EJR European Journal of Rheumatology

DOI:10.5152/eurjrheum.2022.22028

Original Article

# Severe Infections in Patients Treated with Tocilizumab for Systemic Diseases Other Than Rheumatoid Arthritis: A Retrospective Multicenter Observational Study

Florent Broca[1], Odile Souchaud-Debouverie[1], Evelyne Liuu[2,3], Pascal Roblot[1,3], Mickaël Martin[1,3]

## Abstract

**Objective:** This study aimed to describe severe infections in patients treated with tocilizumab for systemic diseases other than rheumatoid arthritis.

**Methods:** Data from patients receiving at least 2 doses of tocilizumab for systemic diseases other than rheumatoid arthritis between January 1, 2012, and July 1, 2020, in the region Poitou-Charentes (France) were retrospectively collected from medical records. Psoriatic arthritis and systemic juvenile idiopathic arthritis were also excluded as usually treated with similar modalities to rheumatoid arthritis.

**Results:** Of 37 patients, mainly suffering from giant cell arteritis, 25 patients (68%) had at least 1 infectious event and 15 severe infections occurred in 6 patients (3.2/100 patient-years), mainly bacterial. Lower respiratory tract and skin were the main sites. Severe bacterial infections were associated with a marked biological inflammatory syndrome, even under a cycle of administration of tocilizumab. Two severe zonas and 1 severe diverticulitis occurred. No tuberculosis or viral hepatitis reactivation was observed.

**Conclusion:** The incidence rate of severe infections was 3.2/100 patient-years and seems lower than that reported in rheumatoid arthritis. C-reactive protein dosage could be helpful for the diagnosis of bacterial infectious adverse events in patients on tocilizumab. Further larger studies are needed to confirm these results to assess potential risk factors for severe infections.

**Keywords:** Tocilizumab, systemic diseases, severe infections

**ORCID iDs of the authors:**
F.B. 0000-0002-9527-1801;
O.S.-D. 0000-0001-7587-0455;
E.L. 0000-0003-2758-5064;
P.R. 0000-0002-3740-3503;
M.M. 0000-0002-3826-4584.

**Cite this article as:** Broca F, Souchaud-Debouverie O, Liuu E, Roblot P, Martin M. Severe infections in patients treated with tocilizumab for systemic diseases other than rheumatoid arthritis: A retrospective multicenter observational study. *Eur J Rheumatol.* 2022; 10.5152/eurjrheum.2022.22028 [Epub Ahead of Print].

[1] Department of Internal Medicine, Poitiers University Hospital, Poitiers, France
[2] Department of Geriatry, Poitiers University Hospital, Poitiers, France
[3] Faculty of Medicine and Pharmacy, University of Poitiers, Poitiers, France

Corresponding author:
Mickael Martin
E-mail: mickael.martin@univ-poitiers.fr

Received: March 17, 2022
Accepted: August 8, 2022
Publication Date: September 16, 2022



## Introduction

Tocilizumab (TCZ) is a humanized immunoglobulin (Ig) G1 monoclonal antibody that selectively neutralizes both the soluble and membrane-bound forms of interleukin (IL)-6 receptor. It was first approved in second-line treatment for rheumatoid arthritis (RA) and polyarticular and systemic juvenile idiopathic arthritis, then more recently for giant cell arteritis (GCA) and polymyalgia rheumatica.[1] Tocilizumab is also used in several other systemic diseases such as Castleman disease,[2] polychondritis,[3] systemic sclerosis,[4] Still disease,[5] and Behçet disease.[6]

Some cases of severe and life-threatening bacterial infections with minimal fever and low biological inflammatory markers, especially C-reactive protein (CRP), were reported in patients treated by TCZ.[7,8] Moreover, several randomized clinical trials and real-life studies in RA suggested that TCZ increased the risk of opportunistic and serious bacterial infection to an extent similar to other biological disease-modifying anti-rheumatic drugs (DMARDs) such as anti-TNF alpha agents.[9-12] Data are however limited by various confounding factors such as comorbidities and the use of other immunosuppressive drugs.[13,14] To the best of our knowledge, except for RA and limited evidence for GCA, there are no available data about severe infections occurring in patients with other systemic diseases treated with TCZ.

