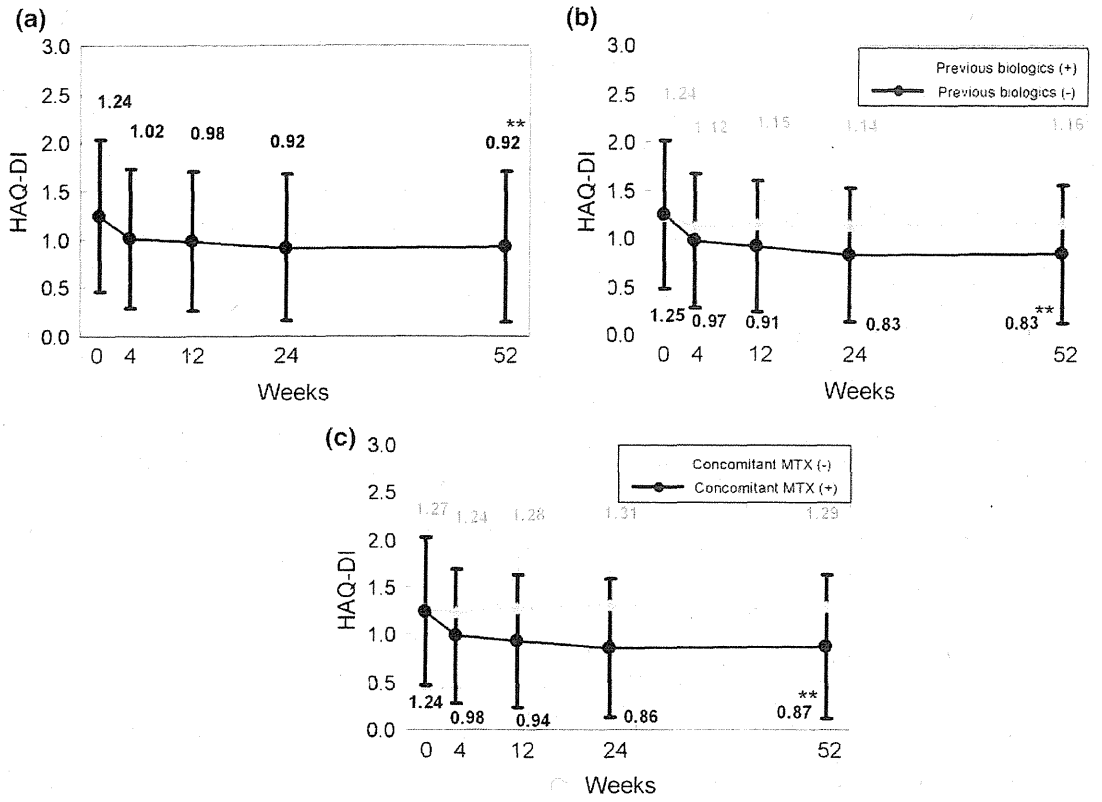

Fig. 3 Time course of Health Assessment Questionnaire—Disability Index (HAQ-DI) over 52 weeks following the initiation of adalimumab treatment. Data were analyzed by the last observation carried forward (LOCF) method. *Points* and *bars* represent the mean and standard deviation, respectively. **a** All patients ($n = 149$), **b** previous biologics (+) ($n = 41$) and (−) ($n = 108$), **c** concomitant MTX (+) ($n = 131$) and (−) ($n = 18$). $^{**}P < 0.0001$ versus baseline by the Wilcoxon signed rank test

The most frequently reported adverse event (SOC) was general disorders and administration site conditions, which were observed at a frequency of 11.40/100 patient-years. ADA therapy was also associated with incidences of infections and infestations at a rate of 10.26/100 patient-years.

Serious adverse events are individually depicted in Table 3. A total of 16 serious adverse events were observed at a rate of 9.12/100 patient-years. Other than the injection site reactions, infections such as *Pneumocystis jiroveci* pneumonia, tuberculosis, nontuberculous mycobacteriosis, and cellulitis were the most frequent serious adverse events. In one patient, perforated colon diverticulum was detected. In another patient, malignant lymphoma was diagnosed. There were no deaths in this study.

Retention rate

In this study, the median duration of ADA treatment was estimated to be 55.9 weeks, with a minimum of 2 weeks and a maximum of 100 weeks ($n = 167$). At week 52, 69.7% of the 165 patients were still undergoing ADA therapy (Fig. 7). A greater percentage of patients in the previous biologics (−) group adhered to the treatment (77.6%) than patients in the previous biologics (+) group (51.0%) during the 52-week period ($P < 0.0001$). Similarly, the retention rate in the concomitant MTX (+) group (73.0%) was significantly higher than that in the concomitant MTX (−) group (50.0%) ($P < 0.05$).

Reasons for withdrawals, including those that occurred after 52 weeks of ADA treatment, are summarized in Table 4. The most common reason for discontinuation was lack of efficacy ($n = 24$), followed by adverse events ($n = 16$). Adverse events that led to discontinuation were *Pneumocystis jiroveci* pneumonia ($n = 1$), miliary tuberculosis ($n = 1$), interstitial pneumonitis ($n = 2$), interstitial pneumonitis/common colds ($n = 1$), generalized rash/nontuberculous mycobacteriosis/upper respiratory inflammation ($n = 1$), cellulitis/injection site reaction ($n = 1$), lymphoproliferative disorder ($n = 1$), perforated colon diverticulum/injection site reaction ($n = 1$), pancytopenia ($n = 1$), malignant lymphoma ($n = 1$), gastrointestinal disorder/injection site reaction ($n = 1$), generalized urticaria/injection site reaction ($n = 1$), and injection site reaction ($n = 3$). Note that 5 patients withdrew after

