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The Emerging Targeted Treatments for Giant Cell Arteritis: Beyond Interleukin-6 Inhibition- A Systematic Literature Review

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ABSTRACT

Giant cell arteritis is a type of granulomatous vasculitis that primarily affects the large vessels, particularly the aortic arch and its main and distal branches, in individuals over the age of 50. The treatment of this condition usually necessitates the use of steroid-sparing agents. Among the traditional immunosuppressive medications, methotrexate is the most commonly used, and some research also indicates that leflunomide may be effective. With the introduction of biologic therapies, new treatment options have become available for managing giant cell arteritis. Although the results with tumor necrosis factor alpha inhibitors have been underwhelming in this condition, the inhibition of interleukin 6 through tocilizumab has proven to be a safe and effective treatment choice for giant cell arteritis. This systematic literature review seeks to compile and evaluate all existing clinical evidence regarding the efficacy and safety of biologic disease-modifying antirheumatic drugs that operate through mechanisms other than tumor necrosis factor alpha and interleukin-6 inhibition (including costimulation modulation, interleukin-1 inhibition, interleukin 12/23 inhibition, interleukin 17 inhibition, interleukin 23 inhibition, granulocyte-monocyte colony-stimulating factor inhibition, and B cell depletion) as well as targeted synthetic disease-modifying antirheumatic drugs, such as Janus kinase inhibitors, in patients diagnosed with giant cell arteritis.

Introduction

Giant cell arteritis (GCA) is a granulomatous large vessel vasculitis that most typically affects aortic arch and its primary and distal branch vesses, which is detected in individuals older than 50 years[1,2]. GCA can lead to significant morbidity if left untreated, including vision loss due to anterior ischemic optic neuropathy and aortic aneurysms, dissection and stenosis in the affected parts of the aorta[3].

Glucocorticoids (GC) are the mainstay treatment for GCA, where initially high doses of glucocorticoids are needed to control the ongoing inflammation in the vessel walls. Subsequently the GC doses are tapered[4]. Although glucocorticoids swiftly suppress the inflammation, they are associated with significant amount of toxicity (such as diabetes, osteoporosis, fracture, and glaucoma) in most patients, when they are used to treat inflammatory diseases[5,6]. A nested case control study performed by Wilson et al demonstrated that higher average daily doses of glucocorticoids were associated with an increased risk of serious adverse effects in GCA patients[7]. Glucocorticoid tapering can also lead to relapses of giant cell arteritis[8]. Therefore steroid sparing agents are often needed in the treatment of GCA.

Methotrexate (MTX) is the conventional immunosuppressive that has the strongest evidence for preventing relapses and reducing the GC dose when used in conjunction with steroids[9-11]. Leflunomide is often used as an alternative agent to methotrexate in daily rheumatology practice in patients that are intolerant to MTX or contraindicated for its use. Two open label studies have demonstrated that leflunomide may have a role as a steroid sparing agent in GCA[12,13].

Among biologic agents, agents that inhibit tumor necrosis factor alpha(TNFα) are not effective in the treatment of GCA, as the placebo controlled studies of infliximab and adalimumab failed to demonstrate additional benefit of these agents over placebo[14,15] whereas the results of the placebo controlled trial of etanercept were inconclusive due to the low number of patients that were enrolled in this study[16].

Tocilizumab, which is a monoclonal antibody directed against interleukin-6 (IL-6) receptor, was the first biologic agent that was demonstrated to have therapeutic efficacy and steroid sparing effect in the treatment of GCA. Two double blind randomized control trials of tocilizumab demonstrated the efficacy of the agent in comparison to GC monotherapy[17,18]. Based on these two studies, tocilizumab received European Medicines Agency and Food and Drug Administration approval for the treatment of adults with GCA in 2017[19,20]. A recent narrative review by Samson et al underlines the benefits of tocilizumab use in giant cell arteritis by achieving sustained remission, reducing disease relapses, enabling glucocorticoid dose reduction as well as improving health related quality of life parameters[21].

Other biologic agents targeting interleukin-6 signalling were also tried in GCA patients. Sirukumab, which is a human anti IL-6 monoclonal antibody was enrolled in a phase 3 GCA trial, but the study was prematurely terminated due to sponsor decision[22]. The phase 3 trial of sarilumab, which is also a monoclonal antibody directed against interleukin-6 receptor, like tocilizumab, was also terminated due to slow recruitment[23].

This systematic literature review aims to analyze the available clinical data about the efficacy and safety of biologic disease modifying anti rheumatic drugs (DMARD) with mechanisms other than tumor necrosis factor alpha and interleukin-6 inhibition, as well as Janus kinase (JAK) inhibitors in patients with GCA.

Method

INFORMATION SOURCES AND ELIGIBILITY CRITERIA

A systematic literature review was performed using the Cochrane Database, MEDLINE (Pubmed), Scopus and Web of Science. Studies published prior to June 2025 were included with no restrictions on language. All patients diagnosed with GCA who received targeted treatment (all biologic DMARDs, except anti IL-6 or anti TNFα) and targeted synthetic DMARDS such as JAK inhibitors) were included in the analysis. Additionally, relevant articles referenced in the collected literature were manually searched. Animal studies and in vitro studies were excluded.

SEARCH STRATEGY

The search strategy was structured as follows: “giant cell arteritis” OR “temporal arteritis” AND “abatacept” OR “anakinra” OR “canakinumab” OR “gevokizumab” OR “rilonacept” OR “rituximab” OR “brodalumab” OR “guselkumab” OR “ixekizumab” OR “mirikizumab” OR “risankizumab” OR “secukinumab” OR “tildrakizumab” OR “ustekinumab” OR “mavrilimumab” OR “JAK inhibitors” OR “baricitinib” OR “tofacitinib” OR “upadacitinib”.

SELECTION PROCESS, DATA COLLECTION PROCESS, DATA ITEMS

Initially, only the abstracts of all results were reviewed. Following this review, studies that met the criteria for screening were identified. The full texts of the selected abstracts were then examined, and duplicates were removed to determine the eligible studies. After a final assessment, the studies to be included were confirmed. The following data was collected from each of the chosen studies: the number of patients with GCA, the age and sex of each patient, clinical findings, extent of the giant cell arteritis (affected organs and systems), laboratory parameters of the patients, previous treatments, dosage and administration route of the targeted therapy, any concurrent conventional immunosuppressives with the targeted treatment modalities, the duration of the targeted therapy, the patients' responses to the targeted agents, and any side effects associated with therapy.

RISK OF BIAS ASSESSMENT, REPORTING BIAS ASSESSMENT AND CERTAINTY ASSESSMENT

This review aims to assemble all the available clinical data on the efficacy and safety of the biologic agents

and JAK inhibitors in GCA patients. Therefore, while we reported the nature of the studies (for example open label, randomized controlled study, case report etc.) , assessments for risk of bias, reporting bias, and certainty were not conducted.

Results

BIOLOGIC AGENTS

Costimulation Modulation with Abatacept

Abatacept is a fusion protein that works as a costimulation modulator. It is composed of the fragment crystallizable (Fc) region of the immunoglobulin G1 fused to the extracellular domain of cytotoxic T lymphocyte-associated antigen (CTLA4). Abatacept is successfully being used in the treatment of rheumatoid arthritis[24].

