methods are expected to be more accurate and sensitive than the clinical composite score, with numerous basic studies in this area [36, 37]. However, this method may have the disadvantages of high cost or being time consuming in practical use. Several research groups have produced unique US-based global scores that targeted limited joint sites to prove these disadvantages [38–44]. At present, there is no consensus as to which score should be used for clinical trials or in daily practice [45]. Additional and confirmatory trials are required to establish a US-based global score. Of note, Backhaus *et al.* produced a unique US-based composite score called the US7, which targets seven joints to reflect disease activity. They reported results of several trials and have steadily progressed in their study of this score [43, 44].

Treat to target (T2T) is a concept of ideal treatment of RA that has become widespread internationally [46]. It emphasizes that RA must be treated in the early phase and tightly controlled by appropriate measurement of disease activity so that patients will receive maximum therapeutic impact and achieve the goal of remission. The US-based global scores have the potential to be useful for the achievement of T2T because US can directly detect changes in synovitis. The various US-based composite scores mentioned here are now in the evaluation process, and additional detailed analyses are anticipated.

Change in SV for assessment of local joints in RA

In our investigation focusing on local joints, we reported that remaining SV at local joints increases the risk of structural deterioration, despite the fact that anti-rheumatoid therapy achieved low disease activity (LDA) clinically at 8 weeks [25, 47]. Interestingly, these joints tended to show improvement in clinical signs such as joint pain or swelling and thus clinical composite scores also showed improvement. Similar findings were reported by another group [48]. Subclinical synovitis and sonography were first reviewed by Bresnihan *et al.* [49], and Brown *et al.* [50, 51] reported that detailed sonographic observation detected subclinical synovitis in patients with long-term clinical remission. These joints with a poor prognosis were asymptomatic or mildly symptomatic but showed positive SV at the local level. Joints with remaining SV might be related to subclinical synovitis. Further longitudinal observation may clarify this relation.

We also reported that joints with a disappearance of SV with simultaneous overall disease improvement showed an improvement in joint prognosis [52]. Dougados *et al.* [53] reported a similar conclusion in their multicentre prospective trial. These results indicate that RA requires both an improvement in overall disease activity and the disappearance of local SV for remission and achievement of T2T. Remaining SV at a local joint indicates ongoing structural alteration. Recently the EULAR published recommendations for the use of joint imaging in RA [54] in which monitoring of inflammatory activity and prediction of response to treatment by imaging were discussed. Although PDS was considered useful for these purposes, more detailed data are needed for PDS to became an established examination tool. We have focused on the response of SV to treatment that may predict structural deterioration in local joints. Multicentre studies are necessary to establish the mechanism of response of SV to treatment.

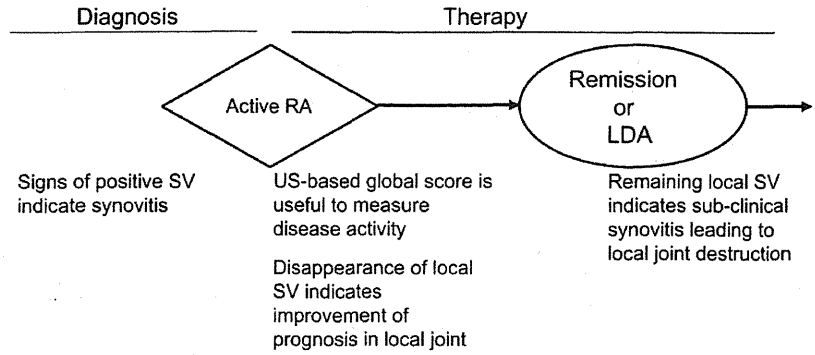
In RA, accumulation of inflammation leads to the progression of joint damage and, logically, time-integrated SV consequently relates to a change in structural alteration. Naredo *et al.* [55] showed that in the body overall, time-integrated joint counts with positive SV are related to the change in total Sharp score. We also reported that local joints showed poor prognosis when SV remained despite achievement of LDA clinically. However, changes in structural alteration of the joint are not related to time-integrated quantitative SV [52]. The reason for this unexpected result is unknown. We speculated that local synovitis might change to heterogeneous inflammation in a condition of LDA that is neither that of simple reduction of acute inflammation nor of prolonged recovery. Further studies are needed to confirm these results.

In daily clinical practice, joints with remaining SV are often detected by PDS, however, there are no definitive methods to treat them. Although these asymptomatic or mildly symptomatic joints with poor prognosis, namely those showing subclinical synovitis, need to be treated, it is unclear whether systemic intensive therapy or topical therapy are effective. Recently a research group called the Targeted Ultrasound Initiative started a multicentre international study called Targeted Ultrasound in RA to investigate the effect of corticosteroid injection in joints with remaining positive SV [56]. T2T emphasizes optimizing treatment by appropriate disease assessment, and clinical composite scores reflecting systemic disease activity are mostly used at present. The use of local assessment with US will help to achieve T2T.

Conclusion

Why should rheumatologists evaluate SV in RA? Early diagnosis and assessment of disease activity are at the heart of the T2T approach in RA. In the early diagnosis of RA, detection of SV to discover synovitis could be used as a screening test for entry into the ACR/EULAR classification algorithm. A US-based global score consisting of both the SV score and synovial hypertrophy score used to assess overall disease activity may be more sensitive and objective than the clinical composite score and thus may be useful as a guide for optimizing disease treatment. Also, changes in local SV have prognostic value for local joint destruction that may lead to meticulous control of inflammation. The evaluation of SV provides various important information and contributes to the clinical practice of RA (Fig. 2).

Fig. 2 Usefulness of SV in the clinical practice of RA.



Information obtained from SV at each clinical point is shown.

Rheumatology key messages

- Abnormal SV is strongly associated with synovitis of RA.
- Detection of SV is useful for proving the presence of synovitis and diagnosing RA.
- RA remission requires an improvement of overall disease activity and disappearance of local SV.

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ORIGINAL ARTICLE

Functional disability can deteriorate despite suppression of disease activity in patients with rheumatoid arthritis: a large observational cohort study

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Abstract
Objective To analyze the relationship between the progression of disability and disease activity in patients with rheumatoid arthritis (RA) in daily practice.
Methods Patients from an observational cohort, IORRA, who completed surveys during 2009–2011 were eligible. Linear regression of disease activity score 28 (DAS28), Japanese version of Health Assessment Questionnaire (J-HAQ), and EQ-5D from baseline were calculated, and the angles of the regression lines were designated DAS28 slope, J-HAQ slope, and EQ-5D slope, respectively, in each patient; averages were compared between treatment groups.
Results A total of 5,038 patients [84.0 % female, mean age 59.4 (SD 13.1) years, disease duration 13.2 (9.6) years, DAS28 3.29 (1.14), and J-HAQ 0.715 (0.760)] were analyzed. The average DAS28 slope indicated improvement in all groups, whereas J-HAQ slopes were negative in patients on methotrexate (MTX), biologics, combination biologics/disease-modifying antirheumatic drugs (DMARDs), and combination biologics/MTX at baseline, but positive in patients on prednisolone >5 mg/day [0.010 (0.153)] and not on MTX at baseline [0.007 (0.122)], representing a worsening of disability.
Conclusion There is some disparity between improvement of disease activity and progression of disability, suggesting that quality of remission must be considered.