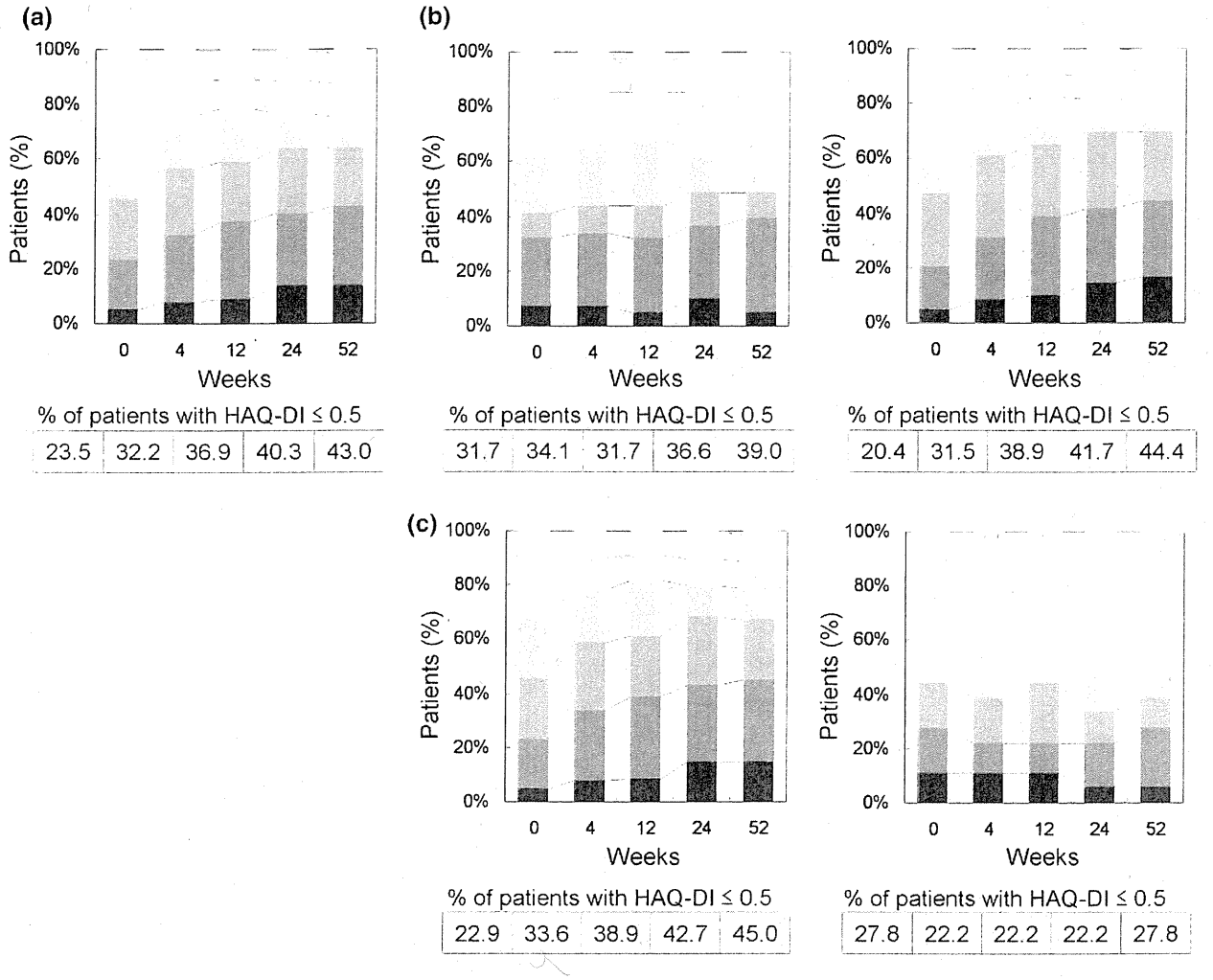

Fig. 4 Time course of the Health Assessment Questionnaire—Disability Index (HAQ-DI) over 52 weeks following the initiation of adalimumab treatment. Data were analyzed by the last observation carried forward (LOCF) method. **a** All patients ($n = 149$), **b** previous biologics (+, *left*) ($n = 41$) and (−, *right*) ($n = 108$), and **c** concomitant MTX (+, *left*) ($n = 131$) and (−, *right*) ($n = 18$). HAQ-DI was categorized as follows

maintaining remission status (DAS28-ESR < 2.6) for more than 24 weeks. The median ADA treatment duration in those 5 patients was 38 weeks (range 28–52 weeks).

Discussion

The present study was carried out to retrospectively analyze the efficacy and safety of ADA in Japanese patients with RA. The study included 167 patients with all individual DAS28-ESR components at baseline. Further, 149 of these had baseline HAQ-DI, and 87 had evaluable radiographic data. For our subjects, ADA therapy provided significant clinical, functional, and radiographic benefits during routine clinical care while also demonstrating generally acceptable safety and tolerability.

The PREMIER study showed that when combination treatment with ADA and MTX is initiated early, it leads to superior clinical, functional, and radiographic outcomes as compared with treatment with MTX alone or ADA alone;

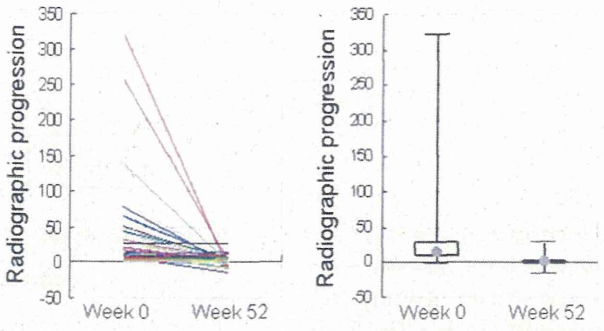

Fig. 5 Yearly progression of TSS in individual patients at weeks 0 and 52 of adalimumab treatment ($n = 87$). Radiographic images were available for 71 of 167 patients at weeks 0 and 52. Linear imputation was used for missing data at week 52 for 16 patients who received adalimumab treatment for at least 180 days. *Right points* and *boxes* represent the median (13.6 at week 0 and 0.0 at week 52) and the interquartile range (8.3–28.9 at week 0 and −0.9 to 2.0 at week 52), respectively. Median reduction in the yearly radiographic progression was 100%. The reduction was statistically significant by the Wilcoxon signed rank test ($P < 0.0001$)

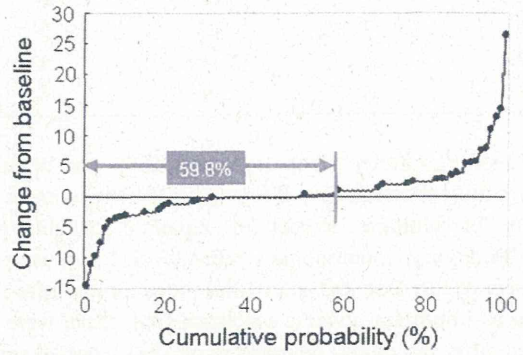

Fig. 6 Cumulative probability plot of change in the total modified Sharp score from baseline to week 52 ($n = 87$). Radiographic images were available for 71 of 167 patients at baseline and week 52. Linear imputation was used for missing data at week 52 for 16 patients who received adalimumab treatment for at least 180 days. In 52 out of the 87 patients (59.8%), the yearly radiographic progression was ≤0.5

adverse event profiles were comparable in all 3 arms [11]. The efficacy confirmed in the CHANGE study should be seen as such [18], since all the ADA-treated patients received ADA monotherapy. The results compared well to those of the DE011 monotherapy study conducted overseas [8]. The present HARMONY study is the first study to demonstrate the efficacy and safety of ADA therapy in combination with MTX in Japanese RA patients. An average of 8.5 mg/week MTX was used at baseline. This study clearly confirmed the superior effectiveness of combination therapy with MTX over ADA monotherapy. Indeed, the impact of concomitant MTX use was greater than that of a lack of history of biologic therapy in terms of both clinical and functional improvement (42.7% DAS28 remission and 45.0% normal function at week 52). Although a rapid