The aim of this study was to describe severe infections occurring in patients treated with TCZ for systemic diseases other than RA.

## Methods

### Study Design and Patient Recruitment

We conducted a retrospective, multicenter observational study including all patients receiving at least 2 doses of TCZ (intravenous or subcutaneous) between January 1, 2012 (which was the date of first use of TCZ in the region regardless of indication) and July 1, 2020, in the former region Poitou-Charentes in France, an administrative region of 1.8 million inhabitants in south-western France, including 1 university hospital (Poitiers) and 4 secondary hospital centers (Niort, Angouleme, Rochefort, and La Rochelle). Patients were screened from the pharmacy of each hospital. The exclusion criteria were age under 18 years, non-systemic disorders (Devic's Neuromyelitis, Graves' orbitopathy), major lack of data (especially about dose of immunosuppressive agents used or patients lost to follow-up), and patients with RA. Psoriatic arthritis and systemic juvenile idiopathic arthritis have also been excluded from this study as usually treated by similar modalities to RA. Cytokine release syndrome associated with chimeric-antigen receptor T cells (CAR T cells) and severe COVID-19 disease were also excluded since a single injection was generally performed. Patients were informed with a booklet on TCZ administration, systematically given upon arrival in the hospital and orally expressed their non-opposition to data collection.

### Data Collection

Biometrical, clinical, and biological data were collected from the patients' medical records of each hospital. The cumulative dose of TCZ (with the protocol used) and glucocorticoids (GCs) was calculated. Use of other immunosuppressants before TCZ introduction was also recorded. Severe infections occurring before and up to at least 6 months after the last injection of TCZ were recorded. An infection was defined as severe if required hospitalization or intravenous treatment, was life-threatening, or led to disability or permanent damage or death. Type(s) of infections, severity, delay since the first TCZ injection, biological inflammatory markers, type and duration of the treatment received, and outcomes were recorded. C-reactive protein was considered increased if greater than 5 mg/L.

### Outcomes

Primary outcome was the frequency of severe infections. Secondary outcomes were the characteristics of patients with severe infections and their description.

### Ethics

This study complies with the Declaration of Helsinki and was approved by the local ethics committee of the University of Poitiers and registered with the French data protection agency (Commission Nationale de l'Informatique et des Libertés, CNIL) (No. CHU86-R2019-11-06). According to French regulations, a non-opposition was obtained from all participants who participated in this study.

### Statistical Analysis

Descriptive analyses were done using the Statview software 5.0 and standardized methods to determine the mean and standard deviations or the median and quartile range value [Q1-Q3] depending on the distribution of the variables studied. No univariate or multivariate analysis was performed due to the small sample size.

## Main Points

- The ratio of severe infections in patients treated with tocilizumab for systemic diseases other than rheumatoid arthritis was 3.2/100 patient-years.
- The main sites of severe infections were the skin and lungs.
- A significant elevation of C-reactive protein was observed in majority of severe bacterial infections.
- The occurrence of severe zonas suggests possible interest in prophylaxis

## Results

### Population Study

Totally 229 patients received TCZ during the inclusion period, of which 192 were excluded according to the inclusion criteria. Finally, 37 patients were included in the study and received the first infusion of TCZ between January 1, 2015, and July 1, 2020 (Figure 1).

Patients' characteristics are depicted in Table 1. Median age at inclusion was 66 years [61-74], and most of them were women (70%). Nearly a third of patients had a history of infection before any immunosuppressive therapy. Seven (19%) had a history of colonic diverticulosis, 2 had a positive QuantiFERON test, and 1 had anti-Hbc antibody positivity with negative viral load before TCZ initiation. Twenty-seven (73%) received vaccines before the first TCZ infusion, mostly against *Streptococcus pneumoniae* (n = 24). The main indication of TCZ was GCA (n = 17), then polymyalgia rheumatica, Takayasu arteritis, Still disease, polychondritis (n = 4 each), and Castleman disease (n = 2) or 2 other vasculitis (Behçet disease and unclassified vasculitis). The median time between the diagnosis of the disease and TCZ initiation was 2 years [1-4]. At TCZ initiation, all patients except 1 were treated by GCs (with a median cumulative dose of 13.7 g prednisone equivalent (p.e.) [6.4-34.4]) and 27 (73%) received other immunosuppressants, mostly methotrexate (n = 23). Mean duration of follow-up during TCZ therapy was 33 ± 19 months with an average cumulative dose of 9.2 ± 5.9 g.