Keywords Rheumatoid arthritis · Disease activity · Physical function · Treatment · Cohort study

Introduction

Treatment of rheumatoid arthritis (RA) has improved over the last ten years, following the introduction of new agents and modification of treatment strategies [1, 2]. As a consequence, clinical remission has become a realistic goal [3, 4]. Suppression of disease activity is the major factor that inhibits the progression of disability [1, 5, 6]. Since the treat-to-target (T2T) initiative first proposed the strategy of remission induction in the management of RA in daily practice [7, 8], the proportion of patients in remission has been increasing. In the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) cohort, which we established at the Institute of Rheumatology, Tokyo Women's Medical University in 2000, the improvement in the disease activity in RA patients has been quite apparent, and nearly 40 % of all patients in 2011 achieved clinical remission [9]. This is thought to be the result of improved patient care following the recognition of the importance of remission induction in preventing joint destruction and preserving activities of daily living. However, disability in patients in the IORRA cohort has not improved as much as disease activity: the average disease activity score 28 (DAS28) improved from 4.16 in 2000 to 3.03 in 2011 (−28 %), while the Japanese version of Health Assessment Questionnaire (J-HAQ) score only improved from 0.80 in 2000 to 0.64 in 2011 (−18 %). This triggers the question of whether the

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remissions achieved by biologics versus corticosteroids yield comparable outcomes with respect to disability.

We hypothesized that the discrepancy between improvement in disease activity and progression of disability might depend on which agents are administered. Indeed, we have previously demonstrated that patients treated with corticosteroids develop progressive disability even when they are in remission, and suggested that there is a difference in the quality of remission between different agent classes [10, 11]. In the study described in this report, we analyzed the relationship between control of disease activity and progression of disability in our observational cohort, IORRA.

Patients and methods

Patients and the IORRA database

We established a prospective observational cohort of RA patients at the Institute of Rheumatology, Tokyo Women's Medical University in October 2000; this is designated the IORRA cohort. Patients with RA who fulfilled the American College of Rheumatology criteria for RA [2, 12, 13] were registered, and their information and data were collected biannually (in April and October) when patients visited the outpatient unit of our institute for consultation. Informed consent was routinely obtained from each patient at each visit.

The IORRA database consists of three components. The first component is the physician's evaluation, which includes the number of tender joints, number of swollen joints, and a visual analogue scale (VAS) of disease activity rated by the physician. The second component is information collected from patients, which includes VAS for pain, VAS for general health, disability level using J-HAQ score [12], height, body weight, and comorbidities in the previous six months. Information about medication actually taken (not just prescribed) during the period was also reported, including corticosteroid use and daily dose, disease-modifying antirheumatic drug (DMARD) use, methotrexate (MTX) use and weekly dose, and biologics use. Patients were asked by the attending physician to answer these questions by completing questionnaire sheets at home and mailing them back in a pre-stamped envelope within two weeks of their visit. The third component is laboratory data, including C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), blood cell count, liver transaminase levels, and urinalysis. All information was integrated into a single database that was used for analysis. DAS28 and EQ-5D scores were calculated according to the original methods [14, 15].

Over 99 % of RA patients in our institute participated in the study during this time period, and over 98 % of patients completed and returned their questionnaires. Patients who participated in the IORRA survey between April 2009 and April 2011 were eligible for this study.

Methods

Institute of Rheumatology, Rheumatoid Arthritis is an observational cohort database in which longitudinal data about disease activity, disability, and treatment have been collected. The linear regressions of DAS28, J-HAQ, and EQ-5D scores from baseline were calculated for each patient, and the angles of the regression lines were designated the DAS28 slope, J-HAQ slope, and EQ-5D slope, respectively. Specifically, for each patient who participated in IORRA at least three times during the study period, a linear regression was conducted with longitudinal DAS28, J-HAQ, and EQ-5D as a response and continuous time, 0, 1, 2, and 3 as an explanatory variable. The DAS28 slope increases as disease activity worsens, the J-HAQ slope increases as disability progresses, and the EQ-5D slope increases as quality of life improves.

Average values for the DAS28 slope, J-HAQ slope, and EQ-5D slope were calculated for different patient groups as follows: (a) patients receiving MTX were classified by MTX dose, (b) patients on oral corticosteroids were classified by equivalent prednisolone (PSL) dose, and (c) patients were classified by agents used at baseline: on conventional DMARDs other than MTX, on MTX, on biologics, and on a combination of DMARDs and biologics or a combination of MTX and biologics. At baseline in April 2009, four biologics were available in Japan: infliximab, etanercept, adalimumab, and tocilizumab. The average DAS28 slope, J-HAQ slope, and EQ-5D slope were compared between treatment groups, respectively. Written consent was obtained from each patient who participated in the study, according to the Declaration of Helsinki (most recently revised at the General Assembly in October 2008), and the study was approved by the local ethics committee at Tokyo Women's Medical University.

Statistical analysis

Means and their standard deviations were used to describe data for continuous variables, and proportions were used to describe data for discrete variables. The time coefficients, representing the degree of progression for each outcome in each patient, were analyzed using the mean and its 95 % confidence interval according to the treatment the patient received. The distributions of the DAS28 slope, J-HAQ slope, and EQ-5D slope were visualized by plotting the

cumulative probability [16–18], a method that has been commonly used to present radiographic progression in RA clinical studies, in order to highlight differences in the DAS28 slope, J-HAQ slope, and EQ-5D slope between treatment groups. All of the calculations were done using the statistical software R (http://cran.r-project.org/, version 2.14.0).

Results

Baseline characteristics

A total of 5,038 patients [84.0 % female, mean age 59.4 (SD 13.1) years, disease duration 13.2 (9.6) years at baseline] whose data from consecutive visits were available were recruited from the cohort.

The average DAS28, J-HAQ, and EQ-5D scores at baseline were 3.29 (1.14), 0.715 (0.760), and 0.760 (0.174), respectively. Patients were subclassified by treatment at baseline (April 2009). The baseline characteristics of these treatment groups are shown in Table 1 and in Tables S1, S2, S3, and S4 of the Electronic supplementary material (ESM).

