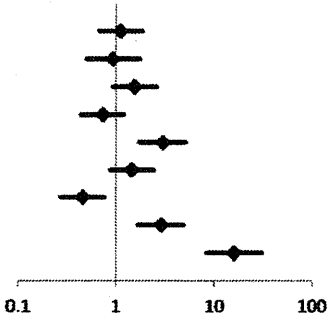
Fig. 2 Factors associated with achievement of low disease activity at 52 weeks

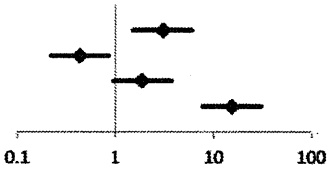
A

Univariate analysis	OR (95% CI)	p-value
Age, <65 years	1.122 (0.679-1.856)	0.652
Male	0.933 (0.495-1.762)	0.831
Disease duration, <10 years	1.563 (0.935-2.611)	0.088
RF positive	0.730 (0.439-1.212)	0.223
no previous biological DMARDs	3.030 (1.792-5.123)	<0.001
concomitant MTX	1.471 (0.888-2.436)	0.134
concomitant PSL	0.455 (0.272-0.758)	0.003
mHAQ, <0.5	2.907 (1.729-4.885)	<0.001
DAS28-CRP at 12 weeks, <3.3	16.040 (8.565-30.040)	<0.001



B

Multivariate analysis	Adjusted OR (95% CI)	p-value
no previous biological DMARDs	3.049 (1.551-5.994)	0.001
concomitant PSL	0.429 (0.218-0.846)	0.015
mHAQ, <0.5	1.880 (0.958-3.689)	0.067
DAS28-CRP at 12 weeks, <3.3	15.244 (7.682-30.249)	<0.001



(**A**) Univariate logistic regression analysis. (**B**) Multivariate logistic regression analysis. PSL: prednisolone; mHAQ: modified HAQ; OR: odds ratio; LDA: low disease activity.

scores at 12 and 24 weeks. The AUC was also almost equivalent at 12 and 24 weeks, and there was no significant difference in the proportion of patients who achieved LDA at 52 weeks. Predictability at baseline and 4 weeks was lower than at those two timepoints. Although a longer observational period allows for a more accurate prediction of long-term response, a longer period of persistent active arthritis leads to irreversible joint destruction and disability. Therefore, a major challenge in the management of RA is to predict long-term response in as short a period as possible to minimize patient exposure to ineffective therapies. It appears that 12 weeks after starting abatacept treatment is an adequate time point for predicting clinical response at 52 weeks. The cut-off DAS28 score of 3.3 at 12 weeks should not be a strict value, but it may help physicians decide whether to continue abatacept therapy in patients who have not achieved LDA at this time.

This report is the first to suggest an adequate observational period before judging and predicting the long-term clinical response to abatacept. Several groups have conducted similar studies to determine the adequate period for predicting the long-term efficacy of TNF blockade therapy [7, 8]. According to those reports, 3 months appeared to be sufficient. The AMPLE trial, a head-to-head comparison of s.c. abatacept *vs* adalimumab for RA, revealed that clinical efficacy and response speed were comparable between these different biologic DMARDs [14]. Our current findings suggest that the long-term clinical efficacy of abatacept can be judged and predicted as early as TNF blockade therapy.

As baseline factors, multivariate logistic regression analysis demonstrated that previous biologic DMARD history and concomitant PSL therapy were independent negative predictors of LDA achievement at 52 weeks. We previously reported that previous biologic DMARD history was negatively associated with LDA at 24 weeks [5]. Abatacept appears to demonstrate its maximal clinical performance when used as a first biologic DMARD, similar to anti-TNF agents [15].

The present study suggests that the long-term response to abatacept may be impaired by concomitant PSL. No data are available on the effect of concomitant steroids on the long-term efficacy of abatacept. The effects of concomitant steroid use on the clinical efficacy of biologic DMARDs differ between agents, and the conclusions are inconsistent [16–18]. Further clinical data would be necessary to resolve these discrepancies.

One important finding in this study was that concomitant MTX was not an independent predictor of clinical response, in contrast to what was found for TNF inhibitors. Previous studies have emphasized that TNF inhibitors required sufficient concomitant MTX therapy to maximize their clinical efficacy against RA [19]. A smaller combined effect with MTX is a unique characteristic of abatacept relative to TNF inhibitors.

This study has several limitations. First, given the retrospective observational setting, a future prospective study would be necessary, especially to verify the external validity of our findings or our DAS28 cut-off score. In addition, the Steinbrocker's stage classification could

have been underestimated, as these classifications were based on each attending physician's report and no data are available on when the radiographs used for evaluation were taken relative to participant entry into this study. In addition, sequential radiographic data were not available. Given the importance of joint protective effects in demonstrating clinical efficacy, evaluating radiographic changes in patients treated with abatacept will be necessary in the future. Finally, the present study findings were all based on the use of i.v. abatacept. However, the use of a new s.c. formulation is now widespread, and further study is needed to identify whether our above results apply to s.c. abatacept as well.

Conclusion

It appears that 12 weeks after starting abatacept treatment is an adequate time point at which clinical response at 52 weeks can be predicted. This strategy comports with the 2013 European League Against Rheumatism recommendation update that a therapy should be adjusted if there is no improvement by at most 3 months after the start of treatment or if the target has not been reached by 6 months [20].

Rheumatology key messages

- DAS28-CRP at 12 weeks independently and strongly predicts low RA disease activity achievement at 52 weeks.
- Twelve weeks is an adequate observational period for predicting abatacept efficacy at 52 weeks in patients with RA.
- Twelve weeks is sufficient to decide on abatacept continuation in patients with RA and fits the EULAR recommendation.

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References

1 Kremer JM, Genant HK, Moreland LW *et al.* Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med 2006;144:865–76.

2 Westhovens R, Robles M, Ximenes AC *et al.* Clinical efficacy and safety of abatacept in methotrexate-naive patients th early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis 2009;68:1870–7.

3 Kremer JM, Russell AS, Emery P *et al.* Long-term safety, efficacy and inhibition of radiographic progression with abatacept treatment in patients with rheumatoid arthritis and an inadequate response to methotrexate: 3-year results from the AIM trial. Ann Rheumatic Dis 2011;70: 1826–30.

4 Leffers HC, Ostergaard M, Glintborg B *et al.* Efficacy of abatacept and tocilizumab in patients with rheumatoid arthritis treated in clinical practice: results from the nationwide Danish DANBIO registry. Ann Rheum Dis 2011; 70:1216–22.

5 Takahashi N, Kojima T, Terabe K *et al.* Clinical efficacy of abatacept in Japanese rheumatoid arthritis patients. Mod Rheumatol 2013;23:904–12.

6 Takahashi N, Kojima T, Kaneko A *et al.* Clinical efficacy of abatacept compared to adalimumab and tocilizumab in rheumatoid arthritis patients with high disease activity. Clin Rheumatol 2014;33:39–47.

7 Vander Cruyssen B, Van Looy S, Wyns B *et al.* Four-year follow-up of infliximab therapy in rheumatoid arthritis patients with long-standing refractory disease: attrition and long-term evolution of disease activity. Arthritis Res Ther 2006;8:R112.

8 van der Heijde D, Keystone EC, Curtis JR *et al.* Timing and magnitude of initial change in disease activity score 28

predicts the likelihood of achieving low disease activity at 1 year in rheumatoid arthritis patients treated with certolizumab pegol: a *post-hoc* analysis of the RAPID 1 trial. J Rheumatol 2012;39:1326–33.

9 Kojima T, Kaneko A, Hirano Y *et al.* Study protocol of a multicenter registry of patients with rheumatoid arthritis starting biologic therapy in Japan: Tsurumai Biologics Communication Registry (TBCR) study. Mod Rheumatol 2012;22:339–45.

10 Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. J Amer Med Assoc 1949; 140:659–62.

11 Matsui T, Kuga Y, Kaneko A *et al.* Disease Activity Score 28 (DAS28) using C-reactive protein underestimates disease activity and overestimates EULAR response criteria compared with DAS28 using erythrocyte sedimentation rate in a large observational cohort of rheumatoid arthritis patients in Japan. Ann Rheum Dis 2007;66:1221–6.

12 Inoue E, Yamanaka H, Hara M, Tomatsu T, Kamatani N. Comparison of Disease Activity Score (DAS)28- erythrocyte sedimentation rate and DAS28- C-reactive protein threshold values. Ann Rheum Dis 2007;66:407–9.

13 Akobeng AK. Understanding diagnostic tests 1: sensitivity, specificity and predictive values. Acta Paediatr 2007;96: 338–41.

14 Weinblatt ME, Schiff M, Valente R *et al.* Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. Arthritis Rheum 2013;65:28–38.

15 Kaneko A, Hirano Y, Fujibayashi T *et al.* Twenty-four-week clinical results of adalimumab therapy in Japanese patients with rheumatoid arthritis: retrospective analysis for the best use of adalimumab in daily practice. Mod Rheumatol 2013;23:466–77.

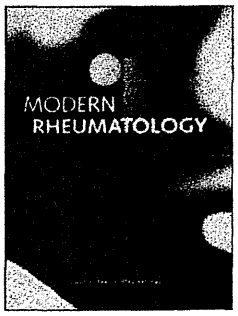
16 Pers YM, Fortunet C, Constant E *et al.* Predictors of response and remission in a large cohort of rheumatoid arthritis patients treated with tocilizumab in clinical practice. Rheumatology 2014;53:76–84.

17 Takeuchi T, Tanaka Y, Amano K *et al.* Clinical, radiographic and functional effectiveness of tocilizumab for rheumatoid arthritis patients—REACTION 52-week study. Rheumatology 2011;50:1908–15.

18 Zintzaras E, Dahabreh IJ, Giannouli S, Voulgarelis M, Moutsopoulos HM. Infliximab and methotrexate in the treatment of rheumatoid arthritis: a systematic review and meta-analysis of dosage regimens. Clin Ther 2008;30: 1939–55.

19 Katchamart W, Johnson S, Lin HJ *et al.* Predictors for remission in rheumatoid arthritis patients: a systematic review. Arthritis Care Res 2010;62:1128–43.

20 Smolen JS, Landewe R, Breedveld FC *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73: 492–509.



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ORIGINAL ARTICLE

High prevalence of cardiovascular comorbidities in patients with rheumatoid arthritis from a population-based cross-sectional study of a Japanese health insurance database

Ryoko Sakai[1,2], Fumio Hirano[1,2], Mari Kihara[1,2], Waka Yokoyama[1,2], Hayato Yamazaki[1,2], Sayoko Harada[1,2], Toshihiro Nanki[1,2], Ryuji Koike[1,2,3], Nobuyuki Miyasaka[4], and Masayoshi Harigai[1,2]

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Abstract

Objective: To reveal any association between rheumatoid arthritis (RA) and cardiovascular comorbidities using a Japanese health insurance database.

