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REVIEW ARTICLES

Efficacy and safety of Tocilizumab in polymyalgia rheumatica: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: The efficacy and safety of tocilizumab in patients with polymyalgia rheumatica (PMR) is not well established.

Methods: We systematically searched PubMed, Cochrane, and Scopus to identify randomized controlled trials (RCTs) evaluating the efficacy and safety of tocilizumab compared with placebo in patients with PMR. The endpoints of interest were glucocorticoid-free remission at week 24, cumulative prednisolone dose at week 24, and adverse effects like risk of infection, gastrointestinal disorders, musculoskeletal and connective tissue disorders. We analyzed binary outcomes using risk ratios (RR) and continuous outcomes using mean difference (MD) with 95% confidence intervals (CI). Statistical analysis was performed using Review Manager 8.13 (Cochrane Collaboration).

Results: Three RCTs with 188 patients were included, of whom 99 (53%) received tocilizumab and 89 (47%) received a placebo. The three RCTs varied significantly regarding patient populations and clinical settings: Bonelli et al. (2022) studied patients with early PMR receiving short-term glucocorticoids (GCs), Devauchelle-Pensec et al. (2022) included patients with GC-dependent PMR and a prespecified GC tapering strategy, and Spiera et al. (2021) analyzed patients with PMR associated with giant cell arteritis (GCA). Tocilizumab was associated with higher glucocorticoid-free remission at week 24 (RR 2.64; 95% CI 1.38 to 5.06; p= 0.003) and a lower cumulative prednisolone dose at week 24 (MD -2.52mg; CI -4.00 to -1.03; p= 0.0009) compared to placebo. However, there were no significant differences between the groups regarding safety outcomes, including the risk of infections (RR 1.19; 95% CI 0.92 to 1.52, p = 0.18), gastrointestinal disorders (RR 1.17; 95% CI 0.72 to 1.89, p = 0.52), and musculoskeletal and connective tissue disorders (RR 1.13; 95% CI 0.53 to 2.42, p = 0.75).

Conclusion: Our findings indicate that tocilizumab significantly improved glucocorticoid-free remission rates and reduced the cumulative prednisolone dose at week 24. Notably, safety outcomes between tocilizumab and placebo groups were comparable. These findings support the efficacy of tocilizumab in treatment of PMR.

Keywords: Tocilizumab; Polymyalgia Rheumatica; Interleukin-6 inhibitors; Glucocorticoid sparing; Cumulative prednisolone dose.

KEY MESSAGES

- Tocilizumab increases glucocorticoid-free remission rates at 24 weeks, highlighting its potential as a glucocorticoid-sparing agent in the management of PMR;
- Tocilizumab reduces the cumulative prednisolone dose at 24 weeks in patients with polymyalgia rheumatica, thereby reducing its side effects;
- The most common adverse effect associated with tocilizumab is an increased risk of infection.

INTRODUCTION

Polymyalgia Rheumatica (PMR) is a chronic systemic inflammatory disease with a rising incidence among individuals aged 50-80 years. Women are more likely to develop PMR, with a lifetime risk of 2.4%, compared to 1.7% in men[1]. While the exact etiology of PMR remains unclear, it is thought to result from a complex interplay between environmental factors and genetic predisposition[2]. Notably, patients with PMR exhibit pain and

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morning stiffness in the proximal regions of the body and elevated IL-6 production without a corresponding increase in TNF-α levels—an observation unique to PMR and Giant Cell Arteritis (GCA), conditions that frequently co-occur[3].

The traditional management of PMR relies on corticosteroid therapy, usually starting with moderate doses and gradually reducing them based on the patient's clinical and laboratory response[4]. While corticosteroids are highly effective in relieving symptoms, their long-term use can lead to significant side effects, including metabolic disorders such as diabetes mellitus, changes in body composition, osteoporosis, and an increased risk of infections[5]. Within this context, biological therapies like tocilizumab are emerging as promising new treatment options, especially in patients with corticosteroid intolerance or frequent relapses[4]. Tocilizumab is a monoclonal antibody that blocks IL-6, proving to play a crucial role in inhibiting inflammatory pathways closely linked to the development of PMR, as well as other rheumatologic conditions such as GCA and RA[6,7]. Recent studies have shown its effectiveness in reducing inflammatory symptoms in PMR patients, particularly those who require high doses of corticosteroids or are resistant to traditional therapies[8].In light of this, we aim to conduct a systematic review and meta-analysis to determine the effectiveness of tocilizumab compared to placebo for the treatment of patients with PMR.

METHODS

Study Design and Protocol

The systematic review and meta-analysis were performed in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines[9,10]. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42025626475.

