Introduction

Recent advances in medication have brought about a substantial paradigm shift in the treatment of rheumatoid arthritis (RA). Biological disease-modifying antirheumatic drugs (bDMARDs) have revolutionized the management of RA and have markedly changed the functional status of patients with RA.

Despite treatment with such agents, structural damage can accumulate over time, and a certain percentage of patients inevitably require surgical intervention (1). Over the years, serious concern has been raised by rheumatologists, orthopedic surgeons, and patients regarding the perioperative complications after orthopedic surgery in patients receiving bDMARDs. The adverse consequences of the inhibition of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), or T cell function may include serious complications such as surgical site infection (SSI) and/or delayed wound healing, especially in patients undergoing total joint replacement. Several articles on this topic have been published in the past decade, although the findings of these articles are conflicting. Considering the huge benefit patients receive from an appropriate surgical intervention, patients, rheumatologists, and orthopedic surgeons should consider the risk–benefit balance based on the evidence of the risks associated with surgical intervention, especially when used with the new medications. Because more evidence recently became available on this topic, we thought that a new systematic literature review using transparent methodology would provide scientifically appropriate conclusions.

This review is part of the clinical practice guidelines for the management of RA in Japan developed in 2014 under the support of Health and Labor Sciences Research Grants for Research on Allergic Disease and Immunology from the Ministry of Health, Labor, and Welfare. We used the GRADE (grading of recommendations, assessment, development, and evaluation) approach to describe the quality of evidence and the strength of recommendations (2, 3). In this article, we focus on the perioperative complications of SSI and wound healing delay in patients receiving bDMARDs compared with those not receiving bDMARDs (mostly receiving conventional synthetic DMARDs, csDMARDs) who underwent orthopedic surgery. We specifically address the following two clinical questions. 1) Does the use of a bDMARD increase the risk of developing an SSI? 2) Does the use of a bDMARD increase the risk of delayed wound healing? We do not discuss other surgical complications such as thromboembolism because there was insufficient literature on these complications at the time of our review.

Materials and Methods

Our review was performed according to the GRADE system (2, 3). The key components of the clinical questions according to the PICO plan (participants, interventions, comparisons, and outcomes) were as follows. The participants were patients with a diagnosis of RA either confirmed by a rheumatologist or using the 1987 or 2010 classification criteria. The intervention examined was the use of bDMARDs and included anti-TNF-α inhibitors (adalimumab, etanercept, golimumab, infliximab), abatacept, and tocilizumab. The comparison arm was any medication except for bDMARDs. All of the participants underwent an elective or compulsory orthopedic surgery with continuation or discontinuation of bDMARDs. We did not ask about perioperative continuation or discontinuation of csDMARDs or steroids.

The types of studies for inclusion in our review were limited to controlled studies, all of which were cohort or observational studies with appropriate control groups. Studies that investigated only patients without RA, interventions with non-bDMARDs, or no orthopedic surgery, and/or studies that did not show separate data for bDMARDs and non-bDMARDs were excluded. Case reports, comments or letters to the editor, and articles with no control group were also excluded from the review. The primary outcomes for this systematic review were SSI and delayed wound healing reported in the literature after an orthopedic surgery.

Search methods to identify the studies

A thorough literature search was performed with a medical librarian to reduce bias by increasing the likelihood of retrieving all relevant studies. The following electronic databases were searched from January 1998 to August 2012: PubMed, Web of Science, and the Cochrane Database of Systematic Reviews (CDSR). Relevant articles were screened for additional references published by the end of December 2013. Articles written in English were considered for review. The search strategy comprised the following components, each of which was defined by a combination of Medical Subject Heading (MeSH) terms and free text terms: (1) arthritis, rheumatoid/surgery; (2) complication, adverse effect, risk factors, wound infection, or treatment outcome; (3) antirheumatic agents or biological agents.

#1. "arthritis, rheumatoid/surgery" [MH] (MH: MeSH Terms)

#2. complication* OR adverse effect* OR risk factors OR wound infection [MH] OR "treatment outcome" [MH]

#3. "antirheumatic agents" [MH] OR (antirheumatic [TIAB] AND agents [TIAB]) OR "antirheumatic agents" [TIAB] OR "antirheumatic agents" [Pharmacological Action] OR biological agent* [TIAB] (TIAB: Title/Abstract)

#4. #1 AND #2 AND #3

#5. #4 Filters: publication date from 1998/01/01 to 2012/08/31; English

In addition, the reference lists of studies identified for inclusion in the review and in previous review papers were searched manually to find additional studies.

Data collection and analysis

Selection of studies

Titles and abstracts were assessed for all records identified through the search strategies. Two review authors (HI, MK) examined each citation, and full papers were retrieved for all those appearing to meet the inclusion criteria. Full reports were also acquired if there was any uncertainty about their inclusion or if abstracts were not available and it was not possible to exclude the study based on the title alone. All full-text articles were screened for the inclusion and exclusion criteria by the two independent review authors (HI, MK), and any disagreements regarding eligibility were resolved by discussion and the involvement of an arbiter where necessary.

