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Targeting interleukin-6 pathways in giant cell arteritis management: A narrative review of evidence

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ABSTRACT

Giant cell arteritis (GCA) is a chronic inflammatory vasculitis with a significant impact on vascular and patient health. It may present with non-specific symptoms and can lead to severe complications if not managed effectively. This narrative review explores the treatment of GCA with interleukin-6 (IL-6) pathway inhibitors, focusing on key studies from selected databases published between 2018 and 2024. The findings reveal that the current treatment primarily involves glucocorticoids (GCs), but their long-term use is associated with adverse effects. Targeting the IL-6 pathway offers therapeutic benefits by reducing inflammation and sparing GC use. Tocilizumab, a humanized immunoglobulin G1κ monoclonal antibody that blocks the IL-6 receptor, has demonstrated efficacy in achieving sustained remission and improving quality of life in people with GCA. However, challenges remain in understanding the optimal duration of therapy, managing relapse upon discontinuation, and addressing long-term structural vascular outcomes. Additional research is needed to further elucidate the complex pathogenesis of GCA and to optimize treatment strategies to achieve sustained remission both clinically and histologically while minimizing adverse effects. This review provides a comprehensive overview of the evidence of IL-6 inhibition in GCA management, highlighting both its therapeutic benefits and the challenges associated with its use.

Take-home notes

Targeting the IL-6 pathway with tocilizumab shows promise in managing giant cell arteritis by reducing inflammation and minimizing glucocorticoid use, but further research is needed to optimize treatment duration and address long-term outcomes.

1. Introduction

Giant cell arteritis (GCA) is a chronic inflammatory vasculitis characterized by extensive granulomatous inflammation of the walls of large arteries, leading to vascular damage, stenosis/occlusion or aneurysms, and associated complications [1]. Globally, GCA is estimated to affect approximately 10 in 100,000 individuals per year over the age of 50, with a higher prevalence in Northern European regions and among

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women [2]. GCA presents with combinations of non-specific systemic symptoms, such as fever and weight loss, and more specific manifestations, such as headache with scalp tenderness, polymyalgia rheumatica [PMR]) and cranial ischemic signs (vision disturbances or loss, jaw claudication, stroke). It has been proposed that GCA and PMR may be part of the same disease spectrum—termed GCA–PMR spectrum disease, where some patients with PMR will go on to develop GCA and vice versa [3,4]. GCA often involves large vessels, especially the thoracic aorta and/or supra-aortic arteries. Patients with large vessel vasculitis (LVV) tend to be younger, experience relapse more often, and require the use of GC-sparing drugs [5–11]. LVV is rarely symptomatic at GCA diagnosis but can impact survival [12] because of its long-term complications that encompass aortic aneurysm, and stenosis/occlusion of major arteries, potentially leading to ischemia [13,14].

The treatment goals in GCA are to achieve sustained remission and prevent acute complications and long-term damage [15,16]. Standard treatment involves glucocorticoids (GCs) [15]. However, over the last six decades, the use of GCs in managing GCA has seen variations in dose, frequency, type, and mode of administration [17]. The more recent shift towards a GC-sparing approach to treatment to reduce long-term side effects has been challenging due to the risk of relapse with shorter GC duration [10,18,19]. Factors such as difficulty in distinguishing mild active disease from adrenal insufficiency upon tapering GC to low doses, overdiagnosis of relapse leading to extended GC use, and persistent subclinical vascular inflammation detected through imaging studies in some patients may have contributed to this pattern and warrant further exploration [17].

The aim of this narrative review was to evaluate the treatment of GCA with approved interleukin (IL)-6 pathway inhibitors, particularly tocilizumab, by assessing their therapeutic benefits, safety, and challenges in disease management. Findings, namely relapse reduction, glucocorticoid-sparing effects, impact on health-related quality of life (HRQoL), and side effects, are discussed. We also address challenges in monitoring, as well as knowledge gaps including optimal duration of therapy, and metabolic and cardiovascular outcomes. Before discussing the results of the narrative review, it is essential to first understand the pathogenesis of GCA and the role of IL-6 in the current treatment landscape.

2. Pathogenesis of GCA

The pathogenesis of GCA is a multi-step process, including several critical cascade pathways of initiation and amplification, namely (1) dendritic cell activation and loss of tolerance [20]; (2) T cell activation and mononuclear cell recruitment [4,13]; and (3) vascular injury and remodeling [21]. This process begins with dendritic cell activation [22], resulting in the recruitment of CD4 T cells and their activation and polarization into T-helper (Th)1 and Th17 cells [23]. Interferon-gamma (IFN-γ), which is produced by Th1 cells, activates vascular smooth cells which produce chemokines leading to the recruitment of subsequent Th1 cells and monocytes that differentiate into macrophages [21,24]. Additionally, these signals lead to further recruitment of immune cells that intensify the immune response [21]. In addition, endothelial cells, vascular smooth muscle cells, myofibroblasts and fibroblasts are active players in vascular inflammation through their ability to support the recruitment and polarization of T cells and to produce pro inflammatory cytokines such as IL-6 [20,24–28]. This vascular inflammation ultimately leads to vascular injury and remodeling, which are characteristic features of GCA [22].

2.1. Dendritic cell activation

The activation of dendritic cells, which are key antigen-presenting cells [22], is driven by Toll-like receptors (TLRs) [1] that are receptors recognizing pathogen-associated molecular patterns as danger signals [23]. Activated dendritic cells then produce chemokines leading to the recruitment of T cells and their subsequent activation [22].

2.2. T-cell activation and mononuclear cell recruitment

The activation of dendritic cells initiates the production of chemokines (chemokine ligand (CCL)19, CCL20, and CCL21) leading to CD4 T-cell recruitment [22]. Then, dendritic cells activate T cells that differentiate into Th1 and Th17 cells, as illustrated in Fig. 1 [20]. Th1 differentiation is driven by IL-12 and reinforced by IFN-γ [29,30], while Th17 development is driven by IL-1β, IL-6, IL-21, and IL-23 [31]. Th17 cells produce IL-17, a pro-inflammatory cytokine [22]. In GCA, peripheral blood Th17 cell numbers increase whereas the number of regulatory T (Treg) cells, which are a subset of T cells regulating the immune response, decrease, causing immune dysregulation. IL-17 expression is positively correlated with GCA activity and response to GC [30,32]. Along this line, previous studies have demonstrated that Treg number and function were altered in patients with GCA under the influence of IL-6, and that GCA-Treg had an increased ability to produce IL-17 thus suggesting a pro-inflammatory rather than an immunosuppressive effect of GCA-Treg [30,33–35]. IFN-γ, which is produced by Th1 cells, activates vascular smooth muscle cells to produce chemokines attracting more T cells and monocytes, and activates macrophages, leading to the formation of multinucleated giant cells, which are the distinctive histological feature of GCA, and contributes to the tissue damage associated with GCA [22].

2.3. Vascular injury and remodeling

In GCA, vascular injury and remodeling are key outcomes of the chronic inflammatory process. As the persistent intramural inflammatory response intensifies, driven by activated T cells and macrophages, ongoing cytokine release leads to significant damage to the arterial wall [22].

Under the influence of mediators produced by mononuclear cells, such as endothelin-1 or platelet-derived growth factor (PDGF) [36–38], smooth muscle cells become activated, change their phenotype and become myofibroblasts that migrate into the neointima, where they proliferate and produce extracellular matrix proteins such as collagen and fibronectin, leading to stenosis or even occlusion of the affected vessels. In addition to their role in vascular remodeling, myofibroblasts are also active players in vascular inflammation through their ability to produce pro-inflammatory cytokines, thereby promoting T-cell polarization towards the Th1 and Th17 pathways [21,22,26]. Recent data also show that fibroblasts are activated in GCA, express senescence markers and produce IL-6. These cells are also capable of differentiating into myofibroblasts, as are smooth muscle cells [25,27,28]. This remodeling process results in endothelial narrowing of the arterial lumen, reduced blood flow, and potentially severe clinical manifestations, such as ischemia [1,22], and in some instances, aneurysm formation [39].