Method: This population-based cross-sectional study was conducted using health insurance data provided by the Japan Medical Data Center Co., Ltd. We identified 2762 RA subjects having RA diagnostic codes (ICD10 codes; M05, M060, M062–63, M068–069) with at least two physician visits more than two months apart between June 2011 and May 2012 (RA group, $n = 2762$). We selected age- (±5 years), sex-, and study period-matched non-RA subjects (non-RA group, $n = 27{,}620$). We compared the prevalence of cardiovascular and related comorbidities (ischemic heart diseases [IHD], cerebral infarction, hypertension [HT], dyslipidemia [DL], and diabetes mellitus [DM]) between these groups and investigated the association between RA and cardiovascular comorbidities using a conditional logistic regression analysis.

Results: The prevalence of all the investigated comorbidities in the RA group was significantly higher compared to the non-RA group. Odds ratios [95% confidence interval] of RA for IHD and cerebral infarction were 2.0 [1.5–2.5] and 3.1 [2.2–4.2] respectively, after adjusting for HT, DL, and DM.

Conclusions: This study revealed for the first time in the Japanese population that RA was significantly associated with cardiovascular comorbidities.

Keywords

Comorbidity, Epidemiology, Rheumatoid arthritis, Prevalence

History

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease with high prevalence and risk of various comorbidities [1–4]. Comorbidities are known to affect prognosis and quality of life of patients with RA [5], impede proper treatment for the primary disease [6,7], and cause work disability [8] and higher medical costs [9]. Among comorbidities in patients with RA, cardiovascular diseases (CVD), including ischemic heart diseases (IHD) and cerebrovascular diseases, have grown in importance for patients and health care providers; this is because excess mortality of patients with RA has been attributed to CVD [10]. The CVD mortality risk of patients with RA was 1.5 times higher than that of the general population [11]. Previous studies in Western countries have reported the incidence rate and risk factors for CVD using RA registries and claims data [11–15]. Not only traditional risk factors, such as older age, obesity, hypertension (HT), and dyslipidemia (DL), but RA-specific risk factors attributable to chronic inflammation, have been associated with accelerated atherosclerosis in RA patients [2,3,16,17]. Treatments for RA also influence the risk for CVD. For example, corticosteroids have been reported to increase the risk of CVD [18–20]. Some epidemiological studies have shown that antirheumatic medications, such as methotrexate (MTX) and tumor necrosis factor inhibitors, significantly decreased the risk for CVD by suppressing chronic inflammation [21–25]. These important lines of evidence help rheumatologists understand the high risk for CVD in patients with RA.

The European League Against Rheumatism has established evidence-based recommendations for cardiovascular risk management in patients with inflammatory arthritis, including RA [26]. In consideration that differences in genetic background, lifestyle, quality of medical service, and healthcare environment could affect the incidence rate and prevalence of cardiovascular comorbidities, it is necessary to investigate cardiovascular comorbidities in various countries for their proper management in patients with RA. In Asia, only one study compared the risk of acute myocardial infarction in RA patients with non-RA controls using the national health insurance database in Taiwan [27]. To date, there have been no reports investigating the prevalence of comorbidities, such as CVD, in Japanese RA patients using a large population-based database.

The aims of this study were to compare the prevalence of cardiovascular and related comorbidities between RA and non-RA

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subjects using data from Japanese insurance claims, and to investigate any association between RA and cardiovascular comorbidities.

Methods

Study population and study design

We used claims data from the Japan Medical Database Center Co., Ltd, Tokyo, Japan (JMDC), the details of which have been described in previous reports [28,29]. Briefly, JMDC has accumulated health insurance claims data since January 2005 and, as of October 2013, the number of subjects reached over one million. The JMDC claims data include medical claims for inpatients, outpatients, and pharmacy benefits from 40 employment-based health insurance societies throughout Japan. We designed a population-based cross-sectional study using claims data between December 2010 and May 2012. We accepted individuals as RA subjects if they had at least two physician visits more than two months apart with RA diagnostic codes [30] (ICD10 codes; M05, M060, M062, M063, M068, and M069) between June 2011 and May 2012 (RA group, $n=2762$). The month that a patient was first given one of the RA diagnostic codes was defined as the index month. Among individuals who did not meet these criteria, we selected age- (±5 years), sex-, and study period-matched non-RA subjects at a ratio of one RA subject to ten non-RA subjects (non-RA group, $n=27,620$). The study period was 12 months at most, to include the 6 months before and after the index month for each patient. This study did not require approval by the institutional review board because we used only unlinkable anonymized data in this study.

Definition of comorbidities

Patients who had the ICD 10 codes (ischemic heart diseases ([IHD) [I20–22, I25], cerebral infarction [I63], HT [I10–I15], DL [E78], and diabetes mellitus (DM) [E10–14]), and were prescribed medicine for the comorbidities at least once during the study period were deemed to have the comorbidities. The medications for the comorbidities, defined according the European Pharmaceutical Marketing Research Association anatomical classification guidelines 2013, were as follows: (i) for IHD: C1D coronary therapy excluding calcium antagonists and nitrites, C1E nitrites and nitrates, C7 beta-blocking agents, C8 calcium antagonists, B1A vitamin K antagonists, B1C platelet aggregation inhibitors, B1E direct thrombin inhibitors, and B1X other antithrombotic agents; (ii) for cerebral infarction: B1A vitamin K antagonists, B1C platelet aggregation inhibitors, B1E direct thrombin inhibitors, and B1X other antithrombotic agents; (iii) for HT: C2 antihypertensives, C3 diuretics, C7 beta-blocking agents, C8 calcium antagonists, C9 agents acting on the renin-angiotension system, and C11 cardiovascular multi-therapy combination products; for DM: A10C human insulin and analogues, A10H sulfonylurea antidiabetics, A10J biguanide antidiabetics, A10K glitazone antidiabetics, A10L alpha-glucosidase inhibitor antidiabetics, A10M glinide antidiabetics, A10N DPP-IV inhibitor antidiabetics, and A10S GLP-1 agonist antidiabetics; and for DL: C10A lipid-regulating/anti-atheroma preparations, C10B anti-atheroma preparations of natural origin, C10C lipid regulators in combination with other lipid regulators, C11A lipid-regulating cardiovascular multi-therapy combination products.

Statistical analysis

Descriptive statistics were used to examine patient characteristics and drug utilization. We calculated odds ratios (ORs) with 95% confidence intervals (95% CIs) for the comorbidities of interest.

Table 1. Characteristics of rheumatoid arthritis and non-rheumatoid arthritis groups.

Characteristics	RA group ($n=2762$)	Non-RA group ($n=27,620$)
Median age, years [interquartile range]	51.0 [42.0–58.0]	51.0 [42.0–59.0]
Age (years)		
≤39, %	19.0	19.2
40–49, %	26.2	24.9
50–59, %	34.3	32.8
≥60, %	20.6	23.2
Female, %	74.1	74.1
Use of corticosteroids*, %	38.8	0.4
Dose of corticosteroids**, mg/day	5.0 [2.5–9.7]	10.0 [5.0–20.0]
Observation period (months)	11.8 ± 0.8	11.8 ± 0.8

RA, rheumatoid arthritis; SD, standard deviation.

*Use of oral corticosteroids was defined as when patients had at least one prescription of these drugs during the index month or the following two months.

**The oral corticosteroid dose was converted to the equivalent prednisolone dosage. Median values [interquartile range] are shown.

We calculated prevalence and ORs for RA versus non-RA separately by age (<45, ≥45 and <60, ≥60) and sex. The associations between RA and comorbidities were investigated adjusting for the presence of HT, DL, and DM using conditional logistic regression analysis. In the RA group, we assessed the associations between drug utilization with comorbidities using logistic analysis. In addition, we used the Benjamini and Hochberg (BH) method [31] to correct for multiple comparisons. The BH method is an approach to multiple comparison problems that controls the False Discovery Rate (FDR). All analyses were performed using SPSS software, version 20.0 (version 20.0, SPSS Inc., Chicago, IL).

Results

Study population

Characteristics of 2762 RA subjects and 27,620 non-RA subjects are shown in Table 1. Both groups were followed for a mean of 11.8 months. In both groups, the median age was 51.0 years and the percentage of females was 74.1%. The percentage of patients given oral corticosteroids was 38.8% in the RA group and 0.4% in the non-RA group. The median prednisolone-equivalent dosage of oral corticosteroids in the RA group was 5.0 mg/day and 10.0 mg/day in the non-RA group. In the RA group, 51.6% of subjects had at least one prescription for conventional synthetic DMARDs and 11.5% for biological DMARDs (Table 2) in the index or the following two months. Methotrexate was prescribed in 32.2% of the RA group at a median dosage of 6.0 mg/week. Tacrolimus, leflunomide, or mizoribine was prescribed in 5.7% of the RA group.

Comparison of prevalence of comorbidities between the RA group and the non-RA group

The prevalence and ORs of the investigated comorbidities for RA and non-RA groups are shown in Table 3; all the ORs [95% CI] were significantly increased, 3.84 [3.15–4.69] for IHD, 4.02 [3.03–5.32] for cerebral infarction, 3.12 [2.83–3.44] for HT, 3.21 [2.89–3.56] for DL, and 2.54 [2.13–3.02] for DM. We then calculated the prevalence and ORs of IHD and cerebral infarction stratified by age and sex (Table 4). In both sexes, ORs of IHD and cerebral infarction were significantly increased (IHD, 3.76 [2.92–4.84] for all females and 4.01 [2.89–5.55] for all males; cerebral infarction, 3.85 [2.72–5.47] for all females, 4.35 [2.71–7.00] for all males).

For both comorbidities stratified by age, the RA group had higher prevalence than the non-RA group in every age stratum in both sexes with higher OR in the younger strata. The prevalence rates of IHD in RA subjects <45 years-old (1.23 [0.63–2.41] for females, 2.39 [1.01–5.40] for males) were numerically higher than that of the non-RA subjects ≥45, <60 years-old (0.73 [0.58–0.93] for females, 1.73 [1.35–2.23] for males). The same pattern was observed when comparing the RA subjects ≥45, <60 years-old (3.62 [2.61–4.99] for females, 9.29 [6.72–12.7] for males), and non-RA subjects ≥60 (3.24 [2.77–3.78] for females, 4.67 [3.76–5.79] for males) (Table 4). For cerebral infarction, the prevalence in the RA subjects <45 years-old (1.23 [0.63–2.41] for females, 2.39 [1.01–5.40] for males) were as high as those of the non-RA subjects ≥60 (1.71 [1.38–2.12] for females, 2.39 [1.76–3.24] for males) (Table 4). Similar results were obtained when stratified by other age categories (<40, ≥40 and <60, ≥60; data not shown).