Among patients with GCA (n = 17), the duration before TCZ was 19 [7.5-24] months and GC daily dose at TCZ initiation was 10 [3.6-13.1] mg/day. Most of them (60%) had uncontrolled GCA with a history of failure of other immunosuppressants (e.g., methotrexate).

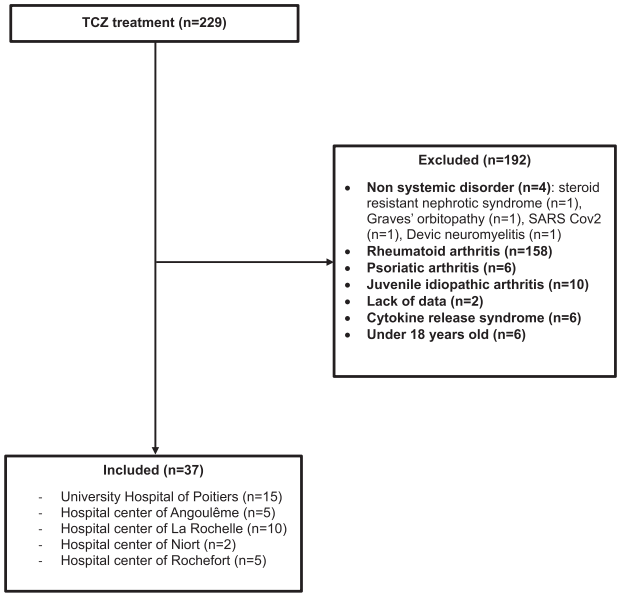


**Figure 1.** Flow chart. TCZ, tocilizumab; SARS Cov2, severe acute respiratory syndrome due to COVID-19.

**Table 1.** Patients' Characteristics

| Characteristics[a] | All Patients (n = 37) |
|---|---|
| Age (years), median [Q1-Q3] | 66 [61-74] |
| Female sex | 26 (70) |
| BMI (kg/m$^2$), mean ± SD | 25.5 ± 5 |
| Diabetes mellitus | 6 (16) |
| Chronic renal insufficiency | 3 (8) |
| Medical history of cancer | 11 (30) |
| Medical history of colic diverticulosis | 7 (19) |
| History of vaccination against *Streptococcus pneumoniae* | 24 (65) |
| History of infections before TCZ introduction[b] | 15 (41) |
| Indication for TCZ | |
| GCA | 17 (46) |
| Takayasu | 4 (11) |
| Polymyalgia rheumatica | 4 (11) |
| Still disease | 4 (11) |
| Polychondritis | 4 (11) |
| Castleman disease | 2 (5) |
| Other vasculitis[c] | 2 (5) |
| Duration of disease before TCZ start (months), median [Q1-Q3] | 19 [6-49] |
| Immunosuppressants used before TCZ start | |
| GCs | 36 (97) |
| Total cumulative dose (g, p.e.), median [Q1-Q3] | 13.7 [6.4-34.4] |
| Daily dose (mg), median [Q1-Q3] | 17.5 [8-30] |
| Methotrexate | 23 (62) |
| Azathioprine | 5 (14) |
| Anakinra | 5 (14) |
| Anti-TFN$\alpha$ | 4 (11) |
| Others[d] | 12 (32) |
| Tocilizumab regimen | |
| Intravenous | 32 (89) |
| Subcutaneous | 12 (33) |
| Total cumulative dose (g), mean ± SD | 9.2 ± 5.9 |
| Duration of TCZ (months), mean ± SD | 33 ± 19 |

[a]All values are expressed in n (%), unless otherwise specified; [b]Urinary tract infections (n = 3), dermohypodermatitis (n = 3), tuberculosis (n = 2), bursitis and tenosynovitis (n = 2), chronic skin Alternaria inflectoria infection (n = 1), hepatitis C (n = 1) (treated with ribavirin and interferon and considered as cured), cholecystitis (n = 2), herpes zoster (n = 1), infectious mononucleosis (n = 1), bacteriemia (n = 1), and bacterial meningitis (n = 1); [c]Behçet disease and unclassified vasculitis; [d]Disulone (n = 3), salazopyrine (n = 3), leflunomide (n = 2), cyclophosphamide, tadekinig-$\alpha$, canakinumab, and rituximab (n = 1 each).
BMI, body mass index; TCZ, tocilizumab; GCA, giant cell arteritis; GCs, glucocorticoids; p.e., prednisone equivalent.

