ANNUAL REVIEWS

Annual Review of Medicine

New Therapeutic Approaches to Large-Vessel Vasculitis

Mahmut S. Kaymakci,[1] Kenneth J. Warrington,[1] and Tanaz A. Kermani[2]

[1]Division of Rheumatology, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA; email: kaymakci.mahmut@mayo.edu, warrington.kenneth@mayo.edu

[2]Division of Rheumatology, Department of Medicine, University of California Los Angeles, Santa Monica, California, USA; email: tkermani@mednet.ucla.edu

Annu. Rev. Med. 2024. 75:427–42

First published as a Review in Advance on September 8, 2023

The *Annual Review of Medicine* is online at med.annualreviews.org

https://doi.org/10.1146/annurev-med-060622-100940

Keywords

giant cell arteritis, Takayasu arteritis, glucocorticoids, immunosuppressive therapies, biologics, tocilizumab

Abstract

Giant cell arteritis (GCA) and Takayasu arteritis (TAK) are large-vessel vasculitides affecting the aorta and its branches. Arterial damage from these diseases may result in ischemic complications, aneurysms, and dissections. Despite their similarities, the management of GCA and TAK differs. Glucocorticoids are used frequently but relapses are common, and glucocorticoid toxicity contributes to significant morbidity. Conventional immunosuppressive therapies can be beneficial in TAK, though their role in the management of GCA remains unclear. Tumor necrosis factor inhibitors improve remission rates and appear to limit vascular damage in TAK; these agents are not beneficial in GCA. Tocilizumab is the first biologic glucocorticoid-sparing agent approved for use in GCA and also appears to be effective in TAK. A better understanding of the pathogenesis of both conditions and the availability of targeted therapies hold much promise for future management.

INTRODUCTION

LVV: large-vessel vasculitis

TCZ: tocilizumab

TNFi: tumor necrosis factor inhibitors

ACR/VF: American College of Rheumatology/ Vasculitis Foundation

EULAR: European League Against Rheumatism

Giant cell arteritis (GCA) and Takayasu arteritis (TAK) are forms of large-vessel vasculitis (LVV) characterized by granulomatous inflammation affecting the aorta and its branches. GCA and TAK share clinical, histopathologic, and radiographic features (1). TAK predominantly affects females below age 50 years while GCA affects individuals over age 50 years (1–4). Clinical presentations vary; they include cranial symptoms with possible vision loss or polymyalgia rheumatica (GCA), constitutional symptoms (GCA or TAK), vascular damage with aortic aneurysms (GCA or TAK), aortic dissections (usually GCA), aortic stenosis (usually TAK), and large-artery stenosis/ occlusions with resultant ischemic manifestations such as stroke, limb claudication, or myocardial infarction (GCA or TAK) (2).

Challenges in the management of GCA and TAK include the relapsing nature and difficulty with disease activity assessment (5, 6). Despite their similarities, clinical trials showing differential responses to the same biologic therapies indicate that these two forms of LVV are distinct (7–10). Glucocorticoids (GC) used for both forms of LVV are associated with significant adverse effects. After many disappointing trials evaluating alternatives to GC in GCA, there was a breakthrough with tocilizumab (TCZ), an interleukin (IL)-6 receptor antagonist showing efficacy. TCZ is the first medication approved by the US Food and Drug Administration (FDA) for the treatment of GCA (11). For TAK, currently, there are no FDA-approved therapies. Given the rarity of TAK, most of the data informing treatment have come from observational studies or open-label trials, though in recent years, two randomized controlled trials (RCTs) have been completed (8, 10, 12). Conventional immunosuppressive medications are added in TAK to allow tapering of GC, but many patients have disease progression despite this (13, 14). Targeted biologic agents such as tumor necrosis factor inhibitors (TNFi) and TCZ are beneficial (13, 14).

In this article, we review the data supporting the current treatment of LVV, including published guidelines from the American College of Rheumatology/Vasculitis Foundation (ACR/VF), and recommendations from the European League Against Rheumatism (EULAR) (13, 14). We also review novel targeted approaches under investigation.