Table 2 Adverse events

MedDRA SOC	Number of events	Events/100 patient-years
Total	60	34.21
Infections and infestations	18	10.26
Respiratory, thoracic, and mediastinal disorders	5	2.85
General disorders and administration site conditions	20	11.40
Hepatobiliary disorders	3	1.71
Gastrointestinal disorders	5	2.85
Skin and subcutaneous tissue disorders	2	1.14
Blood and lymphatic system disorders	1	0.57
Eye disorders	1	0.57
Neoplasms (benign, malignant, and unspecified)	1	0.57
Injury, poisoning, and procedural complications	1	0.57
Investigations	3	1.71

MedDRA SOC Medical Dictionary for Regulatory Activities system organ class

Table 3 Serious adverse events

Adverse events	Number of events	Events/100 patient-years
Total	16	9.12
Injection site reactions[a]	3	1.71
Interstitial pneumonitis	2	1.14
Pneumocystis jiroveci pneumonia	1	0.57
Pneumonia	1	0.57
Miliary tuberculosis	1	0.57
Nontuberculous mycobacteriosis	1	0.57
Cellulitis	1	0.57
Malignant lymphoma	1	0.57
Lymphoproliferative disorder	1	0.57
Perforated colon diverticulum	1	0.57
Generalized rash	1	0.57
Generalized urticaria	1	0.57
Left fibula fracture	1	0.57

Serious adverse events as judged by the attending physicians

[a] Injection site reactions include erythema, itching, hemorrhage, pain, and swelling

response was evident in terms of both HAQ and DAS28 by week 4, the corresponding remission rates tended to increase even after week 24 until week 52, from 35.0 to 42.7%

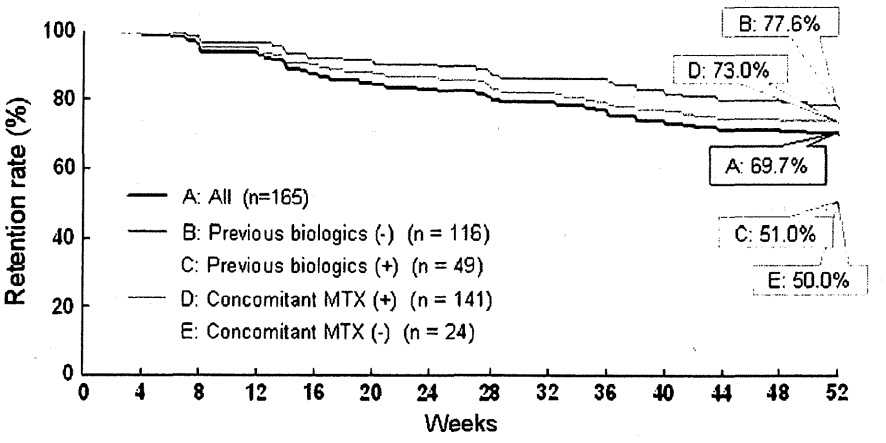

Fig. 7 Retention rates of adalimumab treatment over 52 weeks (Kaplan–Meier plots). Two patients were excluded from the plots because of an unknown date of discontinuation. $P < 0.0001$ between previous biologics (+) versus (−), and $P = 0.0109$ between concomitant MTX (+) versus (−) by the log-rank test

Table 4 Reasons for discontinuation

Two drop-outs with unknown discontinuation date were included. Those who discontinued after 52 weeks of treatment were also included

[a] Other reasons include patient's choice and eye surgery

Variables	All (n = 167)	Previous biologics		Concomitant MTX	
		(+) (n = 49)	(−) (n = 119)	(+) (n = 144)	(−) (n = 24)
Total	55	25	30	42	13
Lack of efficacy	24	14	10	16	8
Adverse events	16	9	7	13	3
Efficacy	5	0	5	4	1
Other reasons[a]	10	2	8	9	1

(DAS28-ESR < 2.6) and from 42.7 to 45.0% (HAQ-DI ≤0.5). Thus, it may be prudent to wait a further 24 weeks to see whether ADA can induce remission in a small portion of patients who responded to ADA at early time points. MTX reduced apparent ADA clearance after multiple dosing in 44% of patients with RA, thereby increasing systemic ADA trough levels [25]. This is because concomitant MTX use is considered to suppress levels of anti-ADA antibodies due to its immunosuppressive effect.

The radiographic outcome presented here is the first evidence of the ability of ADA to significantly limit radiographic progression in Japanese RA patients. Approximately 60% of patients exhibited no radiographic progression in HARMONY, which compares well with the results obtained in the PREMIER study (64 and 51% in the ADA + MTX and ADA monotherapy groups, respectively) [11]. Note that 26 out of the 87 evaluable patients (29.9%) exhibited ΔTSS ≤−0.5, indicating possible radiographic repair.

ADA treatment was generally well tolerated. No anaphylactoid reaction was reported, while injection site reactions occurred at a rate of 11.9% (20/167). This rate was far lower than that reported in the CHANGE study (30.8% in the 40 mg arm). The observed difference may possibly be due to the immunosuppressive effects of the concomitant use of MTX in favor of combination therapy.

Serious infections occurred at a rate of 2.85/100 patient-years (one event of each: *Pneumocystis jiroveci* pneumonia, pneumonia, military tuberculosis, cellulitis, and nontuberculous mycobacteriosis). Recently, the effectiveness and safety of biologic agents in Japanese patients were reviewed, and pneumonia, tuberculosis, *Pneumocystis jiroveci* pneumonia and interstitial pneumonitis were identified as important adverse reactions [26]; these were also observed in our study. Komano et al. [27] reported serious infections at a rate of 6.24/100 patient-years in Japanese patients treated with either infliximab or etanercept for up to 1 year. Although direct comparisons cannot be made among different studies, this may suggest that ADA therapy does not carry an increased risk for serious infections when compared to another anti-TNF therapy.