Search Strategy and Eligibility Criteria

We systematically searched Scopus, Cochrane Central Register of Controlled Trials, and PubMed. We adopted a broad search strategy: "Polymyalgia Rheumatica" AND "Tocilizumab." The database search was performed from inception to 2nd December 2024. Two authors independently performed the search and extracted the data following pre-defined search criteria. Any disagreements were resolved by consensus between the authors.

We included studies that met the following inclusion criteria: (a) RCTs that directly compared tocilizumab with placebo; (b) patients diagnosed with PMR symptoms; (c) no restriction on follow-up duration; (d) a single weekly subcutaneous injection of tocilizumab (162 mg) plus prednisone taper; (e) intravenous infusion of tocilizumab (8 mg/kg) every 4 weeks for 24 weeks plus prednisone taper. We excluded studies involving patients with (a) GCA with PMR and cranial symptoms or cranial symptoms only (b) did not report any clinical outcomes of interest (c) observational studies, cross-sectional studies, and case reports.

We included three randomized controlled trials (RCTs), enrolling a total of 188 patients. However, these trials differed notably in their clinical contexts and inclusion criteria: Bonelli *et al.* (2022) focused on early PMR patients with a short duration of glucocorticoid treatment; Devauchelle-Pensec *et al.* (2022) enrolled GC-dependent PMR patients undergoing a prespecified glucocorticoid tapering protocol; and Spiera *et al.* (2021) evaluated patients with PMR associated with GCA. These contextual differences are critical and were explicitly taken into consideration in interpreting the pooled results.

Endpoints

The endpoints of interest were glucocorticoid-free remission at week 24, cumulative prednisolone dose at week 24, individual outcomes of ESR in patients at week 24, and adverse effects like rate of infection, gastrointestinal disorders, and musculoskeletal and connective tissue disorders.

Study Selection and Data Extraction

After retrieving the studies from the databases, two independent reviewers (B.B. and M.P.) excluded duplicates and screened titles and abstracts. We assessed each remaining study's eligibility based on the articles' full-text review. We also searched for additional studies from references of the included studies. Disagreements were resolved through consensus.

Two authors (M.P and B.B) independently extracted baseline characteristics reported in Table I. Outcomes data were collected, following prespecified criteria for search, data extraction, and quality assessment.

Quality Assessment

The Cochrane Risk of Bias 2 (RoB 2) tool was used to assess the quality of the included RCTs[11]. Two authors (B.B. and M.P.) independently evaluated the risk of bias. Each study was rated as having a high risk, low risk, or some concerns of bias across five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. The risk-of-bias plot was created with Risk-Of-Bias visualization (ROBVIS) tool[12]. Disagreements were resolved through consensus between the authors.

TABLE I. Baseline characteristics of included studies.

	PMR-SPARE, 2022[13]		Spiera, 2021[6]		Devauchelle-Pensec, 2022[8]	
Characteristics	Tocilizumab (n=19)	Placebo (n=17)	Tocilizumab (n=31)	Placebo (n=21)	Tocilizumab (n=49)	Placebo (n=51)
Dose	162 mg SC weekly + prednisone taper	N/A	162 mg SC weekly + prednisone taper	N/A	8 mg/kg IV every 4 weeks for 24 weeks + prednisone taper	N/A
Study Context	New onset PMR, short-term GCs use		PMR associated with GCA		GC-dependent PMR with prespecified GC tapering	
Age (median)†	68.8	71.1	64.2	65.0	68.0	67.0
Female (median)†	10	9	27	12	34	33
Caucasian ethnicity	100 %	100 %	96.8 %	100 %	N/A	N/A
Weight (kg) ‡	81.7 ± 28.5	72.0 ± 13.9	66.6 ± 11.7	75.1 ± 16.0	N/A	N/A
BMI (kg/m2) ‡	26.5 ± 4.5	25.7 ± 3.9	24.6 ± 3.9	25.2 ± 4.1	N/A	N/A
Disease duration at screening (days) ‡	8 ± 5	6 ± 3	216.9 ± 507.4	489.6 ± 698.6	26.66 ± 29.02	19.89 ± 20.59
Current pred. Dose ‡	16.7 ± 3.9	17.2 ± 3.1	15 ± 48.4	12 ± 57.1	11.77 ± 3.82	11.77 ± 3.81
ESR (mm/hr) ‡	24.3 ± 16.4	24.1 ± 18.7	27.6 ± 22.4	21.2 ± 16.3	28.3 ± 33.0	24.3 ± 23.0
CRP (mg/dl) ‡	1.6 ± 2.4	0.98 ± 1.5	0.77 ± 1.07	0.48 ± 0.71	1.01 ± 0.99	1.04 ± 1.67
Pain by VAS (mm) ‡	15.24 ± 20.02	21.14 ± 35.57	N/A	N/A	2.6 ± 2.2	3.6 ± 2.6
Patient Global Assessment of disease activity by VAS (mm) ‡	12.32 ± 17.62	23.59 ± 37.99	46.2 ± 22.2	29.0 ± 25.1	N/A	N/A
Short Form -36 Physical Component Score ‡	55.29 ± 9.77	46.25 ± 6.14	42.3 ± 7.5	44.4 ± 11.0	37.9 ± 4.12	36.4 ± 3.81