3. IL-6 in the current treatment landscape

IL-6 is a cytokine present in both the dendritic cell activation and mononuclear cell recruitment pathways and, in GCA, is associated with the systemic inflammatory process characteristic of the disease [40]. Increased levels of IL-6 have been observed in serum, tissue, and peripheral blood mononuclear cells [40–43]. Monocytes are thought to be the main source of IL-6, but data have shown that activated stromal cells such as myofibroblasts and senescent fibroblasts are important contributors to the production of IL-6 [27,44–47]. It should also be noted that B cells contribute to IL-6 production in blood and tissue [48]. According to its known biologic functions, IL-6 may participate in many steps of the pathogenic cascade. However, mechanistic pre-clinical studies confirming these functions are virtually inexistent.

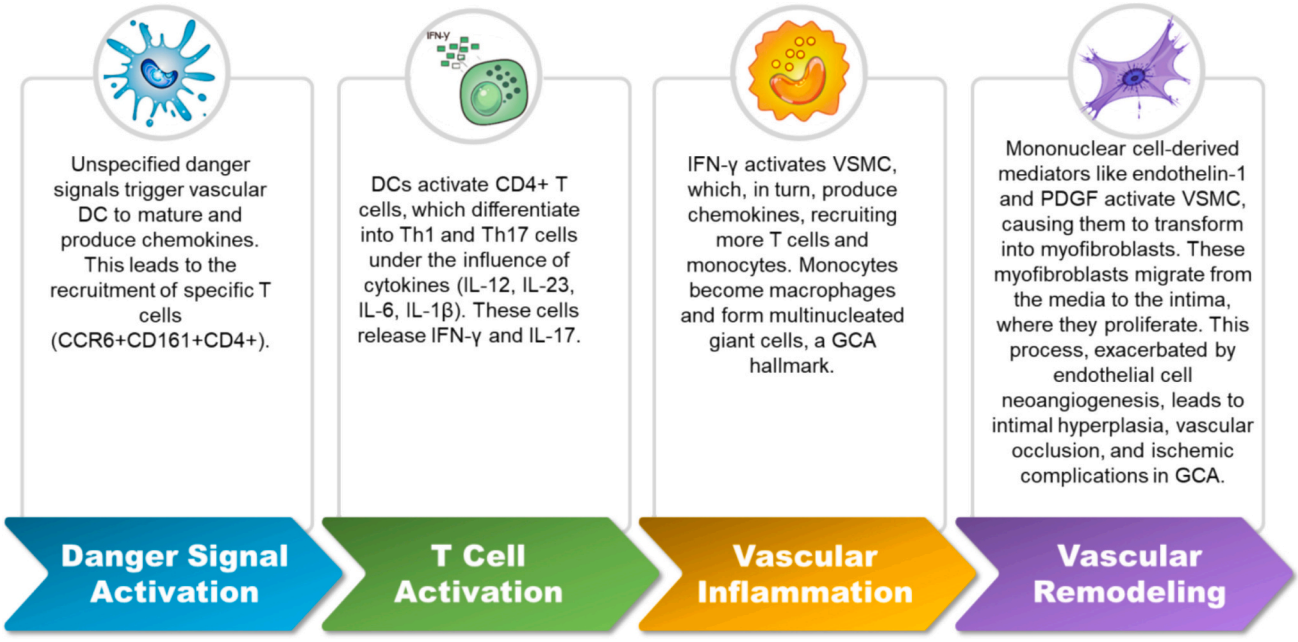

Fig. 1. The pathogenesis cascade of GCA. This schematic outlines the vascular inflammation and remodeling process, from danger signal activation to vascular complications in the pathogenesis of GCA. Unspecified signals prompt DC maturation and chemokine release, recruiting T cells (CCR6 + CD161 + CD4+). Activated CD4+ T cells differentiate into Th1 and Th17 cells, releasing IFN-y and IL-17. IFN-γ activates VSMC, leading to more T-cell and monocyte recruitment. Monocytes differentiate into macrophages, forming multinucleated giant cells. Mononuclear cell-derived mediators further activate VSMC, causing tissue damage, intimal hyperplasia, and vascular occlusion. Note, that the functional role of IL-6 in GCA lesions has not been investigated, only the expression and modulation by other factors have been illustrated. CCR: chemokine receptor; CD: clusters of differentiation; DC: dendritic cells; GCA: giant cell arteritis; IL: interleukin; IFN-γ: interferon-gamma; Th: T helper cells; PDGF: platelet-derived growth factor; VSMC: vascular smooth muscle cells.

3.1. IL-6 signaling pathways and mechanisms

While IL-6 receptor (IL-6R) blockade has shown the ability to delay disease progression in GCA [49], almost no functional studies have delineated the exact role that IL-6 plays in the pathogenesis of GCA. What is known is that consequences of the activation of IL-6 signaling pathways exist in GCA [50]. The IL-6 signaling pathway leads to the activation of immune cells, which may contribute to vascular inflammation, and the production of acute-phase proteins, which are typically elevated in serum from patients with GCA [50]. The Classical pathway elicits the synthesis of acute-phase proteins, and the Trans signaling pathway expands the spectrum of responsive cell types to include all cells expressing the gp130 receptor [21] (Fig. 2).

3.2. IL-6 and Th17/Treg imbalance

Along with other ILs, IL-6 also controls the Th17/Treg imbalance observed in active GCA [48]. IL-6 works in two ways to influence Treg homeostasis. First, it plays a major role in altering immune tolerance by increasing polarization towards Th17 cells at the expense of Treg [35]. Second, IL-6 alters the suppressive function of Treg [33–35]. The Th17/Treg imbalance amplifies the inflammatory process in GCA, leading to vascular damage, arterial wall remodeling, and complications associated with the disease [33]. Interestingly, tocilizumab, a humanized IgG1κ monoclonal antibody (mAb) blocking the IL-6R, has the ability to restore Treg quantities in the blood of patients with GCA and also increase Treg function by restoring expression of exon 2 of FoxP3 (Treg cell master regulator) and calcium influx in Treg cells [33,34]. Current treatments target the Th17 and inflammatory components of GCA, but do not address changes in the Th1-IFN-γ pathway and subsequent vascular lesions, leaving uncertainty regarding the utility of current therapeutic agents in preventing structural vascular disease, including aortic involvement [4]. GC therapy, the standard treatment for GCA, normalizes Th17 cell counts, and clinical trials with IL-17 inhibitors (e.g., secukinumab) have shown promising results in achieving remission and delaying relapse [32]. Recent studies have highlighted different effects of GCs on Treg cells. Some authors found that under their experimental conditions, GCs do not normalize Treg number and function in GCA [34,35]. In contrast, others suggest that GCs can influence the number of Treg cells produced when using minimal kinetic network models [51] and even induce microRNA (miR-342-3p) expression in Treg cells using murine autoimmune and allergic inflammation models [52]. This discrepancy may indicate that more research is needed to clarify the effects of GCs in GCA.

3.3. Clinical impact of IL-6 pathway inhibition

In diseases such as GCA, IL-6 is thought to play a crucial role, amplifying inflammatory cascades that drive vascular inflammation [20,22]. Through its interactions with other immune mediators, IL-6 shapes the inflammatory milieu, leukocyte recruitment, and cytokine production [53]. Clinical trials have also shown that drugs that inhibit the IL-6 pathway are safe and effective and offer the advantage of decreased GC use [6,54–57].

