

# Tocilizumab and the risk of respiratory adverse events in patients with rheumatoid arthritis: a systematic review and meta-analysis of randomised controlled trials

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## ABSTRACT

**Objective.** *The purpose of this study is to evaluate the relative risk (RR) of respiratory adverse events (AEs) among patients with RA treated with TCZ.*

**Methods.** *Databases (PubMed, Embase and Cochrane Library) were searched for randomised controlled trials (RCT) comparing the use of TCZ with placebo (PBO) or active comparator agents in adults with RA published until October 28, 2017. Statistical analyses were conducted to calculate the RR of infectious and non-infectious respiratory AEs and severe AEs (SAEs) using random-effects or fixed-effects models based on the heterogeneity of the included studies.*

**Results.** *Eight trials were ultimately included. TCZ was associated with an increased risk of infectious respiratory AEs relative to comparator agents (RR 1.53, 95% confidence interval [95% CI] 1.04–2.25) but was not associated with an increased risk of non-infectious respiratory AEs (RR 1.19, 95% CI 0.86–1.64). A subgroup analysis revealed similar results for non-infectious AEs and SAEs in the comparisons of TCZ with MTX and adalimumab (ADA), whereas increased risks of these AEs but not SAEs were observed compared with the PBO.*

**Conclusions.** *Our meta-analysis did not reveal an increase in the risk of non-infectious respiratory AEs in adult patients with RA who were treated with TCZ compared with other csDMARDs and bDMARDs in RCTs.*

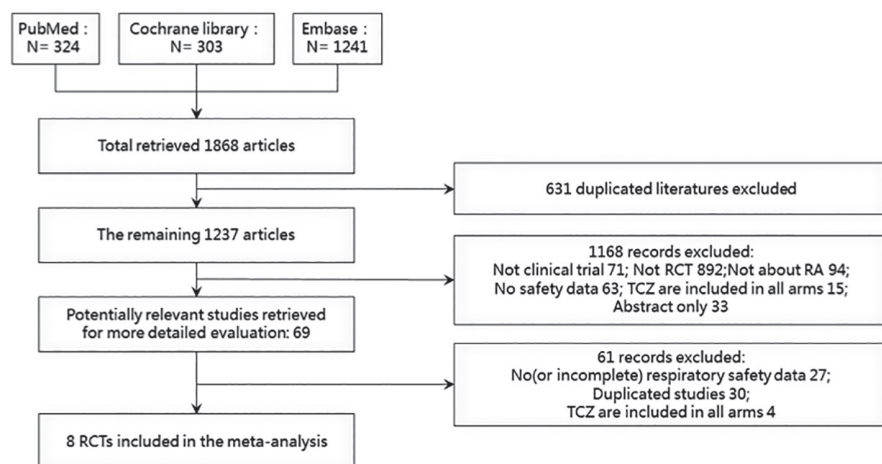
## Introduction

Rheumatoid arthritis (RA) is a systemic disease characterised by persistent synovitis and progressive destruction of the cartilage and bone. It is also associated with extra-articular manifesta-

tions, including interstitial lung disease (ILD) (1). In fact, subclinical interstitial lung abnormalities (ILAs) may be detected in approximately 30–50% of patients with RA, whereas clinically significant RA-ILD occurs in nearly 10% of the RA population and is associated with shorter survival and a more severe underlying disease (2–4). Although overall mortality rates for RA have decreased in recent decades, mortality rates associated with RA-ILD have increased significantly in older age groups (4). In addition, a higher rate of pulmonary infection also contributes to overall and pulmonary-related fatalities in RA patients (5).

Disease-modifying anti-rheumatic drugs (DMARDs), including biologics and non-biological agents, are the mainstay of RA management. Despite their established efficacy, patient and physician concerns regarding possible adverse events (AEs), particularly infections and the risk of pulmonary toxicity, such as ILD, have been raised for these agents (6, 7). In fact, most drugs used as RA treatments have been reported to be associated with the onset or worsening of ILD (8), and these concerns have inevitably limited the optimal use of these medications in clinical practice. Therefore, management of patients with ILD associated with RA remains a challenge for clinicians.