BMI: Body Mass Index; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; PMR: Polymyalgia Rheumatica; GCA: Giant Cell Arteritis; GC: glucocorticoid; VAS: Visual Assessment Score; PCS: Physical Component Score; N/A: not available; kg: kilogram; mm: millimeter; dL: decilitre; m: meter; SC: subcutaneous; IV: intravenous; ‡: mean ± standard deviation; †: median.

Statistical Analysis

Treatment effects for binary endpoints were compared using pooled risk ratios (RRs) with 95% confidence intervals (CI) under a random effects model. Heterogeneity was assessed using I^2 statistics, where $I^2 > 40\%$ was considered significant[9]. p values inferior to 0.05 were considered statistically significant. Leave-one-out sensitivity analysis was performed for high and moderate heterogeneity outcomes to ensure the stability of the pooled treatment effect. All the statistical analyses were performed using Cochrane RevMan version 8.13.0.

RESULTS

Study Selection and Characteristics

The search strategy yielded 382 results (Figure 1). After the removal of duplicate records and studies with an exclusion criterion based on title/abstract review, 23 remained and were fully reviewed for inclusion and exclusion criteria. Three RCTs met all inclusion criteria. These trials differed notably in their clinical contexts and inclusion criteria: Bonelli et al. (2022) focused on early PMR patients with a short duration of glucocorticoid treatment; Devauchelle-Pensec et al. (2022) enrolled GC-dependent PMR patients undergoing a prespecified glucocorticoid tapering protocol; and Spiera et al. (2021) evaluated patients with PMR associated with GCA. These contextual differences are critical and were explicitly taken into consideration in interpreting the pooled results. (A total of 188 patients with PMR were included, of whom 99 received tocilizumab and 89 received placebo. Study characteristics are presented in Table I. The mean patient age was 67.3 years old,