Tocilizumab received European Medicines Agency and Food and Drug Administration approval for the treatment of adults with GCA in 2017 [58,59], based on two pivotal (phase 2 and phase 3) trials [49,60]. Numerous ancillary studies further analyzed data from phase 2 and the GiACTA trial (Giant Cell Arteritis Actemra), a landmark clinical trial assessing tocilizumab safety and efficacy in GCA [60]. The GiACTA trial, which completed data collection in 2018 [61], primarily aimed to determine whether tocilizumab could sustain GC-free remission to one year in patients with GCA undergoing a 26-week prednisone taper [60]. This trial demonstrated significant efficacy.

Nevertheless, clinical trials may not comprehensively represent the real-world situation and included patients are often highly selected. A comparative analysis of data from the GiACTA trial ($N = 251$) and a multicenter patient cohort with GCA from clinical practice ($N = 134$)

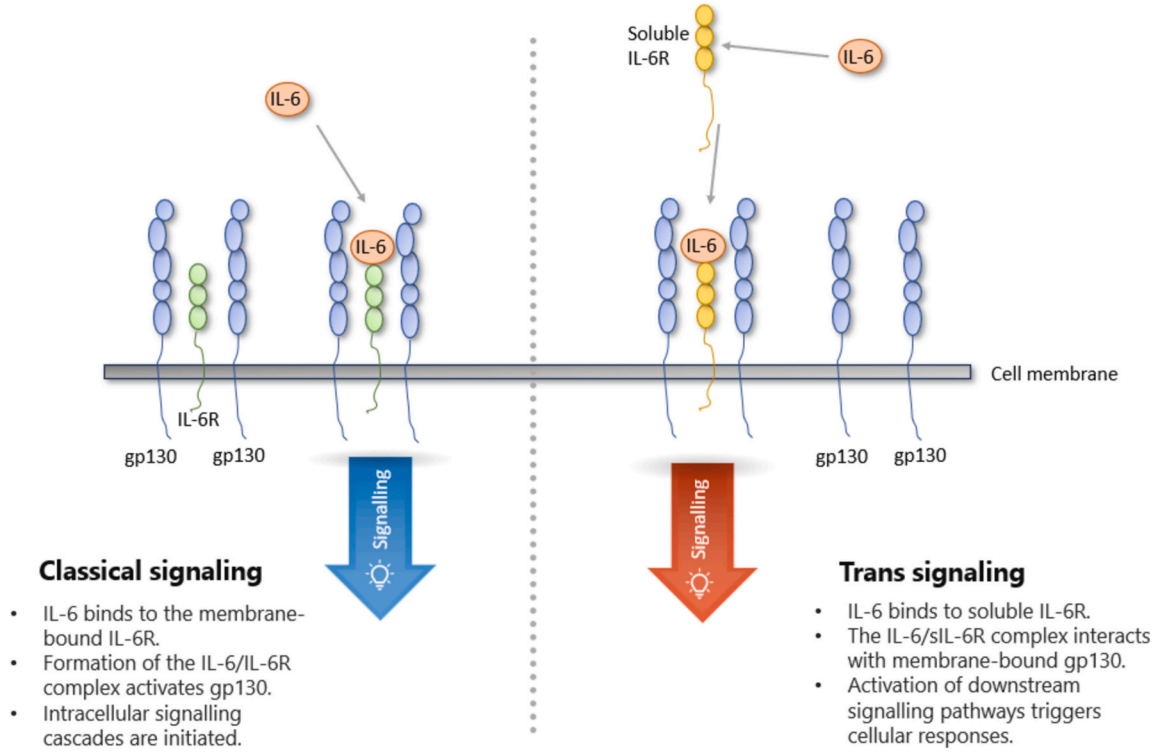

Fig. 2. A comparison of the classical and trans signaling pathways for IL-6 displays the distinct mechanisms and cellular responses mediated by IL-6 and its receptor (IL-6R). In the Classical signaling pathway, IL-6 binds to *membrane-bound* IL-6R, leading to the activation of gp130 proteins and subsequent initiation of intracellular signaling cascades. Classical signaling is limited to monocytes, macrophages, hepatocytes, some T and B cells, megakaryocytes, and endothelial cells. Importantly, hepatocytes, when stimulated by IL-6, are responsible for the production of acute phase reaction proteins such as CRP, fibrinogen, and haptoglobin, which are commonly elevated in patients with active GCA. Conversely, in the Trans signaling pathway, IL-6 associates with *soluble* IL-6R (increased in inflammatory disease), forming a complex that interacts with membrane-bound gp130, thereby triggering downstream signaling pathways and eliciting cellular responses. Trans signaling has larger effects since the expression of gp130 is almost ubiquitous. These pathways are vital for cellular communication and immune modulation. CRP: C-reactive protein; GCA: giant cell arteritis; gp130: glycoprotein 130; IL-6: interleukin 6; IL-6R: IL-6 receptor.

aimed to consider the generalizability of clinical trial results [62]. In the real world, patients receiving tocilizumab were older with extended disease duration and had a higher erythrocyte sedimentation rate (ESR) [62]. Despite this, differences in clinical phenotypes and patient characteristics have not been found to affect the efficacy of tocilizumab in treating GCA [63]. For example, in an ad-hoc analysis of the GiACTA trial, patients with PMR, cranial symptoms, or both, who were treated with tocilizumab consistently showed higher sustained remission rates compared to those who received placebo across all groups (PMR only: 45.2 % vs. 19.0 %, $p = 0.0446$; cranial only: 60.3 % vs. 19.4 %, $p = 0.0001$; PMR and cranial: 55.0 % vs. 11.4 %, $p < 0.0001$) [63]. Additionally, fewer tocilizumab-treated patients experienced disease flares in all groups, further emphasizing the broad efficacy across diverse clinical phenotypes [63].

4. Methods for identifying studies on the treatment of GCA with IL-6 pathway inhibitors

In addition to the aforementioned two pivotal trials, this narrative review included information identified from structured literature searches targeting specific databases and conducted following PRISMA guidelines (Supplemental Fig. S1) to identify studies on the treatment of GCA with IL-6 pathway inhibitors. This methodology provided a flexible, expert-driven approach to reviewing the literature, allowing for focused exploration of specific issues or theories, rapid synthesis of current knowledge, and greater interpretative depth. Unlike a systematic review, it did not aim to systematically capture all available literature but instead selectively included studies deemed most pertinent to the topic. The search was performed across four databases (PubMed/MEDLINE, Cochrane Library, Semantic Scholar, World Cat) and two registries (Cochrane, ClinicalTrials.gov) on October 17, 2023, with an update on August 12, 2024, to include all new articles published since October 17, 2023. Studies were selected using the PICO framework, focusing on patients with GCA treated with IL-6 pathway inhibitors or tocilizumab, compared to other treatments, with all clinical outcomes included. Eligible studies were published between 2018 and 2024 and involved primary research in humans (randomized controlled trials and cross-sectional, prospective, and observational studies). Review articles, grey literature, early-phase studies, in vitro research, irrelevant conditions, and duplicates were excluded (Supplemental Table S1). Search terms included “giant cell arteritis,” “interleukin-6,” and “tocilizumab.” Data extraction included study design, population characteristics, interventions, comparators, and outcomes, with results synthesized into a narrative summary. Tables were used to detail the search strategy and study characteristics (Supplemental Table S2), and no meta-analysis was performed due to the heterogeneity of the studies.

