Association Between Medications and Herpes Zoster in Japanese Patients with Rheumatoid Arthritis: A 5-year Prospective Cohort Study

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ABSTRACT. ***Objective.*** To investigate the association between medications and herpes zoster (HZ) in patients with rheumatoid arthritis (RA) given biological disease-modifying antirheumatic drugs (bDMARD) or conventional synthetic DMARD in the clinical setting during 5 years using the Registry of Japanese Rheumatoid Arthritis Patients on Biologics for Longterm Safety (REAL) database.

Methods. We calculated the crude incidence rate (IR) of HZ treated with systemic antiviral medications in 1987 patients from the REAL database. To estimate the association between HZ and medications, a nested case control study was performed with 1:5 case-control pairs matched for age, sex, observation start year, and comorbidity (HZ case group, n = 43; control group, n = 214). We calculated OR and 95% CI of the use of bDMARD, methotrexate (MTX), and corticosteroids for the occurrence of HZ using a conditional logistic regression analysis.

Results. The median patient age was 60.0 years, female proportion was 81.5%, and median disease duration was 6.0 years. The crude IR (95% CI) of HZ was 6.66 (4.92–8.83)/1000 person-years. The OR (95% CI) of medication use were 2.28 (1.09–4.76) for tumor necrosis factor inhibitor (TNFi) and 1.13 (1.03–1.23) for oral corticosteroids dosage (per 1 mg prednisolone increment), both of which were significantly elevated. The OR of non-TNFi and MTX usage were not elevated.

Conclusion. TNFi use and higher corticosteroids dosage were significantly associated with HZ in Japanese patients with RA in the clinical setting. (First Release April 15 2017; J Rheumatol 2017;44:988–95; doi:10.3899/jrheum.161196)

Key Indexing Terms:
RHEUMATOID ARTHRITIS HERPES ZOSTER ANTIRHEUMATIC AGENTS
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Herpes zoster (HZ) is caused by the reactivation of latent varicella-zoster virus infection and usually responds well to treatment with antiviral drugs. However, HZ often causes postherpetic neuralgia and impairs quality of life in affected individuals, and it can lead to cutaneous dissemination or visceral organ involvement, especially in immunocompromised patients. The risk of HZ was reportedly associated with chronic conditions such as chronic obstructive pulmonary disease, bronchial asthma, chronic kidney disease, and depression, as well as severe immunocompromise[1]. There has been concern about the association between rheumatoid arthritis (RA) and HZ because of the altered immune system of patients with RA and the use of immunosuppressive drugs for treating the disease. Patients with RA showed about a 2-fold increase in the risk of HZ compared to individuals without RA[2]. Previous studies in Europe and the United

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States reported that the incidence rate (IR) of HZ in patients with RA was 8–16/1000 patient-years (PY)[2,3,4,5,6], and older age[3,7] and the use of corticosteroids[2,3,7,8] were identified as significant risk factors. The American College of Rheumatology recommendations state that patients with RA age ≥ 50 years should be given the HZ vaccine before receiving biological disease-modifying antirheumatic drugs (bDMARD)[9]. In Japan, vaccination for HZ was just approved in 2016 for people age ≥ 50 years; however, efficacy and safety in patients with RA has not been demonstrated yet.

Tumor necrosis factor inhibitors (TNFi) have superior clinical efficacy for patients with RA compared to conventional synthetic DMARD (csDMARD) and have become indispensable for the treatment of RA. The use of TNFi is associated with an increased risk of infection[10,11,12,13], and a 4-fold increase in the risk of skin and soft-tissue infections was reported in patients with RA under treatment with TNFi[14]. HZ is a clinically important infection in patients with RA who take TNFi because HZ accounts for more than half of the skin and soft-tissue infections in these patients[13]. Data from population-based studies revealed that the IR of HZ in patients with RA had a tendency to increase after the introduction of aggressive treatments such as bDMARD and high-dose methotrexate (MTX)[2]. Some investigators reported that TNFi use significantly increased the risk of HZ compared to csDMARD use[5,15], whereas others showed a similar risk of HZ between TNFi and csDMARD use[7,8]. Regarding the association of HZ with non-TNFi use, there are a limited number of studies that have investigated it, and 1 study showed a similar risk of HZ between TNFi use and non-TNFi use[16].