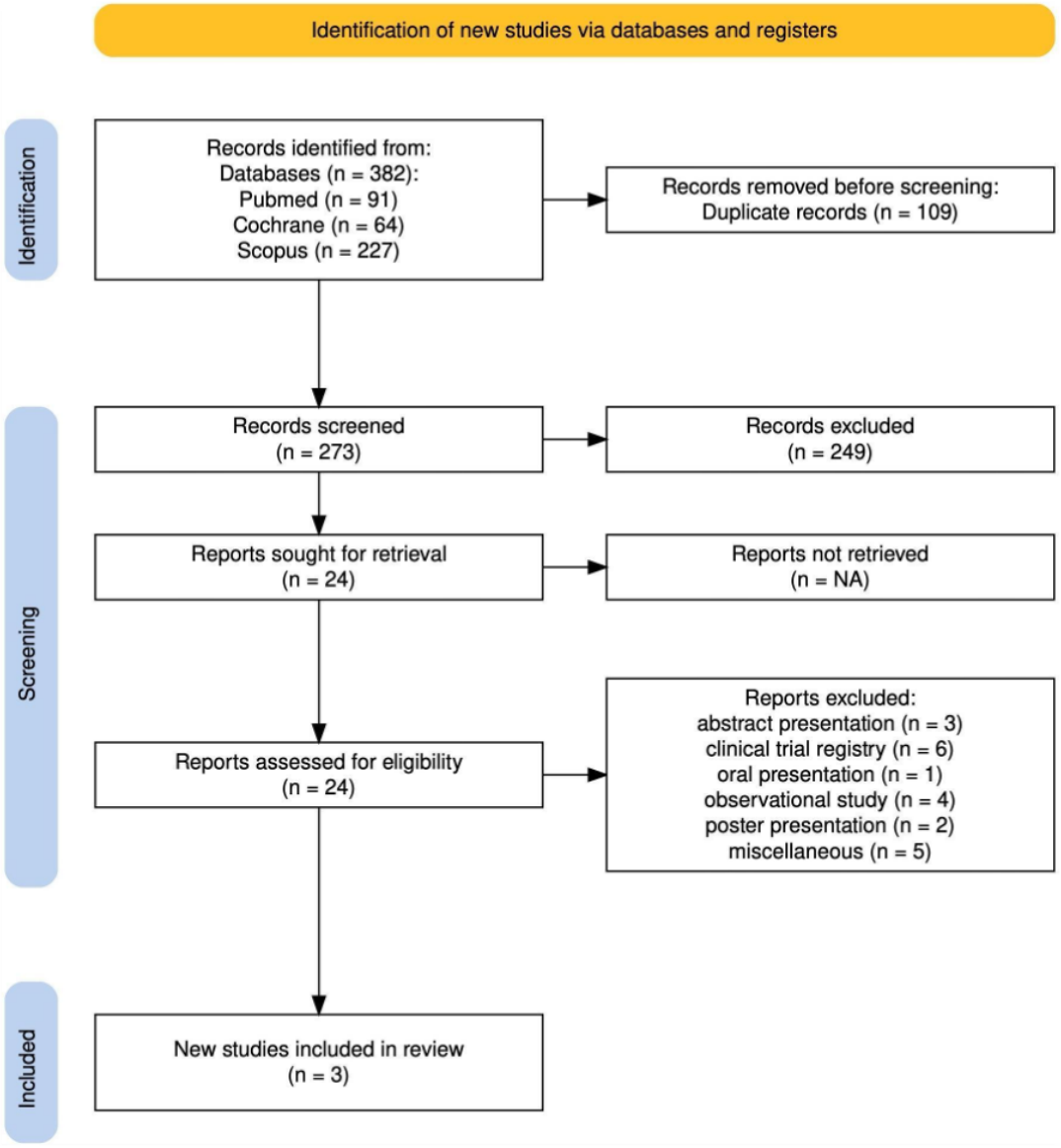

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis flow diagram of study screening and selection.

(63.97%) were female and 99.2% were Caucasians. The average CRP and ESR levels of the included population were 0.98 mg/dl and 24.97 mm/hr respectively.

Efficacy Outcomes

The primary endpoint analyzed was glucocorticoid-free remission at week 24. Tocilizumab significantly increased glucocorticoid-free remission at week 24 (RR 2.64; 95% CI 1.38 to 5.06; p = 0.003; I^2 = 0%; Figure 2). Additionally, tocilizumab significantly decreased the cumulative prednisolone dose at week 24 (RR -2.52; 95% CI -4.00 to -1.03; p = 0.0009, I^2 = 45%; Figure 3). There was no statistically significant difference between groups for individual outcomes of ESR in patients at week 24 (MD -4.32; 95% CI -26.07 to 17.43; p = 0.70; I^2=93%; Figure 4)

Safety Outcomes

There was no statistically significant difference between groups for individual outcomes of, rate of infection (RR 1.19; 95% CI 0.92 to 1.52; p = 0.18; I^2=0%; Figure 5), gastrointestinal disorder (RR 1.17; 95% CI 0.72 to 1.89; p = 0.52; I^2=0%; Figure 6) and musculoskeletal and connective tissue disorders (RR 1.13; 95% CI 0.53 to 2.42; p = 0.75; I^2=76%; Figure 7).

Sensitivity Analysis

One of the primary endpoints, cumulative prednisolone dose at week 24 showed moderate heterogeneity (I^2 = 45%). To address this, we conducted a leave-one-out sensitivity analysis, which confirmed significant differences between the groups. The findings remained ro-

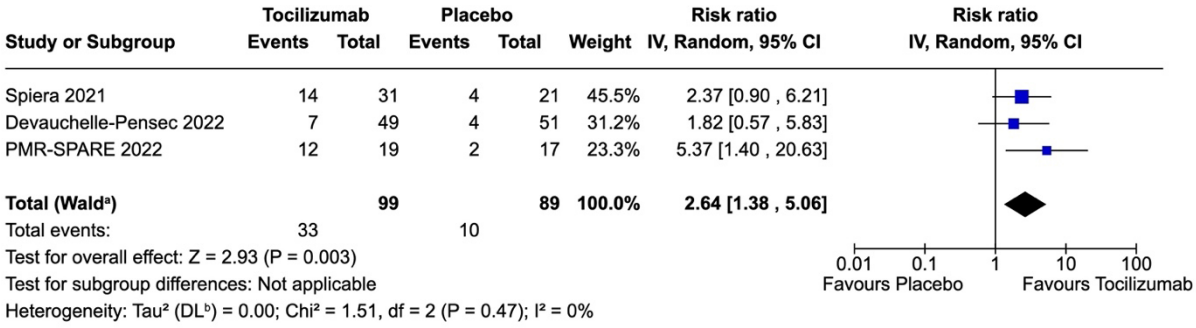

Figure 2. Glucocorticoid-free remission at 24 weeks was significantly increased in the tocilizumab group compared with the placebo. References: [6,8,13]

