Mod Rheumatol
DOI 10.1007/s10165-011-0522-8

ORIGINAL ARTICLE

Treatment discontinuation in patients with very early rheumatoid arthritis in sustained simplified disease activity index remission after synthetic disease-modifying anti-rheumatic drug administration

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Received: 16 March 2011 / Accepted: 17 August 2011

Abstract We aimed to identify whether drug-free remission could be achieved in patients with very early rheumatoid arthritis (RA) with poor prognosis factors by treatment with synthetic disease-modifying antirheumatic drugs (DMARDs). Thirteen patients with very early RA, whose disease was considered to have highly erosive potential, were included. Magnetic resonance imaging (MRI)-proven bone edema and autoantibodies were determined in these patients. A treat-to-target strategy initiated with synthetic DMARDs was employed for 12 months. If the patients achieved simplified disease activity index (SDAI) remission along with a reduction of the RA MRI scoring bone edema score to <33% as compared with baseline at 12 months, DMARD treatment was stopped and the clinical status was further observed for the following 12 months. Synthetic DMARDs were stopped at 12 months in 5 patients. One of the 5 was lost to follow-up because of sustaining an injury that required orthopedic surgery. Three of the remaining 4 patients showed continued SDAI remission that was DMARD-free without any evidence of radiographic progression for the following 12 months. Although this was a small clinical trial, we have shown–for the first time–that true remission of very early RA with poor prognosis factors can be achieved by treatment with synthetic DMARDs.

Keywords Very early RA · Synthetic DMARDs · SDAI · Remission · RAMRIS bone edema score

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Published online: 30 September 2011

Abbreviations

ACR	American College of Rheumatology
Anti-CCP antibodies	Anti-cyclic citrullinated peptide antibodies
BeSt study	Behandelstrategieen study
CRP	C-reactive protein
DAS	Disease activity score
DMARDs	Disease-modifying antirheumatic drugs
IgM-RF	Immunoglobulin M-rheumatoid factor
MMP-3	Matrix metalloproteinase 3
MRI	Magnetic resonance imaging
MTX	Methotrexate
PROMPT study	Probable RA: methotrexate versus placebo treatment study
PIP joint	Proximal interphalangeal joint
RRR study	Remission induction by Remicade in RA study
RA	Rheumatoid arthritis
RAMRIS	RA MRI scoring
SASP	Salazosulfapyridine
SDAI	Simplified disease activity index
Tac	Tacrolimus
T2T	Treat to target

Introduction

Early diagnosis and the treat-to-target (T2T) strategy are now indispensable for the management of rheumatoid arthritis (RA) [1–4]. In particular, these therapeutic options significantly improve the outcome of early-stage RA [1]. The European League Against Rheumatism (EULAR) Task Force has recently developed a consensus on recommendations for the management of RA with synthetic and biological disease-modifying antirheumatic drugs (DMARDs) [5]. These recommendations indicate that for the vast majority of patients with RA, the first treatment approach should include synthetic DMARDs, especially methotrexate (MTX) [5].

As a result of the increasing percentage of patients achieving remission with the introduction of early intensive goal-steered therapy, more often the dilemma is whether a patient with RA in prolonged remission should discontinue DMARDs or whether the treatment should be continued. The Japanese remission induction by Remicade in RA (RRR) study has indicated that approximately half of RA patients were able to discontinue infliximab after attaining low disease activity, as defined by the disease activity score (DAS) 28 [6]. The Behandelstrategieen (BeSt) study has shown that nearly 11% of patients with early-stage RA treated with DMARDs achieve drug-free remission, as defined by the DAS44, even those treated with synthetic DMARDs alone [7]; however, none of the evidence from Japanese RA patients has determined whether drug-free remission can be achieved with synthetic DMARDs.

In the present study, we selected patients with very early RA whose joints, we suspected, would become highly erosive in the later stages of the disease; we used the following criteria for selection: the subjects showed magnetic resonance imaging (MRI)-proven bone edema and tested positive for autoantibodies [8]. None of the patients met the 1987 criteria of the American College of Rheumatology (ACR) for RA [9], but all fulfilled the 2010 RA classification criteria [2, 3] at entry. A tight control approach through the T2T strategy initiated with synthetic DMARDs was adopted in these patients, and we found that drug-free simplified disease activity index (SDAI) remission in the absence of radiographic progression was successfully induced after the patients had been treated with synthetic DMARDs for 12 months.

Patients and methods

Patients

The present study was an investigator-initiated clinical study that attempted to examine the efficacy of the T2T strategy for patients with very early RA with poor prognosis factors. Patients with very early RA were defined in the present study as those who did not meet the 1987 criteria of the ACR for RA [9] but who fulfilled the 2010 RA classification criteria [2, 3] at entry. We recently reported that patients with early undifferentiated arthritis with MRI-proven bone edema and autoantibodies at entry later developed 1987-criteria-fulfilling RA with erosive radiographic changes [8]. Thus, MRI-proven bone edema and serologic autoantibodies are thought to be poor prognostic factors in early arthritis. Accordingly, patients with very early RA who did not meet the 1987 criteria of the ACR for RA but who fulfilled the 2010 RA classification criteria at entry, in addition to having MRI-proven bone edema and serologic autoantibodies, were selected for the present study. We excluded patients who met the international criteria of rheumatic diseases other than RA at baseline. Thirteen patients who met our inclusion criteria were serially recruited from the Early Arthritis Clinic opened in 2001 as part of the Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences. Patients were referred from an area in the western part of

Japan, Nagasaki Prefecture, which has approximately 450,000 inhabitants. These 13 patients were recruited from 2008 to 2009.

Baseline clinical manifestations and variables examined included gender, age, disease duration from onset to study entry, morning stiffness, use of DMARDs, use of glucocorticoids, SDAI, CRP (measured by latex turbidimetric immunosorbent assay; Daiichi Pure Chemicals, Fukuoka, Japan), matrix metalloproteinase 3 (MMP-3; measured by enzyme-linked immunosorbent assay, with cut-off values of 59.7 ng/ml for females and 121.0 ng/ml for males, Daiichi Pure Chemicals), anti-cyclic citrullinated peptide antibodies (anti-CCP Abs) (measured by enzyme-linked immunosorbent assay, cut-off value 4.5 U/ml; DIASTAT Anti-CCP; Axis-Shield, Dundee, UK), IgM-rheumatoid factor (IgM-RF) (measured by latex-enhanced immunonephelometric assay, cut-off value 14 IU/ml; Dade Behring, Marburg, Germany), MRI-proven synovitis, MRI-proven bone edema, MRI-proven bone erosion, and plain radiographs of both hands and both feet. All variables were examined on the same day, as we recently reported [10–13]. Each patient provided a signed consent form to participate in the study, which was approved by the Institutional Review Board of Nagasaki University. All of the above variables except for MRI were also measured every 3 months. MRI and plain radiographs were examined every 6 months, and we followed the above variables for 24 months.

T2T strategy for the treatment of very early RA

In accordance with findings in previous reports, we have employed the T2T strategy for the treatment of very early RA in an attempt to induce SDAI remission [4, 14]. In brief, synthetic DMARDs were initially introduced, and SDAI was evaluated every 3 months. If the SDAI showed moderate disease activity at 3 months or low disease activity after 6 months, the anti-rheumatic therapies were basically modulated. MTX was initiated in 10 of the 13 patients, salazosulfapyridine (SASP) in 2 patients, and tacrolimus (Tac) in 1 patient. SASP and Tac were used in 3 patients because of the presence of interstitial lung disease. Because the officially approved maximum weekly dosage of MTX in Japan was limited to 8 mg, which is much less than that in Europe and the United States [15], the maximum dosage of MTX in our patients was 8 mg per week. After 12 months of treatment with the T2T strategy, if the patients achieved SDAI remission along with a reduction of the RA MRI scoring (RAMRIS) bone edema score to <33% as compared with baseline at 12 months, DMARD treatment was stopped and the clinical status was still observed, as described above.

Radiographic examinations during the treatment

Plain radiographs of both hands and both feet were taken every 6 months and evaluated using Genant-modified Sharp scores. Plain MRIs of both wrists and all finger joints were also examined every 6 months, as we described previously [10–13]. In brief, MRIs of wrists and finger joints were acquired using a 1.5 T system (Sigma, GE Medical Systems, Milwaukee, WI, USA) with an extremity coil. T1-weighted spin echo (TR 450, TE 13) images and short-time inversion recovery (STIR; TR 3,000, TE 12, T1 160) images were simultaneously acquired on the same day. The images were evaluated for synovitis, bone edema, and bone erosion at 15 sites in each finger and wrist: the distal radioulnar joint, the radiocarpal joint, the midcarpal joint, the first carpometacarpal joint, the second-fifth carpometacarpal joints (together), the first-fifth metacarpophalangeal joints (separately), and the first-fifth proximal interphalangeal joints (PIP joints) separately (for a total of 30 sites in both hands), as we have reported recently [10–13]. MRI was evaluated by an experienced radiologist (M.U.), and the severity of MRI-proven joint injury was evaluated by RAMRIS according to the standard method as used for the RAMRIS total score, RAMRIS synovitis score, RAMRIS bone edema score, and RAMRIS erosion score [16, 17]. The RAMRIS score is a semi-quantitative score from 0 to 3 that is used to assess the severity of MRI-proven joint injury [16, 17]. In our experience, the complete resolution of MRI-proven bone edema is a rare event during treatment even if these patients achieve a clinical remission. Therefore, in the present study, we defined a significant improvement of bone edema to be if the RAMRIS bone edema score declined to <33% as compared with the baseline. When this RAMRIS bone edema score was obtained, synthetic DMARD administration was stopped at 12 months, as described above.