In Japan, a retrospective cohort study in a single hospital revealed that the risk of HZ in patients with RA was double that of patients with chronic diseases other than RA[17]. In a single institute-based large prospective cohort of Japanese patients with RA, the crude IR of HZ was 12.1/1000 PY[18]. Older age, higher disease activity, higher corticosteroids dosage, and MTX use were risk factors of HZ, but the use of bDMARD was not[18]. In the Japanese postmarketing surveillance (PMS) programs for patients with RA starting a bDMARD, the percentages of patients who developed HZ during 6 months of observation were 0.8% for etanercept (ETN), 1.1% for tocilizumab (TCZ), 0.9% for adalimumab (ADA), and 1.0% for abatacept (ABA)[19,20,21,22]. These PMS studies, however, could not compare the risk of HZ between bDMARD and csDMARD because of the lack of a comparator arm, and few Japanese studies have addressed this clinical question. Moreover, the higher risk of HZ in patients with RA in Asia including Japan has been reported in clinical trials of tofacitinib[23]. In our study, we assessed the association of bDMARD, MTX, and corticosteroids with occurrence of HZ in Japanese patients with RA using the database of the multiinstitutional prospective cohort.

MATERIALS AND METHODS

Database. We used the Registry of Japanese Rheumatoid Arthritis Patients on Biologics for Longterm Safety (REAL) database. Details of the REAL database have been described[24]. In brief, the REAL is a prospective cohort study that was established to investigate the longterm safety of bDMARD in patients with RA. Twenty-seven institutions including 16 university hospitals and 11 referring hospitals participate in the REAL. The criteria for enrollment to the REAL database include those patients meeting the 1987 American College of Rheumatology criteria for RA[25], written informed consent, and starting or switching treatment with bDMARD or csDMARD at the time of enrollment. Enrollment in the REAL database was started in June 2005 and closed in January 2012. For our study, data were retrieved from the database on March 31, 2013. Our study was in compliance with the Declaration of Helsinki (revised in 2008). The REAL study was approved by the ethics committees of the Tokyo Medical and Dental University Hospital (approval number CHI-16-34) and the other participating institutions.

Data collection. Each patient's recorded baseline data included demographics, disease duration, Steinbrocker class and stage[26], comorbidities, number of previous DMARD, disease activity, and RA treatments. A followup form was submitted every 6 months up to 5 years to the REAL Data Center at the Department of Pharmacovigilance of Tokyo Medical and Dental University by the site investigators to report the occurrence of serious adverse events (SAE), current RA disease activity, treatments, and clinical laboratory data. The investigators in each hospital confirmed the accuracy of their data submitted to the REAL Data Center. The REAL Data Center checked all of the data and made inquiries as needed to verify the data accuracy and improve its quality.

Patients and followup. We analyzed 1987 patients whose baseline and at least 1 set of followup data were fixed until March 31, 2013. The start of the observation was the date that the bDMARD or csDMARD were administrated or switched. The observation period stopped either on the day a patient died or met the exclusion criteria, on March 31, 2013, or 5 years after the start of the observation period, whichever came first. The observation was continued irrespective of treatment changes in our study.

Definition of HZ. In the REAL study, SAE were collected based on the report by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use[27]. Opportunistic infections including HZ were also reported. HZ was clinically diagnosed by the site investigators and reported to the REAL Data Center. We also collected details about distribution of rash, treatment of HZ, and presence of postherpetic neuralgia. In our study, we analyzed confirmed cases that required intravenous or oral administration of antiviral medications.