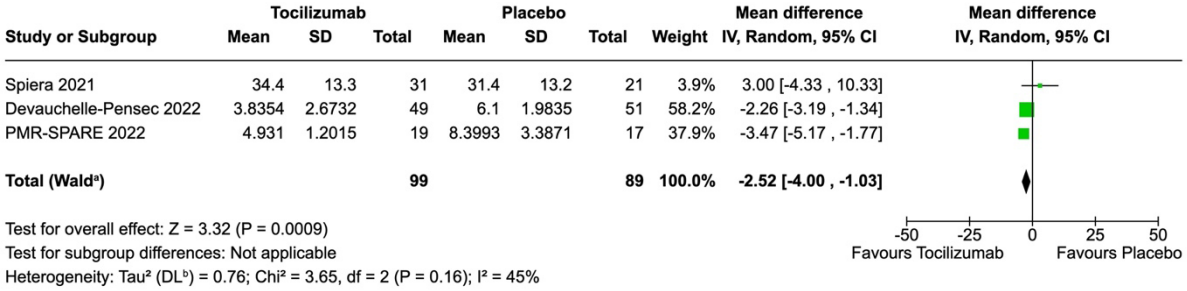

Figure 3. Cumulative prednisolone dose at week 24 was significantly decreased in the tocilizumab group compared with the placebo group. References: [6,8,13]

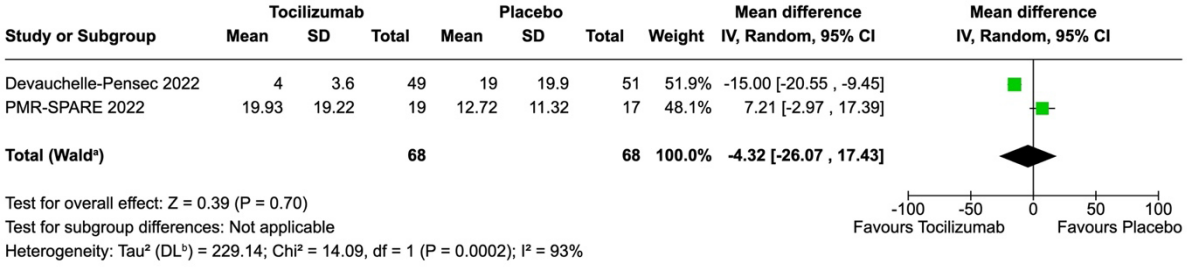

Figure 4. There was no significant difference between groups in ESR levels. References:[8,13]

bust, with a consistent and significant combined effect size between the groups (MD -2.52 mg; 95% CI -3.54 to -1.50), I^2 = 45.3%; Figure 8).

Quality assessment

The appraisal of individual randomized controlled trials (RCTs) is presented in Figure 9. Of the three randomized controlled trials, two demonstrated a low risk of bias across all domains. However, one was rated as having some concerns due to potential bias in the selection of the reported result.

DISCUSSION

In this systematic review and meta-analysis of three RCTs with 188 patients, we compared tocilizumab with placebo in patients with PMR. The main findings from the pooled population analysis were: (a) tocilizumab was associated with glucocorticoid-free remission at week 24 in patients with PMR as compared to placebo; (b) tocilizumab led to a significant decrease in cumulative prednisolone dose up to week 24 in patients with PMR; (c) there was no significant difference between

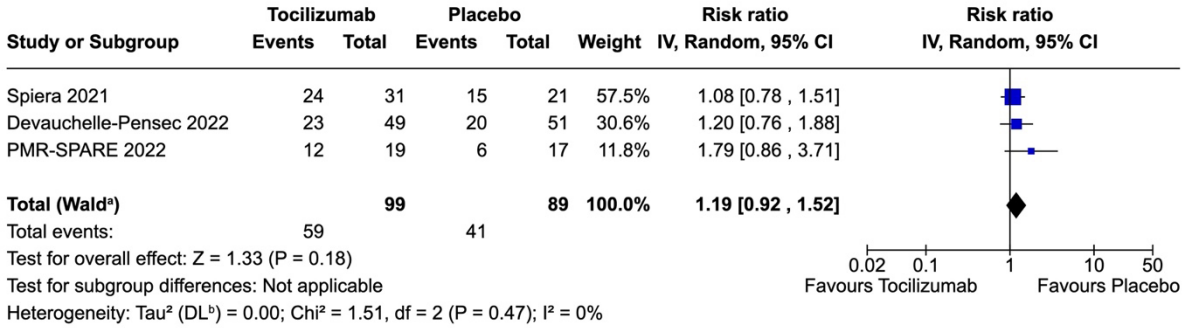

Figure 5. There was no significant difference between the groups regarding the rate of infection.
References: [6,8,13]