5. Treatment of GCA with IL-6 pathway inhibitors

A total of 25 research articles identified from across both searches were retrieved for descriptive narrative synthesis. Over half of these included studies investigated tocilizumab’s efficacy and/or safety in GCA (both mono- and combination therapy) [6,54,57,63–72]. Four studies explored diagnostic tools or biomarkers of disease activity/response to assess disease progression, including serial IL-6 levels, mass spectrometry, ultrasound, and positron emission tomography/computer tomography (PET/CT) scans [73–76]. Four studies focused on disease activity, including relapse, remission, and resolution of inflammation

[55,56,77,78]. However, there was limited research on patient profiles that benefit the most from IL-6 pathway inhibition [62] and the effects of treatment on HRQoL [79]. The data from these studies are summarized in Table 1.

5.1. Benefits and challenges of IL-6 pathway inhibition

5.1.1. Remission and relapse

In the GiACTA trial, sustained remission at Week 52 was observed in 56 % of patients on weekly tocilizumab and 53 % on tocilizumab every other week, compared to in 14 % and 18 % of the placebo groups undergoing 26-week and 52-week prednisone tapers, respectively [60]. In the GiACTA 2-year extension, tocilizumab-treated patients demonstrated sustained GC-free remission [54]. Specifically, 42 % (25 out of 59) of patients initially treated with weekly tocilizumab who were in remission and receiving no treatment at week 52 (entry to the extension trial) maintained remission throughout the extension period [54]. Additionally, remission was maintained during the extension study in 47 % (38 out of 81) of patients initially randomized to receive tocilizumab weekly who were in clinical remission at Week 52 irrespective of whether tocilizumab/GC therapy was ongoing. For those who were initially randomized to receive tocilizumab every other week, 36 % (13 out of 36) maintained remission with or without ongoing tocilizumab/GC therapy [54]. Although flares occurred upon discontinuation of tocilizumab in some patients, retreatment effectively restored remission [54].

Despite the effectiveness of tocilizumab in treating GCA, 20 % of patients will likely experience relapse during therapy [80], and after discontinuation, studies have shown that 30–61 % of patients experience relapse within 12 months [78,81–83], particularly those with large vessel involvement [6,84]. An ongoing clinical trial is investigating the initiation of MTX at the time of tocilizumab discontinuation to sustain remission in patients with GCA [85]. Additionally, "predictive factors" for long-lasting periods of remission are proposed to include experiencing fewer relapses and having been prescribed a smaller total amount of prednisone over time [86]. Others have also suggested that long-term treatment with tocilizumab is required for sustained remission [83]. However, to date, no real-world studies have set the standard duration of tocilizumab therapy [83] or calculated the cost associated with tocilizumab compared to other treatment options.

Of interest, a study presented at the 2023 ACR conference showed that the Asp358Ala polymorphism, which facilitates the proteolytic production of the soluble IL-6R, known to be associated with an increase in the trans signaling of IL-6 [87], was detected in some patients with GCA and associated with LVV involvement and a lower response to tocilizumab [88]. This suggests that the Asp358Ala polymorphism could influence disease characteristics and treatment responses, which then presents opportunities to develop therapies tailored to mitigate its effects.

5.1.2. GC sparing

Currently, many patients will sustain remission on GCs alone (25–66 %), and according to EULAR recommendations, can gradually reduce their GC dose to ≤5 mg/day within 1 year [16]. The remaining 34–75 % of patients do not achieve sustained remission with GC therapy alone and will relapse, including those who experience GC side effects. For those patients who require a GC-sparing strategy due to adverse effects or prolonged treatment duration, EULAR and ACR guidelines recommend tocilizumab as a first-line therapy to control inflammation and induce and maintain remission [15,16]. Additionally, for patients with newly diagnosed GCA or those experiencing relapse with cranial ischemia symptoms, the ACR guidelines conditionally recommend using oral GCs with tocilizumab over oral GCs alone or with MTX [15].

Up to 90 % of patients treated with GC experience adverse events, advancing the need for GC-sparing strategies in clinical practice [19]. In a population-based study of 87,794 patients with immune-mediated

Table 1
Studies included in the review.

Year	Primary author	Study type	Sample size	Main results
Efficacy Outcome				
2024	Harigai M [72]	Multicenter, prospective, phase 4, large-scale, observational	117	Tocilizumab was found to be effective and well-tolerated, with 85.0 % of patients being relapse-free, 94.2 % of relapse-free patients on a glucocorticoid dose of less than 10 mg/day, and common adverse events including neutropenia, leukopenia, and serious infections
2023	Calderón-Goercke M [64]	Retrospective observational multicenter	471	Tocilizumab optimization using dose reduction or increased dose intervals is possible after remission is achieved. After the monitoring period, patients with extended periods of remission (78.2 % vs. 84.2 %; $p = 0.29$) and occurrences of relapses (5.6 % vs. 10.4 %, $p = 0.177$) showed no significant difference between optimized tocilizumab and non-optimized tocilizumab treatments. The non-optimized group exhibited a higher frequency of severe infections (12.9 % vs. 6.6 %; $p = 0.009$)
2023	Patel NJ [65]	Post-hoc analysis GiACTA trial	209	Tocilizumab/GC treatment resulted in a substantial decrease in HbA1c levels compared to GC-only treatment (decrease of 0.5 % [$p < 0.01$] vs. 0.1 % [$p < 0.01$], independent of GC exposure)
2022	Stone JH [66]	RCT (Part 1)	250	Tocilizumab delayed the time to flare. In patients with new-onset and relapsing disease, the median duration until initial flare was 577 and 575 days, respectively, with tocilizumab once a week vs. 179 and 224 days with placebo
2022	Stone JH [66]	Open label extension (Part 2)	250	Tocilizumab reduced the cumulative GC dose in patients with new-onset and relapsing GCA. In patients with new-onset and relapsing disease, the median cumulative glucocorticoid dose was 3068 mg and 2191 mg, respectively, with tocilizumab once a week vs. 4639 mg and 6178 mg with placebo, respectively
2021	Calderón-Goercke M [57]	Retrospective observational multicenter	134	Tocilizumab in monotherapy or combined with conventional immunosuppressive

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Table 1 (*continued*)

