Tocilizumab in rheumatoid arthritis: A case study of safety evaluations of a large postmarketing data set from multiple data sources

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ABSTRACT

Objectives: To evaluate the magnitude of serious adverse events (SAEs) observed in postmarketing reports of tocilizumab (TCZ) for rheumatoid arthritis (RA) in relation to SAEs observed in TCZ clinical trials and external epidemiology data.

Methods: A total of 64,000 patient-years (PY) of TCZ exposure was needed to determine, with 90% power, whether rates of SAEs of interest (eg, death, hepatic, gastrointestinal, and cardiovascular) were ≥50% higher (agreed with the Food and Drug Administration) than expected. Reporting rates were calculated for spontaneously reported SAEs, open-label or unblinded postmarketing clinical trials (phase 3b/4), and a Japanese postmarketing surveillance program in the global postmarketing safety database. Event rates were calculated for the registrational placebo-controlled trials and long-term extension data. External comparators for anti-tumor necrosis factor (aTNF)-treated RA patients were derived from a US-based health care insurance claims database or published literature.

Results: The global postmarketing safety database provided 65,099 PY of TCZ exposure; the aTNF external comparator population provided 53,360 PY. Spontaneous reporting rates per 100 PY (95% confidence interval) were 8.3 (8.1, 8.5) SAEs, 0.39 (0.34, 0.44) deaths, 0.06 (0.04, 0.08) serious hepatic events, 0.15 (0.12, 0.18) serious gastrointestinal events, 0.09 (0.07, 0.12) serious myocardial infarctions, 0.15 (0.12, 0.18) serious strokes, and 0.07 (0.05, 0.09) cardiac deaths in the global postmarketing safety database. These were of similar magnitude to corresponding rates from registrational clinical trials, the aTNF external comparator population, and published literature.

Conclusions: SAE rates observed among postmarketing TCZ users were similar to those of various comparison populations. Predetermined design of studies to compare postmarketing AEs using multiple data sources is a useful strategy that can be applied to other medications.

Introduction

Anti-tumor necrosis factor (aTNF) agents are the most commonly used biologic therapies in patients with rheumatoid arthritis (RA) who have experienced inadequate response (IR) to disease-modifying antirheumatic drugs (DMARDs) (DMARD-IR) [1]. However, therapies that target other mediators in the pathogenesis of RA are needed for these patients because up to 40% may not respond adequately to aTNF agents [2–5].

One such mediator is interleukin-6 (IL-6), a key cytokine involved in RA pathogenesis, with roles in both local and systemic manifestations of the disease [6–8]. Tocilizumab (TCZ) is a humanized, monoclonal, anti-human IL-6 receptor (IL-6R) antibody that binds to membrane-bound and soluble forms of IL-6R [9], thereby blocking IL-6-mediated signaling and its proinflammatory effects [10].

Overall, 5 pivotal phase 3 randomized controlled trials in patients with RA and their long-term extensions (LTEs) demonstrated the efficacy and safety of TCZ in combination therapy with DMARDs [11–14] and as monotherapy [15]. In the clinical trial program, TCZ use was associated with laboratory changes (eg, elevated transaminase and lipid levels and decreased neutrophil and platelet levels) [16], though no temporal relationship has been observed between laboratory changes and clinical events. TCZ was initially approved by the United States Food and Drug Administration (FDA) for patients who did not respond to aTNF.

Clinical trials do not typically enroll a sufficient number of patients for relatively infrequent safety events to be detected. In addition, the populations evaluated are generally homogeneous and may not necessarily represent the diverse nature of the expected postmarketing treatment population. Therefore, greater cumulative exposure in more heterogeneous patient groups is needed for full understanding of the risks associated with any given therapy. Postmarketing surveillance through spontaneous reporting, registries, and postmarketing studies are important resources for the long-term detection of safety events [17,18]. As part of continuous, ongoing pharmacovigilance programs, pharmaceutical companies collect safety information from spontaneous reporting and from postmarketing studies designed to better reflect the real-world treatment setting.

The current analysis describes a safety assessment conducted to measure the rates of serious adverse events (SAEs) of interest [serious hepatic events, serious gastrointestinal (GI) perforations, and serious cardiovascular (CV) events] in the postmarketing setting, where exposure to TCZ was greater than that in registrational clinical trials and their LTEs. These rates were placed in context with background rates observed in a United States aTNF external health care insurance claims database comparator population. This assessment of a large postmarketing safety database was requested by the FDA before approval of the expansion of this new first-in-class product into earlier use in the RA patient population (ie, DMARD-IR patients). The agency agreed that once 64,000 patient-years (PY) of exposure was reached, analysis of the global safety data would provide appropriate sensitivity to quantify the risk for less-frequent SAEs of interest in patients treated with TCZ. The purpose of this report is to illustrate the methodology by which a substantial TCZ postmarketing data set was developed to enable better understanding of the profiles of these less-frequent events in patients treated with TCZ.

