX at doses up to 8 mg/week; newly enrolled patients received weight-tiered 10 mg/kg abatacept monotherapy. Safety and efficacy were assessed.

Results. A total of 217 patients (Phase I, $n = 13$; Phase II, $n = 178$; newly enrolled, $n = 26$) were treated with IV abatacept for a mean of 3 years. Serious adverse events occurred in 67/217 (30.9%) patients. Most adverse events were mild or moderate. For all cohorts combined, American College of Rheumatology 20% response rates ranged from 61.3 to 81.8% for as-observed and last observation carried forward analyses over 192 weeks. Following initial response, clinical and functional outcomes were maintained for up to 3 years.

Conclusions. In Japanese patients with RA, IV abatacept with and without background MTX showed tolerable safety and sustained efficacy over 3 years.

Keywords

abatacept, Japanese, long-term study, rheumatoid arthritis

History

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Introduction

Chronic diseases such as rheumatoid arthritis (RA) require treatments that provide durable efficacy, and which are safe and well tolerated over the long term. While the majority of Japanese patients with RA start their treatment with a conventional disease-modifying antirheumatic drug (DMARD) such as methotrexate (MTX) [1], some patients do not achieve adequate clinical benefit with MTX and may experience serious adverse events such as liver toxicity and bone marrow suppression [2]. Furthermore, MTX should not be administered to some patients due to safety concerns, such as a history of liver or kidney disorders [3]. As many such patients have significant disease activity, additional therapeutic options are necessary. Biologic DMARD therapies for RA provide increased clinical and structural benefit compared with conventional DMARDs [4,5]. First approved more than a decade ago [6], a variety of biologic agents with differing mechanisms of action are currently available.

Abatacept is a fully humanized, soluble, recombinant fusion protein consisting of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and the Fc domain of human immunoglobulin (Ig) G1. It is the only treatment for RA that mimics the naturally occurring homeostatic mechanism of human CTLA-4 and inhibits the interaction of CD28 with CD80/86 on the antigen-presenting cell, thus selectively modulating the co-stimulatory signal required for full T-cell activation [7].

The safety and efficacy of intravenous (IV) abatacept has been well established in the global population, with both short-term and long-term studies. IV abatacept is currently approved in the USA, the European Union, Japan, and several other countries for the treatment of moderate-to-severe RA, and a subcutaneous formulation is becoming more widely available worldwide. The IV formulation of abatacept is effective, with favorable safety, in patients with RA who are MTX-naïve [8], MTX inadequate responders [9,10], or anti-tumor necrosis factor inadequate responders [11].

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IV abatacept has demonstrated favorable tolerability and clinical efficacy benefits among Japanese patients with RA who are MTX inadequate responders [12]. The safety, tolerability, pharmacokinetics, immunogenicity, and preliminary evaluations of the efficacy and pharmacodynamics of abatacept (2, 8, and 16 mg/kg) were examined in a Phase I, multicenter, open-label, dose-escalation study in Japanese patients with RA ($n = 21$; IM101-034) [13]. Abatacept had favorable safety and was well tolerated up to the highest dose of 16 mg/kg over 57–127 days, and pharmacokinetic outcomes were similar to those reported in another open-label clinical study of IV abatacept [14]. Abatacept was found to be effective (as assessed by American College of Rheumatology 20% [ACR20] response) in patients in each of the three dose groups. A Phase II study (IM101-071, NCT00345748) examined the dose response of abatacept (2 and 10 mg/kg) compared with that of placebo and background MTX in Japanese patients with active RA over 24 weeks ($n = 195$) [12]. This study demonstrated significantly greater ACR20, ACR50, and ACR70 responses with abatacept 10 mg/kg compared to those with placebo ($P < 0.0001$), whereas smaller but statistically significant responses were seen in the 2 mg/kg abatacept group. Additionally, abatacept plus MTX was found to be well tolerated.

The primary objective of the present 3-year, long-term study (ClinicalTrials.gov identifier NCT00484289) was to examine the safety of continuous IV abatacept in patients with RA who participated in either the Phase I or the Phase II studies, or were newly enrolled and received abatacept monotherapy due to the inability to tolerate MTX owing to safety concerns and had an inadequate response to other DMARDs. The secondary objectives of this study included assessment of clinical and functional efficacy, health-related quality of life, immunogenicity, and laboratory and pharmacodynamic outcomes.

