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

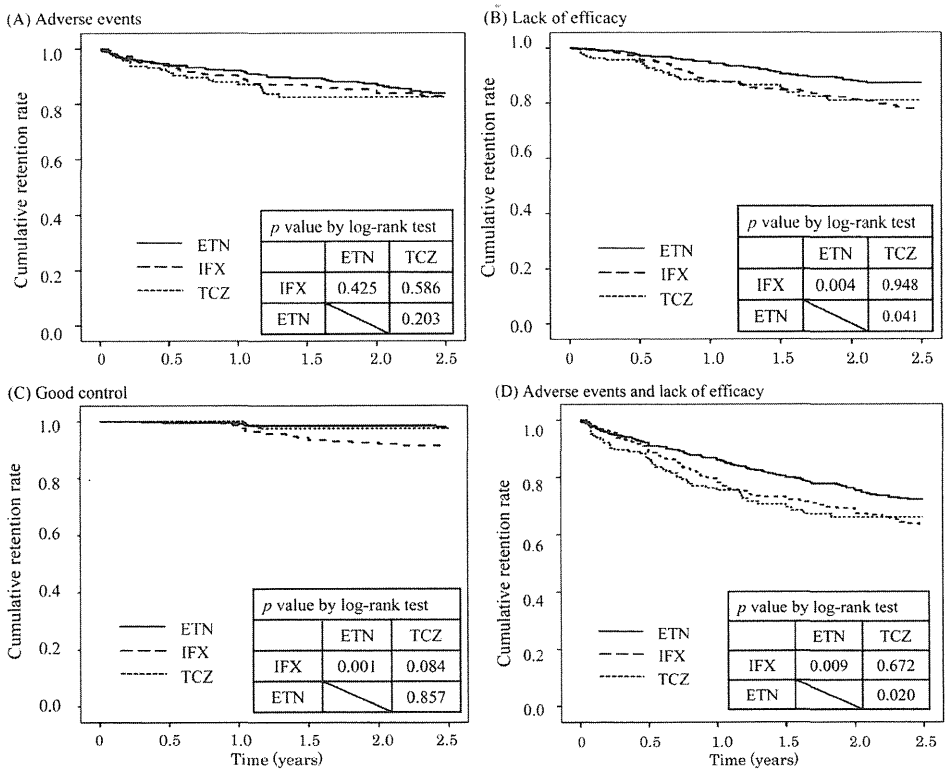

Figure 1 Kaplan-Meier curves for time to discontinuation for each biological agent (etanercept (ETN); infliximab (IFX); tocilizumab (TCZ)). Withdrawal for adverse events (A), lack of efficacy (B), good control (C), and adverse events and lack of efficacy (D) are presented separately. Drug retention rates 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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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)