### Severe infections

During TCZ therapy, 6 patients (17%), all over 65 years of age, had severe infections with a total of 15 severe infections and ratio of 3.2 events/100 patient-years of exposure (Table 2). All necessitated hospitalization and none resulted in death. Of these 6 patients, 2 (33%) had subcutaneous TCZ. Of 15 severe infections, 12 (80%) were currently treated with usual cycle of administration of TCZ (subcutaneous n = 3, intravenous n = 9).

Skin was the main infection site (n = 7) and resulted in permanent sequelae in 4 cases (2 disabling post-zosterian pain and 2 extensive skin wounds due to necrotizing fasciitis). One severe diverticulitis with digestive perforation was recorded. Most infections were documented or considered bacterial (80%) and associated with an increased biological inflammatory syndrome with a median value of CRP of 150 mg/L [61-331]. Among 6 patients, 2 presented several infections (patients 1 and 6), both presenting a history of severe infection on immunosuppressant before TCZ introduction (1 with severe urinary tract infection and 1 with chronic skin *Alternaria inflectora* infection requiring 10 months of antifungal treatment). Only 2 of these patients did not have any infection prior to initiation of TCZ. Median time to severe infection from the start of TCZ was 6 months [3-22]. Except 1, all patients received TCZ in association with GCs only. The median cumulative dose of GCs at TCZ initiation was 22.8 g [9.4-77.8] with a mean dose of 26 ± 17.8 mg per day p.e and a median cumulative dose of 3.8 g [3-4.5] under TCZ course. Two patients had hypogammaglobulinemia around 4 g/L including 1 receiving immunoglobulin supplementation.

## Discussion

Tocilizumab-related infections were mostly evaluated in RA and more recently in GCA. The reported incidence of severe infections in RA varies from 3.9/100 patient-years of exposure to 4.7/100 patient-years of exposure depending on studies and remains the most frequent cause of death in the all-exposed population.[9,15-18] This risk of global infection seems comparable to other biologic agents, although the risk of serious infections seems lower than that observed with TNF antagonists[11] or Rituximab.[19] In GCA, the GiACTA study (Trial Of Tocilizumab in Giant-cell Arteritis) study reported severe infections in 7% of the patients in the TCZ group[1] with corresponding incidence ratios at least 3-fold greater than that reported in patients with RA but may be more related to the disease itself and GCs regimen than TCZ treatment.[20] In our study, 3 patients (8%) with GCA presented serious infections which are in line with the results of GiACTA Study. Another national multicentric observational study reported severe infections in 11.9% (10.6/100 patient-years) of cases of GCA under TCZ,[21] but although age was similar than our 17 patients with GCA (73 vs. 71 years), they had more frequently a history of DMARDs usage (73% vs. 60%) and a greater dose of GCs at TCZ initiation (21.5 vs. 10 mg/day).

In our study, severe infections occurred within 6 months to 2 years after TCZ initiation and affected only people aged over 65 years. The number of severe infections