Tocilizumab (TCZ) is a humanised anti-IL-6 receptor monoclonal antibody. It is one of the first-line biological DMARDs (bDMARDs) used after methotrexate (MTX) failure (9). Monotherapy with TCZ is as effective as combination therapy with MTX, the cornerstone therapy for RA (10, 11). Moreover, according to results from a European collaborative study,



**Fig. 1.** PRISMA flowchart of studies included in the meta-analysis. PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT: randomised controlled trial; RA: rheumatoid arthritis; TCZ: tocilizumab.

treatment with TCZ in combination with or without concomitant synthetic DMARDs resulted in comparable clinical responses, as assessed by changes in the clinical disease activity index (CDAI) (12).

To date, little is known about the risk of ILD in TCZ-treated patients with RA in the real world. Although IL-6 inhibition attenuates pulmonary fibrosis in mice (13), the data from previous case reports and case-control studies of TCZ-treated adult patients with RA are contradictory. One study found that ILD

complications were exacerbated during TCZ therapy for RA (14), whereas others reported RA remission and stability or improvement of ILD in patients with RA-ILD (15, 16). A case-control retrospective study of 163 patients with RA who underwent biological therapy showed that tumour necrosis factor (TNF) inhibitors were administered to more patients with ILD events than to patients without ILD events (88% vs. 60%,  $p < 0.05$ ), but recipients of TCZ or abatacept did not exhibit differences in treatment with TNF inhibitors (17).

According to another recent case-control study, TCZ might be safely administered to patients with RA-ILD. Moreover, acute exacerbation of RA-ILD is due to uncontrolled disease activity rather than an AE caused by the drug (18). However, as with any form of scientific work, case-control studies have limitations, of which selection bias and information bias are among the most common forms. Therefore, a systemic meta-analysis that includes only randomised controlled trials (RCTs) is needed.

The purpose of our study was to evaluate the risk of respiratory AEs, particularly non-infectious AEs, including ILD, associated with TCZ therapy in patients with RA by performing a meta-analysis of RCTs.

**Methods**

*Data sources and searches*

A comprehensive literature search was conducted to identify all relevant articles from the inception of each database until October 28, 2017. The databases searched included PubMed, Embase and Cochrane Library. The search terms included the following keywords: “Arthritis, Rheumatoid”, “tocilizumab” or “monoclonal antibody, MRA” or “atlizumab” or “Actemra”.

**Table I.** Characteristics of the included studies.

Study name	NCT NO.	First author, year, ref.	Medication	TCZ dose	TCZ / comparator, n*	Blinding design	Study duration, weeks	Age, years**	Female, %	Disease duration, years**	TCZ-naive
ADACTA	NCT01119859	Gabay. 2013 (24)	TCZ ADA	8 mg/kg, Q4W	162 / 162	double-blind	24	54.4 / 53.3	79 / 82	7.3 / 6.3	Yes
BREVACTA	NCT01232569	Kivitz. 2014 (20)	TCZ-SC*** PBO-SC	162 mg, Q2W	437 / 218	double-blind	24	52.1 / 52.0	85.8 / 82.6	11.1 / 11.1	Yes
FUNCTION	NCT01007435	Burmester. 2016 (33)	TCZ+PBO MTX+PBO	8 mg/kg, Q4W	292 / 282	double-blind	52	49.9 / 49.6	75 / 79	0.5 / 0.4	Yes
MEASURE	NCT00535782	McInnes. 2015 (22)	TCZ+MTX PBO+MTX	8 mg/kg, Q4W	70 / 62	double-blind	12	57.0 / 57.0	75 / 83	6.8 / 7.0	Yes
OPTION	NCT00106548	Smolen 2008 (23)	TCZ PBO	8 mg/kg, Q4W	206 / 204	double-blind	24	50.8 / 50.6	85 / 78	7.5 / 7.8	Yes
ROSE	NCT00531817	Yazici 2012 (21)	TCZ+DMARDs PBO+DMARDs	8 mg/kg, Q4W	409 / 205	double-blind	24	55.2 / 55.8	79.5 / 83.9	8.6 / 8.5	Yes
U-ACT-EARLY	NCT01034137	Bijlsma 2016 (34)	TCZ+PBO MTX+PBO	8 mg/kg, Q4W	103 / 108	double-blind	104	55.0 / 53.5	76 / 64	25.5 / 27.0	Yes
VISARA	NCT01163747	Bingham 2015 (35)	MTX+TCZ MTX alone	8 mg/kg, Q4W	50 / 24	open-label	8	51.1 / 51.4	41 / 22	13.2 / 8.4	Yes

\*Number of participants analysed for safety data. \*\*Mean or median, as reported in individual studies. TCZ was administered intravenously if not indicated as “TCZ-SC”, which indicates that the drug was administered subcutaneously in this trial. ADA: adalimumab; PBO: placebo; MTX: methotrexate; DMARDs: disease-modifying anti-rheumatic drugs.