The overall retention rate observed in the present study (82.4% at 26 weeks and 69.7% at 52 weeks) falls within the range reported for infliximab (75.6% at 54 weeks) [15], etanercept (85.1% at 6 months) [17], and tocilizumab (79.5% at 24 weeks) [28] in daily clinical practice. However, it is not surprising that the retention rate varies among different biologics, as it is believed to be influenced by numerous factors other than efficacy and safety, such as co-morbidity, concomitant therapy, costs, launch timing, and availability of other therapies [29]. In the literature, it was indicated that the drug survival time of a second TNF inhibitor is shorter than a prior TNF inhibitor, while the survival of anti-TNF treatment was shown to be prolonged with concomitant use of MTX [30–32]. Our own findings in HARMONY resemble these published data, as shown by

week 52 retention rates in the previous biologic (−) and concomitant MTX (+) groups of 77.6 and 73.0%, respectively.

In conclusion, this retrospective study has demonstrated that ADA therapy is highly efficacious at reducing disease activity, improving physical function, and limiting radiographic progression, and is generally safe and tolerable in Japanese RA patients encountered during routine clinical practice. Furthermore, the results of this study demonstrate that ADA in combination with MTX is associated with substantial improvements in clinical, functional, and radiographic responses and retention rate, meaning that this could potentially serve as a first-line treatment.

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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

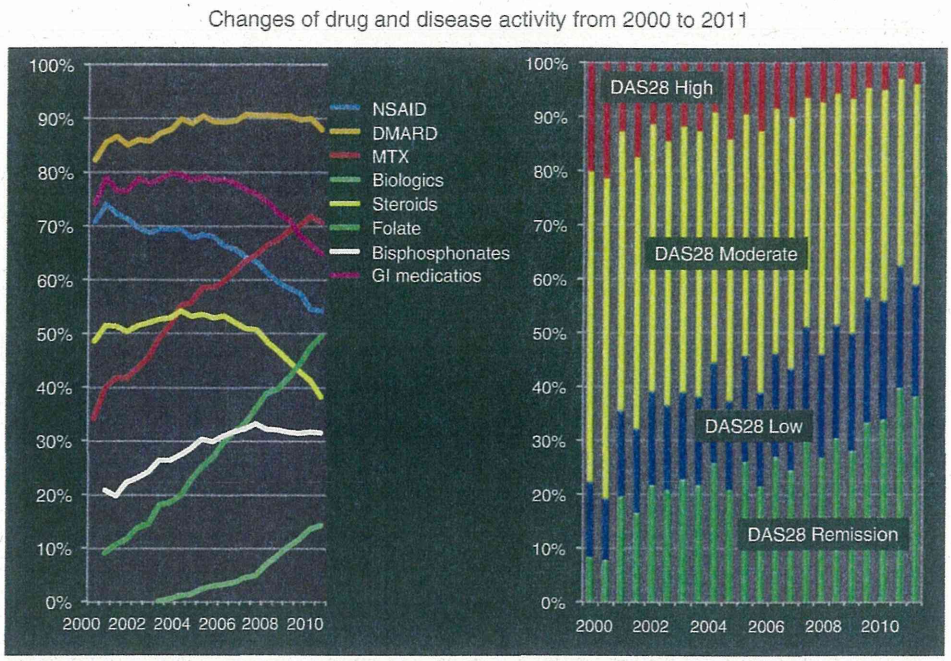

Fig. 1 Changes of drug and disease activity from 2000 to 2011. Changes of drug use and disease activity of RA patients in the IORRA cohort from 2000 to 2011 are shown. Disease activity was categorized by DAS28 according to the standard method

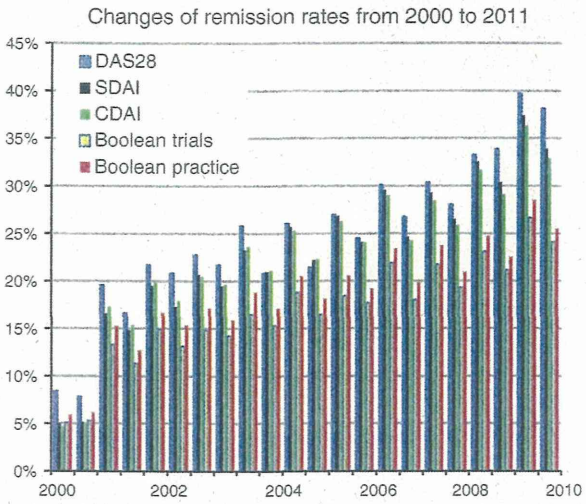

Fig. 2 Changes of remission rates from 2000 to 2011, defined by 5 methods including DAS28, simplified disease activity index (SDAI), clinical disease activity index (CDAI), Boolean trials, and Boolean practice. Definition of remission is based on each criterion

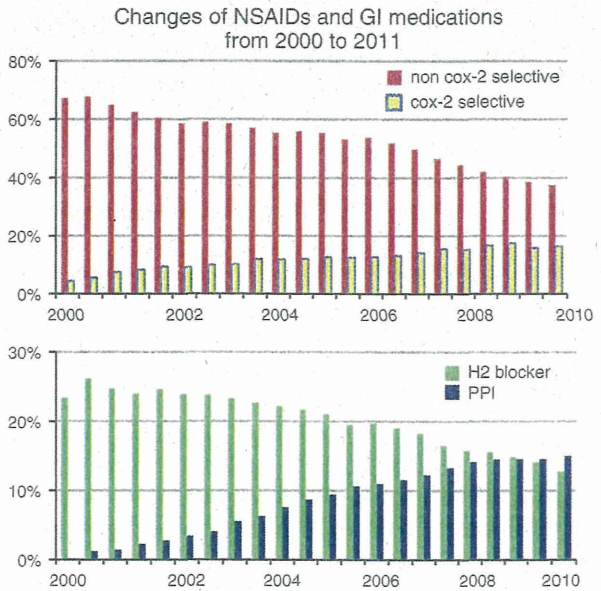

Fig. 3 Changes of use of NSAIDs (*upper column*) and gastrointestinal (GI) medications (*lower column*) from 2000 to 2011. NSAIDs were categorized by cyclooxygenase-2 (COX-2) selectivity as COX-2 selective (celecoxib, meloxicam, and etodolac) or non-COX-2 selective (others). Categorizations of proton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