Statistical analysis. First, we analyzed the demographics and clinical characteristics of the 1987 patients at baseline in our population and calculated the crude IR with 95% CI of HZ per 1000 PY. The cumulative IR of HZ was analyzed using the Kaplan-Meier method. Second, to estimate the association between the occurrence of HZ and the use of medications precisely, we conducted a nested case control (NCC) study because the treatments and dosages of immunosuppressive drugs such as MTX and oral corticosteroids change over time. For each patient who developed HZ during the observation period (case group), the date when HZ occurred was defined as the index date. For a patient who developed HZ multiple times during the observation period, the first date it occurred was defined as the index date. We randomly selected 5 control patients matched for age at index date (± 3 yrs), sex, observation start year (i.e., 2005–2007 or 2008–2011), and comorbidity (pulmonary disease, renal failure or diabetes mellitus) at baseline who had not developed HZ until the index date of each case. We compared the following patient characteristics and drug exposures between the case and control groups using univariate analysis: observation start year, disease duration, Steinbrocker class, Steinbrocker stage, 28-joint Disease Activity Score by C-reactive protein, comorbidity at baseline, the use of bDMARD during the 90 days preceding the index date, the use of MTX during the 7 days preceding the index date, and the use of other DMARD and oral corticosteroids at the index date. In the univariate analyses, we used the

chi-square test for categorical variables and the Student t test or the Mann-Whitney U test for continuous variables depending on the distribution of the data.

To assess the association between the occurrence of HZ and the use of bDMARD, we used conditional logistic regression analysis with a stepwise backward elimination method and calculated OR with 95% CI. Covariates included in the conditional logistic regression model were chosen based on the results of univariate analysis. As sensitivity analyses, we used drug exposure at different timepoints for the multivariate models. Statistical analyses were performed using SPSS (version 22.0; SPSS Inc.). All p values were 2-tailed and p values < 0.05 were considered statistically significant. We evaluated the significance of p values that were obtained with conditional logistic regression analysis using the false discovery rate and the Benjamini and Hochberg method[28].

RESULTS

Patient disposition. Figure 1 shows the number of patients who remained in and dropped out of the analysis by year during the observation. Of the 2033 patients enrolled in the