GENETIC ASSOCIATIONS, PATHOGENESIS, AND THERAPEUTIC IMPLICATIONS

An understanding of the pathogenesis and genetics of LVV has been important to the identification of novel and targeted therapies (**Figure 1**, **Table 1**). The strongest genetic associations are within the major histocompatibility complex (MHC) for both diseases, though GCA is associated with MHC class II polymorphisms (HLA-DRB1*04, HLA-DQA1*03, and HLA-DQB1*03 alleles) whereas TAK susceptibility is associated with MHC class I alleles, particularly HLA B*52:0 (15–17). The non-MHC associations include the IL-12B locus in TAK and PTNP22 (protein tyrosine phosphatase nonreceptor type 22) in GCA (15, 16, 18, 19). However, meta-analysis of genomic data in GCA and TAK found a common non-HLA association within the IL-12B locus (15). IL-12 plays a role in the proliferation of T helper 1 (Th1) cells and is important in the pathogenesis of GCA and TAK (20).

Giant Cell Arteritis

Activation of vascular dendritic cells residing in the adventitial-medial border of the arterial wall and subsequent activation of T cells and macrophages with migration into the vessel wall via the vasa vasorum play an important role (21, 22). Loss of self-tolerance in the adaptive immune system is linked to aberrant signaling in the NOTCH (neurogenic locus notch homolog) pathway