Data extraction and management

For each publication, a review author (HI) retrieved the following details, which were tabulated on a standardized form: assignment to groups; follow-up periods; participants' demographics (age, sex, diagnosis, duration of disease, sample size);

medications for RA (proportions of steroid, use of methotrexate and other DMARDs, and dose of each medication); orthopedic surgery (anatomical site, type of surgery); adverse events or effects; and withdrawals. Another reviewer (MK) then checked the retrieved data and independently searched the original article(s) if there were questions or uncertainty. When the data for a particular study were unclear or missing from the article, we attempted to contact the authors. Only when the accurate data were collected from the authors was the study included for further analyses; otherwise, the study was excluded from our analyses.

Assessment of risk of bias in the included studies

To decide whether each paper retrieved would be included in the review, the two review authors (HI, MK) independently assessed the methodological quality using an adapted version of the Newcastle–Ottawa Scale for Cohort Studies (4). This scale grades the reporting of studies according to the selection, applicability, and comparability of study groups. The maximum score was 8, and the minimum score was 0. A score of 7 or 8 was considered to indicate high methodological quality (low risk of bias), a score of 5 or 6 indicated moderate quality, and 4 or less indicated low quality (high risk of bias) (5).

Statistical analysis

We performed this meta-analysis using the method described previously (5). Briefly, we included in our meta-analysis those studies with unadjusted estimates of SSI and delayed wound healing. After collecting the frequency data, we calculated the relative risk and 95% confidence interval (CI) for the primary outcomes (SSI and delayed wound healing) in the groups that used bDMARDs or any other medication specified. We grouped all of the data, irrespective of the follow-up period or whether the definition of complications was described. We pooled the outcome measures using the random-effects model of DerSimonian and Laird. We weighted all pooled estimates by study size and quantified heterogeneity between studies using the I^2 statistic. To assess publication bias, we constructed funnel plots to examine the sample size versus exposure effect across the included studies. We conducted all statistical analysis using Review Manager 5.1. (Cochrane Collaboration: Review Manager [RevMan; computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

We did not find any reviews in the CDSR on this subject. We next searched PubMed and Web of Science using the terms described in Materials and Methods and then added the manually searched manuscripts published in PubMed by the end of December in 2013, and found 75 articles that matched the search terms and parameters. Forty-four manuscripts were initially included, and 36 of these were excluded after full-text review. The actual numbers of cases reported in the article by Galloway et al. were not found (6), and the authors could not identify them from their record. After repeated correspondence, this manuscript was excluded from the meta-analysis. There was a possibility of duplicated cases between one article (7) and several other articles (8-12), but correspondence with the authors clarified that there were no duplicated cases except for one article (12). The author of the article that was found to have duplicated cases was able to confirm the number of unduplicated cases. There was also a possibility of duplicated cases in two other articles, both of which were published by the same institution (9, 11). The authors could not confirm the number of duplicated cases in the two articles, but most of the cases were reportedly included in the article

by Momohara et al (11). Thus, we decided that this article contained the representative data for the two articles. The full-text review and the correspondence resulted in the inclusion of 10 studies for SSI and five out of 10 for delayed wound healing for further review and meta-analysis (Fig. 1). The structured abstracts of the 10 articles are shown in Table 1.

Surgical site infection

The prospective observational cohort study of Bibbo et al. was the first to report the effects of bDMARDs on SSI (13). The sample numbers were small (72 operations in patients taking a TNF-α inhibitor vs. 69 in those taking csDMARDs) and surgery involved only the foot and ankle. The authors concluded that the use of TNF-α inhibitory agents could be safely undertaken in the perioperative period without increasing the risk of delayed healing or infectious complications (1.4% in both groups). By contrast, in a retrospective observational cohort, Giles et al. showed that the use of TNF-α inhibitors significantly increased the risk of serious postoperative orthopedic infection (20.0% in 35 operations in patients taking a TNF-α inhibitor vs. 5.4% in 56 operations in patients taking csDMARDs) (14).

After these pioneering works, several other studies were published on this subject. Of note, the Committee on Arthritis of the Japanese Orthopaedic Association conducted a nationwide survey on the prevalence of postoperative complications in patients with RA treated in a teaching hospital between January 2004 and November 2008 (7). The association collected 3468 cases of patients taking bDMARDs and 56339 of those taking csDMARDs. The SSI rate after all surgeries was slightly, but not significantly, higher in the bDMARD group (1.3%) compared with the csDMARD group (1.0%). The SSI rate after joint arthroplasty was significantly higher in the bDMARD group (2.1%) compared with the csDMARD group (1.0%). This is the most compelling evidence to date on this issue. Galloway et al. reported the data from the British Society for Rheumatology Biologics Registry (6). The rate of postoperative joint infection (within 90 days) was 0.7%, and the authors concluded that the risk was not significantly increased by anti-TNF-α therapy. Their report included a sufficient number of cases (4390 in the bDMARD group, 481 in the csDMARD group), but the authors of this article did not report on individual cases of infection in both study arms, which resulted in the exclusion of this study from the meta-analysis as described above.

Overall, the incidence rate of SSI was 0% to 20.8% in patients taking bDMARDs, which appeared to be slightly higher than the rate of 0% to 5.4% in the control groups taking csDMARDs or any other drug. The incidence rate of SSI after large joint surgery was 2.1% to 20.8% in patients using bDMARDs, which was higher than that in controls (1.0 to 4.6%). Our meta-analysis showed that the relative risk of bDMARDs was 2.03 with a 95% CI of 1.40 to 2.96 (Fig. 1a). Of note, the patients taking bDMARDs were younger than the controls. Older age is accepted as a risk factor for complications including SSI, and this relative risk provides compelling evidence of the risk of SSI in association with the use of bDMARDs.