Methods

Reporting rates of SAEs of interest—serious hepatic events, serious GI perforations, and serious CV events [myocardial infarction (MI) and stroke]—were estimated in 3 distinct patient data sets (Table 1). The FDA definition of "serious" was used for this analysis [19]. Reported event rates for TCZ were estimated from the global postmarketing safety database population. Event rates were also calculated from the registrational clinical trials all-exposure (including placebo-controlled and LTE phases) population. Background event rates were estimated from the aTNF external health care insurance claims database comparator population, a retrospective cohort of aTNF-treated patients with RA from a United States health care insurance claims database (US MarketScan®). No formal statistical testing was conducted across these data sets because of differences inherent in their compositions. Sample size calculations were performed to allow for stable and precise estimates of event rates.

Sample size calculations were performed to determine the number of TCZ-exposed PY needed to indicate a ≥50% increase in risk (as agreed with the FDA) of SAEs of interest over estimated background rates derived from the aTNF external health care insurance claims database comparator population. Assumptions for the sample size analysis based on a Poisson distribution included an observed rate (TCZ-exposed rate) ≥50% higher than the background rate based on the health care insurance claims database, 2-sided $\alpha = 0.05$, and 90% power. These calculations specified that the amount of TCZ exposure

Table 1
Patient populations

Patient population, n (exposure)	Data included
Global postmarketing safety database population, n = 68,447 (65,099 PY)	Spontaneous reports—all spontaneous reports from TCZ-treated patients with RA, including those with missing or no reported indications cumulative to July 29, 2011
	Published reports from the literature, including those with missing or no reported indications
	In addition, a literature search spanning the period from October 11, 2010 to October 10, 2011 was performed to identify spontaneous reporting of unlisted AEs; 282 publications were identified
	Japanese postmarketing surveillance program
	Data from a 28-week, open-label study and a 3-year ongoing extension (including case report forms and spontaneous reports)
	Open-label/unblinded postmarketing clinical trials (phase 3b/4)
	Completed unblinded trials or ongoing open-label trials
	Excluded from this database were placebo-controlled and LTE studies (these were included in the registrational clinical trials all-exposure population), ongoing RA trials in the TCZ clinical development program, and blinded postmarketing RA trials
Registrational clinical trials all-exposure population, n = 4009 (14,994 PY)	Patient who received ≥1 dose of TCZ in the phase 3 clinical trial program to a cutoff date of April 1, 2011
aTNF external health care insurance claims database comparator population, n = 95,154 (53,360 PY)	Claims data from patients with RA treated with aTNF in a United States health care insurance claims database[a]

aTNF, anti-tumor necrosis factor; LTE, long-term extension; PY, patient-years; RA, rheumatoid arthritis; TCZ, tocilizumab.

[a] Published reports from the literature were used for events that could not be accurately defined in the health care insurance claims database.

Table 2
Required sample size for the lower bound 95% CI to exceed background rates in aTNF external health care insurance claims database comparator population (assuming the observed rate is 50% greater)[a]

Event of interest	aTNF background rate[b] (per 100 PY)	TCZ PY
Serious hepatic events	0.10	63,913
Gastrointestinal perforation	0.14	45,653
Cardiovascular event (myocardial infarction and stroke)	1.74	2744

aTNF, anti-tumor necrosis factor; CI, confidence interval; PY, patient-years; TCZ, tocilizumab.

[a] Assumption included rate ratio of 1.5, α of 0.05, and power of 0.9.
[b] Background rate was based on a cohort of 19,000 aTNF-treated patients with rheumatoid arthritis in the aTNF external health care insurance claims database comparator population.

required to determine with 90% probability that the lower bound of the confidence interval (CI) of the TCZ rate was greater than the background rate (if the observed TCZ rate was 50% higher than the background rate) was approximately 64,000 PY. This calculated minimum exposure was considered sufficient to ensure that overlapping CIs were not merely an effect of too few events or of too small an exposed patient population, which would have resulted in very wide CIs. Background rates and number of PYs needed for the proposed analysis were calculated for each SAE of interest (eg, serious hepatic events, GI perforations, and CV events) (Table 2).