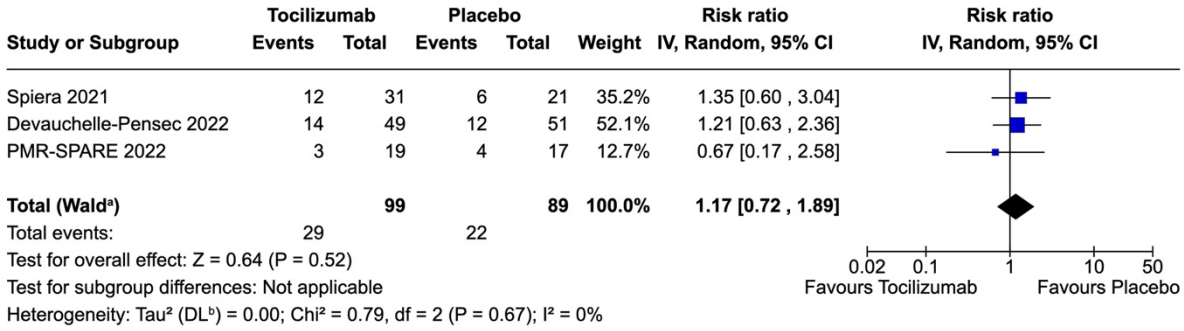

Figure 6. There was no significant difference between the groups regarding the rate of gastrointestinal disorders.
References: [6,8,13]

the groups in ESR levels, rates of infection, gastrointestinal, musculoskeletal, and connective tissue disorders.

In our overall analysis, we observed a significant increase in glucocorticoid-free remission period up to week 24. Bonelli *et al.* 2022 randomized 19 patients to tocilizumab and 17 to placebo, showing significant differences between groups[13]. Glucocorticoid-free remission rates were up to 50% higher in patients treated with tocilizumab compared to those receiving placebo, consistent with findings from the GiACTA trial[14]. Similarly, Spiera *et al.* 2021 randomized 31 patients to tocilizumab and 21 patients to placebo, showing significant differences between the groups. These findings are consistent with our meta-analysis even with the different dosing regimens used. IL-6 is a proinflammatory mediator that plays a major role in initiating and sustaining an inflammatory process[15]. It is responsible for the proliferation and differentiation of T cell and B cell terminal differentiation. It also activates macrophages, osteoclasts and promotes vascular endothelial growth factor along with metalloproteinase production[15]. By inhibiting IL-6, tocilizumab targets multiple pathways involved in the inflammatory cascade in PMR, leading to a reduction in systemic inflammation and symptomatic relief. There are no studies in the current literature that directly evaluate the efficacy of tocilizumab in patients with polymyalgia rheumatica (PMR). However, tocilizumab has demonstrated proven efficacy in other rheumatological conditions, such as rheumatoid arthritis (RA), giant cell arteritis (GCA), and Takayasu arteritis[1,7,16].

In our overall analysis, we observed a significant decrease in the cumulative prednisolone dose up to week 24 with the use of tocilizumab, although moderate heterogeneity was noted (I^2 = 45%). To address this, we performed a leave-one-out sensitivity analysis, which demonstrated significant differences between the groups and was consistent. Spiera et al. (2021) utilized subcutaneous tocilizumab (162 mg) administered weekly or every two weeks, combined with a 26-week prednisone taper. Bonelli *et al.* (2022) administered tocilizumab (162 mg subcutaneous) weekly, alongside a rapid prednisone tapering regimen beginning at 20 mg daily, with a reduction of 2.5 mg per week until a dose of 10 mg/day was reached and maintained for one week. Devauchelle-Pensec *et al.* (2022) used intra-