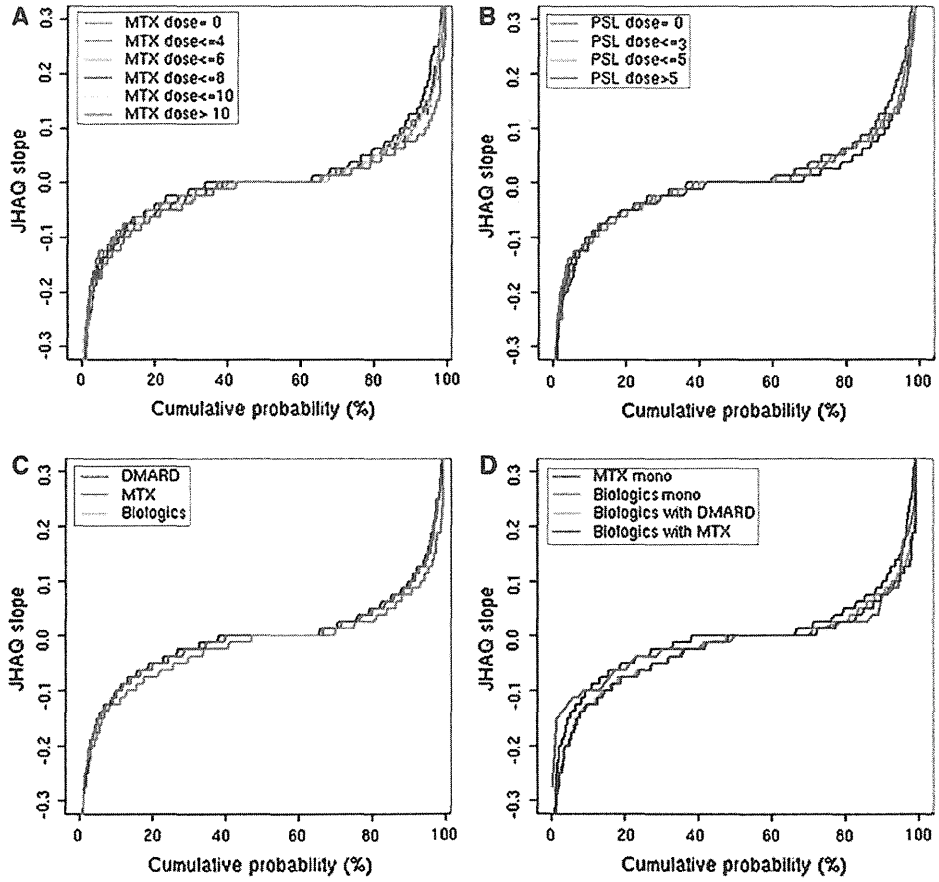

Fig. 1 Probability plots of J-HAQ slopes described for groups subclassified by **a** MTX dose, **b** PSL dose, **c** DMARD, MTX, or biologics users, and **d** monotherapy of MTX/ biologics and combination therapies

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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REVIEW ARTICLE

Management of rheumatoid arthritis: the 2012 perspective

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Abstract Management of rheumatoid arthritis (RA) has improved over the last 10 years. These changes have been monitored in the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) observational cohort, and clinical remission has become a realistic goal. However, we should recognize that the ultimate goal of treatment is to improve long-term outcomes. These improvements have been achieved not only by new drugs, but also by the overall approach toward treating patients. Biologics in RA have been successful; however, safety concerns and pharmacoeconomical issues are still debated. Protein kinase inhibitors have been developed, and can be called "molecular-targeting antirheumatic drugs" (MTARDs), as opposed to "disease-modifying antirheumatic drugs." In comparison with biologics, oral MTARDs should be less expensive; however, their safety profile should be confirmed. Considering the limitations of randomized trials, it is encouraged to conduct studies based on daily practice. It is time to consider the application of the evidence generated from "our" patients to patients in daily practice, namely institute-based medicine as opposed to evidence-based medicine, of which "IORRA-based medicine" would be representative. Finally, there remains much for us rheumatologists to do for our patients, including patient-perspective approaches.

Keywords Outcome · Observational cohort · Biologics · MTARDs · Patient perspective

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What have we achieved since 2000?

The readers of *Modern Rheumatology* know that, over the last 10 years, care of patients with rheumatoid arthritis (RA) has seen impressive improvements. New drugs with novel modes of action have led to improvements not only in signs and symptoms, but also in long-term outcomes, including joint destruction and disability. Therefore, the goal of RA treatment has changed from improving outcomes over the short term to outcomes over the long term. The proposal that there should be a paradigm shift from "care to cure" has become realistic.

The changes generated in the last 10 years have been carefully monitored since 2000 in the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) observational cohort [1, 2]. We previously reported that disease activity in the IORRA cohort improved significantly from 2000 to 2007 [3]; subsequently, there has been constant improvement along with the changes in the drugs employed for therapy (Fig. 1). Clinical remission has become a realistic goal. By any of the 2010 criteria for remission proposed by the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR), the number of patients in remission has increased [4, 5] (Fig. 2). This progress has been the result of the increased use of methotrexate and biologics. Based on data mainly from IORRA, the maximum dose of methotrexate has been raised [6, 7], and this will lead to better patient outcomes over the next decade. It is amazing that changes in disease control have resulted from the use of nonsteroidal anti-inflammatory drugs as well as gastrointestinal medications (Fig. 3).

