

Comparison of serious adverse event profiles
among anti-rheumatic agents using
Japanese Adverse Drug Event Report database

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Abstract

Background. The association between drugs and adverse events (AEs) has been investigated using various AE databases. The aim of this study was to provide useful information for risk minimization of anti-rheumatic agents by investigating the safety profiles of anti-rheumatic agents using the Japanese Adverse Drug Event Report database (JADER), focusing on some important serious AEs (SAEs) and their relation to time. In addition, the influence of aging on SAEs in patients treated with anti-rheumatic agents was examined.

Methods. Tumor necrosis factor-alpha inhibitors (TNF-I), interleukin-6 inhibitors (IL-6-I), and methotrexate (MTX) were selected as anti-rheumatic agents. Infections, malignant tumors, and bone marrow disorders were selected as typical SAEs for rheumatoid arthritis, which are indicated in the guidelines. Disproportionate reporting of these SAEs was evaluated using the reporting odds ratio. Time-to-onset of each SAE was calculated using date information. Further, the relationship between age and AEs such as infections and malignant tumors in patients treated with TNF-I or MTX was evaluated by logistic regression analysis.

Results. Increased reporting odds ratios for infections and malignant tumors were observed in patients treated with TNF-I and IL-6-I, and for infections, malignant tumors, and bone marrow disorders were observed in patients treated with MTX. The median

times-to-onset of the focused SAEs in patients treated with TNF-I were 356, 681, and 254 days, respectively, those in patients treated with IL-6-I were 342, 636, and 116 days, and those in patients treated with MTX were 541, 1,125, and 328 days. These results suggested different time profiles for the focused SAEs. The risk of infections associated with patients treated with TNF-I was higher in the group of patients greater than 70 years old compared to patients 50-59 years old as a reference group, and the risk was lower in the group of patients less than 50 years old. The risk of malignant lymphoma associated with patients treated with MTX was higher in the group of patients 70-79 years old.

Conclusion. The time-to-onset profiles of the SAEs for TNF-I, IL-6-I and MTX as anti-rheumatic agents were different among different SAEs, which suggests that they should be monitored carefully based on the profiles. As for the influence of aging on AEs, for infections associated with patients treated with TNF-I, physicians should observe patients in accordance with their age, with more careful observation in elderly patients. Since JADER is considered to reflect actual clinical practice in the post-marketing stage, the information from JADER is expected to contribute to the minimization of risks of drugs.

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Abbreviations

AE	Adverse Event
CI	Confidence Interval
csDMARDs	conventional synthetic disease-modifying anti-rheumatic drugs
FAERS	FDA Adverse Event Reporting System
FDA	US Food and Drug Administration
IL-6-I	Interleukin-6 Inhibitor
JADER	Japanese Adverse Drug Event Report database
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
PMDA	Pharmaceuticals and Medical Devices Agency
RA	Rheumatoid Arthritis
ROR	Reporting Odds Ratio
SAE	Serious Adverse Event
SMQ	Standard MedDRA Queries
TNF-I	Tumor Necrosis Factor-alpha Inhibitor
WHO	World Health Organization

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of joints and causes joint destruction and disability. In recent years, treatment of RA has shifted to a proactive approach using a combination of a biological product such as an anti-TNF- α antibody and conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), and it is now possible to control disease activity and improve function.

On the other hand, infection has been observed in clinical trials and post-marketing surveillance of biologics, and thus the package inserts and treatment guidelines of biologics contain a statement to call for attention to it. However, little information is available about the time to onset of infection in patients treated with individual biologics in actual clinical practice. Some biologics are said to have a possibility to increase the occurrence of malignant tumors because of their mode of action, and the post-marketing monitoring for this effect has continued. Based on the results, the medical community has been discussing whether treatment with biologics increases the risk of malignant tumors. In addition, although it is expected that the number of elderly RA patients will increase, no studies on the effects of aging on such adverse events (AEs) in patients treated with anti-rheumatic drugs have been reported.

It is well known that there are several limitations in clinical trials conducted

during new drug development, such as an insufficient number of patients, a short treatment period, a restriction of combination therapy and concomitant medication, shortage of pediatric or elderly patients, and an exclusion of patient with liver or kidney diseases [1]. Therefore, it is difficult to fully predict the effectiveness and safety of the product in actual clinical practice. Unexpected AEs often come to light after the launch of a new drug due to the rapid increase in the number of patients who receive the medication and the diversification of patient background. Meanwhile, after the approval of a new drug, use-results survey and post-marketing clinical studies are carried out, and additional safety information is accumulated. Also, spontaneously reported AEs are evaluated in detail. These activities will contribute to identify risk factors for AEs in actual clinical practice. As a result, appropriate safety measures are taken, such as preparing information materials to call for attention, revising packaging inserts, and changing approval contents, which lead to minimizing risks of drugs.

In recent years, various AE databases are available and several studies using such AE databases to evaluate safety of pharmaceutical products have been conducted. AE databases are often used for evaluating the relationship between drugs and AEs, and such databases are maintained by national regulatory authorities including Japan, the United States and Europe, and international organization such as World Health

Organization (WHO).

The Japanese Adverse Drug Event Report database (JADER) is a database of spontaneously reported AEs consisting of information about serious AEs (SAEs) in Japan and is published in the website of the Pharmaceuticals and Medical Devices Agency (PMDA). JADER contains SAE information reported to PMDA as suspected adverse drug reactions since 2004 (Table 1). It has been published since April 2012, and various studies on pharmaceutical safety based on JADER have been reported so far [2, 3]. In research using AE databases, several methods have been developed to analyze the imbalance between drugs and AE reports to identify safety signals, and the crude reporting odds ratio (ROR) is used for this purpose in PMDA and the Pharmacovigilance Center in the Netherlands [4].

Table 1. Overview of the JADER

	JADER
Cases reported to PMDA since	2004
Cases published since	April 2012
Number of cases	Over 680,000 (from 2004 to 2016)
Form of cases reported by physicians and patients	Pharmaceutical safety information report (health care professionals), Patient adverse drug reaction report
Format of shared data	Comma-separated value, latest full set
Frequency of update	Quarterly per year
Medical terminology	MedDRA
Substance name availability	Regulated text-based substance name
Targeted products for reporting	Medicinal products, over-the-counter drugs, combination products with medical devices, vaccines, biologics
Primary suspected drug	Registered by brand name
Concomitant suspected drug	Registered by generic name
Reporter	Physician, pharmacist, other health care professional, patient
Case seriousness for company reporting	Serious cases (concomitant non-serious adverse events can be included)
Country of original report	Japan

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities

Based on these considerations, we performed a database study using JADER to generate information to minimize the risk of anti-rheumatic agents with the aim of contributing to the optimization of benefit to risk balance of these agents. In the studies summarized in study Part 1, we focused on some important SAEs for anti-rheumatic agents and evaluated their profiles, such as the crude ROR and the time-to-onset of AEs based on JADER. In study Part 2, we examined the influence of aging on AEs for anti-rheumatic agents.

This research does not contain any studies with human or animal subjects performed by the author.

2. Part 1

2.1 Background

After the approval of infliximab for the RA indication in July 2003, nine biologics have been launched with RA indication in Japan. Tumor necrosis factor-alpha inhibitors (TNF-I) including infliximab are expected to improve the clinical condition and physical function of RA patients, and to inhibit the progression of joint destruction, by blocking the binding of TNF-alpha to its receptor. Interleukin-6 inhibitors (IL-6-I) are expected to produce similar effects by inhibiting the biological activity of IL-6 in RA patients. Before the launch of these biologics, csDMARDs such as methotrexate (MTX), sulfasalazine, and auranofin were prescribed to improve the disease condition of RA patients. With the advent of biologics, it is now possible to control disease activity and improve function.

Another important factor in evaluation of drugs for RA is their safety profile. For example, infection has been observed in clinical trials and post-marketing surveillance of biologics, and thus the package insert and treatment guidelines of biologics contain a caution about it. However, little information is available about the time-to-onset of infection in patients treated with individual biologics in actual clinical practice. In addition, biologics may increase the occurrence of malignant tumors [5, 6]

due to their mode of action, and the post-marketing monitoring for this has continued.

In recent years, several studies have been conducted using AE databases to evaluate the safety of pharmaceutical products. Now there are various AE databases available including Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), European EudraVigilance, and JADER. In the RA therapeutic area, several studies with these AE databases have been performed. Some research studies used FAERS to investigate the relationship between TNF-I and AEs such as ischemic colitis, inflammatory bowel disease, or neurological events in RA patients [7-9].

JADER is a spontaneous AE database consisting of information about SAEs in Japan, and is published in the website of PMDA [10]. JADER contains SAE information reported to PMDA as suspected adverse drug reactions from 2004. It has been published since April 2012. Nomura compared SAEs in Japanese patients that were reported to PMDA and FDA, and described differences between the reporting in the two databases. Secondly, they described points to consider when using spontaneous AE data for pharmacovigilance activity [11]. JADER contains date information such as the date when the SAEs developed and the date when the administration of the suspected drug started, and thus it is possible to calculate the time-to-onset of each SAE. Sasaoka reported that JADER is more suitable than FAERS for the analysis of

time-to-onset profiles because the input ratio of date data was higher in JADER than in FAERS [12]. This is considered to be one of the advantages of JADER. As studies that focused on the time-to-onset of AEs from drugs, investigations of suicide or diabetes with interferon formulations, osteonecrosis of the jaw with bisphosphonates, and hand-foot syndrome with anti-cancer agents have been reported [12-15].

Weaknesses of spontaneous-report databases, such as over-reporting, under-reporting, and missing data have been pointed out [13, 16]. Since JADER is a spontaneous-report database, we need to recognize the existence of reporting bias, and that some data are missing. Also, no information is available about the total number of patients to whom a drug was administered, and the AE incidence cannot be calculated. Thus, spontaneous-report databases have some weaknesses, but the information from them can be useful for proper use of pharmaceutical products because they reflect the actual clinical practice.