Statistical assessment

We used Fisher's exact probability test and the Mann–Whitney *U*-test to assess differences statistically. Variables with a P value of <0.05 were considered to be significant.

Results

Baseline variables and therapeutic response in the 13 patients

Table 1 summarizes the baseline variables in the 13 patients. The mean disease duration from the onset of symptoms to the initiation of synthetic DMARDs was 13.7 weeks, which is considered to be very early RA. All

of the patients were seropositive for anti-CCP Abs and/or IgM-RF, as described in "Patients and methods". Plain radiographic injury at entry was minimal, as evidenced by the mean Genant-modified Sharp score of 1.8, but all of the 13 patients showed MRI-proven bone edema, as described in "Patients and methods". The RAMRIS scores in the present study appeared to be more severe than those in a similar clinical study–the Ciclosporine, Methotrexate, Steroid in RA (CIMESTRA) trial [18, 19]; in the CIMESTRA trial the mean RAMRIS synovitis score was 10.9, the mean RAMRIS bone edema score was 1.6, and the mean RAMRIS bone erosion score was 1.7. After 12 months' treatment with the T2T strategy, 6 of the 13 patients fulfilled our criteria for quitting the synthetic DMARDs. All 6 of these patients were treated with synthetic DMARDs only, without the addition of biological DMARDs. At 12 months, one patient did not agree to quit the DMARD; however, the synthetic DMARDs were stopped at 12 months in the other 5 patients (in 3 patients treated with MTX, 1 patient treated with SASP, and 1 patient treated with Tac). We compared the baseline variables in the 2 groups (i.e., those quitting and those not quitting synthetic DMARDs), but we were not able to identify any significant intergroup differences (Table 2).

Table 1 Baseline variables in 13 patients

Baseline variables	% Positive or mean ± SD
Gender (female %)	69.20%
Age (years)	59.2 ± 11.0
Disease duration (weeks)	13.7 ± 12.8
Morning stiffness (min)	97.7 ± 133.7
MTX use during 12 months (%)	76.90%
Glucocorticoid use during 12 months (%)	30.80%
SDAI	20.2 ± 10.9
CRP (mg/dl)	1.1 ± 1.0
MMP-3 (ng/ml)	148.7 ± 72.4
Anti-CCP Abs and/or IgM-RF (%)	100%
Genant-modified Sharp score	1.8 ± 2.1
RAMRIS score	
Total	35.8 ± 29.0
Synovitis	12.6 ± 5.2
Bone edema	16.2 ± 17.3
Bone erosion	6.9 ± 10.8

Presentation of the 3 patients who stopped treatment with synthetic DMARDs for 12 months and maintained sustained remission

Of the 5 patients who stopped the synthetic DMARD treatment at 12 months, 1 patient was lost to follow-up (this patient suffered from a femoral bone fracture and was transferred to another hospital at 3 months after stopping the DMARD (SASP); we therefore obtained follow-up data for 4 patients. One patient was required to restart synthetic DMARD treatment (MTX) because of an increase in clinical disease activity at 3 months after stopping MTX. The other 3 patients continued to have a sustained SDAI remission 12 months after quitting the synthetic DMARDs. We have summarized the data for these 3 patients in Table 3. In addition to maintaining the SDAI remission, none of the patients showed progression of radiographic

Table 2 Comparison of baseline variables in patients quitting and those not quitting disease-modifying anti-rheumatic drugs (DMARDs)

Variables	Quitting DMARDs ($n = 5$)	Not quitting DMARDs ($n = 7$)	P value
Gender (female %)	100	57.1	0.2
Age (years)	62.0 ± 11.5	59.7 ± 9.8	1
Disease duration (weeks)	14.4 ± 9.5	13.5 ± 16.3	0.52
Morning stiffness (min)	24.0 ± 25.1	160.0 ± 159.7	0.19
MTX use during 12 months (%)	60	85.7	0.52
Glucocorticoid use during 12 months (%)	20	28.6	1
SDAI	15.9 ± 4.2	24.3 ± 13.4	0.14
CRP (mg/dl)	1.4 ± 1.22	0.97 ± 0.86	0.63
MMP-3 (ng/ml)	179.3 ± 90.0	120.4 ± 55.0	0.26
Genant-modified Sharp score	2.6 ± 2.8	0.84 ± 0.88	0.35
RAMRIS score			
Total	24.2 ± 9.4	39.3 ± 36.5	0.68
Synovitis	13.0 ± 6.0	12.9 ± 5.2	1
Bone edema	9.6 ± 5.9	18.7 ± 22.2	0.81
Bone erosion	1.6 ± 1.1	7.7 ± 11.6	0.46

Table 3 Presentation of the 3 patients in whom DMARDs were stopped for the 12 months following 12-month treatment and who maintained remission

Variables	0 months	Quitting MTX at 12 months	12 Months after quitting MTX (i.e., at 24 months after starting MTX
A. Case 1			
SDAI	22.44	0.04	0.03
CRP (mg/dl)	2.44	0.04	0.03
Genant-modified Sharp score	2	2	2
RAMRIS score			
Total	27	10	6
Synovitis	11	8	4
Bone edema	14	0	0
Bone erosion	2	2	2
B. Case 2			
SDAI	14.26	1.1	0.05
CRP (mg/dl)	0.26	0.1	0.05
Genant-modified Sharp score	0	0	0
RAMRIS score			
Total	9	7	5
Synovitis	4	5	5
Bone edema	3	1	0
Bone erosion	2	1	0
C. Case 3			
SDAI	14.99	0.11	1.31
CRP (mg/dl)	2.69	0.11	1.31
Genant-modified Sharp score	4.4	4.4	4.4
RAMRIS score			
Total	22	6	6
Symmetrical synovitis	18	6	6
Bone edema	3	0	0
Bone erosion	0	0	0

damage, as evaluated by the Genant-modified Sharp score and the RAMRIS bone edema score (Table 3).

Discussion

The clinical efficacy of synthetic DMARDs, especially MTX, in early-stage RA has been established [1, 4, 5]. Stopping DMARDs while maintaining remission would be beneficial with respect to adverse events and costs, but there are few data on the efficacy and safety of quitting synthetic DMARDs in RA [7, 20, 21]. The BeSt study is an intriguing clinical trial that has found that drug-free remission is a realistic goal in patients with early-stage RA treated with synthetic DMARDs [7, 20, 21]. In the BeSt study the patients were treated with synthetic DMARDs for 2 years, and the rate of drug-free remission was 11% [7]. Also, the probable RA: methotrexate versus placebo treatment (PROMPT) study has shown in the earlier stage of disease that patients who had been treated with MTX for 12 months continued with their good disease status after stopping MTX [22]. However, the efficacy of MTX in the PROMPT study may not have been as obvious, because the radiographic progression tended to increase after the cessation of MTX [22]. Therefore, although drug-free remission induced by synthetic DMARDs can be achieved, its precise nature has, until now, remained to be elucidated.

Our present study differs from the BeSt study and the PROMPT study in several ways. First, the definition of RA in our study is based on the 2010 RA classification criteria. This definition appears to be similar to that used in the PROMPT study, but quite different from that used in the BeSt study, which targeted patients fulfilling the 1987 criteria of the ACR at entry [7, 20–22]. None of the patients in the present study fulfilled the 1987 ACR criteria at entry. Second, all of the subjects in our study were seropositive for anti-CCP Abs or IgM-RF. In the BeSt study, 65% of the subjects were seropositive for both antibodies [20, 21]. In the PROMPT study, the prevalence of anti-CCP Abs was 24.5% and that of RF was 35.5% [22]. Third, all of our patients were defined as being positive for MRI-proven bone edema. Previous studies have identified that MRI-proven bone edema reflects a severe disease condition in RA [10, 17]. These data indicate that patients with very early but, nevertheless, severe RA were the subjects of our study, as compared with patients in the BeSt and PROMPT studies. Fourth, we defined the criteria for quitting synthetic DMARDs as achieving SDAI remission as well as a significant improvement in MRI-proven bone edema. Fifth, the doses of the synthetic DMARDs used in our study, especially that of MTX, was quite low as compared with the doses used in Europe and the United States [15]. Therefore, this is the first clinical trial attempting to determine whether the discontinuation of synthetic DMARDs is a realistic goal in Japanese patients with severe but very early RA.