Table 2. Use of disease modifying anti-rheumatic drugs in the RA group*.

DMARDs	RA group (n=2762)
Use of conventional synthetic DMARDs, %	51.6
Methotrexate, %	32.2
Methotrexate, mg/week**	6.0 [5.0–8.0]
Other immunosuppressive DMARDs†, %	5.7
Use of biological DMARDs, %	11.5
Infliximab, %	3.2
Etanercept, %	5.5
Adalimumab, %	1.2
Tocilizumab, %	1.2
Abatacept, %	0.3
Golimumab, %	0.1

DMARDs, disease modifying anti-rheumatic drugs; RA, rheumatoid arthritis.
*Use of drugs was defined as when patients had at least one prescription of these drugs in the index month or the following two months.
**Median values [interquartile range] are shown among MTX users.
†Immunosuppressive DMARDs include tacrolimus, leflunomide, and mizoribine.

Associations between RA and cardiovascular comorbidities

To estimate the associations between RA and cardiovascular comorbidities, a conditional logistic regression analysis was applied (Table 5). ORs [95% CI] (RA versus non-RA group) were significantly elevated after adjusting for HT, DL, and DM (IHD 1.97 [1.54–2.51], $p<0.001$; cerebral infarction 3.06 [2.20–4.24], $p<0.001$). The presence of HT (12.5 [9.57–16.4] for IHD, 6.17 [4.27–8.92] for cerebral infarction), DL (2.83 [2.22–3.61] for IHD, 2.97 [2.12–4.16] for cerebral infarction), and DM (1.43 [1.05–1.95] for IHD, 2.08 [1.39–3.13] for cerebral infarction) were also significantly associated with both comorbidities. After corrections for multiple comparisons using False Discovery Rate and BH methods [31], all ORs remained statistically significant.

Associations between the drug utilization and cardiovascular comorbidities in the RA group

We calculated the ORs of drug utilization for IHD and cerebral infarction using the logistic regression analysis within the RA group to investigate associations between antirheumatic medication and cardiovascular comorbidities (Table 6). The use of biological DMARDs and MTX were not significantly associated with IHD (0.61 [0.28–1.34] for biological DMARDs, 0.97 [0.62–1.51] for MTX) and cerebral infarction (0.47 [0.14–1.57] for biological DMARDs, 0.62 [0.32–1.17] for MTX). The OR for the use of oral corticosteroids was significantly elevated for cerebral infarction (1.68 [1.02–2.78]), but not for IHD (1.32 [0.90–1.94]).

Table 3. Prevalence* of comorbidities** in the RA group.

Comorbidities	RA group (n=2762)	Non-RA group (n=27,620)	Odds ratios (OR) [95% CI]
IHD***	5.00 [4.24–5.87]	1.35 [1.22–1.49]	3.84 [3.15–4.69]
Cerebral infarction	2.50 [1.98–3.15]	0.63 [0.55–0.73]	4.02 [3.03–5.32]
Hypertension	23.6 [22.0–25.2]	8.99 [8.66–9.33]	3.12 [2.83–3.44]
Dyslipidemia	20.1 [18.7–21.7]	7.28 [6.98–7.60]	3.21 [2.89–3.56]
Diabetes mellitus	6.05 [5.22–7.00]	2.47 [2.30–2.66]	2.54 [2.13–3.02]

RA, rheumatoid arthritis; CI, confidence interval; IHD, ischemic heart diseases.
*Prevalence is the number of cases with comorbidity per 100 persons with a 95% confidence interval.
**Comorbidities are defined as when patients had ICD 10 codes of investigated comorbidities with at least one prescription for the comorbidities during the study period.
***Ischemic heart diseases include angina, acute myocardial infarction, and other chronic ischemic heart diseases.

Table 4. Odds ratios for ischemic heart diseases* and cerebral infarction stratified by age and gender in RA and non-RA groups.

Age (years)	RA group			Non-RA group			Odds ratio*	Odds ratio**
	n	Prevalence*	Prevalence**	n	Prevalence*	Prevalence**	[95%CI]	[95%CI]
All female	2046	4.15 [3.37–5.11]	2.15 [1.61–2.87]	20,460	1.14 [1.00–1.29]	0.57 [0.47–0.68]	3.76 [2.92–4.84]	3.85 [2.72–5.47]
<45	649	1.23 [0.63–2.41]	1.23 [0.63–2.41]	6473	0.19 [0.11–0.32]	0.08 [0.03–0.18]	6.72 [2.74–16.5]	16.1 [5.27–49.5]
≥45, <60	967	3.62 [2.61–4.99]	1.45 [0.86–2.42]	9263	0.73 [0.58–0.93]	0.32 [0.23–0.46]	5.08 [3.36–7.68]	4.52 [2.39–8.56]
≥60	430	9.76 [7.31–12.9]	5.11 [3.40–7.62]	4724	3.24 [2.77–3.78]	1.71 [1.38–2.12]	3.23 [2.26–4.62]	3.09 [1.91–5.00]
All male	716	7.40 [5.70–9.56]	3.49 [2.38–5.10]	7160	1.96 [1.66–2.30]	0.82 [0.64–1.06]	4.01 [2.89–5.55]	4.35 [2.71–7.00]
<45	212	2.39 [1.01–5.40]	2.36 [1.01–5.40]	2085	0.14 [0.05–0.42]	0.05 [0.01–0.27]	16.8 [3.98–70.7]	50.3 [5.85–432.9]
≥45, <60	366	9.29 [6.72–12.7]	3.55 [2.09–5.98]	3404	1.73 [1.35–2.23]	0.53 [0.33–0.83]	5.81 [3.75–8.99]	6.93 [3.37–14.3]
≥60	138	10.1 [6.14–16.3]	5.10 [2.48–10.1]	1671	4.67 [3.76–5.79]	2.39 [1.76–3.24]	2.31 [1.27–4.19]	2.18 [0.96–4.96]

RA, rheumatoid arthritis; CI, confidence interval. Prevalence is the number of cases with IHD or cerebral infarction per 100 persons with a 95% confidence interval.
*Ischemic heart diseases include angina, acute myocardial infarction, and other chronic ischemic heart diseases. ** cerebral infarction.

Table 5. Association of RA and cardiovascular comorbidities by conditional logistic regression analyses.

Variables	Odds ratio of IHD*			Odds ratio of cerebral infarction		
	Univariate [95%CI]	Multivariate [95%CI]	*p* Value	Univariate [95%CI]	Multivariate [95%CI]	*p* Value
RA	3.70 [3.04–4.50]	1.97 [1.54–2.51]	<0.001**	4.00 [3.03–5.30]	3.06 [2.20–4.24]	<0.001**
Hypertension	21.6 [16.8–27.7]	12.5 [9.57–16.4]	<0.001**	12.1 [8.67–16.9]	6.17 [4.27–8.92]	<0.001**
Dyslipidemia	8.37 [6.81–10.3]	2.83 [2.22–3.61]	<0.001**	7.66 [5.72–10.3]	2.97 [2.12–4.16]	<0.001**
DM	5.36 [4.18–6.87]	1.43 [1.05–1.95]	0.024**	6.11 [4.33–8.63]	2.08 [1.39–3.13]	<0.001**

RA, rheumatoid arthritis; IHD, ischemic heart disease; CI, confidence interval; DM, diabetes mellitus.
*Ischemic heart diseases include angina, acute myocardial infarction, and other chronic ischemic heart diseases.
**All *p* values in multivariate analysis remained statistically significant after corrections for multiple comparisons using False Discovery Rate and Benjamini and Hochberg (BH) methods [31].

Table 6. Association of drug utilization and cardiovascular comorbidities in the rheumatoid arthritis group by logistic regression analyses.

Variables	Odds ratio of IHD*			Odds ratio of cerebral infarction		
	Univariate [95%CI]	Multivariate [95%CI]	*p* Value	Univariate [95%CI]	Multivariate [95%CI]	*p* Value
Age by decade	2.00 [1.66–2.39]	1.31 [1.06–1.60]	0.011**	1.64 [1.29–2.08]	1.22 [0.94–1.58]	0.125
Female	0.54 [0.38–0.77]	0.57 [0.38–0.84]	0.004**	0.61 [0.37–1.00]	0.70 [0.42–1.19]	0.186
Hypertension	14.4 [9.48–22.0]	8.76 [5.58–13.7]	<0.001**	4.42 [2.72–7.18]	2.30 [1.34–3.95]	0.003**
Dyslipidemia	5.14 [3.63–7.28]	2.45 [1.66–3.61]	<0.001**	4.84 [2.99–7.85]	2.76 [1.62–4.70]	<0.001**
DM	4.55 [2.91–7.13]	1.38 [0.84–2.28]	0.203	5.54 [3.13–9.82]	2.32 [1.24–4.35]	0.009**
Use of biological DMARDs	0.46 [0.22–0.95]	0.61 [0.28–1.34]	0.216	0.34 [0.11–1.10]	0.47 [0.14–1.57]	0.221
Use of MTX	0.68 [0.46–1.00]	0.97 [0.62–1.51]	0.878	0.48 [0.26–0.88]	0.62 [0.32–1.17]	0.138
Use of corticosteroids	1.15 [0.81–1.63]	1.32 [0.90–1.94]	0.154	1.38 [0.85–2.22]	1.68 [1.02–2.78]	0.042

RA, rheumatoid arthritis; IHD, ischemic heart disease; CI, confidence interval; DM, diabetes mellitus; DMARDs, disease modifying anti-rheumatic drugs; MTX, methotrexate.
*Ischemic heart diseases include angina, acute myocardial infarction, and other chronic ischemic heart diseases.
**These *p* values in multivariate analysis remained statistically significant after corrections for multiple comparisons using False Discovery Rate and Benjamini and Hochberg (BH) methods [31].

Age by decade (1.31 [1.06–1.60]) and female sex (0.57 [0.38–0.84]) were significantly associated with IHD; however, there were no associations between these covariates and cerebral infarction (1.22 [0.94–1.58] for age by decade, 0.70 [0.42–1.19] for female sex). The presence of HT or DL was significantly associated with both comorbidities. After corrections for multiple comparisons using False Discovery Rate and BH methods [31], age by decade, sex, HT, DL for IHD, and HT, DL, and DM for cerebral infarction remained significant.

We conducted sub-analyses in RA subjects with at least one prescription of any DMARDs ($n = 1620$) and the matched non-RA subjects ($n = 16{,}200$), and obtained similar results in the higher prevalence of comorbidities of the RA group compared to the non-RA group and associations between RA and cardiovascular comorbidities (data not shown). Although some adjusted ORs did not reach statistical significance due to the small number of cardiovascular events, similar patterns of associations between the drug utilization and cardiovascular comorbidities in the RA group were observed (data not shown).