In study Part 1, we investigated the safety profile of anti-rheumatic agents using the data from JADER, focusing on some important SAEs and their relation to time with the aim of providing useful information for risk minimization of anti-rheumatic agents in the actual clinical practice.

2.2 Method

Search strategy

The JADER database consists of 4 data files, named demo, drug, reac, and hist. Each SAE in the database has specific information in the files, and they are related by identification number. The demo file includes the patients' basic demographic information, the drug file includes information about the administered medicine, the reac file includes the SAE information, and the hist file includes the patient history for the disease. We downloaded JADER data from the PMDA website in February 2017, and created an analysis data set.

We selected anti-rheumatic agents infliximab (Remicade®), etanercept (Enbrel®), adalimumab (Humira®), golimumab (Simponi®), and certolizumab pegol (Cimzia®) as TNF-Is, tocilizumab (Actemra®) as an IL-6-I, and MTX (Rheumatrex®) for our research. When any of these agents was reported as the primary suspected agent, this was counted as an SAE report for that agent. The TNF-Is were approved for RA in Japan in July 2003, January 2005, April 2008, July 2011, and December 2012, respectively; Actemra® was approved in April 2008; and Rheumatrex® was approved in March 1999.

The analysis data set included identification number, primary suspected drug,

SAE, date the SAE developed, patient outcome, date the administration started, purpose of drug use, gender, age, body weight, and reporting fiscal year. The primary suspected drug is registered by its brand name in JADER, and thus we searched the analysis data set using brand names of each product. Although concomitant suspected drugs are registered by their generic name in JADER, we did not include them in the analysis data set.

Some of these biologics are approved for other indications in addition to RA in Japan, and we needed to limit our analysis to SAEs in which the agent was used as an anti-rheumatic agent. To identify such events, we used the purpose-of-drug-use field in the drug-data-file in JADER. Furthermore, MTX is approved under two brand names in Japan; it is approved as Rheumatrex® for RA, and as Methotrexate® for anti-neoplastic indications. We searched for events based on both the purpose-of-drug-use field and the brand name. Therefore, based on this data, we were able to choose SAEs that occurred when the agent was used for RA.

Generic drugs and biosimilars were excluded from this study. If the same AE developed more than once in a patient while taking the same drug, only the first occurrence of the SAE was adopted.

We selected infections, malignant tumors, and bone marrow disorders as the

focused SAEs. Infection has been a focused adverse reaction since the development stage of TNF-Is. Also, it is identified as an SAE in the guidelines for TNF-I [17], for tocilizumab [18], and for MTX [19] by Japan College of Rheumatology. Malignant tumor is described as an important item in the guidelines for TNF-I, and there has been a controversial discussion whether TNF-I treatment increases the risk of malignant tumor or not in the medical community. Bone marrow disorder has been a typical AE of MTX and is identified as an SAE in the guidelines for MTX.

We utilized Medical Dictionary for Regulatory Activities (MedDRA) version 19.1. for identification of these SAEs [20]. We used the preferred-terms belonging to the System Organ Class “infections and infestations” to identify infections. We used Standard MedDRA Queries (SMQ) to identify events of malignant tumors as follows, for malignant tumors (SMQ code: 20000194), for malignant biliary tract tumors (20000196), for malignant breast tumors (20000198), for malignant ovarian tumors (20000200), for malignant prostate tumors (20000202), for malignant skin tumors (20000204), for malignant uterine and fallopian tube tumors (20000206), for malignant liver tumors (20000208), and for malignant lymphomas (20000215). We used SMQ to identify events of bone marrow disorders as follows, for haematopoietic cytopenias affecting more than one type of blood cell (20000028), for haematopoietic erythropenia

(20000029), for haematopoietic leukopenia (20000030), and for haematopoietic thrombocytopenia (20000031) [21]. The narrow scope was used for two SMQs, specifically for malignant tumors (20000194) and malignant biliary tract tumors (20000196); both narrow and broad scope were used for the other SMQs.

Analysis

The relative risk of these SAEs for the respective agents was evaluated by the disproportionate-analysis method of calculating ROR and 95% confidence interval (CI).

The detection of signal was defined as the lower limit of the 95% CI being >1 [22, 23].

These values were calculated according to the formulae in Table 2.

Table 2. Contingency table for calculating disproportionality

	Specific event	All other events
Specific drug	a	b
All other drugs	c	d

“a” means the number of reports of a specific event associated with a specific drug, “b” means the number of reports of all other events associated with the specific drug, “c” means the number of reports of the specific event associated with all other drugs, and “d” means the number of reports of all other events associated with all other drugs.

$$\text{ROR} = (a/c) / (b/d)$$

$$95\% \text{ CI} = \exp[\log(\text{ROR}) \pm 1.96] \sqrt{(1/a + 1/b + 1/c + 1/d)}$$

Moreover, a stratified analysis was performed to assess the impact of age and gender for the focused SAEs. The age categories were less than 40, 40-49, 50-59, 60-69,

70-79, and greater than 80 years. RORs were calculated using all the events regardless of the availability of date information (start of the administration and development of SAEs).

In addition, we selected the SAEs that had both the date the administration started and the date the SAE developed, calculated the time-to-onset, and showed the data as box plots.

In the present study, Microsoft Access® 2010 was used for creating the analysis data set, and Microsoft Excel® 2010 was used for data tabulation and analysis.

2.3 Result

Focused SAEs

We used SAE data reported to PMDA between 1Q 2004 and 2Q 2016. The number of SAEs that were reported for the primary suspected agents is shown in Figure 1. The total number of reported SAEs in the database was 689,137. A total of 8,928 SAEs were in patients treated with TNF-1, among which 3,977 were for infections, 773 for malignant tumors, and 283 for bone marrow disorders. Likewise, a total of 4,088 SAEs were in patients treated with IL-6-I, among which 1,778 were for infections, 251 for malignant tumors, and 249 for bone marrow disorders. Also, 6,255 SAEs were in patients treated with MTX, among which 1,189 were for infections, 967 for malignant tumors, and 1,245 for bone marrow disorders. We did not consider the concomitant suspected drugs.

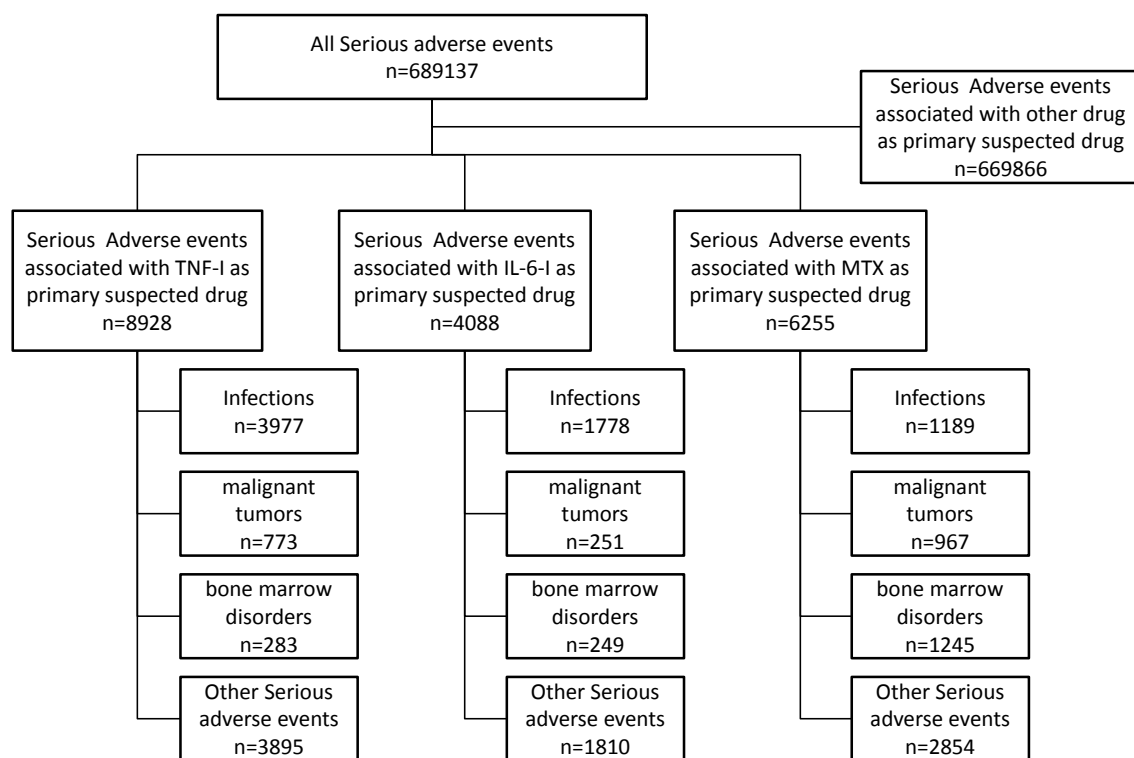


Figure 1. Number of reports of infections, malignant tumors, and bone marrow disorders in patients treated with TNF-I, IL-6-I, or MTX in JADER

The RORs (95% CI) of these events for the groups of patients treated with each agent are shown in Figure 2 and Appendix 1. The RORs (95% CI) of infections, malignant tumors, and bone marrow disorders in patients treated with TNF-I were 10.23 (9.80-10.67), 5.00 (4.64-5.40), and 0.24 (0.22-0.27), respectively. Likewise, the respective RORs for IL-6-I were 9.41 (8.84-10.02), 3.33 (2.93-3.79), and 0.49 (0.43-0.55). The RORs for MTX were 2.82 (2.65-3.01), 9.85 (9.17-10.57), and 1.89 (1.77-2.01), respectively. ROR signals were detected for infections and malignant tumors for both TNF-I and IL-6-I. On the other hand, for MTX, signals were detected for infections, malignant tumors, and bone marrow disorders.