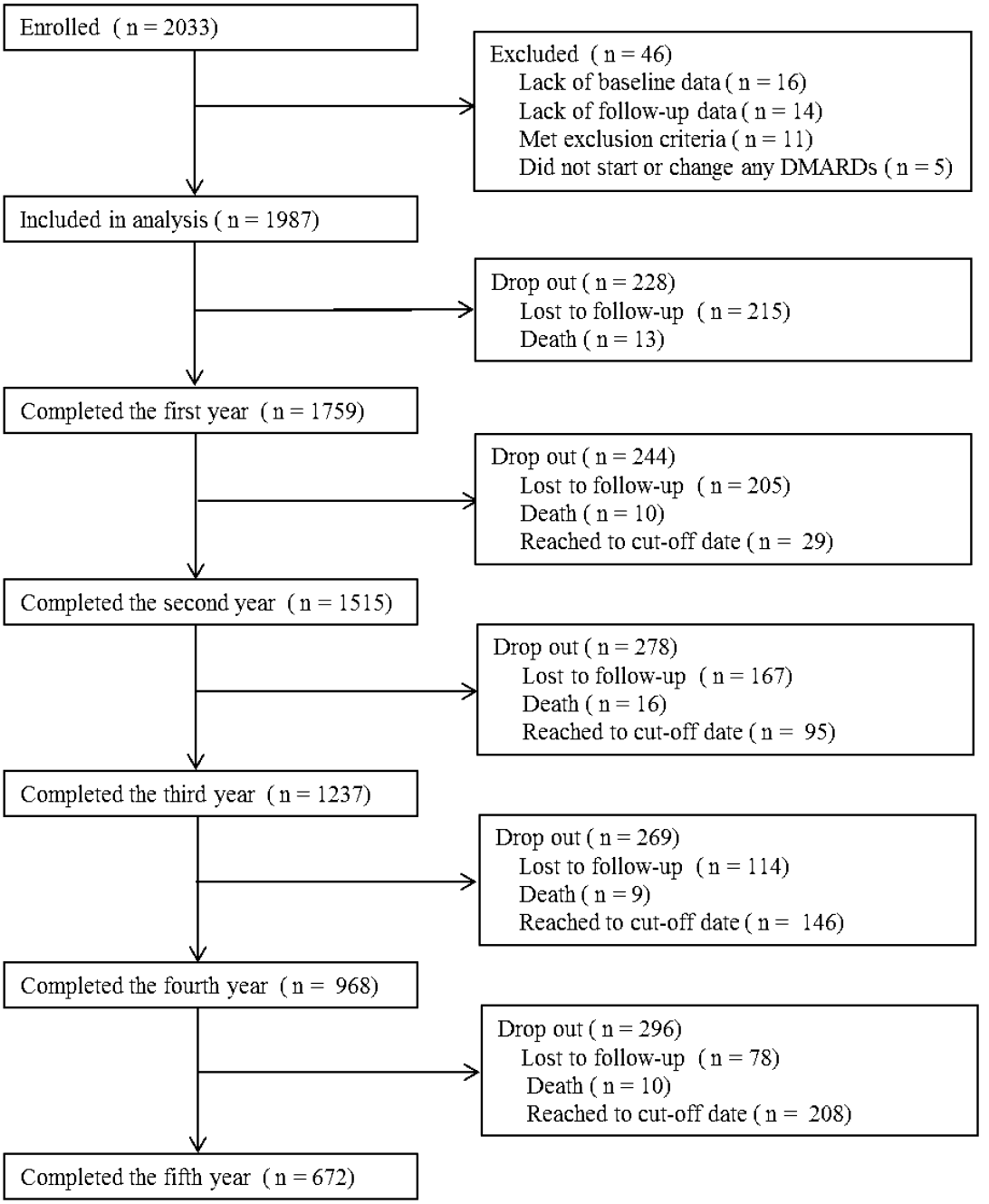

Figure 1. Distribution of numbers of patients during the 5-year observation period in the Registry of Japanese Rheumatoid Arthritis Patients on Biologics for Longterm Safety study. Of the 2033 patients who were registered in the REAL study, 46 were excluded from our study for the described reasons. The remaining 1987 patients were analyzed. Of them, 672 completed 5 years of observation. DMARD: disease-modifying antirheumatic drugs.

REAL study, 46 were excluded from this study and 1987 were included; 672 completed the 5-year observation, 478 reached the cutoff date (i.e., March 31, 2013) before the 5-year observation, 779 were lost to followup, and 58 died.

Baseline characteristics of the patients. The baseline data for the 1987 patients are shown in Table 1. The total followup time was 6753.5 PY and the median [interquartile range (IQR)] was 3.92 years (2.00–5.00). The median (IQR) age was 60.0 years (51.0–68.0), female proportion was 81.5%, and the median (IQR) disease duration was 6.0 years (1.9–13.2). The percentage of patients with comorbidities was 57.4% and the most frequent comorbidity was pulmonary disease (16.9%), followed by diabetes mellitus (9.6%). Of the 1987 patients, 1222 (61.5%) used bDMARD and 1274 (64.1%) used MTX. The median dosage (IQR) of MTX was 8.0 (6.0–8.0) mg/week. Oral corticosteroids were used in 1193 patients (60.0%) and the median dosage (equivalent dose of prednisolone) was 5.0 (4.0–7.0) mg/day.

Incidence rates of HZ. Of the 1987 patients, 43 (45 events; 1 patient had HZ 3 times) developed HZ during the observation period (IR 6.66, 95% CI 4.92–8.83/1000 PY). The second column of Table 2 shows the characteristics of patients who developed HZ. The median (IQR) period from the start of the observation to the index date was 1.7 years (1.1–2.6). The median (IQR) age was 64.0 years (57.0–72.0), the proportion of females was 86.0%, and the median (IQR) disease duration was 8.0 years (2.0–15.0). Figure 2 shows the cumulative IR of HZ. HZ developed at a constant rate during the observation period. The observation was continued as described irrespective of changes in treatments in this Kaplan-Meier analysis. Among the 42 events with the detailed information about HZ, 5 events were reported as disseminated HZ and 12 events were accompanied by postherpetic neuralgia. The types of antiviral medications used were acyclovir (21 events), valacyclovir (18 events), acyclovir and valacyclovir (1 event), and famcyclovir (1 event). The median treatment period (IQR) of 38 events with available information was 7 days (7–7.75).