An IORRA study conducted in the prebiologic era found a standardized mortality ratio (SMR) of 1.46-1.90, which was consistent with findings from Western countries [8]. Advances in drug therapy may improve the survival of RA

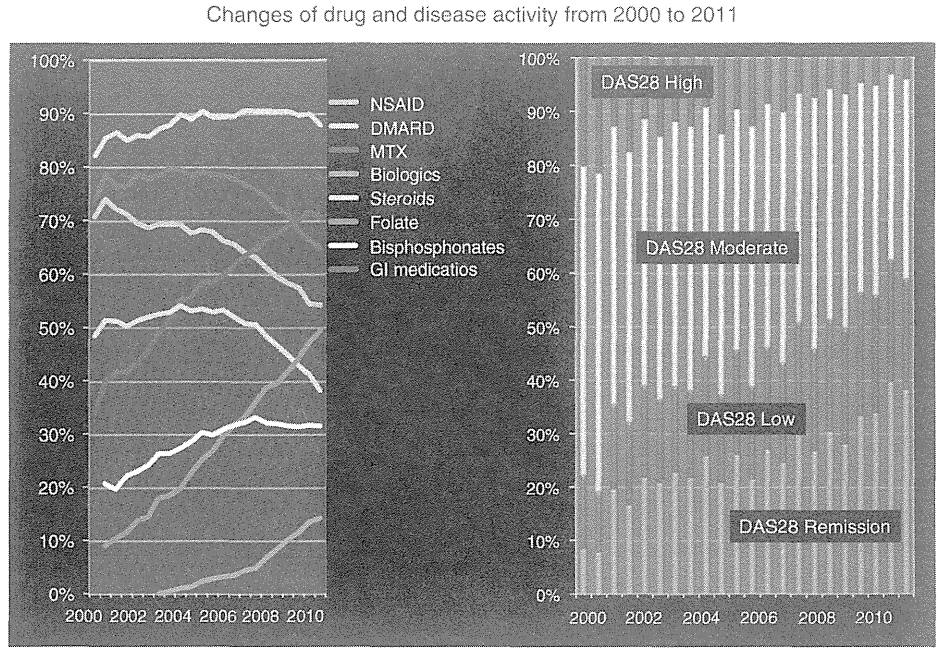

Fig. 1 Changes of drug and disease activity from 2000 to 2011. Changes of drug use and disease activity of RA patients in the IORRA cohort from 2000 to 2011 are shown. Disease activity was categorized by DAS28 according to the standard method

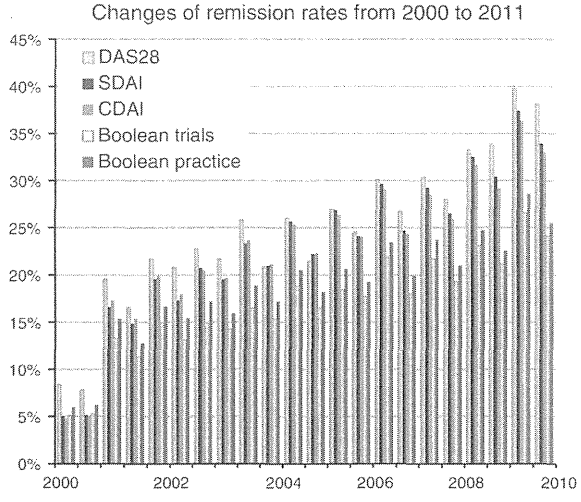

Fig. 2 Changes of remission rates from 2000 to 2011, defined by 5 methods including DAS28, simplified disease activity index (SDAI), clinical disease activity index (CDAI), Boolean trials, and Boolean practice. Definition of remission is based on each criterion