Patients and methods

Patient population

This study comprised three cohorts of patients with RA, including patients who previously participated in either the Japanese Phase I study IM101-034 (February 2004–December 2005) or the Japanese Phase II study IM101-071 (June 2006–November 2007), or new patients enrolling in this study who were MTX-intolerant, had never received abatacept before, and had an inadequate response to DMARDs other than MTX, including biologics. Each cohort consisted of Japanese males and females aged ≥ 20 years with a diagnosis of RA as defined by the American Rheumatism Association (1987) [15] and an ACR functional status of Class I, Class II or Class III [16]. Further eligibility criteria applied to the particular cohorts are described below.

In the Phase I, open-label, dose-escalation study, patients who had been receiving DMARDs at registration were treated with single or multiple doses (Days 1, 15, 29, and 57) of IV abatacept 2, 8, or 16 mg/kg [13]. Patients who were withdrawn from the Phase I study due to safety reasons were excluded from this Phase III study. Between Phase I and Phase III, patients may have been treated with other biologic agents. At registration for this Phase III study, patients from Phase I were required to have undergone the following washout periods: infliximab discontinuation at least 56 days prior to screening and 84 days prior to the first administration of abatacept, and etanercept withdrawal at least 28 days prior to screening.

In the Phase II study, patients with active RA and an inadequate response to MTX were treated with IV abatacept 2 or 10 mg/kg plus MTX, or placebo plus MTX, for 24 weeks [12]. Patients from Phase II must have completed the IM101-071 study to be eligible for the present Phase III study. Additionally, patients from Phase II could not have received any biologics between the completion of IM101-071 and enrollment in the Phase III study.

The new patient cohort with MTX intolerance consisted of patients who could not receive MTX owing to safety reasons. These patients presented with an inadequate response to conventional DMARDs or biologics, and had ≥ 6 swollen joints and ≥ 8 tender joints at the time of screening. In this new patient cohort, infliximab, and etanercept were discontinued as described above for patients from Phase I, and DMARDs were withdrawn at least 28 days prior to screening.

Exclusion criteria for all three cohorts in the current Phase III study included those patients who, at screening, had received unlicensed biologics (excluding abatacept) from previous or ongoing studies in Japan. Additionally, patients who had received any investigational drug (excluding abatacept) within five half-lives of the product or 56 days before screening were excluded. Patients were also excluded if they were currently under treatment with leflunomide, mycophenolate mofetil, calcineurin inhibitors such as cyclosporine and tacrolimus, D-penicillamine, cyclophosphamide, or immunoadsorption columns at screening.

Study design

This was a multicenter, open-label, long-term study that was conducted at 40 sites in Japan. The study was therefore performed in an open-label and uncontrolled manner and no hypotheses were planned. The study was planned to continue until the approval of IV abatacept in Japan, and thus, a specific duration of administration of abatacept was not set. The protocol and patients' informed consent received institutional review board/independent ethics committee approval; the study was conducted in accordance with the Declaration of Helsinki and was consistent with Good Clinical Practice guidelines of the International Conference on Harmonisation.

All patients, regardless of previously received abatacept dose (from Phases I and II), were given abatacept at a weight-tiered dose approximating 10 mg/kg (500 mg for patients weighing < 60 kg, 750 mg for patients weighing 60–100 kg, and 1 g for patients weighing > 100 kg). The dose was administered intravenously at Weeks 0, 2, 4, and every 4 weeks thereafter. From the second year of participation in the study, patients were reweighed once a year and their abatacept dose was checked and adjusted if needed. Concomitant administration of other biologics was prohibited in all patients. New patients with MTX intolerance were not permitted to use concomitant conventional DMARDs during the first 12 weeks, whereas patients enrolled from the Phase I and Phase II studies were permitted to use conventional DMARDs (MTX, < 8 mg/week) from the time of enrollment. In addition, use of corticosteroids (total dose, ≤ 10 mg/day prednisolone equivalent) and non-steroidal anti-inflammatory drugs were permitted in all patients. Patients who discontinued from the study were followed up at the time of discontinuation and for 12 weeks following the last abatacept administration.

Safety assessments

Adverse events (AEs), serious adverse events (SAEs), and laboratory tests were recorded throughout the study. An AE was defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a patient administered abatacept that did not necessarily have a causal relationship with treatment. An SAE was defined as any AE that resulted in death, disability, or hospitalization, or that was life-threatening. If a patient experienced an AE during the study, abatacept was continued only if the AE resolved and was considered not clinically significant.