



Review

A systematic literature review to inform the 2025 EULAR recommendations for the management of polymyalgia rheumatica and primary large vessel vasculitis: management of disease including relapse and complications

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ABSTRACT

Objectives: EULAR recommendations for polymyalgia rheumatica (PMR) and large vessel vasculitis (LVV) were published in 2015 and 2020, respectively. New evidence necessitated an update. We conducted a systematic literature review (SLR) to inform the 2025 EULAR recommendations for PMR and LVV.

Methods: An SLR was conducted on MEDLINE, EMBASE, and CENTRAL on adults with PMR, giant cell arteritis (GCA), or Takayasu arteritis (TAK), using Medical Subject Heading terms related to management strategies on 31 December 2024 (PROSPERO: CRD42024560403). Eligible studies were randomised controlled trials (RCTs) and observational studies published since April 2014 (PMR) or December 2017 (LVV). EULAR 2024 and ACR 2024 abstracts were hand searched. Risk of bias (RoB) was assessed using Cochrane RoB-2 and the Newcastle-Ottawa Scale.

Results: Of 141 included articles (30 RCTs), low RoB GCA RCTs showed superiority of secukinumab (phase II), mavrilimumab (phase II), and upadacitinib (phase III) vs placebo. Phase II trials

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of sarilumab and sirukumab were prematurely terminated. GiACTA secondary analyses reported similar tocilizumab efficacy across cranial and PMR symptoms, with better SF-36 and fatigue improvements than placebo. TAK RCTs reported similar effectiveness of methotrexate or mycophenolate (some concerns about RoB) and superiority of adalimumab over tocilizumab (high RoB). Phase III PMR RCTs showed tocilizumab and sarilumab superiority (low RoB) over placebo; smaller phase II studies supported rituximab (low RoB) and abatacept (some concerns about RoB). One high RoB RCT showed similar efficacy of tofacitinib and GCs.

Conclusions: Multiple phase II and phase III RCTs inform the efficacy and safety of IL-6i, IL-17i, Janus kinase inhibitors, and B cell depletion in GCA and PMR; robust TAK trials remain lacking.

INTRODUCTION

Large vessel vasculitis (LVV) is characterised by inflammation of the aorta and its proximal branches [1]. The 2 types of primary LVV are giant cell arteritis (GCA) and Takayasu arteritis (TAK) [2,3]. PMR is a distinct syndrome of inflammation of the musculo-tendinous junctions characterised clinically by pain and stiffness in the shoulder and pelvic girdles, presenting independently or in association with GCA [4,5]. PMR and GCA are seen in older populations compared with the typical demographic of TAK [2–4].

Therapeutic challenges abound in the management of these conditions, and glucocorticoids (GCs) remain the cornerstone of therapy [2,6,7]. However, prolonged GC exposure is well documented to be associated with toxicities, including osteoporosis, diabetes, cardiovascular disease, and infection risk. Consequently, considerable effort has been directed towards the development and evaluation of GC-sparing agents. This includes trials of conventional and biological disease-modifying agents, as well as the use of targeted synthetic small molecules in these conditions. There has been a paradigm shift in recent years to move towards the aim of GC-free disease control [2–4].

The previous European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of PMR were published in 2015 and LVV in 2018 [8–11]. Since then, substantial new evidence, including from randomised controlled trials (RCTs), has accumulated, particularly regarding targeted therapies. A systematic review of literature was necessitated to inform the 2025 EULAR recommendations for the management of PMR and LVV. In this manuscript, we have focussed on pharmacological and nonpharmacologic interventions in the treatment of PMR and LVV. We have also looked at treatment strategies for the management of relapsing and refractory presentations, as well as commonly encountered complications.

PMR and LVV are commonly associated with a relapsing course [12–14]. The need for avoiding cumulative GC toxicity is even more pertinent in these patients. There is also the need to consider that PMR may relapse as GCA and vice versa. The necessity to protect against ischaemic manifestations, including the indication and methods of revascularisation are also considered here. Collectively, these conditions confer a high degree of morbidity and impact on quality of life. The evidence synthesis from this SLR underpins the 2025 recommendations, produced to support clinicians, researchers, and patients alike in optimising care across the LVV spectrum.

METHODS

This SLR was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. EULAR Standard Operating Procedures (SOP) were followed [15–17].

The protocol was developed by all the authors, and registered in the PROSPERO database of systematic reviews on June 21, 2024 (CRD42024560403) [18]. The research questions were formulated according to the ‘Population, Intervention, Comparator, Outcome’ (PICO) framework to address:

1. Optimal pharmacological and nonpharmacological management options in people diagnosed with LVV and PMR
2. Management of complications, relapse, and refractory disease in patients with LVV and PMR

Search strategy and inclusion criteria

The search strategy was developed by all authors and is available in the Supplementary Material (S1). An online literature search was conducted by an expert librarian (JL) in Medline, Embase, and the Cochrane Library, using relevant Medical Subject Heading (MeSH) terms within the title, keywords, and abstract. Two separate searches were performed pertaining to the treatment of the following: (1) new-onset disease and (2) relapsing disease.

A time restriction was applied based on the search termination date for the previous EULAR recommendations. For studies pertaining to LVV, the search dates were 31 December 2017 until 31 December 2024, and for PMR, 1 April 2014 until 31 December 2024. No language restriction was applied. Conference abstracts were screened separately, with those pertaining to relevant clinical trials presented at the 2024 meetings of the EULAR or American College of Rheumatology Convergence (ACR) checked for full-length publications. Reference lists were hand searched to check for inclusion of all relevant articles.

Adults (≥ 18 years) with a diagnosis of, or patients being assessed for, any primary LVV or PMR, were included. Exclusion criteria were wrong population, wrong disease (including secondary causes of LVV), or wrong age of participant, wrong intervention, wrong outcome, undefined outcome, studies including fewer than 20 patients, and wrong study type (editorials, comments, case reports). All pharmacological and nonpharmacologic (eg, education interventions) treatments were included as interventions, as listed in the search strategy (S1). Comparators were defined as other pharmacological and nonpharmacologic treatments, or no intervention. Outcome categories comprised disease activity state, including relapse, remission, exacerbations and patient-reported outcome measures; disease-related complications and damage, morbidity, and mortality; and treatment concordance.

Selection process, data extraction, and risk of bias assessment

All full-length articles were uploaded into EndNote V.X9 (Clarivate Analytics), with duplicates removed (Fig). Titles, abstracts, and, subsequently, full-text articles were screened by

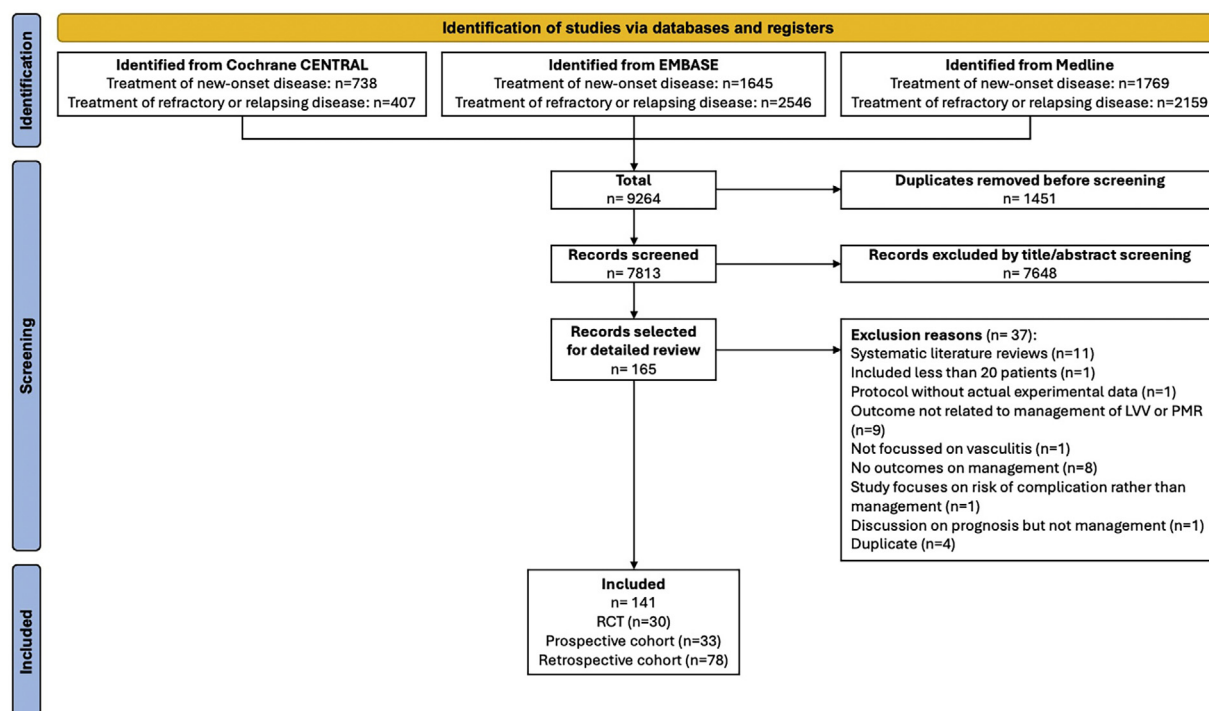


Figure. PRISMA flowchart of included articles.

DPM and AB (new-onset disease) and MD and DPM (relapsing disease) using the online software, Rayyan [19]. Full articles meeting inclusion criteria were then examined in detail, with relevant data extracted, by DPM (treatment of new-onset disease) and MD (treatment of relapsing disease). A 20% cross-validation of extracted information was undertaken by a second author. Conflicts were resolved through discussion with the TF methodologists (EN and PS).

Data were extracted into a preagreed spreadsheet and included: study design and characteristics, population, type of treatment and comparator, and efficacy and safety outcomes. Risk of bias (RoB) was assessed according to Version 2 of the Cochrane RoB tool (RoB 2) for RCTs and the Newcastle-Ottawa Scale for observational studies [20,21].

Data were collated and synthesised using a narrative synthesis.

RESULTS

The initial search yielded 4152 papers on the treatment of new-onset disease and 5112 papers on the treatment of refractory or relapsing disease, giving 9264 papers in total. After deduplication, 7813 papers remained, which were put forward for title and abstract screening; 165 papers were reviewed in detail, with 141 ultimately being included (30 RCTs, 22 prospective cohort studies, and 78 retrospective cohort studies). The Figure presents the PRISMA flowchart detailing study selection.