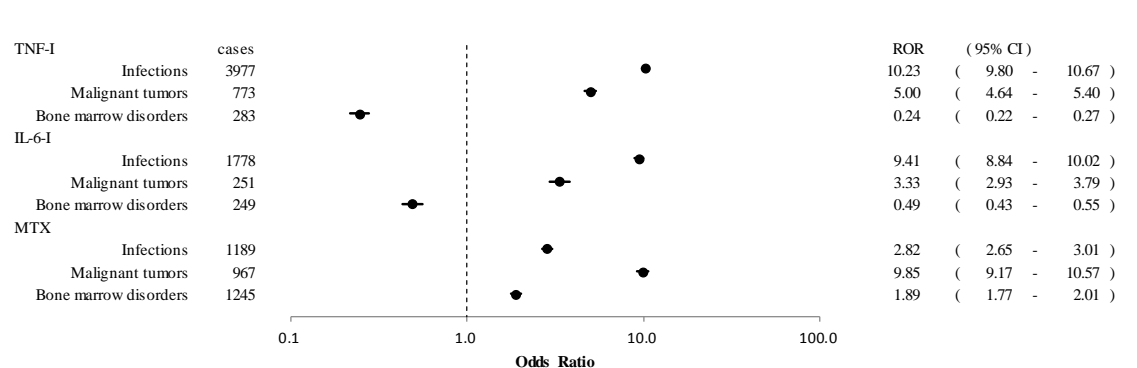


Figure 2. Odds ratio for infections, malignant tumors, and bone marrow disorders in patients treated with TNF-I, IL-6-I, or MTX

Effects of age and gender

The RORs (95% CI) of each focused event for the groups of patients treated with each agent were calculated for the subgroups by patient age and gender (Appendix 2-5.).

For patients given TNF-I, the RORs for each SAE in the subgroups stratified by age and by gender are shown in Figure 3. ROR signals for both infections and malignant tumors were detected for all the classifications of patient age. Also, they were detected for both genders. On the other hand, ROR signals for bone marrow disorders were not detected for any age classification or either gender.

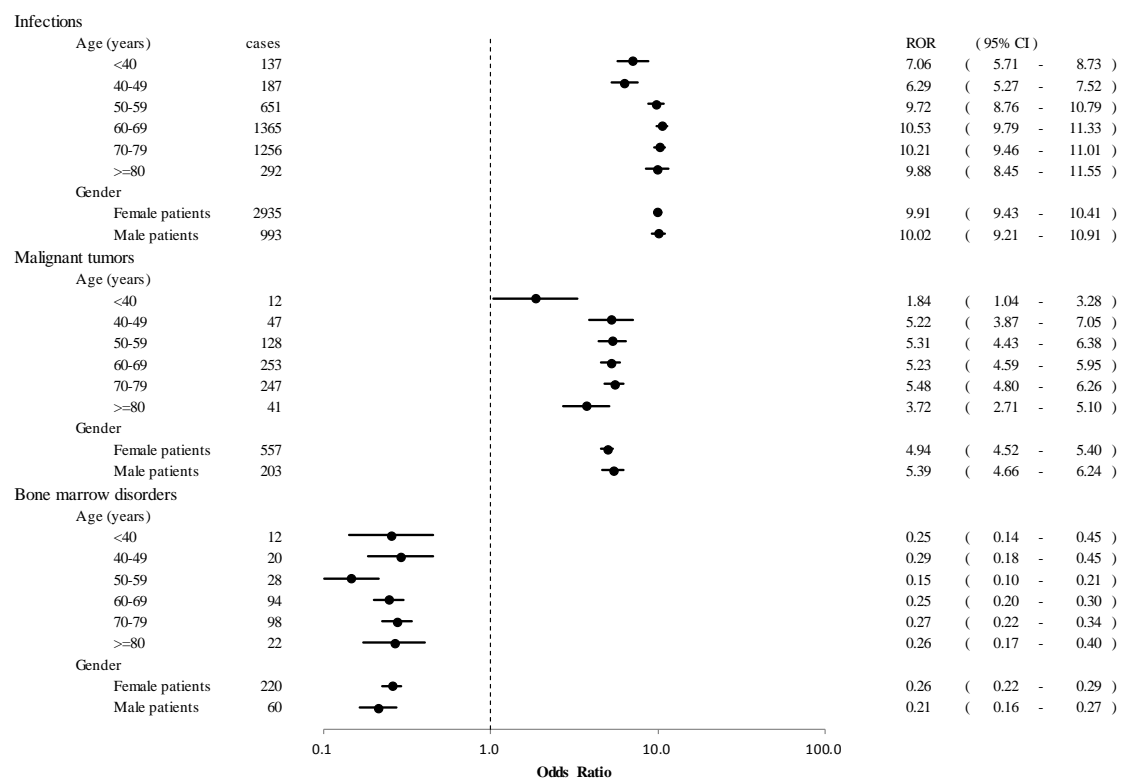


Figure 3. Stratified analysis of infections, malignant tumors, and bone marrow disorders in patients treated with TNF-I

For patients given IL-6-I, the RORs for each SAE in the subgroups stratified by age and by gender are shown in Figure 4. ROR signals for infections were detected for all the classifications of patient age, and also for both genders. ROR signals for malignant tumors were detected for patients 40-49, 50-59, 60-69, 70-79, and greater than 80 years old, and also for both genders. On the other hand, ROR signals for bone marrow disorders were not detected for any age classification or either gender.

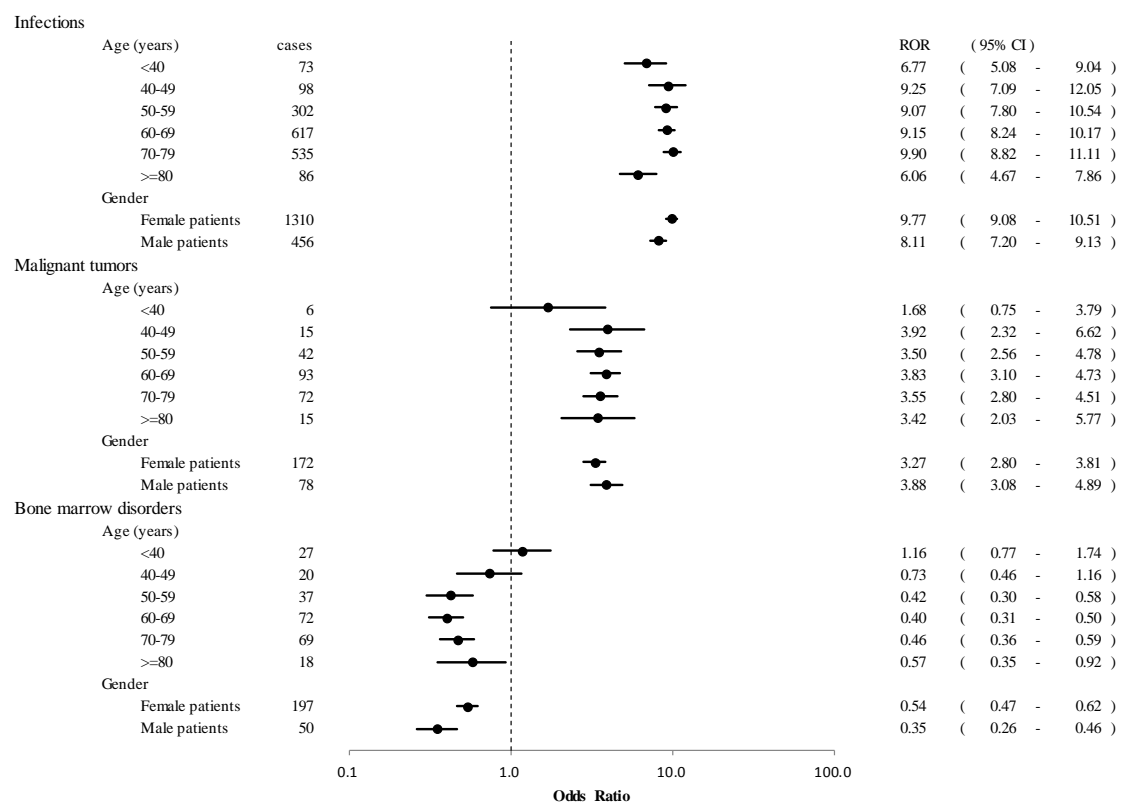


Figure 4. Stratified analysis of infections, malignant tumors, and bone marrow disorders in patients treated with IL-6-I

For patients given MTX, the RORs for each SAE in the subgroups stratified by age and by gender are shown in Figure 5. ROR signals for both infections and malignant tumors were detected for all the classifications of patient age, and also for both genders. ROR signals for bone marrow disorders were detected for patients less than 40, 60-69, 70-79, and greater than 80 years old, and also for both genders.