Year	Primary author	Study type	Sample size	Main results
				agents is safe in patients with GCA. Prevalence of LVV: tocilizumab combination (57 %) vs. tocilizumab monotherapy (34.1 %; $p = 0.007$). Tocilizumab was withdrawn due to prolonged remission in 14.6 % of patients receiving monotherapy after a median of 13 months and in 19.2 % of patients receiving combination therapy after a median of 12 months. The GC sparing effect was similar between both groups
2021	Clément J [56]	Retrospective observational multicenter	43	Tocilizumab is effective for GC sparing. The mean cumulative dose of GC was 2.1 g/year vs. 9.4 g/year before study inclusion ($p < 0.001$), with 28 % patients experiencing relapses on tocilizumab. Remission was sustained in <50 % of patients after tocilizumab discontinuation
2021	Prieto Peña D [74]	Prospective observational	30	83 % of patients on tocilizumab achieved clinical remission, accompanied by a reduction in 18F-fluoro-deoxyglucose vascular update, with an average duration of 10.8 ± 3.7 months. 30 % of patients showed complete remission as reflected in a normal target to background ratio
2021	Schönau V [77]	Retrospective analysis	88	Tocilizumab showed a notable GC-sparing effect. The average cumulative dosage of prednisolone was 5637 mg for prednisone only users, 4418 mg for methotrexate only users, and 2984 mg for tocilizumab only users ($p = 0.002$)
2021	Spiera R [63]	Post-hoc analysis GiACTA trial	250	In patients with polymyalgia rheumatica or cranial symptoms, tocilizumab improved clinical outcomes. By Week 52, tocilizumab treatment resulted in significantly higher rates of sustained remission compared to placebo across all three groups: PMR only (45.2 % vs. 19.0 %, $p = 0.0446$), cranial only (60.3 % vs. 19.4 %, $p = 0.0001$), and PMR and cranial (55.0 % vs. 11.4 %, $p < 0.0001$). Fewer tocilizumab-treated patients experienced ≥1 disease flare compared to placebo recipients across all groups: PMR only (41.9 % vs. 57.1 %), cranial only (20.7 % vs. 47.2 %), and PMR and cranial (31.7 % vs. 81.8 %). The risk of flare after clinical remission was similar between those receiving tocilizumab and those receiving PBO in patients with PMR symptoms only (HR, 0.77; 95 % CI, 0.33–1.78; $p = 0.5389$); 63 % reduced by tocilizumab compared to PBO in patients with cranial symptoms only (HR, 0.37; 95 % CI, 0.17–0.79; $p = 0.0108$); and 82 % reduced by tocilizumab compared to PBO in patients with both symptoms (HR, 0.18; 95 % CI, 0.10–0.34; $p < 0.0001$)
2021	Unizony SH [67]	Post-hoc analysis GiACTA trial	250	Tocilizumab combined with prednisone significantly lowered the risk of treatment failure vs. placebo or prednisone-only groups (OR, 0.2; 95 % CI, 0.1–0.3; $p < 0.0001$).
2020	Banerjee S [69]	Observational prospective	52	Treatment status was measured between visits and categorized as increased, decreased, or unchanged. Treatment change was defined as a change in daily prednisone dose by ≥5 mg, or an additional 50 % dose change of a DMARD or biologic. Increasing tocilizumab treatment notably decreased disease activity as observed through imaging, clinical, and inflammatory markers ($p \leq 0.01$ for each). When treatment remained unchanged, all three evaluations of disease activity showed no significant alterations over 6-month periods. When treatment was reduced, PET activity notably deteriorated ($p = 0.02$), while clinical and serologic activity did not exhibit significant changes
2019	Calderón-Goercke M [70]	Observational, open-label multicenter	134	Tocilizumab improves refractory GCA in clinical practice. Following one month of tocilizumab treatment, 93.9 % of patients experienced clinical improvement. There was a significant reduction in CRP levels from median [inter-quartile range] 1.7

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Table 1 (*continued*)

Year	Primary author	Study type	Sample size	Main results
				[0.4–3.2] to 0.11 [0.05–0.5] mg/dL ($p < 0.0001$), a decrease in ESR from 33 [14.5–61] to 6 [2–12] mm/1st hour ($p < 0.0001$), and a decline in the prevalence of anemia from 16.4 % to 3.8 % ($p < 0.0001$). Clinical improvement leading to remission was observed in 55.5 %, 70.4 %, 69.2 %, and 90 % of patients at 6, 12, 18, and 24 months, respectively.
2019	Adler S [78]	Prospective observational	17	Tocilizumab induced a lasting remission that persisted in half of the patients after stopping 52-weeks' treatment. Eight patients experienced relapses after an average duration of 6.3 months (ranging from 2 to 14 months), with six relapsing within the initial 5 months and two relapsing at months 13 and 14, respectively. Relapsing individuals were younger and exhibited increased indications of mural enhancement in MRA compared to those who did not experience relapses
2019	Stone JH [71]	RCT	250	Tocilizumab combined with prednisone improved GCA control. Among the 149 patients treated with tocilizumab, 24 % experienced flares, of whom 64 % were still using prednisone, typically at a median dosage of 2.0 mg/day. Among the 101 patients treated with placebo and prednisone, 58 % experienced flares, with 76 % still on prednisone, typically at a median dosage of 5.0 mg/day. A substantial number of flares occurred in patients taking prednisone >10 mg/day, accounting for 25 % in the tocilizumab groups and 22 % in the placebo groups. Most flares in the tocilizumab-treated groups (92 %) and a third of those in the placebo + prednisone-treated groups (34 %) occurred despite normal CRP levels
2019	Strand V [79]	Post-hoc analysis GiACTA trial	251	Those treated with tocilizumab every week and prednisone taper for 26 weeks showed a significant and clinically meaningful improvement in SF-36 and FACIT-Fatigue scores compared with those who received prednisone alone
2019	Nannini C [55]	Prospective open-label trial	15	Patients treated with tocilizumab had sustained clinical remission for 6 months after treatment discontinuation. All 15 patients achieved and maintained the remission. In 10 (66.7 %) who were in remission, remission persisted at month 18. Five patients relapsed 2–4 months after treatment discontinuation.
2018	Samson M [6]	Prospective open-label	20	Short-term tocilizumab therapy can be an effective GC sparing strategy in GCA. All patients achieved remission initially. By Week 26, 15 patients (75 %) reached the primary endpoint (percentage of patients in remission with prednisone ≤0.1 mg/kg/day at Week 26). Ten patients experienced relapses during the follow-up period, particularly those with aortitis ($p = 0.048$), CRP levels exceeding 70 mg/L ($p = 0.036$), or hemoglobin levels ≤10 g/dL ($p = 0.015$) at diagnosis. Among the 18 patients who reported a total of 64 adverse events, three events were severe
2017	Stone JH [60]	RCT	251	At Week 52, continuous remission was observed in 56 % of patients receiving weekly tocilizumab with a 26-week prednisone taper and in 53 % of those receiving tocilizumab every other week with a 26-week prednisone taper vs. 14 % and 18 % respectively, in placebo groups with either a 26-week or 52-week prednisone taper, respectively ($p < 0.001$ for both active treatments vs. both placebo regimens). Cumulative median prednisone doses over the 52-week period were 1862 mg in each tocilizumab group (weekly and every other week administration), compared with 3296 mg in the placebo group with 26-week prednisone taper ($p < 0.001$ for both active treatments vs. placebo) and 3818 mg in the placebo group with 52-

(*continued on next page*)

Table 1 (*continued*)

Year	Primary author	Study type	Sample size	Main results
				week prednisone taper ($p < 0.001$ for both active treatments vs. placebo)
2016	Villiger P [49]	Phase 2 RCT	30	Tocilizumab induced and sustained remission in GCA. By Week 12, complete remission was achieved in 17 (85 %) of 20 patients treated with tocilizumab vs. 4 (40 %) of 10 patients given placebo (risk difference 45 %, 95 % CI 11–79; $p = 0.0301$). Relapse-free survival by Week 52 was observed in 17 (85 %) patients in the tocilizumab group vs. 2 (20 %) in the placebo group (risk difference 65 %, 95 % CI 36–94; $p = 0.0010$). The mean difference in time to discontinue GCs favored tocilizumab by 12 weeks (95 % CI 7–17; $p < 0.0001$), resulting in a cumulative prednisolone dose of 43 mg/kg in the tocilizumab group vs. 110 mg/kg in the placebo group after 52 weeks ($p = 0.0005$)
Safety Outcome				
2021	Amsler J [68]	Retrospective observational mono-centric	186	Tocilizumab therapy was associated with a low incidence of vision loss. Visual symptoms were present in 70 (38 %) and vision loss in 21 (11 %) patients treated with tocilizumab. Patients who experienced vision loss were older ($p = 0.032$), had lower levels of CRP ($p = 0.002$), and exhibited a negative correlation with magnetic resonance angiography findings of the aorta ($p = 0.006$)
Other Outcomes				
2019	Berger CT [75]	Prospective observational longitudinal	23	Throughout tocilizumab treatment, CRP, ESR, and white blood cell counts declined and remained suppressed. IL-6 levels increased in those with infections and in some patients who had relapsed. 78 % of patients had a clinically plausible cause for the IL-6 increase
2020	Calderón-Goercke M [62]	Comparative analysis	385	Comparative study of GiACTA trial and real-world tocilizumab-treated patients with GCA. Real-world patients receiving tocilizumab were older, had longer disease duration, higher ESR values, and received more MTX previously. Serious infections were higher in real-world patients. However, tocilizumab was equally effective in both groups
2020	Unizony SH [76]	Post-hoc analysis GiACTA trial	42	Monitoring disease activity in patients with GCA undergoing IL-6 blockade therapy could benefit from utilizing the easily accessible haptoglobin laboratory test. In comparison to tocilizumab-treated patients with inactive disease, those with active disease exhibited notable elevation in various biomarkers such as haptoglobin, haptoglobin precursor, SSA2, and complement factor 4 A, along with reduced levels of peptidase inhibitor 16
2021	Seitz L [73]	Prospective observational	18	A slow and steady decline in intima-media thickness of the temporal arteries was seen with tocilizumab monotherapy