Table 1 Baseline demographic and disease characteristics

Characteristics	Study population (N = 5,038)
Age (years)	59.4 (13.1)
Women (%)	84.0
Duration (years)	13.2 (9.6)
DAS28	3.29 (1.14)
CDAI	7.56 (6.48)
SDAI	8.28 (7.04)
EQ-5D	0.76 (0.17)
J-HAQ (0–3 scale)	0.715 (0.760)
Tender joint count (0–45)	1.8 (3.2)
Swollen joint count (0–45)	1.9 (2.8)
Pain VAS (0–100 scale)	28.7 (25.2)
Patient global VAS (0–100 scale)	30.3 (24.6)
Physician global VAS (0–100 scale)	15.6 (15.2)
CRP (mg/dl)	0.73 (1.27)
ESR (mm/h)	31.7 (22.9)
DMARDs (%)	91.0
MTX (%)	68.5
MTX dose (mg/week)	8.0 (3.1)
Prednisolone (%)	46.8
Prednisolone dose (mg/day)	4.2 (2.9)
Biologics (%)	8.7

Values are the mean (SD) unless indicated otherwise

DAS28 disease activity score 28, *CDAI* clinical disease activity index, *SDAI* simplified disease activity index, *J-HAQ* Japanese version of Health Assessment Questionnaire, *VAS* visual analogue scale, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *DMARDs* disease-modifying anti-rheumatic drugs, *MTX* methotrexate

DAS28 slope

The DAS28 slopes of each treatment group are shown in Table 2. During the observation period, the average DAS28 slope was negative (i.e., it sloped downward) in all subgroups, indicating improvement in disease activity in all subgroups.

J-HAQ slope

The J-HAQ slopes in each treatment group are shown in Table 3. The J-HAQ slope was negative in patients who were receiving MTX, biologics, a combination of biologics and DMARDs, and a combination of biologics and MTX at baseline. In contrast, the J-HAQ slope was positive (i.e., it sloped upward) in patients receiving >5 mg/day of PSL [0.010 (0.153)] and in those without MTX [0.007 (0.122)] at baseline, indicated worsening functional disability.

EQ-5D slope

The EQ-5D slopes in each treatment group are shown in Table 4. The EQ-5D slope was positive in all treatment groups. A significant dose response of EQ-5D was observed in the MTX groups, and the largest improvement in EQ-5D was observed in patients who were on biologics + DMARDs/MTX at baseline. In addition, the increase in EQ-5D slope was larger in the MTX groups than in the PSL groups.

Distribution of the J-HAQ slope

The distribution of the J-HAQ slope was visualized using the probability plot method (Fig. 1). Each plot successfully shows the difference in the J-HAQ slope among groups.

Discussion

In this study, we developed the concept of DAS28 slope, J-HAQ slope, and EQ-5D slope to assess changes over a specified time period. In clinical studies, delta DAS28 and delta HAQ are often used to indicate changes between two time points, i.e., the baseline and endpoint. However, in our longitudinal observational study, DAS28, J-HAQ, and EQ-5D scores were recorded at multiple time points, and these values fluctuated over time; thus, we considered it more logical to evaluate the changes by analyzing linear regression using multiple values at multiple time points. Thus, the DAS28 slope, J-HAQ slope, and EQ-5D slope are

Table 2 DAS28 at baseline and DAS28 slopes

	N	DAS28 (95 % CI)	DAS28 slope (95 % CI)
All	5,038	3.29 (3.26 to 3.33)	−0.071 (−0.080 to −0.061)
Not on MTX	1,586	3.22 (3.16 to 3.28)	−0.041 (−0.058 to −0.025)
MTX 0–4 mg/week	488	3.30 (3.20 to 3.40)	−0.068 (−0.100 to −0.037)
MTX 4–6 mg/week	827	3.28 (3.20 to 3.36)	−0.069 (−0.091 to −0.047)
MTX 6–8 mg/week	966	3.34 (3.26 to 3.41)	−0.083 (−0.104 to −0.062)
MTX 8–10 mg/week	627	3.38 (3.30 to 3.47)	−0.093 (−0.118 to −0.068)
MTX >10 mg/week	521	3.35 (3.26 to 3.44)	−0.106 (−0.131 to −0.081)
Not on PSL	2,682	3.10 (3.06 to 3.15)	−0.056 (−0.068 to −0.044)
PSL 0–3 mg/day	996	3.36 (3.29 to 3.43)	−0.075 (−0.095 to −0.055)
PSL 3–5 mg/day	873	3.56 (3.49 to 3.63)	−0.087 (−0.110 to −0.064)
PSL >5 mg/day	487	3.73 (3.62 to 3.83)	−0.112 (−0.144 to −0.080)
DMARDs	4,587	3.29 (3.26 to 3.33)	−0.071 (−0.080 to −0.061)
MTX	3,429	3.33 (3.29 to 3.37)	−0.083 (−0.094 to −0.072)
Biologics	437	3.28 (3.17 to 3.39)	−0.104 (−0.135 to −0.073)
MTX monotherapy	1,944	3.28 (3.24 to 3.33)	−0.066 (−0.080 to −0.052)
Biologic monotherapy	74	3.28 (3.05 to 3.51)	−0.079 (−0.146 to −0.012)
Biologic with DMARD	363	3.28 (3.15 to 3.41)	−0.109 (−0.144 to −0.074)
Biologic with MTX	345	3.25 (3.12 to 3.38)	−0.107 (−0.143 to −0.071)

CI confidence interval

Table 3 J-HAQ at baseline and J-HAQ slopes

	N	J-HAQ (95 % CI)	J-HAQ slope (95 % CI)
All	5,038	0.715 (0.693 to 0.735)	−0.001 (−0.004 to 0.002)
Not on MTX	1,586	0.690 (0.651 to 0.729)	0.007 (0.000 to 0.013)
MTX 0–4 mg/week	488	0.772 (0.697 to 0.848)	0.001 (−0.010 to 0.011)
MTX 4–6 mg/week	827	0.727 (0.673 to 0.780)	−0.004 (−0.012 to 0.003)
MTX 6–8 mg/week	966	0.733 (0.686 to 0.780)	−0.003 (−0.010 to 0.003)
MTX 8–10 mg/week	627	0.680 (0.628 to 0.732)	−0.005 (−0.014 to 0.004)
MTX >10 mg/week	521	0.703 (0.646 to 0.759)	−0.013 (−0.021 to −0.004)
Not on PSL	2,682	0.542 (0.517 to 0.567)	−0.004 (−0.008 to 0.000)
PSL 0–3 mg/day	996	0.848 (0.797 to 0.897)	0.001 (−0.006 to 0.007)
PSL 3–5 mg/day	873	0.899 (0.847 to 0.952)	0.000 (−0.008 to 0.008)
PSL >5 mg/day	487	1.062 (0.987 to 1.138)	0.010 (−0.004 to 0.024)
DMARDs	4,587	0.705 (0.683 to 0.726)	−0.001 (−0.004 to 0.002)
MTX	3,429	0.723 (0.698 to 0.748)	−0.005 (−0.008 to −0.001)
Biologics	437	0.917 (0.843 to 0.990)	−0.016 (−0.026 to −0.006)
MTX monotherapy	1,944	0.694 (0.661 to 0.727)	−0.002 (−0.007 to 0.003)
Biologic monotherapy	74	1.193 (0.990 to 1.395)	−0.006 (−0.029 to 0.016)
Biologic with DMARD	363	0.861 (0.783 to 0.938)	−0.018 (−0.029 to −0.007)
Biologic with MTX	345	0.853 (0.773 to 0.934)	−0.022 (−0.033 to −0.010)

essentially analogous to delta DAS28, delta J-HAQ, and delta EQ-5D, respectively; however, we consider the former to be more logical indicators of changes over time in the IORRA observational cohort study.

