ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Efficacy and safety of IL-6 inhibitors for polymyalgia rheumatica: a meta-analysis of randomized controlled trials

Eficácia e segurança dos inibidores de IL-6 para polimialgia reumática: uma metanálise de estudos clínicos randomizados

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ABSTRACT

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease, common in older adults, characterized by fatigue, morning stiffness, and pain in the neck, shoulders, and hip girdle. Its pathophysiology is believed to involve abnormal interleukin (IL)-6 activity. Although glucocorticoids are the standard treatment, frequent relapses and long-term adverse effects pose challenges. IL-6 inhibitors may offer an alternative, but their efficacy in isolated PMR, unlike in giant cell arteritis, remains unclear. The present review sought to evaluate the efficacy and safety of IL-6 inhibitors (tocilizumab, sarilumab) combined with glucocorticoids versus glucocorticoids alone in PMR. A systematic review was conducted in the PubMed, Embase, and Cochrane databases to identify randomized controlled trials (RCTs). The primary outcome was the SF-36 Physical Component Score. Secondary outcomes included adverse events, treatment discontinuation, and evaluator global assessment via visual analogue scale (VAS). Analyses were performed in R 4.3.1, with odds ratios (OR) for binary and mean differences (MD) for continuous outcomes, all with 95% confidence intervals (CI). Heterogeneity was assessed using I^2. Four RCTs (n=358; IL-6 inhibitors=188; placebo=170) were included. IL-6 inhibitors significantly improved SF-36 scores (MD 4.75; CI 0.67 to 8.83; p=0.02). No significant differences were found in adverse events (OR 1.69; p=0.16), discontinuation rates (OR

RESUMO

A polimialgia reumática (PMR) é uma doença reumática inflamatória comum em idosos, caracterizada por fadiga, rigidez matinal e dor em região cervical, cintura escapular e pélvica. Sua fisiopatologia parece envolver atividade anormal da interleucina-6 (IL-6). Embora os glicocorticoides sejam o tratamento padrão, recaídas frequentes e efeitos adversos em longo prazo representam desafios. Inibidores de IL-6 podem oferecer uma alternativa, mas sua eficácia em casos isolados de PMR, diferentemente da arterite de células gigantes, ainda é incerta. Este trabalho teve por objetivo avaliar a eficácia e segurança dos inibidores de IL-6 (tocilizumabe, sarilumabe) associados a glicocorticoides, em comparação ao uso isolado de glicocorticoides na PMR. Realizou-se uma revisão sistemática nas bases PubMed, Embase e Cochrane para identificar ensaios clínicos randomizados (ECRs). O desfecho primário foi o escore físico do SF-36. Desfechos secundários incluíram taxa de eventos adversos, descontinuação do tratamento e avaliação global do investigador por escala visual analógica (EVA). As análises foram realizadas no R 4.3.1, utilizando razão de chances (OR) para desfechos binários e diferença média (DM) para contínuos, com intervalos de confiança (IC) de 95%. A heterogeneidade foi avaliada com estatística I^2. Foram incluídos quatro ECRs (n = 358; IL-6i = 188; placebo = 170). Os inibidores de IL-6 melhoraram significativamente o escore físico do SF-36 (DM 4,75; IC 0,67-8,83;

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0.80; p=0.723), or VAS scores (MD -6.51; CI -12.92 to -0.09). IL-6 inhibitors improved physical function without increasing adverse events, supporting their potential use as adjunctive therapy in PMR.

Keywords: Polymyalgia rheumatica, immunology, drug therapy.

p = 0,02). Não houve diferenças significativas nos eventos adversos (OR 1,69; p = 0,16), descontinuações (OR 0,80; p = 0,723) ou EVA (DM -6,51; IC -12,92 a -0,09). Os inibidores de IL-6 melhoraram a função física sem aumento nos eventos adversos, sugerindo seu potencial como terapia adjuvante na PMR.

Descritores: Polimialgia reumática, imunologia, tratamento farmacológico.