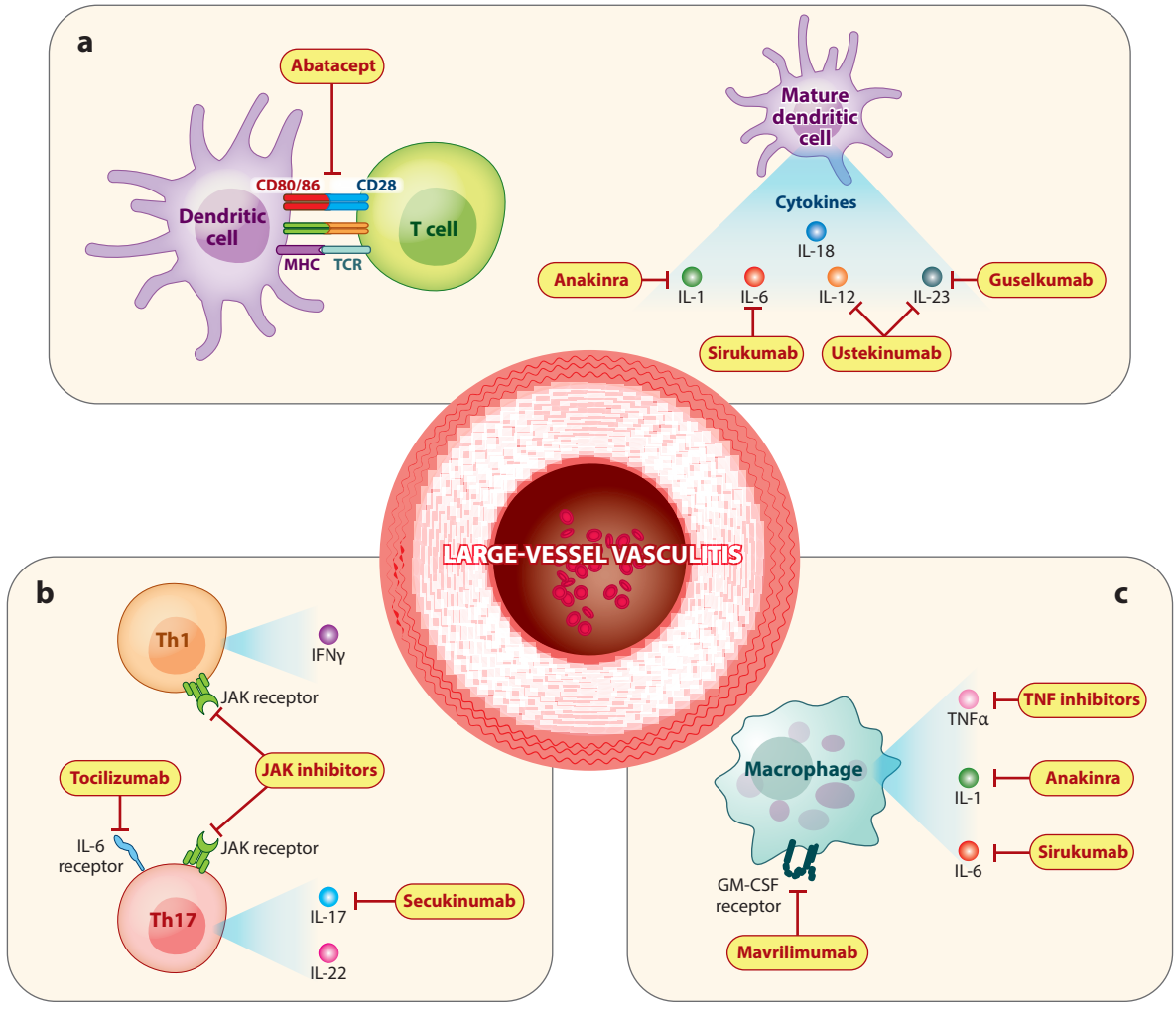

Figure 1

Immune mediators of inflammation in large-vessel vasculitis and available potential therapeutic targets. (*a*) Dendritic cells interact with T cells and also produce cytokines. (*b*) T helper (Th1) cells and Th17 cells and their effector cytokines are important in the pathogenesis of both forms of large-vessel vasculitis. (*c*) Macrophages also play an important role in the production of pro-inflammatory cytokines and amplification of the inflammatory pathways. The role of B cells (not shown) remains unclear. Abbreviations: CD, cluster of differentiation; GM-CSF, granulocyte macrophage-colony stimulating factor; IFN, interferon; IL, interleukin; JAK, Janus kinase; MHC, major histocompatibility complex; TCR, T cell receptor; TNF, tumor necrosis factor. Figure adapted from images created with BioRender.com.

(23). Downregulation of checkpoint inhibitor PDL1 (programmed cell death protein ligand 1) results in increased T cell activation (24). The cytokines produced by dendritic cells drive the differentiation of naïve T cells to Th1 (via IL-12 or IL-18) with production of interferon gamma (IFNγ) or Th17 (via IL-6 and IL-1β) with production of IL-17 (25). While the Th17 arm of the inflammatory cascade is sensitive to GC, the IFNγ-producing Th1 responses persist despite treatment (25). Macrophage activation and granuloma formation are driven by IFNγ and granulocyte-macrophage colony stimulating factor (GM-CSF). GM-CSF and its receptor

Table 1 Summary of targeted therapies for treatment of giant cell arteritis (GCA) and Takayasu arteritis (TAK) with highest level of evidence[a] and upcoming studies

Immune player/pathway	Therapeutic agent	Mechanism of action	Highest published evidence, GCA	Ongoing or upcoming studies, GCA	Highest published evidence, TAK	Ongoing or upcoming studies, TAK
B cells	Rituximab	mAb CD20	None	None	Case series (73–75)	None
T cells	Abatacept	CTLA-4Ig	Double-blinded phase II RCT, positive data (9)	NCT04474847	Double-blinded phase II RCT, no efficacy (10)	None
JAK/STAT	Baricitinib	JAK1/JAK2 inhibitor	Open-label phase II study, positive data (84)	None	Case series, 2 patients (32)	None
	Tofacitinib	JAK1/JAK3 inhibitor	None	None	Prospective observational studies; 1) compared to MTX, possibly superior to MTX (85) 2) compared to LEF, similar efficacy (86)	NCT04299971 NCT05151848 NCT05102448 NCT05749666
	Upadacitinib	JAK1 inhibitor	None	NCT03725202	None	NCT04161898
Cytokines						
IL-1	Anakinra	Recombinant IL-1 receptor antagonist	Case series of 6 patients, reported efficacy (76)	NCT02902731 but status unknown (last updated Feb. 2020)	Case series of 4 patients, no efficacy (77)	None
IL-6	Tocilizumab	IL-6 receptor antagonist	Double-blinded phase III study (63), positive data; FDA-approved therapy	NCT03892785 NCT04239196	Double-blinded phase III study (12), positive data in per protocol analysis	NCT04300686
	Sirukumab	IL-6 inhibitor	Double-blinded phase III RCT (64), terminated early with primary endpoint evaluable in only 28 of 161 randomized patients; reported efficacy	None	None	None
IL-12	Ustekinumab	IL-12/IL-23 inhibitor	Open-label trials (78, 79), one with possible efficacy and another terminated early due to lack of efficacy	NCT03711448	Case series (80), 3 patients with reported efficacy	NCT04882072

(*Continued*)

Table 1 (*Continued*)