To summarize, the relative risk of SSI after orthopedic surgery is marginally higher in patients using bDMARDs compared with those using csDMARDs or any other drug. bDMARD use may increase the relative risk of SSI in patients, especially those undergoing a total joint replacement. All of the reviewed studies were observational studies. The definition of SSI varied between articles, and the differences between deep and superficial infection could not be determined. Most articles dealt with only anti-TNF-α inhibitors. There was little evidence about IL-6 inhibitors and none about T cell function modulators.

Delayed wound healing

The prospective observational cohort study of Bibbo et al. was also the first to report the effects of bDMARDs on wound healing delay (13). They showed that the rate of delayed wound healing for patients taking bDMARDs (0%) was similar to or even lower than that for patients taking csDMARDs (4.3%). Several research groups have reported on this issue since then, and most of the results show similar rates of delayed wound healing for patients taking bDMARDs and controls (8, 10, 12, 15). However, an article published by researchers in Japan reported a higher rate of delayed wound healing (12.4%) in patients taking tocilizumab compared with the rates reported in other articles and experienced in normal clinical practice (16). The article did not have a control group (csDMARDs or other drugs), but the high incidence rate observed in this study should be noted.

Overall, the incidence rate of delayed wound healing was 0% to 5.4% in patients taking bDMARD, which seemed similar to the rate of 0 to 6.8% in controls (csDMARDs or other drugs). Our meta-analysis showed that the relative risk of bDMARDs was 1.09 with a 95% CI of 0.69 to 1.75 (Fig. 1b), indicating that the use of bDMARDs does not increase the risk of delayed wound healing. However, these results were based on only five articles and a relatively a small sample size (605 in the bDMARD groups and 1466 in the controls).

To summarize, the relative risk of delayed wound healing after orthopedic surgery is similar in patients using bDMARDs and those using csDMARDs or any other drugs. The definition of delayed wound healing varied between articles, and most articles dealt with only anti-TNF-α inhibitors. As noted above for SSI, there was little evidence about the effects of IL-6 inhibitors and none about the effects of T cell function inhibitors on the risk of delayed wound healing.

Discussion

Several reports have focused on the increased risk of SSI attributed to bDMARDs and a few review articles have been published (17-21), but their conclusions have been ambiguous and conflicting. Delayed wound healing is a clinical concern for surgeons and patients taking bDMARDs, but few articles have been written on this issue. We, therefore, focused on SSI and delayed wound healing in this systematic review. Our analysis shows that the use of bDMARDs appears to have certain effects on perioperative complications of orthopedic surgery, and thus bDMARDs should be used with appropriate caution. The data from the British national registries of patients with RA receiving bDMARDs showed an increased risk of serious infection, especially within the first 6 months after initiation of treatment (22). Thus, there is a reasonable concern about the increased risk of SSI in patients using bDMARDs compared with csDMARDs.

SSI is one of the most devastating complications after surgery, especially joint-replacement surgery. It is thus important to clarify the effects of bDMARDs on the risk of SSI. Despite the scientific and statistical limitations related to the ethical and clinical aspects of this issue, the current review concludes from the 10 included studies that the use of a bDMARD appears to increase the rate of SSI slightly, especially after large joint-replacement surgery. Several articles have reported infection rates of 0% to 6.5%, although some of these reports lacked controls or sufficient data for statistical analysis (23-29). Johnson recently reported a slightly higher rate of SSI in a group of patients taking anti-TNF-α agents (3.26%, 3/92) compared with a control group (2.10%, 3/143) (30). These results seem to support our conclusion. However, the data are far from sufficient

to justify applying them to specific strategic therapies or preventive interventions in clinical practice. Further collection and analysis of data are needed to be able to draw more reliable, precise conclusions.

Delayed wound healing has received much less attention from physicians because the consequences of this complication are usually less severe than those of SSI. However, delayed wound healing can last a long time and can be annoying to patients. It can also lead to superficial infection, especially in the ankle and foot, and to intractable osteomyelitis or deep infection of an implant in the worst-case scenario. Fewer articles focused on this topic, but the present analysis found that the rates of delayed wound healing are similar between bDMARDs and csDMARDs. One article reported a high rate of this complication in patients taking tocilizumab (16), and clinicians should continuously beware of this topic.

TNF-α inhibitors were first introduced into clinical practice for RA treatment and are used worldwide, and so it is reasonable that there are more data for TNF-α inhibitors than for other bDMARDs. IL-6 inhibitors (e.g., tocilizumab) and T cell or B cell function modifiers are being used increasingly, but reports about these bDMARDs are still lacking. The available data for IL-6 inhibitors appear to show similar infection rates to those for other bDMARDs (7, 8, 11, 12), although Momohara et al. reported a higher rate of delayed wound healing in patients receiving tocilizumab than seen in normal practice (16). This finding and the underlying mechanism require confirmation. Godot et al. recently reported that, of 94 orthopedic surgeries on patients with RA who received rituximab, six patients (6.4%) experienced a superficial or deep infection (31). This rate does not seem higher than that for other bDMARDs. Nishida et al. reported a small case series of treatment with abatacept (32), but the effects of T cell function modifiers should be observed in a large number of cases. This project is now underway.