The search was extended by reviewing reference lists of articles included in the final selection.

#### Study selection and data extraction

Trials were included if they met the following criteria: (1) adult patients (aged  $\geq 18$  years) with RA; (2) English-language publications; (3) RCTs; (4) studies consisting of a minimum of 2 arms, at least 1 of which received TCZ and at least 1 of which did not receive TCZ; and (5) trials in which detailed respiratory AEs were reported separately in the TCZ and comparator groups.

Two investigators independently screened all available studies, and disagreements were discussed and resolved by consensus. Two reviewers independently extracted data from studies using standardised data extraction sheets, and all discrepancies were resolved by consensus. For each study, the following information was recorded: basic information (name of the study, NCT number, first author, and year of publication), study characteristics (design and duration, TCZ dose and usage, and comparator drug dose and usage), study subject characteristics (number of patients in the safety analysis group, age, sex, disease duration, etc.).

As expected, we observed substantial variation in the terminology used to describe respiratory AEs in the included studies. Thus, these AEs were divided into 2 subgroups: infectious and non-infectious AEs, as described in other studies (7, 19). Unfortunately, because of this heterogeneity in terminology, we were unable to directly compare any specific respiratory AEs, including ILD, in this meta-analysis.

#### Assessment of bias

The Cochrane risk of bias tool was used to assess the risks of bias of each trial. The main domains are random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessments, incomplete outcome data, selective reporting and other forms of bias. An  $I^2$  statistic of at least 50% was defined as indicating heterogeneity of outcomes. The assumption of homogeneity was considered invalid for  $p < 0.1$ .

#### Data synthesis and analysis

Review Manager 5.3 software (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) was used to analyse the data, and results are expressed as relative risks (RRs) with 95% confidence intervals (CIs). The pooled estimates were calculated using random-effects or fixed-effects models, depending on the heterogeneity of included studies. If substantial heterogeneity was observed ( $I^2 > 50\%$ ), the pooled estimate was calculated using the random-effects model; otherwise, the fixed-effects model was employed. We also conducted the following prespecified subgroup analyses to explore possible reasons for any observed heterogeneity: 1) the administration of intravenous (IV) TCZ versus subcutaneous (SC) TCZ and 2) the administration of different comparator drugs (placebo (PBO) vs. MTX vs. adalimumab (ADA)).

### Results

#### Study inclusion and characteristics

Our initial search strategy yielded 1,868 citations. Details of the selection process are outlined in Figure 1. Eight RCTs were ultimately selected for analysis, and respiratory AEs were analysed in 2,994 patients. The main characteristics of the included trials are listed in Table I. Across the trials, mean (or median) age and disease duration ranged from 49.6 to 57.0 and 0.4 to 27.0 years, respectively. Study duration ranged from 8 to 104 weeks. The proportions of female subjects ranged from 22 to 85.8 percent. All subjects were TCZ-naïve before participating in the RCT.

#### Risk of bias

The data analysed using the Cochrane risk of bias tool suggested a low risk of bias in the included studies (Supplementary Fig. 1). Most of the bias was contributed by the BREVACTA, MEASURE, OPTION, ROSE and ADACTA studies. In these studies, escape/rescue therapy with TCZ or ADA was permitted from week 12 (20) or 16 (21-24) for patients who did not achieve a 20% or greater improvement in the number of swollen and tender joints from baseline, and the incidence

of AEs in these patients before the escape/rescue therapy was not clearly indicated in the safety data. In addition, in the BREVACTA study, the ratio of patients who withdrew from the TCZ and PBO groups was 28:9, whereas at baseline, 656 patients were randomised into these two groups at a 2:1 ratio. Therefore, bias due to loss to follow-up may exist in this trial. Finally, VISARA was an open-label RCT; therefore, performance bias and detection bias may have existed.

