JPSIM Journal of Pakistan Society of Internal Medicine

Review Article

# Tocilizumab can be a First Line Treatment for Moderate to Severe Rheumatoid Arthritis: A Literature Review and Meta-Analysis of the Safety and Efficacy

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## Abstract

Tocilizumab (TCZ) is a humanized monoclonal antibody that targets receptor alpha for Interleukin (IL)-6. It helps control disease activity, complications, and systemic constitutional symptoms of moderate to severe RA in patients not responding to other biological drugs, including TNF inhibitors. This literature review and meta-analysis aims to search for literature published within the last twelve years to assess infection risk, safety, and efficacy of TCZ use for rheumatoid arthritis.

**Methods:** The review focused on high-quality studies published in the last fifteen years and excludes older studies, low-level research & studies not published in English. Of the 101 reviews found, forty-nine (49) are selected using CASP tools including nine (09) RCTs having 6711 patients for meta-analysis. Med- calc was used for statistical analysis, including odd ratio, 95% confidence interval, p-values, and heterogeneity.

**Results:** TCZ has superior efficacy compared with placebo and other bDMARD with MTX (OR: 4.518, 95% CI: 2.092 to 9.758). However, TCZ has a higher prevalence of total AE (OR 1.67, CI: 1.354 to 2.062, p vale<0.001) & infection risk (OR 1.18, 95% CI: 1.017 to 1.375) but there is no statistically significant difference for serious adverse events (SAE) (OR 1.09, CI: 0.870 to 1.371).

**Conclusion:** Apart from the slightly higher risk of acute bacterial infections and total AEs, TCZ has superior efficacy and similar safety profile for SAE when compared with other DMARDs. TCZ can be a first-line treatment for moderate to severe RA patients.

**Keywords:** Tocilizumab (TCZ) related infections, TCZ safety & efficacy, TCZ adverse events, TCZ monotherapy, TCZ vs. other biological drugs for Rheumatoid arthritis.

**How to cite this:**

Hussain A. Tocilizumab can be a first line treatment for moderate to severe Rheumatoid arthritis: A literature review and meta-analysis of the safety and efficacy. J Pak Soc Intern Med. 2021;2(2): 107-114

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## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory synovitis with or without extra-articular complications. Approximately 30-40% of patients have inadequate disease control by Tumor Necrosis Factor (TNF) inhibitors, and Methotrexate (MTX) combination therapy.[1] Secondly, one-third of patents can't tolerate a combination of csDMARD with Biological drugs due to their comorbidities, intolerance, or side effects and are treated with biological drugs as monotherapy.[2,3]

Tocilizumab (TCZ) is a humanized monoclonal antibody that targets receptor alpha for Interleukin (IL)-6, which is effective and safe for the treatment of moderate to severe RA, both as a monotherapy and in combination with csDMARD.[4] As it blocks IL-6, it also helps control systemic constitutional symptoms of RA. Many trials have shown the safety and effectiveness of TCZ in patients with RA, including its use in patients with multiple comorbidities and those who can't have MTX. It has also been shown that the safety and effectiveness of TCZ are maintained when it is used beyond 24 weeks, and no additional adverse events were reported with prolonged use after 24 weeks. It is effective in the cases not responding to csDMARD and TNF inhibitors treatment.5 Though rates of AEs such as infection are elevated in TCZ monotherapy groups as compared to those with csDMARD, this is potentially due to the comorbidities of the population who can't tolerate MTX due to associated health problems such as lung, liver or renal issues.[6] TCZ monotherapy

has also been proven to be non-inferior to TCZ combination with MTX in controlling moderate to severe RA in patients who have been initially managed with TCZ & MTX. The MTX is discontinued after 24 weeks of treatment after achieving initial control of the disease.[7] Trials to reduce or stop MTX after achieving initial disease control by combination therapy proved monotherapy with TNF inhibitors to be inferior when compared with combination therapy with MTX.[8,9] As TCZ is a humanized antibody and immunogenicity has been proven to be low against it, so MTX is not needed to suppress the immune-related neutralizing response by antibody production against it. TCZ is also effective both as subcutaneous injections and intravenous infusion.[10]

This literature review aimed to shed light on detailed pros & cons of TCZ use in rheumatoid arthritis especially focusing on the following aspects:

- Safety profile of TCZ including adverse events especially risk of infections
- Efficacy of TCZ for use in rheumatoid arthritis patients.