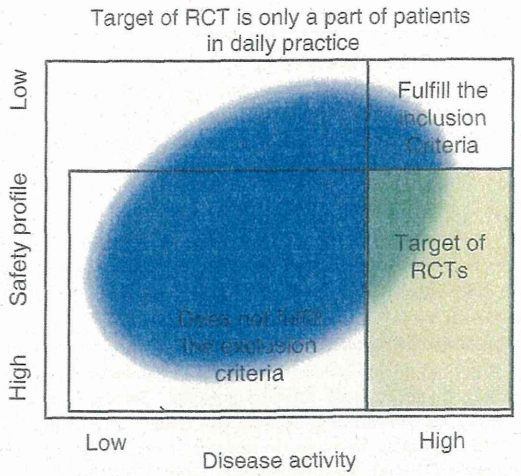

Fig. 4 The target of a RCT is only a part of the patients in daily practice. The target population of most randomized controlled trials (RCTs) is limited by the inclusion and exclusion criteria of the study. In most RCTs for RA, patient inclusion is dependent on disease activity and exclusion is dependent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

No increased mortality in patients with rheumatoid arthritis treated with biologics: results from the biologics register of six rheumatology institutes in Japan

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Abstract
Objective To investigate the influence of biologics on mortality and risk factors for death in rheumatoid arthritis (RA) patients.
Methods RA patients treated with at least one dose of biologics in daily practice in six large rheumatology institutes ("biologics cohort") were observed until 15 May 2010 or death, whichever occurred first. Mortality of the biologics cohort and the "comparator cohort" (comprising patients among the IORRA cohort who had never been treated with biologics) was compared to that of the Japanese general population. Factors associated with mortality were assessed by a Cox model.
Results Among 2683 patients with 6913.0 patient-years of observation, 38 deaths were identified in the biologics cohort. The probability of death in patients lost to follow-up, calculated using the weighted standardized mortality ratio (SMR), was 1.08 [95 % confidence interval (CI) 0.77–1.47] in the biologics cohort and 1.28 (95 % CI 1.17–1.41) in the comparator cohort. Pulmonary involvement was the main cause of death (47.4 %), and the disease-specific SMR of pneumonia was 4.19 (95 % CI 1.81–8.25). Risk factors for death included male gender [hazard ratio (HR) 2.78 (95 % CI 1.24–6.22)], advanced age (HR 1.07, 95 % CI 1.03–1.11), and corticosteroid dose (HR 1.08, 95 % CI 1.01–1.17).
Conclusion Mortality in RA patients exposed to biologics did not exceed that in patients not exposed to biologics, but death from pulmonary manifestations was proportionally increased in RA patients exposed to biologics.

Keywords Biologics · Cause of death · Mortality · Rheumatoid arthritis · Standardized mortality ratio

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that results in worsening physical function and extra-articular manifestations. Due to these manifestations, patients with RA have been reported to experience excessive mortality in Western countries [1–6]. Comparably worse mortality has recently been reported for Japanese patients with RA [7]. However, the cause of death differs

greatly between Western and Japanese RA patients [7]. The main cause of death in Western RA patients is cardiovascular disease (CVD), comprising 40–50 % of deaths. In contrast, one-quarter of Japanese RA patients die from malignancy and respiratory disease, respectively, with pneumonia and interstitial lung disease being the two equivalent primary causes of respiratory disease [7].

Many studies have reported favorable results of biologic treatment of RA in decreasing disease activity, preventing bone destruction, and suppressing CVD events and death [8–11], and possibly improving overall mortality [8, 12, 13] in Western RA patients. However, several reports have demonstrated that use of anti-tumor necrosis factor (TNF) therapy is associated with an increased risk of serious infection, especially in the first six months of treatment [14, 15]. Considering that previous reports [7, 16–18] indicate that the causes of death of Japanese RA patients differ from those of Western RA patients, it is yet to be clarified whether biologic treatment results in the same benefit to Japanese RA patients as that reported for Western RA patients.

We conducted this study to elucidate whether treatment of RA with biologics actually provides an improvement in the mortality of Japanese RA patients and to assess causes of death and risk factors for death in a multicenter observational cohort study.

Patients and methods

Study design

All of the patients with RA who had been treated with at least one dose of a biologic (including infliximab, etanercept, tocilizumab and adalimumab) in daily clinical practice were listed in six rheumatology centers, and these patients were registered into the "biologics cohort" at the start of this observational study in September 2008. Additional new RA patients who were treated with at least one dose of these biologics after September 2008 were introduced into this biologics cohort and both were observed until 15 May 2010 or until death, whichever came first. A query about their survival was sent to the patients who were lost to follow-up at the end of this observational period by the relevant physician. This study was conducted through the cooperation of six large rheumatology centers in Japan: the Institute of Rheumatology of Tokyo Women's Medical University, the Department of Rheumatology and Clinical Immunology of Saitama Medical Center in Saitama Medical University, the First Department of Internal Medicine of the University of Occupational and Environmental Health, Japan, the Department of Orthopedic Surgery and Rheumatology of Nagoya University, the Department of Diabetes, Endocrinology and Rheumatology of Japanese Red Cross Kyoto Daiichi Hospital, and the Division of Rheumatology and Clinical Immunology of Jichi Medical University. This study was conducted after approval was given by the ethical committee at each institute. The use of biologics in daily practice was judged by responsible rheumatologists, with reference to the guideline for the introduction of biologics in practice developed by the Japanese College of Rheumatology.

Assessments

The baseline data of the patients who had received a biologic agent (infliximab, etanercept, tocilizumab, or adalimumab) were collected, including age, sex, disease duration, concomitant methotrexate (MTX) use and dose, concomitant corticosteroid use and dose (converted into the equivalent prednisolone dose) at the initiation of the corresponding biologic, and when and which biologic agent was introduced. Medical history, including tuberculosis, malignancy, CVD, cerebrovascular disease, and gastrointestinal bleeding was reported. Disease activity was assessed by either DAS28 or DAS28-CRP [19] according to their utilization at each institute. Physical function was also measured either by Health Assessment Questionnaire (HAQ), the Japanese version of the HAQ (J-HAQ) [20], or the modified HAQ (M-HAQ). When the biologic agent was discontinued, the time and reason for discontinuation were reported. In cases where the patient had switched biologics, the biologics used during the observational period were recorded. Patients who received at least one dose of a biologic were followed up even if they discontinued the agent or switched to an alternative biologic agent. At the end of this study, on 15 May 2010, the survival of each patient was confirmed as accurately as possible, as described below. Causes of death were collected from each institute and classified according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10).