The overall agreement between reviewers was 99% at the abstract screening stage and 98% at the full paper screening stage. Meta-analysis was deemed inappropriate due to marked heterogeneity arising from differing definitions of remission or relapse, variations in glucocorticoid tapering protocols, and diverse outcome measures used.

TAKAYASU ARTERITIS

Six RCTs (4 phase II trials of drug interventions, including 1 secondary analysis of a trial published previously, 1 trial involving exercise interventions, 1 abstract at ACR 2024), 14 cohort studies

comparing 2 drugs or categories of drugs (3 prospective), 7 cohort studies without a control group (5 prospective), 1 retrospective cohort study each assessing withdrawal of immunosuppressive therapy and the effectiveness of statins, 1 prospective cohort study assessing imaging outcomes, 5 retrospective cohort studies assessing interventions, and 17 cohort studies (3 prospective) assessing complications in patients with TAK were identified.

RCTs of patients with TAK

Six RCTs were identified, 3 with some concerns about RoB and 2 with a high RoB, and 1 a conference abstract (Table 1). An RCT comparing methotrexate with mycophenolate mofetil (MMF) reported similar outcomes with either drug (clinical remission at 9 months in 71.4% on MMF and 63.6% with methotrexate) [22]. Another RCT comparing adalimumab with tocilizumab reported better efficacy at 6 months with adalimumab (18/21) than with tocilizumab (10/19). However, efficacy at 12 months, angiographic retardation, and GC sparing were similar with either drug [23]. A trial of ustekinumab vs placebo had to be terminated prematurely due to poor recruitment [24]. An open-label extension of an RCT of tocilizumab in patients with TAK reported a significant reduction in GC requirement by week 96, angiographic stabilisation in two-thirds and improvement in one-sixth, and significant improvement in quality of life by 96 weeks [25]. Another trial reported a greater magnitude of reduction in disease activity in patients with TAK receiving resistance exercise vs those treated with relaxation control [26]. A conference abstract (ACR 2024), meanwhile published as a full paper, reported better overall response rates with methotrexate and MMF when compared with cyclophosphamide (followed by azathioprine) (Table 1 and Supplementary Table S1) [27,28].

Observational studies of patients with TAK with a control group

Three observational studies (2 at low RoB) comparing conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) reported similar effectiveness of methotrexate and

Table 1
RCTs of patients with TAK

Primary analyses							
Author year	New onset/relapsing	Intervention (n)	Comparator (n)	Primary outcome	Results	Key secondary outcomes	Risk of bias
Li 2022 [26]	Both	Resistance exercise (n = 140)	Relaxation control (n = 138)	Reduction in BVAS	Greater reduction in BVAS for resistance exercise than for relaxation control from wk 4 onwards until wk 12 (end of trial).	Better improvements in ESR, CRP, and TNF-alpha levels over 12 wk were observed with resistance exercise than relaxation control	High
Padiyar 2024 [22]	Both	MMF (n = 26)	MTX (n = 26)	Clinical remission at 9 mo (PP analysis)	15/21 (71.4%) with MMF, 14/22 (63.6%) with MTX	Similar clinical responses on ITT analysis and similar angiographic progression in both groups	Some concerns
Sun 2024 [27,28]	Both	MMF + MTX (n = 74)	CYC (followed by AZA) (n = 37)	Overall response rate at 52 wk (ITT)	OR 2.59 (1.13-5.92)	Similar safety profile for either regimen	NA
Wang 2024 [23]	Both	ADA (n = 21)	TOC (n = 19)	Efficacy rate at 6 m (ITT)	18/21 ADA vs 10/19 TOC	Similar efficacy rates at 12 mo on ITT, similar angiographic progression, and similar glucocorticoid-sparing effect with both drugs	High
Yoshifuji 2025 [24]	Both	UST (n = 6)	PBO (n = 8)	Complete response at 6 m (ITT)	18/21 ADA vs 10/19 TOC		High
				HR for relapse (95% CI) UST vs PBO (ITT)	1.86 (0.41-8.47)	Similar adverse event profile with UST or PBO	
Secondary analyses							
Author year	New onset/relapsing	Intervention (n)	Comparator (n)	Key secondary outcomes		Risk of bias	
Nakaoka 2020 [25]	Relapsing	TOC 162 mg s.c. weekly (n = 36) (LTE)	-	-Reduction in GC dose from 0.223 mg/kg/d at enrolment to 0.131 mg/kg/d at 48 wk and 0.105 mg/kg/d at 96 wk -Stabilisation (67.9%) or improvement (17.9%) of angiographic findings at 96 wk -Improvement in the quality of life assessed using the SF-36 at 96 wk		High	

ADA, adalimumab; AZA, azathioprine; BVAS, Birmingham Vasculitis Activity Score; CYC, cyclophosphamide; GC, glucocorticoid; HR, hazard ratio; ITT, intention to treat; LTE, long-term extension; MMF, mycophenolate mofetil; MTX, methotrexate; NA, not assessable as this was a conference abstract; OR, odds ratio; PBO, placebo; PP, per protocol; SF-36, 36-item short-form health survey; s.c., subcutaneous; TAK, Takayasu arteritis; TOC, tocilizumab; UST, ustekinumab.

azathioprine, a faster response (albeit with similar effectiveness) with leflunomide than methotrexate, and better effectiveness and safety outcomes with leflunomide than cyclophosphamide (Table 2, Supplementary Table S2) [29–31].

Six observational studies compared biologic or targeted synthetic DMARDs (bDMARDs and tsDMARDs; 5 were at low RoB). One study reported higher drug-retention rates with tumour necrosis factor- α inhibitors (TNFi) than tocilizumab, whereas 2 others reported similar clinical responses and safety profiles with either drug. A recent systematic review with meta-analysis of observational studies also reported similar clinical outcomes with TNFi or tocilizumab [32]. Another study reported similar effectiveness but higher relapse rates with subcutaneous than with intravenous tocilizumab. Tomelleri et al [35] reported the need for dose intensification of infliximab beyond 5 mg/kg 8 weekly in two-thirds of patients with TAK. However, similar clinical responses were observed to those treated with a standard dose of infliximab. Another study reported comparable outcomes with the IL-17 inhibitor secukinumab or TNFi (Table 2, Supplementary Table S2) [33–38].

Five observational studies (3 at a low RoB) compared csDMARDs with bDMARDs or tsDMARDs. Similar clinical responses were reported with leflunomide or tofacitinib/adalimumab. Better clinical responses at 12 months and fewer relapses were noted with tofacitinib than methotrexate. However, both treatments were associated with similar GC-sparing or angiographic progression. Tocilizumab was associated with similar responses to cyclophosphamide. Another study comparing tocilizumab with conventional DMARDs in a retrospective cohort reported better vascular event-free survival and fewer relapses with tocilizumab (Table 2, Supplementary Table S2) [39–43].

One retrospective cohort study, with some RoB concerns (Supplementary Table S2), compared the risk of relapses in patients with TAK receiving statins along with GC ($n = 40$) vs those treated with GC alone ($n = 34$). Details on GC use and effect were lacking. The use of statins was associated with a lower risk of relapse (HR 0.26, 95%CI 0.12–0.56) [44].

Observational studies of patients with TAK without a control group

Seven observational studies (all with some concerns about RoB) reported the potential effectiveness of leflunomide, tocilizumab, infliximab, or infliximab biosimilar CPT-13 (Table 2, Supplementary Table S3) [45–51]. Ross et al [52] reported a successful discontinuation of immunosuppressive therapy in 25/65 (38%) patients with TAK over a follow-up of median (IQR) 18 (10–23) years from diagnosis. Relapses were observed only in 3/25 patients after discontinuing immunosuppressive therapy [52]. Banerjee et al [53] reported a significant reduction in 18-F fluorodeoxyglucose (FDG) positron emission tomography (PET) vascular activity on serial imaging upon treatment with tocilizumab or TNFi.

Studies assessing interventions in patients with TAK

Five studies (2 at a low RoB) addressed interventions in patients with TAK (Supplementary Table S4). Two uncontrolled studies reported the feasibility of endovascular angioplasty or stenting in patients with middle aortic syndrome or iliac artery involvement [54,55]. Zheng et al [56] reported fewer complications and perioperative deaths in patients undergoing vascular surgery when treated with GC in the perioperative period (in 1/

24) compared with those not on perioperative GC (in 11/22). Diao et al [57] reported similar primary success with surgical or endovascular interventions. However, surgery was associated with better long-term patency rates [57]. Sun et al [58] reported perioperative stroke/death in 7.5% (3/40) and 10-year survival of 84.4% in patients undergoing surgical repair of thoracoabdominal aneurysms.

Two meta-analyses assessed interventions in TAK. A comparison of open surgical vs endovascular procedures revealed a higher risk of perioperative stroke with open surgical interventions and fewer events of restenosis than endovascular interventions. Mortality was similar in both groups [59]. Another systematic review with meta-analysis reported fewer restenosis but a higher frequency of complications with balloon angioplasty vs stenting of the renal arteries. Both procedures were comparable for other arterial territories [60].

Management of complications in patients with TAK

Seventeen cohort studies (7 at a low RoB, 2 with some concerns about RoB, and 7 at a high RoB) assessed complications in TAK. Renal artery involvement was associated with morbidity (heart failure, hypertension) but not worse mortality or prognosis based on 2 studies [61,62]. Stenting was associated with higher restenosis rates than angioplasty or open surgery [63]. The lack of immunosuppressive therapy or active disease in the perioperative period during renal intervention was associated with worse outcomes [64]. Renal artery involvement is an important cause of hypertension in patients with TAK. One retrospective cohort study suggested that the addition of immunosuppressive therapy might lead to better control of hypertension [65]. While cardiopulmonary involvement overall does not indicate a worse prognosis in TAK, conflicting evidence suggests that pulmonary artery involvement might be associated with adverse prognosis [66–68]. In the presence of aortic regurgitation, surgical management was associated with better outcomes and survival than conservative management [69]. Composite aortic graft replacement might be associated with better outcomes than aortic valve replacement alone in the presence of aortic regurgitation [70]. Percutaneous coronary intervention is associated with higher restenosis rates and worse rates of major adverse cardiovascular events than surgical bypass [71,72]. Coronary artery involvement, aortic regurgitation, and conservative medical management were associated with worse outcomes in the presence of heart failure [73]. Although long-term prognosis was favourable in the presence of neurologic features, surgical treatment in the presence of myocardial ischaemia and neurological symptoms was associated with better outcomes than conservative management [74,75]. The presence of aneurysmal aortitis was associated with a greater risk of future relapses [76]. Overall, the requirement for surgical procedures was associated with a greater risk of mortality in a retrospective cohort of patients with TAK (Supplementary Table S5) [77].