CI: confidence interval, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, GC: glucocorticoids, GCA: giant cell arteritis, HbA1c: glycated hemoglobin, HR: hazard ratio, HRQoL: health-related quality of life, LVV: large vessel vasculitis, MRA: magnetic resonance angiography, MTX: methotrexate, OR: odds ratio, PMR: polymyalgia rheumatica, RCT: randomized controlled trial.

inflammatory diseases, including 25,581 patients with GCA and/or PMR and no history of cardiovascular disease (CVD), even low daily doses of GC (<5 mg prednisone-equivalent) resulted in an increased dose-dependent risk of all-cause CVD and type-specific CVD risk (atrial fibrillation, heart failure, acute myocardial infarction, peripheral artery disease, stroke, and abdominal aortic aneurysm) [89]. This study reported CVD incident rates of 15.3 % over a median of 5 years follow-up [89]. Compared to periods of non-GC use, the use of GC <5.0 mg daily increased all-cause CVD risk (hazard ratio = 1.74; 95 % confidence interval 1.64–1.84) [89]. GC doses ≥25 mg resulted in a 5-year cumulative risk of 28 % [89]. Similarly, osteoporosis [90] and asthma [91] research have also reported that low cumulative exposure (≤500 mg prednisolone-equivalent) to low-dose oral GCs was associated with an increased risk of bone fractures, comorbidities, mortality, and an increase in unscheduled hospitalizations [90,91].

There is a growing body of evidence supporting the reduction in the use of GCs while concurrently reducing disease relapse rates and achieving sustained remission through the inclusion of tocilizumab in the treatment regimen [22,60,63,67,68,77,79]. In addition to allowing tapering of GC doses in patients already receiving GC regimens [6,49,55,60,71], the adjunct use of tocilizumab alongside GCs in the initial 3 months of therapy has also shown positive results in achieving remission and serving as an effective GC-sparing strategy [6,66,92,93]. Similarly, a recent open study reported excellent outcomes with a combination of short course GC (8 weeks) and subcutaneous tocilizumab 162 mg/week for 52 weeks in 30 patients with active GCA [92]. At 52 weeks, 77 % of patients were in prednisone-free sustained remission [92].

However, studies such as GUSTO indicated that a very brief pulse GC therapy (3 days) alongside ongoing tocilizumab treatment might not

effectively control the disease in some patients [93]. In this study, 3 out of 18 patients showed no response to the treatment, 2 discontinued the study because of adverse events (hepatopathy and diverticulitis), and 1 patient developed anterior ischemic optic neuropathy [93]. In contrast, a recent large-scale phase 4 study—tocilizumab combined with continued GC use—demonstrated both effectiveness and good tolerability in Japanese patients with GCA, with 94.2 % of relapse-free patients receiving a concomitant GC dose of <10 mg/day [72]. These findings emphasize the ongoing importance of GC usage and implicate pathways beyond IL-6 in GCA pathogenesis [93].

Two other studies are relevant to the discussion here. First, the TOPAZIO study, a prospective observational study of 18 patients with active large vessel GCA, in which tocilizumab monotherapy was administered after a three-day course of high-dose intravenous methylprednisolone [94]. Notably, this regimen led to significant reductions in the PET vascular activity score (PETVAS) at weeks 24 and 52, with mean reductions of −8.6 (95 % CI −11.5 to −5.7, $P = 0.001$) and − 10.4 (95 % CI −13.6 to −7.2, $P = 0.002$), respectively. Additionally, 56 % of patients achieved relapse-free remission at week 24, decreasing slightly to 47 % at week 52 [94]. In the second proof of concept study, 30 patients received 12 months of tocilizumab in combination with an 8-week prednisone taper [92]. Remarkably, 77 % of participants attained sustained prednisone-free remission by week 52, with an average time to relapse of 15.8 weeks for the seven patients who experienced a relapse. Serious adverse events were reported in 13 % of participants, and no permanent vision loss occurred [92]. These findings collectively suggest that tocilizumab effectively reduces GC exposure while maintaining remission in patients with GCA.

5.1.3. Metabolic effects

Tocilizumab presents therapeutic advantages in GCA management that extend beyond achieving remission. In a post-hoc analysis of the GiACTA trial involving 209 patients, the combination of tocilizumab with GC therapy resulted in a median absolute change of −0.5 % in glycated hemoglobin (HbA1c) levels at 1 year, whereas GC monotherapy led to a median absolute change of −0.1 % [65]. The reductions in mean and median HbA1c values were significantly more pronounced, with six times and five times greater declines, respectively, observed in the tocilizumab plus GC cohort in comparison to the cohort receiving GC therapy alone [65]. Among patients receiving both tocilizumab and GC, 42.5 % transitioned from a prediabetic state to normoglycemic levels, compared to 12.5 % in the GC monotherapy group [65].

When body mass index (BMI) was considered, another post-hoc analysis of the GiACTA trial showed that tocilizumab therapy did not have a significant independent association with changes in BMI over 52 weeks [95]. However, cumulative prednisone exposure was strongly independently associated with increased BMI [95]. Therefore, it is possible that by reducing GC exposure, tocilizumab could have an indirect beneficial effect on BMI in the case of longer follow-up.

When discussing the metabolic effects of IL-6, it is essential to consider the context of systemic inflammation due to the “lipid paradox” in inflammatory diseases. Recently, studies have reported conflicting evidence supporting an increased hyperlipidemia following tocilizumab treatment [96,97]. For example, a retrospective cohort study noted high cholesterol levels (≥5.2 mmol/L) and low-density lipoprotein (LDL) (≥3.37 mmol/L) in 50 % of tocilizumab-treated patients compared to controls (60 months) [96]. Likewise, in a prospective cohort study, post-tocilizumab treatment, total cholesterol (+7.0 %), LDL-cholesterol (+10 %), and non-high-density lipoprotein-cholesterol (+9.9 %) significantly increased [97]. In contrast, tocilizumab therapy has demonstrated some beneficial effects, including reductions in CRP levels, enhancements in lipoprotein-related parameters such as decreased lipoprotein(a) and oxidized low-density lipid levels [97], along with a decrease in intima-media thickness [73]. Consequently, and according to clinical experts, patients prescribed tocilizumab should typically be monitored closely, and their lipid profiles and cardiovascular risk factors managed to minimize potential risks.