Discussion

This is the first population-based cross-sectional study in Japan that demonstrated a significantly higher prevalence of cardiovascular comorbidities, such as IHD, and cerebral infarction in RA patients compared to non-RA patients. This study also determined that the associations between these comorbidities and RA remained significant after adjusting for covariates.

In the general population, the incidence rate (/1000 person-years [PY]) for coronary heart diseases in Japan was lower (3.2 in males and 0.8 in females) [32] than that in Western countries (7.1 in male and 4.2 in female) [33], and mortality due to coronary heart diseases in Japan was approximately one-fourth that of the U.S. [34]. It has been reported that the Japanese population had higher high density lipoprotein cholesterol, lower triglyceride [35], and lower prevalence of DM [36] compared to the American population; this could explain the lower incidence of coronary heart diseases in Japan. In contrast, the incidence rate (/1000PY) of cerebral infarction in the Japanese population (2.7 for males, 1.5 for females) [32] was similar to that of Western populations (2.5 for male, 1.9 for female) [33], but has steadily decreased in Japan in recent years [32]. In this study, the prevalence of comorbidities in the RA and non-RA groups was lower than that reported from Western countries. Halm et al. demonstrated that the prevalence of coronary, cerebral or peripheral arterial diseases was 12.9% in the RA group and 5.0% in the non-RA group without DM in a Dutch cohort [37]; these rates were higher than the sum of the prevalence of IHD and cerebral infarction in this study (5.0% for IHD and 2.5% for cerebral infarction in the RA group, 1.4% for IHD and 0.6% for cerebral infarction in the non-RA group). The prevalence of HT, DL, and DM in this study was 23.6%, 20.1%, and 6.1%, respectively, which was also lower than that from the COMORA study, an international cross-sectional study (40.4% for HT, 31.7% for DL, and 15% for DM, respectively). The lower prevalence of these comorbidities in Japan could be attributed to differences in genetic, environmental, and lifestyle risk factors, demographics of cohorts, recommendations for comorbidities, and definitions of comorbidities. A single-center Japanese RA cohort [38] showed lower mortality rates for stroke (3.6 per 1000 patient-years [PY]) and CVD (2.5 per 1000 PY) than an American RA cohort (5.1 per 1000 PY for stroke, 6.1 per 1000 for any CVD) [38]. A large Japanese RA cohort study also showed that CVD was not a prominent cause of death of RA patients [39]. These data indicate

that the Japanese population has lower risk for CVD compared to the Western population, both in the general population and in RA patients.

In this study, we calculated the unadjusted ORs of IHD and cerebral infarction (RA versus non-RA) when stratified by sex and age. The ORs of these comorbidities were numerically higher in the younger subjects compared to the older, but prevalence increased with age in both groups. It is remarkable that RA subjects <45 years old and between 45 and 60 years old had higher or similar prevalence for IHD and cerebral infarction than the non-RA group between 45 and 60 and >60 years-old. Solomon et al. have reported a pattern similar to ours; the rate ratios of CVD events (RA versus non-RA population) decreased with age [12], but incidence rates of CVD increased with age in both groups. Although we have to consider the possibility that patients with RA are likely to be prescribed medications for comorbidities due to more frequent visits to health care providers, our data strongly suggest that we should be particularly careful to provide special attention to prevention and management of IHD and cerebral infarction in, not only elderly RA patients, but also in young RA patients.

In our study, ischemic heart diseases and cerebral infarction were significantly associated with RA after adjusting for conventional risk factors for CVD, including HT, DL, and DM. In addition to the traditional CVD risk factors, atherosclerosis due to chronic and systemic inflammation has also been reported to increase the risk for CVD in patients with RA [40]. Therefore, it is crucial for rheumatologists to estimate the impact of RA-specific risks for CVD. In this study, the presence of HT, DL, and DM were also significantly associated with both comorbidities. Previous reports showed that these risk factors were significantly associated with the development of CVD in both RA and non-RA groups [41] at a similar level [42], but smoking and past cardiac diseases imparted less risk for the development of CVD to RA patients compared to the non-RA group [42]. Further studies are needed to establish strategies to reduce CVD morbidity in RA patients.

To investigate the associations between cardiovascular comorbidities and treatments for RA, we calculated ORs of antirheumatic medication after adjusting for covariates. In this study, the adjusted OR of MTX or biological DMARDs use for IHD and cerebral infarction were relatively decreased and that of oral corticosteroid use for IHD was slightly elevated, but all of these did not reach statistical significance. Previous reports have shown that use of MTX [22,25,43,44] or biological DMARDs [24,25, 45,46] decreased the risk of CVD significantly. Some reports demonstrated that corticosteroids increased CVD risk [18,20], but others found no significant association between corticosteroids and CVD risk [47,48]. Recent meta-analysis have shown that biological DMARDs and MTX use were associated with about 30% reduction in the risk for CVD, while oral corticosteroid use was associated with 47% increase of the risk for CVD [25]. It was difficult to conclude the associations between treatments and development of cardiovascular comorbidities due to the cross-sectional design of this study. A cohort study with a long observation term is required to ascertain incidence rates and adjusted risk for CVD in Japanese patients with RA.

There are some limitations in this study. First, the JMDC claims data include employees and their dependents, but do not include independent retired populations. Therefore, the median age of this study population was relatively young; this may lead to selection bias in estimating prevalence of comorbidities in elderly populations. Second, in this population, any DMARDs were prescribed in only about half of RA subjects, which was compatible with previous studies using the JMDC claims data [28,29]. We ascertained that low prevalence of DMARDs did not influence the association between RA and comorbidities based on similar results in RA subjects with at least one prescription of DMARDs. Third, we could not investigate the association between the prevalence of comorbidities and RA disease activity, and could not adjust for risk factors, such as smoking and body mass index, because JMDC claims data do not include these data and linkages between several databases are currently prohibited in Japan. Despite the limitations to the study, our population-based design with a large number of Japanese RA patients identified increased prevalence of cardiovascular comorbidities in clinical practice for the first time.

In conclusion, using employment-based health insurance claims data, this study revealed the high prevalence of IHD and cerebral infarction in Japanese RA patients and the significant associations between RA and these cardiovascular comorbidities. Further studies need to be conducted to define the incidence and risk factors for these comorbidities in Japanese patients with RA.

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Conflict of interests

MH received unrestricted research grants for Departments of Pharmacovigilance from Abbvie Japan Co., Ltd., Astellas Pharma Inc., Bristol Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Mitsubishi Tanabe Pharma Co., Ono Pharmaceuticals, Pfizer Japan Inc., Sanofi-Aventis KK., Santen Pharmaceutical Co., Ltd., Sekisui Medical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Teijin Pharma Ltd., and UCB Japan with which TMDU pays salary for ***RS***, ***HY***, ***TN***, and ***MH***. ***NM*** has received research grants from Abbott Japan Co., Ltd., Astellas Pharma Inc., Bristol Myers Squibb, Chugai Pharmaceutical Co., Ltd., Dainihon-Sumitomo Pharma Co. Ltd., Daiichi-Sankyo Co. Ltd., Eisai Co. Ltd., Mitsubishi Tanabe Pharma Co., Novartis Pharma K.K., Ltd., Takeda Pharmaceutical Co., Ltd., Teijin Pharma Ltd and has received consulting fees or honoraria from Abbott Japan Co., Ltd., Bristol Myers Squibb, Janssen Pharmaceutical KK, and Otsuka Pharmaceutical Co. Ltd. ***FH***, ***MK***, ***WY***, and ***RK*** have nothing to declare.

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References

1. Dougados M, Soubrier M, Antunez A, Balint P, Balsa A, Buch M.H, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). Ann Rheum Dis. 2014;73:62–8.
2. Charles-Schoeman C. Cardiovascular disease and rheumatoid arthritis: an update. Curr Rheumatol Rep. 2012;14:455–62.
3. Crowson CS, Liao KP, Davis JM, 3rd, Solomon DH, Matteson EL, Knutson KL, et al. Rheumatoid arthritis and cardiovascular disease. Am Heart J. 2013;166:622–8 e1.
4. Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. Arthritis Res Ther. 2009;11:229
5. Peterson JC, Paget SA, Lachs MS, Reid MC, Charlson ME. The risk of comorbidity. Ann Rheum Dis. 2012;71:635–7.
6. Ranganath VK, Maranian P, Elashoff DA, Woodworth T, Khanna D, Hahn T, et al. Comorbidities are associated with poorer outcomes in