When literature search was performed for "abatacept" AND "giant cell arteritis" OR "temporal arteritis", a total of 347 results were obtained from the aforementioned databases. After exclusion of the irrelevant articles and the elimination of the duplicate results, the following studies were of interest: One randomized double blind phase 2 trial (NCT00556439- Concurrent Pilot Studies in Giant Cell Arteritis and Takayasu's Arteritis to Examine the Safety, Efficacy, and Immunologic Effects of Abatacept in Large Vessel Vasculitis)[25] and two Phase 3 trials (NCT03192969 - A Phase 3 Randomized, Placebo-Controlled, Double-Blind Clinical Trial to Evaluate the Efficacy and Safety of Subcutaneous Abatacept in Combination With Glucocorticoid Treatment Compared to Glucocorticoid Monotherapy in Adults With Giant Cell Arteritis and NCT04474847- Abatacept for the Treatment of Giant Cell Arteritis)[26,27] investigated the efficacy and safety of abatacept in GCA. Results of the phase 2 trial were published by Langford et al[28], but one phase 3 trial[26] was terminated due to "changes in business objectives" before results could be obtained. Second phase 3 trial is currently recruiting patients and study completion is estimated in December 2029[27]. One systematic review and meta-analysis regarding the efficacy and safety of steroid-sparing treatments in giant cell arteritis according to the glucocorticoid tapering regimen included the study by Langford et al[29]. One prospective study compared abatacept and tocilizumab in GCA[30]. One case report described a giant cell arteritis patient where a combination of multiple immunosuppressives (including abatacept) and endovascular treatment modalities were utilized[31].

In their article Langford et al reported the results of the phase 2 trial (NCT00556439)[25] about the efficacy and safety of abatacept in GCA[28]. In this multicenter trial, patients with newly diagnosed or relapsing giant cell arteritis were treated with abatacept 10 mg/kg intravenously on days 1, 15, and 29 and week 8, together with daily prednisone. At week 12, patients in remission underwent a double-blinded randomization to continue to receive abatacept monthly or switch to placebo. Patients in both study arms received a standardized prednisone taper, which was stopped at 28th week. All patients remained on their randomized assignment until meeting criteria for early termination or until 12 months after enrollment of the last patient. The primary endpoint was duration of remission (relapse-free survival rate). Forty-nine eligible patients with GCA were enrolled and treated with prednisone and abatacept; of these patients, 41 reached the week 12 randomization and underwent a blinded randomization to receive abatacept or placebo. Age of diagnosis of the abatacept group was significantly younger than that of the placebo group and placebo group had significantly more female patients compared to placebo. Age of enrollment of the abatacept group was younger at a level close to statistical significance ($p=0.052$) compared to placebo group. Prednisone was tapered using a standardized schedule, reaching a daily dosage of 20 mg at week 12 with discontinuation in all patients at week 28. In the intent-to-treat analysis of the randomized patients, relapse-free survival rate at 12 months was 48% for those receiving abatacept and 31% for those receiving placebo ($p=0.049$). A longer median duration of remission was seen in those receiving abatacept compared to those receiving placebo (median duration 9.9 months versus 3.9 months; $p=0.023$). Covariate analysis examining those variables that were statistically significantly different between the study treatment arms demonstrated that these parameters (namely sex, age at diagnosis, and age at enrollment) did not impact the study results. There was no difference in the frequency or severity of adverse events, including infection, between the treatment arms. No deaths occurred during the study. A total of 33 infections were reported during the trial in 20 patients. Twenty-nine infections occurred in the randomized population, with 4 occurring in patients who did not undergo randomization. Two infections required hospitalization and were reported as serious adverse events. Of the 49 treated patients, 3 developed malignancies during the study period (a papillary urothelial transitional cell carcinoma and an endometrial carcinoma in abatacept group, and a skin squamous cell carcinoma treated in the placebo group). Despite its small sample size, this study presented abatacept as a potential steroid sparing agent for GCA patients[28]. However, the systemic literature review and meta-analysis performed by Gérard et al analyzed the data from the study of Langford[29]. Unlike Langford et al who utilized a one-sided test and obtained a statistical significance near the limit ($p=0.049$)[28], Gérard et al used two-sided tests, which failed to find a beneficial effect of abatacept on relapse rate[29].

In their prospective agent-to-agent real life comparison study, Rossi et al compared the efficacy of abatacept with, which tocilizumab, which is the biologic treatment of choice in GCA patients[30]. Thirty-three consecutive biospy-proven giant cell arteritis patients were prospectively enrolled. Odd patients were assigned to tocilizumab (8 patients received intravenous tocilizumab at the dose of 8 mg/kg/month and 9 patients received subcutaneous tocilizumab at the dose of 162 mg/week, based on patients' preference); and abatacept was administered subcutaneously at the dose of 125 mg/week in 16 even patients (from 2 to 32). All patients received additional oral prednisone. Twenty eight patients received one biologic agent, 5 patients (one patient from tocilizumab group and 4 patients from

abatacept group) had to switch to the other biologic agent. All patients in the intravenous tocilizumab group responded to the treatment (57% complete and 43% partial response), 67 % of subcutaneous tocilizumab group achieved complete response and 16 % achieved partial response; whereas 5 patients (31%) in the abatacept group achieved complete response and 5 other patients in the abatacept group (31%) achieved partial response. At the end of 12 months of treatment all patients in tocilizumab groups but only 43% of the patients in the abatacept group were receiving oral prednisone in doses lower than 7.5 mg/day. No significant difference in outcomes was observed when comparing relapsing patients with newly diagnosed GCA. No significant side effect related to biologic drug administration was recorded. This study's weaknesses included the lack of randomization and its relatively small sample size. Authors emphasized that tocilizumab was more effective than abatacept in remission induction and steroid sparing. With its moderate effect, they offered abatacept as an alternative to patients that have absolute or relative contraindications to tocilizumab[30].

Finally, Travis Caton Jr et al report a GCA case with significant intracranial ischemia that was treated with a combination of high dose glucocorticoids (initially pulse methylprednisolone) and a variety of immunosuppressives which were given subsequently (first tocilizumab, then cyclophosphamide, then tocilizumab a second time, followed by intravenous abatacept) and a total of seven endovascular treatment sessions[31]. In this case report, the duration and dose of abatacept and the dose of concurrent glucocorticoids was not stated. However under abatacept treatment, surveillance magneitc resonance angiography demonstrated new left basal ganglia infarction despite a plateau in symptoms, along with restenosis of supraclinoid left internal carotid artery and new stenosis of petrous segment of left internal carotid artery, which demonstrated that abatacept was not effective in halting the progression of vascular involvement[31].

Interleukin 1 Inhibition

Anakinra, canakinumab, rilonacept and gevokizumab are the biologic agents that inhibit interleukin 1 (IL-1) signalling. Anakinra and canakinumab are the most frequently used interleukin 1 inhibitors which are successfully being used mainly in the treatment of familial Mediterranean fever and other autoinflammatory periodic fever syndromes[32]. Anakinra is a recombinant interleukin-1 receptor antagonist, canakinumab is a neutralizing, IgG1-type monoclonal antibody directed to IL-1 beta, gevokizumab is a humanized monoclonal antibody specific to interleukin-1 beta, whereas rilonacept consists of the extracellular domains of IL-1 receptor 1 and interleukin 1 receptor 3 that are fused to Fc part of human IgG1 that functions as a soluble decoy receptor for interleukin 1 alpha and IL-1 beta[32].

When literature search was performed for "anakinra" OR "canakinumab" OR "rilonacept" OR "gevokizumab" AND " giant cell arteritis" OR "temporal arteritis", a total of 102 results were obtained from the predetermined databases. After exclusion of the irrelevant articles and the elimination of the duplicate results, the following studies were of interest: There was a Phase 3 Trial (NCT02902731- Giant Cell Arteritis and Anakinra Trial (GiAnT)[33]. Unfortunately this study was prematurely terminated due to COVID-19 pandemic, but the results were published by de Boysson et al[34]. Anakinra use in giant cell arteritis was reported in a case series of 6 patients by Deshayes[35] et al and in 3 cases by Ly et al[36]. The retrospective studies about the dilations of aorta in GCA by Gallou et al[37] and about the factors associated with relapse and dependence to glucocorticoids in giant cell arteritis by Dumont et al[38] each reported 2 GCA patients treated with anakinra. In addition, study by Rossi-Semerano et al, reported 2 giant cell arteritis patients that received anakinra[39]. Finally in their retrospective study about large vessel involvement in GCA, de Boysson et al reported anakinra use in 1 patients[40]. Gevokizumab's efficacy in giant cell arteritis was tested in a European Union Clinical Trial (2013-002778-38- A randomised, double-blind, placebo-controlled proof-of concept study of the efficacy and safety of gevokizumab in the treatment of patients with giant cell arteritis)[41]. Three GCA patients were treated with gevokizumab in a retrospective study by Andel et al[42]. Canakinumab use was also reported in the same study by Rossi-Semerano et al in vasculitis (although it is not clear if these vasculitis parients were giant cell arteritis patients)[39]. There was no report of use of rilonacept in GCA.