Global postmarketing safety database population

Reporting rates of the SAEs of interest in the postmarketing setting were based on the experience of TCZ-treated patients recorded in the global postmarketing safety database (Table 3). This database covers a range of sources, including all spontaneously reported adverse event (AE) data arising from the use of TCZ in patients with RA. Spontaneous reports include those received from regulatory authorities, published literature, Internet, lay media (eg, television and newspapers), licensing partners, and other pharmaceutical companies. Postmarketing reports from the Japanese postmarketing surveillance program were also captured in the global postmarketing safety database. Data from ongoing

(cumulative until July 29, 2011) and completed open-label/unblinded clinical trials (phase 3b/4) contributed to the global postmarketing safety database. However, data from the 5 pivotal registrational phase 3 trials and subsequent LTEs were excluded from the global postmarketing safety database to avoid duplication of patient data and were evaluated separately.

Estimation of tocilizumab exposure in the global postmarketing safety database population

The extent of TCZ exposure for the spontaneous reports and for the Japanese postmarketing surveillance program reports that contributed to the global postmarketing safety database population was estimated from global sales data and was used as the denominator for estimating reported rates of SAEs of interest from these sources. The number of spontaneous and/or postmarketing reports of SAEs of interest was used as the numerator. Global sales data included vials sold for use outside the clinical trial setting and in postmarketing clinical trials (including Japanese postmarketing reports) using commercial TCZ until July 29, 2011. Countries were grouped into United States and Canada, Japan, and rest of world (ROW) for TCZ exposure calculations. The estimation of exposure was based on total sales of TCZ and a series of assumptions, including average weight of patients (72.3 kg, United States, Canada, and ROW; 53.2 kg, Japan), average frequency of dosing, and average dose per year (5762 mg, ROW; 5118 mg, United States and Canada; 5069 mg, Japan). Except for average dose, given the differences in the approved TCZ starting dose between ROW and North America (8 mg/kg versus 4 mg/kg), exposure calculations for ROW and the United States and Canada were based on the same assumptions. Japan was treated as a separate region because of more comprehensive data collection regarding exposure to TCZ in the Japanese postmarketing surveillance program. The total amount of TCZ sold per country per year (milligrams) was divided by the average annual dose per patient to give the PY of exposure. Assumptions used were based on data from clinical trials and market research conducted in Europe and the United States. Assumptions used for Japan were based on data collected from the Japanese postmarketing surveillance program (average dose, average body weight, and average number of doses per year). Assumptions used to estimate the average frequency of dosing in ROW were derived from a longitudinal market research study

Table 3
Global postmarketing safety database population sources and exposure rates

Data sources contributing to global postmarketing safety database population	Exposure to TCZ (contribution to database), $n = 68{,}447$			Exposure to TCZ by length of exposure, months (contribution to database)		
Spontaneous reports	$n = 62{,}713$[a]			≥ 24	$n = 8664$	(13.8%)
	US and Canada	8947 PY[b]	(13.7%)	18 to < 24	$n = 5401$	(8.6%)
Published reports from the literature for RA	ROW	26,712 PY[b]	(41.0%)	12 to < 18	$n = 12{,}466$	(19.9%)
Japanese postmarketing surveillance program	Japan	25,095 PY[b]	(38.5%)	6 to < 12	$n = 18{,}247$	(29.1%)
				< 6	$n = 17{,}933$	(28.6%)
Open-label/unblinded postmarketing clinical trials (phase 3b/4)	$n = 5734$[c]			≥ 24	$n = 255$	(4.4%)
	Postmarketing trials	4345 PY[d]	(6.7%)	18 to < 24	$n = 697$	(12.2%)
				12 to < 18	$n = 648$	(11.3%)
				6 to < 12	$n = 1014$	(17.7%)
				< 6	$n = 3120$	(54.4%)
Total		65,099 PY	(100%)			

PY, patient-years; RA, rheumatoid arthritis; ROW, rest of world; TCZ, tocilizumab; US, United States.

[a] Until July 29, 2011.
[b] Simulated data from global sales.
[c] Until August 12, 2011.
[d] Actual data.

conducted in Germany in which 360 patients provided data on 1710 dosing intervals between February 2009 and August 2010.

Calculation of TCZ exposure for patients in open-label/ unblinded postmarketing clinical trials (phase 3b/4) that contributed to the global postmarketing safety database population used reported events as the numerator and extent of TCZ exposure in postmarketing trials in RA patients (calculated using actual exposure data from global and local open-label/unblinded phase 3b/4 clinical trials) as the denominator (Table 3).