Table 1. Baseline characteristics of patients. Data are n (%) unless otherwise specified.

Characteristics	N, total = 1987
Median age, yrs (IQR)	60.0 (51.0–68.0)
Age ≥ 65 yrs	707 (35.6)
Female	1620 (81.5)
Median disease duration, yrs (IQR)	6.0 (1.9–13.2)
Steinbrocker class 3 or 4	422 (21.2)
Steinbrocker stage III or IV	877 (44.1)
Median DAS28 3/CRP (IQR), n = 1699	4.2 (3.3–5.1)
Any comorbidity	1140 (57.4)
Pulmonary disease	336 (16.9)
Liver disease	93 (4.7)
Renal disease	62 (3.1)
Diabetes mellitus	190 (9.6)
Malignancies	11 (0.6)
Use of biological DMARD	1222 (61.5)
Use of MTX	1274 (64.1)
Median dosage of MTX, mg/week (IQR)	8.0 (6.0–8.0)
Use of immunosuppressive DMARD*	209 (10.5)
Use of oral corticosteroids	1193 (60.0)
Median dosage of PSL#, mg/day (IQR)	5.0 (4.0–7.0)

*Immunosuppressive DMARD include tacrolimus, leflunomide, mizoribine, azathioprine, and cyclophosphamide. #The oral corticosteroids dose was converted to the equivalent prednisolone dosage. Steinbrocker classification[26] was used to define rheumatoid arthritis disease stages and classes. Pulmonary diseases include interstitial pneumonia, chronic obstructive pulmonary disease, bronchial asthma, prior pulmonary tuberculosis, and bronchiectasis. IQR: interquartile range; DAS28 3/CRP: Disease Activity Score including 28-joint count and C-reactive protein; DMARD: disease-modifying antirheumatic drugs; MTX: methotrexate; PSL: prednisolone.

NCC analysis. For each patient who developed HZ, 5 patients matched for age at index date, sex, observation start year, and comorbidity (pulmonary disease, renal failure, or diabetes mellitus) at baseline were included in the NCC analysis. One case had only 4 matched controls, and the total number of the control group was 214. The characteristics of the 43 cases and the 214 controls are shown in Table 2. Univariate analyses revealed that disease duration, Steinbrocker class and stage classifications, disease activity, and comorbidities at baseline were not significantly different between the 2 groups. The percentage of the use of bDMARD during the 90 days preceding the index date was significantly higher than that of the control group ($p = 0.034$). The percentages of immunosuppressive DMARD use [i.e., tacrolimus, leflunomide (LEF), mizoribine, azathioprine, and cyclophosphamide], MTX use, and oral corticosteroid use were not significantly different between the 2 groups. The median MTX dosage of the case group was significantly higher than that of the control group ($p = 0.002$), whereas the dosage of oral corticosteroids was similar in the 2 groups (Table 2). A conditional logistic regression analysis with a stepwise backward elimination was applied to estimate the associations between the occurrence of HZ and the medications for RA including bDMARD use (vs no use), MTX dosage, and oral corticosteroids dosage (Table 3). The OR (95% CI) of TNFi use (vs no use) was 2.28 (1.09–4.76), which was significantly elevated. The OR of non-TNFi use (TCZ or ABA; vs no use) was not significant. Oral corticosteroids dosage [per 1 mg increment by equivalent dosage of prednisolone; 1.13 (1.03–1.23)] was also significantly associated with the occurrence of HZ.

As sensitivity analyses, we used MTX treatment during the 14 or 28 days preceding the index date instead of 7 days or the bDMARD use during the 30 days preceding the index date instead of 90 days in the multivariate model and obtained essentially the same results (data not shown).

DISCUSSION

We assessed the association between medication use and HZ occurrence in patients with RA in the clinical setting using

Table 2. Comparison of characteristics of cases and controls of the NCC study. Data are n (%) unless otherwise specified.