"Randomized, Controlled, Double-blind Study of Anakinra Against Placebo in Addition to Steroids in Giant Cell Arteritis" (Giant Cell Arteritis and Anakinra Trial, NCT02902731) was a Phase 3 trial of anakinra aiming to compare the efficacy of anakinra + glucocorticoid combination with placebo+glucocorticoid combination in GCA[33]. Unfortunately this study was discontinued prematurely due to COVID-19 pandemic. Despite this setback, the investigators analyzed and published the results of the 30 patients (17 patients randomized to anakinra and 13 patients randomized to placebo). During the first 16 weeks, the relapse rates was 12% (n = 2) in anakinra group and 23% (n = 3) in placebo group (p = 0.63). At week 26, 12 (40%) patients had relapsed: 8 (47%) in the anakinra group and 4 (31%) in the placebo group (p = 0.47). At the end of 52 weeks, the relapse rate (overall, 50%) did not differ between the anakinra group (53%; 9/17 patients) and the placebo group (46%; 6/13 patients) (p = 1). Two patients in each group discontinued glucocorticoids (p = 0.87). Seven serious adverse events were reported in five patients, including 4 in patients receiving anakinra. The serious adverse events in anakinra group were hematemesis (due to thrombocytopenia), erysipelas, fall, two complicated urinary infections and one COVID-19 infection. This study failed to demonstrate a beneficial effect of anakinra in reducing the relapse risk or glucocorticoid exposure in GCA[34].

Deshayes et al reported retrospective analysis of 6 patients that received anakinra for GCA. Five patients

fulfilled at least 3 American College of Rheumatology criteria of giant cell arteritis with a positive temporal artery biopsy and the sixth patients fulfilled two criteria and had large vessel involvement proven by positron emission tomography/computed tomography (PET/CT). A total of 4 patients had large vessel involvement proven by PET/CT and/or computed tomography (CT) angiography of the aorta. Median duration of anakinra use was 19 (18-32) months. All the patients had complete clinical and biological remission. Among the 4 patients with large vessel involvement, one patient's aortitis disappeared and the three patients had decreased vascular uptake. After a median follow-up of 56 (48–63) months, corticosteroids were discontinued in four patients, and corticosteroid dosage could be decreased to 5 mg/day in two patients. One patient relapsed 13 months after anakinra introduction in the context of increasing the daily anakinra injection interval to every 48 hours. Three patients experienced transient injection-site reactions, and one patient had pneumonia[35]. This report demonstrated that anakinra could be an effective steroid sparing agent in some GCA cases.

Ly et al reported anakinra use in 3 GCA patients. In their discussion, authors stated that in two of these three patients (first patient with aortic and subclavian artery inflammation without temporal artery involvement that received methotrexate and etanercept before anakinra; and the second patient with cranial arteritis who did not previously receive any other steroid sparing agents) anakinra was effective as a steroid sparing agent. Authors claimed that in the third patient (patient with aggressive large artery disease who had hepatotoxicity under dapsone), steroid sparing effect of anakinra was moderate and could be due to a time related sparing effect rather than anakinra related sparing. In these patients anakinra was tolerated well without any infection or malignancy. One patient had injection site skin reaction. Authors underlined the possible efficacy of anakinra, but also stressed the necessity of larger studies with longer observation periods[36].

The retrospective study of Gallou et al reported use of anakinra in 2 GCA patients but efficacy for these patient was not specifically reported[37].

In their study about the factors associated with relapse and dependence to glucocorticoids in GCA, Dumont et al reported 2 giant cell arteritis patients treated with anakinra but specific data for these patients concerning efficacy was not present in their manuscript[38].

In their article about the tolerance and efficacy of off-label anti-interleukin-1 treatments in France, Rossi-Semerano et al reported 4 vasculitis patients (2 with GCA and 2 with polyarteritis nodosa) who were treated with anakinra. Among these patients they reported 2 partial and 1 total response. Two patients switched to canakinumab due to inefficacy/loss of efficacy. Among these patients one responded partially to canakinumab and for the other patient the response was unknown. However it is unclear which patients responded to anakinra, which patients switched to canakinumab and which patients (giant cell arteritis or polyarteritis nodosa) responded partially to canakinumab because of the lack of specific data for each patient[39].

In their retrospective study about GCA patients with large vessel involvement, de Boysson et al reported one patient that was treated with anakinra but the efficacy and safety of anakinra in that patient was not specified[40].

In the randomized double-blind, placebo-controlled proof-of concept study of the efficacy and safety of gevokizumab in the treatment of patients with giant cell arteritis, six GCA patients were randomized to receive gevokizumab and seven giant cell arteritis patients were randomized to receive placebo. All patients received concomitant steroids. Nine patients were withdrawn from the study due to sponsor's decision to prematurely terminate the study and two patients withdrew due to adverse events. During the 24-week double-blind period, the mean treatment duration was 131.0 ± 55.2 days in the gevokizumab group and 159.3 ± 22.6 days in the placebo group. For the patients who entered the 28-week open-label period, the median treatment duration was 85 days. Patients in the gevokizumab group did not have significant acute phase reactant reduction, improvement in polymyalgia rheumatica like/systemic symptoms, in morning stiffness or reduction in glucocorticoid dose. Researchers concluded by stating that the study was severely compromised by the low sample size achieved. No new safety signals were observed and in general gevokizumab was well tolerated. However there were no clear indications of a reduction in glucocorticoids that could be attributed to gevokizumab[41].

In the retrospective study from Southern Norway, Andel et al reported all the patients diagnosed with GCA between 2006 and 2019 in their single center fast-track clinic. Among the 77 patients that they identified, 3 patients were treated with gevokizumab but information concerning the efficacy and safety of gevokizumab was not present[42].

Interleukin 12/23 Inhibition

Ustekinumab is a fully human monoclonal IgG1 antibody that binds to the p40 subunit of IL-12 and IL-23[43]. When literature review was performed for "ustekinumab" AND "giant cell arteritis" OR "temporal arteritis", a total of 200 results were obtained. After exclusion of the irrelevant articles and the elimination of the duplicate results, the following studies were of interest: There was one Phase 1-Phase 2, prospective, single center, single arm, open-label trial (Ustekinumab for the Treatment of Giant Cell Arteritis, UGCA, NCT02955147)[44]. Results of this trial was published by Matza et al[45]. There was also a Phase 2 trial (Ustekinumab for the Treatment of Relapse of Refractory Giant Cell Arteritis, ULTRA, NCT03711448)[46]. Conway et al reported the preliminary data of 14 GCA patients that were treated with ustekinumab in their prospective registry[47]. Later, the same author and his colleagues reported a larger cohort of 25 GCA patients treated with ustekinumab with a minimum follow up duration of 12 months[48]. Samson et al reported a

giant cell arteritis case where ustekinumab successfully inhibited Th1 and Th17 polarization[49]. Abdalla et al repoted a GCA case with aortitis that was treated with ustekinumab[50]. In their case control study about association of large vessel vasculitis and inflammatory bowel disease, Maillet et al reported a GCA patient treated with ustekinumab[51]. Finally Sandler et al reported paradoxical GCA development in a psoriatic arthritis patient treated with ustekinumab[52].