GIANT CELL ARTERITIS

Nine RCTs on the management of GCA were identified, comprising 3 phase III trials and 2 phase II trials of drug interventions, 2 secondary analyses of a trial of tocilizumab, 4 secondary analyses of another trial of tocilizumab, and 1 secondary analysis of a trial of methotrexate, as well as 1 abstract at ACR 2024; 10 cohort studies with a control group (3 prospective) and 23 cohort studies without a control group (9 prospective) assessing the effectiveness of drugs were also identified. A further 5

Table 2
Observational studies of patients with TAK

Controlled studies						
Author year, prospective/retrospective	New onset/relapsing	Intervention (n)	Comparator (n)	Key outcomes	Conclusion	Risk of bias
Comparisons between conventional DMARDs						
Dai 2020, retrospective [29]	New onset, relapsing	LEF (n = 53)	CYC (n = 78)	At 9 mo - CR before matching 84.6% with LEF and 59% with CYC, after matching 95.7% with LEF and 63% with CYC - Effectiveness rate (CR + PR) before matching 94.2% with LEF and 74.4% with CYC, after matching 100% with LEF and 83.3% with CYC - Adverse events 4/53 with LEF, 34/78 with CYC	Leflunomide was more effective with better safety profile than cyclophosphamide in patients with TAK.	Low
Kaymaz-Tahra 2024, retrospective [31]	New onset	MTX (n = 204)	AZA (n = 77)	At the last visit, CR 48/110 with MTX and 18/57 with AZA In matched analyses, remission 19/48 with MTX and 19/48 with AZA, relapses 16/35 with MTX and 24/38 with AZA, vascular surgery 2/48 on MTX and 14/48 on AZA, deaths 2/46 on MTX and 3/45 on AZA	MTX and AZA were associated with similar clinical responses and relapses. More patients on AZA required vascular interventions.	Low
Wu 2020, retrospective [30]	New onset	MTX (n = 28)	LEF (n = 40)	At 6 mo, CR 15/28 with MTX and 29/40 with LEF, PR 6/28 with MTX and 5/40 with LEF. At 12 mo, CR 18/26 with MTX and 29/37 with LEF, PR 5/26 with MTX and 3/37 with LEF. Relapses 3/26 with MTX and 2/37 with LEF. Angiographic progression 3/26 with MTX and 4/37 with LEF. Adverse events 6/28 with MTX and 9/40 with LEF	Leflunomide was associated with faster response than methotrexate, long-term response, angiographic progression and safety were similar.	Some concerns
Comparison between biologic/targeted synthetic DMARDs						
Alibaz-Oner 2021, retrospective [33]	Relapsing	TNFi (n = 88)	TOC (n = 23)	At last visit, CR 28/61 with TNFi and 9/18 with TOC, PR 15/61 with TNFi and 2/18 with TOC. Angiographic progression 17/88 with TNFi and 9/23 with TOC	Similar clinical responses with TNFi or TOC	Low
Campochiaro 2020, retrospective [34]	New onset, relapsing	TNFi (n = 61)	TOC (n = 17)	Drug-retention rates 67.2% with TNFi vs 41.1% with TOC (log-rank p value = .028)	Drug-retention rates were better with TNFi than TOC.	Some concerns
Mekinian 2022, retrospective [37]	New onset, relapsing	TNFi (n = 132)	TOC (n = 77)	HR for relapse TNFi vs TOC 1.03 (0.67-1.61). Adverse events 21% with TNFi vs 17% with TOC	Similar clinical response and safety profile with TNFi or TOC	Low
Mekinian 2023, retrospective [38]	New onset, relapsing	Subcutaneous TOC (n = 18)	Intravenous TOC (n = 91)	HR subcutaneous vs intravenous TOC for CR 1.04 (0.32-3.35), relapses 2.55 (1.08-6.02)	Similar effectiveness but greater risk of relapses with subcutaneous than intravenous TOC	Low
Tian 2023, prospective [36]	Relapsing	SEC (n = 19)	TNFi (n = 34)	Overall response at 24 wk - ITT analysis 0/19 with SEC vs 22/34 with TNFi. - PP analysis 10/15 with SEC vs 21/34 with TNFi. - Adverse events. 2/19 with SEC vs 2/34 with TOC	Similar clinical responses and adverse events with SEC or TNFi	Low
Tomelleri 2022, retrospective [35]	New onset, relapsing	Standard-dose IFX (n = 13)	Intensified dose IFX (n = 28)	Standard vs intensified dose IFX treatment failure 2/13 vs 7/28, mean relapse rate per y 0.3 vs 0.8, serious infections 0/13 vs 3/28	>2/3 TAK treated with IFX required treatment escalation to higher dose; however, response rates were similar.	Low
Comparison between conventional and biologic/ targeted synthetic DMARDs						
Kong 2018, retrospective [40]	New onset, relapsing	TOC (n = 24)	CYC (n = 9)	Remission by NIH criteria at 6 mo TOC 8/9 vs CYC 13/15, improvement in angiography TOC 3/9 vs CYC 2/15.	Similar responses with TOC and CYC	Some concerns
Kong 2022, prospective [41]	New onset, relapsing	TOFA (n = 27)	MTX (n = 26)	At 12 mo, CR + PR 23/26 with TOFA and 15/23 with MTX. Relapses 3/26 with TOFA and 8/23 with MTX. Prednisone dose ≤7.5mg/d 16/26 with TOFA and 5/23 with MTX. Angiographic stabilisation 19/27 with TOFA and 24/26 with MTX. Adverse events 1/27 with TOFA and 4/26	TOFA was better than MTX for clinical response at 12 mo, with fewer relapses, better corticosteroid-sparing effect and similar effect on angiographic progression	Low

(continued on next page)

Table 2 (Continued)

Author year, prospective/retrospective	New onset/relapsing	Intervention (n)	Comparator (n)	Controlled studies		Risk of bias
				Key outcomes	Conclusion	
Mekinian 2018, retrospective [39]	New onset, relapsing	TOC (n = 46)	cDMARDs (n = 46)	3-y vascular event-free survival TOC 80% vs cDMARDs 50%, cumulative relapses TOC 6.3% vs cDMARDs 34.6%	TOC was associated with better vascular event-free survival and fewer relapses than cDMARDs.	Some concerns
Peron Filho 2024, retrospective [43]	New onset, relapsing	LEF (n = 44)	ADA (n = 16)	Complete response at the last follow-up visit 62.5% with ADA vs 78.3% with LEF. HR for relapse ADA vs LEF 1.007 (0.366-2.768)	Similar clinical responses and relapses with LEF or ADA	Low
Wang 2022, prospective [42]	New onset, relapsing	LEF (n = 35)	TOFA (n = 32)	At 12 mo, CR + PR 25/35 with LEF and 23/32 with TOFA. Angiographic improvement 2/35 with LEF and 8/32 with TOFA.	Similar clinical responses with LEF or TOFA. Better angiographic responses with TOFA	Low
Uncontrolled studies						
Campochiaro 2021, prospective [45]	New onset, relapsing	IFX biosimilar CT-P13 (n = 23)	-	Active disease at 6 mo: 5/21 vs 4/21 at baseline ADRs at 12 mo: 10/19	IFX biosimilar was similarly effective to the innovator molecule upon switching.	Some concerns
Cui 2019, prospective [46]	New onset, relapsing	LEF (n = 56)	-	RR at 6 mo 47/56 (83.93%) RR at 12 mo 39/56 (69.64%)	LEF was effective in two-thirds.	Some concerns
Erbasan 2021, retrospective [49]	New onset, relapsing	IFX (n = 9), TOC (n = 6), IFX + TOC (n = 6)	-	Mean (SD) NIH disease activity score before 1.8 (1.4), after 0.4 (0.9) Mean (SD) CARDS before 4.4 (3.1), after 3.4 (2.9) Angiographic regression 15/21 (71.4%) Vascular progression 3/21 (14.3%) Serious infections 3/21 (14.28%)	Biologic DMARDs could effectively suppress disease activity and angiographic progression in most patients with TAK.	Some concerns
Harigai 2023, prospective [51]	New onset, relapsing	TOC (n = 120)	-	- Drug-retention rate - wk 12: 112/120 (93.3%); wk 24: 104/120 (86.7%); wk 36: 101/120 (84.2%); wk 52: 94/120 (78.3%). - Adverse events: 49/120 (40.8%); serious adverse events: 19/120 (15.8%); adverse drug reactions: 28/120 (23.3%) - Relapse until the last observation; 24/120 (20%)	TOC was safe and effective in a real-life cohort of TAK.	Some concerns
Mertz 2020, prospective [47]	New onset, relapsing	IFX (n = 23)	-	Reduction in glucocorticoid dose (median [IQR]): at inclusion 10 (10-25) mg, at 6 mo 9 (5-10) mg, at 12 mo 5 (5-10) mg, at 24 mo 5 (5-5) mg	IFX had steroid-sparing efficacy in TAK.	Some concerns
Mustapha 2021, retrospective [48]	New onset, relapsing	LEF (n = 9)	-	Efficacy at 6 mo 8/9 Sustained remission at 12 mo 8/9 sustained remission at 24 mo 7/8	LEF was effective in a majority of patients.	Some concerns
Wu 2021, prospective [50]	New onset, relapsing	TOC (n = 33)	-	At 6 mo: RR 29/33 (88%), angiographic improvement 6/33 (18%), angiographic progression 5/33 (15%). At 12 mo: angiographic improvement 6/31 (19%), angiographic progression 3/31 (10%)	TOC was effective in 88% with a fifth showing angiographic improvement.	Some concerns

ADA, adalimumab; ADR, adverse drug reactions; AZA, azathioprine; CARDS, combined arteritis damage score; CYC, cyclophosphamide; DMARDs, disease-modifying antirheumatic drugs; IFX, infliximab; IQR, interquartile range; ITT, intention to treat; LEF, leflunomide; MTX, methotrexate; NIH, National Institutes of Health; PP, per protocol; RR, response rate (complete or partial response); SEC, secukinumab; TNFi, tumour necrosis factor- α inhibitors; TOC, tocilizumab; TOFA, tofacitinib.

cohort studies (4 prospective) assessed imaging outcomes, while 8 cohort studies (1 prospective) assessed complications in GCA.

RCTs of patients with GCA

Nine RCTs were identified, 4 at a low RoB, 1 with some concerns about RoB, and 3 with a high RoB and 1 a conference abstract (Table 3). The SELECT-GCA RCT, investigating the effect of upadacitinib, reported higher sustained remission from weeks 12 to 52 with upadacitinib 15 mg once daily (37%) but not at 7.5 mg once daily (26%), when compared with placebo (16%), with no adverse safety signals [78].