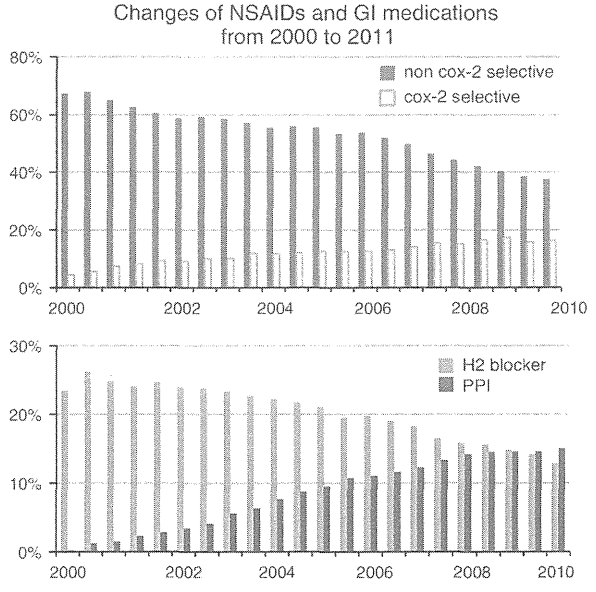

Fig. 3 Changes of use of NSAIDs (*upper column*) and gastrointestinal (GI) medications (*lower column*) from 2000 to 2011. NSAIDs were categorized by cyclooxygenase-2 (COX-2) selectivity as COX-2 selective (celecoxib, meloxicam, and etodolac) or non-COX-2 selective (others). Categorizations of proton pomp inhibitor (PPI) and H2 blocker are based on label information

patients [9]. We recently undertook a nationwide study to estimate the mortality rate of RA patients treated using biologics (Nakajima A, et al. submitted); our findings need confirmation by a more precise study. It is extremely important to recognize that the ultimate goal of the treatment of patients with RA is to improve long-term outcomes, including mortality and quality-adjusted life years (QALYs) [10].

We would like to emphasize that improvements in patient management have been achieved not only by new drugs. It is apparent that new drugs initiated these changes, but in addition, major improvements have been achieved in the overall approach toward treating patients with RA. The establishment of treatment recommendations [11, 12] for management of RA, and the introduction of new criteria for classification [13] and remission [4, 5], are important

platforms for introducing novel treatments into daily practice.

We previously reported several findings that support the concept that strict control of disease activity by maintaining the disease activity score using 28 joint count (DAS28) at a low value can inhibit the progression of disability in patients with RA [3, 14]. This target-driven therapeutic strategy ("treat to target") has become familiar as the T2T movement since recommendations for achieving optimal outcomes were published in 2010 [15]; we first reported on use of "treat to target" in 2007 [3].

Progress in the technology of imaging modalities, including ultrasound and magnetic resonance imaging (MRI), has led to increased accuracy of diagnosis. As suggested by the new classification criteria for polymyalgia rheumatica [16], the addition of ultrasound information will increase the sensitivity and specificity of the diagnosis of early rheumatoid arthritis. Although there remains the problem of feasibility, ultrasound should be widely implemented for routine care of RA patients [17]. These diagnostic strategies were established based on the results of several clinical studies, predominantly randomized controlled trials (RCTs) [18]. Comparing the study patients in RCTs with patients in daily practice is debatable, which we return to later in this review.

When we consider the changes that have occurred over the last 10 years, we can see that the strategies of RA treatment have changed dramatically as a result of the productive collaboration of academic expertise and innovative companies.

The future of the biologic era

Everyone can agree that molecular targeting is one of the best ways to control disease activity for a disease in which the target molecule has been identified. RA is phenotypically a quite heterogeneous disease, but the pathophysiology is quite uniform. Although many molecules are involved in the pathogenesis of RA, there are only a few key molecules that can be targeted for treatment. Tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) have been most successfully targeted, and the introduction of monoclonal antibodies and receptor-fusion proteins has successfully led to suppression of RA disease activity [19, 20].

There are several other candidate molecules that may be targeted for RA treatment, including CD86, CD20, CD22, and B cell activating factor (BAFF), which are functional surface molecules of T cells or B cells; and IL-17 and IL-12/23, which are proinflammatory cytokines [21, 22]. Antibodies and/or fusion proteins with activity against those molecules have been developed and are in clinical trials. In the near future, we may have more than 10 effective drugs for treatment of RA. The efficacy and safety profiles of these biologics may differ according to their target molecules, but an essential characteristic of these drugs is their ability to suppress joint destruction and improve long-term outcomes. Improvement in the signs and symptoms of each RA patient is a minimum requirement, but will not be sufficient for a candidate drug to become a useful therapeutic option.