**Table 2.** Description of Serious Infections

| Sex | Disease | Age at First Infection (Years) | Therapies Before TCZ | Infections Before TCZ (n) | TCZ Regimen | Time Since TCZ Start (Months) | Time Since Last TCZ (Days) | GC Dose (mg/day) | Infections | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Site | Micro organism | CRP (mg/L) | Outcomes |
| M[a] | Unclassified vasculitis | 82 | GC, ANA, MTX, AZA, DIS | 3 | IV | 16 | 12 | 5 | ORL | No | 140 | Healing |
| | | | | | | 24 | 6 | 9 | Urinary | *E. coli* | 161 | Healing |
| | | | | | | 31 | 28 | 15 | Pulmonary | No | 331 | Healing |
| | | | | | | 34 | 23 | 15 | Skin | No | 340 | Healing |
| | | | | | | 37 | 76 | 15 | Skin | No | 187 | Healing |
| M | GCA | 75 | GC, ANA | 0 | SC | 5 | 4 | 20 | Pulmonary | No | 368 | Healing |
| M | Castelman | 88 | No | 0 | IV | 1 | 9 | 0 | Digestive (diverticulitis) | No | 36 | Healing |
| F | Relapsing polychondritis | 73 | GC, DIS, MTX, AZA | 1 | IV | 3 | 5 | 30 | Skin | VZV | NA | Post-zosterian pain |
| F | GCA | 66 | GC, MTX | 1 | SC | 3 | 7 | 12 | Digestive (oesophagitis) | Candida | 2 | Healing |
| | | | | | | 15 | 4 | 2 | Skin | VZV | <1 | Post-zosterian pain |
| M[b] | GCA | 65 | GC, MTX | 3 | IV | 1 | 13 | 50 | Skin | *E. cloacae* | NA | Skin wound |
| | | | | | | 3 | 8 | 30 | Skin | *E. coli* | 61 | Skin wound |
| | | | | | | 3 | 21 | 30 | Bacteriemia | *P. aeruginosa* | NA | Healing |
| | | | | | | 6 | 117 | 8 | Pulmonary | HRSV, *E. cloacae* | 126 | Healing |
| | | | | | | 7 | 160 | 6 | Skin | *P. aeruginosa, S. aureus, S. pyogenes* | 47 | Healing |

[a]Had non-substituted hypogammaglobulinemia; [b]Had substituted hypogammaglobulinemia.
M, male; F, female; GCA, giant cell arteritis; TCZ, tocilizumab; GC, glucocorticoids; ANA, anakinra; MTX, methotrexate; AZA, azathioprine; DIS, disulone; IV, intravenous; SC, subcutaneous; *E. coli, Escherichia coli*; VZV, varicella zoster virus; *E. cloacae, Enterobacter cloacae*; *P. aeruginosa, Pseudomonas aeruginosa*; HRSV, human respiratory syncytial virus; *S. aureus, Staphylococcus aureus*; *S. pyogenes, Streptococcus pyogenes*; CRP, C-reactive protein; NA, not available.

was greater after TCZ initiation than during the use of conventional immunosuppressive therapy. This result should be interpreted with caution because of the very small sample of patients and the biases related to other infectious risk factors that may be associated with the occurrence of such episodes after initiation of TCZ, especially concomitant treatment with GCs which is known to be associated with an increased risk of severe infections in patients treated with TCZ.[22] In contrast to the literature, these infections occurred in patients without long-standing disease. History of infections seems to be an important factor for the occurrence of severe infections, since 4 out of 6 patients had such a history, 2 of whom had recurrent severe infections. Among the 4 patients with available data about gamma globulin level, 2 had hypogammaglobulinemia around 4 g/L including 1 receiving immunoglobulin supplementation.

In agreement with the literature on RA, most infections were respiratory and skin infections.[13,17,23] Importantly, contrary to previous clinical cases report,[7,8] our study shows that patients with various systemic diseases who develop severe bacterial infections on TCZ mostly had associated marked biological inflammatory syndrome, even under usual cycle of administration of TCZ (Table 2). This has only been described in one other study on 6/8 patients with RA and severe infections.[13] This could be helpful for the diagnosis of bacterial infectious adverse events in patients on TCZ, but larger studies are needed to confirm this observation.

Our study found only one but severe case of diverticulitis with lower intestinal perforation. This is in line with the well-known increased risk of lower intestinal perforation related to diverticulitis in patients treated with TCZ compared with all other DMARDs.[24] Interestingly, while the risk of herpes zoster infection is similar to that of other immunosuppressive agents such as TNF alpha inhibitors,[18] 2 severe de novo zonas occurred in our study resulting in disabling post-zosterian pain. No case of tuberculosis or reactivation of chronic viral hepatitis was found, which is in agreement with the literature on RA.[9,11,25]