Safety analysis in the global postmarketing safety database population

The safety analysis estimated reporting rates of exposure for deaths, overall SAEs, and 3 SAEs of interest for TCZ [serious hepatic events, serious GI perforation, and serious CV events (MI and stroke)]. Multiple occurrences of SAEs were counted multiple times. Transient ischemic attacks were excluded from the calculation for stroke rates because they are generally assessed separately from stroke in epidemiological studies of CV events in patients with RA [20]. SAEs of interest were defined using published Standardised MedDRA Queries, MedDRA High Level Terms, AE grouped terms developed by the sponsor, and/or medical review. All SAE reporting rates were expressed per 100 PY and included 95% CIs for the overall medical concept.

Based on size estimations from the aTNF external health care insurance claims database comparator population, analysis of the global postmarketing safety database was performed once it was calculated that at least 64,000 PY of TCZ exposure had been reached.

Registrational clinical trials all-exposure population

Pooled event rates in the placebo-controlled and LTE periods of TCZ registrational clinical trials were estimated using 4009 patients who received at least 1 dose of double-blind and/or open-label TCZ in the phase 3 clinical program until a cutoff date of April 1, 2011. Patients who were DMARD-IR naive ($n = 2904$), aTNF-IR naive ($n = 464$), or methotrexate (MTX) naive ($n = 417$) were included.

Calculation of tocilizumab exposure in the registrational clinical trials all-exposure population

Event rates in the registrational clinical trials all-exposure population were calculated using events reported in the trials as the numerator and total PY of TCZ exposure in the trials as the denominator. Total TCZ exposure was calculated as the sum of individual patient exposure from TCZ registrational clinical trials (which did not contribute to the global postmarketing safety database population). The extent of exposure (PY) until April 1, 2011, was calculated as the number of infusions actually received (missed doses excluded) plus up to 28 days per infusion. Duration of the study (PY) until April 1, 2011 was calculated as the date of the last safety observation minus the date of the first dose plus 1.

Safety analysis in the registrational clinical trials all-exposure population

Event rates were estimated for deaths, SAEs, and SAEs of interest. SAEs occurring more than 90 days after the last dose of TCZ were reported only if they were considered by the investigator to be related to treatment. Multiple occurrences of SAEs were counted multiple times. The total PY used to calculate the rate of death in the TCZ group was different from the PY used for other SAEs because the time on escape therapy (escape to TCZ 8 mg/kg

was permitted per protocol in some studies for patients who did not respond) was included for the group in which it occurred.

aTNF external health care insurance claims database comparator population

To provide an expected background rate of events and to compare reported rates in TCZ-treated RA patients with expected rates in biologic-treated RA patients, event rates of the SAEs of interest were calculated using data from the aTNF external health care insurance claims database comparator population. These data were based on claims from patients treated with aTNF biologics licensed for the treatment of RA patients who were DMARD-IR. Events that could not be accurately identified in health insurance claims data (eg, "any" SAE or death) were compared with event rates published in the literature. Background event rates of SAEs of interest were calculated using events identified through *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnostic and National Drug Code for Healthcare Common Procedure Coding System procedure codes as the numerator and the total PY of exposure included in the aTNF external health care insurance claims database comparator population as the denominator. RA patients receiving aTNF agents were classified as having SAEs of interest if the patient had a hospital claim with overnight stay and an *ICD-9-CM* diagnosis code indicative of the SAE of interest. Emergency room visits without overnight stay were not counted as SAEs. Hospital stays involving diagnostic codes associated with AEs of interest were used in previously published epidemiological studies as proxies for categorizing AEs as serious [21–23]. The index date for follow-up was defined as the first aTNF prescription after RA diagnosis. Retrospectively collected patient health care insurance claims records [for all patients in the intent-to-treat population (those who discontinued treatment or who switched to another biologic agent)] were followed up from the index date until the first occurrence of the AE of interest or until disenrollment from the database.

Results

Patient characteristics

An estimated 68,447 patients were included in the global postmarketing safety database population—62,713 from global sales data (including the Japanese postmarketing surveillance program) and 5734 from the open-label or unblinded postmarketing clinical trials (phase 3b/4) (Table 3). Most patients reporting an event were from Japan (37.5%), Europe (32.2%), and North America (15.2%). Demographic data and baseline disease characteristics of patients contributing to the global postmarketing safety database are not consistently reported. However, available data indicate that median age was 59 years and that most reports were for female patients (79.2%), consistent with data for the RA population in general [24]. The total extent of exposure to TCZ in the global postmarketing safety database population was an estimated 65,099 PY, most (80%) of which was based on sales data from ROW and Japan. Based on analysis of the global sales data, approximately 59% of patients were exposed to TCZ for an average of ≤ 12 months, 28% were exposed for 12–24 months, and 13% were exposed for ≥ 24 months (Table 3).