Although the number of patients in the present study was very small, 3 out of 4 patients successfully achieved drug-free SDAI remission for 12 months after the cessation of synthetic DMARDs. Plain radiographic progression as well as increases in the RAMRIS bone edema score were completely suppressed in these 3 patients. These data are excellent as compared with those from the BeSt study and the PROMPT study. Our criteria for quitting synthetic DMARDs, i.e., achieving SDAI remission along with a

significant improvement in MRI-proven bone edema, may have led to the better results. Accordingly, SDAI remission is believed to be a more stringent requirement than DAS remission [14]. We and other investigators have found that MRI-proven bone edema is a very strong predictor of further plain radiographic progression [8, 18, 19]. However, as the sample size of the present study was small, our criteria for quitting synthetic DMARDs could be changed if the present patients show radiographic progression in a further follow-up period. Of note, biomarkers reflecting the clinical characteristics might be present in the patients' serum or plasma, and such biomarkers may be of value in making the decision to quit DMARD treatment. Future prospective studies will be necessary to guide the rationale for quitting DMARDs in patients in whom clinical remission has been achieved.

Synthetic DMARD use in Japan is quite different from that in western countries; the present study, however, has shown–for the first time–that, in patients with very early RA with poor prognosis factors, true remission can be achieved by treatment with synthetic DMARDs. Evaluation of disease activity by the SDAI and MRI-proven bone edema is thought to be very valuable for identifying whether sustained remission has been achieved.

Acknowledgments This study was supported in part by a grant from The Ministry of Health, Labour and Welfare, Japan.

Conflict of interest None.

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RHEUMATOLOGY

Rheumatology 2011;50:962–965
doi:10.1093/rheumatology/keq415
Advance Access publication 23 December 2010

Concise report

The power Doppler ultrasonography score from 24 synovial sites or 6 simplified synovial sites, including the metacarpophalangeal joints, reflects the clinical disease activity and level of serum biomarkers in patients with rheumatoid arthritis

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Abstract

Objective. We evaluated the significance of the power Doppler ultrasonography (PDUS) score by comparing it with serum biomarkers and clinical disease activity.

Methods. We measured the PDUS scores of 24 synovial sites in 12 joints in 22 RA patients. For convenience, the PDUS scores of six synovial sites in six joints were also examined. Each joint was scored for a power Doppler (PD) signal on a scale from 0 to 3. The PDUS scores are the sums of the PD signal scores for the 24 synovial sites or the 6 synovial sites. On the same day, serum variables as well as clinical disease activity were evaluated.

Results. The PDUS scores from the 24 joint sites were significantly positively correlated with DAS of 28 joints (DAS-28), simplified disease activity index (SDAI), clinical disease activity index (CDAI) and serum biomarkers including MMP-3, VEGF and tissue inhibitor of metalloproteinases-1 (TIMP-1). Accordingly, the PDUS scores from the six synovial sites greatly correlated with those from the 24 joint sites. Clinical disease activities as well as serum variables were also clearly correlated with the PDUS scores from the six synovial sites.

Conclusion. The standard as well as the simplified PDUS scores well reflected clinical disease activity and serum variables, including angiogenic factors. Our data reaffirm the utility of ultrasonography for monitoring disease activity in patients with RA.

Key words: Ultrasonography, Power Doppler, Rheumatoid arthritis, Vascular endothelial growth factor.

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Submitted 9 June 2010; revised version accepted 16 November 2010.

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Introduction

The greater resolution of superficial musculoskeletal structures offered with the use of high-frequency transducers, along with the high sensitivity of current colour Doppler and power Doppler (PD) US, have led to increasing use of US in rheumatic diseases [1]. Naredo *et al.* [2] reported 12-joint simplified PD ultrasonographic assessment as the original US scoring system. Recently, Kurosaka *et al.* [3] examined a relatively large number of patients and found a correlation of PD signal intensity with

DAS of 28 joints (DAS-28) and serum angiogenic factors, although they did not include the power Doppler ultrasonography (PDUS) score of the finger joints of the hand, which are frequently affected by RA.

We focused on the association of the PDUS score including the MCP joints with serum biomarkers as well as clinical disease activity. We found that the PDUS score of 24 synovial sites at 12 joints reflects the clinical disease activity and serum biomarkers. Second, for convenience, we reduced the number of joints to six synovial sites at six joints and also found that the PDUS score of six synovial sites at six joints is clearly correlated with the clinical disease activity and serum biomarkers.

Materials and methods

RA patient and healthy control samples

Twenty-two RA patients were selected to be enrolled in the present study from the Unit of Translational Medicine, Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University. All of the patients fulfilled the 1987 criteria of the ACR for RA [4]. The patients underwent clinical, laboratory and PDUS evaluation on the same day. We also collected serum samples from eight healthy controls without musculoskeletal disorder. Subjects' written consent was obtained according to the Declaration of Helsinki, and the design of the work was approved by the Institutional Review Board of Nagasaki University.

Clinical and laboratory assessment

Clinical evaluation was performed by Japan College of Rheumatology-certified rheumatologists (A.K. and K.E.), who were blinded to the PDUS findings. Disease activity was evaluated by DAS-28, simplified disease activity index (SDAI) and clinical disease activity index (CDAI). In using DAS-28, we followed the criteria set by the European League against Rheumatism (EULAR), and in using CDAI and SDAI, we followed the method recommended by Smolen and colleagues [5].

The following laboratory variables were assessed: RF (Dade Behring, Marburg, Germany; cut-off value, 14 IU/ml), anti-CCP antibodies (DIASTAT Anti-CCP, Axis-Shield, Dundee, UK; cut-off value, 4.5 U/ml), CRP (Eiken Chemical Co. Ltd, Tokyo, Japan), ESR, VEGF (Quantikine, R&D Systems, Abingdon, UK), MMP-3 (Daiichi Pure Chemicals, Fukuoka, Japan), MMP-9 (Biotrak ELISA System, GE Healthcare, USA) and tissue inhibitor of metalloproteinases-1 (TIMP-1; Biotrak ELISA System, GE Healthcare, USA). Clinical disease activity as well as serum variables were evaluated on the same day as US examination.

US examination

Each patient underwent a US assessment by a Japan College of Rheumatology-certified rheumatologist (S.K.), who was blinded to the clinical and laboratory findings. Images from all the examinations were stored, and the US scoring reliability was examined by assessing 24 synovial sites in randomly selected patients at the end of the study. This assessment was carried out by Japan College of Rheumatology-certified rheumatologists (S.K., N.I., K.F. and T.O.) with consensus. A systematic multiplanar grey scale (GS) and PD examination of 12 joints was performed with the same scanner (TOSHIBA AplioXG; Toshiba Medical Systems Corporation, Tochigi, Japan) using a multifrequency linear transducer (12 MHz) according to the EULAR guidelines [6]. The US score included the following 24 synovial sites at 12 joints: bilateral elbows (anterior and posterior recess), wrists (dorsal and carpal recess), second and third MCP joints (dorsal and palmar recess), knees (suprapatellar and lateral parapatellar recess) and ankles (anterior tibiotalar recess, medial tendon sheaths and lateral tendon sheaths). Signs of OA were not detected by US and X-ray in the examined joints.

The IA, tenosynovial and intrabursal PD signals were graded on a semi-quantitative scale from 0 to 3 (Grade 0 = absence, no synovial flow; Grade 1 = mild, $\leqslant$3 isolated singles; Grade 2 = moderate, >3 isolated singles or confluent signal in less than half of the synovial area; Grade 3 = marked, signals in more than half of the synovial area). These scores corresponded to the maximum score for PD signals obtained from any of the synovial sites evaluated at each joint, as documented by Naredo *et al.* [2]. The sum of the PD signal scores obtained from each joint was used as the PDUS score, as reported by Naredo *et al.* [2]. The 12-joint (12j)-PDUS score was the sum of the scores of the above 24 synovial sites at 12 joints. In an attempt to expand the convenience of ultrasonography in clinical practice, we have chosen six synovial sites from six joints including the bilateral wrists (dorsal recess) and second and third MCP joints (dorsal recess). The six-joint (6j)-PDUS score was the sum of the six synovial sites.

Statistical analyses

Within-group comparisons were made using the Mann–Whitney *U*-test. Correlations were assessed with Spearman's correlation coefficient test. The overall significance level for statistical analysis was 5% (two-sided). $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

The demographic and clinical characteristics of 22 RA patients (5 males and 17 females) are as follows. The mean (S.D.) (range) age of the patients was 64 (9) (48–81) years. The mean (S.D.) (range) of disease duration was 2.3 (2.5) (0.25–10) years, which corresponded to relatively early-stage disease. RF and anti-CCP antibodies were positive in 15 (68.2%) and 18 (81.8%) patients, respectively. They received either synthetic DMARDs ($n = 14$), a combination of synthetic DMARDs plus TNF inhibitor ($n = 1$) or TNF inhibitor monotherapy ($n = 1$). Six patients were not treated with DMARDs. The mean tender joint counts (TJCs), swollen joint counts (SJCs), ESR, CRP, DAS-28, SDAI and CDAI were 9.2, 8.0, 58.8, 2.38, 5.69, 30.6 and 28.3, respectively, which indicate that

patients with relatively high disease activity were included in the present study.