## Methods

**Search strategy and study selection:** The author searched for the recent high-quality studies published in last twelve years regarding the benefits and risks of TCZ in RA patients including the risk of infections by using access to study material through USW library subscription, membership ship to American College of Rheumatology, various rheumatology journals, New England Journal of Medicine (rheumatology section), PubMed, Research gate to find and analyze related studies.

Any studies which are older than fifteen years or low-level research, such as case studies, case series, are excluded. Also, the studies not published in English or those which are just abstracts are excluded. Those studies which are included are initially assessed using the CASP tools protocol, and only the studies meeting the inclusion criteria are used for the review. Keywords for the search included: Tocilizumab (TCZ) related infections, TCZ safety & efficacy, TCZ adverse events, subcutaneous TCZ vs. IV TCZ, TCZ monotherapy, TCZ pharmacokinetics, TCZ vs. other biological drugs for Rheumatoid arthritis.

Data search was conducted between 15/02/2020 and 15/04/2020. A total of 101 studies were found related to the TCZ, its efficacy, and infection risks. Fifty-two studies were excluded based on the exclusion criteria as mentioned earlier and were not mainly focusing on TCZ related aspects of the rheumatoid arthritis patients. Remaining studies (49) were assessed for suitability, analyzed, and read in detail for the literature review to find out the information regarding the safety, efficacy, and infection risk of TCZ (Fig.1). Then the data was analyzed for the next month till 15/07/2020, and the writing up started, which took another two weeks.

For the purpose of meta-analysis, nine (09) RCTs were found out of forty-nine (49) selected studies, relevant to the aims and objectives of this review (Table1).

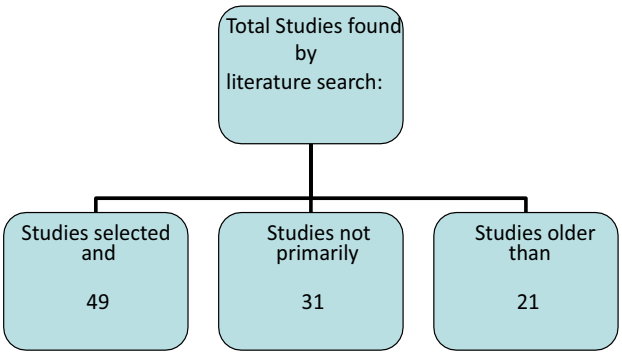


**Fig.1:** *Studies Selection*

**Table 1:** *RCTs for Meta-Analysis:*

| RCT | Description | Duration | Sample Size | Mean Age | Previous Treatment |
|---|---|---|---|---|---|
| Jones (AMBITION), 2010 | Phase 3 RCT | 24 weeks | 673 | 50.0-50.7 | MTX-naive |
| Kremer (LITHE), 2011 | Phase 3, RCT | 1 year | 1190 | 51.3-53.4 | MTX-IR |
| Gabay (ADACTA), 2013 | Phase 4 RCT | 24 weeks | 326 | 53.3-54.4 | MTX-IR |
| Ryoko S, et al. (2015). | Head-to-Head RCT | 1 year | 606 | 50.6-51.4 | MTX-IR |
| Emery (RADIATE), 2008 | Phase 3 RCT | 24 weeks | 499 | 50.9-53.9 | TNFi-IR |
| Yazici (ROSE), 2012 | Phase 3b RCT | 24 weeks | 619 | 55.2-55.8 | DMARD-IR |
| Genovese,2008 | Phase 3 | 24 weeks | 1220 | 53-54 | csDMARD-IR |
| Nishimoto (SATORI), 2009; | Phase 3 RCT | 24 weeks | 125 | 50.8-52.6 | MTX-IR |
| Shunsuke M, (2017). | RCT | 1 year | 1596 | 60.1 | csDMARD-IR |

Abbreviations: DMARD (Disease Modifying Anti Rheumatoid Drugs), MTX (Methotrexate), IR (Inadequate Response), RCT (Randomized Control Trial).