The baseline characteristics of the treatment groups in this analysis differed, so it is not appropriate to compare the results between treatment groups. This is an inherent limitation of observational studies, in contrast to well-designed clinical trials [19]. It may be possible to compare outcomes by matching patients with comparable disease activity or disability, as done in propensity score matching [20], in order to determine which treatment is superior for

Table 4 EQ-5D at baseline and EQ-5D slopes

	N	EQ-5D (95 % CI)	EQ-5D slope (95 % CI)
All	5,038	0.76 (0.76 to 0.76)	0.0046 (0.0032 to 0.0059)
Not on MTX	1,586	0.77 (0.76 to 0.78)	−0.0008 (−0.0037 to 0.0022)
MTX 0–4 mg/week	488	0.76 (0.74 to 0.78)	0.0046 (0.0005 to 0.0086)
MTX 4–6 mg/week	827	0.76 (0.75 to 0.78)	0.0061 (0.0027 to 0.0095)
MTX 6–8 mg/week	966	0.75 (0.74 to 0.76)	0.0072 (0.0043 to 0.0100)
MTX 8–10 mg/week	627	0.76 (0.74 to 0.77)	0.0075 (0.0042 to 0.0108)
MTX >10 mg/week	521	0.75 (0.73 to 0.76)	0.0082 (0.0049 to 0.0115)
Not on PSL	2,682	0.80 (0.79 to 0.81)	0.0051 (0.0032 to 0.0069)
PSL 0–3 mg/day	996	0.74 (0.73 to 0.75)	0.0047 (0.0018 to 0.0076)
PSL 3–5 mg/day	873	0.72 (0.71 to 0.73)	0.0042 (0.0009 to 0.0074)
PSL >5 mg/day	487	0.67 (0.66 to 0.69)	0.0022 (−0.0034 to 0.0077)
DMARDs	4,587	0.76 (0.76 to 0.77)	0.0049 (0.0035 to 0.0063)
MTX	3,429	0.76 (0.75 to 0.76)	0.0068 (0.0053 to 0.0083)
Biologics	437	0.73 (0.71 to 0.74)	0.0120 (0.0074 to 0.0165)
MTX monotherapy	1,944	0.76 (0.75 to 0.77)	0.0053 (0.0033 to 0.0073)
Biologic monotherapy	74	0.69 (0.65 to 0.73)	0.0079 (−0.0045 to 0.0203)
Biologic with DMARD	363	0.73 (0.71 to 0.75)	0.0128 (0.0079 to 0.0177)
Biologic with MTX	345	0.73 (0.72 to 0.75)	0.0135 (0.0084 to 0.0186)

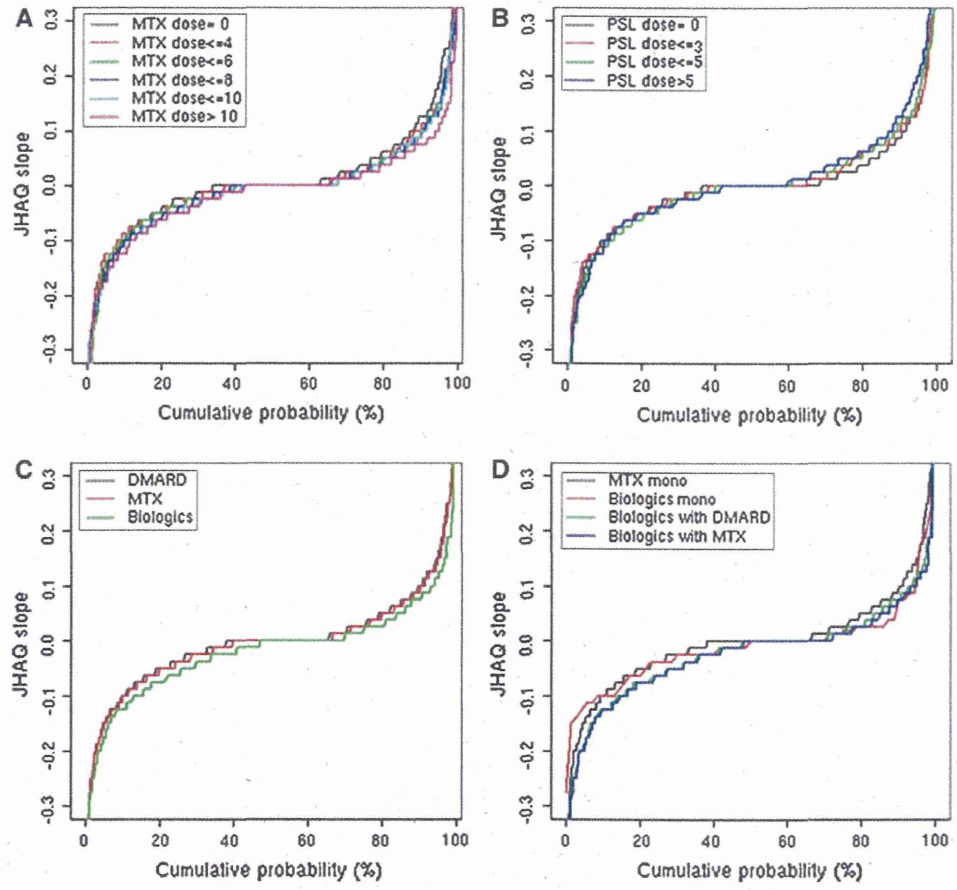

Fig. 1 Probability plots of J-HAQ slopes described for groups subclassified by **a** MTX dose, **b** PSL dose, **c** DMARD, MTX, or biologics users, and **d** monotherapy of MTX/ biologics and combination therapies

the prevention of disability. However, the goal of this study was to examine the differences between control of disease activity as estimated by DAS28 and progression of disability as estimated by J-HAQ among the different treatment groups.

As indicated by the DAS28 slope shown in Table 2, an improvement in DAS28 was observed in every treatment group during the two years from baseline, indicating that the treatment successfully improved the signs and symptoms of RA. Biologics strikingly decreased DAS28 with or without DMARDs, and PSL also decreased DAS28 in a dose-dependent manner. As indicated by the EQ-5D slope, patient QOL also improved during the observation period. However, the J-HAQ slopes differed markedly between treatment groups. Dramatic decreases in the J-HAQ slope were seen in patients on biologics, as well as in patients on MTX (in a dose-dependent manner), whereas increases were observed in patients on PSL dosed at >5 mg/day, indicating worsening functional disability.

These data were also visualized using probability plots. As this method has been frequently used to visualize the distribution of the progression of bone damage as assessed by X-ray scoring methods, we elected to utilize it to show progression of disability. Biologics, sufficiently dosed MTX, and low-dose PSL suppressed this ratio, indicating that patients in these groups are treated properly with respect to preventing the progression of disability. While similar results have been reported from clinical trials [21], the present data reflect patients seen in actual clinical practice.