Twelve j-PDUS scores and serum biomarkers

The median (range) of PDUS scores was 13.5 (1–39). Serum VEGF, MMP-3, MMP-9 and TIMP-1 were significantly higher in RA patients than in healthy controls—the mean levels of serum biomarkers; RA patients *vs* healthy controls (*P*-value, Mann–Whitney *U*-test)—VEGF; 695 *vs* 308 pg/ml ($P < 0.0001$), MMP-3; 185 *vs* 30 U/l ($P < 0.001$), MMP-9; 1962 *vs* 55 pg/ml ($P < 0.0001$) and TIMP-1; 214 *vs* 160 pg/ml ($P < 0.05$).

The correlations of 12j-PDUS scores with disease activity and serum biomarkers

The correlation of DAS-28 with SDAI or CDAI was extremely high, indicating that the physical examination was well performed (Table 1). The 12j-PDUS scores from 24 synovial sites were significantly positively correlated with TJC, SJC, ESR, CRP, DAS-28, SDAI, CDAI, serum VEGF, MMP-3 and TIMP-1, whereas they were not correlated with serum MMP-9 (Table 2). In particular, DAS-28 ($r = 0.72$, $P < 0.001$) and serum VEGF ($r = 0.62$, $P < 0.01$) strongly correlated with PDUS scores.

The correlations between clinical disease activity and serum biomarkers are shown in Table 1. All serum biomarkers correlated with inflammatory markers such as CRP and ESR. With regard to angiogenic factors, VEGF correlated well with the variables other than MMP-9 or TIMP-1 (Table 1).

Six j-PDUS scores can be an alternative for 12j-PDUS scores

The 6j-PDUS scores were strongly correlated with 12j-PDUS scores ($r = 0.92$, $P < 0.0001$). Accordingly, 6j-PDUS scores were significantly correlated with TJC ($r = 0.50$, $P < 0.05$), SJC ($r = 0.44$, $P < 0.05$), ESR ($r = 0.57$, $P < 0.05$), DAS-28 ($r = 0.67$, $P < 0.01$), SDAI ($r = 0.55$, $P < 0.05$), CDAI ($r = 0.54$, $P < 0.05$) and serum VEGF ($r = 0.62$, $P < 0.01$), whereas they were not correlated with serum MMP-3, MMP-9 and TIMP-1. Although these associations were slightly weaker than those with 12j-PDUS scores, the tendencies of 6j-PDUS and 12j-PDUS scores were very similar to each other.

Discussion

We have verified additional information regarding PDUS scores in patients with RA. First, our data included the small MCP joints. Since the second and third MCP joints are considered to be important areas for radiographic imaging of RA, as reported by Naredo *et al.* for US [2] and by OMERACT for MRI [7], our present data may reinforce the utility of PDUS. Although our present study includes relatively elderly patients, signs of OA were not detected in the examined joints, indicating that our results reflect rheumatoid inflammatory change.

Second, we have chosen other biomarkers. MMP-9 is important for the budding of endothelial cells, and TIMP-1 is an inhibitor of MMP-9; both are elevated in serum as well as in the synovial tissues of RA [8, 9]. As suspected, TIMP-1 was correlated with PDUS score and several other biomarkers, although its correlation was weaker than that of VEGF. MMP-9 tended to correlate with PDUS score; however, it did not reach statistical significance. Since the budding of endothelial cells is an early step in angiogenesis, MMP-9 may be important in the early phase of rheumatoid synovitis. The selection of very early-stage RA may be necessary to identify any association of MMP-9 with PDUS score.

Third, we have assessed SDAI and CDAI in the present study. The present study has revealed a clear correlation of PDUS score with SDAI and CDAI, although that of DAS-28 ESR was better. These data reinforce the validity of PDUS for the measurement of the disease activity of RA.

Fourth, for better clinical availability, we have reduced the number of sites examined by US to only six sites of the wrist and finger joints. These methods are simple and can save time that would be spent on scanning. Since the correlation of disease activity and PDUS was weaker than those with 24 synovial sites, further studies with larger numbers of patients should be necessary.

Recent investigations have found that the presence of the PDUS signal is a better predictor of further radiographic joint destruction than DAS-28 [10, 11].

TABLE 1 Correlations between disease activity and serum biomarkers

	DAS-28	SDAI	CDAI	ESR	CRP	VEGF	MMP-3	MMP-9
SDAI	0.93***							
CDAI	0.93***	0.99***						
ESR	0.64**	0.44*	0.43					
CRP	0.64**	0.64**	0.59**	0.71**				
VEGF	0.59**	0.54*	0.51*	0.62**	0.70**			
MMP-3	0.61**	0.58**	0.55*	0.57**	0.68**	0.60**		
MMP-9	0.27	0.23	0.18	0.43*	0.49*	0.29	0.39	
TIMP-1	0.39	0.42	0.37	0.52*	0.71**	0.58**	0.69**	0.38

Correlations were assessed with Spearman's correlation coefficient test. *$P < 0.05$, **$P < 0.01$, ***$P < 0.0001$.

TABLE 2 Correlations of PDUS score with disease activity and serum biomarkers

Characteristics	r	P-value
Tender joints	0.52	0.017
Swollen joints	0.48	0.028
ESR	0.62	0.005
CRP	0.47	0.03
DAS-28	0.72	<0.001
SDAI	0.6	0.006
CDAI	0.6	0.006
Serum VEGF levels	0.62	0.005
Serum MMP-3 levels	0.47	0.03
Serum MMP-9 levels	0.38	0.08
Serum TIMP-1 levels	0.54	0.014

Correlations were assessed with Spearman's correlation coefficient test.

Therefore, it is very important to search the variables that correlate with PDUS score. Among the biomarkers and clinical disease activity indices in the present study, however, DAS-28 was the strongest variable that correlates with PDUS scores. VEGF was best in the biomarkers although it was weaker than that of DAS-28. These data may suggest that comprehensive analysis is necessary to identify the best biomarkers to reflect the severity of the PDUS score.

In conclusion, PDUS, especially when focused on the area of the wrist and finger joints, is an excellent tool for the evaluation of disease activity in patients with RA. Our six-site evaluation method can be adequately tolerated in clinical practice.

Rheumatology key messages

- Standard as well as simplified PDUS scores reflected clinical disease activity and serum variables, including angiogenic factors.
- Our six-site evaluation method can be adequately tolerated in clinical practice.

Disclosure statement: The authors have declared no conflicts of interest.

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ARTHRITIS & RHEUMATISM
Vol. 63, No. 7, July 2011, pp 2149–2150

LETTERS

DOI 10.1002/art.30370

A graphic demonstration that the Disease Activity Score in 28 joints using the erythrocyte sedimentation rate is overly sensitive when erythrocyte sedimentation rates are low: comment on the article by Smolen and Aletaha

To the Editor:

In the January 2011 issue of *Arthritis & Rheumatism*, Smolen et al (1) reported the problem with the Disease Activity Score in 28 joints (2) using the erythrocyte sedimentation rate (DAS28-ESR) in patients treated with tocilizumab. The authors stated that the DAS28-ESR was too sensitive to changes in the ESR, even within its normal range. This is somewhat imprecise. Here, we provide graphic evidence that the DAS28-ESR is overly sensitive to subtle changes in the ESR, particularly in its lower-normal range.

The DAS28-ESR is calculated as follows (3): DAS28 = $0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.70 \times \ln(ESR) + 0.014 \times GH$, where TJC28 = total joint count using 28 joints, SJC28 = swollen joint count using 28 joints, and GH = global health as reported by the patient. The natural logarithm (ln) of the ESR multiplied by 0.7 contributes to the score. When plotted against the ESR, the characteristics of natural logarithms give an interesting result. An ESR decrement of 1 causes the value for $0.70 \times \ln(ESR)$ to decrease more prominently in the lower-normal range of the ESR.

Therefore, a decrease in the ESR from 6 mm/hour to 2 mm/hour lowers the DAS28-ESR by −0.77, whereas a decrease in the ESR from 26 mm/hour to 22 mm/hour lowers the value by only −0.12 (Figure 1). In a hypothetical patient with a TJC of 2, a SJC of 2, a GH score of 10, and an ESR of 6 mm/hour, the DAS28-ESR is 2.58, representing disease in remission. If the ESR is lowered to 2 mm/hour, the DAS28-ESR becomes 1.81, which allows disease remission to continue in a patient with a GH score as high as 65, a SJC of up to 17, or a TJC of up to 7.