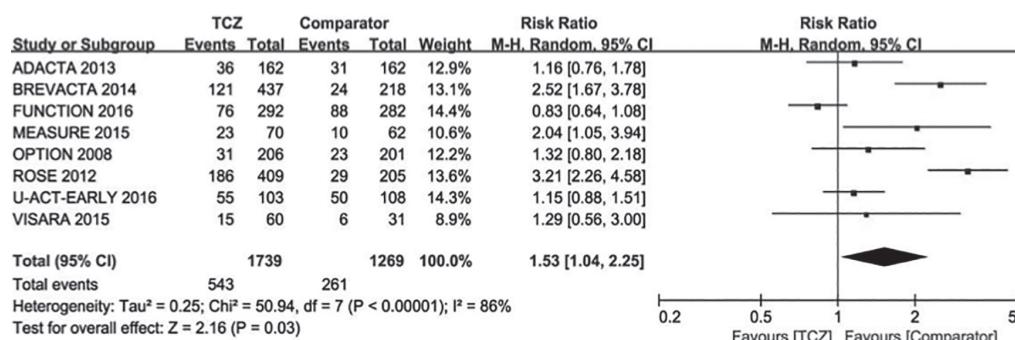
#### Risk of respiratory AEs

TCZ was associated with an increased risk of total infectious respiratory AEs compared to comparator agents (RR 1.53 (95% CI 1.04–2.25,  $p=0.03$ ),  $I^2=86\%$ ; Fig. 2). Among these infectious respiratory AEs, the most frequent were “upper respiratory tract infection”, “nasopharyngitis”, “sinusitis” and “bronchitis” for both TCZ and the comparator agents group. TCZ was not associated with an increased risk of total non-infectious respiratory AEs (RR 1.19 (95% CI 0.86–1.64,  $p=0.30$ ),  $I^2=18\%$ ; Fig. 3). Moreover, no significant differences were observed in the risk of infectious serious AEs (SAEs) (RR 1.43 (95% CI 0.74–2.76,  $p=0.28$ ),  $I^2=0\%$ ; Supplementary Fig. 2A) and non-infectious SAEs (RR 2.15 (95% CI 0.89–5.18,  $p=0.09$ ),  $I^2=0\%$ ; Supplementary Fig. 2B) between the TCZ group and the group treated with comparator agents.

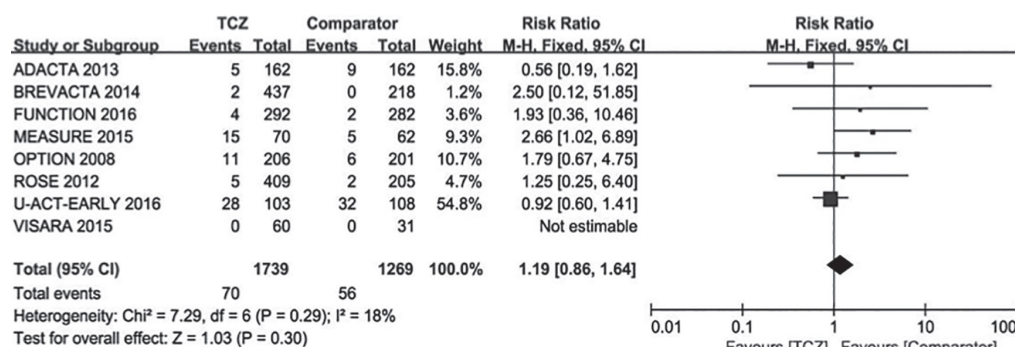
#### Subgroup analyses

Subgroup analyses were performed according to 1) the use of different comparator agents in these trials and 2) the route by which TCZ as administered to determine whether the difference in the risk of respiratory AEs was influenced by study design. Notably, the open-label VISARA trial, in which the patients were randomly assigned at a 2:1 ratio to receive TCZ plus MTX or MTX alone, was also included in the PBO subgroup.

Compared with MTX and ADA, TCZ was not associated with an increased risk of infectious respiratory AEs (RR=0.98,  $p=0.89$  and RR=1.16,  $p=0.49$ , respectively, Supplementary



**Fig. 2.** Relative risk of infectious respiratory AEs for tocilizumab compared with comparator agents. M-H: Mantel-Haenszel test; df: degrees of freedom.