As proposed in the T2T initiative, the primary target for treatment of RA should be clinical remission [1–4]. As mentioned above, we previously reported that patients treated with corticosteroids experience progression of disability even when they are in remission, and we suggested that there is a difference in the quality of remission between different agent classes [10, 11]. The present study supports this finding and suggests that there should be some discrepancy between suppression of disease activity and maintenance of physical function.

Another mechanism of joint damage prevention in well-controlled RA patients may be the consequence of residual disease activity [22, 23]. We have used DAS28 as a measure of disease activity; however, the progression of disability may be caused by the involvement of joints other than the 28 joints used in this assessment.

A major limitation of this study is the observational nature of the study design; thus, outcomes could not be accurately compared between treatment groups. Indeed, it is also true that the selection of the baseline treatment may be strongly associated with the baseline patients' comorbidities or previous drug histories, etc. Therefore, these background characteristics may influence the outcomes of groups categorized according to the type of agent selected. Our present data do not indicate that corticosteroid should never be given on any occasion in daily practice, or that corticosteroid itself worsens functional disability. In addition, treatment group assignment was based on the treatment at baseline, so the effects of changes in treatment during the observational period could not be assessed.

In conclusion, there is considerable disparity between control of disease activity and progression of disability in RA patients, and this disparity is correlated with the type and dosage of agent used. Remission is a realistic target under current management guidelines; however, differences in the quality of remission must also be considered.

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EXTENDED REPORT

Drug retention rates and relevant risk factors for drug discontinuation due to adverse events in rheumatoid arthritis patients receiving anticytokine therapy with different target molecules

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► Additional supplementary data are published online only. To view these files please visit the journal online (http://ard.bmj.com/content/early/recent)

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ABSTRACT

Objective To compare reasons for discontinuation and drug retention rates per reason among anticytokine therapies, infliximab, etanercept and tocilizumab, and the risk of discontinuation of biological agents due to adverse events (AE) in patients with rheumatoid arthritis (RA).

Method This prospective cohort study included Japanese RA patients who started infliximab (n=412, 636.0 patient-years (PY)), etanercept (n=442, 765.3 PY), or tocilizumab (n=168, 206.5 PY) as the first biological therapy after their enrolment in the Registry of Japanese Rheumatoid Arthritis Patients for Long-term Safety (REAL) database. Drug retention rates were calculated using the Kaplan–Meier method. To compare risks of drug discontinuation due to AE for patients treated with these biological agents, the Cox proportional hazard model was applied.

Results The authors found significant differences among the three therapeutic groups in demography, clinical status, comorbidities and usage of concomitant drugs. Development of AE was the most frequent reason for discontinuation of biological agents in the etanercept and tocilizumab groups, and the second most frequent reason in the infliximab group. Discontinuation due to good control was observed most frequently in the infliximab group. Compared with etanercept, the use of infliximab (HR 1.69; 95% CI 1.14 to 2.51) and tocilizumab (HR 1.98; 95% CI 1.04 to 3.76) was significantly associated with a higher risk of discontinuation of biological agents due to AE.

Conclusions Reasons for discontinuation are significantly different among biological agents. The use of infliximab and tocilizumab was significantly associated with treatment discontinuation due to AE compared with etanercept.

Biological disease-modifying antirheumatic drugs (biological agents) are a standard treatment for rheumatoid arthritis (RA).[1 2] A number of clinical trials have demonstrated that biological agents significantly improve signs and symptoms of RA patients with both early and established disease, and that remission of RA can be achieved with biological agents not only in early RA patients, but also in established RA patients who have shown inadequate responses to conventional non-biological disease-modifying antirheumatic drugs (DMARD).

In Japan, six biological agents have been approved for the treatment of RA, infliximab in 2002, etanercept in 2005, tocilizumab and adalimumab in 2008, abatacept in 2010 and golimumab in 2011. These drugs are widely used in clinical practice according to treatment guidelines for biological agents by the Japan College of Rheumatology[3 4] and Japanese drug package inserts. Postmarketing surveillance and some clinical studies have shown short-term effectiveness and safety of these biological agents for Japanese RA patients.[5–8] The European League Against Rheumatism recommendations for the management of RA state that a tumour necrosis factor (TNF) antagonist should be administered as the first biological DMARD for patients who fail to respond to non-biological DMARD, including methotrexate,[9] whereas Japanese guidelines do not clearly specify the precedence of biological agents.

Some RA patients treated with biological agents are compelled to stop the administration of these drugs because of lack of efficacy (LOE), adverse events (AE), or financial reasons. In addition, some RA patients discontinue biological agents in the hope of a biological-free remission or biological-free low disease activity status.[10–12] In general, drugs with high retention rates have a good balance between long-term effectiveness and tolerability, reflecting the satisfaction of patients and doctors with the treatment. Because treatment for RA continues for many years or is life-long in the majority of patients, the examination of long-term drug retention rates using a prospective cohort study is important for the evaluation of biological agents.

To establish better treatment strategies for RA, it is important to identify reasons and risk factors causing the discontinuation of a drug, especially for biological agents. Several studies have shown that

Table 1 Characteristics of RA patients treated with infliximab, etanercept or tocilizumab at the start of the observation period

	Infliximab group (n=412)	Etanercept group (n=442)	Tocilizumab group (n=168)	p Value
Age, years	53.6±13.5	58.5±13.0	59.8±13.4	<0.001
Female, %	85.9	78.1	80.4	0.011
Disease duration, years	7.9±7.8	10.3±8.9	10.3±9.6	<0.001
Steinbrocker's class (3 or 4), %	24.8	31.2	27.4	0.108
Steinbrocker's stage (III or IV), %	43.9	57.0	46.4	<0.001
DAS28 (3/CRP)	4.5±1.2 (n=411)	4.5±1.3 (n=440)	5.1±3.4 (n=167)	0.056
Use of ≥3 previous non-biological DMARD, %	41.0	54.5	31.5	<0.001
Biological—naive, %	96.4	83.9	46.4	<0.001
Methotrexate use, %	99.3	44.6	44.0	<0.001
Methotrexate dose, mg/week	8.0±2.1	7.0±2.0	8.2±2.9	<0.001
Use of immunosuppressive drugs, except for methotrexate, %	1.9	5.7	14.9	<0.001
Oral corticosteroid use, %	68.9	73.1	60.1	0.008
Prednisolone-equivalent dose of corticosteroids (mg/day)	5.4±2.6	6.1±3.3	4.9±2.2	<0.001
Chronic pulmonary disease, %	22.6	36.7	40.5	<0.001
Diabetes mellitus, %	8.5	14.9	12.5	0.015

CRP, C-reactive protein; DAS28, disease activity score including 28-joint count; DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis

a frequent reason for the discontinuation of biological agents is the development of AE.[5–7 13–16] Mid to long-term tolerability of TNF inhibitors[6 13 14 16–24] and tocilizumab[7 15 25] has been reported, and some studies have directly compared drug retention rates among TNF inhibitors or between TNF inhibitors and other biological agents.[14 16 17 25–27] To summarise, infliximab had the lowest overall retention rate among infliximab, etanercept and adalimumab[14 16 17] and among infliximab, etanercept and anakinra.[26] A recent report from the CORRONA registry demonstrated the highest retention rate of infliximab compared with etanercept and adalimumab.[27] However, drug retention rates have not been compared between TNF inhibitors and the interleukin-6 receptor inhibitor, tocilizumab, in the real world. In addition, the risk factors causing drug discontinuation due to AE for patients given these biological agents have not been thoroughly evaluated.