Immune player/pathway	Therapeutic agent	Mechanism of action	Highest published evidence, GCA	Ongoing or upcoming studies, GCA	Highest published evidence, TAK	Ongoing or upcoming studies, TAK
IL-17	Secukinumab	IL-17 inhibitor	Double-blinded phase II study (81), positive data	NCT04930094 NCT05380453	Prospective open-label study (82) comparing secukinumab to TNFi, comparable efficacy	None
IL-23	Guselkumab	IL-23 inhibitor	None	NCT04633447	None	None
	Ustekinumab	IL-12/IL-23 inhibitor	As above	As above	As above	As above
TNFα	Adalimumab	Human mAb inhibitor of TNFα	Double-blinded phase III RCT (55), no efficacy	None	Data available in meta-analyses showing efficacy of this class of medications	NCT04300686 NCT05151848
	Infliximab	Chimeric mAb inhibitor of TNFα	Double-blinded phase II RCT (53), no efficacy	None	Open-label prospective study (60), reported efficacy	NCT04564001
	Etanercept	Fusion protein inhibitor of TNFα	Double-blinded phase II RCT (54), study too small to draw conclusions	None	Open-label prospective study (60), reported efficacy	None
	Golimumab	Human mAb inhibitor of TNFα	None	None	Data available in meta-analyses showing efficacy of this class of medications	None
GM-CSF	Mavrilimumab	GM-CSF receptor antagonist	Double-blinded phase II RCT (83), positive data	None	None	None

[a]Only case series or higher level of evidence considered; case reports not included.

Abbreviations: CTLA4-Ig, cytotoxic T lymphocyte–associated antigen 4 immunoglobulin; FDA, US Food and Drug Administration; GM-CSF, granulocyte macrophage-colony stimulating factor; IL, interleukin; JAK, Janus kinase; LEF, leflunomide; mAb, monoclonal antibody; MTX, methotrexate; RCT, randomized controlled trial; STAT, signal transducer and activator of transcription; TNFα, tumor necrosis factor alpha; TNFi, tumor necrosis factor inhibitors.

(GM-CSFRα) are upregulated in the arterial wall in GCA (26). Activation of the JAK2/STAT5 (Janus kinase 2 signal transducer and activator of transcription 5) signaling pathway for GM-CSF is seen in GCA temporal arteries (26). Activated macrophages produce proinflammatory cytokines (IL-1, IL-6, tumor necrosis factor α), matrix metalloproteinases, reactive oxygen species, fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor, which amplify the inflammatory pathways and contribute to vascular damage and remodeling (22). B cells can be present in GCA lesions, where they occasionally form tertiary lymphoid organs, particularly in aortic tissue, but the functional significance is currently unknown (27, 28).

Takayasu Arteritis

The pathogenesis of TAK shares many similarities with GCA, notably the predominant role of Th1/Th17 cells and increased expression of NOTCH1 in $CD4^+$ T cells (29, 30). However, the increased number of $CD8^+$ T cells and the prominent role of natural killer cells in TAK distinguish it from GCA (31). Similar to GCA, the JAK/STAT pathway plays an important role in the pathogenesis of TAK (32). Th1 and Th17 cell differentiation depends on type 1 and type 2 cytokines, and they act through the JAK/STAT pathway (30). In contrast to GCA, the Th1 pathway is responsive to GC treatment in TAK, and the Th17 pathway persists (30). B cells are also thought to play a role in the pathogenesis of TAK. Patients with active TAK are found to have higher plasmablasts than those with inactive TAK (33). Furthermore, highly reactive antiendothelial antibodies were detected in the sera of patients with TAK (34).

GLUCOCORTICOID THERAPY

GC are potent anti-inflammatory and immunosuppressive medications used for the treatment of GCA and TAK due to their rapid onset of action (35).

Giant Cell Arteritis

Since the initial publication in 1957 showing efficacy of cortisone in GCA including in the prevention of vision loss, GC have been the mainstay of treatment (36). Given the risk of vision loss in GCA from arteritic anterior ischemic optic neuropathy, a sudden and often irreversible complication, it is important to initiate therapy with GC promptly while awaiting additional diagnostic studies to confirm the diagnosis (2). Despite their widespread use, the optimal dose, taper, and duration of therapy remain unknown. There are scant prospective data evaluating the efficacy of intravenous (IV) GC in patients with severe ischemic manifestations including vision loss (8). Both the EULAR recommendations and the ACR/VF guideline recommend initiation of high-dose GC (prednisone or equivalent 40–60 mg or 1 mg/kg up to 80 mg) in patients with active GCA (13, 14). Despite the absence of high-quality data, both recommend consideration of IV methylprednisolone for patients with vision loss (13, 14).

GC taper has not been studied prospectively, though there are data from the RCT of TCZ in GCA (GiACTA) (11). GiACTA included two placebo arms, a rapid 26-week GC taper, and a 52-week GC taper. Relapses were noted in 68% of subjects in the placebo group with the 26-week taper and 49% of those in the placebo group with the 52-week taper. Interestingly, the cumulative GC doses at the end of the study were similar in both placebo arms (3.3 g in the 26-week group and 3.8 g in the 52-week group), likely reflecting relapses in the 26-week arm requiring increases in GC dose. If GC monotherapy is used, a more gradual GC taper may be beneficial, whereas in patients receiving TCZ, the 26-week GC taper as in the clinical trial is used in clinical practice (11).