Except for partial data in GCA detailled above, our real-life multicentric study is the first to describe sevre infections in patients treated with TCZ for systemic diseases other than RA. The other strengths of our study are its multicentric and real-life design. In addition, the monitoring period offered a long-term follow-up under treatment, which allowed to have sufficient perspective about the occurrence of infections. Our study has several limitations. First, the small sample size limited the interpretability of the results and did not allow statistical analysis, especially for evaluation of

the main clinical factors associated with severe infections and adjustment of confounding factors, especially concomitant GC exposure. Indeed, a real-world database multicentric study found a statistically significant increased risk associated with each 1-g increase in cumulative glucocorticoid exposure for glucocorticoid-related serious infections and for infectious adverse events related to TCZ.[22] It is noteworthy that 9/15 severe infections occurred in patients receiving a daily dose of GC >10 mg p.e. in our study. Secondly, the retrospective design may have underestimated the number of infectious events, especially mild ones, and therefore, our study focused on severe infections only. Furthermore, we did not conduct an imputability investigation to conclude that TCZ is an independent risk factor for severe infections.

## Conclusion

The incidence rate of severe infections was 3.2/100 patient-years and seemed lower than that reported in RA. Severe infections were mostly bacterial with a significant elevation of CRP in the majority of cases. The occurrence of severe zonas suggests the possible interest in prophylaxis in patients treated with TCZ. A larger study should be carried out to confirm these results and to assess potential risk factors of severe infections in patients with systemic diseases treated by TCZ.

**Ethics Committee Approval:** Ethical committee approval was received from the Local Ethics Committee of the University of Poitiers and registered with the French data protection agency (Commission Nationale de l'Informatique et des Libertés, CNIL) (No. CHU86-R2019-11-06).

**Informed Consent:** Written informed consent was obtained from all participants who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – O.S.D.; Design – O.S.D., M.M., P.R.; Supervision – O.S.D., M.M.; Funding – NA; Materials – O.S.D., F.B.; Data Collection and/or Processing – F.B., E.L.; Literature Review – F.B., M.M.; Writting – F.B., O.S.D., M.M; Critical Review – O.S.D., E.L., P.R., M.M.

**Acknowledgments:** The authors would like to thank Dr Mélanie Catroux, Bruno Gombert, Dr Elisabeth Brottier-Mancini, Dr Lydia Faba, Dr Quentin Bodard, Dr Antoine Brigaud, Dr Elisabetta Manciano, Dr Aurélie Grados, Dr Guillaume Denis, Dr Céline Dieval, Dr Cédric Landron, Dr Frédérique Roy-Peaud, Dr Luminita Luca, Dr Florence Berthelemy, and the pharmacists of each hospital (Dr Pauline Lazaro, Dr Victoire Delbee, Dr Agnes Tran) for their participation to data collection.