Introduction

Polymyalgia rheumatica (PMR) is a rheumatic disorder of inflammatory origin, characterized by pain and stiffness in the neck, shoulders, and hips. It is the second most common inflammatory systemic rheumatic disease after rheumatoid arthritis (RA).[1] Evidence suggests a genetic susceptibility to PMR, with shared genetic risk factors such as the HLA-DRB1*01 and HLA-DRB1*04 alleles.[2,3] PMR also shares pathophysiological mechanisms with other systemic inflammatory disorders, including elevated levels of proinflammatory cytokines such as interleukin-6 (IL-6).[4,5]

The mainstay of PMR management is long-term glucocorticoid (GC) therapy, with a mean duration of 1.8 years of therapy in PMR.[6] The starting daily prednisone equivalent dose is recommended to range between 12.5 and 25 mg; the minimum effective dose should be used.[7] The response to GCs in PMR is usually rapid and the GC tapering regimen should be individualized. Despite the striking initial response to GCs in most cases, disease relapses are common, and the burden of long-term GC therapy has an impact on the development of comorbidities in patients with PMR.[8] A systematic review and meta-analysis has shown that 77%, 51%, and 25% of PMR patients remain on GC therapy at 1, 2, and 5 years, respectively.[9]

Since the 1990s, IL-6 has been recognized as a key driver of inflammation in PMR.[6,7] Elevated IL-6 levels are strongly associated with disease activity, underscoring its critical role in the pathogenesis of this condition. IL-6 inhibitors (IL6i), initially developed for the treatment of RA, block the interaction between IL-6 and its receptors and effectively suppress IL-6-mediated inflammation. Given the aforementioned central role of IL-6 in PMR pathophysiology, targeting this pathway holds promise for reducing disease activity.[9-12]

Within this context, we carried out a systematic literature review and meta-analysis to assess the efficacy and safety of IL6i compared with placebo in patients with PMR already receiving GC therapy.

Material and Methods

This systematic review and meta-analysis followed the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.[13,14] This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) in December 2024 (ID CRD42024629302).[15]

Outcomes of Interest and Eligibility Criteria

The primary outcome was disease remission. The secondary efficacy outcome was cumulative GC dose. Secondary safety outcomes included (i) overall adverse event rate, (ii) occurrence of neutropenia, and (iii) occurrence of infections (Table 1). Inclusion in this meta-analysis was restricted to studies that met all the following eligibility criteria: randomized controlled trials (RCT), inclusion of patients with an established clinical diagnosis of PMR, and comparison of adjunctive IL6i therapy with placebo. Studies without a control group that did not report at least one outcome of interest were also excluded. No language restrictions were applied. Abstracts, editorials, letters to the editor, reviews, systematic reviews, and meta-analyses were excluded from the sample.

Search Strategy and Data Extraction

We systematically searched PubMed, Embase, and the Cochrane Library in November 2024 using the following search strategy: ("IL-6 inhibitors" OR Tocilizumab OR Sarilumab OR Satralizumab OR Siltuximab) AND ("Polymyalgia rheumatica" OR PMR

OR "Giant Cell arteritis" OR GCA). We also conducted a hand search of references from the included manuscripts, previous systematic reviews, and meta-analyses for additional studies that might warrant inclusion. Our search strategy encompassed studies on giant cell arteritis (GCA) due to the significant

Table 1
Details of the included randomized controlled trials

Study and Type of Infection	Intervention (n)	Control (n)
Bonelli- Common cold	6	4
Bonelli- Conjunctivitis	3	0
Bonelli- Respiratory Infection	2	1
Bonelli- Abscess/suppurative focus teeth	1	1
Bonelli- Fever blister	1	0
Bonelli- Erysipela	1	0
Spiera- Opportunistic infections	2	2
Spiera- Bacterial cystitis	1	0
Spiera- Intervertebral discitis	1	0
Spiera- COVID-19	0	1
Spiera- Erysipela	0	1
Spiera- Bacterial Urinary tract infection	1	0
Spiera- Pneumonia	1	0
Devauchelle-Pensec- Abscess limb	1	0
Devauchelle-Pensec- Bronchitis	5	4
Devauchelle-Pensec- Conjuctivitis	1	0
Devauchelle-Pensec- Cystitis Klebsiella	1	0
Devauchelle-Pensec- Gastroenteritis	3	0
Devauchelle-Pensec- Herpes	6	2
Devauchelle-Pensec- Dermatophytosis of nails	0	1
Devauchelle-Pensec- Fungal infection	0	4
Devauchelle-Pensec- Hordeolum	0	1
Devauchelle-Pensec- Laryngitis	0	1
Devauchelle-Pensec- Site of injection abcess	1	0
Devauchelle-Pensec- Influenza	0	1
Devauchelle-Pensec- Nasopharyngitis	1	3
Devauchelle-Pensec- Pharyngitis	1	0
Devauchelle-Pensec- Pyelonephritis	0	1
Devauchelle-Pensec- Rhinitis	2	2
Devauchelle-Pensec- Sinusitis	3	1
Devauchelle-Pensec- Tonsilitis	1	0
Devauchelle-Pensec- Abscess/suppurative focus teeth	2	1
Devauchelle-Pensec- Teeth infection	2	1
Devauchelle-Pensec- Tracheitis	1	1
Devauchelle-Pensec- Urinary tract infection	0	4
Devauchelle-Pensec- Viral infection	2	0
Devauchelle-Pensec- Bacterial wound infection	1	1