A total of 49 studies were included in the review (Fig.1). As the main focus was TCZ related infection, almost half of the studies of the studies (24 out of 49) are related to the risk of infections imposed by the use of TCZ in RA. Studies reviewed for other aspects of TCZ are for other adverse events, safety profile, TCZ as a monotherapy, subcutaneous use of TCZ, and basic pharmacological properties of the drug.

Data (number of events and total sample size) for meta-analysis was collected regarding adverse events (AE), serious adverse events (SAE), infections and safety from nine (09) RCTs, then organized as two by two tables and processed by using MedCalc software to calculate odd ratios (OR), 95% confidence intervals (95% CI), p-Values, combined effects and heterogeneity statistics (Q, I2) for variable effect meta-analysis. From these statistical values, forest plots for treatment effect size (OR) and funnel plots for publication bias were produced.

## Results

A total of 9 RCTs (done on 6711 patients) were included for meta-analysis. TCZ has statistically significant greater efficacy for moderate to severe cases of rheumatoid arthritis in comparison with placebo or other bDMARD with MTX (OR: 4.518, 95% CI: 2.092 to 9.758). However, TCZ also has higher prevalence of total AE when compared with other bDMARD or placebo with MTX (OR 1.67, CI: 1.354 to 2.062, p vale<0.001). Similarly, the rate of infection is slightly more in TCZ group (OR 1.18, 95% CI: 1.017 to 1.375). However, there is no statistically significant difference for serious adverse events including serious infections needing hospitalization in TCZ group com-pared with other treatment options (OR 1.09, CI: 0.870 to 1.371). Results are summarized as forest plots figures (2-5) & table (2).

**Table 2:** *Summarized Results for Meta-Analysis*

| Result | Infections | AE | SAE | Efficacy |
|---|---|---|---|---|
| Studies related to | 09 | 07 | 09 | 07 |
| TCZ group (n) | 3543 | 2846 | 3543 | 2549 |
| Control group (n) | 3168 | 1663 | 3168 | 1502 |
| OR | 1.18 | 1.67 | 1.09 | 3.87 |
| 95% CI | 1.017 to 1.375 | 1.354 to 2.062 | 0.870 to 1.371 | 3.211 to 4.684 |
| P value | <0.029 | <0.001 | <0.448 | <0.001 |
| Inconsistency(I2)% | 0.00% | 43.2% | 0.00% | 91.8% |

Abbreviations: AE (Adverse Events), 95 % CI (95% Confidence Interval), Sample size (n), OR (Odd Ratio), SAE (Serious Adverse Events), TCZ (Tocilizumab arm).