**Declaration of Interests:** The authors have no conflicts of interest to declare.

**Funding:** The authors declared that this study has received no financial support.

## References

1. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of tocilizumab in giant-cell arteritis. *N Engl J Med*. 2017;377(4) :317-328. [CrossRef]
2. van Rhee F, Voorhees P, Dispenzieri A, et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. *Blood*. 2018;132(20):2115-2124. [CrossRef]
3. Moulis G, Pugnet G, Costedoat-Chalumeau N, et al. Efficacy and safety of biologics in relapsing polychondritis: a French national multicentre study. *Ann Rheum Dis*. 2018;77(8):1172-1178. [CrossRef]
4. Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2020;8(10):963-974. [CrossRef]
5. Kaneko Y, Kameda H, Ikeda K, et al. Tocilizumab in patients with adult-onset Still's disease refractory to glucocorticoid treatment: a randomised, double-blind, placebo-controlled phase III trial. *Ann Rheum Dis*. 2018;77(12):1720-1729. [CrossRef]
6. Akiyama M, Kaneko Y, Takeuchi T. Effectiveness of tocilizumab in Behcet's disease: A systematic literature review. *Semin Arthritis Rheum*. 2020;50(4):797-804. [CrossRef]
7. Nguyen MTT, Pødenphant J, Ravn P. Three cases of severely disseminated Staphylococcus aureus infection in patients treated with tocilizumab. *BMJ Case Rep*. 2013;2013:bcr2012007413. [CrossRef]
8. Bari SF, Khan A, Lawson T. C reactive protein may not be reliable as a marker of severe bacterial infection in patients receiving tocilizumab. *Case Rep*. 2013;2013:bcr2013010423. [CrossRef]
9. Navarro-Millán I, Singh JA, Curtis JR. Systematic review of tocilizumab for rheumatoid arthritis: a new biologic agent targeting the interleukin-6 receptor. *Clin Ther*. 2012;34(4):788-802.e3. [CrossRef]
10. Koike T, Harigai M, Inokuma S, et al. Effectiveness and safety of tocilizumab: postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan. *J Rheumatol*. 2014;41(1):15-23. [CrossRef]
11. Campbell L, Chen C, Bhagat SS, Parker RA, Östör AJK. Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: a systematic literature review and meta-analysis of randomized controlled trials. *Rheumatol (Oxf Engl)*. 2011;50(3):552-562. [CrossRef]
12. Sakai R, Cho SK, Nanki T, et al. Head-to-head comparison of the safety of tocilizumab and tumor necrosis factor inhibitors in rheumatoid arthritis patients (RA) in clinical practice: results from the registry of Japanese RA patients on biologics for long-term safety (REAL) registry. *Arthritis Res Ther*. 2015;17:74. [CrossRef]
13. Lang VR, Englbrecht M, Rech J, Schuch F. Risk of infections in rheumatoid arthritis patients treated with tocilizumab. *Rheumatology (Oxford)*. 2012;51(5):852-857. [CrossRef]
14. Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. *Rheumatology (Oxford)*. 2013;52(1):53-61. [CrossRef]
15. Genovese MC, Rubbert-Roth A, Smolen JS, et al. Longterm safety and efficacy of tocilizumab in patients with rheumatoid arthritis: a cumulative analysis of UP to 4.6 years of exposure. *J Rheumatol*. 2013;40(6):768-780. [CrossRef]
16. Jones G, Ding C. Tocilizumab: a review of its safety and efficacy in rheumatoid arthritis. *Clin Med Insights Arthritis Musculoskelet Disord*. 2010;3:81-89. [CrossRef]
17. Morel J, Constantin A, Baron G, et al. Risk factors of serious infections in patients with rheumatoid arthritis treated with tocilizumab in the French Registry REGATE. *Rheumatology (Oxford)*. 2017;56(10):1746-1754. [CrossRef]
18. Pawar A, Desai RJ, Solomon DH, et al. Risk of serious infections in tocilizumab versus other biologic drugs in patients with rheumatoid arthritis: a multidatabase cohort study. *Ann Rheum Dis*. 2019;78(4):456-464. [CrossRef]
19. Grøn KL, Arkema EV, Glintborg B, et al. Risk of serious infections in patients with rheumatoid arthritis treated in routine care with abatacept, rituximab and tocilizumab in Denmark and Sweden. *Ann Rheum Dis*. 2019;78(3):320-327. [CrossRef]
20. Gale S, Trinh H, Tuckwell K, et al. Adverse events in giant cell arteritis and rheumatoid arthritis patient populations: analyses of tocilizumab clinical trials and claims data. *Rheumatol Ther*. 2019;6(1):77-88. [CrossRef]
21. Calderón-Goercke M, Loricera J, Aldasoro V, et al. Tocilizumab in giant cell arteritis. Observational, open-label multicenter study of 134 patients in clinical practice. *Semin Arthritis Rheum*. 2019;49(1):126-135. [CrossRef]
22. Gale S, Wilson JC, Chia J, et al. Risk associated with cumulative oral glucocorticoid use in patients with giant cell arteritis in real-world databases from the USA and UK. *Rheumatol Ther*. 2018;5(2):327-340. [CrossRef]
23. Rutherford AI, Subesinghe S, Hyrich KL, Galloway JB. Serious infection across biologic-treated patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Ann Rheum Dis*. 2018;77(6):905-910. [CrossRef]
24. Strangfeld A, Richter A, Siegmund B, et al. Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs. *Ann Rheum Dis*. 2017;76(3):504-510. [CrossRef]
25. Ahn SS, Jung SM, Song JJ, Park YB, Park JY, Lee SW. Safety of tocilizumab in rheumatoid arthritis patients with resolved hepatitis B virus infection: data from real-world experience. *Yonsei Med J*. 2018;59(3):452-456. [CrossRef]