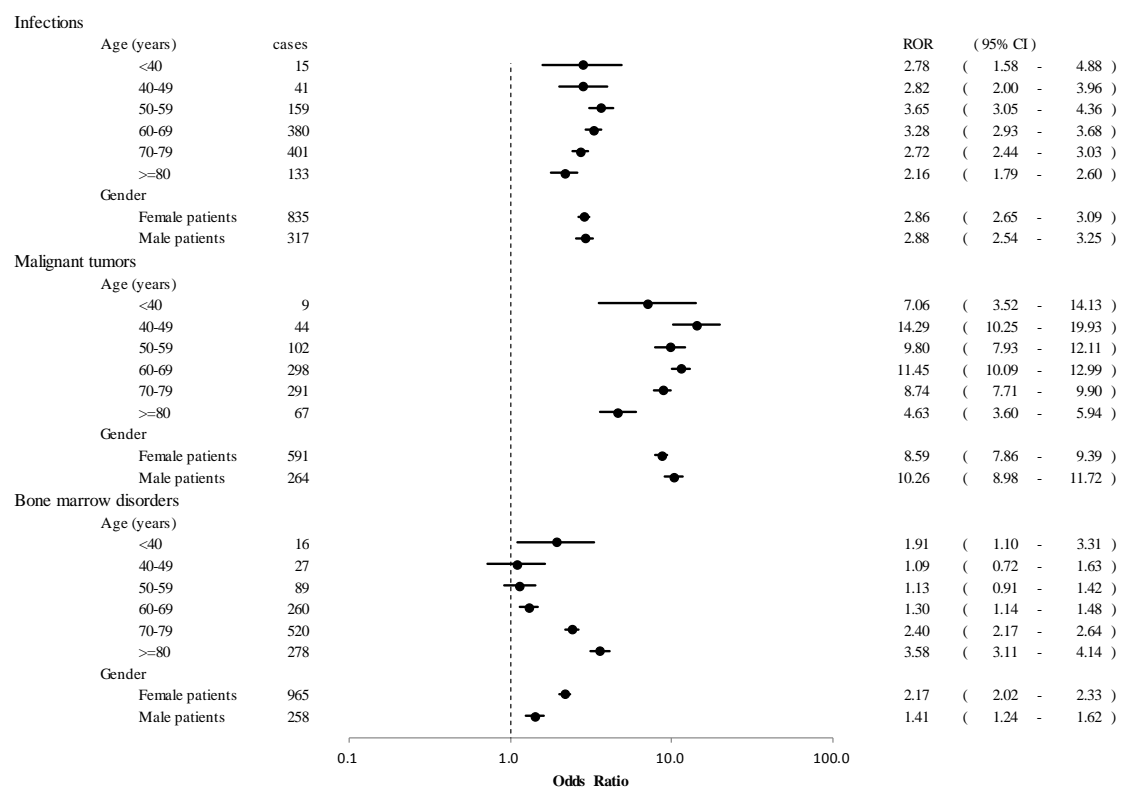


Figure 5. Stratified analysis of infections, malignant tumors, and bone marrow disorders in patients treated with MTX

Time-to-onset of SAE

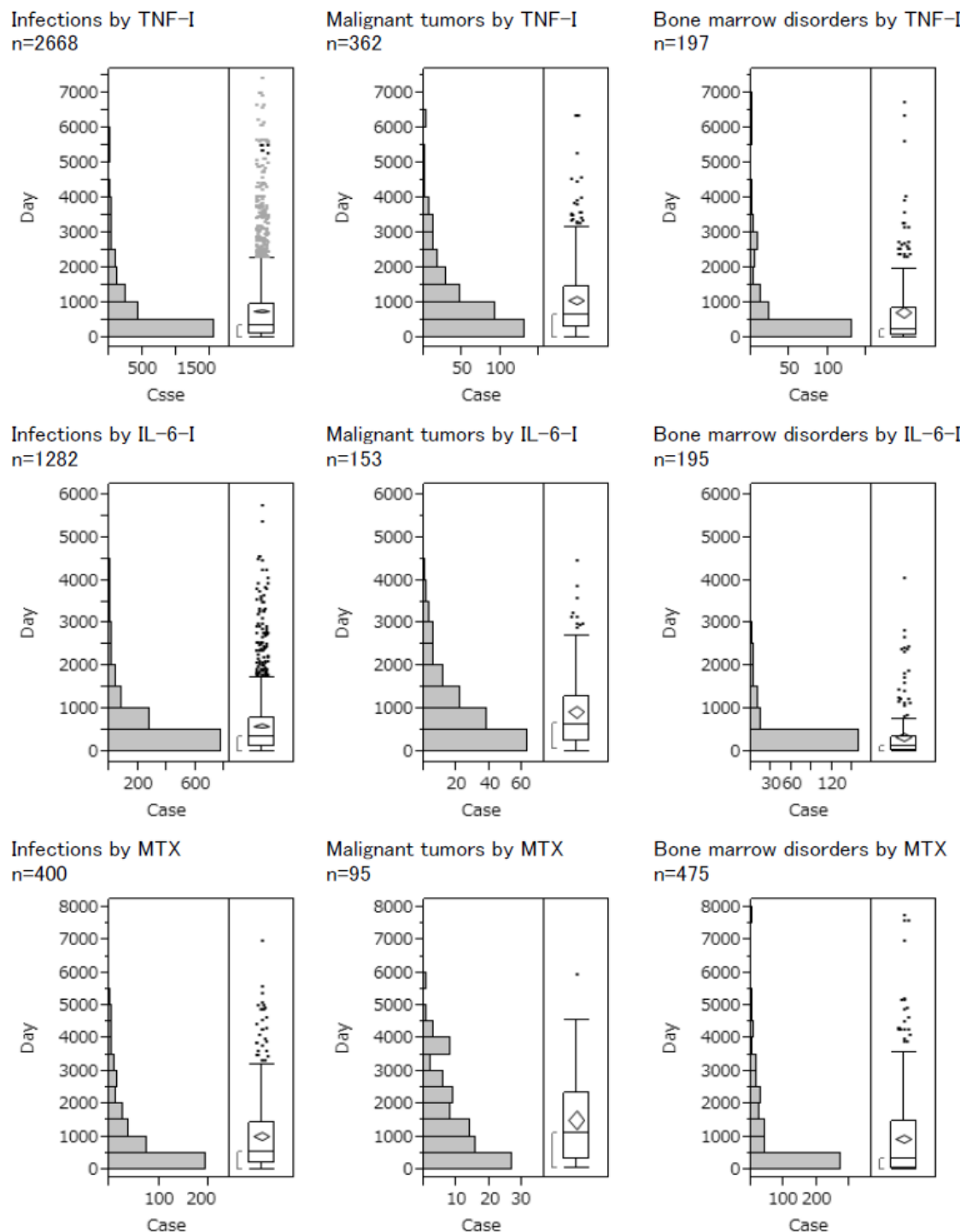
The time-to-onset was calculated for 6,785 events (76.0%) in patients treated with TNF-I, 3,274 events (80.1%) in patients treated with IL-6-I, and 2,305 events (36.9%) in patients treated with MTX. Figure 6 summarizes the time-to-onset of the SAEs.

For SAEs in patients treated with TNF-I, the median and quartile range of time-to-onset of each SAE were 356 (124-994) days for infections, 681 (336-1,485) days for malignant tumors, and 254 (88-866) days for bone marrow disorders. The onset of malignant tumors was later than that of infections or bone marrow disorders, and the range was the widest. The onset of bone marrow disorders was earlier and more focused than that for infections or malignant tumors.

Likewise, for SAEs in patients treated with IL-6-I, the median and quartile range of time-to-onset of each SAE were 342 (123-779) days for infections, 636 (265-1,289) days for malignant tumors, and 116 (28-344) days for bone marrow disorders. The onset of malignant tumors was later than that of infections or bone marrow disorders, and the range was the widest. The onset of bone marrow disorders was earlier and more focused than that for infections or malignant tumors.

Also, likewise for SAEs in patients treated with MTX, the median and quartile

range of time-to-onset of each SAE were 541 (182-1,428) days for infections, 1,125 (334-2,282) days for malignant tumors, and 328 (32-1,481) days for bone marrow disorders. The onset of malignant tumors was later than that of infections or bone marrow disorders, and the range was the widest. The onset of bone marrow disorders was earlier than that for infections or malignant tumors.



n= Number of cases for which both the date the administration started and the date the SAE developed were known. The boxes include half of values from the first quartile to the third quartile. The whiskers indicate the limit value of 1.5 times the interquartile range from the box. The open symbols represent outliers. Left bracket indicates the narrowest range including a half of cases.

Figure 6. Distribution of time-to-onset for infections, malignant tumors, and bone marrow disorders in patients treated with TNF-I, IL-6-I, or MTX

2.4 Discussion

The biologics and MTX, which are recommended in the RA treatment guidelines, play an important role in medication for RA [24, 25]. For effective drug treatment, the benefit to risk balance of each drug must be maximized, which can be achieved by understanding the AE profiles in actual clinical practice and minimizing risk through detecting the AEs earlier and giving appropriate treatment. Generally, an AE in patients treated with a drug is studied in detail under certain conditions in clinical trials. The AE data obtained in the drug development phase serve as an important basis for safety measures in the post-marketing stage, but they have limitations from different aspects. After a drug is launched, various AEs are sometimes increased and reported due to the expansion of the targeted population of patients. We are able to use the knowledge from a database of spontaneously reported AEs with recognition of the limitations. This becomes an important source for actual clinical practice.

In the present study, safety signals were detected between specified SAEs and agents used for treatment of RA. Specifically, imbalances in reporting odds ratio were observed in both infections and malignant tumors associated with patients treated with TNF-I and IL-6-I, and in infections, malignant tumors, and bone marrow disorders associated with patients treated with MTX, as demonstrated by disproportionality

analysis. These AEs have been identified previously. For example, infection is identified as an SAE in the guidelines for TNF-I [17], for tocilizumab [18], and for MTX [19] by Japan College of Rheumatology, malignant tumor is described as an important item in the guidelines for TNF-I, and bone marrow disorder is identified as an SAE in the guidelines for MTX [19]. This may be one of the reasons why the ROR values of bone marrow disorder associated with patients treated with TNF-I and IL-6-I were lower than that with MTX. It can be said that it reflects the data from actual clinical practice. On the other hand, malignant tumors, which are not described in the guidelines for tocilizumab, were detected as a signal among SAEs for IL-6-I, and malignant tumors, which are not described in the guidelines for MTX, were detected as a signal among SAEs for MTX. The relationship between malignant tumors and use of biologics is unclear because the results from several cohort studies and meta-analyses were contradictory [5, 6, 26]. In the present study using an SAE database, increased risk of malignant tumors associated with patients treated with biologics is indicated based on the ROR values.

Based on the result of the present study, we would suggest that these SAEs be carefully observed in clinical practice. The results of our research are considered to be information that could help medical care for RA.