5.1.4. Cardiovascular effects

Data show that long-term GC treatment is associated with an increased risk of major cardiovascular events (MACE) [89], comorbidities, and mortality [91]. Tocilizumab, through its GC-sparing effect, could therefore reduce this cardiovascular risk, especially as phase 4 trials in RA have shown that the risk for MACE was not significantly increased in patients treated with tocilizumab (hazard ratio 1.05 compared to TNF inhibitors) [98] unlike tofacitinib (hazard ratio 1.33 compared to TNF inhibitors) [99]. Similarly, results of a network meta-analysis identified no significant difference in major cardiovascular outcomes between tocilizumab and other biological disease-modifying antirheumatic drugs in people with rheumatoid arthritis but a lower risk of myocardial infarction compared to abatacept [100]. These findings are notable given the observed increase in cholesterol levels with tocilizumab, and the cardiovascular risk associated with tocilizumab remains the subject of ongoing discussion [100].

5.1.5. HRQoL and safety

Further advantages extend to HRQoL indicators, including physical and mental health status, pain, health perceptions, social functioning, role limitations, disease activity, and energy and fatigue levels [79]. Evidence from the GiACTA trial showed that patients receiving tocilizumab and a 52-week GC taper-to-stop regimen had a statistically significant and clinically meaningful improvement in short-form survey (SF)-36 and Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue scores compared to those receiving GC alone [79]. Tocilizumab might also be effective in preventing new visual complications and transient visual loss in GCA [101], potential benefits that are currently under investigation in a prospective controlled trial (NCT04239196) [102].

The safety of tocilizumab use in GCA has been determined [6,63,70,103]. Still, mild-to-moderate adverse events have been reported in one-third of patients with GCA using tocilizumab [104], including injection site reactions [105] and opportunistic infections, although small numbers of patients have experienced serious adverse events of gastrointestinal perforation or drug-induced liver toxicity [106,107]. In the GiACTA study, serious infections were observed in 4 % of patients who received tocilizumab every other week and in 7 % of patients on weekly tocilizumab [60]. This incidence compared favorably with that in patients on placebo and GC taper, in whom serious infections were reported in 4 % receiving placebo and 26-week GC taper, and 12 % receiving placebo and 52-week GC taper [60].

5.2. Monitoring disease activity in tocilizumab-treated patients

Monitoring disease activity in patients with GCA treated with tocilizumab and other IL-6 pathway inhibitors poses a significant challenge. While symptoms such as typical headaches, scalp tenderness jaw claudication and PMR are relatively specific to GCA, other symptoms frequently observed during relapse, such as atypical headaches and constitutional symptoms are less specific, and may be caused by other conditions [2,80], and may not definitively indicate disease activity. Therefore, clinical assessments alone may be insufficient to detect relapse, particularly when GCA symptoms are vague and varied. Consequently, a multi-faceted approach that includes both clinical evaluations and objective measures is essential for effective monitoring.

5.2.1. Biomarkers for disease activity

Recently, biomarkers have emerged as a priority area to investigate, offering insights for differential diagnosis, predicting relapses, and monitoring disease activity [108]. By blocking IL-6 signaling, IL-6 pathway inhibitors effectively suppress the production of key inflammatory markers, including CRP, fibrinogen, and ESR [62,75], commonly used to measure disease activity. These laboratory investigations for

GCA are therefore unreliable in patients treated with IL-6R blockers, necessitating alternative monitoring strategies to assess disease activity effectively [2,71]. Serum calprotectin, an S100 A8/A9 protein, and osteopontin, a glycoprotein, are not influenced by IL-6 pathway inhibition therapy and have been linked to GCA disease activity and correlated to CRP [109–111]. However, insufficient evidence exists to quantify calprotectin or osteopontin as routine follow-up parameters, and the associated costs of these biomarkers hinder widespread clinical use [110–112].

5.2.2. Role of vascular imaging

The European Alliance of Associations for Rheumatology (EULAR) recommendations outline ultrasound as the first-line imaging modality to support the diagnosis of GCA [113]. Other imaging modalities, such as magnetic resonance imaging (MRI), 18F-fluorodeoxyglucose (FDG) PET-CT, and CT angiography are particularly helpful in assessing large vessel involvement and disease activity in GCA [113,114]. MRI and PET have also proven their ability to assess cranial arteries [115,116], but challenges exist in incorporating particularly FDG PET-CT into the standard clinical diagnosis of LVV because of restricted access to scanners and elevated expenses [83,117]. These procedures, ultrasound, MRI, and FDG-PET, may help to estimate the risk of aortic aneurysm if identified at diagnosis [118].

For individuals on tocilizumab who are in clinical remission with normal inflammatory markers, there is a chance that subclinical LVV may remain undetected, and the potential clinical consequences remain uncertain [119]. The retrospective RIGA study showed a reduction in imaging signs of vascular inflammation with tocilizumab, as well as with GCs and MTX, compared to GC monotherapy [77]. Ultrasound results, assessed by intima-media thickness of temporal and axillary arteries, may vary according to disease activity with tocilizumab treatment, therefore it is important to consider integrating multiple assessment methods to ensure comprehensive monitoring [73]. Similarly, FDG PET/CT results, assessed by PET Vasculitis Activity Score or Total Vascular Score (TVS), vary according to disease activity at a given time and have limited value in guiding management decisions or predicting relapse risk in patients with GCA on tocilizumab [119–122].

In a prospective study of 100 patients with GCA, those with positive vascular FDG PET scans at diagnosis experienced a greater increase in thoracic aortic dimensions compared to those with negative scans [14]. Higher TVS on PET were associated with increased aortic dimensions and a higher risk of thoracic aortic aneurysms, suggesting that PET imaging at diagnosis could help estimate the risk of aortic aneurysm formation [14]. Therefore, imaging assessment of disease activity may be useful to clinicians in particular patients, yet there is a persistent lack of strong evidence for any specific method, uncertainty about diagnostic accuracy, and variability in how results are analyzed.

5.3. Other therapeutic targets

Treatment with other mAbs against the IL-6 pathway is probably relevant but has not shown conclusive results. For instance, sirukumab was tested in a GCA phase 3 randomized trial; however, the study was terminated early due to a sponsor decision [123]. Similarly, a phase 3 trial of sarilumab in GCA was terminated due to slow recruitment [124].

MTX was evaluated as a GC-sparing strategy in older trials and has shown contradictory results, possibly due to differences in design and doses [125–127]. Data gathered in a meta-analysis demonstrated that MTX reduced the risk of relapse and the cumulative dose of GC (842 mg in 48 weeks) in newly diagnosed patients with GCA, albeit with minimal steroid-sparing effects [128]. Additionally, in a retrospective study of 134 patients treated in clinical practice, higher long-lasting remission rates were seen with tocilizumab in combination with GC and, predominantly, MTX (92.3 % of the combination therapy group; the remaining patients received azathioprine or leflunomide) compared to tocilizumab monotherapy at 12 months, even though patients receiving combination therapy had more severe GCA [57]. Overall remission and relapse rates, and the incidence of serious adverse events were similar between the two groups [57]. The efficacy and safety of MTX in active GCA (newly diagnosed or relapsing) is currently being compared to those of tocilizumab in a phase 3 prospective randomized clinical trial (NCT03892785) [129].

Moreover, TNF-α inhibition with infliximab failed to provide a consistent or robust therapeutic benefit in 44 patients with GCA treatment in a placebo-controlled trial [130]. Similarly, a randomized controlled trial involving 70 patients with GCA showed no effect of adalimumab versus placebo, both in combination with prednisone [131], and a third trial involving a small number of patients with GCA ($N = 17$) did not show a significant advantage for etanercept after 1 year of treatment [132].