Given the efficacy of TCZ, studies evaluating the shortest exposure to GC are of interest. In a small proof-of-concept study, 18 patients with newly diagnosed GCA were treated with IV methylprednisolone 500 mg for 3 consecutive days without further GC (37). All patients received one infusion of TCZ 8 mg/kg followed by TCZ 162 mg subcutaneously weekly for 52 weeks. The primary endpoint of percentage of patients in remission at day 31 was met in only 25%, though 78% were in remission within 24 weeks. Additionally, 17% required rescue GC treatment due to persistent symptoms, and 1 patient developed vision loss from arteritic anterior ischemic optic neuropathy at day 15 (37).

MTX: methotrexate

LEF: leflunomide

EULAR recommendations suggest tapering GC to 15–20 mg/day within 2–3 months with a goal of ≤5 mg by the end of 1 year, while the ACR/VF guideline emphasizes minimizing GC exposure but recommends this be a joint discussion guided by the patient's values and preferences (13, 14).

Takayasu Arteritis

There are no well-designed studies evaluating the efficacy of GC in TAK (7). A favorable response to GC has been observed in clinical practice (38); however, the optimal treatment regimen of GC in TAK is still largely unknown. The prospective data we have on GC monotherapy are from the GC/placebo arms of the abatacept and TCZ trials, both of which reported a high relapse rate of 60% (10, 12).

The ACR/VF guideline and EULAR recommendations advise starting high-dose GC for patients with active TAK (40–60 mg/day prednisone or equivalent per EULAR; prednisone 1 mg/kg/day up to 80 mg or equivalent per ACR/VF) (13, 14). EULAR recommends a target GC dose of ≤10 mg/day after 1 year of treatment for patients in remission, whereas ACR/VF recommends tapering off GC for patients in remission after 6–12 months of treatment (13, 14).

ADJUNCTIVE THERAPY

GC therapy, while effective, is also associated with significant adverse effects (39, 40). Furthermore, despite treatment, relapses are frequent and new vascular damage can occur (41–43). EULAR recommends adjunctive immunosuppression with TCZ in patients with GCA and refractory or relapsing disease, or in patients at increased risk of GC adverse effects, while the ACR/VF guideline recommends the initiation of TCZ with GC in all patients with newly diagnosed GCA (13, 14). In contrast, for TAK, both guidelines recommend starting conventional immunosuppressive agents concomitantly with GC, with the ACR/VF guideline also considering TNFi as a first-line option (13, 14).

CONVENTIONAL IMMUNOSUPPRESSION

Giant Cell Arteritis

Three RCTs evaluating methotrexate (MTX) in patients with newly diagnosed GCA yielded conflicting results (44–46). However, the doses ranged from 7.5 to 15 mg/week, limiting the interpretation. A subsequent meta-analysis showed some benefit of MTX in lowering relapses and allowing GC sparing (47). MTX may be considered in patients with contraindications to TCZ, or in cases where cost may be a barrier to TCZ.

A recent prospective, open-label study evaluated leflunomide (LEF) in 215 patients with newly diagnosed GCA (48). However, at week 12, patients were offered LEF 10 mg/day and opted in or out. In the 151 patients treated with LEF and 64 patients who continued in the GC monotherapy,

relapses after initiation of LEF were fewer in the treatment arm (15%) than in the GC arm (45%). The study design, however, makes the benefits of LEF difficult to assess.

There are no well-designed clinical studies to support the routine clinical use of cyclosporine, azathioprine or cyclophosphamide (8).

Takayasu Arteritis

The current evidence regarding efficacy of conventional immunosuppressive therapy in TAK is based on retrospective or small, open-label studies. In an open-label pilot study, 16 patients with TAK refractory to GC monotherapy were treated with weekly MTX (mean dose of 17.1 mg) and GC (49). Thirteen (81%) patients achieved remission, although 44% of the patients experienced relapse upon GC taper or discontinuation (49).

A retrospective study compared the efficacy of LEF and MTX in 68 patients with TAK (50). Patients were treated with MTX and GC ($n = 28$) or LEF and GC ($n = 40$). At the end of 12 months of follow-up, there was no difference in the rate of complete remission between the MTX and LEF groups (69.23% versus 78.38%, $p = 0.21$), though the LEF group had fewer relapses than the MTX group (7.24% versus 16.67%, $p = 0.03$) (50).