In the registrational clinical trials all-exposure population, 4009 patients received at least 1 dose of TCZ. Demographic and baseline disease characteristics among RA patients who were MTX-naive, DMARD-IR, and aTNF-IR were comparable. Slight numerical differences in disease parameters reflect differences in duration and severity of disease among these 3 subpopulations. Median age at

randomization into the original trials ranged from 51 to 54 years, and most (≥80%) patients were women. Patients had moderate to severe active RA, as indicated by a median Disease Activity Score using 28 joints ranging from 6.3 to 6.8. The extent of exposure to TCZ in the registrational clinical trials all-exposure population was 13,503 PY (from the first dose of TCZ); of the 4009 patients, 700 (17%) were exposed for ≤ 12 months, 884 (22%) were exposed for 13–48 months, and 2425 (61%) were exposed for ≥4 years. The DMARD-IR subpopulation contributed 11,126 PY of the total 14,994 PY duration of exposure. Median duration during the trial was 4.56 years.

In the aTNF external health care insurance claims database comparator population, of the 95,154 patients with at least one diagnosis code for RA who were 18 years of age or older, 69,246 (72.8%) were women; approximately 17% were younger than 45 years of age, 52% were 45–64 years of age, and 31% were older than 65 years of age. Average observation time for these patients was approximately 2.8 years. The 19,000 patients who were treated with one or more aTNF agents provided a maximum of 53,360 PY of cumulative follow-up (PY of follow-up varied slightly for different types of AEs because of censoring of event occurrence) after the initiation of aTNF therapy.

Safety analyses

Reporting event rates in the global postmarketing safety database population, event rates in the registrational clinical trials all-exposure population, and event rates in the aTNF external health care insurance claims database comparator population (or published data, where applicable) are shown in Table 4 [25,26]. Safety results for the global postmarketing database population are also detailed in Table 4.

In the global postmarketing safety database population, 253 patients were reported to have died after TCZ administration. Therefore, the reporting rate of death was estimated to be at least 0.39 (95% CI: 0.34, 0.44) deaths per 100 PY. Death rates calculated using a published meta-analysis of data from 17 clinical trials of aTNF-treated RA patients [26] were reported as 0.61 per 100 PY (95% CI: 0.38, 0.91). For many patients, more than 1 AE was recorded in the safety database as having led to death (401 events were recorded for 253 deaths). Based on all recorded AEs leading to death, the most common causes of death were infections and infestations (89 patients with 114 AEs) and cardiac disorders (46 patients with 52 events).

The reported rate of overall SAEs in the global postmarketing safety database population was estimated to be at least 8.30 (95% CI: 8.08, 8.52) events per 100 PY; infections and infestations were the most frequently reported SAEs [2.31 (95% CI: 2.20, 2.43) per 100 PY]. The overall SAE rate in the registrational clinical trials all-exposure population and the rate estimated from a published meta-analysis of 18 clinical trials in aTNF-treated RA patients [26] were 14.63 (95% CI: 14.03, 15.26) and 16.46 (95% CI: 15.05, 17.97) per 100 PY, respectively.

The reported rate of serious hepatic events in the global postmarketing safety database population was estimated to be at least 0.06 (95% CI: 0.04, 0.08) events per 100 PY, based on a total of 36 events reported in 31 patients. The event rate of serious hepatic events in the registrational clinical trials all-exposure population and in the aTNF external health care insurance claims database population was 0.04 (95%: 0.01, 0.09) and 0.10 (95% CI: 0.08, 0.13) per 100 PY, respectively (Table 4). The reported rate for serious GI perforations in the registrational clinical trials all-exposure population was 0.34, (95% CI: 0.24, 0.47) per 100 PY using AE terms in the Standard MedDRA Query (SMQ) for gastrointestinal perforation. However, this SMQ is relatively nonspecific (it includes abscesses) and may potentially overestimate the true rate of perforation. Therefore, a medical review of each case was performed to determine whether it was a true perforation (see Supplemental Material for criteria for medical confirmation). The rate of medically confirmed events was 0.20 (95% CI: 0.13, 0.29).