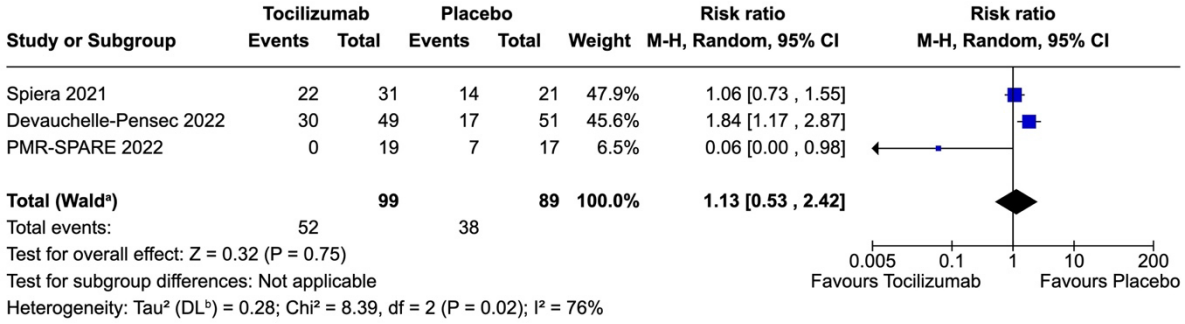

Figure 7. There was no significant difference between groups regarding the rate of musculoskeletal and connective tissue disorders. References: [6,8,13]

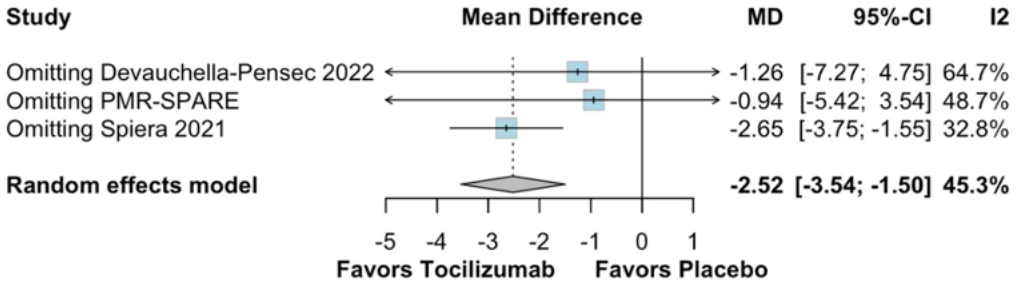

Figure 8. Leave one out analysis of cumulative prednisolone dose at week 24
Even after conducting the leave-one-out analysis, the study remained consistent with a significant difference between the group's combined effect (MD -2.52 mg, 95% CI [-3.54; -1.50])

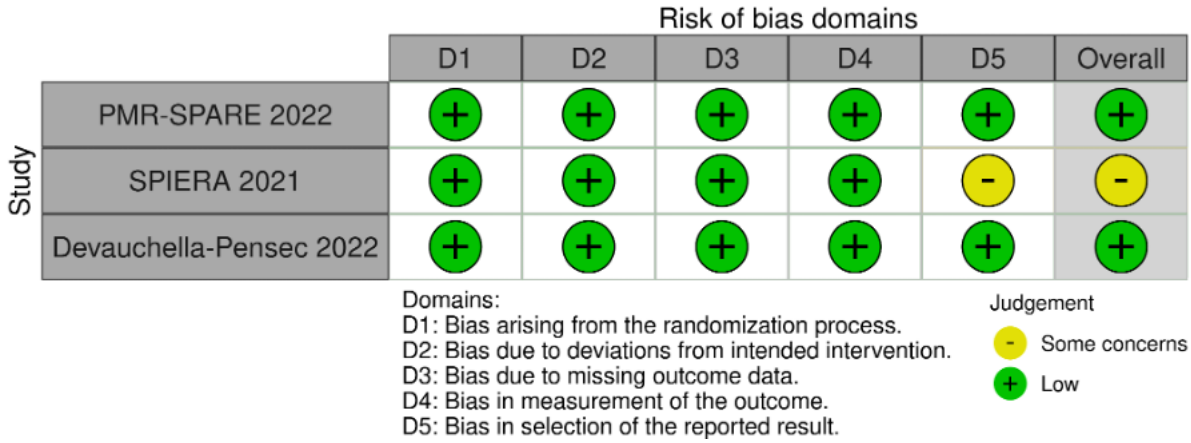

Figure 9. RoB-2 tool for risk of bias assessment. References: [6,8,13]

venous tocilizumab (8 mg/kg) every four weeks for 24 weeks, combined with a prednisone taper beginning after week 8. For prednisone doses >10 mg/day, the tapering occurred in 5 mg decrements per study visit. For doses <10 mg/day, if the C-reactive protein-based Polymyalgia Rheumatica Activity Score (CRP-PMR-AS) was <10, the dose was reduced by 2 mg per week.

These regimens differ in route of administration, dosing frequency, and corticosteroid tapering strategy, potentially contributing to the observed heterogeneity in our analysis. Subcutaneous versus intravenous administration may result in differing pharmacokinetics, leading to variable degrees of interleukin-6 suppression and cumulative prednisone reduction. Such variability

in treatment protocols can influence efficacy, safety, and glucocorticoid-sparing effects, thereby impacting the clinical interpretation of pooled results.