Characteristics	Case group, n = 43	Control group, n = 214[##]	p
Median age*, yrs (IQR)	64.0 (57.0–72.0)	63.5 (56.0–71.0)	—
Female	37 (86.0)	184 (86.0)	—
Observation start year after 2008[#]	15 (34.9)	74 (34.6)	—
Median disease duration, yrs[#] (IQR)	8.0 (2.0–15.0)	7.0 (2.3–14.1)	0.674
Steinbrocker class 3 or 4[#]	12 (27.9)	77 (36.0)	0.310
Steinbrocker stage III or IV[#]	26 (60.5)	113 (52.8)	0.358
Median DAS28 3/CRP[#] (IQR)	4.4 (3.6–5.6), n = 39	4.2 (3.3–5.2), n = 173	0.169
Any comorbidity[#]	29 (67.4)	132 (61.7)	0.476
Pulmonary disease, renal failure, or diabetes mellitus	14 (32.6)	69 (32.2)	—
Pulmonary disease	13 (30.2)	65 (30.4)	0.985
Liver disease	1 (2.3)	6 (2.8)	0.668
Renal failure	1 (2.3)	7 (3.3)	0.602
Diabetes mellitus	5 (11.6)	26 (12.1)	0.924
Malignancies	1 (2.3)	1 (0.5)	0.307
Autoimmune disease other than RA	7 (16.3)	19 (8.9)	0.119
Others	17 (39.5)	79 (36.9)	0.746
Use of biological DMARD*	34 (79.1)	133 (62.1)	0.034
TNFi	30 (69.8)	110 (51.4)	0.027
Infliximab	7 (16.3)	40 (18.7)	0.709
Adalimumab	4 (9.3)	15 (7.0)	0.396
Etanercept	19 (44.2)	55 (25.7)	0.015
Non-TNFi	4 (9.3)	23 (10.7)	0.516
Tocilizumab	4 (9.3)	21 (9.8)	0.590
Abatacept	0 (0.0)	2 (0.9)	0.693
Use of immunosuppressive DMARD* ^	5 (11.6)	31 (14.5)	0.622
Use of MTX*	23 (53.5)	133 (62.1)	0.289
Median dosage of MTX, mg/week (IQR)	8.0 (8.0–10.0)	8.0 (6.0–8.0)	0.002
MTX > 8 mg/week	8 (18.6)	23 (10.7)	0.149
Use of oral corticosteroids*	27 (62.8)	120 (56.1)	0.417
Median dosage of PSL**, mg/day (IQR)	5.0 (3.0–10.0)	5.0 (3.0–5.8)	0.153
PSL ≥ 5 mg/day**	15 (34.9)	65 (30.4)	0.560

*Data on age and oral corticosteroids use were recorded at index date; biological DMARD use during the 90 days preceding the index date; immunosuppressive DMARD use at the index date; and methotrexate use during the 7 days preceding the index date. [#]Data were collected at baseline on the observation start year, disease duration, Steinbrocker class, Steinbrocker stage, DAS28 3/CRP, and comorbidity. ^Immunosuppressive DMARD include tacrolimus, leflunomide, mizoribine, azathioprine, and cyclophosphamide. **The oral corticosteroids dosage was converted to the equivalent prednisolone dosage. [##]One case had only 4 matched controls. Steinbrocker classification[26] was used to define RA disease stages and classes. IQR: interquartile range; DAS28 3/CRP: Disease Activity Score including 28-joint count and C-reactive protein; RA: rheumatoid arthritis; DMARD: disease-modifying antirheumatic drugs; MTX: methotrexate; PSL: prednisolone; NCC: nested case control.

the REAL database. In this patient population with RA, HZ developed at a constant rate and the crude IR of HZ was 6.66/1000 PY. The NCC and conditional logistic regression analysis revealed that TNFi use and higher oral corticosteroids dosage were the significant risk factors for the occurrence of HZ.