clinical overlap between PMR and GCA, as well as to the inclusion of individuals with symptoms of both conditions in some trials, which were later excluded.

Two authors (O.C.M. and B.A.A.H.M.) independently conducted the search, imported the results into Zotero software (version 6.0.26)[16], and performed triage. In cases of disagreement, a third author (M.M.S.) adjudicated. Data extraction was performed independently by two authors (O.C.M. and B.A.A.H.M); if the included studies did not provide the mean and standard deviation, the values were estimated using the reported median and range, based on Luo et al. and Wan et al.[17,18]

Risk of bias and evidence quality assessment

Risk of bias assessment was performed by two independent authors (B.A. A. H. M. and M. L. R. D.), using the second version of the Cochrane Risk of Bias Assessment Tool (RoB 2).[19] We evaluated five domains for each outcome of the selected studies: (1) bias in the randomization process, (2) bias due to deviations from the intended interventions, (3) bias due to missing data, (4) bias in outcome measurement, and (5) bias in the selection of the reported results.

The overall risk-of-bias assessment for each trial outcome was based on individual domain judgments, with any disagreements resolved through consensus after a critical debate on the reasons for unconformity.

Statistical Analysis

The risk ratio (RR) was used to compare the treatment effects for dichotomous endpoints, whereas the mean difference (MD) with 95% confidence intervals (95% CI) was used for continuous outcomes. Statistical significance was accepted at p-values < 0.05. We assessed heterogeneity using the I^2 statistic and Cochran's Q test; a p-value < 0.10 or I^2 > 25% were regarded as significant for heterogeneity. Sensitivity analyses were conducted using a leave-one-out plot in the presence of significant heterogeneity (I^2 > 25%). DerSimonian and Laird random effects models were used for all outcomes. R software version 4.3.2 was used for statistical analysis.[20]

Results

Study selection and characteristics

The initial search yielded 2079 results, as shown in Figure 1. After removing duplicate records and ineligible studies, 31 remained and were reviewed in full. Of these, 3 RCTs with 254 patients (128 on IL6i vs. 126 on placebo) were included. Initially, the search strategy also included GCA, as both PMR and GCA are related conditions and a substantial proportion of PMR patients present with subclinical GCA or progress to overt GCA after some time of disease.[21]

Tocilizumab and sarilumab were administered to 136 and 118 participants, respectively. The dose regimen and route of administration differed between trials for the former: one RCT evaluated tocilizumab given intravenously at a monthly dose of 8 mg/kg, whereas the other RCT assessed tocilizumab given via the subcutaneous route at a dose of 162 mg weekly. Details of the included RCTs are shown in Table 2.

The mean age of the patients was 69 years at baseline and 168 (66%) were women. The total treatment duration also differed between the RCTs, ranging from 24 weeks in both RCTs assessing tocilizumab to 52 weeks in the RCT evaluating sarilumab.

Pooled analysis of all studies

Primary outcome

The definition of disease remission in PMR remains heterogeneous across studies, reflecting the ongoing challenge of establishing standardized outcome measures. Devauchelle-Pensec[22] defined remission based on inflammatory markers, specifically a C-Reactive Protein Polymyalgia Rheumatica Activity Score (CRP-PMR-AS) below 1.5. In contrast, Bonelli[23] adopted a strictly clinical approach, defining remission as the absence of shoulder and/or hip girdle stiffness attributable to active PMR as determined by a blinded investigator. Although CRP levels were measured at each visit, Bonelli's criteria excluded inflammatory markers from remission assessments, instead relying on clinical parameters such as patient and assessor global scores, patient pain score, morning stiffness (all assessed via 100 mm visual analog scales [VAS]), 'Elevation of the Upper Limb Score' (a semiquantitative scale), the Health Assessment Questionnaire Disability Index (HAQ), and the Short Form-36 (SF-36). Spiera[24] integrated both clinical and laboratory findings, defining remission as the resolution of PMR symptoms accompanied by CRP normalization (<10 mg/L). Recognizing these discrepancies, Dejaco conducted an international Delphi survey among PMR experts to establish consensus criteria for remission and disease