The primary outcome measure in this study was mortality. The notification of death and the cause of death were acquired from the relevant physician at each rheumatology institute. When the patient's survival was uncertain at the end of this study period, a letter to confirm their survival was sent by the affiliated institute. When the death of the patient was approved, cause of death and time were reported.

Comparison cohorts

Patients with RA who were enrolled in the IORRA (Institute of Rheumatology, Rheumatoid Arthritis) cohort after April 2003 (around which time the first biologic agent

became available in daily practice in Japan) and who had never been treated with any biologics until 15 May 2010 were included in the "comparison cohort" (nonbiologics IORRA) in this study. IORRA is a large observational cohort established in 2000 at the Institute of Rheumatology, Tokyo Women's Medical University, with the primary aim being to assess standard RA outcomes in accordance with the current treatments used in daily practice, as reported precisely previously [7, 21, 22]. The IORRA cohort basically comprises all RA patients who attended the Institute of Rheumatology, Tokyo Women's Medical University, and fulfilled the classification criteria of the American College of Rheumatology for RA [23] in principle after informed consent was obtained. The IORRA survey is conducted biannually (in April and May and in October and November). Disease activity evaluated by DAS28 [19], physical function evaluated by J-HAQ [20], and laboratory data used in daily practice were collected. Medications, including disease-modifying antirheumatic drugs (DMARDs), MTX, corticosteroids, and biologics used within the previous six months were also reported. Active follow-up by mail was conducted for patients who did not attend the subsequent IORRA survey. The cause and the time of the death were collected from the physicians at the affiliated hospitals, from residual family members through active follow-up inquiry by mail, and from the police when it was sudden or accidental.

Statistical analysis

Mortality

The mortality of patients in this biologics cohort was compared to the mortality of the Japanese general population reported by Japanese Health and Wealth (**http://www.stat.go.jp/data/nihon/02.htm**) via standardized mortality ratios (SMRs) and confidence intervals (95 % CIs). Standardization was conducted by the calendar year of recruitment, gender, and age. Since this biologics cohort study was observational, patients were not completely followed unless an active effort was made to capture their survival status. Nonresponse to mailed queries is a potential source of bias in this type of research survey. Thus, to assess mortality, we attempted to statistically analyze it as follows. First, we assumed that all patients who were lost to follow-up at the end of the observation period were alive; the SMR was then calculated and compared to the Japanese general population (analysis 1). Second, we assumed that patients who were ascertained to be alive at three months (analysis 2) or six months (analysis 3) before the end of the observation period were alive at the end of the observational period; these data were compared to those of the Japanese general population. Finally, as Kauppi et al. [24] reported that patients with RA who did not respond to mailed queries were 1.65 times more likely to have died over the two-year follow-up period compared to responders, we statistically determined that patients who were lost to follow-up would have died at this rate (analysis 4), and these data were compared to those of the Japanese population.

The mortality of the patients in the comparison cohort (non-biologics IORRA) was analyzed using SMR with the same weighting as in analysis 4, assuming the patients who were lost to follow-up were 1.65 times more likely to have died over the two-year follow-up period than the Japanese general population (analysis 5).

Causes of death and disease-specific mortality

The causes of death in this biologics cohort were collected and cause-specific mortality was analyzed for malignancy, pneumonia, and respiratory diseases including pneumonia. Death within three months of the last use of biologics was considered "death on biologics." For patients who were ascertained to have died due to a specific cause of death, the disease-specific mortality rate and SMR were calculated by comparing to the mortality of the Japanese general population reported by Japanese Health and Wealth (**http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/suii01/deth10.html**).

Risk factors for mortality

To assess the risk factors for mortality among patients who had been exposed to at least one dose of a biologic, variables including sex, age (year), body mass index (BMI) (kg/m^2), disease duration (year), disease activity (DAS28), MTX dose (mg/week), and corticosteroid dose (mg/day) at the initiation of the first biologics were analyzed using a Cox model.

Results

Overall, 2683 patients with RA who had been exposed to biologics were registered into the biologics cohort. The first biologics used in these patients included infliximab ($n = 1112$, 41.2 %), etanercept ($n = 1053$, 39.0 %), adalimumab ($n = 345$, 12.8 %), tocilizumab ($n = 173$, 6.4 %), and abatacept ($n = 4$, 0.1 %). The mean (SD) age was 56.0 (13.9) years, mean disease duration was 10.1 (10.1) years, and 84.0 % of patients were women (Table 1). Baseline disease activity was 5.6 (1.2) as evaluated by DAS28 or 4.9 (1.2) by DAS28-CRP. MTX and corticosteroids were concomitantly prescribed in 77.7 and 54.2 % of patients, respectively. Discontinuation of the

Table 1 Baseline characteristics of the biologics cohort

	Percentage or mean	SD
Female (%)	84.0	
Age (years)	56.0	13.9
Disease duration (years)	10.1	10.1
BMI (kg/m^2)	21.5	3.4
General VAS	57.0	23.5
Disease activity		
DAS28	5.6	1.2
DAS28-CRP	4.9	1.2
ESR (mm/h)	54.9	30.2
CRP (mg/dl)	3.10	3.40
RF (IU/ml)	202.4	348.2
Physical dysfunction (HAQ, J-HAQ, MHAQ)	1.17	0.81
EQ-5D	0.62	0.13
Past history		
Pulmonary tuberculosis (%)	3.4	
Malignancies (%)	4.5	
Ischemic heart diseases (%)	1.4	
Cerebrovascular disease (%)	1.3	
GI bleeding (%)	1.0	
MTX use (%)	77.7	
MTX dose (mg/week)	7.6	3.2
Corticosteroid use (%)	54.2	
Prednisolone dose (mg/day)	3.9	3.4

Data shown are the % or mean (standard deviation) values, as appropriate

VAS visual analogue scale, *DAS28* disease activity score 28, *ESR* erythrocyte sedimentation rate, *CRP* C reactive protein, *RF* rheumatoid factor, *HAQ* health assessment questionnaire, *EQ-5D* EuroQoL 5 dimension, *GI* gastrointestinal, *MTX* methotrexate

first biologic was reported in 36.1 % of patients. Reasons for discontinuation of biologics included great response (7.1 %), insufficient effect (38.6 %), side effects (19.8 %), and economic reasons (2.9 %). Among patients who discontinued their first biologic, 43.2 % of patients switched to a second biologic. During this observation period, 64.8 % of patients were treated with one biologic, 17.2 % were treated with two biologics, and 18.0 % were treated with three or more biologics.