It should be recognized that these macromolecular drugs cannot cross cell membranes, and are active extracellularly. Therefore, these biologics are quite safe with regard to hepatotoxicity, nephrotoxicity, and hematotoxicity. Concerns regarding the safety of biologics focus on the immunogenic reactions against exogenous proteins and the results of the suppression of target molecules. Preclinical and clinical data accumulated over the last 10 years have demonstrated that hypersensitivity to these macromolecules occurs at a tolerable level, and is manageable in daily practice. However, suppression of target molecules is a major problem affecting the safety profiles of these biologics; For example, TNF-α is part of the endogenous line of defense against tuberculosis infection, and suppression of TNF-α has resulted in increases in reactivation of occult tuberculosis infection [23]. Thus, it very important to predict the possible side-effects of any biologic by considering the role of its target molecule. However, all of the target molecules of the biologics used to treat RA are associated with the immune system of the host, and therefore susceptibility to infection is an unavoidable issue. Efforts have been made to identify patients highly susceptible to infection, so that an effective prophylactic regimen can be instituted; however, prevention of opportunistic infections, including pneumocystis pneumonia, remains an important concern [24].

Use of biologics to treat RA is a pharmacoeconomical issue. These macromolecules are quite expensive compared with other drug classes, because they are produced using advanced technology. The outpatient costs incurred from 2000 to 2007 for 8,982 RA patients (34,839 patient-years) enrolled in the IORRA study were evaluated. The mean annual outpatient cost increased from 287,626 JPY in 2000 to 366,964 JPY in 2007 (+27.6 %). The cost of medications and injections over those 7.5 years increased 39.0 and 1215 %, respectively. Costs increased in association with aging, increased DAS28 values, and increased Japanese Health Assessment Questionnaire (J-HAQ) scores. Levels of disability and use of biologics were the most significant factors associated with cost increases. Outpatient care costs for patients with RA also increased over the last 7.5-year period, especially after the introduction of biologics [25].

Extensive pharmacoeconomical analysis has demonstrated that biologics are cost-effective when work

productivity is taken into consideration, but cost is an obvious barrier to RA patients who have lost their job because of their disease. Our recent data have shown that biologics are most cost-effective when used in patients with early RA and with moderate disability (J-HAQ = 1.0–1.5) (Tanaka E, et al. submitted). In the effort to improve patient quality of life (QOL), this use of biologics for earlier disease is needed for effective utilization of limited medical resources.

Another promising approach for improving the cost benefits of biologics is the development of generic biologics, also known as biosimilar products [26]. Clinical studies of these biosimilar products are now being conducted in many countries, including Japan.

Antirheumatic drugs: DMARD to MTARD

Control of disease activity in RA had its origins in the empirical use of gold compounds in clinical practice, and was not the result of scientific evaluations. Gold compounds belong to the class of drugs called disease-modifying antirheumatic drugs (DMARDs). The target molecules of DMARDs, including gold compounds, D-penicillamine, sulfasalazine, bucillamine, and actarit, have not been clearly identified, but the targets of methotrexate, leflunomide, mizoribine, and tacrolimus have been well defined. Now there is a new class of drugs, including protein kinase inhibitors, which target unique molecules that regulate cell functions. Many of these drugs have been classified as immunosuppressive drugs. We propose a tentative generation-based classification of these immunosuppressive drugs according to when they were discovered (Table 1).

The molecular targets of the drugs in the 1st to 3rd generations were identified after discovery of the drug; however, the 4th generation of immunosuppressive drugs is a novel class of antirheumatic drugs that have been developed based on molecular targets. Thus, we would like to propose the designation "molecular-targeting antirheumatic drugs" (MTARDs), as opposed to "disease-modifying antirheumatic drugs" (DMARDs).