One RCT reported lower risk of relapses with mavrilimumab compared with placebo (HR 0.38 95% CI 0.15–0.92) [79]. Another RCT reported better rates of sustained remission at 28 weeks with secukinumab than placebo (risk ratio 3.43, 95% CI 2.10–5.87) [80]. Two RCTs of interleukin-6 (IL-6) inhibitors, sirukumab and sarilumab, had to be prematurely terminated due to poor recruitment resulting from the coronavirus disease-19 pandemic, precluding any definitive conclusions about the efficacy of either drug [81,82].

Secondary analyses of the GiACTA trial reported lower rates of complete response on angiography despite complete clinical response and relapses in about one-half of patients upon withdrawal of tocilizumab [83,84]. Other secondary analyses of the GiACTA trial of tocilizumab in GCA reported similar responses in those with cranial symptoms, PMR symptoms, or both. Compared with placebo, tocilizumab was also associated with lower odds of treatment failure, lower risk of relapse with weekly tocilizumab (but not 2-weekly tocilizumab), and greater reductions in HbA1c [85–88].

A secondary analysis of a trial of methotrexate vs placebo reported greater reductions in erythrocyte sedimentation rate with methotrexate over 24 months [89]. A conference abstract (ACR 2024) reported similar relapse-free survival and safety profile with anakinra or placebo in patients with GCA (Tables 3, Supplementary Table S6) [90].

Observational studies of patients with GCA with a control group

Ten studies were identified (6 with low risk and 4 with some concerns about RoB, Supplementary Table S7). Two studies reported a reduction in relapses and better GC-sparing with leflunomide, while another reported fewer relapses with the addition of methotrexate, compared with GCs alone [91–93]. Fewer relapses and faster GC sparing were observed with the addition of methotrexate or cyclophosphamide to GCs [94]. One study reported similar effectiveness with methotrexate or leflunomide [95]. Tocilizumab was more cost-effective than GCs alone, while 2 studies reported faster reductions in halos and better GC sparing with tocilizumab compared with methotrexate [96–98]. A shorter time to relapse was observed when tocilizumab was abruptly discontinued in patients in remission, as opposed to a gradual taper. However, both groups had similar proportions of relapses overall (27/59 with abrupt cessation and 8/57 with a gradual taper) [99]. An individually optimised regimen of tocilizumab after attaining remission was associated with fewer infections (7% in the optimised group vs 13% in a protocolised regimen) and similar clinical response (78% vs 84%) (Table 4) [100].

Observational studies of patients with GCA without a control group

Twenty-eight studies were identified (all with some concerns about the RoB, Supplementary Table S8). One study reported that 58% patients with GCA continue to be on GCs long-term [101]. Five studies assessed GC-tapering strategies with differing results. One study reported remission in nearly 90% at 1 year when treated with monotherapy with a GC-tapering strategy, dependent on the clinical response [102]. Two studies reported remission in 33% to 47% of individuals with a GC taper over 26 weeks [103,104]. One study reported sustained remission in 77% of patients when treated with a GC taper over 8 weeks along with tocilizumab [105]. Another study reported relapse-free remission in 47% when treated with 3 days of intravenous methylprednisolone and tocilizumab without oral prednisolone [106]. Two studies reported the effectiveness of methotrexate or MMF to reduce relapses in patients with GCA [107,108]. Eight observational studies confirmed the effectiveness of tocilizumab, 1 of which reported similar rates of sustained remission in a real-life cohort to that observed in the GiACTA trial [12,109–115]. Two studies reported similar rates of clinical remission and relapses in GCA, irrespective of a presentation with cranial symptoms, extracranial symptoms or both [14,116]. One study reported relapses in half of patients with GCA 2 years after stopping tocilizumab [117].

With regard to Janus kinase (JAK) inhibitors, 1 study reported the effectiveness and safety of baricitinib in relapsing GCA, while another reported remission in about half of patients with relapsing GCA treated with tofacitinib, baricitinib, or upadacitinib [118,119]. Two studies reported contrasting results with ustekinumab in patients with GCA. Conway et al [120] reported a significant GC-sparing effect with ustekinumab, whereas Matza et al [121] reported relapses in greater than 50% with less than a quarter off GCs at 1 year (Table 4).

Five observational studies assessed imaging outcomes in GCA. Banerjee et al [53] reported a significant reduction in PET vascular activity on serial imaging in patients with TAK upon treatment with tocilizumab but not TNFi. Quinn et al [122] reported reductions in FDG PET vascular activity with tocilizumab. However, an increase in PET activity was noted following the cessation of tocilizumab [122]. Ponte et al [123] reported a decrease in halos on treatment with GCs, with faster resolution in temporal than axillary artery halos [124]. Monti et al [125] reported the persistence of halos in a fifth of patients despite treatment with GCs or other DMARDs (Table 4).

Management of complications in patients with GCA

Eight cohort studies (2 at a low RoB and 3 with some concerns or at a high RoB) assessed complications in GCA. Monti et al [126] reported a higher risk of visual loss, aortic aneurysm, and serious infections in older patients with GCA. Two studies reported visual symptoms, vertebral artery involvement, or aortic dilatation in a third of patients [127–129]. One study reported progression to blindness in about a third of patients with visual symptoms at presentation [127]. Two studies suggested a protective effect of tocilizumab in preventing worsening visual symptoms or new-onset aortic dilatation [130,131]. A population-based cohort study reported that treatment with intravenous methylprednisolone was not associated with visual improvement in GCA but was associated with a higher risk of developing diabetes mellitus [132]. One study reported that limb involvement in GCA was associated with a greater risk of

Table 3
RCTs of patients with GCA

Primary analyses							
Author, year	New onset/ relapsing	Intervention (n)	Comparator (n)	Primary outcome	Results	Key secondary outcomes	Risk of bias
Blockmans 2025 [78]	New onset, relapsing	UPA 15 mg (n = 209) UPA 7.5 mg (n = 107)	PBO (n = 112)	Sustained remission from wk 12 to wk 52	Sustained complete remission from wk 12 to wk 52: UPA 15: 37.1%, UPA 7.5: 26.2%, PBO: 16.1%	Cumulative GC exposure till wk 52, time to first flare and proportion with at least one flare till wk 52 all favoured UPA 15 mg vs placebo	Low
Cid 2022 [79]	New onset, relapsing	MAV (n = 42)	PBO (n = 28)	Time to flare (weeks) (ITT)	HR 0.38 (0.15-0.92)	HR for sustained remission at 26 wk 33.3 (10.7-55.8)	Low
de Boysson 2024 [90]	Not defined	ANAK (n = 17)	PBO (n = 13)	Relapse-free survival	Similar for ANAK or PBO - log-rank <i>P</i> value .65	Relapses at wk 26: ANAK 8/17 (47%), PBO 4/13 (31%) Relapses at wk 52: ANAK 9/17 (53%), PBO 6/13 (46%) Adverse events: ANAK (n = 4), PBO (n = 3)	NA
Schmidt 2020 [81]	New onset, relapsing	SIR100 + 6M GC taper (n = 42) SIR100 + 3M GC taper (n = 39) SIR50 + 3M GC taper (n = 26)	6M GC taper (n = 27) 3M GC taper (n = 27)	Sustained remission at 52 wk	3/17 with SIR100 + 6M GC taper, 2/13 with SIR100 + 3M GC taper, 1/11 with SIR50 + 3M GC taper, 0/7 with 6M GC taper, 0/7 with 3M GC taper	Statistical analyses not performed due to premature termination	High
Schmidt 2023 [82]	New onset, relapsing	SAR200 + 26W GC taper (n = 27) SAR150 + 26W GC taper (n = 14)	PBO + 52W GC taper (n = 28) PBO + 26W GC taper (n = 14)	Sustained remission at 52 wk	6/13 with SAR200 + 26W GC taper, 3/ 7 with SAR150 + 26W GC taper, 3/ 10 with PBO + 52W GC taper, 0/6 with PBO + 26W GC taper	Statistical analyses not performed due to premature termination	High
Venhoff 2023 [80]	New onset, relapsing	SEC (n = 27)	PBO (n = 25)	Sustained remission at wk 28 (ITT) Using Bayesian summary statis- tics, and nonresponder impu- tation and noninformative priors in both treatment groups (ITT)	RD 0.50 (0.29-0.67) RR 3.43 (2.10-5.87) RD 0.45 (0.20-0.66) RR 2.85 (1.50-6.72) OR 7.52 (3.35-16.86)	Fewer flares, similar adverse events with SEC and PBO	Low
Secondary analyses							
Author year	New onset/relapsing	Intervention (n)	Comparator (n)	Key secondary outcomes		Risk of bias	
Adler 2019 [84]	New onset, relapsing	TOC (n = 17)	-	All 17 patients were in remission at 52 wk. Upon withdrawal of TOC, relapses occurred in 8/17 patients over mean (range) follow-up of 28.1 (17-44) mo. Younger age, more areas of mural enhancement were associated with relapses.		Some concerns	
Reichenbach 2018 [83]	New onset, relapsing	TOC (n = 20)	PBO (n = 10)	Complete clinical response at 3 mo in 9/9 on TOC and 3/4 on PBO. However, complete remission of vasculitis on MRA at 3 mo in 3/9 on TOC and 1/4 on PBO. Complete remission of vasculitis at end of trial in 9/9 on TOC and 2/4 on PBO. However, complete remission of vasculitis on MRA at end of trial in 3/9 on TOC and 1/4 on PBO.		Some concerns	
Spiera 2021 [85]	New onset, relapsing	TOC (n = 149)	PBO (n = 101)	Sustained remission at wk 52 in those with PMR symptoms only (14/31 TOC vs 4/21 PBO), with cranial symptoms only (35/58 TOC vs 7/36 PBO), with both PMR and cranial symptoms (33/60 TOC vs 5/44 PBO).		Low	
Stone 2022 [87]	New onset, relapsing	TOC 162 mg s.c. weekly (n = 100),	PBO (n = 91)	In new-onset disease, HR for flare with weekly TOC (0.51, 0.30-0.87), with 2-weekly TOC (HR 0.76, 0.43-1.35) vs PBO.		Low	

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Table 3 (Continued)

Author year	Secondary analyses				Risk of bias
	New onset/relapsing	Intervention (n)	Comparator (n)	Key secondary outcomes	
Patel 2023 [88]	New onset, relapsing	TOC 162 mg s.c. 2-weekly (n = 49) TOC (n = 121)	PBO (n = 88)	In relapsing disease, HR for flare with weekly TOC (0.55, 0.34-0.90), with 2-weekly TOC (HR 0.80, 0.44-1.46) vs PBO.Cumulative GC dose lower with weekly (but not 2-weekly) TOC vs PBO Change in HbA1C -0.54 (0.63) ($P < .001$ vs baseline) with TOC and -0.09 (1.06) ($P < .001$ vs baseline) with PBO	Low
Unizony 2021 [86]	New onset, relapsing	TOC (n = 130)	PBO (n = 94)	Adjusted OR for treatment failure (Inability to attain remission by 12 wk, or relapse between wk 12 and 52) with TOC vs placebo 0.2 (0.1-0.3)	Low
Perez-Sancristobal 2024 [89]	New onset, relapsing	MTX (n = 21)	PBO (n = 21)	Changes in ESR with treatment over 24 mo (AUC, mean with SD) 19,598.4 (8117) with MTX and 28,461.7 (12326) with PBO	High

ANAK, anakinra; AUC, area under the receiver operating characteristics curve; GC, glucocorticoid; HR, hazard ratio; ITT, intention to treat; LfE, long-term extension; MAV, mavrilumab; MRA, magnetic resonance angiography; MTX, methotrexate; NA, not assessable as this was a conference abstract; OR, odds ratio; PBO, placebo; PMR, polymyalgia rheumatica; RD, risk difference; RR, risk ratio; SAR, sarilumab; S.C., subcutaneous; SD, standard deviation; SEC, secukinumab; SF-36, 36-item short-form health survey; TOC, tocilizumab; UPA, upadacitinib.

cardiovascular involvement and vascular surgery (Supplementary Table S9) [133].