Mortality

Thirty-eight deaths were recorded among 6913.0 patient-years (1072.4 patient-years for males and 5840.6 patient-years for females) of observation in the biologics cohort, and 537 patients (20.0 %) were lost to follow-up. SMRs were calculated with several assumptions (Table 2). When assuming that all of the patients lost to follow-up were alive, the SMR of RA patients treated with biologics did not exceed that of the Japanese general population [analysis 1, SMR 1.02 (95 % CI 0.72–1.40)]. When assuming that the patients who were ascertained to be alive at three months (analysis 2) or six months (analysis 3) before the end of the observation period were alive, the assumed SMR for the general population was 2.17 (95 % CI 1.73–2.70) in analysis 2 and 1.96 (95 % CI 1.54–2.46) in analysis 3. Upon weighting for patients lost to follow-up at the end of the observation period using the 1.65 times death assumption (as described in "Patients and methods"), the SMR in this biologics cohort (analysis 4) was 1.08 (95 % CI 0.77–1.47) compared with that of the Japanese general population [1.45 (95 % CI 0.86–2.30) in males and 0.90 (95 % CI 0.57–1.35) in females].

When the same weighting for patients lost to follow-up was applied to the nonbiologics IORRA cohort, the assumed SMR was 1.28 (95 % CI 1.17–1.41) for all subjects [1.31 (95 % CI 1.11–1.53) for males and 1.27 (95 % CI 1.13–1.43) for females] as compared to the Japanese general population.

Causes of death and cause-specific mortality

The most frequent cause of death was respiratory disease (47.4 %), including pneumonia (21.1 %) and interstitial lung disease (18.4 %), followed by infection other than pneumonia and malignancies (Table 3). When only deaths that occurred within three months of the last administration of biologics were considered, deaths from respiratory disease (58.8 %) including pneumonia (23.5 %) and interstitial pneumonia (23.5 %) were most prominent.

Concerning disease-specific mortality, deaths from malignancy in RA patients treated with biologics did not exceed those in the Japanese general population [malignancy-specific SMR, 0.30 (95 % CI 0.10–0.69)]; however, deaths from pneumonia (pneumonia-specific SMR 4.19, 95 % CI 1.81–8.25) and respiratory disease (respiratory-specific SMR 9.42, 95 % CI 5.58–14.88) were much higher than those in the Japanese general population (Table 4).

Risk factors for mortality

Risk factors for mortality (analyzed by a Cox proportional hazards model) were male gender [hazard ratio (HR) 2.78 (95 % CI 1.24–6.22), $p < 0.05$], older age [HR 1.07 (95 % CI 1.03–1.11), $p < 0.001$], and corticosteroid dose [HR 1.08 (95 % CI 1.01–1.17), $p < 0.05$], as shown in Table 5.

Discussion

This is the first study to deal with mortality in patients with RA treated with biologics in Japan. In general, the

Table 2 Adjusted mortality rates and standardized mortality ratios (SMRs) of biologics-treated rheumatoid arthritis patients ("biologics cohort") and rheumatoid arthritis patients among the IORRA cohort who had never taken biologics ("nonbiologics IORRA cohort") as compared to the Japanese general population

	Observed	Observation (patient-years)	Crude rate/100,000 patient-years	Adjusted mortality rate			SMR		
				Per 100,000 patient-years	95 % lower	95 % upper	SMR	95 % lower	95 % upper
Analysis 1: biologics cohort (assuming that all patients who were lost to follow-up at the end of observation period are alive)									
Total	38	6913.03	834.29	423.60	228.50	717.67	1.02	0.72	1.40
Male	17	1072.41	921.50	672.03	301.05	1292.97	1.40	0.81	2.24
Female	21	5840.62	751.05	186.49	93.43	332.87	0.84	0.52	1.28
Analysis 2: biologics cohort (assuming that all patients who were ascertained to be alive at three months before the end of the observation period were alive)									
Total	81	6913.03	834.29	700.08	470.12	1003.22	2.17	1.73	2.70
Male	23	1072.41	921.50	846.01	434.85	1483.29	1.89	1.20	2.84
Female	58	5840.62	751.05	560.79	393.21	775.65	2.31	1.76	2.99
Analysis 3: biologics cohort (assuming that all patients who were ascertained to be alive at six months before the end of the observation period were alive)									
Total	73	6913.03	834.29	628.58	406.84	927.81	1.96	1.54	2.46
Male	22	1072.41	921.50	821.43	414.13	1459.73	1.81	1.13	2.74
Female	51	5840.62	751.05	444.52	307.90	621.07	2.03	1.51	2.67
Analysis 4: biologics cohort (assuming that patients who were lost to follow-up were 1.65 times more prone to die)									
Total	40.20	6913.03	834.29	442.73	243.45	739.70	1.08	0.77	1.47
Male	17.65	1072.41	921.50	691.31	314.95	1315.47	1.45	0.86	2.30
Female	22.55	5840.62	751.05	205.47	102.56	367.66	0.90	0.57	1.35
Analysis 5: nonbiologics IORRA cohort (assuming that patient who were lost to follow-up was 1.65 times more prone to die)									
Total	445.86	39078.17	1140.94	743.37	628.64	872.98	1.28	1.17	1.41
Male	161.19	6775.95	2378.91	814.48	648.09	1010.55	1.31	1.11	1.53
Female	284.66	32302.21	881.25	675.50	522.91	858.72	1.27	1.13	1.43

investigation of mortality is conducted by accessing death certificates or death records provided by the government or local government. However, there is no national death database in Japan, and it is quite difficult to access death certificates, even from local governments. Thus, we attempted to register as many cases as possible from the institutes that participated in this study, and to monitor death information actively in each clinical environment. IORRA was used as an external control population, since the IORRA cohort is considered to be representative of Japanese RA patients in a real-world setting and is the only cohort in which mortality of RA patients has been analyzed and published [7]. In this study, we demonstrated that the mortality of Japanese RA patients treated with at least one dose of biologics in daily practice did not exceed that in the Japanese general population, whereas the mortality of patients among the IORRA cohort who had never been treated with biologics slightly exceeded that seen in the Japanese general population. Even though these two cohorts came from different populations, it is hoped that treatment with biologics may improve the mortality of patients who can be treated with biologics. This result is comparable to recent reports from Western countries [12, 13, 25]. In those countries, information on comorbidity, hospitalization, and death can be obtained from nationwide registries, making it possible to calculate mortality more accurately, even though patients lost to follow-up are not mentioned. In this study, the number of patients who were lost to follow-up was relatively large, so the sensitivity analysis need to be executed by using assumption according to the report of Kauppi et al. How best to manage patients who are lost to follow-up (which inevitably occurs in this type of study) is a major issue to be solved.