Limited data suggest efficacy of mycophenolate mofetil in TAK. A meta-analysis of two observational studies showed clinical improvement in 29 patients, including a decrease in the level of acute phase reactants and GC dosage (51). Two additional patients had severe adverse events from mycophenolate mofetil requiring discontinuation of treatment.

A prospective study of 15 patients with newly diagnosed TAK treated with azathioprine and GC for 1 year found efficacy. All patients experienced an improvement in their systemic symptoms in 3 months, with reduction in acute phase reactants and angiographic stability at 1 year (52).

Although several studies showed the efficacy of cyclophosphamide in TAK, its severe side effect profile (hemorrhagic cystitis, infertility, etc.) limits its use in this young patient population (7, 13, 14). There is currently an ongoing RCT evaluating LEF (NCT02981979) and two efficacy studies comparing MTX to other targeted therapies (NCT05102448, NCT04299971).

Given the absence of good comparison studies, in clinical practice the decision regarding which medication to use takes into consideration comorbidities, any contraindications, and factors such as plans for pregnancy.

TARGETED THERAPIES: TUMOR NECROSIS FACTOR INHIBITORS

Despite the importance of macrophages and TNFα in the pathogenesis of GCA, studies evaluating three different TNFi failed to show efficacy in GCA (53–55). In contrast to the disappointing results in GCA, TNFi have been extensively used for the treatment of TAK, with several retrospective studies showing efficacy (7, 56–61). A multicenter, open-label, prospective study of infliximab found GC-sparing effects with a reduction of disease activity in 64% of treated patients (62). In another prospective, open-label study, 10 of 15 patients with relapsing TAK had sustained remission with TNFi and were able to discontinue GC (60). Further supporting the efficacy of TNFi in TAK, a population-based study from Norway of 78 patients found higher sustained remission rates among those treated with TNFi versus conventional immunosuppressive agents (42% versus 20%, $p = 0.03$) (58). Moreover, fewer patients treated with TNFi developed new vascular lesions within the first 2 years after initiation of therapy compared to other immunosuppressive agents and GC monotherapy (10%, 40%, and 92%, respectively) (58). In a meta-analysis of 15 studies involving 208 patients with TAK treated with TNFi, at least a partial response to treatment was noted in 81% of the patients, with significant heterogeneity across the studies. Among 148 patients with radiographic data, 86% had stabilization (57).

The ACR/VF guideline suggests use of TNFi as a possible first-line alternative to other immunosuppressive agents, while EULAR recommends TNFi for relapsing or refractory disease (13, 14).

TARGETED THERAPIES: INTERLEUKIN-6 INHIBITION

Giant Cell Arteritis

Two prospective, randomized trials demonstrated efficacy of TCZ, an IL-6 receptor antagonist, in GCA (11, 63). In a phase II, double-blind, placebo-controlled trial, 30 patients with GCA were randomized to TCZ 8 mg/kg intravenously every 4 weeks for 52 weeks ($n = 20$) and GC, or placebo and GC ($n = 10$) (63). The primary endpoint of complete remission on a prednisolone dose of $\leq$0.1 mg/kg/day at week 12 was met in 85% of patients in the TCZ group compared to 40% in the placebo group ($p = 0.03$) (63). In GiACTA (11), a multicenter, phase III RCT, 251 patients with newly diagnosed or relapsing GCA were randomized to placebo with a 26-week prednisone taper (50 patients), placebo with a 52-week prednisone taper (51 patients), subcutaneous TCZ 162 mg every other week with a 26-week prednisone taper (50 patients), or TCZ 162 mg weekly with a 26-week prednisone taper (100 patients). The primary endpoint of sustained GC-free remission at week 52 was met in 56% of patients in the TCZ-weekly arm and 53% in the TCZ-every-other-week arm, compared to 14% for placebo-26-week prednisone taper and 18% for placebo-52-week prednisone taper ($p < 0.001$). Relapses were lower in the treatment arms: 23% in the weekly-TCZ arm and 26% in the TCZ-every-other-week arm compared to 68% in the placebo group with 26-week prednisone taper and 49% in the placebo group with 52-week prednisone taper. Median cumulative GC dose at the end of 52 weeks in patients treated with TCZ was 1,862 mg in each of the TCZ groups compared with 3,296 mg in the placebo-26-week group and 3,818 mg in the placebo-52-week group (11).