Thus far, five oral compounds including kinase inhibitors (tofacitinib, fostamatinib, VX-509), an S1P lyase inhibitor (LX 3305), and a chemokine receptor-1 antagonist (CCX354-C) have been developed [27, 28]. Because there are many target molecules involved in regulating cell function in the immune system, many novel drugs classified as MTARDs should be discovered (Table 2).

MTARDs are small-molecule compounds with high specificity for the target molecule. In comparison with biologics, MTARDs are administered orally, and their production should be less expensive. Therefore, if they are noninferior to DMARDs, MTARDs would provide advantages over biologics, since biologics are not administered orally and are expensive.

Table 1 Immunosuppressants

Generation	Mode of action	Drugs
1st	DNA damaging agents	Cyclophosphamide, alkylating agents
2nd	Purine/pyrimidine antimetabolites	Methotrexate, leflunomide, mizoribine, azathioprine
3rd	Calcineurin inhibitors	Cyclosporine, tacrolimus
4th	Protein kinase inhibitors	Tofacitinib, fostamatinib

Table 2 Comparison of DMARDs and MTARDs

Class		Definition	Drugs
DMARDs	Disease-modifying antirheumatic drugs	Target molecule is unknown, or was identified after drug development	Gold, D-penicillamine, sulfasalazine, bucillamine, methotrexate, leflunomide, tacrolimus, etc.
MTARDs	Molecular-targeting antirheumatic drugs	Drug was developed directly to target the molecule	Tofacitinib, fostamatinib, etc.

The safety profile of MTARDs is a concern. MTARD actions occur intracellularly, and MTARDs must cross the cell membrane. Thus, cytotoxicity may be inevitable if MTARDs must be administered in high concentrations. In addition, regulation of intracellular protein kinases, the target molecules, is thought to be sensitive to concentration; therefore, changes in levels of protein kinases may lead to side-effects [29]. Since kinases are phosphotransferases, these kinase-inhibiting drugs will inhibit adenosine triphosphate (ATP) binding at the catalytic sites of kinases [30], and may nonspecifically inhibit ATP binding. In vivo and in vitro experiments should be performed for clarification. The results of phase 1–3 clinical trials of the first MTARD, tofacitinib, indicate that it was relatively well tolerated, and it has been submitted for approval in the USA, European Union, and Japan [31].

Importance of practice-based clinical studies

As mentioned earlier in this review, there are many guidelines and recommendations regarding therapeutic strategies for daily practice that have been established, including the most recent ACR recommendation [12]; however, it is important that these have been established based on the results of many clinical studies, including

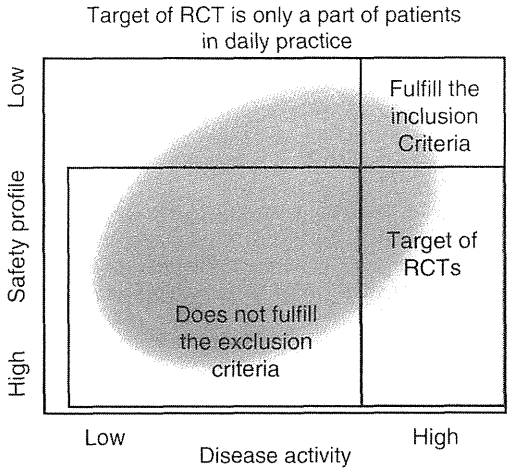

Fig. 4 The target of a RCT is only a part of the patients in daily practice. The target population of most randomized controlled trials (RCTs) is limited by the inclusion and exclusion criteria of the study. In most RCTs for RA, patient inclusion is dependent on disease activity and exclusion is dependent on safety profiles

many RCTs. RCTs are quite appropriate for determining the efficacy and safety profile of a drug or therapeutic strategy, but the population of study patients is usually restricted because of the study inclusion and exclusion criteria (Fig. 3).