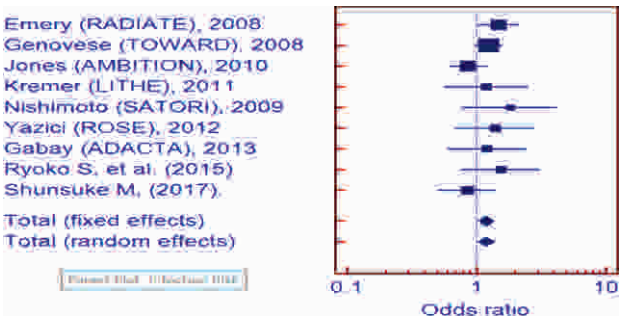


**Fig.2:** *Forest Plot (Infection Risk).*

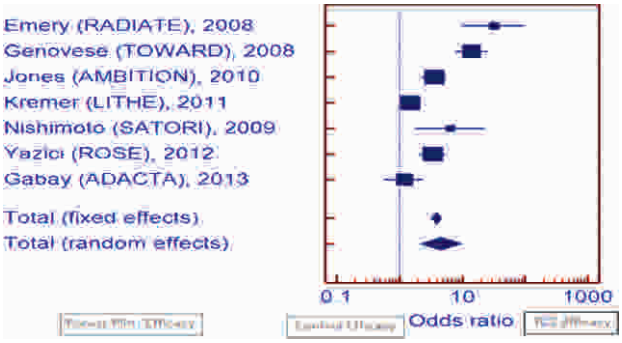


**Fig.3:** *Forest Plot (Efficacy):*

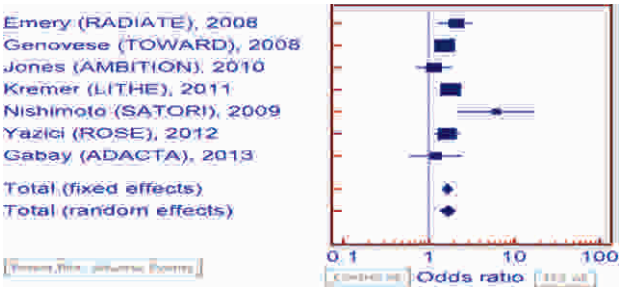


**Fig. 4:** *Forest Plot (Adverse Effect):*

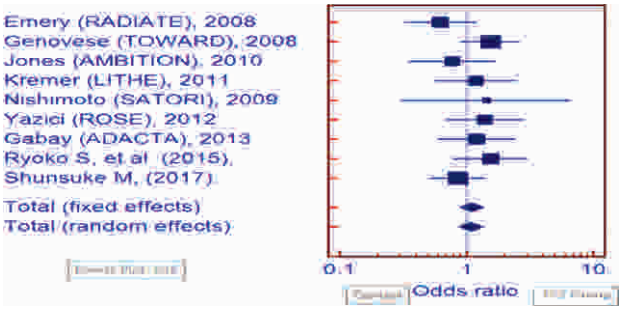


**Fig.5:** *Forest Plot (Serios Adverse Effects):*

***Pros & Cons of Tocilizumab (TCZ) for Rheumatoid Arthritis:*** Almost half to two-third of rheumatoid arthritis patients don't have an adequate response to Tumor Necrosis Factor Inhibitors (TNFi), and this is where non-TNF biological drugs such as TCZ has provided us with the option to control the disease for such cases.[11] Tocilizumab was initially recommended for moderate to severe RA with inadequate response or intolerance to other conventional Disease Modifying Anti Rheumatoid Drugs (csDMARDs) or anti TNF.[6]

The LITHE trial showed that long term efficacy and safety of TCZ were maintained for five years.[12].

***Intravenous (IV) vs. subcutaneous (S.C) TCZ in patients with Rheumatoid Arthritis:*** When S/C TCZ was approved, patients preferred s.c TCZ due to the convenience of self-injecting at home by using pre-filled syringes. SUMMACTA study using s.c TCZ (162 mg weekly) vs. TCZ IV (8mg/kg monthly), both options in combination with csDMARDs showed non-inferiority for achieving 20% ACR improvement response at 24 weeks.[13] MUSASHI study also showed non- inferiority of s.c TCZ (162 mg every fortnightly) vs. IV TCZ (8 mg /kg monthly) for achieving 20% ACR improvement at 24 weeks. S.c TCZ was also well tolerated with similar side effect profile and safety as IV TCZ.[14] Even long- term extension studies, 84 to 108 weeks, have shown that efficacy and safety have been shown for s.c TCZ.[15] TOZURA has shown that subcutaneous TCZ has the same efficacy as IV with similar side effects profile. These studies concluded that the efficacy of s.c TCZ in real-world cases over one year follow up was similar to that of IV TCZ.[16]