It was reported that the IR of HZ in patients with RA was 8–16/1000 PY[2,3,4,5,6,29] using the health insurance claims data or the RA registries from Western countries, whereas the IR of HZ in our study was 6.66/1000 PY and relatively low. The differences in the IR of HZ between these studies and ours could be explained by several factors. First, the ethnic difference in the susceptibility to HZ could explain the results. The incidence of HZ in the general population, however, was 4.15/1000 PY in Miyazaki prefecture in Japan[30], which was quite similar to those of the United States (3.7/1000 PY[6] and 5.4/1000 PY[2]) and the United Kingdom (4.1/1000 PY[6]). Second, the age distribution of the study subjects could influence the IR of HZ because age was an established significant risk factor of HZ[3,7]. In our study, the proportion of patients ≥ 65 years of age was 35.6%, whereas in the study using the health insurance claims database of the United Kingdom, the proportion of elderly patients was 41.8%[6], which could lead to the higher IR of HZ (10.6/1000 PY). Third, it was also shown that corticosteroid use was a risk factor of HZ[2,3,7,8]. The rate of patients with RA using

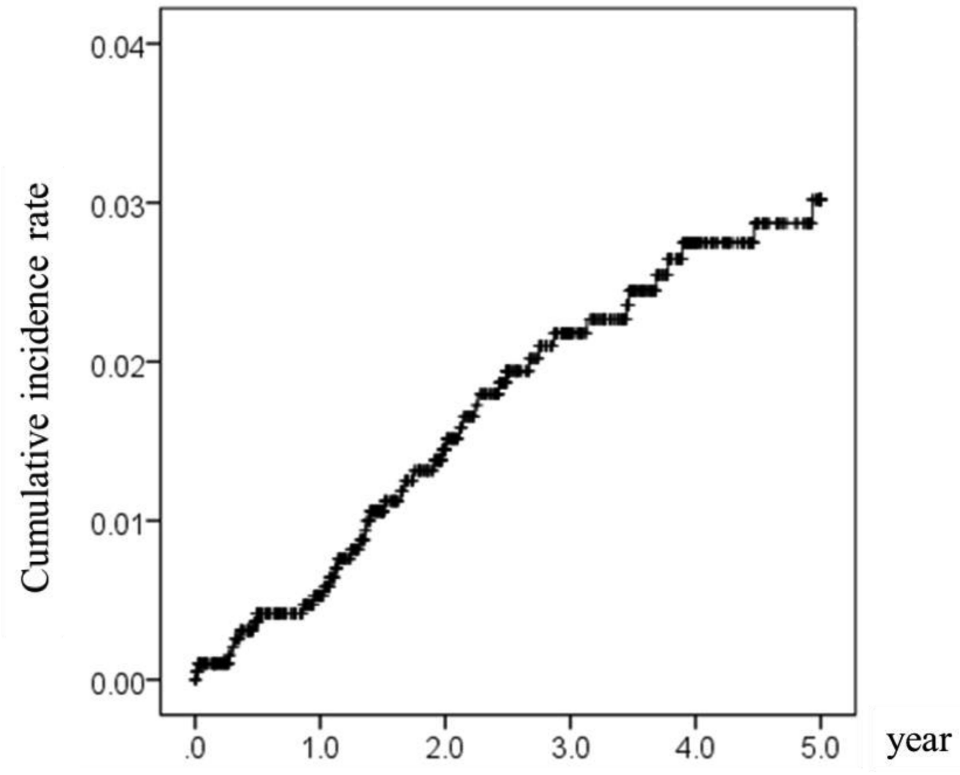

Figure 2. Cumulative incidence rates of herpes zoster (HZ). The Kaplan-Meier curves show the cumulative incidence rate of HZ in the 1987 patients during the observation period. The observation was continued irrespective of changes in treatments.

Table 3. Association between the medications for RA and HZ in the NCC study.