The result that patients who were treated with at least one dose of biologics have a better outcome needs to be interpreted carefully, because we compared SMRs from different sources. The potential for selection bias in this study should be considered. First of all, patients who were candidates for biologics treatment were expected to tolerate the biological therapy. Second, patients who receive biologics were carefully screened for occult infections, malignancies, and comorbidities such as respiratory diseases before treatment. Thirdly, they were also monitored more extensively during the treatment, so adverse events, including upper respiratory infections and malignancies,

were more likely to have been identified in the biologic cohort beforehand. However, this possible selection bias favoring less severe complications in the biologic cohort does not completely explain our results. Additional considerations include the fact that 25.9 % of patients discontinued biologics during the observation period, and the average 2.6 years of the observation performed in this study may not have been long enough to sufficiently evaluate mortality.

Respiratory diseases, primarily pneumonia and interstitial lung disease, were the predominant causes of death in this biologics cohort, followed by infections other than pneumonia, malignancy, and CVD. In Western countries, CVD is the major cause of death in the general population, and it affects a larger proportion of patients with RA. Biologics, mainly anti-TNF agents, are expected to reduce the incidence and risk of cardiovascular events and improve mortality [11, 26], but CVD is still the main cause of death in Western RA patients treated with biologics. In contrast, rates of respiratory diseases (especially pneumonia) in this biologics cohort were significantly high, and the disease-specific SMR for pneumonia was about four times higher than that of the Japanese general population. When we considered deaths limited to within three months of the last use of biologics, 58 % of these particular RA patients died from respiratory diseases, including pneumonia; in other words, pneumonia and respiratory diseases tended to occur while using biologics. Interstitial lung disease is one of the major causes of death in Japanese patients with RA, accounting for half of all cases of respiratory disease; this was also true in this biologics cohort. Recently, interstitial lung disease has been extensively discussed in the context

Table 3 Causes of death classified according to ICD-10 chapter number in patients with rheumatoid arthritis treated with biologics

Chapter	Blocks	Chapter title	Total deaths ($N = 38$), n (%)	Death within three months after the last use of biologics ($N = 17$), n (%)
I	A00–B99	Certain infections and parasitic diseases	6 (15.8)	2 (11.8)
II	C00–D48	Malignancies	5 (13.2)	2 (11.8)
IV	E00–E90	Endocrine, nutritional and metabolic diseases	1 (2.6)	
IX	I00–I99	Diseases of the circulatory system	5 (13.2)	1 (5.9)
	I20–I25	Ischemic heart diseases	2 (5.3)	1 (5.9)
	I60–I69	Cerebrovascular diseases	2 (5.3)	
X	J00–J99	Diseases of the respiratory system	18 (47.4)	10 (58.8)
	J10–J18	Influenza and pneumonia	8 (21.1)	4 (23.5)
	J99	Rheumatoid lung disease	7 (18.4)	4 (23.5)
XVIII	R00–R99	Symptoms, signs and abnormal clinical and laboratory findings not classified elsewhere	3 (7.9)	2 (11.8)

ICD-10 International Statistical Classification of Disease and Related Health Problems, Tenth Revision

Table 4 Disease-specific mortalities and standardized mortality ratios (SMRs) of patients treated with at least one dose of biologics

Observed	Patient-years	Adjusted mortality rate	Per 100,000 patient-years	95 % CI	SMR	95 % CI
Malignancies						
Total	5	6913.03	44.92	10.90–121.78	0.30	0.10–0.69
Male	2	1072.41	65.79	7.94–237.93	0.37	0.04–1.33
Female	3	5840.62	24.93	5.09–73.15	0.26	0.05–0.76
Pneumonia						
Total	8	6913.03	189.42	62.16–439.46	4.19	1.81–8.25
Male	5	1072.41	317.29	82.41–832.08	6.82	2.21–15.91
Female	3	5840.62	66.96	5.81–270.49	2.55	0.52–7.44
Respiratory diseases						
Total	18	6913.03	309.65	151.55–561.60	9.42	5.58–14.88
Male	9	1072.41	455.74	177.50–957.40	12.27	5.61–23.29
Female	9	5840.62	169.72	51.81–409.58	7.64	3.49–14.51

SMR standardized mortality ratio, *95 % CI* 95 % confidence intervals

Table 5 The risk factors for death in patients with rheumatoid arthritis treated with at least one dose of biologics

	Coefficient	HR	95 % CI	*p*
Male sex	1.021	2.78	1.24–6.22	0.013
Age (years)	0.068	1.07	1.03–1.11	<0.001
Disease duration (year)	−0.024	0.98	0.93–1.02	0.291
DAS28	−0.133	0.88	0.64–1.20	0.404
Methotrexate dose (mg/week)	−0.042	0.96	0.87–1.06	0.389
Steroid dose (mg/day)	0.081	1.08	1.01–1.17	0.029

HR hazard ratio, *95 % CI* 95 % confidence interval, *DAS28* 28-joints disease activity score

of treatment with or without biologics [6, 27, 28]; thus, reducing the incidence and mortality of interstitial lung disease in this patient population is an important issue.

We have demonstrated that risks for mortality included age, male gender, and corticosteroid dose at the initiation of the first biologic in this biologics cohort. Jacobsson reported that disability, VAS for pain, and presence of comorbidity (COPD, diabetes, or CVD) were strong predictors of mortality according to time-dependent proportional hazards models. In this study, we could not perform time-dependent analysis because it was difficult to obtain all of the required data on physical function and VAS for pain. In addition, as we did not establish any central adjudicative committee for this study, each institution needed to authorize the recording of data on comorbidity and death. Thus, it was difficult to obtain that information in this study. However, we found that the dose of corticosteroids at the initiation of the first biologic was a risk factor for mortality. It is the consensus that the concomitant use of corticosteroids is a risk factor for mortality in patients with RA, even though corticosteroids are more likely to be prescribed to patients in whom immunosuppressants—including biologics—are not indicated due to comorbidities.

In conclusion, this study demonstrated that no increase in mortality was associated with the introduction of biologics during RA treatment in Japan. This important issue should be further studied through an improved methodology for assessing mortality, including access to death certificates.

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