According to the stratified analysis, we found the impact of age and gender on these SAEs. The risk for both infections and malignant tumors in patients given TNF-I increased in all age categories and both genders. The risk for these SAEs with IL-6-I increased in the almost similar populations. For MTX, the risk for these two AEs increased in all age categories and both genders, and the risk for bone marrow disorders increased in the relatively older populations and in both genders.

The distribution of time-to-onset for infections, malignant tumors, and bone marrow disorders associated with patients treated with TNF-I, IL-6-I, and MTX showed different patterns. For each of the agents, the time-to-onset for bone marrow disorders was shorter, and the distribution of time-to-onset for malignant tumors was broad. The bone marrow disorders associated with patients treated with TNF-I and IL-6-I developed a lot earlier after starting agent administration compared with infections and malignant tumors. These findings would be helpful for treatment of RA patients, because no information about time-to-onset is described in the RA guidelines. During treatment with anti-rheumatic agents, physicians should observe patients carefully to look for SAEs for various periods which are different depending on the respective agent and SAEs. These focused SAEs associated with patients treated with TNF-I or IL-6-I should be closely monitored for 2 years. On the other hand, those associated with

patients treated with MTX should be closely monitored for 3 years. Since the AEs sometimes developed beyond the periods described above, it is preferable to carefully detect them early and to treat them properly and continuously.

Sasaoka reported that, in her study of the time-to-onset for hand-foot syndrome during treatment with anti-cancer agents, for which they used JADER and FAERS, the input ratio of time-to-onset information of SAEs with capecitabine was 78% in JADER, and 49% in FAERS [12]. The reporting ratios of time-to-onset information with TNF-I and IL-6-I in our study were similar to that for capecitabine in the previous study, but the ratio for MTX was lower. We suspect that, because MTX had been administered as off-label use long before the approval for the RA indication, the safety profile of MTX was considered to have been established to some extent. SAEs have been reported to the Japan healthcare authority since 1980, but SAEs reported before March 2004 are not included in JADER. Therefore, JADER does not include SAE information which was reported during 5 years after approval of MTX for RA indication in March 1999. On the other hand, the biologics were approved for RA indication after April 2004 except infliximab, so more data on date might be included in JADER.

The time-to-onset of AEs, which can be calculated from the data in JADER, provides important information. For example, the onset and development of SAEs can

be examined, and can be compared those profiles with similar drugs. Although, in this study, we evaluated several specific agents and SAEs, this approach would be used to investigate other drugs or other SAEs. Our results suggest that this approach using JADER, with consideration of the limitations of database research and the features of JADER, could contribute to planning the actual safety measures for the clinical use.

3. Part 2

3.1 Background

As of October 2016, the total population of Japan was 126.7 million, of which the population over 65 years-old was 34.5 million. The proportion of the elderly in the total population is 27.3%, which has been increasing every year since 1950[27]. As life expectancy extends, and now that the aged society has arrived, it is expected that the number of elderly people with inflammatory rheumatic diseases will continue to increase. Fukuda reported, based on a study for 777 Japanese RA patients, that the average age of RA patients was 64.2 years, and that the percentage of patients over 70 years old was 37.7%, indicating that the proportion of elderly RA patients is higher than that of elderly people in Japan [28]. TNF-Is have not been proactively studied in elderly RA patients, who have different clinical features compared to younger patients, while research studies report that the potential risk of developing drug-associated AEs in elderly patients is increasing [28-30]. Clement reported that renewed scientific attention in recent years should promote more widespread use of biologics; however, he also mentioned that attention to their safety in these elderly patients should not diminish [31]. The efficacy and safety information about anti-rheumatic agents in elderly RA patients is limited because elderly patients are often excluded from Ph2 and/or Ph3 studies in the

development stage of new drugs. Therefore the information from AE databases becomes useful for health care professionals. In the TNF-I guideline, aging is described as a risk factor for pneumonia and serious infectious diseases, but specific information by stratified age is not stated [17].

Various studies on the impact of aging on AEs have been reported, such as the relation between dabigatran and hemorrhagic events using FAERS [32], the relation between bevacizumab and thromboembolic events using JADER [33], and the relation between concomitant administration of clopidogrel, aspirin and proton-pump inhibitors and cardiovascular (embolic/thrombotic) events using FAERS [34]. However, no studies on the relationship between AEs in patients treated with anti-rheumatic agents and aging have been reported.

The widespread use of biologics is expected as the number of elderly RA patients increases; recent findings suggest that the use of TNF-I for elderly patients has become more aggressive [31]. Therefore, we examined the influence of aging on AEs in patients treated with TNF-I or MTX by logistic regression analysis using data from JADER.

3.2 Method

Search strategy

We selected anti-rheumatic agents infliximab (Remicade®), etanercept (Enbrel®), adalimumab (Humira®), golimumab (Simponi®), and certolizumab pegol (Cimzia®) as TNF-Is and MTX (Rheumatrex®) for our research. When one of these agents was reported as a primary suspected agent, this was counted as an SAE report for that agent. The TNF-Is were approved for RA in Japan in July 2003, January 2005, April 2008, July 2011, and December 2012; Rheumatrex® was approved in March 1999.

We downloaded JADER data from the PMDA website in February 2017, and created an analysis data set [10]. It included identification number, suspected drug, SAE, purpose of drug use, gender, and age. The primary suspected drug is registered by its brand name in JADER, and thus we searched the analysis data set using the brand names of each product. Although concomitant suspected drugs are registered by their generic name in JADER, we did not include them in the analysis data set. We searched for events based on both the purpose-of-drug-use field and the brand name. Therefore, based on this data, we were able to choose SAEs that occurred when the agent was used for RA. Generic drugs and biosimilars were excluded from this study. If the same AE

developed more than once in a patient while taking the same drug, only the first occurrence of the SAE was adopted.

We selected infections and malignant tumors as the focused SAEs. Furthermore, we selected tuberculosis and *pneumocystis jirovecii* pneumonia because they were identified as SAEs in the guidelines for TNF-I [17] by Japan College of Rheumatology. In addition, malignant lymphoma was selected as a hematologic cancer because it is reported to be associated with patients treated with TNF-I administration [35].

We utilized MedDRA version 19.1. to identify these SAEs [20]. We used the preferred-terms belonging to the system organ class “infections and infestations” to identify events of infections, the preferred-terms belonging to the high-level-term “tuberculosis infections” to identify events of tuberculosis, and the preferred-terms code (10073755) to identify events of *pneumocystis jirovecii* pneumonia. We used SMQ to identify events of malignant tumors as follows, for malignant tumors (SMQ code: 20000194), for malignant biliary tract tumors (20000196), for malignant breast tumors (20000198), for malignant ovarian tumors (20000200), for malignant prostate tumors (20000202), for malignant skin tumors (20000204), for malignant uterine and fallopian tube tumors (20000206), for malignant liver tumors (20000208), and for malignant lymphomas (20000215) [21].

Analysis

The relative risk of these SAEs for the respective agents was evaluated by the disproportionate-analysis method of calculating ROR and 95% CI. The detection of a signal was defined as the lower limit of the 95% CI being >1 [22, 23]. These values were calculated according to the formulae in Table 2.

We examined the influence of AEs in patients treated with TNF-I or MTX by age classification. After adjusting for gender and stratified age groups, the adjusted RORs were calculated by logistic regression analysis by the following model [32, 36, 37]. To construct the logistic model, the drugs and stratified age groups were coded. We calculated adjusted ROR for each age group using the 50-59 age group as a reference group, because the median age at the time of onset of RA was reported to be 55, 56, or 58 years old [28, 38, 39].

$$\text{Log (odds)} = \beta_0 + \beta_1 G + \beta_2 D + \beta_3 A + \beta_4 D * A$$

(G = gender, D = drug (TNF-I or MTX), and A = stratified age group)

In the present study, Microsoft Access® 2010 was used for creating the analysis data set, Microsoft Excel® 2010 was used for data tabulation and analysis, and R software, version 3.4.0. was used for data analysis [40].

3.3 Result

We used SAE data reported to PMDA between 1Q 2004 and 2Q 2016. The total number of reported SAEs in the database was 689,137. A total of 8,928 SAEs were in patients treated with TNF-1, and 6,255 SAEs were in patients treated with MTX. We did not consider the concomitant suspected drugs.

The adjusted RORs of infections for the groups of patients treated with TNF-I or MTX are summarized in Table 3, and the adjusted RORs of malignant tumors are shown in Table 4. The adjusted RORs (95% CI) for infections in patients treated with TNF-I for the group of patients less than 50, 70-79, and greater than 80 years old were 0.697 (0.586-0.830), 1.163 (1.019-1.328), and 1.569 (1.295-1.901), respectively. The risk was higher in the group of patients greater than 70 years old compared to those 50-59 years old as a reference group, and lower in the group of patients less than 50 years old compared to that of the reference group. Likewise, the adjusted ROR for tuberculosis for the group of patients greater than 80 years old was 1.737 (1.081-2.792), and the risk was higher compared to that of the reference group. The other adjusted RORs for tuberculosis did not meet the criteria for the signal. Also, the adjusted RORs for *pneumocystis jirovecii* pneumonia for the group of patients less than 50 years old, and greater than 80 years old were 0.558 (0.330-0.943) and 2.317 (1.455-3.689), the

risk was higher in the group of patients greater than 80 years old compared to that of the reference group, and lower in the group of patients less than 50 years old compared to that of the reference group. The other adjusted RORs for *pneumocystis jirovecii* pneumonia did not meet the criteria for the signal.