POLYMYALGIA RHEUMATICA

In total, 27 articles were identified regarding the treatment of new-onset disease, comprising 11 RCTs, 10 retrospective cohort studies, and 6 prospective cohort studies. A further RCT was identified regarding the treatment of refractory or relapsing PMR. Additionally, 1 conference abstract (RCT) was identified on the treatment of new-onset PMR.

RCTs of patients with PMR

Of the 13 RCTs, 8 had a low RoB, 2 had some concerns, and 2 had a high RoB (Table 5, Supplementary Table S10). It was not possible to assess the RoB for the conference abstract. Two studies examined the use of prednisolone in the treatment of new-onset PMR, 1 looking at oral prednisolone vs IV methylprednisolone, and the second comparing modified release (MR) with immediate-release (IR) preparations [134,135]. Viapiana et al [135] reported similar biochemical and clinical responses with prednisolone (89% of participants achieved clinical response within 2 weeks) or methylprednisolone (100%). However, patients treated with methylprednisolone have a faster onset of response (15.2 vs 20.3 days). Of note, this study was deemed to have a high RoB, mainly due to concerns regarding the randomisation process and deviations from the intended interventions [135]. Cutolo et al [134] reported similar complete response to treatment at 4 weeks with MR or IR prednisone, although some of the secondary outcomes (ie, a partial response) favoured MR preparations. Only 1 RCT was identified on the use of csDMARDs for the treatment of new-onset PMR, specifically methotrexate—this found similar results to placebo for GC-sparing and prevention of relapses [136].

Two phase II RCTs assessed the use of tocilizumab for the treatment of new-onset PMR. Results from the PMR-SPARE trial demonstrated tocilizumab to be efficacious for GC sparing and prevention of relapses, compared with GCs alone [137]. GC-free remission at week 16 was achieved in 12/19 patients on tocilizumab (63.2%) and 2 of 17 patients taking a placebo (11.8%, $P = .002$). Time to the first relapse was also significantly longer for patients on tocilizumab compared with placebo. The SEMAPHORE trial found similar results in a cohort which also included relapsing and refractory cases. Of 11 reported secondary endpoints at 24 weeks, 7 showed significant differences favouring tocilizumab (compared with placebo), including mean CRP PMR-activity score (PMR-AS) score (7.5 [95% CI, 5.4-9.6] vs 14.9 [95% CI, 11.4-18.4]), and the percentage of patients no longer receiving prednisone (49.0% vs 19.6%) [138]. In the SEMAPHORE trial, 26 of 33 patients who had attained remission on tocilizumab at 24 weeks discontinued the drug. Twenty-four of these 26 patients experienced relapses, suggesting that treatment with tocilizumab for 6 months was inadequate to prevent relapses [139].

Spiera et al [140] reported results from a phase III RCT on the treatment of refractory or relapsing PMR, using sarilumab. Sarilumab showed significant efficacy in achieving sustained remission (28% vs 10% in the sarilumab vs placebo group) and reducing cumulative GC dose in patients with PMR relapse, compared with placebo [140].

The BACHELOR trial assessed the use of baricitinib in new-onset PMR. Baricitinib was more effective than placebo in newly diagnosed patients, without adverse safety signals. The primary

Table 4
Observational studies of patients with GCA

Controlled studies						
Author, year, prospective/retrospective	New onset/relapsing	Intervention (n)	Comparator (n)	Key outcomes	Conclusion	Risk of bias
Calderón-Goercke 2023 [100], Retrospective	New onset, relapsing	Optimised TOC regimen (n = 125)	Nonoptimised TOC regimen (n = 106)	Prolonged remission at the end of follow-up in optimised 78.2% (relapses 5.6%, severe infections 6.6%) vs 84.2% (relapses 10.4%, severe infections 12.9%) in nonoptimised regimen. Optimised regimen had lower annual cost.	Fewer serious infections and lower cost with the optimised regimen of TOC despite similar clinical efficacy to the nonoptimised regimen.	Some concerns
Carbonella 2016 [94], retrospective	New onset, relapsing	GC + MTX/CYC (n = 23)	GC alone (n = 24)	Relapses on GC + MTX/CYC 3/23 vs 10/24 on GC alone. Mean time to reach a prednisolone dose of 5 mg 5.4 mo with GC + MTX/CYC vs 10/4 mo on GC alone	Addition of MTX/CYC was associated with fewer relapses and better GC sparing than GC alone.	Some concerns
Grazzini 2023 [97] prospective	New onset	TOC (n = 20)	MTX (n = 9)	Reductions in OGUS/ halo count at 3 and 6 mo were significant with TOC but not with MTX. At 12 mo, reductions in OGUS/ halo count were significant with either TOC or MTX.	TOC was associated with faster reductions in OGUS and halo count than MTX.	Low
Hocevar 2019 [91] prospective	New onset	LEF + GC (n = 30)	GC alone (n = 46)	Relapse by 96 wk 13.5% with LEF + GC vs 39.1% with GC alone Median cumulative GC dose 4390 mg with LEF + GC vs 5340 mg with GC alone	Fewer relapses and greater glucocorticoid-sparing effect were observed with LEF combined with GC than GC alone.	Low
Jogimahanti 2021 [96], Retrospective	Not defined	TOC + GC (n = 16)	GC alone (n = 16)	TOC 26 wk/ 52 wk with mild/severe prednisone side effects compared with class I/II prednisone side effects was more cost-effective.	TOC was more cost-effective than GC alone.	Low
Kramaric 2022 [92] Prospective	New onset	LEF + GC (n = 151)	GC alone (n = 64)	Relapse at weeks 14.6% with LEF + GC vs 45.3% with GC alone Median cumulative GC dose 7 grams with LEF + GC vs 7.7 grams with GC alone	Fewer relapses were observed with LEF combined with GC than GC alone.	Low
Koster 2019 [93], Retrospective	New onset	MTX + GC (n = 83)	GC alone (n = 83)	RR for relapse after vs before MTX 0.32 (0.24-0.41) HR for relapse after vs before MTX (adjusted for starting dose of GC and GC use on follow-up): 0.36 (0.27-0.48)	The addition of MTX was associated with a lower risk of relapses.	Low
Nielsen 2024 [99], Retrospective	New onset, relapsing	TOC tapering (n = 57)	TOC abrupt discontinuation (n = 59)	Relapses 46% with tapering vs 47% with abrupt discontinuation Time to relapse was shorter for abrupt discontinuation than tapering (log-rank <i>P</i> value = .02).	Overall relapses were similar, but faster relapses were observed with abrupt discontinuation of TOC than with tapering.	Low
Quartuccio 2024 [98], Retrospective	New onset	MTX (n = 81)	TOC (n = 31)	Sustained GC-free remission at 6 mo 0% with MTX and 16.1% with TOC, at 12 mo 11.1% with MTX and 64.5% with TOC	TOC had better GC-sparing effect than MTX	Some concerns
Tengesdal 2019 [95], Retrospective	New onset, relapsing	LEF (n = 27)	MTX (n = 24)	Remission in 7/27 on LEF and 5/24 on MTX	Similar responses were observed with LEF or MTX.	Some concerns
Uncontrolled studies						
Studies assessing clinical outcomes						
Blanco 2024 [14], Retrospective	Relapsing	TOC (n = 471)	-	Clinical remission at 24 mo 79% for cranial GCA, 81% for extracranial GCA and 89% for mixed GCA. Relapses 13% for cranial GCA, 15% for extracranial GCA and 13% for mixed GCA	Similar responses were observed with TOC, irrespective of the presentation of GCA.	Some concerns
Conway 2018 [120], Prospective	Relapsing	UST (n = 25)	-	Reduction in median (IQR) glucocorticoid dose from last relapse to at 52 wk of UST15 (5-20) mg to 5 (2.5-5) mg (<i>P</i> < .001). Relapses 0/25 and GC cessation 6/24 at 52 wk	UST was effective with significant GC sparing at 1 y.	Some concerns

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Table 4 (Continued)