community patients with rheumatoid arthritis. Rheumatology (Oxford). 2013;52:1809–17.
7. Tiippana-Kinnunen T, Kautiainen H, Paimela L, Leirisalo-Repo M. Co-morbidities in Finnish patients with rheumatoid arthritis: 15-year follow-up. Scand J Rheumatol. 2013;42:451–6.
8. Radner H, Smolen JS, Aletaha D. Impact of comorbidity on physical function in patients with rheumatoid arthritis. Ann Rheum Dis. 2010;69:536–41.
9. Joyce AT, Smith P, Khandker R, Melin JM, Singh A. Hidden cost of rheumatoid arthritis (RA): estimating cost of comorbid cardiovascular disease and depression among patients with RA. J Rheumatol. 2009;36:743–52.
10. Semb AG, Rollefstad S, van Riel P, Kitas GD, Matteson EL, Gabriel SE. Cardiovascular disease assessment in rheumatoid arthritis: a guide to translating knowledge of cardiovascular risk into clinical practice. Ann Rheum Dis. 2014;73:1284–8.
11. Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum. 2008;59:1690–7.
12. Solomon DH, Goodson NJ, Katz JN, Weinblatt ME, Avorn J, Setoguchi S, et al. Patterns of cardiovascular risk in rheumatoid arthritis. Ann Rheum Dis. 2006;65:1608–12.
13. Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis. 2012;71:1524–9.
14. Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum. 2005;52:402–11.
15. Solomon DH, Avorn J, Katz JN, Weinblatt ME, Setoguchi S, Levin R, et al. Immunosuppressive medications and hospitalization for cardiovascular events in patients with rheumatoid arthritis. Arthritis Rheum. 2006;54:3790–8.
16. van der Stoep DF, Klop B, van Zeben D, Hazes JM, Castro Cabezas M. Cardiovascular risk in rheumatoid arthritis: how to lower the risk? Atherosclerosis. 2013;231:163–72.
17. Zhang J, Chen L, Delzell E, Muntner P, Hillegass WB, Safford MM, et al. The association between inflammatory markers, serum lipids and the risk of cardiovascular events in patients with rheumatoid arthritis. Ann Rheum Dis. 2014;73:1301–8.
18. Souverein PC, Berard A, Van Staa TP, Cooper C, Egberts AC, Leufkens HG, et al. Use of oral glucocorticoids and risk of cardiovascular and cerebrovascular disease in a population based case-control study. Heart. 2004;90:859–65.
19. Avina-Zubieta JA, Abrahamowicz M, De Vera MA, Choi HK, Sayre EC, Rahman MM, et al. Immediate and past cumulative effects of oral glucocorticoids on the risk of acute myocardial infarction in rheumatoid arthritis: a population-based study. Rheumatology (Oxford). 2013;52:68–75.
20. Davis JM III, Maradit Kremers H, Crowson CS, Nicola PJ, Ballman KV, Therneau TM, et al. Glucocorticoids and cardiovascular events in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum. 2007;56:820–30.
21. Prodanovich S, Ma F, Taylor JR, Pezon C, Fasihi T, Kirsner RS. Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid arthritis. J Am Acad Dermatol. 2005;52:262–7.
22. Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet. 2002;359:1173–7.
23. Bili A, Tang X, Pranesh S, Bozaite R, Morris SJ, Antohe JL, et al. Tumor necrosis factor α inhibitor use and decreased risk for incident coronary events in rheumatoid arthritis. Arthritis Care Res (Hoboken). 2014;66:355–63.
24. Greenberg JD, Kremer JM, Curtis JR, Hochberg MC, Reed G, Tsao P, et al. Tumour necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. Ann Rheum Dis. 2011;70:576–82.
25. Roubille C, Richer V, Starnino T, McCourt C, McFarlane A, Fleming P, et al. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. Ann Rheum Dis. 2015;74:480–9.
26. Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis. 2010;69:325–31.
27. Chung WS, Lin CL, Peng CL, Chen YF, Lu CC, Sung FC, et al. Rheumatoid arthritis and risk of acute myocardial infarction-a nationwide retrospective cohort study. Int J Cardiol. 2013;168:4750–4.
28. Yamanaka H, Sugiyama N, Inoue E, Taniguchi A, Momohara S. Estimates of the prevalence of and current treatment practices for rheumatoid arthritis in Japan using reimbursement data from health insurance societies and the IORRA cohort (I). Mod Rheumatol. 2014;24:33–40.
29. Katada H, Yukawa N, Urushihara H, Tanaka S, Mimori T, Kawakami K. Prescription patterns and trends in anti-rheumatic drug use based on a large-scale claims database in Japan. Clin Rheumatol. 2014.
30. Lacaille D, Anis AH, Guh DP, Esdaile JM. Gaps in care for rheumatoid arthritis: a population study. Arthritis Rheum. 2005;53:241–8.
31. Benjamini YHY. Controlling the False Discovery Rate – a Practical and Powerful Approach to Multiple Testing. J Roy Stat Soc B Met. 1995;57:289–300.
32. Hata J, Ninomiya T, Hirakawa Y, Nagata M, Mukai N, Gotoh S, et al. Secular trends in cardiovascular disease and its risk factors in Japanese: half-century data from the Hisayama Study (1961–2009). Circulation. 2013;128:1198–205.
33. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. Am Heart J. 1986;111:383–90.
34. Kitamura A, Sato S, Kiyama M, Imano H, Iso H, Okada T, et al. Trends in the incidence of coronary heart disease and stroke and their risk factors in Japan, 1964 to 2003: the Akita-Osaka study. J Am Coll Cardiol. 2008;52:71–9.
35. Sekikawa A, Ueshima H, Sutton-Tyrrell K, Kadowaki T, El-Saed A, Okamura T, et al. Intima-media thickness of the carotid artery and the distribution of lipoprotein subclasses in men aged 40 to 49 years between whites in the United States and the Japanese in Japan for the ERA JUMP study. Metab. Clin. Exp. 2008;57:177–82.
36. Iso H. Changes in coronary heart disease risk among Japanese. Circulation. 2008;118:2725–9.
37. van Halm VP, Peters MJ, Voskuyl AE, Boers M, Lems WF, Visser M, et al. Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. Ann Rheum Dis. 2009;68:1395–400.
38. Masuda H, Miyazaki T, Shimada K, Tamura N, Matsudaira R, Yoshihara T, et al. Disease duration and severity impacts on long-term cardiovascular events in Japanese patients with rheumatoid arthritis. J Cardiol. 2014.
39. Nakajima A, Inoue E, Tanaka E, Singh G, Sato E, Hoshi D, et al. Mortality and cause of death in Japanese patients with rheumatoid arthritis based on a large observational cohort, IORRA. Scand J Rheumatol. 2010;39:360–7.
40. Dessein PH, Joffe BI, Veller MG, Stevens BA, Tobias M, Reddi K, et al. Traditional and nontraditional cardiovascular risk factors are associated with atherosclerosis in rheumatoid arthritis. J Rheumatol. 2005;32:435–42.
41. Barbhaiya M, Solomon DH. Rheumatoid arthritis and cardiovascular disease: an update on treatment issues. Curr Opin Rheumatol. 2013;25:317–24.
42. Gonzalez A, Maradit Kremers H, Crowson CS, Ballman KV, Roger VL, Jacobsen SJ, et al. Do cardiovascular risk factors confer the same risk for cardiovascular outcomes in rheumatoid arthritis patients as in non-rheumatoid arthritis patients? Ann Rheum Dis. 2008;67:64–9.
43. Naranjo A, Sokka T, Descalzo MA, Calvo-Alen J, Horslev-Petersen K, Luukkainen RK, et al. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. Arthritis Res Ther. 2008;10:R30.
44. Micha R, Imamura F, Wyler von Ballmoos M, Solomon D.H, Hernan MA, Ridker PM, et al. Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease. Am J Cardiol. 2011;108:1362–70.
45. Ljung L, Askling J, Rantapaa-Dahlqvist S, Jacobsson L. The risk of acute coronary syndrome in rheumatoid arthritis in relation to tumour

necrosis factor inhibitors and the risk in the general population: a national cohort study. Arthritis Res Ther. 2014;16:R127.
46. Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. Am J Med. 2004;116:305–11.
47. Avina-Zubieta JA, Abrahamowicz M, Choi HK, Rahman MM, Sylvestre MP, Esdaile JM, et al. Risk of cerebrovascular disease associated with the use of glucocorticoids in patients with incident rheumatoid arthritis: a population-based study. Ann Rheum Dis. 2011;70:990–5.
48. Nadareishvili Z, Michaud K, Hallenbeck JM, Wolfe F. Cardiovascular, rheumatologic, and pharmacologic predictors of stroke in patients with rheumatoid arthritis: a nested, case-control study. Arthritis Rheum. 2008;59:1090–6.

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RESEARCH ARTICLE Open Access

Head-to-head comparison of the safety of tocilizumab and tumor necrosis factor inhibitors in rheumatoid arthritis patients (RA) in clinical practice: results from the registry of Japanese RA patients on biologics for long-term safety (REAL) registry

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Abstract

Introduction: The objective of this study was to directly compare the safety of tocilizumab (TCZ) and TNF inhibitors (TNFIs) in rheumatoid arthritis (RA) patients in clinical practice.

Methods: This prospective cohort study included RA patients starting TCZ [TCZ group, n = 302, 224.68 patient-years (PY)] or TNFIs [TNFI group, n = 304, 231.01 PY] from 2008 to 2011 in the registry of Japanese RA patients on biologics for long-term safety registry. We assessed types and incidence rates (IRs) of serious adverse events (SAEs) and serious infections (SIs) during the first year of treatment. Risks of the biologics for SAEs or SIs were calculated using the Cox regression hazard analysis.

Results: Patients in the TCZ group had longer disease duration ($P < 0.001$), higher disease activity ($P = 0.019$) and more frequently used concomitant corticosteroids ($P < 0.001$) than those in the TNFI group. The crude IR (/100 PY) of SIs [TCZ 10.68 vs. TNFI 3.03; IR ratio (95% confidence interval [CI]), 3.53 (1.52 to 8.18)], but not SAEs [21.36 vs. 14.72; 1.45 (0.94 to 2.25)], was significantly higher in the TCZ group compared with the TNFI group. However, after adjusting for covariates using the Cox regression hazard analysis, treatment with TCZ was not associated with higher risk for SAEs [hazard ratio (HR) 1.28, 95% CI 0.75 to 2.19] or SIs (HR 2.23, 95% CI 0.93 to 5.37).

Conclusions: The adjusted risks for SAEs and SIs were not significantly different between TCZ and TNFIs, indicating an influence of clinical characteristics of the patients on the safety profile of the biologics in clinical practice.

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Introduction

Tocilizumab (TCZ), which is a humanized antibody against the interleukin 6 (IL-6) receptor [1], inhibits signaling mediated by IL-6 [2] and was first approved to treat rheumatoid arthritis (RA) in Japan in 2008. The superior efficacy of TCZ compared to a control drug or placebo in RA patients has been demonstrated by a series of clinical trials [3-12]. In clinical practice, TCZ showed excellent effectiveness in patients with established RA [13]. Safety profiles of TCZ in patients with RA were clarified by the Japanese post-marketing surveillance (PMS) program [14] and a meta-analysis [15]. In the PMS of TCZ, the most frequent category of serious adverse events (SAEs) was infection and the most common infection was pneumonia. The incidence rate (IR) of serious infections (SIs) per 100 patient-years (PY) was 9.1, with older age, longer disease duration, respiratory diseases, and prednisolone dose ≥5 mg/day at baseline identified as significant risk factors for development of SIs during the first six months of treatment with TCZ [14]. The favorable benefit-risk balance of TCZ has led to the worldwide use of this biologic for treating RA [16].

In 2013, the European League Against Rheumatism recommendations for the management of RA were updated [17]. They now express no preference for the use of a specific biological agent; this indicates that TCZ, as well as tumor necrosis factor inhibitors (TNFIs) and abatacept, can be first line biologics. Therefore, for the clinical selection of biologics, it is necessary to compare the efficacy and safety of TCZ with those of other biologics. Systematic reviews [18,19] and meta-analyses [20] indirectly comparing efficacy of TCZ with other biologics showed that TCZ had similar response rates in patients with RA. Results from a clinical trial or study comparing TCZ with another biologic have been reported. Gabay *et al.* demonstrated that TCZ monotherapy was superior to adalimumab monotherapy in RA patients who are intolerant to methotrexate [21]. A Danish registry reported the comparison of effectiveness between TCZ and abatacept (ABA) [22] and found that declines in disease activity during 48 weeks were similar between the drugs.

There are few data comparing the safety of TCZ with other biologics. A meta-analysis found no significant difference in the risk of SIs between TCZ and other biologics [23]. Using a Japanese single institution registry with a relatively small number of patients, Yoshida *et al.* reported the safety profiles of TCZ and TNFIs; IRs of SAE were 15.9/100 PY in the TCZ group and 13.9/100PY in the TNFI group [24]. However, to date, no detailed comparison of SAEs between TCZ and TNFIs, particularly the types and incidence of SIs, has been reported. Additional direct observational studies are needed to clarify the risk of use of TCZ versus TNFIs for the development of SAEs and SIs in clinical practice.