The adjusted RORs for malignant lymphoma for the group of patients less than 50 years old was 0.396 (0.214-0.733), and the risk was lower compared to that of the reference group. No adjusted ROR met the criteria for the signal for malignant tumors in patients treated with TNF-I for any stratified age groups. Although the adjusted RORs of infections, tuberculosis and *pneumocystis jirovecii* pneumonia in patients treated with TNF-I increased numerically with increasing age, they did not meet the criteria for the signal except the group of patients over 80 years old. (Figure 7 (a)). On the other hand, no such trend was observed in the adjusted RORs for malignant tumors and malignant lymphomas in patients treated with TNF-I (Figure 7 (b)).

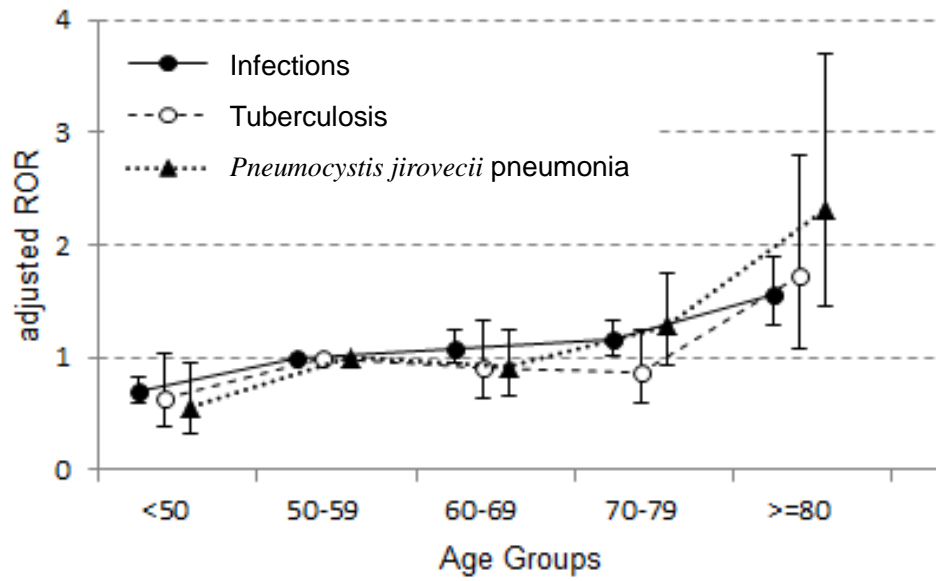
Table 3. Adjusted ROR for infections, tuberculosis and *pneumocystis jirovecii* pneumonias

	Infections				Tuberculosis				<i>Pneumocystis jirovecii</i> pneumonias			
	Adjusted ROR	(95% CI)			Adjusted ROR	(95% CI)			Adjusted ROR	(95% CI)		
(Intercept)	0.091	(0.089	-	0.093)	0.002	(0.001	-	0.002)	0.003	(0.002	-	0.003)
TNF-I	9.996	(8.980	-	11.127)	34.358	(24.974	-	47.269)	20.857	(16.051	-	27.102)
MTX	3.708	(3.093	-	4.445)	11.846	(6.180	-	22.708)	13.301	(8.667	-	20.414)
Gender female	0.878	(0.861	-	0.895)	0.656	(0.593	-	0.726)	1.050	(0.962	-	1.146)
AGE												
<50	0.985	(0.955	-	1.017)	1.418	(1.149	-	1.750)	0.696	(0.587	-	0.825)
50-59 (as reference)	1	1		1	1	1		1	1		1	1
60-69	0.971	(0.940	-	1.002)	1.380	(1.114	-	1.709)	1.135	(0.967	-	1.332)
70-79	0.880	(0.852	-	0.909)	1.454	(1.177	-	1.796)	1.016	(0.864	-	1.194)
>=80	0.648	(0.623	-	0.675)	1.000	(0.773	-	1.295)	0.455	(0.360	-	0.575)
interaction term TNF-I * AGE												
TNF-I * <50	0.697	(0.586	-	0.830)	0.640	(0.395	-	1.037)	0.558	(0.330	-	0.943)
TNF-I * 50-59 (as reference)	1	1		1	1	1		1	1		1	1
TNF-I * 60-69	1.086	(0.953	-	1.238)	0.914	(0.628	-	1.329)	0.913	(0.664	-	1.254)
TNF-I * 70-79	1.163	(1.019	-	1.328)	0.861	(0.591	-	1.253)	1.280	(0.935	-	1.753)
TNF-I * >=80	1.569	(1.295	-	1.901)	1.737	(1.081	-	2.792)	2.317	(1.455	-	3.689)
interaction term MTX * AGE												
MTX * <50	0.806	(0.572	-	1.137)	0.842	(0.280	-	2.538)	0.403	(0.119	-	1.365)
MTX * 50-59 (as reference)	1	1		1	1	1		1	1		1	1
MTX * 60-69	0.934	(0.753	-	1.158)	0.597	(0.273	-	1.305)	1.176	(0.720	-	1.920)
MTX * 70-79	0.854	(0.691	-	1.057)	0.491	(0.226	-	1.068)	1.342	(0.829	-	2.171)
MTX * >=80	0.927	(0.714	-	1.203)	0.626	(0.237	-	1.652)	1.487	(0.784	-	2.817)

Table 4. Adjusted ROR for malignant tumors and malignant lymphomas

	Malignant tumors				Malignant lymphomas			
	Adjusted ROR	(95% CI)			Adjusted ROR	(95% CI)		
(Intercept)	0.020	(0.019	-	0.021)	0.004	(0.003	-	0.004)
TNF-I	5.549	(4.594	-	6.704)	9.813	(7.210	-	13.354)
MTX	10.156	(8.172	-	12.621)	36.954	(28.400	-	48.084)
Gender female	0.834	(0.803	-	0.866)	0.997	(0.921	-	1.079)
AGE								
<50	0.714	(0.668	-	0.763)	1.139	(0.993	-	1.307)
50-59 (as reference)	1	1		1	1	1		1
60-69	1.049	(0.985	-	1.118)	0.899	(0.776	-	1.041)
70-79	0.892	(0.836	-	0.952)	0.647	(0.554	-	0.756)
>=80	0.698	(0.645	-	0.757)	0.367	(0.293	-	0.458)
interaction term TNF-I * AGE								
TNF-I * <50	1.018	(0.734	-	1.412)	0.396	(0.214	-	0.733)
TNF-I * 50-59 (as reference)	1	1		1	1	1		1
TNF-I * 60-69	0.914	(0.725	-	1.152)	0.884	(0.598	-	1.306)
TNF-I * 70-79	1.133	(0.897	-	1.430)	1.162	(0.777	-	1.737)
TNF-I * >=80	0.990	(0.681	-	1.438)	1.235	(0.600	-	2.543)
interaction term MTX * AGE								
MTX * <50	1.766	(1.218	-	2.560)	1.035	(0.670	-	1.598)
MTX * 50-59 (as reference)	1	1		1	1	1		1
MTX * 60-69	1.085	(0.842	-	1.397)	1.331	(0.976	-	1.814)
MTX * 70-79	0.981	(0.762	-	1.264)	1.483	(1.084	-	2.028)
MTX * >=80	0.678	(0.484	-	0.949)	1.476	(0.968	-	2.250)

(a)



(b)

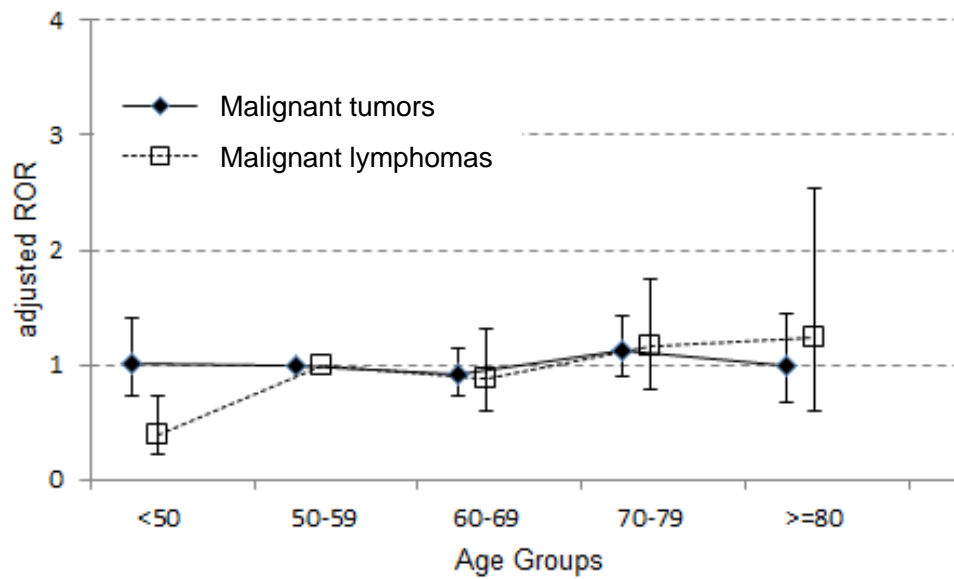
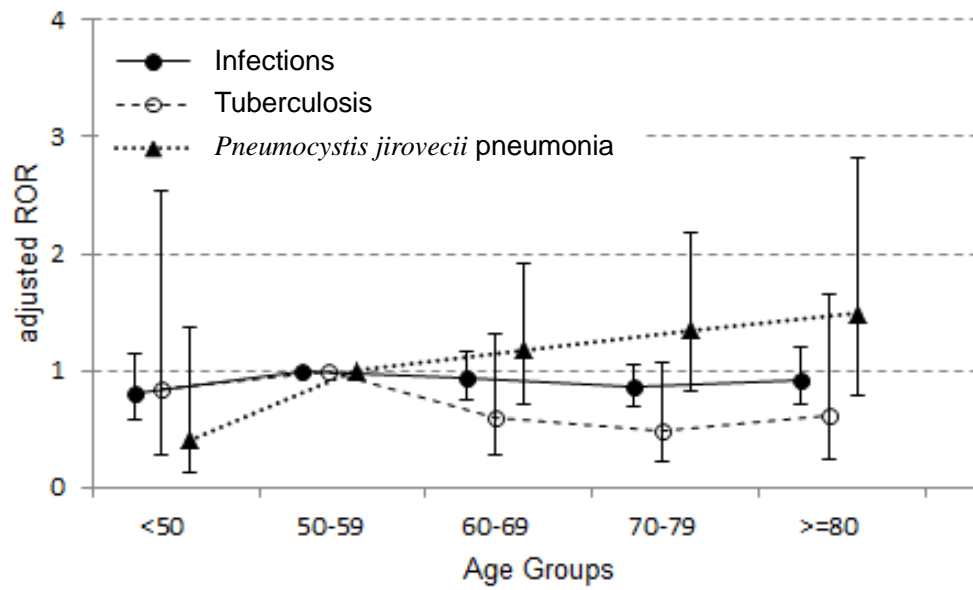