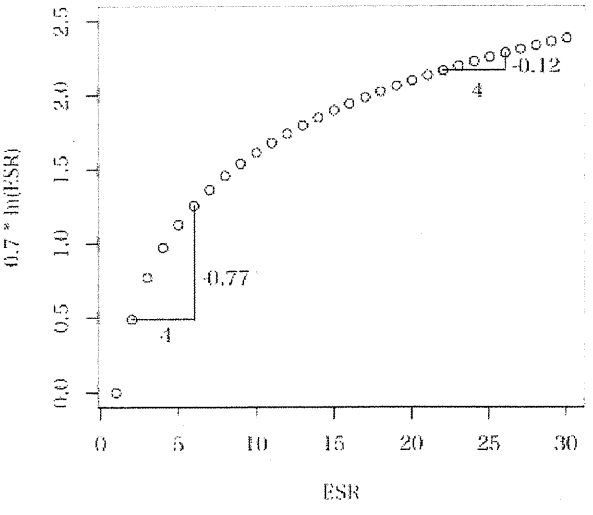

Figure 1. Contribution of the erythrocyte sedimentation rate (ESR) to the Disease Activity Score in 28 joints.

This demonstrates that the DAS28-ESR is not an accurate tool when the ESR is very low. In addition, an important thing to remember is that the DAS28-ESR was developed to discriminate between high and low disease activity (2) and was not designed to assess disease remission. Adaptation of the new American College of Rheumatology/European League Against Rheumatism remission criteria (4) is mandatory in the era of tight control, when remission is a realistic goal.

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DOI 10.1002/art.30369

Reply

To the Editor:

Dr. Yoshida and colleagues nicely confirm our finding that small changes in the ESR within its normal range have a large impact on the DAS28. Indeed, we and other investigators have presented graphs similar to theirs in previous discussions on the DAS28 (1,2), revealing that the steepest portion of the curve of the transformed ESR values is within the normal range. However, from our point of view, the equally or even more important issue is the low weight given to the swollen

Yoshida *et al. Arthritis Research & Therapy* 2011, 13:N
http://arthritis-research.com/content/13/4/N

arthritis research&therapy

LETTER

Remission by Disease Activity Score 28-CRP and Disease Activity Score 28-ESR

Kazuki Yoshida[1]*, Kazuo Matsui[1], Hiroto Nakano[1], Hideto Oshikawa[1], Masako Utsunomiya[1], Tatsuo Kobayashi[1], Makiko Kimura[1], Gautam A. Deshpande[2] and Mitsumasa Kishimoto[3]

See related research by Lee *et al.*, http://arthritis-research.com/content/13/3/R83

[AU Query: Check and confirm meaning of text remains OK throughout]

We read with interest the report by Lee and colleagues in the June issue of *Arthritis Research & Therapy* [1]. The study compared the C-reactive protein Disease Activity Score in 28 joints (DAS28-CRP) versus American College of Rheumatology/European League Against Rheumatism remission in terms of residual pain **[AU Query: Confirm sentence is OK]**. The authors stated that DAS28-CRP remission criteria allowed for persistence of pain in more than 10% of patients, whereas there were very few complaints of pain among patients in American College of Rheumatology/European League Against Rheumatism remission. This is a very important finding as it clearly demonstrated incompetence of the DAS28-CRP remission criteria in defining remission that is meaningful for patients, thus encouraging transition to new American College of Rheumatology/European League Against Rheumatism remission criteria.

One factor, however, that was not mentioned in the article and which may be of interest is the erythrocyte sedimentation rate Disease Activity Score in 28 joints (DAS28-ESR) **[AU Query: Confirm sentence is OK]**. Although the DAS28-CRP is a validated score demonstrating good correlation with the DAS28-ESR [2], the DAS28-CRP frequently results in lower scores than its erythrocyte sedimentation rate counterpart [2,3]. Inoue and colleagues thus suggested a different cut-off point of 2.3 for the DAS28-CRP [3]. This tendency was also demonstrated in our cohort of 265 rheumatoid arthritis patients taking biologics (Figure 1). When plotted against the DAS28-ESR, the DAS28-CRP resulted in lower values (below the diagonal line, indicating complete agreement) more often than not. Also noteworthy is that the DAS28-CRP is never lower than 0.96, which is the constant term in the following equation [4]:

$$\text{DAS28-CRP} = 0.56 \times \sqrt{\text{TJC28}} + 0.28 \times \sqrt{\text{SJC28}} + 0.36 \times \ln(\text{CRP} + 1) + 0.014 \times \text{GH} + 0.96$$

in which TJC stands for tender joint count, SJC for swollen joint count, ln for natural logarithm, CRP for C-reactive protein, and GH for global health as reported by the patient.

We therefore wonder whether Lee and colleagues performed the same analysis with DAS28-ESR remission

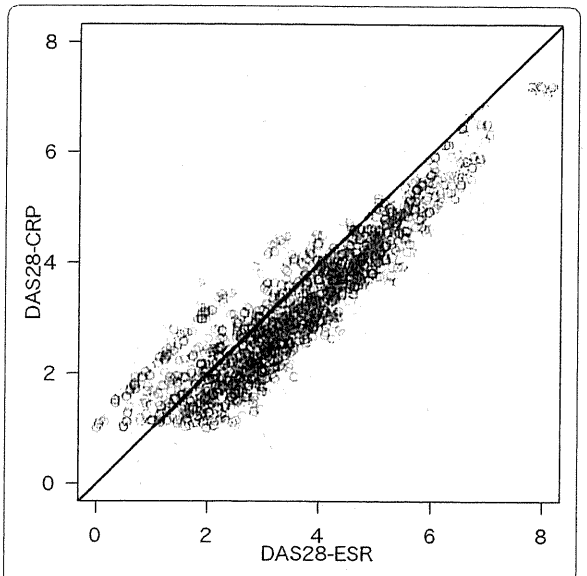

Figure 1. Relationship between the C-reactive protein and erythrocyte sedimentation rate Disease Activity Scores in 28 joints. Relationship between the C-reactive protein Disease Activity Score in 28 joints (DAS28-CRP) and the erythrocyte sedimentation rate Disease Activity Score in 28 joints (DAS28-ESR) in our biologic cohort. **[AU Query: Confirm caption]**

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criteria. We think it may be interesting to perform the same analysis with DAS28-ESR remission criteria or a stricter DAS28-CRP cut-off point of 2.3.

Abbreviations

DAS28-CRP, C-reactive protein Disease Activity Score in 28 joints; DAS28-ESR, erythrocyte sedimentation rate Disease Activity Score in 28 joints. **[AU Query: Confirm definitions]**

Competing interests

The authors declare that they have no competing interests.

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Published: X Month 2011

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doi:10.1186/ar3393
Cite this article as: Yoshida K, *et al.*: Remission by Disease Activity Score 28-CRP and Disease Activity Score 28-ESR. *Arthritis Research & Therapy* 2011, 13:4??.

RHEUMATOLOGY

Rheumatology 2011;50:2093–2099
doi:10.1093/rheumatology/ker295
Advance Access publication 2 September 2011

Original article

An observational study of tocilizumab and TNF-α inhibitor use in a Japanese community hospital: different remission rates, similar drug survival and safety

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Abstract

Objective. To assess the effectiveness, drug survival and safety of tocilizumab compared with TNF-α inhibitors in clinical practice.

Methods. Patients in the Cohort of Arthritis Biologic Users at Kameda Institute (CABUKI) registry who were on biologics during July 2003 to October 2010 were included. Remission rates at 6 months, Kaplan–Meier drug survival estimates and serious adverse event (SAE) rates were compared.

Results. A total of 247 RA patients were analysed. For first-line biologic users, the 6-month 28-joint DAS (DAS-28)-ESR remission rates were 66.7% for tocilizumab *vs* 25.8% for TNF inhibitors ($P < 0.001$, Fisher's exact test). This advantage disappeared with the application of the newly suggested Boolean remission criterion for clinical trials: 0% for tocilizumab *vs* 8.2% for TNF inhibitors ($P = 0.367$, Fisher's exact test). Tocilizumab users in DAS-28-ESR remission had lower mean ESR (3.9 mm/h for tocilizumab *vs* 7.9 mm/h for TNF inhibitors, $P = 0.026$, *t*-test) and higher mean swollen joint count (2.6 for tocilizumab *vs* 1.3 for TNF inhibitors, $P = 0.036$, *t*-test), thus failing to meet the more stringent Boolean criteria. First- and second-line tocilizumab users showed similar drug survival and SAE rates compared with TNF inhibitor users.

Conclusion. Tocilizumab had drug survival and safety profiles similar to those of TNF inhibitors in this Japanese single-centre registry. Tocilizumab was superior to TNF inhibitors when compared at 6 months by DAS-28-ESR remission. However, the newly suggested Boolean criteria are more appropriate measures of effectiveness as DAS-28-ESR remission by tocilizumab was mainly due to very low ESR in our study population.

Key words: Tocilizumab, TNF inhibitors, Rheumatoid arthritis, Benefit, Safety, Treatment outcome, DAS-28, Boolean remission criteria.

Introduction

RA is a multisystem inflammatory disorder, characterized by severe synovial involvement, the treatment of which has advanced substantially in the past two decades. Use of TNF inhibitors, such as infliximab, etanercept and adalimumab, results in remission in certain patients in clinical practice [1]. Given their effectiveness, TNF inhibitor use has become part of formal treatment recommendations [2, 3]. Despite this, a considerable number of patients fail to go into remission on TNF inhibitors, and require other treatments.