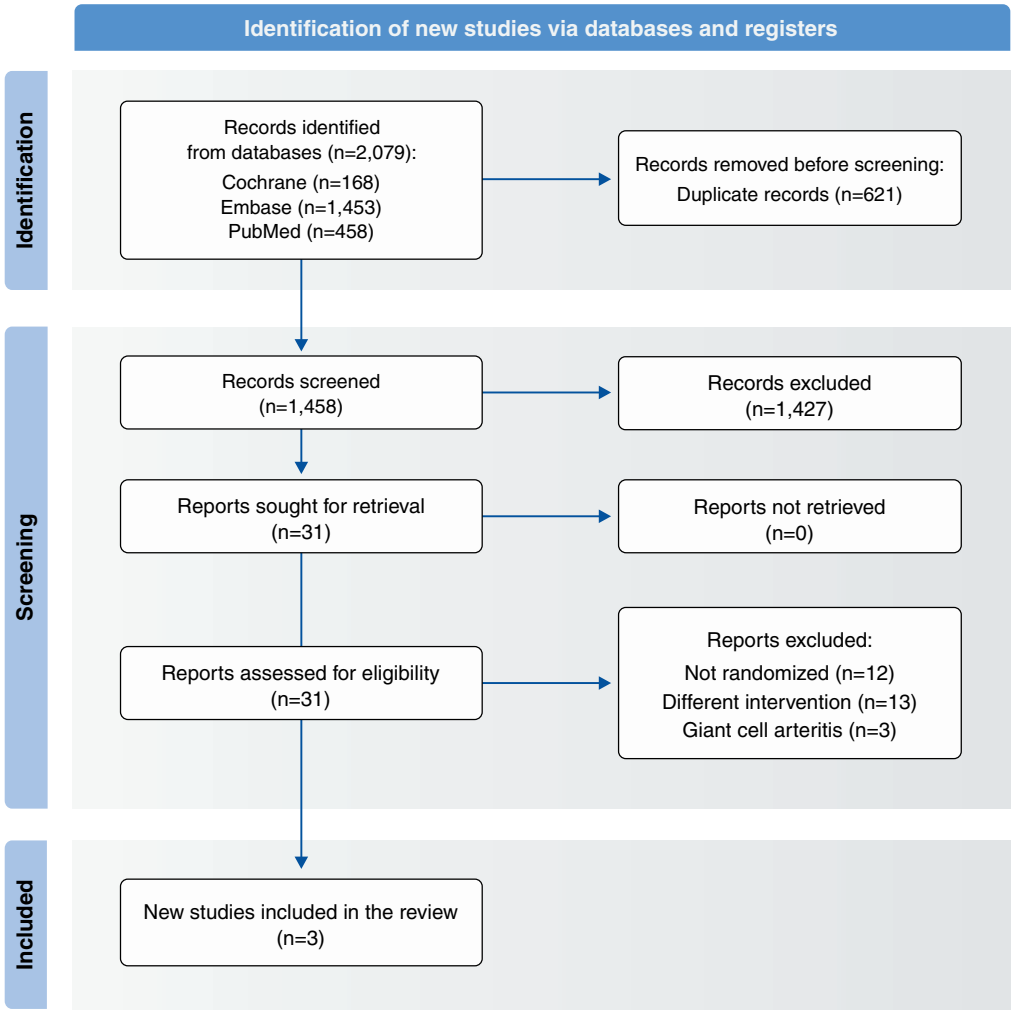

Figure 1
PRISMA flow diagram of study selection

Table 2
Baseline characteristics of included studies

Study	IL6i	IL6i Dose	Groups	Sample size	Age, years[a]	Female, n (%)	Total treatment time (weeks)
Devauhelle-Pensec et al., 2022	Tocilizumab	8 mg/kg every 4 weeks	IL6i + GC Placebo + GC	49 51	68 67	34 (69.4) 33 (64.7)	24 weeks
Spiera et al., 2023	Sarilumab	200 mg every other week	IL6i + GC Placebo + GC	60 58	69 70	45 (75) 37 (64)	52 weeks
Bonelli et al., 2021	Tocilizumab	162 mg weekly	IL6i + GC Placebo + GC	19 17	68.8 71.1	10 (52.6) 9 (52.9)	24 weeks