In this study, we utilized the database of the registry of Japanese RA patients on biologics for long-term safety (REAL), a prospective, multi-center cohort with a large number of patients, and herein report IRs for each category of SAEs for TCZ with hazard ratios (HRs) for SAEs and SIs from the use of TCZ compared to the use of TNFIs.

Methods

Database

The REAL is a prospective cohort established to investigate the long-term safety of biologics in RA patients. Details of the REAL have been previously described [25]. In brief, 27 institutions participate in the REAL, including 16 university hospitals and 11 referring hospitals. The criteria for enrollment in the REAL include patients meeting the 1987 American College of Rheumatology criteria for RA [26], written informed consent, and starting or switching treatment with biologics or starting, adding or switching non-biologics at the time of enrollment in the study. Enrollment in the REAL database was started in June 2005 and closed in January 2012. Data were retrieved from the REAL database on 5 March 2012 for this study. This study was in compliance with the Helsinki Declaration (revised in 2008). The REAL study was approved by the ethics committees of the Tokyo Medical and Dental University Hospital and all other participating institutions. All ethical bodies that approved this study are shown in the Acknowledgements section.

Data collection

Recorded baseline data for each patient includes demography, disease activity, physical disability, comorbidities, treatments, and laboratory data at the beginning of the observation period. A follow-up form was submitted every six months to the REAL Data Center at the Department of Pharmacovigilance of Tokyo Medical and Dental University by site investigators to report the occurrence of SAEs, current RA disease activity, treatments, and clinical laboratory data [25]. Steinbrocker's classification [27] was used as the baseline measurement for the physical disability of each patient instead of the Health Assessment Questionnaire Disability Index [28]. The investigators in each hospital confirmed the accuracy of their data submitted to the REAL Data Center. The center examined all data sent by site investigators and made inquiries if needed to verify accuracy of the data.

Patients

A flow chart of patients enrolled in this study from the REAL is shown in Figure 1. By March 2012, 1,945 patients with RA were registered in the REAL. Of 1,236 patients who started infliximab (IFX), etanercept (ETN), adalimumab (ADA) or TCZ at the time of enrollment or

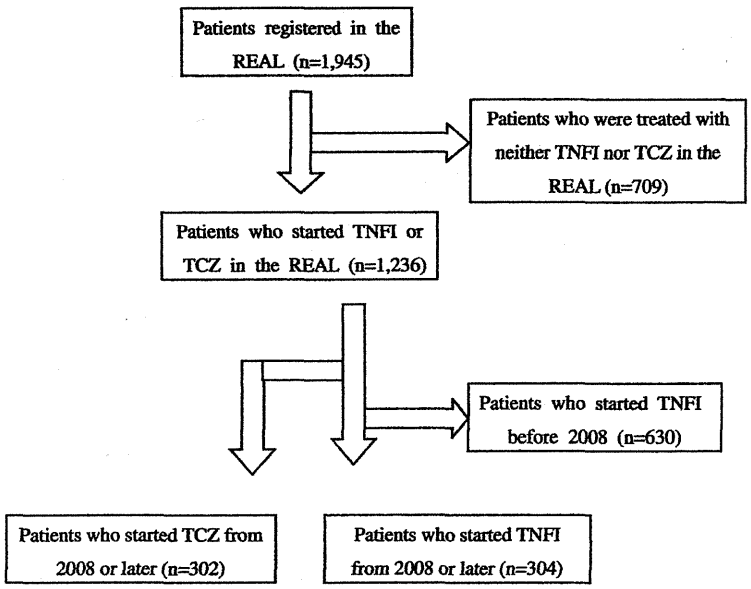

Figure 1 Flow chart of rheumatoid arthritis (RA) patients enrolled in this study from the REAL.

after enrollment in the REAL, we identified 302 patients who started TCZ (TCZ group). Patients who used both TCZ and TNFIs at different periods were assigned to the TCZ group. We then excluded 630 patients who had started any of the TNFIs before 2008 because TCZ was approved for RA in Japan in 2008, and identified 304 patients who started only TNFIs between 2008 and 2011 (TNFI group). The first TNFI of each patient in the TNFI group was IFX for 117 patients, ETN for 80, and ADA for 107. No patients started abatacept, golimumab, or certolizumab pegol in the REAL during the time our data were compiled for this study.

Follow-up

For patients in the TCZ group, the start date for the observation period was the date TCZ was first administered. For patients in the TNFI group, the start of the observation period was the date of the first administration of TNFI from 2008 to 2011. Observation was ended at either 1.0 year after the start of the observation period, or on the date of death of a patient, loss to follow up, enrollment in clinical trials, when therapy with a biologic of interest was discontinued for more than 90 days, or on 5 March 2012, whichever came first. The period following switching to another biologic was excluded from this study. The date of the last administration of each biologic was retrieved from medical records and reported by the site investigators.

Definition of serious adverse events

Our definition of a SAE, including SIs, was based on the report by the International Conference on Harmonization [29]. In addition, bacterial infections that required intravenous administration of antibiotics and opportunistic infections were regarded as SAEs [30,31]. SAEs were classified using the System Organ Class (SOC) of the medical dictionary for regulatory activities (MedDRA version 16.0).

Statistical analysis

The chi-square test for categorical variables and Student's t-test or the Mann–Whitney test for continuous variables were used for comparisons among groups. The IR per 100 PY and incidence rate ratios (IRR) with their 95% confidence intervals (CIs) were calculated. Kaplan-Meier methods and log-rank tests were used to compare drug retention rates between the groups. The Cox regression hazard model with the forced entry method was used to calculate HRs of use of TCZ versus TNFIs for SAEs and SIs. As a sensitivity analysis, we performed the same analysis in patients treated with methotrexate (MTX) at baseline, considering substantial differences in clinical characteristics between MTX users and non-users. 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

Demographic and clinical baseline characteristics of patients

Baseline data for the patients are shown in Table 1. Compared to the TNFI group, the TCZ group had longer disease duration ($P < 0.001$), higher disease activity ($P = 0.019$), more advanced disease stage ($P < 0.001$), and

Table 1 Demographic and clinical characteristics of RA patients treated with TCZ or TNFIs

Characteristics	TCZ group (number = 302)	TNFI group (number = 304)	*P* value
Age, years	59.20 ± 13.04	57.33 ± 15.18	0.275
Female, %	82.5	82.8	0.425
Disease duration, years	10.20 ± 8.64	7.96 ± 8.70	<0.001
Steinbrocker's stage[a] (III or IV), %	51.0	35.2	<0.001
Steinbrocker's class[a] (3 or 4), %	29.1	19.4	0.005
Previous biologic use, %	70.5	10.5	<0.001
Number of previous non-biological DMARDs ≥3, %	47.0	38.5	0.034
DAS28CRP (3)[b]	4.50 ± 1.23 (n = 233)	4.25 ± 1.24 (n = 279)	0.019
Pulmonary diseases[c], %	20.2	15.5	0.128
Diabetes mellitus, %	10.9	10.5	0.873
Liver diseases[d], %	6.6	4.6	0.281
Kidney diseases[e], %	3.6	0.7	0.011
MTX use, %	53.0	85.5	<0.001
MTX dose, mg/week	8.41 ± 2.80	8.54 ± 2.28	0.237
Oral corticosteroids use, %	65.6	51.0	<0.001
PSL-equivalent dose[f], mg/day	5.32 ± 3.19	4.99 ± 3.05	0.433

[a]Steinbrocker's classification was used to define RA disease stages and classes; [b]DAS28CRP (3) was calculated based on three variables: swollen and tender 28-joint counts and CRP; [c]pulmonary diseases included interstitial lung disease, chronic obstructive pulmonary disease, and asthma; [d]liver diseases included hepatitis B carrier, hepatitis C carrier, fatty liver, hepatitis, primary biliary cirrhosis, positive anti-hepatitis C antibody, cholelithiasis, and abnormal liver function tests; [e]kidney diseases included nephrotic syndrome, nephritis, renal failure, chronic kidney disease, renal hypertension, hemi-kidney, and elevation of serum creatinine; [f]the oral corticosteroids dose was converted to the equivalent prednisolone dosage. CRP; C-reactive protein; DAS28, disease activity score including 28-joint count; DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate; PSL, prednisolone; RA, rheumatoid arthritis; TCZ, tocilizumab; TNFIs, tumor necrosis factor inhibitors.

poorer physical function ($P = 0.005$). Age did not differ significantly between the groups. A significantly higher rate of the patients in the TCZ group had received three or more non-biological disease-modifying anti-rheumatic drugs before starting the biologic ($P = 0.034$), was biologic non-naive ($P < 0.001$), and was treated with oral corticosteroids ($P < 0.001$). The proportion of patients treated with MTX in the TCZ group was significantly ($P < 0.001$) lower than in the TNFI group (n = 160 (53.0%) versus n = 260 (85.5%)). We also compared characteristics of MTX users at baseline. Patients in the TCZ group had significantly longer disease duration ($P = 0.003$), more advanced stage ($P = 0.005$) and poorer physical function ($P = 0.042$) than those in the TNFI group (Additional file 1: Table S1).

Retention rates for TCZ and TNFIs

The median (interquartile (IQR)) treatment period was 1.00 (0.50 to 1.00) year for the TCZ group and 1.00 (0.51 to 1.00) year for the TNFI group. The number of patients who discontinued biologics for any reason during the observation period was 81 (26.8%) in the TCZ group and 62 (20.4%) in the TNFI group, not a significant difference ($P = 0.062$ by chi-square). The development of AEs was the most frequent reason for discontinuation in both the TCZ group (n = 41, 50.6%) and the TNFI group (n = 24, 38.7%). There was no significant difference in the retention rates of the biologics for one year between the two groups (71.0% in the TCZ group, 76.1% in the TNFI group, $P = 0.082$ by Kaplan-Meier analysis and log-rank test) (Figure 2).

Types and occurrence of SAEs

The IRs for SAEs are summarized in Table 2. Among the 606 patients, 82 SAEs were reported during the observation period; 48 in the TCZ group and 34 in the TNFI group. The crude IRR, comparing the TCZ group with the TNFI group for SAEs, was 1.45 (95% CI, 0.94 to 2.25) and for SIs was 3.53 (95% CI, 1.52 to 8.18). There were no significant differences in the IR of SAEs among the three TNFIs (data not shown). For patients using MTX at baseline, the IR of SAEs in the TCZ group was not significantly higher than that in the TNFI group (IRR 1.48 95% CI, 0.85 to 2.61), whereas, the IR of SIs was significantly higher in the TCZ group compared to the TNFI group (IRR 2.88 95% CI, 1.13 to 7.32). The IR of SIs in the TCZ group was significantly higher than that in the TNFI group in patients with previous biologics exposure (4.4 (1.7 to 11.6)), but not for SAEs (1.6 (0.8 to 3.0)).