Tocilizumab is a humanized mAb against the IL-6 receptor, blocking its activity through competitive receptor binding [4]. Tocilizumab monotherapy was compared with MTX in the Study of Active controlled TOcilizumab

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Submitted 7 April 2011; revised version accepted 14 July 2011.

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monotherapy for Rheumatoid arthritis patients with an Inadequate response to methotrexate (SATORI) trial [5] in Japanese patients refractory to MTX therapy, and showed effectiveness in disease activity suppression. Recently, a systematic review by Singh *et al.* [6] concluded that tocilizumab was effective based on the eight clinical trials reviewed.

Attempts to compare different biologic agents both directly and indirectly have gained popularity in rheumatology. For example, Hetland *et al.* [1] reported a direct comparison of three TNF inhibitors using a nationwide registry in Denmark, finding that etanercept had the best drug survival rates, while adalimumab showed the best treatment response. Tocilizumab was not included in the study. Bergman *et al.* [7] compared tocilizumab's ACR response with that of other biologic agents indirectly via a systematic literature review. They concluded that tocilizumab had similar ACR 20 and ACR 50 response rates, but a higher ACR 70 response rate. In a more recent meta-analysis by Salliot *et al.* [8], clinical trials of biologic agents used in TNF inhibitor-refractory cases were reviewed. Tocilizumab as well as rituximab, abatacept and golimumab were found to be equally effective. However, data on comparison of biologic agents in a routine practice setting are scarce to date.

Clinical experience with tocilizumab has accumulated in Japan, where it was developed and first approved. In this Japanese single-centre, registry-based observational study, we report on the effectiveness, drug survival and safety of tocilizumab in comparison with TNF inhibitors.

Materials and methods

The present study was conducted at Kameda Medical Center, a community-based teaching hospital in a rural area of Japan. Approval of the ethics committee of the hospital was obtained (Institutional Review Board of Kameda Medical Center). Individual patient informed consent was not required under Japanese law, as the present study was purely observational.

The Cohort of Arthritis Biologic Users at Kameda Institute registry

We enrolled RA patients who started biologic treatment under our care into the Cohort of Arthritis Biologic Users at Kameda Institute (CABUKI) registry. This comprehensive database contains information on baseline characteristics of patients and disease activity at initial and follow-up visits. Serious adverse events (SAEs), defined as hospitalization or the need for i.v. antibiotics, were also recorded. The treating rheumatologist was responsible for data entry. Data were collected from the initiation of the biologic therapy to the discontinuation of the agent for any reason for >3 months.

Eligibility criteria

Patients who were clinically diagnosed with RA and treated with biologics between July 2003 and October 2010 were potentially eligible. Patients were excluded if the agent of choice was abatacept, as its use in Japan began towards the end of the inclusion period. Patients were also excluded if their biologics had been commenced at other institutions. Patients were grouped into first-, second- and third-line biologic groups. The first-line group was comprised of patients who were biologic naïve. Patients in the second- and third-line groups had used one or two previous biologic agents, respectively.

Effectiveness measures

Effectiveness was compared between the tocilizumab group and TNF inhibitors-combined group, which comprised infliximab, etanercept and adalimumab users, at 6 months by four remission criteria: DAS-28-ESR < 2.6, DAS-28-CRP < 2.3 and the Boolean remission criteria for both clinical practice and trials. The same comparison was done between first- and second-line tocilizumab and TNF inhibitor users. As DAS-28-CRP tends to be lower than DAS-28-ESR, we utilized the cut-off of 2.3 as suggested by Inoue *et al.* [9]. The Boolean criteria for clinical trials and practice were announced at the ACR annual meeting 2010 and recently published [10, 11]. Remission criteria for clinical trials are defined as tender joint count (TJC) $\leqslant 1$, swollen joint count (SJC) $\leqslant 1$, patient's global assessment (PGA) $\leqslant 1$ out of 10 and CRP $\leqslant 1$ mg/dl. Boolean criteria without CRP may be used in clinical practice until better measures become available. For patients with follow-up duration <6 months, the 6-month data were supplied using the last observation carried forward (LOCF) method. Since prominent discrepancy exists between DAS-28-ESR and Boolean remission criteria, particularly in the first-line tocilizumab group, we performed additional comparisons of patients in DAS-28-ESR remission between the first-line tocilizumab group and the TNF inhibitors-combined group.

Statistical analyses

Continuous and categorical baseline variables were analysed using *t*-test and Fisher's exact test, respectively. Of these baseline variables, ones with univariate $P < 0.2$ or with clinical significance (tocilizumab use, male sex, age >65 years, current smoking status, RA disease duration, prednisolone use, MTX use, previous exposure to other biologics and DAS-28-ESR without PGA) were included in the models for multivariate analyses for remission, drug survival and SAE rate. Baseline DAS-28-ESR without PGA [DAS-28-ESR (three variables)] was used for multivariate analyses, as PGA was missing in 42 patients [12].

Baseline predictors of DAS-28-ESR and Boolean remission for clinical trials and practice at 6 months were determined with logistic regression models. Explanatory variables included in the Boolean remission prediction models were tocilizumab use, sex, age >65 years, current smoking status, RA disease duration, prednisolone use, MTX use, previous exposure to other biologics and DAS-28-ESR (three variables) at baseline. DAS-28-ESR remission prediction models were adjusted for these variables plus baseline lung disease and diabetes. Longitudinal changes in DAS-28-ESR were compared between the tocilizumab

group and TNF inhibitors-combined group with linear mixed models including prednisolone dose and MTX dose as random effects.

Kaplan–Meier drug survival estimates of tocilizumab and TNF inhibitors-combined groups were analysed with a log-rank test. Baseline predictors of poor drug survival were determined using multivariable-adjusted Cox regression models adjusted for tocilizumab use, sex, age >65 years, BMI, current smoking status, RA disease duration, RF/ACPA positivity, lung disease, diabetes, concomitant autoimmune diseases, prednisolone use, MTX use, NSAID use, previous exposure to biologic agents and baseline DAS-28-ESR (three variables).

We also examined the rates of SAEs per 100 person-years (PY) of drug usage. Analysis by *t*-test compared the mean SAE rate (SAE/100 PY of drug usage) for each group. Baseline characteristics associated with SAE were analysed with linear regression models with the SAE rate as the response variable. Adjustment was done for baseline variables included in the Cox regression models, with the exception of BMI.

All statistical analyses were performed with R version 2.12 (http://www.r-project.org), except for linear mixed models, for which PASW Statistics version 18 (SPSS Inc., Chicago, IL, USA) was used. All tests were two-sided when applicable. $P < 0.05$ was considered statistically significant.

Results

We identified 255 potentially eligible RA patients who were or had been on biologics. One patient on abatacept and seven patients whose biologic agents had been started at other hospitals were excluded, leaving 247 patients meeting inclusion criteria for the safety and drug survival analyses. There were 192 first-, 44 second- and 11 third-line biologic users. Seventeen patients without 6-month response data were excluded from the effectiveness analyses ($n = 17$, first-line infliximab 7, first-line etanercept 8, second-line etanercept 1 and second-line tocilizumab 1). Baseline characteristics of the overall cohort and first-line biologic users are shown in Table 1. Mean follow-up duration, mean MTX dose, prior history of malignancy and MTX use showed significant differences between the first-line biologic groups, whereas mean follow-up duration [tocilizumab group 10.3 (8.7) months *vs* TNF inhibitors-combined group 18.9 (13.2) months, $P = 0.015$] and mean age [tocilizumab group 62.9 (10.8) years *vs* TNF inhibitors-combined group 53.2 (16.7) years, $P = 0.030$] differed significantly in second-line tocilizumab ($n = 22$) and TNF inhibitor users ($n = 22$, infliximab 3, etanercept 17 and adalimumab 2). Characteristics of third-line biologic users did not differ between the tocilizumab ($n = 7$) and TNF inhibitors-combined group ($n = 4$, infliximab 1 and etanercept 3).

Effectiveness comparison

Comparisons of remission rates at 6 months are shown in Fig. 1 ($n = 230$: tocilizumab 46, infliximab 92, etanercept 87 and adalimumab 5), demonstrating a statistically significant difference by DAS-28-ESR remission criteria only. For first-line biologic users ($n = 177$: tocilizumab 18, infliximab 88, etanercept 68 and adalimumab 3), remission rates are shown in Fig. 2. Statistically significant differences existed in remission rates between the tocilizumab group and TNF inhibitors-combined group with regards to DAS-28-ESR and DAS-28-CRP remission criteria, but not with Boolean criteria. In the additional analysis, tocilizumab users in DAS-28-ESR remission had a significantly higher SJC and lower ESR compared with TNF inhibitor users in DAS-28-ESR remission (Table 2).

For second-line biologic users ($n = 42$: tocilizumab 21, infliximab 3, etanercept 16 and adalimumab 2), remission rates were 33.3, 14.3, 0 and 0% in the tocilizumab group, and 28.6, 38.1, 14.3 and 14.3% in the TNF inhibitors-combined group by DAS-28-ESR, DAS-28-CRP, Boolean criteria for clinical practice and Boolean criteria for clinical trials, respectively. No statistically significant difference was found between the two groups regardless of the criteria used.