[a]: Mean or median.
IL6i: IL-6 inhibitors; GC: Glucocorticoid; NA: Not available.

flare. The study highlighted a key limitation of CRP and ESR: up to 20% of PMR patients exhibit normal inflammatory markers at diagnosis, underscoring the critical role of clinical assessment in defining true disease remission.[25-28]

In the RCTs included herein, disease remission was significantly higher in the 52-week IL6i group than in the placebo group (RR: 2.81; 95% CI: 1.52, 5.20; p<0.01; I^2=0%) (Figure 2). In the subgroup analyzed at 24 weeks, disease remission was also significantly higher in the IL6i group (RR: 2.96; 95% CI: 1.03; 8.55; p= 0.04; I^2= 30.2%) (Figure 3). No individual study influenced the overall results regarding induction of disease remission (Figure 4).

Secondary efficacy outcome

The cumulative GC dose for the 52-week treatment group (i.e., sarilumab vs. placebo RCTs) showed no statistically significant difference between groups (MD: -741.19 mg; 95% CI: -1562, -80.28; p= 0.08; I^2= 98.3%) (Figure 5). In the 24-week subgroup (i.e., both RCTs assessing tocilizumab vs. placebo), the cumulative GC dose was significantly lower in the IL6i group (MD: -374.65 mg; 95% CI: -736.47, -12.82; p= 0.04; I^2= 81.4%) (Figure 6). Leave-one-out analysis showed that Spiera (2023)[24] contributed the most to heterogeneity in these outcomes (Figure 7).

Secondary safety outcomes

There was no significant difference in the overall adverse event rate between all IL6i groups and placebo (RR: 1.17; 95% CI: 0.89; 1.54; p= 0.26; I^2= 72.7%) (Figure 8C), nor in the rate of infections (RR: 1.32; 95% CI: 0.91; 1.93; p= 0.15; I^2= 0; Figure 8A). However, the incidence of neutropenia was significantly higher in the IL6i group than in the placebo group (RR: 14.56; 95% CI: 1.95; 108.80; p<0.01; I^2= 0%) (Figure 8B). Leave-one-out analysis revealed that, again, Spiera (2023)[24] contributed the most to heterogeneity in the overall adverse event rate (Figure 9).

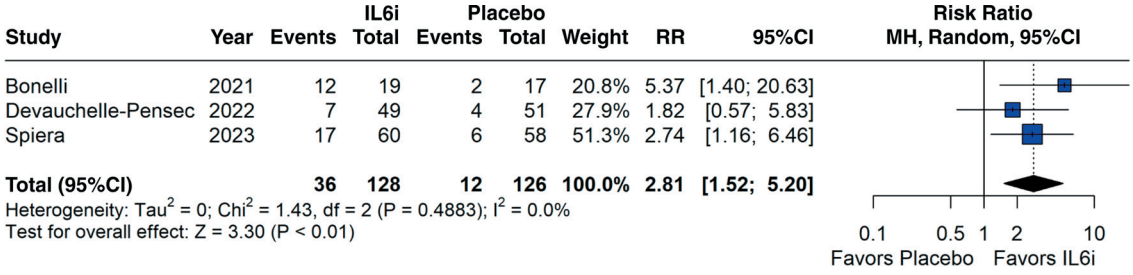

Figure 2
Disease remission was significantly more frequent in the IL6i group

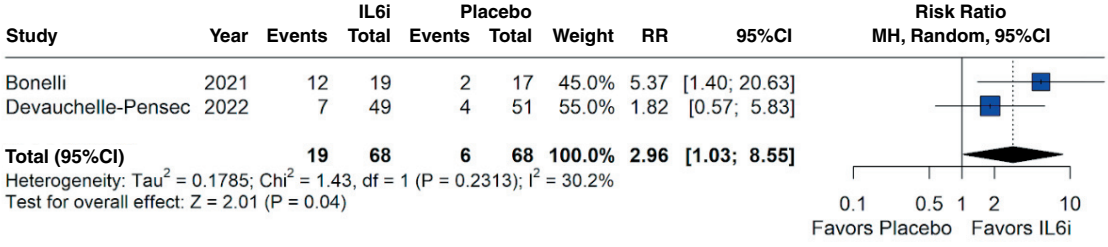

Figure 3
Disease remission was significantly more frequent with IL6i in the 24-week subgroup