Figure 7. Adjusted ROR and 95% confidence interval value of each SAE in patients treated with TNF-I by age group ((a): Infections, (b): Malignant tumors)

The adjusted RORs for malignant tumors in the group of patients treated with MTX less than 50 years old, and greater than 80 years old were 1.766 (1.218-2.560) and 0.678 (0.484-0.949), respectively; the risk was higher in the group of patients less than 50 years old, and lower in the group of patients greater than 80 years old compared to that of the reference group. No adjusted ROR met the criteria for the signal for infections in patients treated with MTX for any stratified age groups. Likewise, the adjusted ROR for malignant lymphoma for the group of patients 70-79 years old was 1.483 (1.084-2.028), and the risk was higher compared to that of the reference group. No definite increasing trend was observed in the adjusted RORs for infections, tuberculosis, *pneumocystis jirovecii* pneumonia, malignant tumors or malignant lymphomas in patients treated with MTX (Figure 8(a), (b)). The relative risk of each AE in patients treated with TNF-I or MTX by age group mentioned above is shown in Figure 9.

(a)



(b)

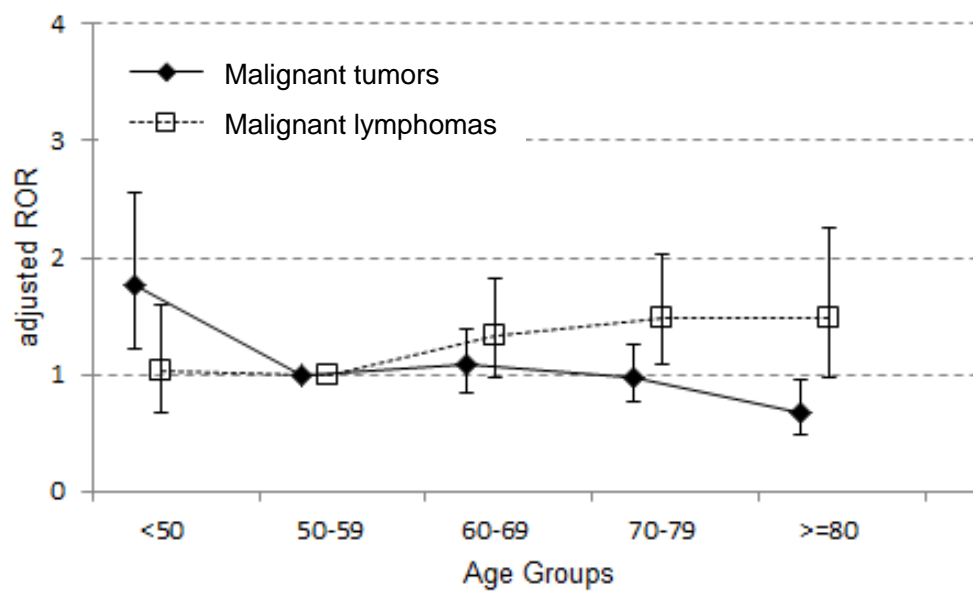


Figure 8. Adjusted ROR and 95% confidence interval value of each SAE in patients treated with MTX by age group ((a): Infections, (b): Malignant tumors)

Drug	SAE	Age (years)				
		<50	50-59	60-69	70-79	>=80
TNF-I	infections		reference			
	tuberculosis		reference			
	<i>pneumocystis jirovecii</i> pneumonias		reference			
	malignant tumors		reference			
	malignant lymphomas		reference			
MTX	infections		reference			
	tuberculosis		reference			
	<i>pneumocystis jirovecii</i> pneumonias		reference			
	malignant tumors		reference			
	malignant lymphomas		reference			



: Lower risk than reference,



: Higher risk than reference

Figure 9. Map of risk by age group

3.4 Discussion

Based on an observational study in patients with RA, Filippini reported that many serious AEs such as severe infection, cancer, allergy, and lupus-like reaction were observed in the elderly patients (greater than 65 years old, n=311) compared to younger patients (18-65 years old, n=803) [41]. Ornetti reported that, from a literature review, although no definite increase in risk was observed for elderly RA patients treated with etanercept, there was a possibility that the risk increased in elderly RA patients [42]. Generally, elderly people are assumed to have a higher risk than non-elderly people because of reduction in immunity, decline of renal function and numerous complications, so it is necessary to take care of them sufficiently.

We evaluated the relationship between aging and AEs in patients treated with TNF-I or MTX by logistic regression analysis. As a result, it was suggested that the risk of infections, tuberculosis and *pneumocystis jirovecii* pneumonia associated with patients treated with TNF-I was higher in elderly patients compared to those who were 50-59 years old. This finding supports the results of studies by other researchers in which there were more severe infections in elderly people [41, 43]. On the other hand, the risk of infections and *pneumocystis jirovecii* pneumonia was lower in patients less than 50 years old. It was shown in study Part 1 that infections developed earlier than

malignant tumors during TNF-I administration, and therefore identification of risks by age category may be possible for SAEs with a shorter time to onset from the start of drug administration. For infections associated with patients treated with TNF-I, it was suggested that a close observation should be made especially in elderly patients.

For malignant tumors and malignant lymphomas associated with patients treated with TNF-I, increased risks were not suggested in the groups of elderly patients compared to the 50-59 years old group. For malignant lymphomas, the risk was lower in the group of patients less than 50 years old. According to the result shown in study Part 1, it is considered that the risk did not increase in the group of the elderly because development of malignant tumors requires long periods and various factors may affect during that period.

For infections, tuberculosis and *pneumocystis jirovecii* pneumonia associated with patients treated with MTX, although the risk was neither higher nor lower in any age groups, and no tendency to suggest higher risk in elderly patients compared to the 50-59 years old group was shown, observation of patients by physician is required throughout the age groups because signals were detected for all the classifications of patient age. For malignant tumors, younger patients had a trend of higher risk compared to the 50-59 years old group, and the group of elderly patients had a trend of lower risk.

For malignant lymphomas, the risk was higher in the groups of elderly patients. JADER is a spontaneous AE database that contains SAE information reported to PMDA as suspected adverse drug reactions from 2004. Therefore, it does not include SAE information of MTX which was reported during the first 5 years after the approval of RA indication. It was considered that insufficient data was one of the reasons for the opposite result.

No research has been reported that investigated the association between aging and the occurrence of AEs during treatment with anti-rheumatic agents using logistic regression analysis. We demonstrated that the risk of infections associated with patients treated with TNF-I was higher in elderly patients compared to 50-59 years old patients.

4. Overall Discussion

In study Part 1, imbalances in reporting odds ratio were observed in both infections and malignant tumors associated with patients treated with TNF-I and IL-6-I, and in infections, malignant tumors, and bone marrow disorders associated with patients treated with MTX. Our results are considered reasonable because many of the AEs for which these imbalances were observed have already been identified as safety issues requiring attention by the RA guideline and package inserts of the products. Although the risk of developing malignant tumors during treatment with biologics is controversial, our study based on the AE database demonstrated an increased risk for malignant tumors. It is desirable to conduct additional clinical trials, surveys, or other database research focusing on this issue, and to start working on revising the guidelines if necessary.

The time-to-onset for infections, malignant tumors, and bone marrow disorders associated with patients treated with focused agents, TNF-I, IL-6-I, and MTX, showed different patterns. These findings would be helpful for the treatment of RA patients, because no information about time-to-onset of these adverse drug reactions is described in the RA guidelines nor in the package insert of the products.

In study Part 2, we found the influences of aging on AEs associated with patients

treated with anti-rheumatic agents; it was suggested that the risk of infections, tuberculosis and *pneumocystis jirovecii* pneumonia associated with patients treated with TNF-I was higher in elderly patients compared to those who were 50-59 years old. This is the first research to investigate the relationship between aging and some specific AEs by logistic regression analysis using data from JADER.

Elderly patients have different clinical features compared to younger patients. Also, the data about medicines used in elderly patients is very limited during the drug development stage, and such data accumulates through the post-marketing experience. Therefore, it is possible to provide important information for effective medication in the elderly patients by maximizing the utilization of actual clinical data from the post-marketing period.

The AE databases can be used for routine signal management of drugs. In Japan, PMDA uses JADER to manage signals for marketed drugs, and also in the US and Europe, the industry, government and academia use FAERS and EudraVigilance for signal management. In addition, it is possible, by referring AE databases of similar drugs, to predict the post-marketing actual usage conditions and AE reporting of a drug under development. At the same time, we need to recognize the fact that they are databases of spontaneously reported AEs. It is difficult to use them for absolute risk

assessment of a drug because we cannot calculate the incidence of AEs without the information on the total number of patients exposed to the drug [44].

Most of the SAE information compiled in the JADER is reported by pharmaceutical companies. Generic companies are generally considered lacking sufficient system for collecting and reporting SAE information of their own products compared to original drug companies. We were concerned that these differences might affect the evaluation of SAE, and we excluded generic drugs from this study.