"Ustekinumab for the Treatment of Giant Cell Arteritis" (UGCA, NCT02955147) was an open label study performed to test the safety and efficacy of ustekinumab in GCA patients. All patients received a 24-week prednisone taper and subcutaneous ustekinumab 90 mg at baseline, weeks 4, 12, 20, 28, 36 and 44. The primary endpoint, prednisone-free remission, was defined as the absence of relapse through week 52 and normalization of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Relapse was defined as the recurrence of giant cell arteritis symptoms requiring treatment intensification[44]. Matza et al reported the results of the study. The study enrolled 13 patients. Enrollment was closed prematurely after 7 of the initial 10 patients relapsed. Five patients had new-onset disease. The initial prednisone doses were 20 mg (1 patient), 40mg (9 patients), and 60 mg (3 patients). All patients entered disease remission within 4 weeks of baseline. Only 3 (23%) achieved the primary endpoint. Of the 10 (77%) patients who failed to achieve the primary endpoint, 7 relapsed after a mean period of 23 weeks. The remaining 3 patients met the alternative definition of prednisone-free remission that did not require ESR/CRP normalization. One serious adverse event occurred (mild diverticulitis requiring hospitalization). Authors concluded that although ustekinumab was well tolerated, it did not prevent disease relapse in a significant proportion of GCA patients once prednisone was discontinued or tapered[45]. However the commentaries on this article by Samson[53] and Conway[54] both underlined that it was early to draw conclusions from this study and that the rate of relapse could be due to the rather short prednisone regimen with accelerated taper which was used in this study.

Ustekinumab for the treatment of relapse of refractory giant cell arteritis (ULTRA, NCT03711448) is a randomized controlled phase 2 study that aims to compare ustekinumab with placebo. Both groups concomitantly received glucocroticoids. Primary outcome is percentage of living patients who enter a period of remission after inclusion, without a new relapse and without deviation from the steroid tapering protocol of the study. Even though the study is labelled as "completed", no results are posted[46].

In their proof of concept, uncontrolled, unblinded study, Conway et al reported ustekinumab use in 14 refractory GCA patients. In this study "refractory disease" was defined as an inability to taper glucocorticoids to <10 mg/day due to symptoms of active giant cell arteritis, with a minimum of two relapses. In a median duration of 13.5 months, no patient had a relapse of GCA while receiving ustekinumab. Seven of the 14 patients had large vessel vasculitis prior to ustekinumab use. Ustekinumab enabled significant reduction in glucocorticoid dose and cessation of other immunosupressants in refractory GCA patiens. Six adverse events occurred but a definite relationship to ustekinumab could not be confirmed in any case. Three patients stopped ustekinumab due to adverse events, two of whom subsequently had flares of polymyalgia rheumatica[47]. Later Conway et al reported their experience with ustekinumab in 25 giant cell arteritis patients that were under follow up, for a duration of at least 12 months. All patients had failed to taper glucocorticoids despite addition of a median of 1 other immunosuppressive agent. At week 52, median daily prednisolone dose decreased from 20 mg to 5 mg ($p<0.001$). Six patients stopped prednisolone completely. No patient experienced a relapse of GCA while receiving ustekinumab. Median CRP decreased significantly from 12.9 to 6 mg/L ($p=0.006$). Large vessel involvement was present in 10 patients in the beginning. After ustekinumab therapy, repeat imaging with computed tomography angiography was performed in 8 patients, which demonstrated improvement of large vessel vasculitis in all patients studied. No unexpected adverse events were observed with ustekinumab. The majority of adverse events were minor infections, most commonly respiratory tract infections. Three patients discontinued ustekinumab over the course of the study due to adverse events. (1 due to recurrent respiratory tract infections, 1 due to alopecia, and 1 due to non-dermatomal limb paraesthesia.) All adverse events resolved following ustekinumab cessation. Two of these 3 patients subsequently had flares of polymyalgia rheumatica 4 and 5 months respectively after stopping ustekinumab. Authors concluded that ustekinumab could be effective for GCA treatment and that it needed to be assessed with randomized controlled trials[48].

Samson et al reported a GCA patient who previously received azathioprine and methotrexate as steroid sparing agents. When patient relapsed under 20 mg/week dose of methotrexate, tocilizumab could not be considered in this patient due to his history of sigmoiditis. Therefore ustekinumab was initiated. At the fourth month of ustekinumab, patient's methylprednisolone dose was reduced to 8 mg/day and CRP was 12 mg/l. This case is noteworthy as the authors demonstrated the inhibition of Th1 and Th17 polarization at the sixteenth week of ustekinumab therapy[49].

In their case report, Abdalla et al reported a relapsed GCA case with aortic involvement that was treated with high dose glucocorticoids and at the second month ustekinumab was added. At the sixth month, patient was well and prednisolone dose was reduced to 5 mg/day[50].

In their case control study about association of large vessel vasculitis and inflammatory bowel disease, Maillet et al reported a GCA patient treated with ustekinumab but specific information regarding its efficacy was absent in the text[51].

Finally, Sandler et al reported paradoxical GCA development in a psoriatic arthritis patient treated with ustekinumab. This is the first report where ustekinumab therapy caused paradoxical giant cell arteritis that was proven with temporal artery biopsy[52].

Interleukin 17 Inhibition

Secukinumab and ixekizumab are interleukin 17A inhibitors whereas brodalumab is a monoclonal antibody directed against interleukin 17 receptor[55]. When literature review was performed for "secukinumab" OR "ixekizumab" OR "brodalumab AND "giant cell arteritis" OR "temporal arteritis", a total of 192 results were obtained. After exclusion of the irrelevant articles and the elimination of the duplicate results, the following studies were of interest: There was a phase 1 study for evaluation of the pharmacokinetics, safety and tolerability of intravenous secukinumab in GCA or polymyalgia rheumatica patients (NCT06130540)[56]. There was a placebo-controlled phase 2 trial to investigate the safety and efficacy of secukinumab in giant cell arteritis (TitAIN, NCT03765788)[57]. This trial's protocol was published by Venhoff et al[58] and its results were published by the same author in 2023[59]. Two phase 3 trials (NCT04930094 , NCT05380453)[60,61] for secukinumab were present. Tomelleri et al reported secukinumab use in a case series of 6 giant cell arteritis patients with tocilizumab failure[62]. Rotar[63] and Sammut[64] each reported a GCA patient who concomitantly had psoriatic arthritis and was successfully treated with secukinumab. Use of ixekizumab was reported only in a case report where a giant cell arteritis patient with concomitant psoriasis was treated with ixekizumab[65]. There was no reported use of brodalumab in GCA.

An open-label, multicenter study to evaluate the pharmacokinetics, safety and tolerability of intravenous secukinumab infusion in adults with GCA or polymyalgia rheumatica (PMR) (NCT06130540) was a 12-week, open-label, multicenter, basket design study followed by an 8-week follow-up period in two cohorts of participants, one cohort with giant cell arteritis and one cohort with PMR. This study had 3 phases: screening, treatment and follow-up.. Although status of the study seems "completed", no results have been posted[56].

Placebo controlled phase 2 trial (TitAIN, NCT03765788) aimed to investigate the safety and efficacy of secukinumab in GCA[57]. This was a randomized, parallel-group, double-blind, placebo-controlled, multi-center, phase 2 study in which patients, treating physicians, and the associated clinical staff as well as the sponsor clinical team were blinded. It was designed to evaluate the efficacy and safety of secukinumab compared to placebo in combination with an open label prednisolone taper regimen. Patients included were naïve to biological therapy and had newly diagnosed or relapsing giant cell arteritis. Fifty patients were randomly assigned in a 1:1 ratio to receive either 300 mg secukinumab or placebo subcutaneously at baseline, weeks 1, 2 and 3, and every 4 weeks from week 4. Patients in both treatment arms received a 26-week prednisolone taper regimen. The study consisted of a maximum 6-week screening period, a 52 week treatment period (including the 26-week tapering), and an 8-week safety follow-up, with primary and secondary endpoint assessments at week 28. The primary efficacy endpoint was the proportion of GCA patients in sustained remission at week 28. Secondary endpoints included remission rate at week 12, time to first flare of giant cell arteritis after clinical remission up to week 52, cumulative prednisolone dose up to weeks 28 and 52, proportion of patients with sustained remission at week 52, proportion of patients with prednisolone dose < 5 mg/day at weeks 19, 28 and 52 and changes from baseline ESR and CRP at weeks 4, 8, 12, 16, 20, 24, 28, 36, 44 and 52[58].