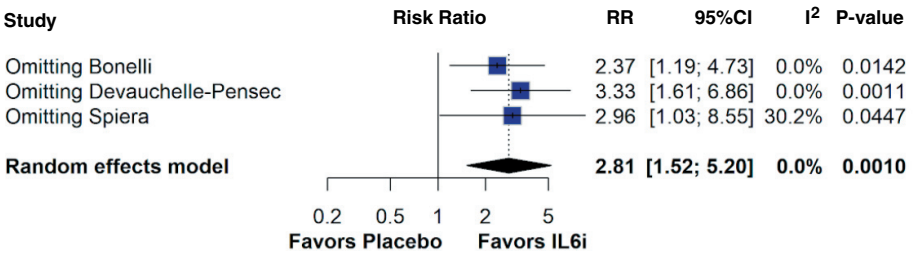

Figure 4
Leave-one-out plot of disease remission

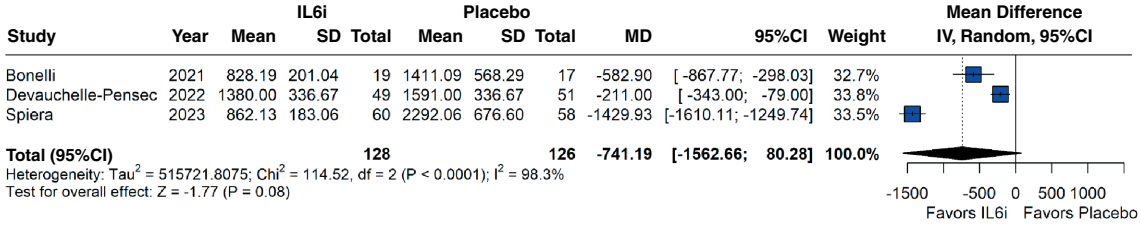

Figure 5
The cumulative glucocorticoid dose was significantly lower in the IL6i group

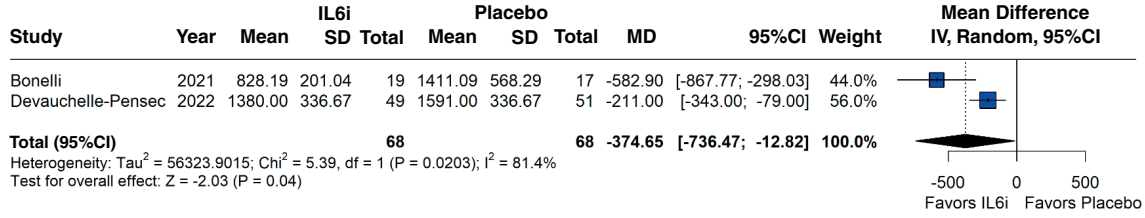

Figure 6
The cumulative glucocorticoid dose was not significantly different in the 24-week subgroup