Medications	OR (95% CI)	p
Use of TNFi# **	2.28 (1.09–4.76)	0.028*
PSL dosage (per 1 mg/day increment) **	1.13 (1.03–1.23)	0.008*

To assess the association of the medications for RA and HZ, use of TNFi, and use of non-TNFi, MTX dosage and PSL dosage were put into the conditional logistic model as dependent variables with a stepwise backward elimination method. *Statistically significant after correction for multiple testing using false discovery rate and Benjamini and Hochberg method[28]. #Versus no use of biological DMARD. **Use of TNFi during the 90 days preceding the index date was collected. Prednisolone dosages were collected at the index date. The eliminated variable (i.e., use of non-TNFi and MTX) was collected as shown in the legend of Table 2. RA: rheumatoid arthritis; HZ: herpes zoster; NCC: nested case control; TNFi: tumor necrosis factor inhibitor; MTX: methotrexate; PSL: prednisolone; DMARD: disease-modifying antirheumatic drugs.

oral corticosteroids in Olmsted County, Minnesota, USA was higher than that of our study (77% vs 60.0%, respectively), and the IR was 12.1/1000 PY[2]. Fourth, the presence of chronic lung disease, renal failure, liver disease, and malignancy also increased the risk of HZ[3]. The low percentage of comorbidities in the REAL database could be one of the reasons for the low IR of HZ. In addition, the differences in definition of HZ among the studies should be considered. The IR of HZ defined by diagnosis code alone was 20%–30% higher than that of HZ defined by treatment and diagnosis codes[8]. The study using the US health insurance claims database defined the HZ by diagnosis code only and reported a higher IR of HZ (9.8/1000 PY) than this study, in which HZ was confirmed by the medical records and use of antiviral drugs[6].

Changes in drug exposure during the observation period were not considered in most of the previous studies. Because treatments for RA can change during the clinical course, we implemented the NCC study to precisely evaluate the association between treatments for RA and HZ occurrence. In our study, TNFi use was identified as a significant risk factor for the occurrence of HZ. Some studies showed the same results[3,4,5,15,31], whereas others did not[8,18]. Winthrop, *et al* reported that the risk of HZ in TNFi users was similar to that in csDMARD users (HR 1.00, 95% CI 0.77–1.29)[8]. The discordance of the risk of TNFi between this and the Winthrop study could be derived from the difference in the treatment of the comparator; about 40% of the csDMARD users had LEF in the previous study, whereas in our study, only 10.5% of all patients had immunosuppressive DMARD including LEF. Nakajima, *et al* reported that bDMARD use was not a risk factor for HZ (HR 1.16, 95% CI 0.74–1.81)[18].

In that study, data on the use of medications for RA were collected twice a year (i.e., in April and October) for all patients and these data were used for time-adjusted Cox regression analysis. Hence, there could be a time lag of up to 6 months between the collection of medication data and the occurrence of HZ. This and other differences in the statistical methods might affect the risk of the medications for occurrence of HZ and could explain the difference in the risk of TNFi between the studies.

In our study, not using TNFi was not identified as a risk factor for the occurrence of HZ. The number of non-TNFi users in the case group was only 4, which was apparently smaller than the corresponding numbers of TNFi users. In addition, the incidence of HZ in the Japanese PMS programs was similar across the bDMARD[19,20,21,22]. These data indicate that it is necessary to conduct further study to determine more precisely the risk of nonuse of TNFi for HZ.

Our study has several limitations. First, we have to consider selection bias. The REAL study was implemented in institutions dedicated to the treatment of RA. The relatively low incidence of HZ in this study might be related to appropriate risk management for patients with RA in these institutions. Second, if the patients visited other institutions at the occurrence of HZ and did not report the occurrence of HZ to their attending physicians, the IR of HZ could be underestimated. Third, we have to consider the influence of the patients who were lost to followup during the observation period on the incidence of HZ. Fourth, we could not include disease activity, comorbidity, structural damage, and physical function at the index dates in our statistical model because of a lack of data. Fifth, the number of events was relatively small in this study, so we could not compare the risk for HZ between different bDMARD users. To overcome some of these limitations, it is necessary to examine the incidence and risk factors of HZ using a larger database in the near future.

We showed that TNFi use and higher corticosteroid dosage were significantly associated with the occurrence of HZ. Our results suggest that careful monitoring for HZ is necessary in patients with RA using these drugs.

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APPENDIX 1.

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