Patients with polymyalgia rheumatica (PMR) are frequently exposed to high cumulative doses of glucocorticoids due to the chronic and relapsing nature of the disease[17]. Consequently, glucocorticoid-related toxicities are common in this patient population, manifesting as cataracts, gastric ulceration, osteoporosis, diabetes mellitus, and an increased risk of infection. The use of tocilizumab may help mitigate these toxicities by reducing the glucocorticoid burden required for disease management[5].

ESR and CRP are essential markers in the diagnosis and management of PMR; however, their levels may remain normal in a subset of patients, presenting diagnostic challenges[18]. While ESR is a stronger predictor of relapse, CRP is more sensitive to current disease activity[19]. In our study, tocilizumab did not significantly reduce ESR levels in patients with PMR, which may be attributed to suboptimal dosing or timing of tocilizumab, or potentially due to an interaction between tocilizumab and glucocorticoids, where the latter's potent anti-inflammatory effects could have masked the additional benefit of tocilizumab. Bonelli *et al.* (2022) randomized 19 patients to receive tocilizumab and 17 to placebo, reporting no significant differences in outcomes between the groups. The authors suggest that the higher rates of glucocorticoid use in the placebo group may have masked the anti-inflammatory effects of tocilizumab. Similarly, Devauchelle-Pensec et al. (2022) also demonstrated no significant differences between the groups. These findings align with our meta-analysis, highlighting the need for caution when interpreting the overall effect of tocilizumab on ESR.

In our study, there was no statistically significant difference in adverse event rates between tocilizumab and placebo groups. This finding is consistent with those reported by Bonelli *et al.* (2022) and Devauchelle-Pensec et al. (2022), who also observed no significant differences in adverse events between treatment arms likely attributable to the immunosuppressive effects of tocilizumab[20,21]. Our meta-analysis reinforces these observations, further supporting the safety profile of tocilizumab in this clinical context. By blocking interleukin-6 (IL-6), tocilizumab impairs immune system functionality, reducing the body's ability to defend against bacterial, viral, and other infections. Additionally, patients with polymyalgia rheumatica (PMR) are often on glucocorticoids, which further suppress immune responses, compounding the risk of infection[22].2015 recommendations for the management of PMR by the European League Against Rheumatism (EULAR)/ American College of Rheumatology (ACR) collaborative Initiative guideline does not recommend biologics stating its potential risk of harm rather than benefit due to lack of clinical trials[23]. The panel strongly recommended against the use of TNF α blockers in patients with PMR at the time because there was no evidence of benefit. Therefore, no recommendations were made for other biologic agents like tocilizumab due to lack of clinical trials. They also proposed that the recommendation would change in the future if robust data regarding biologics were available. Hence, this research may be helpful for future recommendations.

LIMITATIONS

This study has several important limitations. First, the dosing regimens of tocilizumab varied across the three included randomized controlled trials (Table I), which may have contributed to heterogeneity in treatment effects. To address this, we conducted a leave-one-out sensitivity analysis to assess the robustness of the pooled results. Second, the meta-analysis included only three RCTs with a total of 188 patients, resulting in a relatively small sample size and limited statistical power. As such, the findings should be interpreted with caution when applied to clinical practice. Third, polymyalgia rheumatica (PMR) is a chronic, relapsing disease that requires long-term management; however, all included trials had a follow-up duration limited to 24 weeks. This short-term follow-up may underestimate relapse rates, fail to capture late-onset flares, and inadequately reflect the long-term steroid-sparing potential of tocilizumab. Furthermore, it may not allow for comprehensive assessment of delayed adverse effects such as osteoporosis, diabetes mellitus, and cardiovascular events. Finally, short-duration studies may not provide insight into the durability of remission following discontinuation of therapy, which is critical for long-term disease management. Fourth, clinical heterogeneity was present among the included trials, particularly in patient selection criteria, treatment regimens, and clinical settings. As a result, the generalizability of our findings should be interpreted with caution. Clinicians should carefully consider these variations when applying the results to individual patient care and clinical decision-making.

CONCLUSION

This meta-analysis, which included 188 patients with PMR, demonstrated that tocilizumab was associated with greater efficacy, as evidenced by a higher rate of glucocorticoid-free remission at 24 weeks and a sig-

nificant reduction in cumulative prednisolone dose at the same time point. In terms of safety, there was no significant difference in adverse events between the tocilizumab and placebo groups.

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