Uncontrolled studies						
Studies assessing clinical outcomes						
Calderón-Goercke 2020 [12], Retrospective	New onset, relapsing	TOC (real-life cohort, n = 134, GACTA cohort, n = 251)	-	Sustained remission in real-life cohort 70.4% vs 54.6% in GACTA cohort	TOC was similarly effective in real-life and trial settings.	Some concerns
Christ 2021 [109], Prospective	New onset	TOC (n = 18)	-	Remission at d 31 without relapses at wk 24 3/12, relapse-free remission at wk 52 in 13/18	About a fourth of patients remained in remission on TOC at 1 y.	Some concerns
Clement 2021 [110], Retrospective	New onset, relapsing	TOC (n = 43)	-	Relapses on TOC 26/43.	Relapses were observed in 60% on TOC.	Some concerns
Cronin 2022 [111], Retrospective	New onset	TOC ± GC (n = 63)	-	Cessation of long-term GC in 5/63, relapses of GCA in 16/63	One-fourth of newly diagnosed GCA relapsed while on GC.	Some concerns
Harigai 2024 [112], Retrospective	New onset, relapsing	TOC (n = 117)	-	Drug-retention rates 82.9% at 12 wk, 79.5% at 24 wk, 76.1% at 36 wk, and 73.5% at 52 wk. ADRs in 28.2%, serious ADRs in 11.1%. Relapse-free at the last follow-up 85%, on GC at last follow-up 22.1%	Three-fourths of patients continued to be on TOC at 1 y.	Some concerns
Karabayas 2020 [102], Retrospective	New onset, relapsing	Stratified GC therapy (n = 73)	-	At 1 y, new vision loss in 1/73, remission in 64/73. GC-related complications in 15/73	GC taper dependent on clinical response was associated with good outcomes.	Some concerns
Karabayas 2020 [107], Retrospective	New onset, relapsing	MMF (n = 37)	-	Relapse at 1 y in 16.2% and 2 y in 27%	MMF was effective in GCA over 2 y.	Some concerns
Koster 2022 [118], Prospective	Relapsing	BARI (n = 15)	-	At wk 52, AE in 14/15, serious AE in 1/15 (thrombocytopenia), relapses 1/14, GC discontinuation in 13/14	BARI was safe and effective over 52 wk of follow-up.	Some concerns
Lavergne 2023 [108], Retrospective	New onset, relapsing	MTX (n = 49)	-	GC discontinuation after median 20.5 mo in 24/49 Relapses per mo before MTX 0.14, on MTX 0.01, upon stopping MTX 0.03	Fewer relapses were observed on MTX than historically. GC could be discontinued in one-half on MTX.	Some concerns
Loricera 2024 [119], retrospective	New onset, relapsing	BARI (2-4mg OD, n = 15), TOFA (5mg BD, n = 10), UPA (15mg OD, n = 10)	-	At a mean of 11 mo of follow-up, 20 attained clinical remission (16 complete remission)	About one-half of patients attained remission on treatment with Janus kinase inhibitors.	Low
Matza 2021 [121], prospective	Relapsing	UST (n = 13)	-	At wk 52, GC-free remission in 3/13, disease flares in 7/13	UST was associated with treatment failure at 1 y in one-half.	Some concerns
Mensch 2023 [103], retrospective	New onset, relapsing	GC taper and stop by 26 wk (n = 47)	-	At 1 y, GC cessation in 9/47, relapses in 32/47. GC-related AE in 19/47	One-fifth are able to discontinue GC at 1 y.	Some concerns
Muratore 2024 [104], prospective	New onset	26-wk GC taper (n = 22)	-	Relapse-free remission at wk 52 in 10/22. Relapse-free remission off GC at wk 52 in 5/22	About one-half remained in remission at 1 y. despite a rapid GC taper.	Some concerns
Muratore 2024 [106], prospective	New onset, relapsing	IVMP 3 d (no oral GC) + TOC wk 4 to 52 (n = 18)	-	Significant reduction in PETVAS at wk 24 (mean change -8.6, <i>P</i> = .001) and 52 (mean change -10.4, <i>P</i> = .002). Relapse-free remission at 24 wk—56% (95% CI 31–78) and 52 wk—47% (95% CI 23–72)	TOC with ultrashort GC regimen could successfully ameliorate inflammation in GCA.	Some concerns
Nagase 2025 [113], retrospective	New onset, relapsing	TOC (n = 62)	-	Relapses on TOC 10/62 (16%), 39 adverse events in 28/62 (45%)	Relapses occurred in a fifth treated with TOC.	Some concerns
Quick 2024 [117], retrospective	New onset, relapsing	TOC (n = 336)	-	After stopping TOC, relapses at 6 mo 21.4%, 12 mo 35.4%, and 48.6% at 24 mo	Relapses were observed in one-half by 2 y after stopping TOC.	Some concerns
Samson 2018 [114], prospective	New onset, relapsing	TOC (n = 20)	-	Remission at wk 26 on prednisone ≤0.1 mg/kg/d 15/20, relapses by wk 26 in 5/20	Three-fourths were in remission on TOC over 6 mo.	Some concerns
Sebastian 2020 [115], retrospective	New onset, relapsing	TOC (n = 22)	-	One relapse over 12-52 wk, 2 discontinued due to adverse effects	Few relapses were observed on TOC.	Low
Tomelleri 2022 [116], retrospective	New onset, relapsing	GC with DMARDs (n = 116)	-	Cumulative GC dose, relapse-free survival, relapse rate, and incidence of aneurysms were not significantly different between extracranial or cranial GCA	Similar outcomes irrespective of cranial or extracranial GCA.	Some concerns
Tsalapaki 2024 [101], prospective	New onset, relapsing	GC (n = 243)	-	On GC at the last follow-up 58%, relapses at 2 y in 27%	Only 40% are able to discontinue GC in the long-term.	Some concerns
Unizony 2023 [105], prospective	New onset, relapsing	TOC with 8-wk GC taper (n = 30)	-	At wk 52, sustained remission in 23/30 (77%), relapses in 7/30 (23%)	Despite rapid GC taper, treatment with TOC was associated with remission in three-fourths at 1 y.	Some concerns

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Table 4 (Continued)

Uncontrolled studies						
Studies assessing clinical outcomes						
Studies assessing imaging outcomes alone						
Banerjee 2020 [53], prospective	New onset, relapsing	TOC (n = 17), TNFi (n = 3)	-	Reduction in PETVAS on TOC from 25 to 21.5, normalisation of PET in 3/17. Improvement in PET and clinical activity in 1/3 on TNFi	TOC reduced PET activity but not TNFi.	Some concerns
Monti 2018 [125], retrospective	New onset, relapsing	GC ± DMARDs (n = 89)		Active disease on routine scans in asymptomatic individual: 19/89 (21%). Patients with GCA with possible relapse with active disease on US: 29/78 (37%).	US findings might persist in a fifth despite the lack of symptoms	Some concerns
Ponte 2020 [123], prospective	New onset, relapsing	GC (n = 226)	-	Smaller halo size with more days of GC treatment ($r = -0.30$, $P = .001$). Statistically significant difference in temporal artery halo between baseline and ≥ 4 d of GC treatment ($P = .003$). No significant difference in axillary artery halos with days of GC treatment.	Halo size decreases with GC treatment, more so for temporal artery halos.	Some concerns
Ponte 2021 [124], prospective	New onset, relapsing	GC (n = 49)	-	A significant reduction in temporal artery halo was observed from wk 1 and axillary artery halo from wk 6 of treatment	Temporal artery halo starts resolving faster than axillary artery halos.	Some concerns
Quinn 2021 [122], prospective	New onset, relapsing	TOC (n = 25)	-	Clinical disease activity at the most recent visit in 3/25 (12%), discordant with persistent FDG activity in 11/25 (44%) Reduction in PETVAS from 24 (22.3-27) at baseline to 18.5 (15.3-23.8) at last visit. Significant reduction in PETVAS over 2 y of treatment After TOC discontinuation (n = 6), PETVAS changes from 18.5 (16.5-21) at discontinuation to 21.5 (17.3-23) 6 mo later.	TOC is associated with significant reductions in FDG PET activity. However, an increase in FDG PET activity was observed after stopping TOC.	Some concerns

ADR, adverse drug reactions; AE, adverse events; BARI, baricitinib; DMARDs, disease-modifying antirheumatic drugs; FDG, fluorodeoxyglucose; GC, glucocorticoids; GCA, giant cell arteritis; HR, hazard ratio; LEF, leflunomide; MMF, mycophenolate; MTX, methotrexate; OGUS, OMERACT GCA ultrasound score; PET, positron emission tomography; PETVAS, PET Vasculitis Activity Score; RR, risk ratio; TOFA, tofacitinib; TOC, tocilizumab; US, ultrasound; UPA, upadacitinib; UST, ustekinumab.

Table 5
RCTs of patients with PMR

Author year	New onset/ relapsing	Intervention (n)	Comparator (n)	Primary outcome	Results	Key secondary outcomes	Risk of bias
Primary analyses							
Bonelli 2022 [137]	New onset	TOC 162 mg SC weekly for 16 wk (n = 19)	PBO (n = 17)	GC-free remission at wk 16	OR 12.9 (2.2-73.6)	TOC was more effective for GC sparing and prevention of relapses compared with GC alone.	Low
Cutolo 2017 [134]	New onset	MR PRED (n = 32)	IR PRED (n = 30)	Complete response at 4 wk	Clinical response: MR (53.8%) vs IR (40.9%). Treatment difference 12.22 (95%CI 15.82% -40.25%) did not met the criteria for noninferiority (-15%).	Some secondary outcomes favoured use of MR PRED: PMR-VAS, global pain scale, and IL-6 levels.	Low
Devauchelle-Pen-sec 2022 [138]	New onset, relapsing	TOC (n = 49)	PBO (n = 51)	CRP PMR-AS <10 with daily PRED ≤5 mg/d or reduction in PRED dose from baseline ≥10 mg/d at wk 24 (ITT).	TOC had better steroid-sparing effect than PBO. RR 2.3 (1.5-3.6).	Significant reduction in CRP PMR-AS and ESR PMR-AS. Comparable adverse event profile	Low
Ma 2023 [142]	New onset	TOFA (n = 35)	GC (n = 32)	PMR-AS <10 at wk 12 and 24	100% in both groups	Similar clinical outcomes were observed with TOFA or GC at 24 wk.	High
Marsman 2021 [143]	New onset, relapsing	Single-dose RTX 1000 mg (n = 23)	PBO (n = 24)	GC-free remission at wk 21	Absolute risk difference (one sided 95%CI): 27(4)% RR: 2.3 (1.1)	Mean change in PMR-AS: absolute difference -10 (-2.2). GC dose 5 mg/d: absolute difference 46% (20%), RR 1.8 (1.3). Any adverse event (number of events): rate ratio 1.0 (0.8). Infections: rate ratio 2.0 (1.0). Infusion-related events: rate ratio 3.5 (1.3).	Low
Saraux 2023 [146]	New onset	ABA (n = 16)	PBO (n = 18)	Low disease activity (CRP PMR-AS ≤10) at wk 12 without GC and without rescue treatment	RR 2.2 (0.9-5.5)	Similar clinical responses with ABA or PBO, including AS, fatigue, pain, and morning stiffness.	Some concerns
Saraux 2025 [141]	New onset	BARI 4 mg OD until wk 12, and 2 mg OD from wk 12- 24 (n = 18)	PBO (n = 16)	CRP PMR-AS ≤10 without GC at wk 12	BARI was more effective than PBO in newly diagnosed patients with PMR without adverse safety signals (remission 14/18 [78%] in BARI vs 2/15 [13%] in PBO).	Secondary endpoints including ESR PMR-AS, pain VAS, SF-36, and EQ-5D favoured BARI over PBO.	Low
Spiera 2023 [140]	Relapsing	SAR 200 mg SC 2- weekly (n = 59)	PBO (n = 58)	Sustained remission	28% in SAR group; 10% in PBO group. SAR showed significant efficacy in achieving sustained remission.	Cumulative GC dose at 52 wk significantly lower in SAR group. Most common AEs with SAR: neutropenia, arthralgia, diarrhoea	Low
Spiera 2025 [147]	New onset	ABBV-154 40 mg (n = 42) ABBV-154 150 mg (n = 45) ABBV-154 340 mg (n = 44)	PBO (n = 50)	HR for flare	ABBV-154 340mg was better than PBO for reducing relapses in steroid-dependent PMR (HR 0.20 [95% CI 0.09-0.42])	Trial was terminated early by the sponsor.	Some concerns
Viapiana 2015 [135]	New onset	PRED (n = 26)	IVMP (n = 24)	Clinical response at wk 2	Similar clinical and biochemical response at 2 wk with PRED (89%) or IVMP (100%) at 2 wk; mean time to remission slightly less with IVMP vs PRED (15.2 vs 20.3 d).	Similar reductions in ESR and CRP at 2 wk and 3, 6, or 12 mo.	High