***Monotherapy vs. with csDMARD for Rheumatoid Arthritis:*** The efficacy of TCZ in the ACT-MOVE study was similar to monotherapy or in combination with csDMARDs.[17] In COMP-ACT Trial for 52 weeks, discontinuation of MTX at 24 weeks and continuing TCZ as monotherapy was shown non-inferior to a combination of MTX with TCZ monitored by DAS[28] score from 24 weeks onward. There were also no significant changes for bone erosions, synovitis, osteitis, and cartilage damage from 24 weeks to 40 weeks, [2017]. A study conducted by Gabay et al. showed that TCZ. as a single drug therapy was better than Adalimumab single-drug therapy in Rheumatoid patients who didn't tolerate MTX.[18]

***Efficacy of TCZ in Patients of Rheumatoid Arthritis:*** EULAR guidelines 2013 for treatment of Rheumatoid Arthritis express no preference of any specific biological DMARD, which means that either TCZ or TNFi can be used as the first line for moderate to severe RA cases. Hence main factors in choosing the biological agents are efficacy, safety profile, and comorbidities. Long term follow-up (4.6years) in a cumulative analysis study for more than 4000 patients of moderate to severe RA showed consistency in the efficacy of TCZ and long-term safety profile for TCZ use. Infections were the most common and serious adverse events.[19] Comparison of the effectiveness of TCZ vs. Abatacept reported by the Danish Registry found that disease control over 48 weeks was similar to both the drugs[20]. Many clinical studies proved the efficacy of Tocilizumab for reducing the signs and symptoms in RA.[21] ACT-MOVE study conducted in the UK as a part of multinational study TOZURA showed that TCZ either as monotherapy or TCZ as a combination therapy with csDMARDs was effective in reducing disease activity.

Efficacy of TCZ for symptoms and signs of RA is generally with longer-term follow up, and it plateaus around 12-24 months of treatment, unlike other biological agents with efficacy peak at 12-24 weeks requiring a longer period of treatment in those with inadequate response at the start. Similarly, the radiographic progression response noted in the second year of treatment, though there may be some progression in the first year of treatment with TCZ.[22] However, attempts to withdraw treatment or reduce the dose based on the high rate of remissions over time, led to higher relapses of the disease, more in those who were on monotherapy. Also, it's shown that a higher dose has greater efficacy, and that's why most centers use 162 mg weekly or 8mg/kg monthly regimen. TCZ also helps in reducing the need for corticosteroids in long term studies.[23] A trial also showed that those moderate to severe RA patients who failed first TNFi could respond to second TNFi, but non-TNF biological drugs such as TCZ is superior for signs and symptoms control.[24] A meta-analysis of Clinical Trials also suggests that the RA factor is also an indicator of the greater efficacy of TCZ.[25]

The persistence of efficacy in the long-term follow-up has been shown in the AMBITION Trial, and there were no issues with loss of response when the drug was continued over a long period for more than 24 months. Also, this sustained response was less affected by stopping the MTX or csDMARD therapy for TCZ.[26]

***Safety Profile & Adverse Events (AE) with TCZ:*** Safety of s.c and IV TCZ monotherapy or TCZ combined with csDMARDs has been established for more than one decade in many studies. The most common adverse reaction was respiratory infection (11%, same with both drugs). Side effects were 12% vs. 10% TCZ vs. Adalimumab groups, respectively.[18]

A large prospective, multi-center study of 1236 patients with Rheumatoid arthritis in clinical practice was conducted in Japan for comparison of TCZ vs. TNFi. Unadjusted incidence ratio (IR) of serious infections (SI) was 3.5-fold higher in the TCZ group than the TNFi group. However, adjusted results for serious adverse events (SAEs) or severe infections (SIs) were not higher in the TCZ group. [27]

***Cardio-vascular (CVS) Safety of TCZ:*** TCZ increases cholesterol level but also reduces CRP. It also reduces SSA types of inflammatory proteins, which can restore the anti-atherogenic function of HDL-C. Studies so far had not shown any increase in CVS mortality or CVS events. Longer-term studies in the use of TCZ

didn't show any increase in CVS events.[26] Some recent studies have shown reassuring data regarding CVS major adverse events with TCZ compared to other biological disease- modifying anti rheumatoid arthritis drugs (bDMARDs).[24] A meta-analysis of 29 relevant studies shows that TCZ has similar CVS outcomes compared with other bDMARDs and csDMARDs.[28]