Results of TitAIN were published in 2023. A total of 52 patients were enrolled (27 received secukinumab) and 25 received placebo). Four of 27 patients in the secukinumab group and eight of 25 patients in the placebo group discontinued treatment by week 28 of the study. On the basis of the Bayesian analysis, the median proportion of patients in sustained remission until week 28 was 70% in the secukinumab group versus 20% in the placebo group. The incidence of adverse events was similar in the secukinumab (all 27 patients had any adverse event) and placebo groups (24 of 25 patients had any adverse event); the most common adverse events were hypertension (six of 27 patients in the secukinumab group and eight of 25 patients in the placebo group) and nasopharyngitis (five of 27 patients in the secukinumab group and five of 25 patients in the placebo group). Two patients (one in each group) died during the study, neither of which was considered to be related to study treatment. Authors concluded that active GCA patients had higher sustained remission rate in the secukinumab group than in the placebo group at week 28, in combination with glucocorticoid taper regimen. Secukinumab was tolerated well, with no new safety concerns. This study supported secukinumab as a treatment option for patients with giant cell arteritis[59].

Promising results of this phase 2 trial have led to two phase 3 trials. First one is "a randomized, parallel-group, double-blind, placebo-controlled, multi-center, phase 3 study to evaluate the efficacy and safety of secukinumab 300 mg and 150 mg administered subcutaneously versus placebo, in combination with a glucocorticoid taper regimen, in patients with giant cell arteritis" (GCAptAIN, NCT04930094)[60]. This study's status is "active, not recruiting" with no results posted. Second one is "a randomized, parallel-group, double-blind, placebo-controlled, multicenter trial to investigate the efficacy and safety of subcutaneously administered secukinumab in patients with new-onset of giant cell arteritis who are in clinical remission and eligible for treatment with glucocorticoid-monotherapy" (GigAINt, NCT05380453). This study is also in "active, not recruiting" status and so far no results have been posted[61].

Tomelleri et al reported 6 GCA patients who were treated with secukinumab after responding inadequately to tocilizumab. All patients were female

with a median age of 72 years. At disease onset, all patients had cranial symptoms, and four experienced constitutional symptoms. Tocilizumab failure occurred after a median period of 14 months. Following secukinumab initiation, all patients achieved clinical and laboratory remission within six months. Imaging confirmed complete resolution of vasculitis in four patients with documented active disease before start of secukinumab. Three patients successfully discontinued glucocorticoids within four months, while the remaining three patients continued low-dose prednisone (5mg/day or less). No adverse events were reported during secukinumab treatment. Authors concluded that these preliminary real-world findings supported the potential role of IL-17A inhibition in GCA management, particularly in cases of inadequate response to IL-6 blockade and underlined the need of larger studies to confirm these observations[62].

Finally Rotar[63] and Sammut[64] each reported a GCA patient who concomitantly had psoriatic arthritis and was successfully treated with secukinumab. Patient in Rotar's case report was a 67 year old female with temporal artery and large vessel involvement who developed giant cell arteritis when she was under methotrexate and etanercept treatment for psoriatic arthritis. After GCA diagnosis, she was switched to a combination of leflunomide and steroids. When steroid dose was reduced, disease relapsed and tocilizumab was added. However psoriatic arthritis flared under tocilizumab. Then leflunomide and tocilizumab were stopped and the patient received secukinumab. Secukinumab was highly successful in controlling both diseases and in enabling steroid discontinuation[63]. Sammut reported a 70 year old male patient who received adalimumab for psoriatic arthritis. When patient presented with fever, occipital headache, dry cough and elevated CRP, he underwent an extensive work up. Finally temporal artery biopsy revealed the diagnosis of giant cell arteritis. He received high dose steroids in addition to adalimumab but steroid requirement for GCA remained high and psoriatic arthritis flared. In order to control both diseases, adalimumab was switched to secukinumab which effectively controlled both diseases and at the 9th month of treatment patient was well with normal acute phase reactants and using low dose steroids[64].

Tomelleri et al reported a patient that had both GCA and psoriasis. This 64 year old male patient had temporal artery involvement with halo sign in Doppler USG, as well as left common carotid, left subclavian and bilateral femoral artery involvement documented by PET/CT. This patient recevied methotrexate in addition to glucocorticoids. At the seventh month, patient had a polymyalgic flare with elevated acute phase reactants. At that point methotrexate was switched to tocilizumab which controlled the disease and enabled glucocorticoid withdrawal. Later, when patients suffered a psoriatic flare, tocilizumab was switched to ixekizumab, which treated the psoriatic flare and for 12 months under ixekizumab, patient was GCA symptom-free with normal acute phase reactants and a normal PET/CT scan[65].

Interleukin 23 Inhibition

Guselkumab, tildrakizumab, risankizumab and mirikizumab are interleukin 23 inhibitors[66]. When literature review was performed for "guselkumab" OR "tildrakizumab" OR "risankizumab" OR "mirikiziumab" AND "giant cell arteritis" OR "temporal arteritis", a total 29 results were obtained. After exclusion of the irrelevant articles and the elimination of the duplicate results, the following studies were of interest: There was a phase 2 study of guselkumab in GCA patients (A Study to Evaluate Guselkumab for the Treatment of Participants With New-onset or Relapsing Giant Cell-Arteritis, THEIA, NCT 04633447)[67]. There were no results concerning the use of tildrakizumab, risankizumab or mirikizumab in GCA patients.

In the phase 2, randomized controlled study of guselkumab in GCA, new onset or relapsed giant cell arteritis patients were randomized to receive guselkumab or placebo. Primary endpoint was percentage of patients achieving glucocorticoid free remission at week 28. Secondary outcomes included percentage of patients achieving glucocorticoid free remission at weeks 32, 36, 40, 44, 48, 52; percentage of participants achieving both glucocorticoid-free remission and normalization of erythrocyte sedimentation rate, CRP or both at weeks 28, 32, 36, 40, 44, 48, 52; cumulative glucocorticoid dose; time to first GCA disease flare or discontinuation of study intervention due to adverse event of worsening of giant cell arteritis; number of patients with GCA disease flare or discontinuation of study intervention due to adverse event of worsening of giant cell arteritis and number of participants with treatment-emergent adverse events. This study was terminated because the primary endpoint was not met[67].

Granulocyte-Monocyte Colony-Stimulating Factor Inhibition

Mavrilimumab is a monoclonal antibody directed against granulocyte-monocyte colony stimulating factor (GM-CSF)[68]. When literature review was performed for "mavrilimumab" AND "giant cell arteritis" OR "temporal arteritis", 82 results were obtained. After exclusion of the irrelevant articles and the elimination of the duplicate results, the following studies were of interest: There was one phase 2 study about the efficacy and safety of mavrilimumab in GCA (NCT03827018)[69]. Protocol of this study was published by Pupim[70] et al and results were published bu Cid et al[71,72]. Unizony et al reported the utility of acute phase reactants in the diagnosis of giant cell arteritis in the same trial[73].