(continued on next page)

Table 5 (Continued)

Author year	New onset/ relapsing	Intervention (n)	Comparator (n)	Primary outcome	Results	Key secondary outcomes	Risk of bias
Secondary analyses							
Allard 2024 [145]	New onset	ABA (n = 13)	PBO (n = 17)	Clinical remission at wk 12	Similar responses on clinical assessment between patients treated with ABA and PBO.	Similar changes in PET-CT in all areas in those treated with ABA or PBO.	Some concerns
Bolhuis 2023 [144]	New onset, relapsing	Single-dose RTX 1000 mg (n = 23)	PBO (n = 24)	GC-free remission at 1 y	RR for GC-free remission at 1 year 2.5 (1.0-6.0) for RTX vs PBO.	Median PMR-AS at 1 y 4.2 with TOC and 7.2 with PBO. Lower cumulative GC dose with RTX (1595 mg) than PBO (2302 mg)	Low

ABA, abatacept; ABBV-154, adalimumab conjugated to a glucocorticoid receptor modulator; AE, adverse event; AS, activity score; BARI, baricitinib; EQ-5D, EuroQol 5 Dimension; GC, glucocorticoid; HR, hazard ratio; IR, immediate-release; ITT, intention to treat; IVMP, intravenous methylprednisolone; MR, modified release; PBO, placebo; PRED, prednisolone; RR, relative risk; RTX, rituximab; SAR, sarilumab; SF-36, short-form 36-question questionnaire; SC, subcutaneous; TOC, tocilizumab; TOFA, tofacitinib; VAS, visual analogue scale.

endpoint (CRP PMR-AS ≤10 at week 12, without oral GC use from week 1 to 12) was reached by 14/18 participants (78%) taking baricitinib, and 2 of 15 participants (13%) in the placebo arm (RR 5.8 [95% CI 3.2-10.6], *P* = .0004) [141]. Another open-label study on the use of JAK inhibitors, assessing tofacitinib (EAST PMR), found similar clinical outcomes between tofacitinib or GCs after 24 weeks. However, this study was deemed to have a high RoB, mainly due to concerns around deviations from the intended protocol, as well as the randomisation process and outcome measurement [142].

The BRIDGE-PMR RCT assessed the use of rituximab in both new-onset and refractory or relapsing cases of PMR. The first results from this phase II trial demonstrated rituximab was effective for GC sparing, with better improvements in morning stiffness and PMR-AS, compared with placebo [143]. The extension study subsequently demonstrated that a single dose of rituximab had a significant GC-sparing effect and ability to attain lower disease activity than placebo at 1 year (RR 2.5 [95% CI 1.0-6.0]) [144].

Results from the ALORS study showed similar clinical responses between patients taking abatacept vs placebo (RR 2.2 [95% CI 0.9-5.5]), including changes on PET-CT imaging [145,146].

The novel agent, ABBV-154 (adalimumab conjugated to a GC receptor), was assessed for the treatment of 154 patients with relapsing PMR. ABBV-154 340 mg was better than placebo for reducing relapses in steroid-dependent PMR (HR for flare 0.20 [95% CI 0.09-0.42]). However, the trial was terminated early by the sponsor due to strategic considerations [147].

Observational studies of the treatment of PMR

Of the 16 included observational studies, 10 were retrospective and 6 were prospective, with an overall RoB score ranging from 4 to 8 out of a maximum of 9 (Table 6, Supplementary Table S11).

Six studies (3 prospective, 3 retrospective) assessed the use of GCs in the treatment of new-onset disease [148–153]. All had an uncertain RoB. In a cohort comprising PMR (n = 64) and GCA (n = 10), an early complete response was obtained with prednisolone in two-thirds of patients overall, with improvements in inflammatory markers, global assessment of disease activity (patient and physician), and ultimately, a successful reduction in prednisolone dose[152,153]. However, there was an increase in the proportion of obese patients by week 40. Of note, in a cohort of 34 patients with PMR, one-third were in remission at 1 year, with two-thirds relapsing [149]. A further study reported younger patients with PMR as having greater dependence on GC and DMARDs than elderly-onset PMR [150].

Five studies assessed the use of csDMARDs in new-onset PMR with a control group, summarised in Table 6 [143,154–157]. When assessing the use of methotrexate with GCs, compared with GCs alone, de la Torre et al [154] reported fewer relapses after commencing methotrexate compared with before treatment, whereas Marsman et al [143] reported no reduction in flares. In a retrospective cohort study comparing methotrexate with leflunomide, a greater proportion of patients with PMR attained remission with leflunomide than with methotrexate (although patients on leflunomide had shorter follow-up duration; OR 2.96 [95% CI 1.29-6.78]) [157]. A greater GC-sparing effect was observed with leflunomide compared with methotrexate.

Four observational studies did not have a control group, including 3 assessing the use of tocilizumab [158–161].. All

Table 6
Observational studies of patients with PMR

Author year Prospective/ retrospective	New onset/ relapsing	Intervention (n)	Comparator (n)	Key outcomes	Conclusion	Risk of bias
Albrecht 2018, prospective [148]	New onset, relapsing	GC use in cohort of patients with PMR, GCA or both (n = 1858; PMR = 922)	n/a	Proportion with glucocorticoid use—75.7% (75.8% with PMR, 73.5% with PMR + GCA) PMR (n = 922): GC use 88.8% at cohort entry, 86.3% at 1 y, 79.7% at 2 y, 75% at 3 y. Clinical remission 62.4% at 1 y, 70% at 2 y, 65% at 3 y.	GCs were used in 3/4 of patients with PMR with or without GCA, nearly a fourth of whom were on GCs at 3 y with clinical remission in 55.8%-80%.	Some concerns
Assaraf 2024, retrospective [158]	New onset, relapsing	TOC (n = 53)	n/a	Proportion of patients able to taper GC to ≤ 5 mg/d by 6 mo: 34/45 (75.6%, 95%CI 62.2-88.6)	TOC was effective for GC sparing in patients with PMR (with or without GCA).	Some concerns
Castrejon 2018, retrospective [149]	New onset, relapsing	PRED (n = 34)	n/a	At mean (SD) follow-up of 15.5 (6.4) mo, significant reduction in RAPID3 at most recent visit compared with baseline (SRM = 0.58). Significant reduction in MDHAQ-function, MDHAQ-Pain, MDHAQ patient global estimate, total RADAI, morning stiffness (in minutes), ESR, and PRED dose at most recent visit compared with baseline	Significant responses were observed in patients with PMR when assessed using the RAPID3.	Some concerns
Charpentier 2018, retrospective [150]	New onset, relapsing	PRED Young PMR (age <60 years) (n = 14) Elderly PMR (n = 28)	n/a	Dependence on corticosteroids: 64.3% in young PMR vs 17.9% in elderly PMR. Requiring a DMARD to maintain remission: 35.7% in young PMR vs 10.7% in elderly PMR	Younger patients with PMR have a GC dependence and more requirement for DMARDs than elderly-onset PMR.	Some concerns
de la Torre 2020, prospective [154]	New onset	MTX + GC (n = 41)	GC alone (n = 53)	Before MTX vs after MTX: relapses 81.4% vs 8.16%, GC dose 6 mg vs 2 mg, similar time to relapse and time free of relapse	Fewer relapses were observed after starting MTX, compared with before treatment with MTX.	Low
Devauchelle-Pensec 2016, prospective [159a]	New onset, relapsing	TOC (n = 20)	n/a	Primary outcome—PMR-AS ≤ 10 by 12 wk—20/20 Significant improvements in PMR-AS, CRP, ESR, VAS for pain, fatigue, disease activity by wk 12 and wk 24 compared with baseline Improvements noted in FDG uptake and/or MRI findings in uptake at hip/ shoulders by wk 2 and wk 12.	Monotherapy with TOC is feasible with clinical response in a majority of patients with new-onset PMR.	Some concerns
Do 2018, retrospective [151]	New onset, relapsing	PRED (n = 34)	n/a	Remission rate at 1 year: 35.3% (12/34) Relapses observed in 23/34 (67.6%) patients during initial taper of PRED Multivariate analysis predictor of remission failure: history of relapse (OR 6.81, 95%CI 1.04-44.80)	1/3 PMR were in remission at 1 y. Relapses were frequent, seen in 2/3.	Some concerns
Emamifar 2021, prospective [153b]	New onset, relapsing	GC (PMR: n = 64; PMR + GCA: n = 10)	n/a	Complete response at wk 4: 68.7%; at wk 16: 62.9%; at wk 28: 44.1%; at wk 40: 33.3%	An early complete response was obtained with GCs in 2/3 patients with PMR and/or GCA.	Some concerns
Emamifar 2021, prospective [152b]	New onset, relapsing	GC (PMR: n = 64; PMR + GCA: n = 10)	n/a	Following treatment with GC, patients with PMR and/or GCA had improvements in inflammatory markers, global assessment of disease activity (patient or physician), successful reduction in prednisolone dose, improvement in aortic pulse wave velocity, while there was an increase in the proportion of obese patients by wk 40 of treatment.	GC treatment led to early clinical response albeit with increased prevalence of obesity at wk 40.	Some concerns
Giollo 2019, retrospective [162]	New onset, relapsing	GC + bisphosphonates (n = 240)	GC without bisphosphonates (n = 145)	Use of bisphosphonates with GC associated with reduced risk of persistent treatment with GCA on MVA analyses (adjusted for age, initial prednisone dose, number of flares, peripheral involvement, CRP, haemoglobin and osteoporosis): HR 0.65 (0.49-0.85)	Use of bisphosphonates with GC was associated with reduced risk of persistent treatment with GC in patients with PMR.	Some concerns