It has been argued that only a small fraction of patients in daily practice would satisfy the inclusion and exclusion criteria of the clinical studies of biologics [17]; therefore, the therapeutic strategies established by clinical studies are acceptable but not ideal for implementation in daily practice. As Professor Furst has commented, "Well-designed clinical studies and observational cohorts, we need them both" [32]. Many RCTs have been conducted by pharmaceutical companies, but it is extremely difficult for a company to organize and maintain an observational cohort based on daily practice. There are many registries and observational cohorts of RA patients, including IORRA, CORRONA [33], NOR [34], and SRR [35]. We believe that consideration should be given to basing the guidelines and recommendations for RA therapeutic strategies on these practice-oriented databases. In addition, we would like to encourage clinical studies based on all the patients seen in daily practice (Fig. 4).

One of the pitfalls of evidence-based medicine (EBM) has been the application of the results of clinical studies that were conducted under medical conditions different from those of the patients in our daily practice. Even if the essential baseline characteristics are similar, the study patients might be of different ethnicities, with different comorbid diseases, concomitant medications, methotrexate doses, financial support, or medical insurance. These are the limitations of EBM, and we have to think about the application of evidence generated from "our" patients to patients in daily practice. We have established a large cohort of IORRA patients with RA, and various evidence-based findings can be generated by appropriate analyses; therefore, it is possible to apply the data from the IORRA cohort to our patients in IORRA. We call this approach "institute-based medicine" (IBM) or "IORRA-based medicine" (also IBM). It may not be feasible to apply this concept to all patients in all clinical situations, but we think that we have to try to improve the quality of evidence by considering the medical circumstances of each patient.

Thoughts on a patient-friendly program

The aim of RA treatment is the well-being of RA patients. Patient self-care is needed to prevent disease progression; however, RA is essentially not a lifestyle-related disease where patient effort yields a better outcome. Thus, medical professionals, including rheumatologists, must modify the course of the disease so that it leads to the best outcome. If patients are not educated about their disease, or are depressed by a poor disease outcome, effective treatment cannot be delivered. As treatment goals have become more optimistic over the years since the introduction of rigorous control of disease activity, there is also a tendency to administer stronger immunosuppression to patients. Both patients and health professionals have to be acutely aware of the early signs and symptoms of adverse events, including opportunistic infections, since anticytokine therapy may sometimes mask those signs [36].

Considering these issues, our IORRA cohort has been established essentially based on information from patients [1–3]. OMERACT has been conducting workshops on patients' perspectives for over 10 years [37], which has led to a recently published definition of RA remission from the patient perspective [38]. Thus, patient education and participation has become increasingly important. As a part of the T2T program, the patient version of the T2T program has been published [37] and translated into many languages, including Japanese. Furthermore, product-specific campaigns that focus on patients who are prescribed a specific drug have been developed, with an aim of specifying the important issues of care in daily life. These are welcome developments in the management of RA and may lead to better patient outcomes. Thus, rheumatologists must share their experience with their patients.

Future perspectives

It has been proposed that medicine of the future should be described by the 4 Ps: predictive, personalized, preventive,

and participatory [39]. Using this perspective, what we have to develop for management of rheumatoid arthritis is: better prediction of disease onset, progression, and response to treatment; a personalized therapeutic strategy; prevention of disease onset, worse outcomes, and side-effects; and participation of all rheumatologists and patients. In the future, use of genomic information [39–47] from individual patients should become important for predicting the disease and its course in each patient.

Furthermore, when thinking about the characteristics of medicine in 2020, we should include the developments of a postgenomic society, and of nanotechnology, smart IT, and enhanced performance [48]. It has been suggested that both medicine and healthcare should be incorporated into the big wave of technology investment.

In conclusion, management of RA has progressed remarkably over the last 10 years. However, there remains much for us rheumatologists to do for our patients.

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Conflict of interest H.Y. has been received speaking fee and/or consulting fee from Abbott, AstraZeneca, Bristol-Myers, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Janssen Pharmaceutical, Mitsubishi Tanabe, Otsuka Pharmaceutical, Pfizer Japan, Takeda Pharmaceutical, Teijin, and UCB. All other authors have declared no conflicts of interest.

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