A multicenter, phase III RCT evaluating sirukumab, a monoclonal antibody IL-6 antagonist, was terminated early (sponsor decision) (64). Only 28 of the 161 patients who were randomized had data at week 52 when the primary endpoint was assessed, limiting interpretation.

The duration of treatment with TCZ remains unknown. In the GiACTA trial, at the end of the 52-week study, patients entered a 104-week open-label arm with continuation of GC, MTX, and/or TCZ or discontinuation of therapy at the discretion of the investigator (65). Given the nonrandomized nature of the open label, the data need to be interpreted with caution, but only 42% of patients in the weekly-TCZ arm who were in clinical remission at week 52 off all treatment were able to stay in drug-free remission (65). Therefore, a subset of patients with GCA may require long-term therapy with TCZ, though optimal duration of treatment is unknown. The impact of TCZ on long-term outcomes such as aortic aneurysms or vascular damage is also unknown at this time.

Takayasu Arteritis

Since the FDA approval of TCZ for GCA in 2017, several studies have assessed its efficacy in TAK, including a double-blinded RCT (TAKT) and its open-label extension study (12, 66–70). In the TAKT trial (12), 36 patients with active TAK were randomized to weekly TCZ ($n = 18$) or placebo ($n = 18$) with GC taper by 10% per week to a minimum of 0.1 mg/kg/day. The study did not meet its primary endpoint of time to relapse in the intention-to-treat analysis, though a per-protocol analysis showed a difference in favor of TCZ. Additionally, the relapse rate at 24 weeks was 51% in the placebo arm compared to 23% in the TCZ arm, suggesting benefit (12).

Other studies suggest efficacy of TCZ in both treatment-naïve and treatment-refractory TAK (12, 40, 66, 67, 69, 70). A meta-analysis of 20 uncontrolled studies in TAK treated with TCZ

showed a clinical response in 85% of the patients, and the pooled analysis of 12 studies showed angiographic stabilization in 82% (68).

Retrospective studies suggest similar efficacy between TNFi and TCZ in TAK (66–68). A large observational cohort of 209 patients with TAK treated with TNFi (132 patients) or TCZ (77 patients) found equivalent efficacy, relapse, and retention rates with no difference in adverse effects (67). Another meta-analysis of six comparative studies revealed comparable clinical remission, angiographic stabilization, and adverse events among patients treated with TNFi versus TCZ (68).

One of the challenges with TCZ is the normalization of acute phase reactants, particularly the C-reactive protein, which can hinder disease assessment. There are reports of clinical and radiographic disease progression in patients on treatment with normal markers of inflammation (71). In a post hoc analysis of 28 patients from the TAKT clinical trial with imaging at week 96, new lesions were noted in 29%, suggesting a need for more frequent radiographic evaluation, at least initially (72).

EULAR recommends TNFi or TCZ for refractory disease, whereas the ACR/VF guideline favors TNFi over TCZ in TAK (13, 14).

OTHER THERAPIES UNDER INVESTIGATION

Despite the currently available therapies, relapses still occur. Furthermore, while many of the treatments allow reduction of GC, options that allow discontinuation of GC in TAK should be prioritized. There may be contraindications to the currently available treatments or adverse events that limit their use. As a result, there has been much interest in finding other options. **Table 1** includes other targeted therapies under investigation.

T Cell Target: Abatacept

Abatacept is a cytotoxic T lymphocyte–associated antigen 4 immunoglobulin (CTLA-4Ig) that binds to CD80 and CD86, blocking the interaction with CD28, and acts as a negative regulator of CD28-mediated T cell costimulation. In a randomized, phase II, double-blind, multicenter trial by Langford et al., 49 patients with newly diagnosed or relapsing GCA were treated with IV abatacept on days 1, 15, and 29 and week 8 with a standardized prednisone taper (9). At week 12, patients in remission were randomized to either abatacept monthly with continued GC taper or placebo with GC taper. The relapse-free survival at 12 months was 48% for the abatacept group compared to 31% for the placebo group ($p = 0.049$) (9). A phase III study is currently underway (NCT04474847).

Using the same design as in their GCA trial, Langford et al. conducted a randomized, phase II, double-blind, multicenter trial of abatacept for TAK (10). Thirty-four newly diagnosed or relapsing patients with TAK were included. The primary endpoint of relapse-free survival at 12 months was not met (22% for the abatacept group, 40% for the placebo group; $p = 0.853$) (10). This is an interesting although disappointing finding, given the role of T cells in the pathogenesis of TAK.