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Table 6 (Continued)

Author year Prospective/ retrospective	New onset/ relapsing	Intervention (n)	Comparator (n)	Key outcomes	Conclusion	Risk of bias
Izumi 2021, retro- spective [155]	New onset, relapsing	MTX + GC (n = 32) TOC + GC (n = 15)	GC alone (n = 177)	Median prednisolone dose at the last visit MTX vs TOC:3.5 (1.6-6.0) vs 0 (0-0) Discontinuation of prednisolone at the last visit MTX vs TOC: 6/32 (18.8%) vs 12/15 (80%) Relapses: 2/32 with MTX vs 0/15 with TOC	TOC had better corticosteroid-sparing effect than MTX.	Some concerns
Marsman 2021, ret- rospective [166]	New onset, relapsing	MTX + GC (n = 39)	GC alone (n = 201)	IRR of flares (MTX vs GC alone): 0.80 (95%CI 0.45-1.42) IRR of flares after vs before MTX use: 0.35 (95% CI 0.23-0.52)	No reduction in flares with MTX vs no MTX in patients with PMR, although flares were lesser in the group on MTX after starting MTX when compared with before. Patients on MTX had a higher GC usage.	Low
Palard-Novello 2016, prospec- tive [160]a	New onset, relapsing	TOC (n = 20)	n/a	Median PMR-AS decreased from 38.2 (wk 0) to 15.7 (wk 2) to 3.9 (wk 12). Median CRP decreased from 65.2 mg/L (wk 0) to 0.4 mg/L (wk 2) to 0.2 mg/L (wk 12). In the patient-based analysis, median (IQR) SUVmax decreased from 5.8 (0.8) (wk 0) to 5.2 (1.4) (wk 2) and 4.7 (1.2) (wk 12). Significant reductions in SUVmax at the left hip, right hip, left ischial tuberosity, right ischial tuberosity, and lumbar spi- nous processes	Treatment with TOC as first-line agent was associated with significant but moderate reductions in FDG uptake on PET-CT in patients with active PMR.	Some concerns
Quartuccio 2018, retrospective [161]	New onset, relapsing	MTX + GC (n = 100)	n/a	Remission at 12 mo with prednisone $\leq$ 2.5 mg/d: 59/100 Remission at 12 mo with prednisone $\leq$ 5 mg/d: 73/100 Remission with stoppage of GC at mo 12: 38/100 Remission with stoppage of GC at mo 24: 33/73 Remission with stoppage of GC and MTX at last follow-up: 23/ 100 Number of relapses: 54/100	Use of MTX in PMR was associated with clinical responses in nearly 2/3 patients by 1 y. However, only about 40% of patients were able to come off GC.	Some concerns
Shiraishi 2018, ret- rospective [156]	New onset, relapsing	MTX (n = 10)	Mizoribine (n = 14)	Similar clinical responses, flare rate, and GC-sparing effect were observed with mizoribine or MTX in patients with PMR.	No significantly observed differences between treatment groups.	Low
Vinicki 2024, retro- spective [157]	New onset, relapsing	MTX (n = 143)	LEF (n = 43)	MVA showed LEF was associated with a significantly better odds of remission than methotrexate (2.96, 95% CI 1.29 –6.78).	Greater proportion of patients with PMR attained remis- sion with LEF than MTX (although patients on LEF had shorter follow-up duration). Greater GC-sparing effect observed with LEF than with MTX	Low

AS, activity score; DMARD, disease-modifying antirheumatic drug; GC, glucocorticoid; IRR, incident rate ratio; LEF, leflunomide; MDHAQ, Multidimensional Health Assessment Questionnaire; MTX, methotrexate; MVA, multivariate analysis; PBO, placebo; PRED, prednisolone; RAPID3, Routine Assessment of Patient Index Data 3; SRM, standardised response mean; TOC, tocilizumab; VAS, visual analogue scale.

^aThese studies were analyses from the same cohort.

^bThese studies were analyses from the same cohort.

had an uncertain RoB. Tocilizumab was found to lead to significant improvements in clinical, patient-reported, and imaging responses, as well as GC-sparing [158–160]. The final study, with uncertain RoB, assessed the use of GCs with and without coprescription of bisphosphonates. Use of bisphosphonates with GCs was associated with a reduced risk of persistent treatment with GCs in patients with PMR (HR 0.65 [95% CI 0.49–0.85]) [162].

DISCUSSION

This SLR demonstrates substantial progress in the evidence base for the management of GCA and PMR, especially with the emergence of targeted therapies. Multiple phase II and III RCTs provide robust evidence supporting the efficacy of IL-6 inhibitors in both conditions, alongside promising results for IL-17 inhibition in a phase 2 trial and, more recently, JAK inhibition with upadacitinib. Additional data suggest potential benefits with B cell depletion and T cell costimulation modulation in selected patients. In contrast, the therapeutic landscape for TAK remains limited, with only small, heterogeneous trials and mixed results for conventional immunosuppressive agents and bDMARDs. Collectively, the findings reinforce the central role of IL-6 blockade and emerging role of JAK inhibition in GCA and PMR, while highlighting a pipeline of emerging bDMARDs and tsDMARDs, and the persisting need for high-quality evidence in TAK.

Multiple RCTs were identified for the management of GCA. Secondary analyses of 2 RCTs of tocilizumab, which were included in the previous EULAR recommendations, confirmed the efficacy of tocilizumab to reduce treatment failure and effectiveness irrespective of the phenotype at presentation with cranial symptoms, PMR symptoms or both, or in those with new-onset or relapsing disease [85–87]. Another secondary analysis reported relapses in about half of patients upon withdrawal of tocilizumab [84]. A large phase III RCT supported the use of upadacitinib at a dose of 15 mg once daily in patients with GCA, significant for the ease of oral administration of this drug with a once daily dosing [78]. However, the labels from different regulatory agencies about the risk of cardiovascular events with JAK inhibitors need to be interpreted in the appropriate context [163]. Primary analyses of phase II RCTs provided preliminary evidence for the use of mavrilimumab and secukinumab in GCA, consistent with the role of IL-17, macrophages, and neutrophils in driving the pathogenesis of GCA [79,80,164,165].

New RCT evidence supports the use of tocilizumab in PMR from 2 phase II trials and sarilumab in PMR from a single phase III trial, in line with the role of IL-6 in driving the pathogenesis of PMR [13,137,138]. A phase II RCT reported the potential utility of a single dose of rituximab for PMR [166]. Two phase II RCTs also supported the use of the oral JAK inhibitors baricitinib and tofacitinib. However, the latter had a high RoB, and their utility must be interpreted in the context of warnings about the use of JAK inhibitors in those with cardiovascular risk factors [141,142,163]. A trial of abatacept in PMR demonstrated inefficacy, and another of ABBV-154 in PMR reported promising results, but the development of this drug was discontinued by the sponsor [146,147]. An important consideration, when interpreting trials in PMR, is the increasing recognition of imaging-detected LVV in a subset of patients with otherwise typical PMR. As vascular imaging was not systematically performed across all included RCTs, the extent to which treatment effects may reflect efficacy in overlapping PMR-LVV phenotypes remains uncertain.

Limited evidence was uncovered to support the management of TAK. An open-label extension of a trial of tocilizumab which had met its secondary but not primary endpoints reported significant reductions in GC requirement and quality of life in the longer term, with angiographic stabilisation in two-thirds [25]. A prematurely terminated RCT of ustekinumab failed to demonstrate efficacy [24]. A trial with some concerns about RoB reported similar outcomes with methotrexate or MMF [22]. Another trial at a high RoB due to concerns about the reported outcome showed better efficacy of adalimumab over tocilizumab for primary but not secondary outcomes [23,167]. All of this must be interpreted in the context that neither methotrexate, MMF, adalimumab, nor tocilizumab has been demonstrated to be effective in TAK, compared with placebo [6].

Strengths and limitations

The identified evidence from this SLR had its limitations. The evidence was heterogeneous and of mixed quality therefore did not permit a meta-analysis. No significant RCT evidence was uncovered to guide the use of interventions in LVV or the management of complications in LVV and PMR. Since there are existing or ongoing recommendations/points to consider from EULAR for the management of complications related to metabolic or bone health, a specific search to address this topic was not included in our review. This SLR highlights the lack of high-quality, adequately powered, multicentric RCTs to guide the management of TAK and PMR. There is also a need to evaluate dosing regimens for GCs in LVV and PMR, as their use is guided largely by expert opinion. Recent literature also highlights the fragility of the results of RCTs in LVV—this aspect was not specifically explored in this SLR [168]. The SLR identified gaps in the literature for the management of LVV and PMR, which should form the basis for future research. However, the use of 2 separate search strategies to identify studies on the treatment of both new-onset and also refractory disease, across the LVV spectrum, makes this a highly comprehensive review of the current literature, imperative for informing the updated EULAR guidelines and best practice in the field.

CONCLUSION

In conclusion, this SLR demonstrates considerable advances in the therapeutic landscape for GCA and PMR, with IL-6 inhibition now supported by multiple high-quality trials, as an effective GC-sparing strategy in both new-onset and relapsing disease. In new-onset GCA, IL-6 blockade has shown rapid and sustained disease control, while in refractory or relapsing cases, it has been proven to reduce flare frequency and cumulative GC exposure. For PMR, phase III trials have established IL-6 inhibitors as an effective targeted therapy with consistent benefit, beyond methotrexate, which continues to have a modest role, especially in relapsing disease. New evidence is emerging for a role of JAK inhibition in both GCA and PMR. Evidence for TAK remains poor, based on small heterogeneous trials and inconsistent findings across both csDMARDs and bDMARDs, leaving clinicians with few high-quality data to guide treatment in this population.

Despite these advances, several challenges remain. Many trials have short follow-up durations, leaving uncertainty around sustained remission, relapse risk, and long-term safety, especially in older, comorbid patients. Heterogeneity in trial design and outcome measures limits comparability across studies. Future research must prioritise longer term and comparative

effectiveness trials, as well as studies to determine optimal tapering and switching strategies. A greater focus is needed in TAK, where high-quality trials remain absent. Collectively, these priorities, as well as the findings presented here, will shape the next iteration of the EULAR recommendations, enabling clinicians to offer more effective, safer, and perhaps, in future, more individualised therapies for patients with GCA, PMR, and TAK.

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