One of the current interests in relation to the use of bDMARDs is the perioperative discontinuation of these drugs. If bDMARDs increase the rates of SSI and delayed wound healing, it may be better to stop these drugs before surgery. This is one reason why some guidelines suggest discontinuation of bDMARDs for a certain time before and after an operation (33, 34). Conversely, several reports have shown that continuation of bDMARDs does not increase the rate of SSI and suggested justification of continuation of the drug when it is needed (15, 23-26, 28, 30, 35), while otherwise was documented by an article (36). There is insufficient literature on this subject (21), and further studies are required to draw a definite conclusion. Given that the most serious concern about discontinuation of bDMARDs is a flare-up of disease activity, compared with the most serious concern about continuation, namely SSI, our analysis suggests that discontinuation during the perioperative period should be considered unless a reasonable factor to warrant continuation exists.

This study has several limitations. First, the articles reviewed were mostly retrospective single-center observational cohort studies. One prospective cohort study had only a small sample size with high bias (13). Prospective randomized studies cannot be conducted from an ethical point of view, and the level of evidence was, and will always be, less than optimum. Second, surgery inevitably involves a variety of uncontrollable biases, such as surgical indications and the backgrounds of the patient and surgeon. This unavoidably leads to ambiguity when drawing conclusions from this type of study, even in a systematic review. We conducted a meta-analysis, but the results should be interpreted with caution in mind. Third, the definitions of SSI and delayed wound healing are inconsistent between studies, and several articles included in our analysis did not describe the definitions

sufficiently. Finally, new medications are being developed, and the indications for medication change accordingly. Therefore, at any given time, there will always be insufficient evidence on newly developed drugs. However, information about new drugs should be collected and published as soon as practical to help surgeons avoid surgical complications.

In summary, the use of bDMARDs appears to increase the rate of SSI slightly, especially after large joint-replacement surgery. The risk of delayed wound healing does not appear to be increased by the use of bDMARDs. The use of bDMARDs appears to have certain effects on perioperative complications of orthopedic surgery, and these medications should be used with appropriate caution. The slight increase in the risk of SSI in patients taking bDMARDs should not prevent consideration of an appropriate combination of bDMARDs and orthopedic surgery.

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Conflict of interest

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Figure legends

Figure 1. Literature search of 75 articles. Twelve articles were met the inclusion criteria. Ten articles were used for meta-analyses.