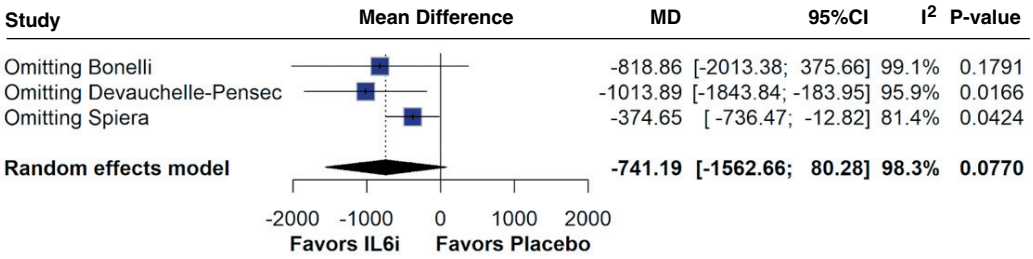

Figure 7
Leave-one-out plot of cumulative glucocorticoid dose

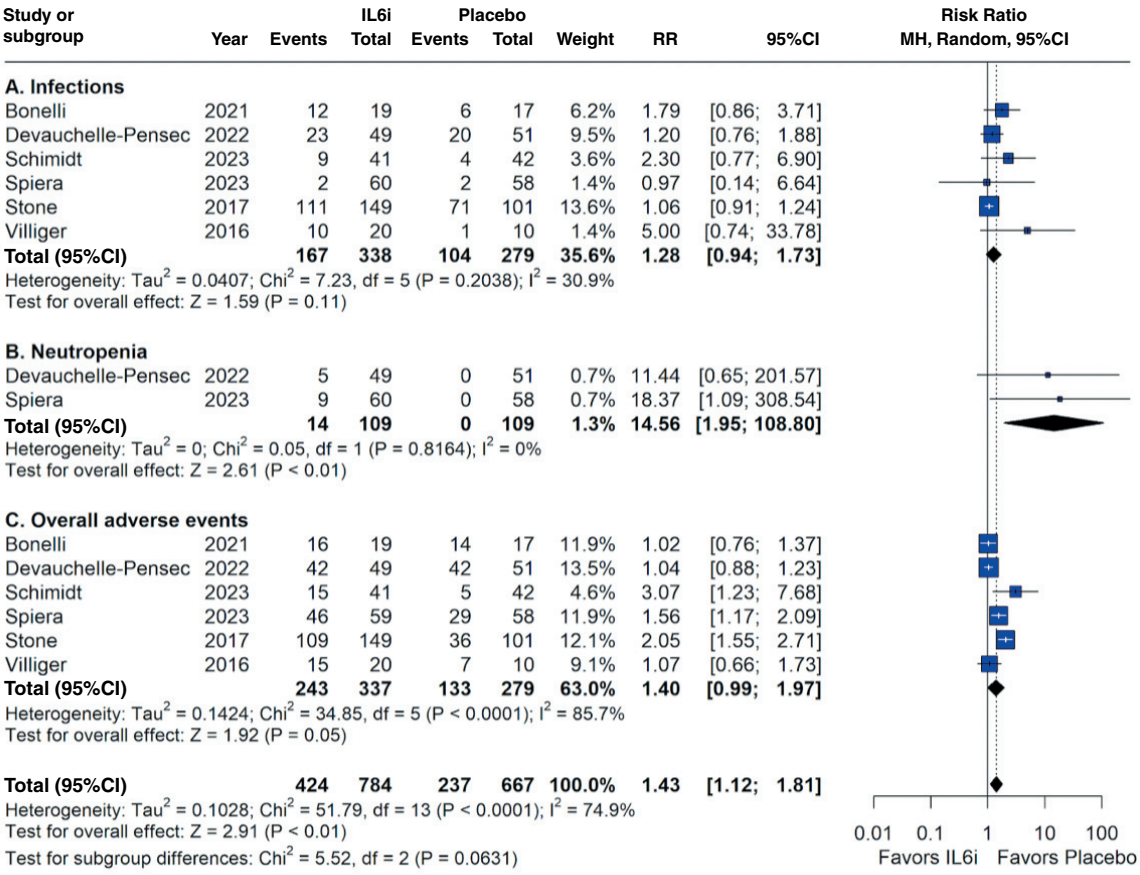

Figure 8
No significant between-group differences were found in infections (A) or overall adverse events (B); however, neutropenia (C) was significantly higher in the IL6i group compared with placebo

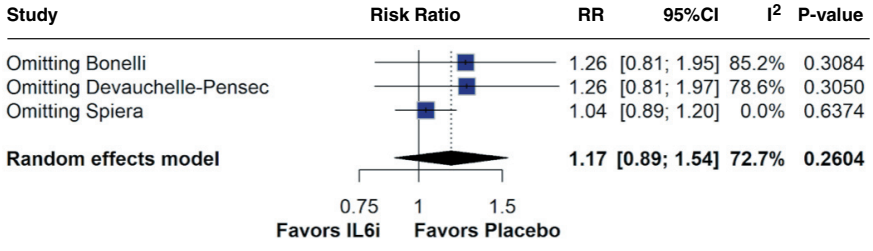

Figure 9
Leave-one-out plot of overall adverse events

Quality assessment

Figure 10 shows the quality assessment of each RCT included in this meta-analysis. All three RCTs were classified as having a low risk of bias.