The purpose of this study was to compare drug retention rates and reasons for discontinuation of infliximab, etanercept and tocilizumab among Japanese RA patients, and to investigate the association of the use of these biological agents and other clinical characteristics with drug discontinuation due to AE.

PATIENTS AND METHODS

Database

The Registry of Japanese Rheumatoid Arthritis Patients for Long-term Safety (REAL) is an ongoing prospective cohort established to investigate the long-term safety of biological agents in RA patients. Twenty-seven institutions participate, including 16 university hospitals and 11 referring hospitals. Details of REAL have previously been described.[28 29] Briefly, the criteria for enrolment in REAL include patients meeting the 1987 American College of Rheumatology criteria for RA, written informed consent, and starting or switching treatment with biological agents or starting, adding or switching non-biological DMARD at the time of enrolment in the study. Enrolment in the REAL database was started in June 2005 and closed in January 2012. To facilitate enrolment to the REAL registry, participating physicians were asked to enrol their patients already registered in postmarketing surveillance programmes previously implemented by pharmaceutical companies for biological agents.[5 8] In addition, our investigators were also encouraged to enrol as many patients as possible who fulfilled the inclusion criteria.[29]

Data were retrieved from the REAL database on 4 April 2011 for this study. The REAL study was approved by the ethics committees of the Tokyo Medical and Dental University Hospital and other participating institutions.

Data collection

Each patient's recorded baseline data included demography, disease activity, physical disability, comorbidities, treatments and laboratory data at the beginning of the observation period. A follow-up form was submitted by the site investigators every 6 months to the REAL data centre at the Department of Pharmacovigilance of Tokyo Medical and Dental University to report the occurrence of serious AE, current RA disease activity, treatments and clinical laboratory data.[28 29] We collected the Steinbrocker class[30] as the baseline measurement for each patient's physical disability, instead of the health assessment questionnaire disability index.[31] The investigators in each hospital confirmed the accuracy of their data submitted to the REAL data centre. The centre examined all the data sent by site investigators and sent queries if necessary to verify the accuracy of the data.

Patients

By April 2011, 2067 RA patients were registered in REAL, of these 1044 patients started treatment with infliximab, etanercept or tocilizumab at the time of enrolment or after enrolment in REAL. Four patients were excluded from this study because the reason for discontinuation of the initial biological agents was not identified. Eighteen patients who were enrolled in another clinical study requiring the discontinuation of infliximab were also excluded. We did not include patients who used adalimumab, abatacept or golimumab as the first biological agent in REAL because we did not have sufficient numbers of patients on adalimumab in the database (n=98) compared with infliximab and etanercept and had no patients given abatacept or golimumab in the database at the time our data were compiled. Our analysis included 412 patients who started infliximab, 442 patients who started etanercept and 168 patients who started tocilizumab.

Follow-up

For patients who initiated biological agents (infliximab, etanercept, or tocilizumab) at enrolment in REAL, the start date

Table 2 Reasons for drug discontinuation in RA patients treated with infliximab, etanercept or tocilizumab*

Reason for discontinuation	Infliximab (n=157)†	Etanercept (n=130)†	Tocilizumab (n=51)†
Adverse events	57 Cases (36.3%)	57 Cases (43.8%)	23 Cases (45.1%)
Infection	20 Cases (12.7%)	22 Cases (16.9%)	8 Cases (15.7%)
Pulmonary diseases except infection‡	7 Cases (4.5%)	7 Cases (4%)	3 Cases (5.9%)
Infusion reaction	6 Cases (3.8%)	NA	0 Case (0%)
Allergy except infusion reaction	7 Cases (4.5%)	12 Cases (9.2%)	6 Cases (11.8%)
Malignancy	6 Cases (3.8%)	3 Cases (2.3%)	1 Case (2%)
Cardiovascular system disease	2 Cases (1.3%)	2 Cases (1.5%)	2 Cases (3.9%)
Others	9 Cases (5.7%)	11 Cases (8.5%)	3 Cases (5.9%)
Lack of efficacy	68 Cases (43.3%)	47 Cases (36.2%)	23 Cases (45.1%)
Good control	21 Cases (13.4%)	7 Cases (5.4%)	2 Cases (3.9%)
Miscellaneous§	11 Cases (7.0%)	19 Cases (14.6%) §	3 Cases (5.9%)

The χ^2 test was applied to assess differences in the proportion of causes for discontinuation (ie, adverse event, lack of efficacy, good control and miscellaneous), and the adjusted residuals were calculated. A significant difference among the three groups (p=0.026) was observed. The adjusted residuals indicated that significantly higher percentages of patients in the infliximab group stopped the treatment due to good disease control compared with the other two groups (p<0.05).
*Values are the number (percentage) of patients who discontinued use because of each reason.
†Number of patients who discontinued their first biological DMARD for any reason.
‡Pulmonary diseases except for infection included interstitial pneumonia (three cases for infliximab, five for etanercept, two for tocilizumab) and other pulmonary diseases (four for infliximab, two for etanercept, one for tocilizumab).
§Miscellaneous reasons for drug discontinuation include patients' preference, financial reasons, and pregnancy.
DMARD, disease-modifying antirheumatic drugs; RA, rheumatoid arthritis.
NA, not applicable

of the observation period was the date these agents were first administered. For patients who started non-biological DMARD at the time of entry in REAL and who later started treatment with biological agents, the start of the observation period was the date of the first administration of biological agents in REAL. Observation was stopped either at 2.5 years after the start of the observation period, on the date of death of a patient, loss to follow up, enrolment in clinical trials, or when therapy was stopped with the first biological agent in REAL for more than 90 days, or on 4 April 2011, whichever came first. The period following switching to a second biological agent was excluded from this study. We defined termination of treatment with biological agents as stopping treatment with the agent for more than 90 days. The date of the last administration of each biological DMARD was retrieved from medical records and reported by the site investigators. Reasons for drug discontinuation were obtained from case report forms of REAL supplemented by medical records, if necessary, and classified into AE, good control, LOE or miscellaneous. We did not discriminate between a primary and secondary LOE. Note that we collected only serious AE in REAL, but also collected AE in this study if it was the main reason for the discontinuation of a biological agent. When a patient had two or more reasons for drug discontinuation, site investigators assigned precedence and we used the primary reason contributing to drug discontinuation for that patient.