**Fig. 3.** Relative risk of non-infectious respiratory AEs for tocilizumab compared with comparator agents.

Fig. 3A), although a statistically significant difference was observed when we compared TCZ with PBO (RR=2.08,  $p=0.0001$ , Supplementary Fig. 3A). Similarly, TCZ was not associated with an increased risk of non-infectious respiratory AEs compared with MTX and ADA (RR=0.98,  $p=0.92$  and RR=0.56,  $p=0.28$ , respectively, Supplementary Fig. 3B), but it was associated with a significantly increased risk compared with PBO (RR=2.04,  $p=0.02$ , Supplementary Fig. 3B). Regarding the SAEs, our meta-analysis did not reveal significant differences in RRs of infectious (PBO: RR=2.07,  $p=0.10$ ; MTX: RR=0.57,  $p=0.37$ ; ADA: RR=3.00,  $p=0.50$ , Supplementary Fig. 3C) or non-infectious respiratory SAEs (PBO: RR=1.81,  $p=0.33$ ; MTX: RR=2.57,  $p=0.20$ ; ADA: RR=3.00,  $p=0.50$ , Supplementary Fig. 3D) between the groups treated with TCZ and comparator agents. Among the non-infectious SAEs, only three cases of ILD or pulmonary fibrosis were reported, one in the MTX group and two in the TCZ-IV group.

In the TCZ-SC subgroup, infectious respiratory complications were significantly more likely to develop in patients treated with TCZ (RR=2.52,  $p=0.00$ , Supplementary Fig. 4A), whereas in

the TCZ-IV subgroup, significant differences in RRs of infectious respiratory AEs were not observed between groups treated with TCZ and comparator agents (RR=1.42,  $p=0.09$ , Supplementary Fig. 4A). Regarding the infectious SAEs and non-infectious AEs and SAEs, the RRs were not significantly different in either subgroup (IV group: RR=1.65,  $p=0.21$ ; RR=1.17,  $p=0.35$ ; RR=2.11,  $p=0.11$ ; SC group: RR=1.00,  $p=1.00$ ; RR=2.50,  $p=0.55$ ; RR=2.50,  $p=0.55$ , Supplementary Fig. 4B, C, D).

#### Sensitivity analysis

According to the sensitivity analysis performed using Stata/SE software (v. 11.0, StataCorp LLC), the exclusion of any single trial had little effect on the pooled results (Supplementary Fig. 5A-B-C-D). Thus, the results of this meta-analysis are quite stable.

#### Discussion

In general, we did not observe increased risks of non-infectious respiratory AEs or SAEs in patients with RA who were treated with TCZ. The subgroup analysis revealed similar results for the comparisons of TCZ with MTX and ADA, although increased risks of these AEs but not SAEs were observed for TCZ compared with PBO. Nota-

bly, MTX was not associated with an increased risk of total non-infectious respiratory AEs compared with other bDMARDs and sDMARDs in a recent meta-analysis (19).

In the present study, TCZ was associated with a significant increase in total infectious respiratory AEs, whereas the subgroup analysis showed that this statistically significant difference was observed only when the TCZ group was compared to the PBO group. This finding is not surprising because infections are among the most frequently occurring AEs during TCZ therapy, similar to other biological or non-biological DMARDs. A previous meta-analysis of six initial trials and five long-term extensions found that the MedDRA system organ class in which AEs occurred most frequently was "infections and infestations", among which respiratory AEs, such as upper respiratory infection, bronchitis and pneumonia, rated first, fourth and sixth most frequent AEs, respectively (25). Our study showed a similar pattern of infections, with "upper respiratory tract infection" as the most common. In addition, nearly all of these upper respiratory tract infections were AEs rather than SAEs, except for one event. As expected, compared with other DMARDs, such as MTX and the