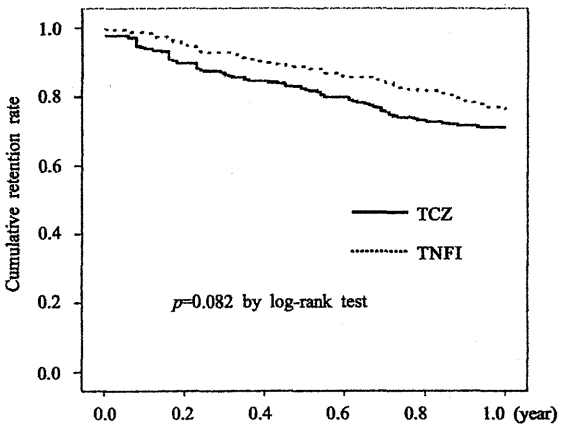

Figure 2 Kaplan-Meier curves for time to discontinuation for each group. Drug retention rates were compared using the log-rank test between tocilizumab (TCZ) and tumor necrosis factor inhibitors (TNFIs). The y axis shows the cumulative retention rates.

In the TCZ group, 53% of patients had received MTX at baseline; there were no significant differences in the unadjusted IR of SAEs and SIs between MTX users and non-users (data not shown). In the TCZ group, 70% of the patients had previously used biologics; these patients had safety profiles similar to the biologics-naïve patients (data not shown).

In the TCZ group, there were 24 SIs including five cases of opportunistic infections (herpes zoster (two); Pneumocystis pneumonia (PCP) (one); pulmonary aspergillosis (one); and esophageal candidiasis (one)) and 19 non-opportunistic infections. In the TNFI group, of seven cases with SIs, three were opportunistic infections (herpes zoster (one); PCP (one); and pulmonary cryptococcosis (one)), and four non-opportunistic infections. The respiratory system was the most frequent site of infection in both groups (TCZ (seven) and TNFI (three)), followed in the TCZ group by five in bone and joints and four in skin and subcutaneous tissue. There were no significant differences in the IR for pulmonary infection (IRR 2.40 95% CI, 0.62 to 9.28), but the IR for non-pulmonary infections was significantly higher in the TCZ group compared to the TNFI group (IRR 4.37 95% CI, 1.47 to 13.0). One perforation of the upper gastrointestinal tract developed in the TCZ group. No anaphylactic reactions were reported in either group.

Evaluation of risk of TCZ for development of SAEs compared to TNFI

We compared patients who had and had not experienced SAEs using a univariate analysis and selected variables for the multivariate Cox regression hazard analysis to evaluate the risk of the use of TCZ for the development of a SAE. After adjusting for age, gender, disease activity score including 28-joint count C-reactive protein (3), comorbidity, use of oral corticosteroids (prednisolone-equivalent dose) ≥5 mg/day, and Steinbrocker's class, the hazard ratio (HR) of the use of TCZ compared to the use of TNFI for developing SAEs was 1.28 (95% CI, 0.75 to 2.19, $P = 0.370$), not significantly elevated (Table 3). Significant risk factors influencing the development of SAEs

Table 2 Occurrence of SAEs in patients with RA treated with TCZ or TNFIs[a]

Types of SAEs	TCZ group, 224.68 PY IR (/100PY)	TNFI group, 231.01 PY IR (/100PY)	TCZ versus TNFI Crude IRR (95% CI)
Total SAEs	21.36 (15.94 to 28.07)	14.72 (10.37 to 20.32)	1.45 (0.94 to 2.25)
Serious infection (SI)	10.68 (7.02 to 15.63)	3.03 (1.35 to 5.95)	3.53 (1.52 to 8.18)
Pulmonary infection	3.12 (1.39 to 6.12)	1.30 (0.36 to 3.46)	2.40 (0.62 to 9.28)
Non-pulmonary infection	7.57 (4.57 to 11.84)	1.73 (0.58 to 4.12)	4.37 (1.47 to 12.99)
Skin infection	1.78 (0.60 to 4.23)	0.43 (0.04 to 2.02)	4.11 (0.46 to 36.80)
Urinary tract infection	0.89 (0.18 to 2.85)	0.43 (0.04 to 2.02)	2.06 (0.19 to 22.68)
Gastrointestinal infection	0.89 (0.18 to 2.85)	0.43 (0.04 to 2.02)	2.06 (0.19 to 22.68)
Bone and joint infections	2.23 (0.84 to 4.88)	0	NA
Sepsis	1.34 (0.37 to 3.56)	0	NA
Other infection	0.45 (0.04 to 2.08)	0.43 (0.04 to 2.02)	1.03 (0.06 to 16.44)
Pulmonary disease, except infection	2.23 (0.84 to 4.88)	2.16 (0.82 to 4.74)	1.03 (0.30 to 3.55)
Cardiovascular or cerebrovascular disease	0.45 (0.04 to 2.08)	2.16 (0.82 to 4.74)	0.21 (0.02 to 1.76)
Malignancy	0.89 (0.18 to 2.85)	1.30 (0.36 to 3.46)	0.69 (0.11 to 4.10)
Death	1.78 (0.60 to 4.23)	0.87 (0.17 to 2.78)	2.06 (0.38 to 11.23)
Others	7.12 (4.24 to 11.29)	6.06 (3.47 to 9.90)	1.18 (0.57 to 2.41)

[a]Crude incidence rate per 100 PYs and crude incidence rate ratio with their 95% CI were calculated for each category of serious adverse events. CI: confidence interval; IR: incidence rate; IRR: incidence rate ratio; NA: not applicable; PY: patient-year; RA: rheumatoid arthritis; SAEs: serious adverse events; TCZ: tocilizumab; TNFIs: tumor necrosis factor inhibitors.

Table 3 Factors influencing development of SAEs in patients with RA treated with TCZ or TNFIs[a]

Variable	All patients		MTX users	
	HR (95% CI)[c]	P value[c]	HR (95% CI)[d]	P value[d]
Age by decade	1.47 (1.15 to 1.88)	0.002	1.58 (1.07 to 2.35)	0.022
Female	0.74 (0.40 to 1.38)	0.345	0.96 (0.38 to 2.47)	0.940
DAS28CRP (3)	1.06 (0.98 to 1.14)	0.151	1.06 (0.76 to 1.48)	0.744
Comorbidity[b]	1.86 (1.07 to 3.24)	0.029	2.10 (0.92 to 4.79)	0.077
PSL ≥5 (mg/day)	1.72 (1.01 to 2.93)	0.047	1.64 (0.74 to 3.63)	0.223
Steinbrocker's Class 3 or 4	1.37 (0.77 to 2.43)	0.287	1.10 (0.47 to 2.60)	0.825
Tocilizumab	1.28 (0.75 to 2.19)	0.370	1.21 (0.55 to 2.65)	0.632

[a]Cox regression analysis with the independent variables included in the Table; [b]comorbidity included pulmonary diseases, diabetes mellitus, liver diseases, and kidney diseases; [c]Cox regression analysis was applied in all patients; [d]Cox regression analysis was applied in patients who were treated with MTX at baseline. CI: confidence interval; CRP: C-reactive protein; DAS28CRP (3): 3-variable disease activity score including 28-joint count; HR: hazard ratio; MTX: methotrexate; PSL: prednisolone RA: rheumatoid arthritis; SAEs: serious adverse events; TCZ: tocilizumab; TNFIs: tumor necrosis factor inhibitors.

were age by decade (HR 1.47, 95% CI, 1.15 to 1.88, $P = 0.002$), the presence of a comorbidity (HR 1.86, 95% CI, 1.07 to 3.24, $P = 0.029$), and the use of oral corticosteroids (prednisolone-equivalent dose) ≥5 mg/day (HR 1.72, 95% CI, 1.01 to 2.93, $P = 0.047$) (Table 3). We evaluated the risk of use of TCZ for development of SAEs in patients given MTX at baseline as a sensitivity analysis, and found the HR of use of TCZ was 1.21 (0.55 to 2.65, $P = 0.632$) compared to the use of TNFI (Table 3).

Evaluation of risk of TCZ for development of SIs compared to TNFIs

We next investigated the risk of use of TCZ compared to the use of TNFI for development of SIs. After comparing patients who had and had not experienced SIs using a univariate analysis, we selected adjusting factors for the multivariate analysis. The HRs for using TCZ compared with TNFI were 2.23 (95% CI, 0.93 to 5.37; $P = 0.074$) in all the patients and 1.93 (95% CI, 0.72 to 5.17; $P = 0.190$) in patients treated with MTX at baseline (Table 4). The use of oral corticosteroids (prednisolone-equivalent dose) ≥5 mg/day was a significant risk factor influencing the development of SIs (HR 2.26, 95% CI, 1.02 to 5.01, $P = 0.046$).

Discussion

In this study, we conducted a direct comparison of the safety of TCZ with TNFIs in clinical practice, using a prospective, multi-center cohort with the largest possible number of patients. We demonstrated that the unadjusted IR of SAEs was not significantly higher in the TCZ group compared with the TNFI group, whereas the unadjusted IR of SIs of the TCZ group was 3.5-fold higher than the TNFI group. However, after adjusting for covariates, the use of TCZ compared to the use of TNFIs was not significantly associated with the development of SAEs or SIs.

Some studies have investigated the safety of TCZ in RA patients [4,13,15,32-35]. It has been reported that the IR of SAEs was 20 to 30/100PY and that the most frequent SAE was infection (5 to 9/100PY) [4,14,15,36]. In the present study, the IRs of SAEs (21.36/100PY) and SIs (10.68/100PY) were similar to those of previous reports. The most frequently reported category of SAE in our study was infection and the incidence rate of non-pulmonary infection in the TCZ group was conspicuously higher compared to the TNFI group (7.57/100PY versus 1.73/100PY). Among non-pulmonary infections, skin and bone and joints were common sites in the TCZ

Table 4 Factors influencing development of SI in patients with RA treated with TCZ or TNFIs[a]

Variable	All patients		MTX users	
	HR (95% CI)[c]	P value[c]	HR (95% CI)[d]	P value[d]
Age by decade	1.34 (0.95 to 1.89)	0.093	1.31 (0.86 to 2.00)	0.210
Female	3.27 (0.77 to 13.98)	0.110	2.20 (0.49 to 9.93)	0.305
Comorbidity[b]	2.20 (0.95 to 5.11)	0.067	2.49 (0.87 to 7.10)	0.088
PSL ≥5 (mg/day)	2.26 (1.02 to 5.01)	0.046	2.04 (0.77 to 5.44)	0.154
Tocilizumab	2.23 (0.93 to 5.37)	0.074	1.93 (0.72 to 5.17)	0.190

[a]Cox regression hazard models were performed using the independent variables included in the Table; [b]comorbidity included pulmonary diseases, diabetes mellitus, liver diseases, and kidney diseases; [c]Cox regression analysis was applied in all patients; [d]Cox regression analysis was applied in patients who were treated with MTX at baseline. CI: confidence interval; HR: hazard ratio; MTX: methotrexate; PSL: prednisolone; RA: rheumatoid arthritis; SI: serious infection; TCZ: tocilizumab; TNFIs: tumor necrosis factor inhibitors.

group. Previous studies also reported that skin infections, as well as pulmonary infections, were frequently observed in patients treated with TCZ [4,15,24,33,37,38]. Although the reasons for the high incidence rates of these types of infections in patients given TCZ have not been explained, special attention should be paid, not only to pulmonary infections, but also to skin infections in TCZ users.