NCT03827018 was a phase 2, randomized, double-blind placebo-controlled study to test the efficacy and safety of KPL-301 (mavrilimumab) in GCA[69]. Patients with new onset or relapsing/refractory giant cell arteritis and ESR>30 mm/hr or CRP≥1 mg/dl) were randomized in 3:2 ratio to receive subcutaneous mavrilimumab or placebo together with prednisone (given with a 26 week taper program). Primary outcome was time to GCA flare. Secondary outcomes included cumulative steroid dose, acute phase reactants, time to signs and symptoms of giant cell arteritis, time to elevated erythrocyte sedimentation rate or C-reactive

protein[69,70]. Among 42 patients that received mavrilimumab, flare occurred in 19% (n=8) and among 28 placebo receiving patients flare occurred in 46% (n=13). Median time to flare was 25.1 weeks in the placebo group, but the median was not reached in the mavrilimumab group (HR 0.38; p=0.026). Sustained remission at week 26 was 83% for mavrilimumab and 50% for placebo recipients (p=0.0038). Adverse events occurred in 78.6% (n=33) of mavrilimumab and 89.3% (n=25) of placebo recipients. No deaths or vision loss occurred in either group. Cid et al concluded that mavrilimumab+steroid combination was superior to placebo+steroids for time to flare by week 26 and sustained remission in GCA patients. Mavrilimumab was well tolerated, and no new safety signals were observed. Authors underlined the need of longer treatment to determine response durability and steroid sparing potential of the drug[71,72]. Unizony et al aimed to analyze the relationship between CRP/ESR and clinical disease activity in giant cell arteritis patients treated with mavrilimumab in this study. They reported similar frequency and magnitude of erythrocyte sedimentation rate and C-reactive protein elevations at relapse in both treatment arms, suggesting that these acute phase reactants remained useful in assessment of disease activity in patients that were treated with mavrilimumab. Acute phase elevations without GCA related clinical symptoms or signs occurred more frequently in patients treated with placebo[73].

B-Cell Depletion with Rituximab

Rituximab is a monoclonal mouse–human chimeric anti-CD20 IgG1 antibody that induces depletion of mature and memory B cells, via an apoptotic process mediated by antibody- and complement-dependent cytotoxicity[74]. When literature review was performed for "rituximab" AND "giant cell arteritis" OR "temporal arteritis", 590 results were obtained. After exclusion of the irrelevant articles and the elimination of the duplicate results, the following studies were of interest: One phase 2 trial (NCT05168475) included GCA patients that were treated with rituximab[75]. Rest of the evidence concerning use of rituximab in giant cell arteritis is derived from numerous case reports and case series[76-88].

"Biologics in refractory vasculitis (BIOVAS): a pragmatic, randomised, double-blind, placebo-controlled, modified-crossover trial of biologic therapy for refractory primary non-antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis in adults and children" (NCT05168475) is a phase 2 trial which aimed to investigate infliximab, rituximab, tocilizumab, and placebos to each, in the treatment of refractory non-ANCA-associated vasculitis. This trial was terminated due to withdrawal of funding. Results of the completed phases have been published. Among the seven patients who were treated with rituximab, one patient had GCA but that patient's response to rituximab was not specified in the posted results[75].

Bhatia et al reported a 82 year old woman with GCA and accompanying polymyalgia rheumatica with a visual defect. She initially received azathioprine but it was not effective as a steroid sparing agent. Then, she received 500 mg IV cyclophosphamide, followed by 1 g rituximab. Four days after rituximab administration, patient had respiratory failure and was transferred to intensive care unit where chest x-ray demonstrated bilateral lobar consolidation. 6 months later, patient had no GCA symptoms and mildly elevated CRP[76]. Mayrbaeurl et al reported a 67 year old man with biopsy proven giant cell arteritis and mild neutropenia who was treated with rituximab as a steroid sparing agent. Patient had no adverse events as of first month of rituximab, but a longer time was needed to assess rituximab's efficacy[77]. Ruch et al reported a 64 year old man diagnosed with temporal arteritis based on clinical symptoms who initially received methotrexate as a steroid sparing agent. When this patient developed renal failure, methotrexate was stopped, work up revealed mixed cyogloblinemia and he received rituximab. This patient's giant cell arteritis did not recur under rituximab, his cryoprecipitate disappeared but he later developed catastrophic multiple organ ischemia due to an anti-Pr cold agglutinin development[78]. Lu-Emerson et al reported a 64 year old female giant cell arteritis patient with multiple ischemic strokes, whose clinical condition deteriorated despite receiving high dose glucocorticoids, 5 infusions of cyclophosphamide and rituximab, with new infarcts and she eventually passed away[79]. Larivière et al reported a 61 year old female, biopsy proven GCA patient with multiple small infarcts who initially received glucocorticoids. During steroid taper new infarcts emerged and steroid dose was increased with initiation of concomitant cyclophosphamide therapy. When patient relapsed again, rituximab was utilized. However she had new ischemic lesions under rituximab which was switched to azathioprine. Azathioprine was later switched to tocilizumab, which caused neutropenia. Patient was finally given mycophenolate mofetil with a 15 mg/day prednisone and had severe cognitive impairment[80]. In the retrospective, longitudinal follow-up study of Czihal et al, 43 patients were diagnosed with giant cell arteritis. One patient was received rituximab but there was no data about the efficacy or safety of rituximab[81]. Pradhan et al reported a very interesting case where a 83 year old female patient presented with vaginal bleeding. An endometrium polyp was detected. Polypectomy revealed well differentiated endometrioid adenocarcinoma. Subsequent hysterectomy and bilateral salpingo-oopherectomy revealed well differentiated endometrioid adenocaricnoma with accompanying findings of classic GCA that involved numerous small to medium sized arteries. Later, same patient had leukocytosis and lymphocytosis and atypical lymphoid cells were detected in peripheral blood. Bone marrow biopsy revelaed marginal zone lymphoma with rare 20q deletion. Bilateral temporal artery biopsies were also compatible with giant cell arteritis, with findings that were similar to those discovered in the genital tract. Patient received rituximab for lymphoma and corticosteroids-methotrexate combination for GCA and polymyalgia rheumatica. Patient was doing well after 3 years of follow-up, with normal acute phase reactants and not receiving any steroids[82]. Ng et al reported an 80 year old female with scleroderma who received rituximab 2 months before the presentation of giant cell arteritis. In this case rituximab could not

prevent emergence of GCA[83]. Hassane et al reported co-existence of giant cell arteritis and granulomatosis with polyangiitis in a 67 year old female who was treated with steroids and rituximab but this patient's response to treatment was not specified[84]. Mulhearn et al reported a 67 year old woman with seropositive rheumatoid arthritis who received low dose methotrexate and rituximab during onset of GCA/PMR symptoms. Rituximab could not resolve the symptoms and patient had to switch to tocilizumab[85]. Shibata et al reported a 73 year old male patient who had temporal artery biopsy proven giant cell arteritis and comcomitant ANCA positive vasculitis who was successfully treated with steroids and rituximab[86]. Coattrenec et al reported 5 granulomatosis with polyangiitis patients with accompanying large vessel vasculitides. One of these patients was a 66 year old female with aortitis and three patients had biopsy proven temporal arteritis. Among these patients 3 patients received rituximab together with glucocorticoids (one patient for induction, and the other 2 for relapses). Patient who received rituximab as induction treatment had improvement in symptoms and inflammatory markers. Efficacy of rituximab in other 2 patients who received it for relapses was not specified[87]. Finally, in their study about GCA patients with vertebral artery involvement, Prünte et al reported one patient treated with rituximab. This patient received rituximab for 2 years until he was switched to tocilizumab 3.3 years after GCA diagnosis[88].