Statistical analysis

The primary outcome of this study was the investigation of the association of the use of infliximab, etanercept and tocilizumab with drug discontinuation due to AE. We also sought to identify other risk factors for drug discontinuation due to AE. Drug retention rates were calculated by the Kaplan–Meier method and compared using the log-rank test among groups. For univariate analysis, the χ^2 test was used for comparison of categorical variables and the Kruskal–Wallis test was used for continuous variables among the three agents. For multivariate analysis, the Cox regression hazard model with the forced entry method was employed to compare risks for drug discontinuation due to AE. The validity of the proportional hazards assumption was confirmed by the log-minus-log survival function. We followed the STROBE statement[32] for clear reporting except for 'the number and reasons for non-participation' in this study.

These statistical analyses were conducted using SPSS (version 16.0Illinois,). All p values were two-tailed and p<0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the patients

This analysis included 412 patients in the infliximab group (636.0 patient-years (PY)), 442 in the etanercept group (765.3 PY) and 168 in the tocilizumab group (206.5 PY). Table 1 shows the baseline characteristics of the groups. There were significant differences in age, gender, disease duration and clinical status of the patients. The etanercept and tocilizumab groups had longer disease duration (p<0.001) and higher percentages of comorbidities than the infliximab group (p<0.001 for chronic pulmonary disease, p=0.011 for diabetes mellitus). The rates of biological-naive patients (96.4% for the infliximab group, 83.9% for the etanercept group and 46.4% for the tocilizumab group) (p<0.001) and of the use of three or more non-biological DMARD (p<0.001) in the tocilizumab group were the lowest among the three groups. The rate of the use (p=0.007) and dose (p<0.001) of oral corticosteroids of the etanercept group were higher than those for the other two groups. Disease activity did not differ significantly among the groups.

Occurrence of treatment termination

The median IQR of the observation period for each group was 1.50 (0.74–2.50) years for the infliximab group, 2.1 (0.98–2.50) years for the etanercept group and 1.0 (0.5–2.0) years for the tocilizumab group. The number of patients who discontinued biological agents for any reason during the observation period was 157 (38.1%) for the infliximab group, 130 (29.4%) for the etanercept group and 51 (30.4%) for the tocilizumab group (p=0.019 by χ^2). Table 2 shows the reasons for drug discontinuation for each group. A significant difference among the three groups (p=0.026 by χ^2) was seen in the proportions of reasons for discontinuation, and the adjusted residuals indicated that significantly higher percentages of patients in the infliximab group stopped treatment due to good disease control compared with the other two groups (p<0.05). The most frequently reported

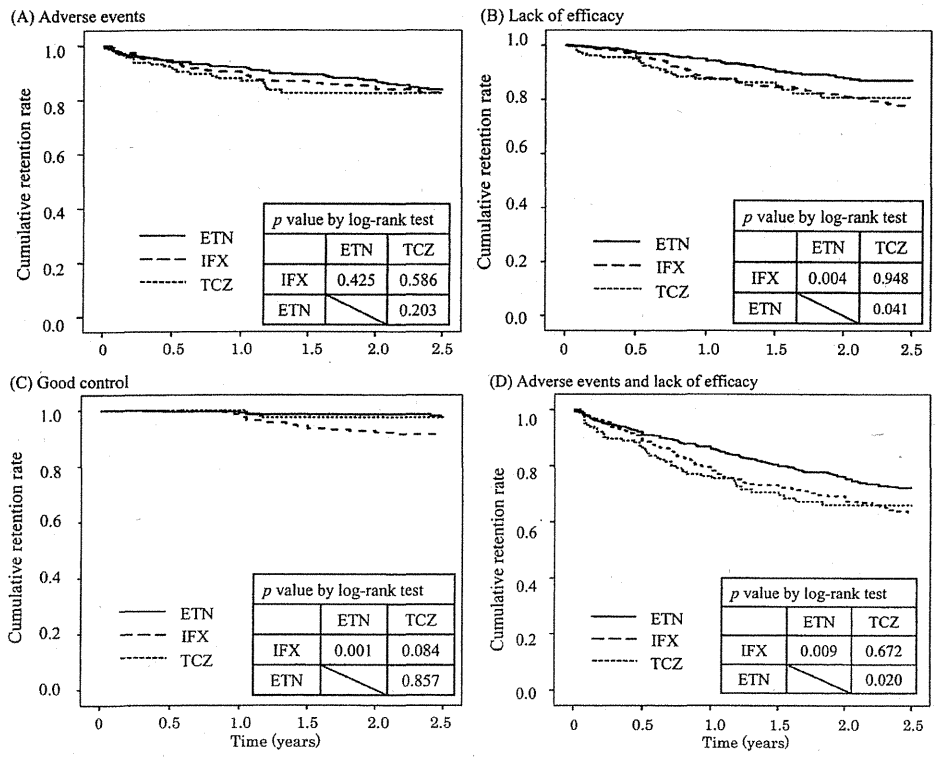

Figure 1 Kaplan-Meier curves for time to discontinuation for each biological agent (etanercept (ETN); infliximab (IFX); tocilizumab (TCZ)). Withdrawal for adverse events (A), lack of efficacy (B), good control (C), and adverse events and lack of efficacy (D) are presented separately. Drug retention rates are compared using the long-rank test among groups. The y axis shows the cumulative retention rates.

reason for discontinuation was LOE in the infliximab group, development of AE in the etanercept group and both in the tocilizumab group (table 2).

The retention rates of biological agents

Because the distribution of reasons for drug discontinuation was significantly different among these biological agents (table 2), we investigated drug retention rates per reason for discontinuation. Kaplan–Meier curves for time to discontinuation for each agent due to AE and LOE are shown in figure 1A,B, respectively. No significant differences existed among the three drugs for treatment discontinuation due to AE. The discontinuation rate due to LOE was significantly lower for etanercept compared with that of infliximab (p=0.004, log-rank test) and tocilizumab (p=0.041) (figure 1B), and the discontinuation rate for infliximab due to good control was significantly higher than that for etanercept (p=0.001, log-rank test) (figure 1C). We combined withdrawals due to AE and LOE to assess treatment failure; etanercept had a significantly lower discontinuation rate due to treatment failure compared with the other two agents (p=0.009 vs infliximab, p=0.020 vs tocilizumab, log-rank test) (figure 1D). To evaluate the possible effects of previous treatment with biological agents on drug discontinuation due to AE and LOE, we compared the retention rates per reason except for good control in the etanercept and tocilizumab groups between biological-naive and non-naive patients (see supplementary figures, available online only). In both groups, there was no significant difference in drug retention rates between biological-naive and non-naive patients. However, we found a numerically higher discontinuation rate of biological agent non-naive patients due to LOE in the tocilizumab group (see supplementary figure S3, available online only).

Multivariate analysis of the risk for discontinuation of biological agents due to AE

We compared patients who discontinued treatment with biological agents due to AE and remaining patients using a univariate analysis (see supplementary table S1, available online only) and used the same variables for the multivariate analysis of table 3. Although we found no significant difference in the use of infliximab and tocilizumab in the univariate analysis (table S1, available online only), the Cox regression hazard model revealed that the adjusted risk for discontinuation due to AE was significantly higher in patients using infliximab (HR 1.69; 95% CI 1.14 to 2.51) and tocilizumab (HR 1.98; 95% CI 1.04 to 3.76) compared with etanercept (table 3). Among the other variables, the risk of discontinuation due to AE was also significantly higher in patients with increasing age by decade (HR 1.64; 95% CI 1.38 to 1.97) and with the previous use of three or more non-biological DMARD (HR 1.86; 95% CI 1.30 to 2.67).