***TCZ use in pregnancy:*** It should be avoided in pregnancy as no sufficient data is available. TCZ can cause miscarriages and preterm births.[29]

***Gastrointestinal Perforations (GIP) with TCZ:*** The incidence of diverticular perforations is much higher in patients treated with TCZ (2.7 events/1000 PYs) than in those treated with TNFi (0.5 events/1000 PYs), Rituximab (0.2 events /1000 PYs) or abatacept (0.5 events/ 1000 PYs). The number needed to harm with TCZ, csDMARD, and TNFi was 371, 1647 & 1911, respectively.30

***Malignancies Risk with TCZ:*** Japanese studies 31 indicating cases of malignancies including solid organ, non-melanoma skin cancers and hematological malignancies in cases who had exposure to TCZ but the rate of these malignancies in such cases was similar to the incidence in the general population and RA patients without exposure to TCZ.[32]

***Risk of Infections with TCZ use In RA Patients:*** A direct comparison of Etanercept, Infliximab, Adalimumab, abatacept, and Tocilizumab didn't find any significant difference in hospitalized infections attributable to the types of biological drugs used. Still, the risk of serious infections was mainly attributable to patient-specific risk factors.[33] Another literature review and meta-analysis found that it has a small but significantly higher risk of the adverse event but is comparable with other biological drugs.[34]

In a post-marketing surveillance program (PMS) of TCZ, the reported incidence of infection per 100 patients-years (PY) was 9.1.[35] Another multicenter, randomized trial reported that the incidence of serious infections (SIs) in the TCZ group after adjusting variables was similar to the TNFi group.27 French registry Orencia and RA (ORA) & Autoimmunity and Rituximab (AIR) reported rate of serious infections was 4.1, 5% & 3-6% for abatacept, Rituximab and anti-TNF drugs, respectively. However, it's suspected that the rate of infection with TCZ may be higher than other biological medications used for Rheumatoid Arthritis.[36] One study showed the rate of infection with TCZ in RA patients was 4.7% with regular frequency during 27.6 months follow up.[37] Risk of infection in real life Clinical patients on Tocilizumab was higher in studies conducted on non-trial patients than in trial patients, possibly due to selection criteria.[38] A meta-analysis of six RCT & five long term extension studies in Japan, rate of severe infections of 6.22% PYs.[31]

British Society of Rheumatology noted significantly increased risk of serious infections in RA patients treated with TCZ compared with Etanercept even after excluding prior use of other biological DMARDs. TOZURA & ACT-MOVE trials showed an infection rate of 3.6% PY.[16]

The most common infections reported were lung infections and skin/soft tissue infections.[39]. The non-TB opportunistic organism has no significant difference b/w various biological drugs.[40] Staphylococcus and Streptococcus were the most commonly identified infections in patients of RA treated with TCZ. The mean duration of these infections from the start of TCZ treatment was 12.8 months (SD10.6). This remained stable over three years of follow up.[39] A post marketing surveillance showed that most opportunistic infections in rheumatoid arthritis patients treated with TCZ included mycobacterium TB, non-TB mycobacterium, and invasive candidiasis pneumocystis jirvocii, cryptococcus, herpes zoster, and cytomegalovirus type infections.[35]

Old age and comorbidities, along with polypharmacy, are common patients related issues increasing the infection risk. Ryoko S et.al[27] conducted a large multi-Centre RCT on 1229 Clinical patients showed that important risk factors for serious infections (SIs) in TCZ group were the use of oral prednisolone >5 mg/day & presence of comorbidities also increase the risk of infections. Post marketing surveillance (PMS) of TCZ in Japan identified the following risk factors for serious infections during the first six months of use of TCZ in patients of RA: older age of the patients, longer disease duration, pre- existing lung disease, and prednisolone use more than 5 mg/day, concomitant therapies such as corticosteroids, DMARDs, prior use of Rituximab, and baseline high diseases activity calculated by DAS28 scoring system.[35]