In clinical practice, experts report that leflunomide is sometimes used as an alternative to MTX. A single-center, prospective, observational, non-randomized study of leflunomide as adjunctive therapy to GCs versus GCs in patients with GCA, demonstrated some benefits for leflunomide [133,134]. In the initial group of patients ($n = 76$), 13.3 % of leflunomide-treated and 39.1 % of GC-only-treated patients relapsed during a median follow-up of 96 weeks ($p = 0.010$ between treatment groups), and a significant GC-sparing effect was seen for leflunomide ($p = 0.01$) [134]. After a longer study period and in a greater number of patients ($N = 215$), the relapse rate was 14.6 % and 45.3 %, respectively, and at 96 weeks ($p < 0.001$) a significant steroid-sparing effect was again seen ($p = 0.009$) [133]. Of note, during this extension period, 27.2 % of patients in the leflunomide group discontinued treatment due to one or more adverse events, which led to discontinuation after a median (interquartile range) of 18 weeks of treatment [133].

With the treatment landscape for GCA rapidly evolving, encouraging outcomes have emerged from phase 2 studies for inhibitors of IL-17 A (secukinumab [135]; phase 3 in progress), selective T-cells (abatacept [136]; phase 3 in progress), and granulocyte-macrophage colony-stimulating factor receptor (mavrilimumab [137]). In addition, Janus kinase inhibitors have shown promise in treating GCA, including baricitinib in a small prospective pilot study [138] and upadacitinib (an inhibitor of IL-6 signaling among others) in a phase 3 trial (NCT03725202) [139]. Results show that 46 % of those treated with upadacitinib 15 mg/day and 6 months prednisone taper achieved sustained remission at 52 weeks compared to 29 % who received a placebo and 12 months prednisone taper [139]. Lastly, ustekinumab (anti IL-12/23 p40) has shown positive outcomes in a prospective cohort study [140], but the findings of a non-comparative open study suggested that there was no significant effect in active GCA [141]. Ustekinumab is still under evaluation in a phase 2 randomized controlled trial for relapsing GCA (NCT03711448) [142]. IL-23p19-inhibition with guselkumab was tried in a phase-2 randomized controlled trial (NCT04633447); however, this trial has been recently terminated due to the primary study endpoint—GC-free remission—not being met [143].

5.4. Knowledge gaps

Despite the promising outcomes associated with IL-6 pathway inhibition, several critical gaps in knowledge remain (Table 2).

Firstly, there is a need for better predictors of response to IL-6 pathway inhibition, as limited research exists on patient profiles that benefit the most from this treatment [8,62,86,88]. Understanding the optimal duration and tapering of therapy is also critical and study results suggest long-term administration may be necessary for sustained remission [78,81–83]. Furthermore, the long-term safety and efficacy of continued drug administration remains uncertain, particularly concerning the risk of relapses after discontinuation, which can occur in 30–61 % of patients within 12 months [61,62,78,81–83]. In addition to these concerns, the impact on large vessel complications of GCA needs further investigation [7,8], especially as studies indicate that flares and relapses are highly likely in patients with large vessel involvement

Table 2
Knowledge gaps related to treatments for GCA.

Category	Identified Gaps
Predictors of response	Limited research on the patient profiles that benefit the most from IL-6 inhibition [8,62,86,88].
Duration of therapy	Further research is needed on the optimal duration and tapering schedules for tocilizumab treatment in GCA, and study results suggest long-term administration may be necessary for sustained remission [83].
Efficacy of tocilizumab	Need for standardized duration of tocilizumab therapy and associated costs compared to other treatments. Relapse rates during and after tocilizumab therapy require more comprehensive studies [78,81–83].
Safety Profile of tocilizumab	Limited understanding of the long-term safety profile of tocilizumab in GCA treatment, especially regarding serious adverse events like gastrointestinal perforation and drug-induced liver toxicity [61,62,82]. Need for larger studies to assess the frequency and types of adverse events in a real-world setting.
Impact of large vessel complications	This needs further investigation, especially as studies indicate that flares are more likely in patients with large vessel involvement [5–11,54].
HRQoL Outcomes	Insufficient data on the effects of treatment on HRQoL [79]. Need for studies assessing long-term HRQoL in patients treated with tocilizumab.
Biomarkers for Disease Monitoring	Current biomarkers (e.g., CRP, fibrinogen, ESR) may not be reliable in patients treated with IL-6 inhibitors, necessitating the exploration of alternative biomarkers [44,76,110]. Limited evidence for the routine use of serum calprotectin and osteopontin in clinical practice due to costs and insufficient validation [109,111].
Cardiovascular Effects	Ongoing discussion regarding the cardiovascular risks associated with tocilizumab despite observed cholesterol increases [89,91,98,100]. Need for longitudinal studies assessing cardiovascular outcomes in patients receiving tocilizumab compared to traditional therapies.
GC-Sparing Strategies	Need for more evidence on the long-term effectiveness of GC-sparing strategies using tocilizumab or other treatments in diverse patient populations [19,22,60,63,67,68,77,79,89]. Lack of consensus on the best approach for tapering GC doses in patients receiving tocilizumab [93].

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, FDG PET-CT: fluorodeoxyglucose positron emission tomography-computed tomography, GCA: giant cell arteritis, HRQoL: health-related quality of life, IL-6: interleukin-6, mAbs: monoclonal antibodies.

[5–11,54]. Compounding these issues, there is a need to identify appropriate biomarkers to replace traditional measures such as CRP and ESR for monitoring disease activity in patients on IL-6 pathway inhibitors, given that these markers may be unreliable in this context [44,76,109–111].

Another critical knowledge gap pertains to the mechanisms underlying the effects of IL-6 pathway inhibitors. Although there is a growing body of evidence which outlines the immunomodulatory effects of IL-6 pathway inhibition, the precise biological processes involved remain insufficiently understood [4].

Furthermore, the effects of IL-6 pathway inhibition on patients' HRQoL and functional status have not been comprehensively studied, and only briefly explored using the GiACTA data [79]. While clinical outcomes are of foremost importance, understanding how IL-6 pathway inhibitors impact daily functioning and overall well-being is equally important [79]. There is a notable lack of research evaluating these outcomes over extended periods, which is crucial for informing treatment protocols that prioritize patient-centered care [79].

Addressing these knowledge gaps through focused research is essential to harness the full therapeutic potential of IL-6 pathway inhibitors and ensure their safe and effective application in diverse patient populations.

6. Limitations

The limitations of a narrative review include potential bias in study selection, as it does not aim to systematically capture all relevant literature. It may overlook important studies outside the chosen databases, time frame and search criteria, leading to incomplete coverage. Additionally, the lack of formal quality assessment or meta-analysis reduces the ability to quantify and compare findings across studies. The narrative synthesis may also introduce subjectivity in interpreting results, and without a structured protocol, reproducibility is limited.

7. Conclusion

GCA, characterized by extensive granulomatous inflammation of arterial walls, poses significant challenges in management due to its chronic inflammatory nature and associated complications. The treatment goal is sustained remission without complications or long-term damage. Standard therapy primarily involves GCs, with varying responses and relapse rates. Elevated IL-6 levels are a typical feature of GCA, which led to the experimentation of IL-6R blockers in GCA, successful trials, and in turn, approval of tocilizumab, a mAb against the IL-6R and a useful therapeutic option. However, challenges persist in the treatment of GCA. These include uncertainty regarding the optimal duration of therapy, the occurrence of high relapse rates post-discontinuation, difficulties in accurately monitoring disease activity, and potential cardiovascular risk associated with tocilizumab. Additionally, it is important to evaluate the cost-effectiveness of IL-6 pathway inhibition, which patient profiles benefit most from the therapy and the impact on HRQoL in clinical practice. Challenges in monitoring disease activity, particularly in detecting subclinical LVV and predicting relapse, underscore the need for robust biomarkers and imaging modalities. In the face of these challenges, the advancements in understanding GCA pathogenesis and the availability of biosimilars of targeted therapies offer hope for cost-effective options with improved outcomes for patients with this complex disease.

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Data availability

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Appendix A. Supplementary data

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