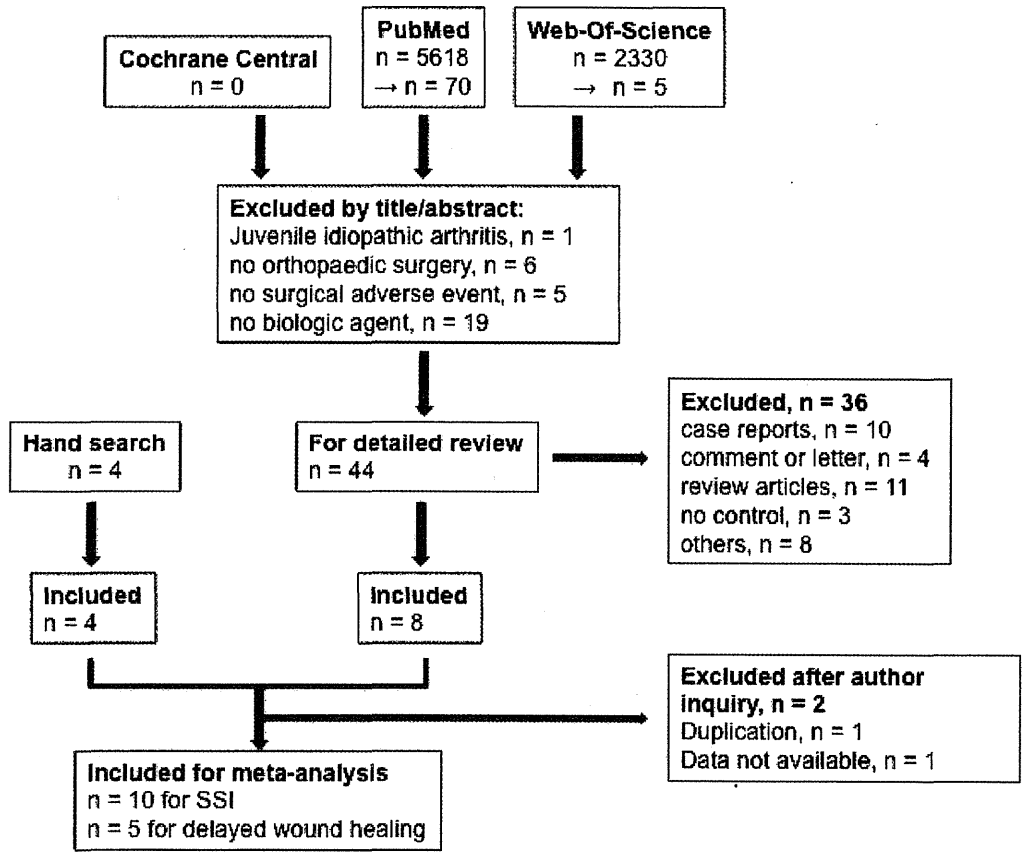

Figure 2. Meta-analyses of SSI and delayed wound healing

Fig. 2a

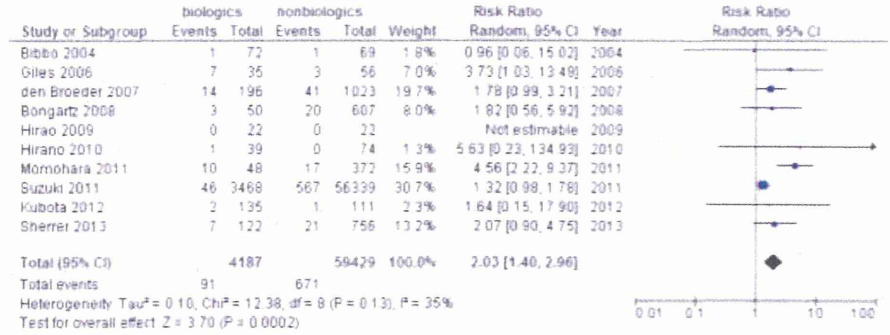

Fig. 2b

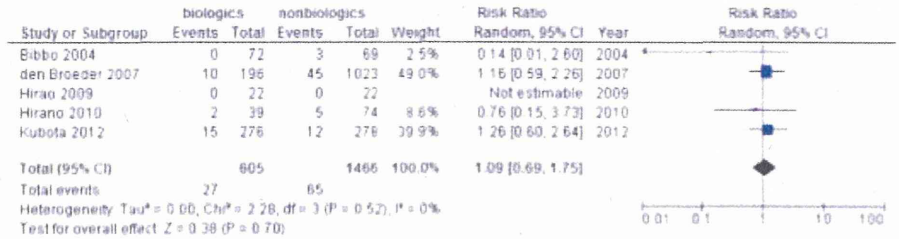

Table legends

Table 1. Study and patient characteristics for the included studies

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SHORT COMMUNICATION

The risk of serious infection in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors decreased over time: a report from the registry of Japanese rheumatoid arthritis patients on biologics for long-term safety (REAL) database

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Abstract To investigate changes in the risk for serious infections (SIs) over time in Japanese rheumatoid arthritis (RA) patients treated with tumor necrosis factor inhibitors (TNFIs). This prospective cohort study included Japanese RA patients who began treatment with a TNFI from 2005 to 2007 (2005 group, $n = 716$, 634.2 patient years [PY]) and from 2008 to 2011 (2008 group, $n = 352$, 270.1 PY) at the time or after their enrollment in the registry of Japanese RA patients on biologics for long-term safety (REAL) database. Patients were observed for 12 months or until discontinuation of their initial TNFI in the REAL database. Drug discontinuation reasons and retention rates were analyzed. Incidence rates of serious adverse events (SAEs) were calculated with 95 % confidence intervals (CIs). The Cox proportional hazard model was applied to estimate the risk for SIs. The retention rate in the 2008 group was significantly lower than the 2005 group ($p < 0.001$). Discontinuation rates due to lack of efficacy or good control for the 2008 group were significantly higher than the 2005 group ($p < 0.001$). The crude incidence rate ratios comparing the 2008 group with the 2005 group for SAEs were 0.93 (95 % CI 0.65–1.34) and for SIs were 0.50 (0.24–1.03). The 2008 group had significantly lower risk for SIs than the 2005 group after adjusting for covariates (hazard ratio: 0.43 [0.20–0.93]). These results indicate significant decrease of the risk for SIs with TNFI treatment over time; this may be explained by evidence-based risk management of RA patients given TNFIs.

Keywords Rheumatoid arthritis · Epidemiology · Tumor necrosis factor inhibitor · Infection · Risk

Ryoko Sakai and Soo-Kyung Cho have contributed equally to this work.

For the REAL study group. The REAL study group is given in "Appendix".

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Introduction

Tumor necrosis factor inhibitor (TNFI), the first approved biological disease-modifying antirheumatic drug (biological DMARD), has been widely used to treat patients with rheumatoid arthritis (RA) [1–3]. In 2003, infliximab (IFX) was the first approved biological DMARD for treatment of RA in Japan, followed by etanercept (ETN) in 2005, adalimumab (ADA) in 2008, golimumab in 2012, and certolizumab pegol in 2013 [4]. The data from postmarketing surveillance programs (PMS) implemented for these TNFIs by pharmaceutical companies [5–7], and those from prospective cohort studies for RA patients given TNFIs [8–10] have provided indispensable evidence for clinical practice.

The effectiveness and safety of a drug are strongly influenced by the selection of patients for whom it is prescribed. The launch of a new drug with indications similar to those of an older drug creates a situation where patients with a most suitable profile are "channeled" into the new therapy, thus creating differences in baseline clinical profiles from patients who were treated with the original drug. Such differences cause potential bias in estimation of drug effectiveness and safety [11]. The emergence of new clinical evidence leads to changes in the prescription practice of physicians, which may also over time affect treatment response or drug safety. It has been reported that treatment responses to TNFIs were significantly improved by changing patterns in prescriptions of TNFIs [12]. However, changes in the safety profile of TNFIs have not been described.