Also, high CRP, ESR, high neutrophils, patients who have longer disease duration, exposure to more than three DMARDS, concomitant use of PPI, concomitant use of prednisone &/or Leflunomide, prior use of Rituximab and high DAS28 score were associated with increased infections. A five unit increase in disease activity led to a 7.7% increased risk of serious infections.[35] Another study demonstrated a linear relationship between the DAS-28 score and the risk of infections. Overall, a one-unit increased DAS28 score can increase the infection risk of up to 27%,[41]. ACPA has an important role in infections as ACPA positive and ACPA negative RA have different outcomes.[39] The patient's physical function is associated with infections in rheumatoid arthritis patients, and a decline in functional

capacity is a significant risk factor for pre-disposing them to infections.[42] Disease severity is an independent risk factor for serious infections irrespective of disability.[43] A combination of DMARDs with TCZ is a known risk factor for infections, as proved in the TOWARD study.[44] ESCMID conclusions regarding the risk of infections and preventive strategies for TCZ suggested: that infection risk is similar to other biological drugs.[45]

## Discussion

A detailed literature search was done to assess the safety and efficacy of TCZ with a special focus for the infections in adult patients using TCZ for rheumatoid arthritis. Many studies showed variable results, with some showing that the infection risk is higher in TCZ groups especially the risk for acute bacterial infections.[46] The incidence of these infections doesn't increase when TCZ is continued for long term treatment beyond 24 weeks. Though the risk for acute infection is high in the TCZ group, the risk for opportunistic infections such as mycobacterium TB or non-TB mycobacterium in patients treated with TCZ is similar to other biological drugs for RA. Common risk factors identified making such patients at higher risk for infections were patients related factors (old age, decreased functioning, disabilities), disease-related factors (high disease activity, disease-related disability, longer disease duration, abnormal neutrophil count, high ACR score or DAS28 score and other scoring used for assessing disease activity), concomitant drug therapies (leflunomide, corticosteroids, previous use of other biological drugs especially Rituximab) & drug-related factors (decreased IL-6 activity, higher dose).[27] However, common clues used such as fever, increased CRP, and neutrophilia are often absent in patients receiving TCZ for rheumatoid arthritis, so the assessment for infections shouldn't be based on these parameters alone.[47] Procalcitonin is another inflammatory marker that can help in such situations as it is not affected by TCZ.

Other concerns with TCZ are altered lipid profile and deranged liver enzymes.[48] which remain stable with the continuation of treatment. There has not been a significantly higher incidence in, major cardiovascular events, risk of malignancies, immunogenicity due to the drug or significant issues related to antibody production against the drug, or reducing its efficacy in the long-term follow-up studies.[26,32,49] Monotherapy with TCZ after discontinuing MTX beyond 24 weeks of treatment has been proven non-inferior to continue MTX with TCZ. So, patients who can't continue csDMARDs for many reasons can have reasonable disease control by TCZ monotherapy.[16]

TCZ has well-established long-term safety, persistent efficacy, and acceptable adverse events profile. It's also convenient to use as it has the option to self-inject by the prefilled drug at home without losing effectiveness or increasing side effects.[15] Although the outcome of the meta-analysis is clearly indicating the superior efficacy of Tocilizumab but there are not enough head- to-head trials of the tocilizumab with other available biological drugs.

## Conclusion

The metanalysis shows that TCZ has a slightly higher risk of acute bacterial infections and total AEs but no significant difference in serious adverse events, including serious infections when compared with other DMARDs. It's clearly more effective than other DMARDs, especially TNFi, for moderate to severe rheumatoid arthritis patients. Based on the findings of this review, TCZ can be the first line of treatment for moderate to severe RA patients, but the management of potential minor infections should also be considered as part of any treatment plan using TCZ. Further head-to-head comparison of Tocilizumab with other biological drugs is needed to establish its use as a first line therapy for moderate to severe RA.

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