Table 4
Rates of SAEs in the analysis populations

	Reporting Rate (95% CI) per 100 PY			
	Reporting event rate in TCZ global postmarketing safety database population[a]	Event rate in TCZ registrational clinical trials all-exposure population[b]	Event rate in aTNF external health care insurance claims database comparator population[b]	Event rate in aTNF published literature[b]
Deaths	0.39 (0.34–0.44)	0.57 (0.45–0.70)	–	0.61 (0.38–0.91)[c]
SAEs	8.30 (8.08–8.52)	14.63 (14.03–15.26)	–	16.46 (15.05–17.97)[d]
Serious hepatic events	0.06 (0.04–0.08)	0.04 (0.01–0.09)	0.10 (0.08–0.13)[e]	–
Serious gastrointestinal perforations				
Overall	0.15 (0.12–0.18)[f]	0.20 (0.13–0.29)[f]	0.14 (0.11–0.18)[e]	–
With corticosteroids	–	–	0.15 (0.11–0.19)	–
Without corticosteroids	–	–	0.10 (0.03–0.24)	–
Serious myocardial infarction events	0.09 (0.07–0.12)	0.25 (0.18–0.35)	0.64 (0.58–0.71)[e,g]	–
Serious stroke events	0.15 (0.12–0.18)[h]	0.25 (0.17–0.34)	0.69 (0.62–0.76)[e]	–
Cardiac deaths	0.07 (0.05–0.09)	0.13 (0.08–0.21)	–	0.24 (0.10–0.50)[i]

aTNF, anti-tumor necrosis factor; CI, confidence interval; MI, myocardial infarction; PY, patient-years; RA, rheumatoid arthritis; SAEs, serious adverse events; TCZ, tocilizumab.

[a] Simulated data from global sales.
[b] Actual data.
[c] Unadjusted mortality rate of aTNF-treated RA patients; based on meta-analysis data of 17 trials with 23 combined deaths over 3800 combined PY of exposure in 4097 patients [26].
[d] Based on unadjusted event rate of aTNF-treated RA patients from 18 randomized trials with 499 combined SAEs over a cumulative 3032 PY of follow-up in 3581 patients [26].
[e] aTNF external health care insurance claims database population.
[f] Medically confirmed rate.
[g] Includes all codes for acute MI, including codes for asymptomatic MI diagnosed on electrocardiogram or other special investigation.
[h] Excluding transient ischemic attacks.
[i] Estimated mortality rate from cardiovascular disease causes from published data in a biologic (aTNF) registry in Spain [35].

The reported rate of serious GI perforation in the global post-marketing safety database population was estimated to be at least 0.23 (95% CI: 0.19, 0.27) events per 100 PY, derived from 149 events in 120 patients based on the SMQ wide (i.e., broad terms); the medically confirmed rate was 0.15 (95% CI: 0.12, 0.18). In the aTNF external health care insurance claims database population, the reported rate was 0.14 (95% CI: 0.11, 0.18) per 100 PY (Table 4). The reported rate of serious MI was estimated to be at least 0.09 (95% CI: 0.07, 0.12) events per 100 PY in the global postmarketing safety database population; this rate is based on 60 events in 59 patients. Serious stroke events (ischemic and hemorrhagic events were combined; transient ischemic attacks were excluded) were reported at a rate estimated to be at least 0.15 (95% CI: 0.12, 0.18) events per 100 PY, based on 96 events in 87 patients.

Reporting rates of serious MI and stroke in the registrational clinical trials all-exposure population and in the aTNF external health care insurance claims database population can be found in Table 4. A total of 46 deaths were reported in association with cardiac events; therefore, the corresponding reporting rate of cardiac deaths was estimated to be at least 0.07 (95% CI: 0.05, 0.09) events per 100 PY. Given that more than 1 event resulting in death could be reported per patient, it is possible that not all 46 deaths were of direct cardiac origin.

Discussion

Characterization of less-frequent safety events from purely clinical trial data is limited by the number of patients enrolled and the enrollment criteria that may not be representative of the expected real-world postmarketing treatment population. The approach described here attempted to overcome such challenges in generating a data set of sufficient exposure to define the expected risk for less-frequent events in patients with RA treated with TCZ. A TCZ postmarketing population with 64,000 PY of exposure was formed by evaluating data from a variety of post-marketing data sources (spontaneous reports, published reports from the RA literature, postmarketing trials in patients with RA, and a Japanese postmarketing surveillance program). Patients with RA who are DMARD-IR are usually prescribed aTNF biologics [1]; therefore, background rates of SAEs of interest for TCZ were estimated in a large aTNF external health care insurance claims database comparator population or in the published literature. This gave an indication of the number of PY of exposure to TCZ that would be needed to confidently ascertain that the rates of SAEs of interest were neither underreported nor overreported in the postmarketing setting or from the registrational clinical trial data.