Discussion

In this systematic review and meta-analysis of three RCTs[22-24] encompassing 254 patients, we conducted a comparative analysis of the efficacy of adjunctive use of IL6 inhibitors as a steroid-sparing strategy in patients with PMR. The main findings were as follows: (1) IL6i therapy was associated with a higher disease remission rate, (2) the use of IL6i was associated with a reduced cumulative GC dose at 24 weeks, and (3) there was no difference in overall adverse events between IL6i and placebo; however, the incidence of neutropenia was higher in patients receiving IL6i therapy.

A recent meta-analysis conducted by Floris et al.[29] demonstrated that GCs are effective in managing PMR, with a significant number of patients achieving remission. However, long-term therapy is necessary and relapse rates remain substantial, making the wide-ranging side-effect profile that comes with long-term GC exposure a concern.

Oral GCs are a well-proven therapy that is widely used for autoimmune and rheumatic diseases; however, the optimal initial dose and tapering regimens are unknown.[30] The EULAR/ACR recommends using the minimum effective daily dose, ranging from 12.5 to 25 mg of prednisone as initial treatment. GCs inhibit B and T cells and phagocytes, thereby affecting the innate and adaptive immune systems through genomic and nongenomic mechanisms. Their use is associated with various side effects (including cumulative dose-related effects), such as weight gain, dyspepsia, osteoporosis, hyperglycemia, cardiovascular diseases, and infections.[31]

In a previously published meta-analysis evaluating the relationship between long-term GC therapy and relapse rates in individuals with PMR, a relapse rate of 40% was observed in the first year, with rates increasing to 67% over a 6-year follow-up period. This contributes to prolonged GC use and increased exposure to the severe side effects associated with such treatment in these patients.[29,32]

The EULAR/ACR recommendations for PMR treatment suggest methotrexate be added to GCs for patients with a high risk of relapse, those under prolonged GC therapy, or those at high risk of developing adverse effects to GCs.[31,33]

Although IL-6 inhibition represents the use of a biologic therapy in a predominantly older PMR population, its clinical appeal lies in its glucocorticoid-sparing effect. IL-6 inhibitors are associated with a higher incidence of neutropenia, although there is no clear evidence that they increase the rate of infection.

A prospective study by Lally proved IL6i to be safe, effective, and well tolerated for patients newly diagnosed with PMR, with a significant steroid-sparing effect.[34] Another retrospective study suggested that IL6i were safer and more effective than other biologic disease-modifying antirheumatic drugs (bDMRADs) in reducing GC exposure in PMR.[35,36]

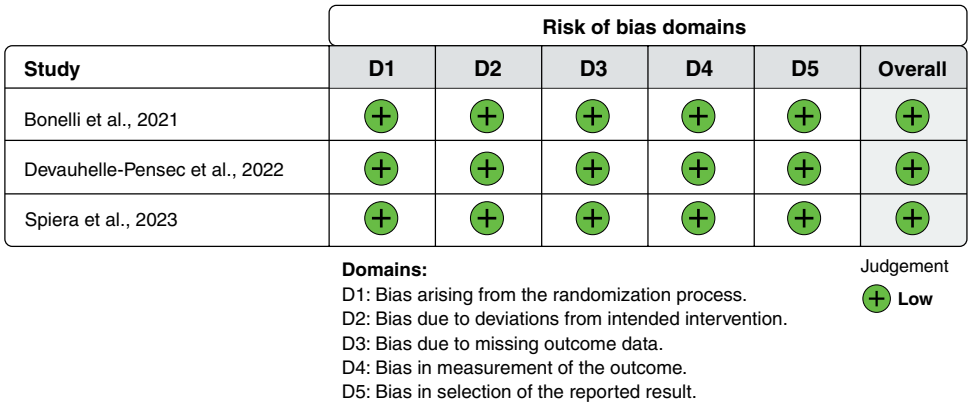

Figure 10
The Cochrane collaboration's tool for assessing the risk of bias in randomized trials (RoB 2)

Our meta-analysis is subject to limitations, including the small number of published RCTs and the relatively modest sample sizes of these studies. Additionally, substantial heterogeneity was observed in outcomes related to cumulative GC doses and overall adverse events, likely due to variations in study design and treatment protocols. These findings emphasize the need for a harmonized, evidence-based definition that balances both clinical and biochemical parameters to improve disease monitoring and treatment outcomes in PMR.

Conclusion

IL6i can be safely added to steroid tapering regimens to increase the disease remission rate in patients with PMR under GC therapy.

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