TARGETED SYNTHETIC DRUGS

Janus Kinase Inhibitors

The Janus kinase family of nonreceptor protein-tyrosine kinases consists of JAK1, JAK2, JAK3, and TYK2 (Tyrosine Kinase 2)[89]. Janus kinase inhibitors are increasingly used in daily rheumatology practice. Tofacitinib is selective for JAK1 and JAK3, while baricitinib is selective for JAK1 and JAK2 and upadacitinib is a selective janus kinase 1 inhibitor[90]. Baricitinib is currently approved for rheumatoid arthritis whereas both tofacitinib and upadacitinib are approved for treatment of rheuatoid arthritis, axial spondylarthritis and psoriatic arthritis[91]. Ruxolitinib is an oral selective Janus kinase 1 and 2 inhibitor first approved for use in myelofibrosis[92].

When literature review was performed for "tofacitinib" OR "baricitinib" OR "upadacitinib" OR "JAK inhibitors" AND "giant cell arteritis" OR "temporal arteritis", 425 results were obtained. After exclusion of the irrelevant articles and the elimination of the duplicate results, the following studies were of interest: There was one phase 2 trial of baricitinib in GCA (NCT03026504)[93], and the results of this study were published by Koster et al[94]. Regent[95] and Prigent[96] each reported one giant cell arteritis patient treated with baricitinib. Camellino et al reported a case series of GCA and/or polymyalgia rheumatica patients treated with baricitinib[97]. There was a phase 3 trial of upadacitinib (NCT03725202)[98] and its results were published by Blockmans et al[99]. Sanada et al reported a case with both giant cell arteritis and psoriatic arthritis who was treated with upadacitinib[100]. In their article about outcomes with tocilizumab in GCA, Matza et al reported a giant cell arteritis patient treated with tofacitinib[101]. Article of Eriksson et al reported GCA patients treated with tofacitinib and baricitinib[102]. Loricera et al reported their real life experience in giant cell arteritis with tofacitinib, baricitinib and upadacitinib[103]. Herlihy et al reported ruxolitinib use, in combination with azacytidine for a case with chronic neutrophilic leukemia and associated giant cell arteritis[104].

In the trial "Baricitinib in relapsing giant cell arteritis (GCA): A phase 2, single-institution, open-label pilot study" (NCT03026504), relapsed giant cell arteritis patients were treated with baricitinib. Primary outcome was the percentage of subjects who experienced greater than or equal to one adverse event and the secondary outcomes were the number of subjects to experience relapse of GCA at 24 weeks and 52 weeks and acute phase reactant (CRP, ESR) levels[93]. Results of this study were published by Koster et al. Fifteen patients were enrolled (11 female) with a mean age at entry of 72.4 ± 7.2 years, median GCA duration of 9 months, and a median of 1 prior relapse. Four (27%) patients entered the study on prednisone at 30 mg/day, 6 (40%) at 20 mg/day, and 5 (33%) at 10 mg/day. Fourteen patients completed 52 weeks of baricitinib treatment. At week 52, 14/15 (93%) patients had ≥1 adverse events, with the most frequent events including: infection not requiring antibiotics (n=8), infection requiring antibiotics (n=5), nausea (n=6), leg swelling (n=2), fatigue (n=2), diarrhea (n=1). One subject required baricitinib discontinuation due to adverse event (reduction in estimated glomerular filtration rate). One serious adverse event was recorded. Only 1 of 14 (7%) patients relapsed during the study. The remaining 13 patients achieved steroid discontinuation and remained in disease remission during the 52-week study duration. Authors concluded that in this proof-of-concept study, baricitinib at 4 mg/day was well-tolerated and allowed glucocorticoid discontinuation in most patients with relapsing GCA, underlying the necessity of larger randomized clinical trials to determine the utility of JAK inhibition in giant cell arteritis[94].

Regent reported a 52 year old woman with contitutional symptoms, left subclavian murmur, mildly elevated C-reactive protein and PET/CT scan demonstrating significant vascular uptake of the left subclavian artery and the aorta. The diagnosis was large vessel vasculitis (overlapping between GCA and Takayasu arteritis). She received glucocorticoids, methotrexate, tocilizumab, infliximab and cyclophosphamide but vasculitis progressed and new onset symptomatic mesenteric involvement occurred. She was finally treated with baricitinib which enabled dramatic symptomatic improvement, successful glucocorticoid taper, normalized acute phase reactants and improved PET/CT uptake. She did not report any side effects during the 6 months of follow up[95]. Prigent reported a 76 year old GCA patient with accompanying PET/CT proven large vessel vasculitis, who failed to achieve remission under methotrexate and tocilizumab. She responded favorably to baricitinib both clinically and radiologically[96]. Camellino et al reported 6 patients with giant cell arteritis and/or PMR who were treated

with baricitinib. Four patients had GCA (one with cranial features, 3 with large vessel vasculitis- with 2 that had accompanying polymyalgia rheumatica). All four priorly received tocilizumab, two received methotrexate and one patient priorly received both cyclophosphamide and mycophanolate mofetil. After baricitinib treatment, two patients were in remission, where one patient was able to discontinue steroids. One patient was stable but when a PET/CT was performed to evaluate low limb claudication, large vessel vasculitis was detected which caused a switch from baricitinib back to tocilizumab. And although the fourth patient remained clinically stable under baricitinib and was able to reduce prednisolone initially, she reported constitutional symptoms at the third month and when PET/CT was performed a slight reduction in the uptake of arteries was and pulmonary uptake compatible with pneumonia were noted. She received antibiotics and was later switched back to tocilizumab[97].

The phase 3 trial "multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of upadacitinib in subjects with giant cell arteritis: SELECT-GCA" (NCT03725202) consisted of two periods. Period 1 aimed to evaluate the efficacy of upadacitinib in combination with a 26-week GC taper regimen compared to placebo in combination with a 52-week glucocorticoid taper regimen, as measured by the proportion of participants in sustained remission at week 52, and to assess the safety and tolerability of upadacitinib in GCA patients. Period 2 aimed to evaluate the safety and efficacy of continuing versus withdrawing upadacitinib in maintaining remission in participants who achieved sustained remission in period 1. Primary outcome was the percentage of participants achieving sustained remission at week 52. Secondary outcomes included the percentage of participants achieving sustained complete remission from week 12 through week 52, cumulative GC exposure through week 52, time to first disease flare through week 52, percentage of participants in complete remission at week 24 and week 52, the rate of glucocorticoid related adverse events through week 52 and patient reported outcomes regarding quality of life[98]. Blockmans published the results of this study. A total of 209 patients received 15 mg/day upadacitinib, 107 received 7.5 mg/day, and 112 received placebo; 70% of the patients had new-onset giant-cell arteritis. Upadacitinib at a dose of 15 mg/day showed superiority over placebo with respect to the primary endpoint (46.4% vs. 29.0%, p = 0.002). Upadacitinib at a dose of 15 mg was superior to placebo in the analysis of the hierarchically prespecified and multiplicity-controlled key secondary endpoints of sustained complete remission, time to a disease flare, cumulative glucocorticoid exposure, and patient-reported outcomes. Upadacitinib at a dose of 7.5 mg was not superior to placebo with respect to the primary endpoint. Safety outcomes during the treatment period of 52 weeks were similar in the upadacitinib and placebo groups. Although cardiovascular risk is a potential concern with JAK inhibitors, no major adverse cardiovascular events occurred in the upadacitinib groups. Authors concluded by underlining the superiority of 15 mg/day dose of upadacitinib in giant cell arteritis patients in comparison to placebo[99].

In addition to this study, Sanada et al reported a 72 year old female GCA patients with both temporal artery and aortic involvement. Patient also had concomitant psoriatic arthritis for which she previously received sulfasalazine. She was treated with 15 mg/day upadacitinib and high dose glucocorticoids which achieved remission of both diseases. She was able to discontinue steroids and maintained remission over a period of 7.5 months[100].

In their article about outcomes with tocilizumab in GCA, Matza et al reported a GCA patient treated with tocilizumab who previously had inadequate responses to abatacept, tofacitinib and secukinumab[101].