Remission predictors

Male sex was associated with a better chance of remission by the Boolean criteria for clinical trials [$P = 0.004$; odds ratio (OR) = 6.96, 95% CI 1.91, 28.11] and clinical practice ($P = 0.011$; OR = 4.70, 95% CI 1.42, 16.16). Using TNF inhibitors-combined as the reference, tocilizumab use was not a negative predictor by either of the Boolean criteria. Predictors of DAS-28-ESR remission at 6 months were tocilizumab use ($P < 0.001$, OR = 4.79, 95% CI 1.95, 12.52), male sex ($P = 0.009$, OR = 3.04, 95% CI 1.33, 7.17), age >65 years ($P = 0.008$, OR = 0.29, 95% CI 0.11, 0.70) and baseline DAS-28-ESR (three variables) ($P < 0.001$, OR = 0.53, 95% CI 0.36, 0.74).

In longitudinal analyses of DAS-28-ESR changes with linear mixed models, first-line tocilizumab users had significantly lower DAS-28-ESR (−1.25/12 months of drug usage, $P = 0.011$) compared with first-line TNF inhibitor users. The same held true for second-line tocilizumab users (−1.26/12 months, $P < 0.001$).

Drug survival and safety

No significant difference was found in drug survival time as shown in Fig. 3 ($P = 0.879$, log-rank test) between the tocilizumab group and TNF inhibitors-combined group ($n = 247$, tocilizumab 47, infliximab 99, etanercept 96 and adalimumab 5). Between the first-line tocilizumab group and TNF inhibitors-combined group ($n = 192$, tocilizumab 18, infliximab 95, etanercept 76 and adalimumab 3), there was also no statistically significant difference (Fig. 4, $P = 0.860$, log-rank test). At 6 and 12 months, respectively, 69.6 and 59.7% remained on first-line tocilizumab, whereas 71.5 and 53.2% remained on TNF inhibitors. Reasons for drug discontinuation in each group were similar. Drug survival was also comparable ($P = 0.354$, log-rank test) between the second-line tocilizumab group ($n = 22$; 72.6% at 6 months, 60.5% at 12 months) and TNF inhibitors-combined group ($n = 22$; 81.8% at 6 months, 76.7% at 12 months), with similar reasons for discontinuation.

TABLE 1 Baseline characteristics for the overall cohort and first-line biologic users

Baseline characteristics	Overall cohort (n = 247)			First-line users (n = 192)		
	TCZ (n = 47)	TNFi (n = 200)		TCZ (n = 18)	TNFi (n = 174)	
Continuous variables, mean (S.D.)			P, t-test			P, t-test
Follow-up duration, months	9.6 (7.4)	16.8 (15.6)	<0.001*	9.4 (6.6)	16.6 (16)	0.001*
Age, year	60.3 (11.4)	57.7 (14.3)	0.179	60.6 (8.9)	58.1 (14)	0.303
BMI[a]	23.9 (4.2)	22.9 (3.8)	0.133	22.6 (4.0)	22.8 (3.7)	0.889
RA disease duration, year	8.8 (7.3)	8.1 (9.2)	0.640	9.1 (8.6)	7.9 (9.4)	0.616
Prednisolone dose, mg	7.3 (4.3)	7.0 (4.4)	0.684	7.0 (5.7)	6.8 (4.5)	0.876
MTX dose, mg/week	6.9 (4.7)	7.0 (3.8)	0.894	4.3 (4.0)	6.9 (3.6)	0.015*
DAS-28-ESR (three variables)	4.8 (1.1)	4.9 (1.2)	0.552	4.9 (1.2)	5.0 (1.2)	0.781
DAS-28-ESR (four variables)[b]	5.0 (1.2)	5.1 (1.3)	0.503	5.0 (1.3)	5.2 (1.3)	0.660
Categorical variables, %			P, Fisher's exact test			P, Fisher's exact test
Male	19.1	25.0	0.452	22.2	25.9	1.000
Elderly (age >65 year)	36.2	34.5	0.866	38.9	33.9	0.795
Current smoker[c]	17.4	16.7	1.000	11.1	16.7	1.000
RF/ACPA positivity	89.4	89.0	1.000	94.4	88.5	0.699
Chronic kidney disease	12.8	7.5	0.250	11.1	7.5	0.637
Lung disease	25.5	27.0	1.000	27.8	25.9	0.786
Heart disease	4.3	3.5	0.682	0.0	3.4	1.000
Diabetes mellitus	21.3	19.5	0.839	11.1	19.5	0.534
Isoniazid prophylaxis	63.8	69.0	0.492	61.1	70.7	0.424
Concomitant autoimmune disease	21.3	15.5	0.383	27.8	14.9	0.178
FM	6.4	6.5	1.000	0.0	6.3	0.604
Prior history of malignancy	10.6	3.5	0.056	22.2	3.4	0.008*
Prednisolone use	91.5	91.0	1.000	83.3	89.7	0.424
MTX use	74.5	85.0	0.089	55.6	85.6	0.004*
NSAIDs use	44.7	56.0	0.194	61.1	56.9	0.806

[a]Not available in eight patients. [b]Not available in 42 patients. [c]Not available in 21 patients. *Statistically significant. TCZ: tocilizumab; TNFi: TNF inhibitors.

FIG. 1 Remission rates (%) by criteria for toclizumab *vs* TNF inhibitor groups (overall cohort). Pract Boolean: Boolean remission criterion for clinical practice; Trial Boolean: Boolean remission criterion for clinical trials; TCZ: tocilizumab; TNFi: TNF inhibitors.

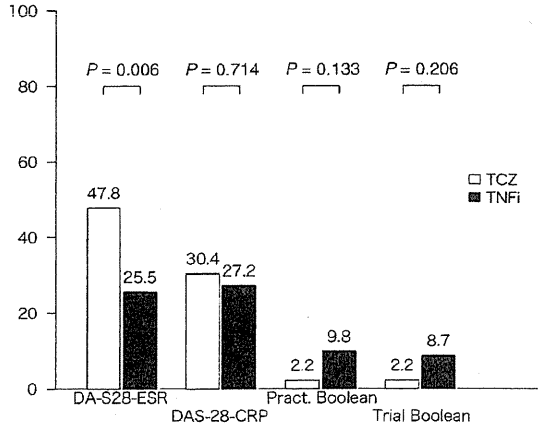


FIG. 2 Remission rates (%) by criteria for toclizumab *vs* TNF inhibitor groups (first-line users). Pract Boolean: Boolean remission criterion for clinical practice; Trial Boolean: Boolean remission criterion for clinical trials; TCZ: tocilizumab; TNFi: TNF inhibitors.

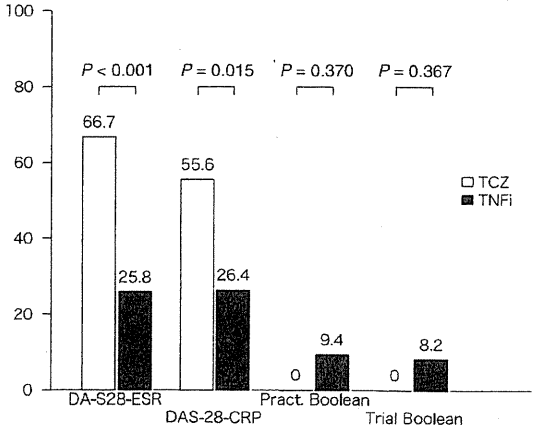
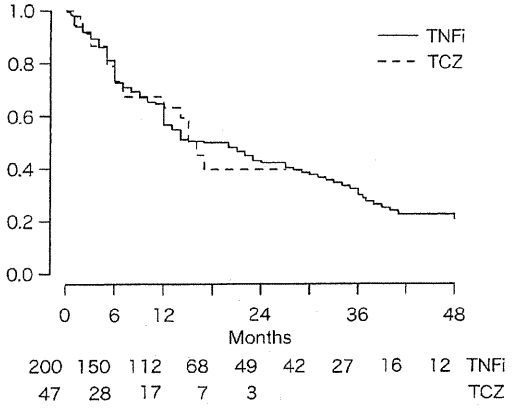


TABLE 2 Comparison of mean values between first-line tocilizumab and TNF inhibitor users in DAS-28-ESR remission

DAS-28-ESR components	TCZ	TNFi	*P*, *t*-test
TJC (0-28)	0.7	0.3	0.139
SJC (0-28)	2.6	1.3	0.036*
PGA (0-10)	17.3	14.6	0.531
ESR, mm/h	3.9	7.9	0.026*

*Statistically significant. TCZ: tocilizumab; TNFi: TNF inhibitors.