In the current analysis, estimates of event rates in TCZ-treated patients were from a heterogeneous and substantial global postmarketing safety data set with approximately 65,000 PY of exposure, thus reflecting the use of TCZ in real-life clinical practice. The minimum exposure required to rule out a 50% increase in risk compared with background rates based on the aTNF external health care insurance claims database comparator population was estimated to be at least 64,000 PY. This volume of data produced tight CIs across all end points of interest. Additional exposure would make those CIs smaller; however, this would be unlikely to produce any additional clinical insight. The study sponsor felt that detecting a 50% increase in risk associated with TCZ for the key safety events was a reasonable approach, given the tradeoff between providing the information using the data available versus delaying the analysis while waiting for addi-tional data to accrue. This proposal was made to the FDA in a pre-supplemental biologics license application meeting and was approved. In future studies designed to meet pharmacovigilance needs, alternative approaches such as testing a non-inferiority

hypothesis for safety events compared with an alternative exposure (eg, anti-TNF agents) might also be considered.

Estimates based on all events from the Japanese postmarketing surveillance program and the postmarketing open-label phase of unblinded studies were obtained directly from the data collected on case report forms during postmarketing programs and were thus considered reliable.

Event rates of SAEs of interest calculated in the large aTNF external health care insurance claims database comparator pop-ulation were based on more than 50,000 PY of exposure from more than 19,000 RA patients treated with aTNF agents in real-world clinical practice, including a sample of the elderly (≥65 years of age) RA population representative of the United States general population. The aTNF external health care insurance claims database population in the current analysis provided more than 50,000 PY of follow-up in aTNF agent-exposed patients, which allowed for the detection of relatively infrequent events that cannot be identified in smaller, existing observational RA registries that enroll aTNF agent-treated patients.

Incidence rates of SAEs of interest in the aTNF external health care insurance claims database used in the current analysis were in line with the limited published data. Analysis of 2 health care databases (PharMetrics and Protocare) reported serious hepatic event rates of 0.05 per 100 PY for biologic and nonbiologic DMARD-treated patients with RA [21]. In the health care insurance claims database in the current analysis, which used a similar definition of serious hepatic events, the incidence rate was 0.10 per 100 PY (95% CI: 0.08, 0.13). The overall incidence rates of GI perforations in the health care insurance claims database [0.14 per 100 PY (95% CI: 0.11, 0.18)] were within published ranges of 0.19 and 0.10 per 100 PY in patients with RA treated with biologic therapies with or without concomitant corticosteroids, respec-tively [27]. In patients treated with corticosteroids, the incidence rate of GI perforations in the current health care insurance claims database analysis [0.15 (95% CI: 0.11, 0.19) per 100 PY] was within the range of previously published rates (0.11–0.19 per 100 PY) [22,28]. Reports from the British Rheumatology Society Biologics Registry estimated rates of MI and stroke among aTNF-treated patients to be 0.48 per 100 PY (95% CI: 0.37, 0.61) and 0.39 per 100 PY (95% CI: 0.29, 0.53), respectively [29,30]. Incidence rates of MI and stroke in the health care insurance claims database in the current analysis were 0.64 per 100 PY (95% CI: 0.58, 0.71) and 0.69 per 100 PY (95% CI: 0.62, 0.76), respectively. Certain advantages and limitations are associated with estimating background rates using health care insurance claims data. Such data sources have been used increasingly in pharmacovigilance for active safety monitoring of new therapies during the postmarketing period. Advantages of using electronic health care utilization records include rapid and cost-efficient access to health and drug pre-scription records, availability of diagnostic and drug prescription information recorded using standard coding systems (eg, *ICD-9-CM* and National Drug Code), and large, population-based samples of real-world health care utilization data [31–33]. Although health care claims data are valuable for efficient and effective examina-tion of health care outcomes, most health care claims databases have inherent limitations because they are collected primarily for the purpose of reimbursement for health services and not for research. Such limitations include potential miscoding of medical events or occasional inclusion of diagnostic codes related to rule out diagnostic workups. Therefore, to increase the specificity in outcome identification, hospitalization was required for all out-come events in the current analysis [21–23]. In addition, *ICD-9-CM* diagnostic codes were used for these conditions from published epidemiological studies, and some claims-based algorithms are based on high-quality validation studies (eg, myocardial infarction and stroke; see Appendices A and B in Supplementary Materials

for diagnostic, treatment, and Healthcare Common Procedure Coding System/National Drug codes used) though the outcomes in these analyses were not validated.