Eriksson et al reported the retrospective data of 15 GCA patients who were treated with Janus kinase inhibitors (tofacitinib/baricitinib). Mean daily dose of baricitinib was 3.86 (range 2−4) mg, and the patients receiving tofacitinib were all prescribed a dose of 10 mg/day . Mean age at JAK inhibitor initiation was 70.1 years and the mean exposure to Janus kinase inhibitors was 19 months. From initiation, significant reductions in CRP were seen already at 3 (p= 0.02) and 6 (p= 0.02) months. A slower decrease was observed regarding ESR at 3 (p= 0.12) and 6 (p= 0.02) months. Daily prednisolone doses were reduced at 3 (p= 0.02) and 6 (p= 0.004) months. No giant cell arteritis relapses were observed during the observed time. At the 3-month follow-up, 9 of 15 (60%) subjects fulfilled the definition of therapeutic benefit. This percentage increased at the 6-month follow-up when 11 of 15 (73%) individuals fulfilled the same outcome. At the last follow-up, 12 of 15 (80%) patients were still on daily treatment with Janus kinase inhibitors. Three patients had ceased JAK inhibitors due to sustained remission after having been on the drug for more than 2 years (range 26−29 months) One of these patients experienced a giant cell arteritis relapse with headache, jaw claudication, and temporal tenderness 1 month after ending the drug. However, baricitinib 4 mg daily was reintroduced promptly in combination with a low dose of prednisolone (7.5 mg/day) to bring his symptoms under control. Consequently, he improved, and the remaining prednisolone could be tapered out over time. During the study, no cases of malignancy nor gastrointestinal perforation were observed. Only minor effects were observed on blood cell counts over time. Alterations of blood lipid profile, resulting in the initiation of statin therapy, were not observed in any subject. Moreover, no elevation of liver enzymes was seen, and no cases of herpes zoster were found. Nevertheless, two patients were affected by serious side effects (*Aspergillus fumigatus* infection and *Enterococcus faecalis* bacteremia, respectively). JAK inhibitor therapy of these patients was retained or reintroduced after recovery[102].

In their article, Loricera et al evaluated the effectiveness of JAK inhibitors in relapsing giant cell arteritis patients in a real-world setting. They retrospectively analyzed GCA patients treated with Janus kinase inhibitors for relapsing disease at thirteen centers in Spain and one center in United States (time period: 01/2017-

12/2022). Outcomes assessed included clinical remission, complete remission and safety. Clinical remission was defined as the absence of giant cell arteritis signs and symptoms regardless of the ESR and CRP values. Complete remission was defined as the absence of GCA signs and symptoms along with normal acute phase reactants. Thirty-five patients (86% females, mean age 72.3) with relapsing giant cell arteritis received Janus kinase inhibitor therapy (baricitinib, n = 15; tofacitinib, n = 10; upadacitinib, n = 10). GCA was confirmed by temporal artery biopsy in 15 (62%) patients and by vascular imaging in 24 (69%) patients. Vascular ultrasonography was performed in 15 patients, vasculitis signs were observed in 7 of them. Before JAK inhibitor therapy, 22 (63%) patients had received conventional synthetic immunosuppressants, and 30 (86%) previously received biologic agents. Without considering concomitant glucocorticoid use, Janus kinase inhibitors were prescribed as monotherapy in 34 (97%) patients, and were combined with methotrexate in one patient. Thus, only one patient who started treatment with baricitinib concurrently used methotrexate at a dose of 10 mg per week and prednisone at a dose of 5 mg/day. Thirty-one patients started treatment with JAK inhibitors in combination with glucocorticoids, and three patients initiated Janus kinase inhibitor therapy alone. After a median follow-up of 11 (6-15.5) months, with 35 patients followed for at least one month, 33 patients followed for at least three months, 28 patients followed for at least six months and 20 patients followed for at least twelve months; most patients experienced improvement of clinical manifestations and laboratory parameters over time following JAK inhibitor therapy. Clinical remission was observed at one, three, six and twelve months in 18/35 (51%), 18/33 (54%), 17/28 (61%) and 14/20 (70%) patients, respectively.

Complete remission was observed at one, three, six and twelve months in 15/35 (43%), 16/33 (48%), 16/28 (57%) and 13/20 (65%) patients, respectively. Effectiveness was similar across all Janus kinase inhibitors. Median ESR declined significantly but the decrease in CRP was not significant. The median daily dose of prednisone decreased from 16.2 (8.7–30) mg at baseline to 5 (0-12.5) mg at last follow up ($p < 0.001$) with seven patients stopping glucocorticoids. Overall, eleven (31%) patients discontinued JAK inhibitor therapy due to relapse or persistence of active disease. Of these eleven patients, five were on tofacitinib, four on baricitinib, and two on upadacitinib. Adverse events were reported in five (14%) patients during Janus kinase inhibitor therapy, leading to JAK inhibitor discontinuation in 4 patients (causes of discontinuation included elevated liver enzymes, disseminated herpes zoster and glioblastoma multiforme diagnosis). No thromboembolism, major adverse cardiovascular events, or significant cytopenias were observed during follow-up. No cases of giant cell arteritis related permanent vision loss were reported either. This study's results encouraged the use of JAK inhibitors in GCA patients that failed tocilizumab and methotrexate therapy[103].

Finally Herlihy et al reported a 75 year old woman with seropositive rheumatoid arthritis who presented with GCA, aortitis and leukocytoclastic vasculitis, which was refractory to methylpredinisolone, methotrexate and mycophenolate mofetil. She also had alarming constitutional symptoms. During treatment with cyclophosphamide, she developed a marked neutrophilia. Bone marrow biopsy demonstrated a hypercellular marrow with markedly increased granulopoesis, dysgranulopoesis and megakaryocyte atypia, reduced erythropoesis and prominent eosinophils without basophilia. In addition, mutations supporting chronic neutrophilic leukemia were detected. She initially received hydroxycarbamide, which was ineffective. She then underwent leukapheresis, which was followed by cytarabine-ruxolitinib combination. This combination was rapidly effective in normalizing neutrophils, decreasing CRP and resolving uptake of aortitis in PET/CT. Due to this favorable response authors concluded that aortitis was a secondary paraneoplastic process to chronic neutrophilic leukemia[104].

Conclusion

Emergence of many targeted treatment modalities (biologic agents and JAK inhibitors) have greatly improved rheumatologists' ability to control inflammation in many patients with various rheumatic diseases that responded inadequately to conventional immunosuppressives. Such is also true for giant cell arteritis. GCA guidelines currently recommend tocilizumab (in relapsing refractory cases in European Alliance of Associations for Rheumatology 2018 guideline[105] and both in refractory cases and new onset disease in American College of Rheumatology 2021 guideline[106] as an effective treatment modality.

This literature review explored the efficacy and safety of many targeted treatment modalities beyond interleukin 6 inhibition in GCA and there are some hopeful new candidates. Success of upadacitinib's phase 3 trial is the most encouraging progress in this field. With the positive results of the phase 2 trial of secukinumab, results of its two ongoing phase 3 results are also eagerly awaited. Mavrilimumab and baricitinib each have one positive phase 2 clinical trials but so far, no phase 3 trial for either molecule is planned. Although phase 2 trial of abatacept was encouraging, real life data demonstrated it to be somewhat inferior to tocilizumab, reserving the molecule for patients that are contraindicated to receive tocilizumab. Ongoing phase 3 trial of abatacept in giant cell arteritis will provide more information about its efficacy once it is completed. Even though ustekinumab failed its phase 2 study in GCA, that trial was criticized for its short prednisone regimen with accelerated taper. Since there are refractory giant cell arteritis cases that responded to ustekinumab in real life setting and there are important implications of interleukin 12/23 blockade in GCA pathogenesis, it would be prudent to design a new trial of ustekinumab in giant cell arteritis patients, with a slower steroid taper regimen.

Conflict of Interest: None.

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