DISCUSSION

To our knowledge, this is the first report comparing drug retention rates among TNF inhibitors and tocilizumab and identifying risk factors causing drug discontinuation due to AE. The major findings of this study are: (1) the reasons for discontinuation were significantly different among the three biological agents studied; (2) the risk of discontinuation due to AE was significantly higher in patients using infliximab and tocilizumab compared with etanercept; and (3) other significant risk factors for the discontinuation due to AE were increasing age and the previous use of three or more non-biological DMARD.

There are some reports describing drug retention rates and reasons for drug discontinuations in patients treated with TNF

Table 3 Multivariate analysis for drug discontinuation due to adverse events in RA patients treated with infliximab, etanercept or tocilizumab*

	HR (95% CI)	p Value
Infliximab (vs etanercept)	1.69 (1.14 to 2.51)	0.009
Tocilizumab (vs etanercept)	1.98 (1.04 to 3.76)	0.037
Age by decade	1.64 (1.38 to 1.97)	<0.001
Class 3 or 4 (vs class 1 or 2)	1.07 (0.74 to 1.54)	0.727
DAS28 (3/CRP) at baseline (per 1.0 increment)	1.03 (0.92 to 1.17)	0.585
Chronic pulmonary disease	1.19 (0.83 to 1.70)	0.336
Diabetes mellitus	0.95 (0.58 to 1.56)	0.841
Concomitant use of oral corticosteroids at baseline	1.15 (0.78 to 1.70)	0.489
Concomitant use of immunosuppressive drugs except for methotrexate at baseline	0.56 (0.20 to 1.55)	0.262
Previous use of three or more non-biological DMARD	1.86 (1.30 to 2.67)	0.001
Previous use of biological agents	1.05 (0.64 to 1.72)	0.842

*Cox regression hazard model analysis, adjusted for the variables included in the table, gender and calendar year.
Class, Steinbrocker's class; CRP, C-reactive protein;
DAS28, disease activity score including 28-joint count; DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis.

inhibitors.[14 16–18 20 22 24 26 27 33–35] Among patients stopping treatment with TNF inhibitors due to any reason, approximately half of those discontinued due to AE, and the proportions of patients who discontinued the agents due to AE or LOE were similar in each group in the Swiss[14] and the French[16] registries. In this study, AE and LOE were the two major reported reasons for discontinuation, with similar percentages also for all three groups, but the discontinuation rate due to good control in the infliximab group was significantly higher than those in the other two groups. Several studies have shown successful discontinuation of treatment with infliximab[10 36–40] and tocilizumab[41] without flare of RA, but the reported percentage of patients who could discontinue infliximab was higher compared with tocilizumab. In contrast, there is no evidence of the successful discontinuation of treatment for etanercept to date. Therefore, our results might be influenced by physicians' expectations for successful discontinuation of biological agents based on previous reports.

We observed a significantly lower discontinuation rate due to LOE in the etanercept group compared with infliximab and tocilizumab (figure.1B), which can be explained by the following reasons. First, treatment with infliximab induces the formation of human antichimeric antibody in some patients, which may lead to LOE or adverse drug reactions.[42 43] The prevalence of antidrug antibodies in RA patients who were treated with infliximab is much higher compared with etanercept[44 45] and tocilizumab.[15 46] Second, the tocilizumab group had a significantly lower percentage of biological-naive patients, which may be associated with a less favourable response to treatment.[47 48] In the tocilizumab group, we confirmed that the discontinuation rate due to LOE was numerically lower in the biological-naive patients compared with biological agent non-naive patients (see supplementary figure S3, available online only).

In this study, we limited our multivariate analyses to the risk factors associated with discontinuation due to AE. Some previous studies identified risk factors for overall discontinuation in patients treated with TNF inhibitors.[6 17 26] Because treatments with biological agents are discontinued for various reasons, as shown in table 1, we postulated that it would not be appropriate to build a multivariate model for overall discontinuation from a medical point of view. In REAL, we did not collect measures of patients' disease activity, such as the disease activity score in 28 joints (DAS28), when patients stopped treatment with biological agents, and we could not define discontinuation due to LOE by using objective criteria. Therefore, we opted not to analyse risk factors for discontinuation due to LOE. The number of patients who discontinued the agents due to good control was too small to analyse associated factors using multivariate analysis.

Increasing age was also identified as a risk factor associated with the discontinuation of biological agents due to AE, data supported by a previous report.[16] In all three groups, infections were most frequent among AE leading to drug discontinuation (table 2). It is plausible that increasing age contributes to discontinuation because of an increasing risk of RA patients for infection[29 49] with age. Higher numbers of previous non-biological DMARD use suggests cases difficult to treat, with high disease activity or long-standing disease. Compatible with this possibility, patients who had been treated with three or more non-biological DMARD before enrolment in REAL had a significantly longer disease duration with more advanced disease stages and classes than those receiving less than three non-biological DMARD (data not shown). It has been reported that advanced stage or higher disease activity was reported as a risk for infections.[8 29 50]

Our study has limitations. First, we have to mention the possibility of selection bias in this study. However, because almost all patients who were registered from the participating hospitals of our study to the all-cases postmarketing surveillance programmes for each biological DMARD were enrolled in REAL, selection bias was substantially decreased. Second, we analysed the first biological agent administered to each patient at or after enrolment in REAL. However, these biological agents were not necessarily truly the first one used for each patient; rates of biological-naive patients were significantly different among the three groups (table 1), indicating the presence of channelling bias. Therefore, we adjusted for the previous use of biological agents in the multivariate analysis.

In conclusion, we have presented the first epidemiological data that directly compare TNF inhibitors and tocilizumab in a single cohort. We demonstrated that reasons for discontinuation were significantly different among the biological agents and that the use of infliximab and tocilizumab had a significantly higher risk of treatment discontinuation due to AE compared with etanercept after adjusting for various confounding factors.

Values are the mean±SD, unless otherwise stated. For univariate analysis, the χ^2 test for categorical variables and the Student's t test or Mann–Whitney test were used to compare continuous variables among groups.

Steinbrocker's classification[30] was used to definite RA disease stages and classes.

The immunosuppressive drugs used were tacrolimus, leflunomide, mizoribine and ciclosporin.

The oral corticosteroid dose was converted to the equivalent prednisolone dosage. Methotrexate and corticosteroid doses are shown as the mean±SD among users of these drugs.

Chronic pulmonary diseases include interstitial pneumonia, chronic obstructive pulmonary disease, bronchial asthma, previous pulmonary tuberculosis and bronchiectasis.

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Drug retention rates and relevant risk factors for drug discontinuation due to adverse events in rheumatoid arthritis patients receiving anticytokine therapy with different target molecules

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