In this study, we hypothesized that safety profiles of treatment with TNFIs have improved over time. Thus, we compared risk for SAEs, including serious infections (SIs) between patients who started TNFIs from 2005 to 2007, shortly after the approval of the first TNFI in Japan, and from 2008 to 2011.

Patients and methods

Database

The registry of Japanese RA patients on biologics for long-term safety (REAL) is a prospective cohort established to investigate the long-term safety of biologicals in RA patients. Details of the REAL have been previously described [8]. Briefly, the criteria for enrollment in the REAL include patients meeting the 1987 American College of Rheumatology (ACR) criteria for RA, and starting or switching to treatment with biologicals or starting, adding or switching to non-biological DMARDs at the time of enrollment in the database, which was started in June 2005 and closed in January 2012.

Data were retrieved from the REAL database on March 5, 2012, for this study. The REAL study was approved by the ethics committees of the participating 27 institutions. The procedures followed were in accordance with the

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Japanese guidelines for epidemiological studies and with the Helsinki Declaration of 1975, as revised in 1983. All patients in the REAL signed an informed consent form at enrollment in the REAL.

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 to the REAL data center every six months by site investigators to report occurrence of SAEs, current RA disease activity, treatments, and laboratory data [8].

Patients

By March 2012, 1,945 RA patients were registered in the REAL, of these 1,069 patients started administration of IFX, ETN, or ADA at the time of enrollment or after enrollment in the REAL. Our analysis included 716 patients who started IFX or ETN in 2005–2007 (2005 group) and 353 patients who started IFX, ETN, or ADA in 2008–2011 (2008 group).

Follow-up

The start date of the observation was the date an initial TNFI was administered to a patient. Observation was terminated: (1) 12 months after the start of the observation period, (2) on the date of death or loss to follow-up, (3) on enrollment in a clinical trial, (4) on the date of the last administration of TNFI, if therapy with the initial TNFI in the REAL was discontinued for more than 90 days, (5) on the date when the initial TNFI in the REAL was changed to another biologic, or (6) on March 5, 2012, whichever came first.

Definition of serious adverse events (SAEs)

Our definition of SAEs, including SIs, was in accordance with the International Conference on Harmonization [13]. Bacterial infections requiring intravenous administration of antibiotics and opportunistic infections were also regarded as SIs [14].

Statistical analysis

Drug retention rates were calculated by the Kaplan–Meier method and compared using the log-rank test between the two groups. Risk factors for SIs during continuous treatment with the TNFI for up to 1 year were identified using the Cox regression hazard model with the forced entry method. These statistical analyses were conducted using SPSS (version 20.0, SPSS Inc., Chicago, IL USA). All p values were two-tailed, and $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics of patients

Baseline data for the two groups are shown in Table 1. Compared with the 2005 group, the 2008 group had shorter disease duration ($p = 0.001$) and lower disease activity ($p = 0.001$) and was treated with higher doses of methotrexate ($p = 0.010$) and lower dosage of oral corticosteroids ($p < 0.001$). The rate of previous use of three or more non-biological DMARDs was lower in the 2008 group ($p = 0.001$) (Table 1). The median duration of follow-up (interquartile [IQR]) was 1.00 (IQR 0.51, 1.00) year in the 2005 group and 1.00 (IQR 1.00, 1.00) year in the 2008 group.

Types and occurrence of SAEs

During the observation period, 103 SAEs and 42 SIs in the 2005 group and 41 SAEs and 9 SIs in the 2008 group were observed. The crude incidence rate ratio (IRR) comparing the 2005 group with the 2008 group for all SAEs was 0.93 [95 % confidence interval (95 % CI) 0.65–1.34] and for SIs was 0.50 (95 % CI 0.24–1.03) (Table 2).

Drug discontinuation reasons and retention rates

There were significant differences in the reasons for discontinuation between the two groups ($p = 0.049$ by χ^2 test). The adjusted residuals indicate that a significantly higher percentage of patients in the 2008 group discontinued TNFI due to good control (Supplementary Table 1). The discontinuation rate for the 2008 group due to good control ($p < 0.001$, log-rank test) or to lack of efficacy ($p < 0.001$, log-rank test) was significantly higher than that for the 2005 group (Supplementary Figure 1).

Starting years of TNFI associated with risk for serious infection

We initially performed univariate analyses to compare patients who did and did not develop SIs (data not shown) and selected the following variables for multivariate analysis with consideration of medical significance: age, gender, presence of comorbidities, patient group (2008 vs. 2005), type of TNFI (monoclonal antibody vs. soluble receptor), and the use of oral corticosteroids at baseline. Cox