We found no increased risk for the use of TCZ compared to the use of TNFIs for the development of SIs after adjusting for covariates at baseline. It is notable that the unadjusted IR of SIs in the TCZ group (10.7 (7.02 to 15.6)) was significantly increased compared to the TNFI group (3.53 95%CI, 1.52 to 8.18); this can be explained by several factors. The multivariate analysis indicated that the differences in clinical characteristics of the patients between the two groups influenced the difference in IRs of SIs (Table 4). The use of oral corticosteroids (prednisolone-equivalent dose) ≥5 mg/day was a significant risk factor for SIs in our study. Previous studies have reported that use of oral corticosteroids significantly increased the risk of SIs in patients undergoing treatment with biologics [29,39,40]. Patients in the TCZ group of our study used concomitant corticosteroids more frequently. It has been shown that the presence of comorbidities increased the risk of SIs in RA patients [41]. Although the HR of comorbidities was 2.20 in our study, it did not achieve statistical significance ($P = 0.067$). Relatively more patients in the TCZ group than in the TNFI group had at least one comorbidity (34.1% for the TCZ group, 27.3% for the TNFI group, $P = 0.069$). These data indicate that patients in the TCZ group may be more predisposed to infections than those in the TNFI group.

The low IR of SIs in the TNFI group apparently contributed to the increased IRR of SIs. The IR of SIs in the TNFI group in our study (3.03/100 PY) was lower than in previous studies (5 to 6/100PY) [25,29,42,43], resulting in an increased IRR when comparing TCZ and TNFIs. We previously reported a significant decrease over time of the risk for SIs with TNFI treatment, possibly explained by evidence-based risk management of RA patients given TNFIs [44]. In the present study, patients in the TNFI group started TNFIs in or after 2008, five years after the approval of IFX for RA in Japan. Information about risk of SIs in patients given TNFIs from observational studies has been extensively shared among Japanese rheumatologists, leading to improved risk management and, in consequence, lowered IRs for SIs in the TNFI group [44]. To accurately compare the outcome between a new drug and an existing one, differences in the calendar year of drug approval should be considered. Therefore, in our study, we compared the use of two biologics, TCZ and TNFIs, in clinical practice during the same time period.

There are potential limitations of this study. First, we have to mention the possibility of selection bias. The patients in this study were enrolled from university hospitals or referral hospitals that are dedicated to the treatments of RA, which may indicate unidentified selection bias. However, because almost all patients who were registered from the participating hospitals to the all-cases post-marketing surveillance programs for each biological DMARD were enrolled in the REAL, selection bias was substantially low. Second, although there is concern about information bias, such as recall bias and reporting bias, in epidemiological studies in general, we collected patient data using the same case report form prospectively, which should overcome the misclassification and underestimation of SAEs derived from these types of bias. Third, clinical practice is always accompanied by the indication bias occurring when a drug is preferentially prescribed to patients with different baseline characteristics. In this study, it was notable that the difference in the percentage of patients who were given MTX at baseline between the two groups was significant, which would have affected the results of our study. To address this possibility, we estimated the risk of SAEs and SIs in patients with concomitant MTX in addition to the whole study population, and found them to be similar. Fourth, we did not investigate the comparison of effectiveness between the two groups due to incomplete data about disease activity in some patients.

Conclusions

The adjusted risks for SAEs and SIs between TCZ and TNFI were not significantly different in clinical practice, although significantly higher IRs for SIs were observed in the TCZ group, possibly attributable to more infection susceptible clinical characteristics of the patients in the TCZ group.

Additional file

Additional file 1: Demographic and clinical characteristics of RA patients treated with methotrexate at baseline. This file provides demographic and clinical characteristics of RA patients given methotrexate at baseline in this study.

Abbreviations

ABA: abatacept; ADA: adalimumab; CI: confidence interval; CRP: C-reactive protein; DAS28: disease activity score including 28-joint count; ETN: etanercept; HR: hazard ratio; IFX: infliximab; IL: interleukin; IQR: interquartile range; IR: incidence rate; IRR: incidence rate ratio; MTX: methotrexate; PCP: *Pneumocystis jirovecii* pneumonia; PMS: post-marketing surveillance; PSL: prednisolone; PY: patient-year; RA: rheumatoid arthritis; REAL: Japanese Rheumatoid Arthritis Patients on biologics for Long-Term Safety; SAE: serious adverse event; SI: serious infection; TCZ: tocilizumab; TNFI: tumor necrosis factor inhibitors.

Competing interests

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Authors' contributions

KR, MN, and HM conceived of the study, and participated in its design and coordination. SR and CSK participated in study design, data analysis, coordination and manuscript preparation. NT, WK, YH, TM, KR, TY, SK, HS, AK, NH, SumidaT, HT, SugiharaT, DH, YS, SawadaT, EK, UA, FT, MK, MN, and HM participated in data acquisition, data analysis, and revising the manuscript critically for important intellectual content. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

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References

1. Mihara M, Kasutani K, Okazaki M, Nakamura A, Kawai S, Sugimoto M, et al. Tocilizumab inhibits signal transduction mediated by both mIL-6R and sIL-6R, but not by the receptors of other members of IL-6 cytokine family. Int Immunopharmacol. 2005;5:1731–40.
2. Nishimoto N, Kishimoto T. Humanized antihuman IL-6 receptor antibody, tocilizumab. Handb Exp Pharmacol. 2008;181:151–60.
3. Maini RN, Taylor PC, Szechinski J, Pavelka K, Broll J, Balint G, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Arthritis Rheum. 2006;54:2817–29.
4. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J. Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis (the STREAM study): evidence of safety and efficacy in a 5-year extension study. Ann Rheum Dis. 2009;68:1580–4.
5. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis. 2010;69:88–96.
6. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. 2008;371:987–97.
7. Garnero P, Thompson E, Woodworth T, Smolen JS. Rapid and sustained improvement in bone and cartilage turnover markers with the anti-interleukin-6 receptor inhibitor tocilizumab plus methotrexate in rheumatoid arthritis patients with an inadequate response to methotrexate: results from a substudy of the multicenter double-blind, placebo-controlled trial of tocilizumab in inadequate responders to methotrexate alone. Arthritis Rheum. 2010;62:33–43.
8. Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum. 2008;58:2968–80.
9. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008;67:1516–23.
10. Kremer JM, Blanco R, Brzosko M, Burgos-Vargas R, Halland AM, Vernon E, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Arthritis Rheum. 2011;63:609–21.
11. Nishimoto N, Hashimoto J, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis. 2007;66:1162–7.
12. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol. 2009;19:12–9.
13. Takeuchi T, Tanaka Y, Amano K, Hoshi D, Nawata M, Nagasawa H, et al. Clinical, radiographic and functional effectiveness of tocilizumab for rheumatoid arthritis patients–REACTION 52-week study. Rheumatology (Oxford). 2011;50:1908–15.
14. Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, et al. Effectiveness and safety of tocilizumab: postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan. J Rheumatol. 2014;41:15–23.
15. Nishimoto N, Ito K, Takagi N. Safety and efficacy profiles of tocilizumab monotherapy in Japanese patients with rheumatoid arthritis: meta-analysis of six initial trials and five long-term extensions. Mod Rheumatol. 2010;20:222–32.
16. Smolen JS, Schoels MM, Nishimoto N, Breedveld FC, Burmester GR, Dougados M, et al. Consensus statement on blocking the effects of interleukin-6 and in particular by interleukin-6 receptor inhibition in rheumatoid arthritis and other inflammatory conditions. Ann Rheum Dis. 2013;72:482–92.
17. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. 2014;73:492–509.
18. Schoels M, Wong J, Scott DL, Zink A, Richards P, Landewe R, et al. Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2010;69:995–1003.
19. Schoels M, Aletaha D, Smolen JS, Bijlsma JW, Burmester G, Breedveld FC, et al. Follow-up standards and treatment targets in rheumatoid arthritis: results of a questionnaire at the EULAR 2008. Ann Rheum Dis. 2010;69:575–8.
20. Schoels M, Aletaha D, Smolen JS, Wong JB. Comparative effectiveness and safety of biological treatment options after tumour necrosis factor alpha inhibitor failure in rheumatoid arthritis: systematic review and indirect pairwise meta-analysis. Ann Rheum Dis. 2012;71:1303–8.
21. Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet. 2013;381:1541–50.
22. Leffers HC, Ostergaard M, Glintborg B, Krogh NS, Foged H, Tarp U, et al. Efficacy of abatacept and tocilizumab in patients with rheumatoid arthritis treated in clinical practice: results from the nationwide Danish DANBIO registry. Ann Rheum Dis. 2011;70:1216–22.
23. Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev. 2011;2, CD008794.
24. Yoshida K, Tokuda Y, Oshikawa H, Utsunomiya M, Kobayashi T, Kimura M, et al. An observational study of tocilizumab and TNF-alpha inhibitor use in a Japanese community hospital: different remission rates, similar drug survival and safety. Rheumatology (Oxford). 2011;50:2093–9.
25. Komano Y, Tanaka M, Nanki T, Koike R, Sakai R, Kameda H, et al. Incidence and risk factors for serious infection in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors: a report from the Registry of Japanese Rheumatoid Arthritis Patients for Longterm Safety. J Rheumatol. 2011;38:1258–64.
26. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315–24.
27. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. J Am Med Assoc. 1949;140:659–62.
28. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions and practical applications. Health Qual Life Outcomes. 2003;1:20.
29. Sakai R, Komano Y, Tanaka M, Nanki T, Koike R, Nagasawa H, et al. Time-dependent increased risk for serious infection from continuous use of tumor necrosis factor antagonists over three years in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012;64:1125–34.
30. Aringer M, Burkhardt H, Burmester GR, Fischer-Betz R, Fleck M, Graninger W, et al. Current state of evidence on 'off-label' therapeutic options for systemic lupus erythematosus, including biological immunosuppressive agents, in Germany, Austria and Switzerland–a consensus report. Lupus. 2012;21:386–401.
31. Furst DE, Keystone EC, Braun J, Breedveld FC, Burmester GR, De Benedetti F, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2011. Ann Rheum Dis. 2012;71:i2–45.
32. Bykerk VP, Ostor AJ, Alvaro-Gracia J, Pavelka K, Ivorra JA, Graninger W, et al. Tocilizumab in patients with active rheumatoid arthritis and inadequate