In order to promote proper use of pharmaceutical products and to enhance safety measures, it is important to understand their safety profiles, including typical features such as safety signals, time-to-onset of AEs, and impact of aging on AEs. Healthcare professionals and patients as well as pharmaceutical companies will be able to predict whether AEs will develop by recognizing these safety profiles, and therefore it is considered that this information will be useful to minimize the risks through early detection of AEs and proper treatment.

There are several limitations in the present study. JADER is a spontaneous-report database, and it needs to be recognized that it has various reporting biases. Also, it does not have enough detailed patient information [13, 16, 45-47]. Since data on the total number of prescriptions are not available, incidence of AEs cannot be

calculated. With these limitations in mind, we should interpret the results carefully.

5. Conclusion

By using the data from JADER, the characteristics of SAEs in actual clinical practice for TNF-I, IL-6-I and MTX for treatment of RA were investigated. As a result, it was suggested that the SAEs should be evaluated carefully because their time-to-onset was different for different agents. As for the influence of aging on AEs, physicians should carefully observe patients treated with TNF-I for infections across the age groups, but more attention should be devoted to elderly patients.

Since JADER is considered to reflect actual clinical practice in the post-marketing stage, it is important to make maximum use of these data and to grasp the situation and characteristics of SAEs associated with drug treatment. This is expected to contribute to the risk minimization of drugs in actual clinical practice.

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Appendix

Appendix 1. The RORs of infections, malignant tumors, and bone marrow disorders in patients treated with TNF-I, IL-6-I, or MTX

Drug	Adverse Event	Suspected drug		All other drugs		ROR (ad/bc)	95% CI		
		Cases (a)	Non-cases (b)	Cases (c)	Non-cases (d)				
TNF-I									
	Infections	3977	4951	48501	617452	10.23	(9.80	- 10.67)
	Malignant tumors	773	8155	12386	653567	5.00	(4.64	- 5.40)
	Bone marrow disorders	283	8645	78754	587199	0.24	(0.22	- 0.27)
IL-6-I									
	Infections	1778	2310	50700	620093	9.41	(8.84	- 10.02)
	Malignant tumors	251	3837	12908	657885	3.33	(2.93	- 3.79)
	Bone marrow disorders	249	3839	78788	592005	0.49	(0.43	- 0.55)
MTX									
	Infections	1189	5066	51289	617337	2.82	(2.65	- 3.01)
	Malignant tumors	967	5288	12192	656434	9.85	(9.17	- 10.57)
	Bone marrow disorders	1245	5010	77792	590834	1.89	(1.77	- 2.01)

Appendix 2. Number of cases and ROR of infections, malignant tumors, and bone marrow disorders in patients treated with TNF-I stratified by age

Drug	Adverse Event	Age years	Suspected drug		All other drugs		ROR (ad/bc)	95% CI			
			Cases (a)	Non-cases (b)	Cases (c)	Non-cases (d)					
TNF-I											
	Infections										
		<40	137	227	49993	585179	7.06	(5.71	-	8.73)
		40-49	187	348	49943	585058	6.29	(5.27	-	7.52)
		50-59	651	791	49479	584615	9.72	(8.76	-	10.79)
		60-69	1365	1552	48765	583854	10.53	(9.79	-	11.33)
		70-79	1256	1470	48874	583936	10.21	(9.46	-	11.01)
		>=80	292	347	49838	585059	9.88	(8.45	-	11.55)
	Malignant tumors										
		<40	12	352	11532	623640	1.84	(1.04	-	3.28)
		40-49	47	488	11497	623504	5.22	(3.87	-	7.05)
		50-59	128	1314	11416	622678	5.31	(4.43	-	6.38)
		60-69	253	2664	11291	621328	5.23	(4.59	-	5.95)
		70-79	247	2479	11297	621513	5.48	(4.80	-	6.26)
		>=80	41	598	11503	623394	3.72	(2.71	-	5.10)
	Bone marrow disorders										
		<40	12	352	75689	559483	0.25	(0.14	-	0.45)
		40-49	20	515	75681	559320	0.29	(0.18	-	0.45)
		50-59	28	1414	75673	558421	0.15	(0.10	-	0.21)
		60-69	94	2823	75607	557012	0.25	(0.20	-	0.30)
		70-79	98	2628	75603	557207	0.27	(0.22	-	0.34)
		>=80	22	617	75679	559218	0.26	(0.17	-	0.40)

Appendix 3. Number of cases and ROR of infections, malignant tumors, and bone marrow disorders in patients treated with IL-6-I stratified by age

Drug	Adverse Event	Age years	Suspected drug		All other drugs		ROR (ad/bc)	95% CI		
			Cases (a)	Non-cases (b)	Cases (c)	Non-cases (d)				
IL-6-I										
	Infections									
		<40	73	126	50057	585280	6.77	(5.08	- 9.04)
		40-49	98	124	50032	585282	9.25	(7.09	- 12.05)
		50-59	302	391	49828	585015	9.07	(7.80	- 10.54)
		60-69	617	796	49513	584610	9.15	(8.24	- 10.17)
		70-79	535	637	49595	584769	9.90	(8.82	- 11.11)
		>=80	86	166	50044	585240	6.06	(4.67	- 7.86)
	Malignant tumors									
		<40	6	193	11538	623799	1.68	(0.75	- 3.79)
		40-49	15	207	11529	623785	3.92	(2.32	- 6.62)
		50-59	42	651	11502	623341	3.50	(2.56	- 4.78)
		60-69	93	1320	11451	622672	3.83	(3.10	- 4.73)
		70-79	72	1100	11472	622892	3.55	(2.80	- 4.51)
		>=80	15	237	11529	623755	3.42	(2.03	- 5.77)
	Bone marrow disorders									
		<40	27	172	75674	559663	1.16	(0.77	- 1.74)
		40-49	20	202	75681	559633	0.73	(0.46	- 1.16)
		50-59	37	656	75664	559179	0.42	(0.30	- 0.58)
		60-69	72	1341	75629	558494	0.40	(0.31	- 0.50)
		70-79	69	1103	75632	558732	0.46	(0.36	- 0.59)
		>=80	18	234	75683	559601	0.57	(0.35	- 0.92)

Appendix 4. Number of cases and ROR of infections, malignant tumors, and bone marrow disorders in patients treated with MTX stratified by age

Drug	Adverse Event	Age years	Suspected drug		All other drugs		ROR (ad/bc)	95% CI			
			Cases (a)	Non-cases (b)	Cases (c)	Non-cases (d)					
MTX											
	Infections										
		<40	15	63	50115	585343	2.78	(1.58	-	4.88)
		40-49	41	170	50089	585236	2.82	(2.00	-	3.96)
		50-59	159	510	49971	584896	3.65	(3.05	-	4.36)
		60-69	380	1359	49750	584047	3.28	(2.93	-	3.68)
		70-79	401	1731	49729	583675	2.72	(2.44	-	3.03)
		>=80	133	720	49997	584686	2.16	(1.79	-	2.60)
	Malignant tumors										
		<40	9	69	11535	623923	7.06	(3.52	-	14.13)
		40-49	44	167	11500	623825	14.29	(10.25	-	19.93)
		50-59	102	567	11442	623425	9.80	(7.93	-	12.11)
		60-69	298	1441	11246	622551	11.45	(10.09	-	12.99)
		70-79	291	1841	11253	622151	8.74	(7.71	-	9.90)
		>=80	67	786	11477	623206	4.63	(3.60	-	5.94)
	Bone marrow disorders										
		<40	16	62	75685	559773	1.91	(1.10	-	3.31)
		40-49	27	184	75674	559651	1.09	(0.72	-	1.63)
		50-59	89	580	75612	559255	1.13	(0.91	-	1.42)
		60-69	260	1479	75441	558356	1.30	(1.14	-	1.48)
		70-79	520	1612	75181	558223	2.40	(2.17	-	2.64)
		>=80	278	575	75423	559260	3.58	(3.11	-	4.14)

Appendix 5 .Number of cases and ROR of infections, malignant tumors, and bone marrow disorders in patients treated with TNF-I, IL-6-I, or MTX stratified by gender

Drug	Adverse Event	Gender	Suspected drug		All other drugs		ROR (ad/bc)	95% CI			
			Cases (a)	Non-cases (b)	Cases (c)	Non-cases (d)					
TNF-I											
	Infections										
		Female patients	2935	3703	48127	601523	9.91	(9.43	-	10.41)
		Male patients	993	1195	50069	604031	10.02	(9.21	-	10.91)
	Malignant tumors										
		Female patients	557	6081	11823	637827	4.94	(4.52	-	5.40)
		Male patients	203	1985	12177	641923	5.39	(4.66	-	6.24)
	Bone marrow disorders										
		Female patients	220	6418	76951	572699	0.26	(0.22	-	0.29)
		Male patients	60	2128	77111	576989	0.21	(0.16	-	0.27)
IL-6-I											
	Infections										
		Female patients	1310	1627	49752	603599	9.77	(9.08	-	10.51)
		Male patients	456	672	50606	604554	8.11	(7.20	-	9.13)
	Malignant tumors										
		Female patients	172	2765	12208	641143	3.27	(2.80	-	3.81)
		Male patients	78	1050	12302	642858	3.88	(3.08	-	4.89)
	Bone marrow disorders										
		Female patients	197	2740	76974	576377	0.54	(0.47	-	0.62)
		Male patients	50	1078	77121	578039	0.35	(0.26	-	0.46)
MTX											
	Infections										
		Female patients	835	3492	50227	601734	2.86	(2.65	-	3.09)
		Male patients	317	1312	50745	603914	2.88	(2.54	-	3.25)
	Malignant tumors										
		Female patients	591	3736	11789	640172	8.59	(7.86	-	9.39)
		Male patients	264	1365	12116	642543	10.26	(8.98	-	11.72)
	Bone marrow disorders										
		Female patients	965	3362	76206	575755	2.17	(2.02	-	2.33)
		Male patients	258	1371	76913	577746	1.41	(1.24	-	1.62)