Table 1 Patient characteristics at the start of the observation period

	2005 group ($n = 716$)	2008 group ($n = 352$)	p value
Age (years)	56.1 ± 13.3	57.9 ± 14.8	0.021
Gender [female (%)]	81.8	81.2	0.814
Disease duration (years)[a]	7.0 (2.9, 14.0)	4.9 (1.8, 12.6)	0.001
DAS28(3/CRP) (number)	4.6 ± 1.2 ($n = 702$)	4.3 ± 1.3 ($n = 313$)	0.001
Steinbrocker's stage III or IV (%)[b]	53.6	37.5	<0.001
Steinbrocker's class 3 or 4 (%)[b]	29.5	21.0	0.003
Previous biologicals use (%)	11.2	17.3	0.005
Number of previous non-biological DMARDs ≥3 (%)	51.0	35.5	<0.001
MTX use (%)	68.6	80.7	<0.001
MTX dosage (mg/week)	7.5 ± 2.1	8.0 ± 2.4	0.010
Oral corticosteroid use (%)	71.2	53.7	<0.001
Corticosteroid (mg/day)[c]	5.8 ± 2.8	5.1 ± 2.5	<0.001
IFX use (%)	45.3	38.9	<0.001
ETN use (%)	54.7	26.7	
ADA use (%)	0	34.4	
Any comorbidities (%)	32.1	33.0	0.785
Chronic pulmonary diseases (%)[d]	21.2	21.9	0.809
Diabetes mellitus (%)	11.2	10.5	0.745
Liver diseases (%)	4.9	4.5	0.805
Kidney diseases (%)	3.6	1.1	0.020
TMP-SMX use (%)	2.4	19.0	<0.001

TNFI tumor necrosis factor inhibitor, *DAS28* disease activity score including 28-joint count, *CRP* C-reactive protein, *DMARDs* disease-modifying antirheumatic drugs, *MTX* methotrexate, *IFX* infliximab, *ADA* adalimumab, *ETN* etanercept, *TMP-SMX* trimethoprim-sulfamethoxazole

Values are mean ± SD unless otherwise indicated. For univariate analysis, the chi-square test for categorical variables and Mann–Whitney test were used to compare continuous variables between the two groups

[a] Values are median (interquartile)

[b] Steinbrocker classification was used to define RA disease stages and classes

[c] The oral corticosteroid dose was converted to the equivalent prednisolone dosage

[d] Pulmonary diseases include interstitial pneumonia, chronic obstructive pulmonary disease, bronchial asthma, prior pulmonary tuberculosis, and bronchiectasis

regression models reveal that the 2008 group had significantly lower risk for SIs than the 2005 group (hazard ratio: 0.43 [95 % CI 0.20–0.93], $p = 0.032$) after adjusting for the covariates (Table 3).

Comparison of disease activities between the groups

In patients with DAS28 (3/CRP) data at baseline and year 1 ($n = 540$ for 2005 group, $n = 178$ for 2008 group), the 2005 group had significantly higher DAS28 (3/CRP) scores than the 2008 group at both times (mean ± standard deviation in 2005 vs. 2008; 4.59 ± 1.23 vs. 4.32 ± 1.25 at baseline, $p = 0.011$; 2.80 ± 1.08 vs. 2.50 ± 0.97 at year 1, $p = 0.001$). A significantly higher percentage of patients in the 2008 group achieved low disease activity (DAS28 [3/CRP] <3.2) at year 1 compared with the 2005 group (80.9 % in the 2008 group, 68.7 % in the 2005 group, $p = 0.002$).

Discussion

In this study, the IR of SIs in the 2005 group was consistent with previous reports [9, 14], while the 2008 group showed a 50 % reduction in the IR of SIs, without statistical significance. Patients in the 2005 group appeared to be more susceptible to SIs than those in the 2008 group because of higher dosage of oral corticosteroids, higher disease activity, more advanced disease, and poorer physical function at baseline, all of which were identified as risk factors for SIs [8, 15]. After adjusting for these baseline characteristics, patients in the 2008 group had significantly lower risk for SIs (Table 3) than those in the 2005 group.

Several factors can be considered as determinants of the decreased risk for SIs. The first contributing factor is the safety results from PMS studies. The PMS studies of TNFIs in Japan revealed the types, incidence rates, and risk factors for infections [5–7]. Risk factors, such as older age,

Table 2 Number and incidence rates of serious adverse events in rheumatoid arthritis patients

	TNFI 2005 634.2 PY IR (/100PY)	TNFI 2008 270.1PY IR (/100PY)	TNFI 2008 vs. TNFI 2005, Crude IRR[a] (95 % CI)
ALL SAEs			
Number of events	103	41	0.93 (0.65–1.34)
IR/100 PY (95 % CI)	16.2 (13.3–19.6)	15.2 (11.1–20.4)	
Serious infections (SIs)			
Number of events	42	9	0.50 (0.24–1.03)
IR/100 PY (95 % CI)	6.62 (4.84–8.86)	3.33 (1.65–6.08)	
Serious respiratory tract infections			
Number of events	27	5	0.43 (0.17–1.13)
IR/100 PY (95 % CI)	4.26 (2.87–6.10)	1.85 (0.70–4.06)	
Other infections			
Number of events	15	4	0.63 (0.21–1.89)
IR/100 PY (95 % CI)	2.37 (1.38–3.80)	1.48 (0.50–3.52)	
Pulmonary diseases except for infection			
Number of events	11	6	1.28 (0.47–3.46)
IR/100 PY (95 % CI)	1.73 (0.92–3.00)	2.22 (0.92–4.58)	
Malignancies			
Number of events	3	5	3.91 (0.93–16.38)
IR/100 PY (95 % CI)	0.47 (0.13–1.26)	1.85 (0.70–4.06)	
Others			
Number of events	47	21	1.05 (0.63–1.75)
IR/100 PY (95 % CI)	7.41 (5.51–9.76)	7.77 (4.96–11.66)	