Despite its strengths, the methodology used in the current analysis of the global postmarketing safety database and registrational clinical trials all-exposure population also has limitations. First, the event rates were obtained from various sources with different methods of event definition, identification, and reporting. For example, in the global postmarketing safety database, data from the postmarketing setting is subject to underreporting because of the voluntary nature of safety reporting [34], whereas the Japanese postmarketing surveillance program and the postmarketing clinical trials are more akin to a registry and are subject to strict and structured reporting of events [35]. This may account for the higher proportion of events reported from Japan (37.5%) compared with those reported from the United States and Canada (15.2%). Additionally, the United States and Canada together contributed only 14% of the total TCZ exposure in the global postmarketing safety database, whereas Japan and ROW contributed 39% and 41%, respectively; this might also have contributed to the higher proportions of events observed in these regions compared with the United States and Canada. Furthermore, a key and well-known limitation in the analysis of spontaneous reports is that assumptions were made to estimate patients and PY of exposure from sales data. Certain additional assumptions were used in exposure calculations. For example, the estimates of average annual patient exposure were based on 3 regions: United States and Canada, Japan, and ROW; however, the average body weight for the United States, Canada, and ROW were estimated from market research conducted in the top 5 European countries. The same average dose was used regardless of region, but average weight likely varied per region/country.

Because of variations in the different analysis populations, inconsistencies between patient characteristics and demography are inherently probable. Although the populations were similar with regard to age, sex, and duration on treatment, regional variations in disease and treatment characteristics and potential differences in general health status and comorbidities among patients in the health care insurance claims database and in the global postmarketing safety database may confound comparisons of the incidence of SAEs.

Postmarketing rates of SAEs were comparable in an analysis between Japan and ROW, except for reported rates of gastric cancer, lymphoma, hematophagic histiocytosis, *Pneumocystis jiroveci* pneumonia, atypical mycobacterial infection, bacterial pneumonia, intestinal lung disease, and organizing pneumonia (data not shown). As is the nature of all spontaneously reported data, there is no ability to adjust for potential confounders in the TCZ global postmarketing safety database population.

Case numerator is defined differently by the health care insurance claims database, the global postmarketing safety database, and the registrational clinical trials all-exposure population. Therefore, diagnoses of events and conditions differ among the sources and may differ among regions and countries, which may indirectly impact event identification and reporting. The demographics of the full global postmarketing safety database population could not be characterized because of the nature of spontaneously reported data; only the demographics of patients reporting an event were known. This limits comparisons between the global postmarketing safety database population and other patient populations in the current study and in other published studies. An additional challenge was that postmarketing data were assessed cumulatively until a single point, which did not allow for assessment of changes in rates over time. TCZ has been available to prescribers for a relatively short time, so average exposure to TCZ in our study was comparatively short; approximately 59% of the patients reporting an event were exposed for an average of 12 months or less. Information on the effects of longer cumulative exposure to tocilizumab is limited.

In summary, despite the significant advantage of providing a large data set for this disease area, analysis of long-term safety for DMARD-IR patients with RA in the postmarketing setting continues to be challenging. There are inherent difficulties in assessing the exposed population given the spontaneous nature of safety event reporting, with limited epidemiological data on background rates and rates in the exposed population (particularly for the early postmarketing period). Addressing such challenges has necessitated the use of different cross-disciplinary (pharmacovigilance, biostatistical, and epidemiological) techniques, different data sources for estimation of the exposed population, and calculation of background rates of safety events for comparison with postmarketing data.

Overall, analysis of background event rates from the aTNF external health care insurance claims database comparator population and the published literature suggested that the reporting rates of SAEs—including death and hepatic, gastrointestinal, and CV events—estimated in the TCZ global postmarketing safety database were not higher than the background rates expected in aTNF-treated patients with RA. Furthermore, the observed rates of events determined from the TCZ global postmarketing safety database population were no greater than rates in the registrational clinical trials all-exposure population using placebo-controlled and LTE data.

Conclusions

The analyses presented illustrate an example of an integrated approach with which postmarketing pharmacovigilance data can be analyzed to improve understanding of a treatment's safety profile in the context of less-frequent events. They form the most comprehensive and rigorous evaluation of TCZ safety to date and were conducted to identify whether there was a $\geq 50\%$ increase in risk compared with background rates in patients treated with aTNF. Limitations of postmarketing data, particularly spontaneous reporting (for which underreporting and missing data are expected and exposures are based on assumptions), prevent accurate comparison with other, more reliable, data sets. Conclusions that event rates in the real world are consistent with those observed in clinical trials, therefore, should be drawn with these factors in mind. Nevertheless, in this case, analysis of a global and substantial postmarketing database was informative in that it did not identify greater risk for SAEs of interest for TCZ [serious hepatic events, serious GI perforations, and serious CV events (MI and stroke)] in the real-world setting. Long-term pharmacovigilance will continue to inform the safety profile.

Acknowledgments

Appendix A.　Supporting Information

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.semarthrit.2014.07.006.

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