TNF- $\alpha$  inhibitor ADA examined in this study, differences in infectious respiratory AEs or SAEs were not observed. Notably, in the TCZ subgroup, infectious respiratory complications were significantly more likely to develop in patients treated with TCZ-SC, but not TCZ-IV. The possible explanation for this finding is that only one trial analysed the TCZ-SC subgroup, and the only comparator agent for TCZ-SC was PBO; for the TCZ-IV subgroup, seven trials compared this treatment with different comparator agents. Therefore, this result must be interpreted with caution. In addition, in a recent review comparing the safety profile of the SC formulation of TCZ with the original IV formulation in patients with RA, McLaughlin *et al.* concluded that the safety data for TCZ-SC are similar to the IV form, although with a higher frequency of injection site reactions (26). TCZ is an effective treatment for RA. It was first approved in Japan in 2008 and in the European Union in 2009. During the last decade, TCZ has been approved as a treatment for RA in >100 countries worldwide (27). The administration of TCZ-SC or -IV as a monotherapy or in combination with conventional synthetic DMARDs (csDMARDs) provided rapid and sustained improvements in clinical and radiographic outcomes and health-related quality of life. These formulations were generally well-tolerated in clinical trials and clinical practice (28). In addition to its well-recognised efficacy and safety, TCZ has several special advantages. First, other biological DMARDs, such as TNF inhibitors, must be used in combination with MTX for patients with RA to achieve maximum benefits (29, 30), whereas TCZ is clinically, functionally, and radiographically effective and safe both with and without low-dose MTX (11). Consequently, TCZ monotherapy represents a valuable alternative strategy for patients with RA who cannot tolerate MTX and other csDMARDs. Second, the immunogenic risk of TCZ-SC and TCZ-IV treatments is low, either as monotherapy or in combination with csDMARDs (31). Moreover, a small proportion of patients develop anti-TCZ antibodies, but they have no evident impact on PK,

efficacy or safety (31). Considering the abovementioned advantages of TCZ in the clinical setting, practitioners must distinguish TCZ-induced lung toxicity from RA-associated lung disease.

Our study has important clinical implications. To the best of our knowledge, this meta-analysis, which includes a large number of patients (more than 2,900), is the first to show that RA patients treated with TCZ did not exhibit an increased risk of non-infectious respiratory AEs compared to those treated with other csDMARDs and biological agents. Although we were not able to directly evaluate any specific respiratory AE, including ILD, in this meta-analysis because of the heterogeneity in terminology, we believe our meta-analysis may to some extent help ameliorate clinician concerns regarding TCZ usage and therefore benefit patients with RA, especially those who cannot tolerate csDMARDs.

As with any study, ours has some limitations. A major limitation may be the relatively small number of studies included in our meta-analysis. Although several RCTs assessed TCZ, only a few studies provided complete information regarding all respiratory AEs (both infectious and non-infectious). We tried to include only high-quality studies that provided detailed information on the relevant data to minimise the effect of data collection errors. Another limitation is that although only three cases of ILD or pulmonary fibrosis were found in our analysis, these data may be biased by the selection of patients in the RCTs, which typically exclude patients with preexisting lung diseases. In addition, because ILD sometimes needs years to develop clinically, we believe that additional “real world” studies with long periods of detailed observation are needed. A final limitation is that only studies administering 8 mg/kg TCZ-IV every four weeks and 162 mg TCZ-SC weekly were analysed. We had two reasons for employing this strategy. 1) Among the eight trials analysed in our study, only one (OPTION) contained a 4 mg/kg arm. 2) In most countries, such as European countries, Japan and China, the recommended IV dosage of TCZ for patients with moderate to se-

vere RA is 8 mg/kg once every 4 weeks, whereas in the United States, the recommended initial dose is 4 mg/kg once every 4 weeks, which may subsequently be increased to 8 mg/kg based on the clinical response at the physician’s discretion (32). However, according to analyses from the Corrona Registry in the US, 77% of patients actually received 8 mg/kg TCZ every 4 weeks for 6 months after treatment initiation in real-world settings (32). Thus, the AEs occurring in the 8 mg/kg group may be more likely to reflect the AEs observed in the real-world clinical setting.

### Conclusions

In summary, the results of our work provide an up-to-date summary of the infectious and non-infectious respiratory AEs in adults with RA who are treated with TCZ. We did not observe an increased risk of non-infectious respiratory AEs in patients with RA who were treated with TCZ compared with other csDMARDs and biological agents, although an increased risk of infectious respiratory AEs was identified with TCZ treatment compared to comparator agents. These findings have important implications for clinicians who are treating patients with RA, and may assist practitioners with disease-management decisions. Nevertheless, more studies are warranted in the future to improve our knowledge of the safety of IL-6R blockade therapy among patients with RA.

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