TNFI tumor necrosis factor inhibitor, *PY* patient year, *IR* incidence rate, *IRR* incidence rate ratio, *CI* confidence interval, *SAE* serious adverse event

[a] Crude incidence rate per 100 PY and crude incidence rate ratio with their 95 % CI were calculated for each category of serious adverse events occurring from the first to the last dose of infliximab, etanercept, or adalimumab

Table 3 Multivariate analysis of independent risk factors for serious infections in rheumatoid arthritis patients

All values at baseline	Hazard ratio (95 %CI)	*p* value
Age by decade	1.76 (1.31–2.39)	<0.001
Gender (male)	0.45 (0.18–1.16)	0.099
Steinbrocker's class 3 or 4 (vs. 1 or 2)	1.26 (0.68–2.32)	0.460
Comorbidities yes (vs. no)[a]	2.23 (1.18–4.22)	0.014
Concomitant use of corticosteroid	1.79 (0.85–3.75)	0.126
2008 group (vs. 2005)	0.43 (0.20–0.93)	0.032
IFX or ADA (vs. ETN)	1.63 (0.88–3.03)	0.124

Cox hazard model analysis, adjusted for the variables included in the table

CI confidence interval, *IFX* infliximab, *ADA* adalimumab, *ETN* etanercept

[a] Comorbidities include pulmonary, liver, kidney diseases, and diabetes mellitus

presence of diabetes mellitus, or pulmonary diseases, were incorporated into the Japanese guidelines for treatment with TNFIs [3] and updated periodically thereafter. Japanese guidelines for treatments with TNFIs state that administration of TNFIs to patients with any of the above risk factors should be carefully considered. The guidelines have enabled Japanese rheumatologists to select appropriate patients for TNFI therapy. The second factor is the improved risk management of RA patients given these drugs. Bacterial pneumonia has been identified as the most frequent infection in Japanese RA patients given TNFIs, and Japanese RA patients have relatively higher incidence of tuberculosis and *Pneumocystis jirovecii* pneumonia than RA patients in other countries [5–7]. Hence, pneumococcal vaccination and chemoprophylaxis with isoniazid or trimethoprim-sulfamethoxazole (TMP-SMX) for high-risk patients have been recommended in the Japanese guidelines for treatment with TNFIs since 2007 [3]. In the patient population of this study, a significantly higher percentage of patients received TMP-SMX in the 2008 group compared with the 2005 group (Table 1). The third factor is the approval of alternative treatments, such as tocilizumab and abatacept. In this population, the discontinuation rate for the 2008 group due to lack of efficacy was significantly higher than that for the 2005 group (Supplementary Figure 1). In the 2008 group, some patients whose disease activities could not be sufficiently controlled by TNFIs were switched to other classes of biological DMARDs and excluded from this analysis.

Recent changes in treatment for RA are possible unadjusted confounders of the lower risk for SIs seen in the 2008 group. The ACR 2008 recommendations for the use

of non-biological and biological DMARDs in RA [16], the European League Against Rheumatism (EULAR) 2010 recommendations for the management of RA [17], and the updated guideline for TNFIs by the Japan College of Rheumatology (JCR) in 2012 [18] have enabled rheumatologists to begin treatment with a TNFI at an earlier stage. Although patients in the 2008 group in this study were not influenced by the updated JCR guideline, because they started TNFIs between 2008 and 2011, the ACR and EULAR recommendations may have influenced the use of TNFIs in that group. Disease duration in the 2008 group was significantly shorter than that in the 2005 group (Table 1), indicating that the rheumatologists in the participating institutions started TNFIs for their RA patients earlier in the course of disease. Generally, patients with shorter disease durations tend to have lower prevalence of comorbidities, earlier stages of RA, better physical function, and lower rates and dosages of concomitant corticosteroids than those with longer disease duration [19]. However, we had already incorporated these factors as covariates in the multivariate analysis.

There are limitations to this study. First, the number of patients in the 2008 group was smaller than in the 2005 group, which could affect the sensitivity of the analysis. Second, we could not adjust for control of disease activity in the multivariate analysis because data were lacking for year 1 in some patients. Because it has been reported that higher disease activity was associated with the development of SIs [8, 20], better control of disease activity in the 2008 group may have led to reduced risk for SIs. Third, we could not use the history of previous infections and health assessment questionnaire scores as covariates in the multivariate analysis because the REAL database lacks these data.

In conclusion, the adjusted risk for SIs in Japanese RA patients receiving TNFIs decreased significantly over time. This observation may partly be explained by the progress in evidence-based risk management during treatment with TNFI and indicates that continuing pharmacovigilance activity is a requisite for proper use of TNFIs in clinical practice.

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Appendix

The investigators of the REAL study group and their affiliates who contributed to data collection were Michi Tanaka (Tokyo Medical and Dental University); Shintaro Hirata, Kazuyoshi Saito (University of Occupational and Environmental Health); Taichi Hayashi (University of Tsukuba); Yoshiaki Ishigatsubo (Yokohama City University); Tatsuya Atsumi (Hokkaido University); Shoko