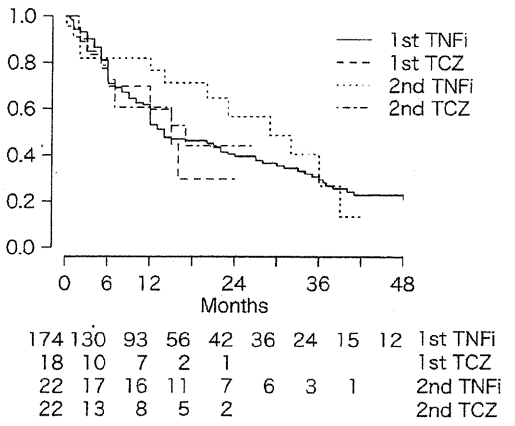
FIG. 3 Kaplan-Meier drug survival estimates for all biologic users. Number at risk in each group is shown at the bottom. TCZ: tocilizumab; TNFi: TNF inhibitors.



Baseline factors associated with an increased risk of drug discontinuation were BMI [$P = 0.013$, hazard ratio (HR) = 1.06 for each 1-point increase in BMI, 95% CI 1.01, 1.11]. In contrast, previous exposure to other biologics ($P = 0.016$, HR = 0.52, 95% CI 0.31, 0.88), concomitant autoimmune disease ($P = 0.042$, HR = 0.56, 95% CI 0.32, 0.98) and NSAID use ($P = 0.005$, HR = 0.57, 95% CI 0.38, 0.84) were associated with decreased risk. Compared with TNF inhibitors-combined, tocilizumab use was not associated with changes in risk ($P = 0.357$, HR = 1.30, 95% CI 0.74, 2.27).

Differences in mean SAE rate for each group were not statistically significant: 43.1/100 PY of drug usage for the tocilizumab group and 35.2/100 PY of drug usage for the TNF inhibitors-combined group ($P = 0.730$, *t*-test). When calculated by dividing the total number of SAEs by the total duration of drug usage, the SAE rates were 15.9/100 PY for the tocilizumab group and 13.9/100 PY for the TNF inhibitors-combined group. No baseline characteristics were associated with a significant increase in SAE rate. RF/ACPA positivity [$P = 0.084$, regression coefficient (RC) = −54.6/100 PY, 95% CI −116.6, 7.4], concomitant

FIG. 4 Kaplan-Meier drug survival estimates for first- and second-line biologic users. Number at risk in each group is shown at the bottom. TCZ: tocilizumab; TNFi: TNF inhibitors.



autoimmune disease ($P = 0.099$, RC = −46.6/100 PY, 95% CI −102.0, 8.8) and NSAIDs use ($P = 0.062$, RC = −3.1/100 PY, 95% CI −80.0, 1.9) were associated with a non-significant trend towards decreased risk of SAEs. Tocilizumab use (TNF inhibitors-combined as the reference) was not a significant predictor ($P = 0.685$, RC = +11.1/100 PY, 95% CI −42.7, 64.9).

The most common SAEs in the TNF inhibitors-combined group were pneumonia (14 events) followed by urinary tract infection (UTI) (4 events), worsening of interstitial lung diseases (3 events), malignancy (3 events) and pulmonary haemorrhage (3 events), whereas soft-tissue infections (2 events), UTI (2 events) and vasculitis (2 events) occurred in the tocilizumab group. One event of vasculitis and two events of soft-tissue infections also occurred in the TNF inhibitors-combined group.

Discussion

The present study assessed the effectiveness, drug survival and safety of tocilizumab in clinical practice compared with TNF inhibitors. In the effectiveness analysis, we found that first-line tocilizumab achieved higher remission rates than first-line TNF inhibitor use by both DAS-28-ESR and DAS-28-CRP remission criteria, but not by the new Boolean remission criteria. In the drug survival analysis, tocilizumab was comparable with TNF inhibitors both in first- and second-line use. In the safety analysis, SAE rates were similar between the tocilizumab and the TNF inhibitors-combined groups.

Tocilizumab achieved a higher 6-month remission rate than TNF inhibitors by DAS-28-ESR remission criterion. Tocilizumab users also achieved lower DAS-28-ESR values in the longitudinal analysis. Interestingly, none of the first-line tocilizumab users in DAS-28-ESR remission met the Boolean remission criteria. In fact, more patients in the TNF inhibitor groups were in remission by these new

criteria, although the difference was not statistically significant.

Lower ESRs in first-line tocilizumab users in DAS-28-ESR remission caused this intriguing discrepancy. ESR was lower by 4 mm/h in this group (3.9 mm/h) compared with first-line TNF inhibitor users (7.9 mm/h) in DAS-28-ESR remission. ESR is heavily weighted in DAS-28-ESR [13]. More importantly, its weight rapidly decreases as ESR approaches zero, which commonly occurs in tocilizumab users. Thus a 4 mm/h decrease in ESR in this range causes DAS-28-ESR to decrease by approximately −0.49, effectively allowing patients to have an additional two to three swollen joints and still remain in remission by DAS-28-ESR criteria. As the Boolean remission criteria require the SJC to be $\leqslant 1$, these first-line tocilizumab users in DAS-28-ESR remission failed to meet Boolean criteria.

Several groups have reported similar results comparing DAS-28-ESR remission with remission defined by the simple disease activity index (SDAI) and the clinical disease activity index (CDAI) [14, 15] in clinical trials. Nishimoto *et al.* [16] reported good correlation between DAS-28-ESR and SDAI/CDAI in the SATORI study, although remission rates at Week 24 by DAS-28-ESR (47.2%) and SDAI/CDAI (17.0 and 15.1%, respectively) showed differences. Smolen *et al.* [17] reported that tocilizumab achieved four times more DAS-28-ESR remission compared with CDAI remission, whereas TNF inhibitors achieved two times more DAS-28-ESR remission. They stated that although this discordance was most prominent with tocilizumab, it also happened with TNF inhibitors and MTX. We confirmed the new Boolean remission criteria are as stringent as SDAI/CDAI remission criteria. The problematic laxity of the DAS-28-ESR remission criterion, which affects all biologics, but appears to favour tocilizumab, may be avoided with the use of these new criteria.

The present study also confirmed that the drug survival of tocilizumab was comparable with the TNF inhibitors, both in first- and second-line use. The drug survival rate of tocilizumab was 69.6% at 6 months in first-line users, whereas 72.6% remained on tocilizumab at 6 months in the second-line group. This is similar to values reported in the REtrospective ACTemra Investigation for Optimal Needs of RA Patients (REACTION) study [18], in which 6-month drug survival rates of 78.5% for first-line users and 77.6% for the TNF inhibitor failure group were observed.

No pneumonia was observed in the tocilizumab group during the study period, whereas the number of serious soft-tissue infections was similar between these groups, even though the tocilizumab group had fewer patients and a shorter follow-up duration. This might suggest that infections associated with tocilizumab use are different from those associated with TNF inhibitor use. On the other hand, Campbell *et al.* [19] reported that most common infections occurring with tocilizumab use were skin and subcutaneous infections and respiratory tract infections, and similar infection profiles were observed in TNF inhibitor users. Japanese post-marketing surveillance yielded similar results; respiratory tract infections were the most common infectious complications, followed by soft-tissue infections [20]. At this point, special attention to both pneumonia and soft-tissue infections in tocilizumab users is required.

The limitations of the present study mainly arise from its observational design. Channelling or allocation bias [21], resulting from preferential use of a particular agent in patients with a better or worse prognosis, should be considered in the present study. First-line tocilizumab users were less often on concurrent MTX therapy. It is likely that treating physicians chose patients who could not tolerate MTX as candidates for tocilizumab therapy. These MTX-naïve patients may have been more likely to respond to any further treatment compared with MTX-refractory patients. We addressed this problem with logistic regression models adjusted for MTX use after which tocilizumab use was still associated with a higher OR of attaining DAS-28-ESR remission. This indicates that the higher DAS-28-ESR remission rates observed in the first-line tocilizumab group were due to medication rather than patient selection. Finally, the tocilizumab group was substantially smaller than the TNF inhibitors-combined group and had a shorter follow-up period. This is likely due to shorter experience with tocilizumab, approved in Japan in 2008, compared with TNF inhibitors, which have been in clinical use since 2003. As clinical experience with tocilizumab grows, future follow-up studies are warranted.

In conclusion, the present study suggests tocilizumab has drug survival and safety profiles similar to those of TNF inhibitors in clinical practice. Although a higher rate of DAS-28-ESR remission was observed in the tocilizumab group, DAS-28-ESR remission achieved with tocilizumab may be different from that achieved with TNF inhibitors, given that the ESR component of the composite score was heavily affected by tocilizumab. This problem may be addressed by using the newly suggested Boolean remission criteria, which we anticipate will be the preferred method, along with SDAI and CDAI, in the years to come. Further studies are needed to clarify the clinical implications of discrepant remission rates and the validity of the new remission criteria.

Rheumatology key messages

- Tocilizumab had drug survival and safety profiles similar to TNF inhibitors.
- DAS-28, but not the Boolean remission rate was higher with tocilizumab compared with TNF inhibitors.
- Decreased ESR with tocilizumab might explain the discordant remission rate.

Disclosure statement: M.K. has received honoraria from Tanabe-Mitsubishi Pharma, Pfizer, Eisai and Chugai Pharma. All other authors have declared no conflicts of interest.

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