B Cell Target: Rituximab

There are no convincing data on rituximab, a monoclonal anti-CD20 antibody, for the treatment of GCA. The role of B cells in the pathogenesis of GCA remains unclear and this may not be an important therapeutic target. However, studies have implicated B lymphocytes in the pathophysiology of TAK (2). The current evidence of the efficacy of rituximab for TAK is based on case reports and small case series in patients with refractory disease (73–75). In a review of 27 cases

treated with rituximab, 73% had a clinical response, and among 13 patients who had radiographic evaluation before and after rituximab therapy, 9 (69%) showed improvement in imaging findings (75). Prospective clinical trials are needed to further characterize the efficacy of rituximab in TAK.

Cytokine Inhibition: IL-1

A case series of six patients with GCA showed possible efficacy of anakinra, a recombinant IL-1 receptor antagonist. Clinical and biologic remission was reported in all patients, including radiographic improvement in four patients with LVV (76). A prospective RCT is underway (NCT02902731).

A retrospective, single-center study evaluating biologic therapies in TAK reported four patients treated with kineret, but all discontinued the therapy due to inefficacy (77). It is difficult to draw any conclusions and there are no current studies evaluating this therapeutic target in TAK.

Cytokine Inhibition: IL-12 and IL-23

Two open-label trials in GCA evaluated ustekinumab, a humanized IgG1 monoclonal antibody that binds to the p40 subunit of IL-12 and IL-23. The two reached contradictory results but also included different populations (78, 79). A prospective, open-label study of 25 patients with refractory GCA treated with ustekinumab found a GC-sparing effect in all patients, with no relapses while on treatment (78). A recent, open-label trial of 13 patients with new-onset or relapsing GCA treated with ustekinumab with a 24-week rapid GC taper prematurely closed enrollment after 7 of the 10 patients experienced a relapse and 77% of patients failed to meet the primary endpoint of prednisone-free remission (79). Despite the disappointing results, a randomized, double-blind, proof-of-concept study using guselkumab, a monoclonal antibody that binds to the p19 subunit of IL-23, is underway (NCT 04633447).

Similarly, based on the importance of IL-12 and IL-23 in the pathogenesis of TAK, and polymorphisms in the IL-12 gene, ustekinumab may be beneficial in TAK. A study of three patients treated with ustekinumab reported promising results (80). An ongoing phase III trial in Japan with an estimated enrollment of 50 participants is underway (NCT04882072).

Cytokine Inhibition: IL-17

Secukinumab is a monoclonal antibody that selectively binds IL-17A. In a multicenter, phase II, double-blind RCT, patients with new-onset or relapsing GCA were randomized to secukinumab and GC (27 patients) or placebo and GC (25 patients) (81). The results are available only in abstract form but show promise and require confirmation in larger trials. A phase III study is currently underway (NCT04930094).

A prospective, open-label study compared the efficacy of adding secukinumab ($n = 19$) versus TNFi ($n = 34$) to the treatment of patients with refractory TAK who were on immunosuppressive agents. In intention-to-treat analysis, complete response rates (clinical remission, no progression on imaging, normal markers of inflammation, and GC dose <15 mg) were similar: at 12 weeks, 31.6% in the secukinumab group versus 52.9% in the TNFi group; at 24 weeks, 47.3% in the secukinumab group and 55.9% in the TNFi group (82). These results suggest that secukinumab may be a useful treatment for refractory TAK.

Cytokine Inhibition: Granulocyte Macrophage-Colony Stimulating Factor

Mavrilimumab is an IgG4 monoclonal antibody that binds to the GM-CSFRα. In a phase II, multicenter, randomized, double-blind, placebo-controlled trial, 70 patients with new-onset or

relapsing GCA were treated with mavrilimumab and GC ($n = 42$) or placebo and GC ($n = 28$) (83). A greater proportion of patients in the treatment arm met the primary endpoint of sustained remission at week 26 (83%) compared to the placebo arm (50%) (83). There are no studies evaluating this treatment for TAK, but given the mechanism of action and the pathogenesis of TAK, mavrilimumab may be an option worth exploring.

Signal Inhibition: JAK-STAT Inhibitors

In an open-label study, 15 patients with relapsing GCA were treated with baricitinib (a JAK1/JAK2 inhibitor). Only 1 of the 14 patients who completed the study had relapsed at week 52, and the remaining 13 patients were able to completely discontinue GC (84). Four of 14 patients (29%) flared in the 12-week follow-up after baricitinib discontinuation (84). A phase III study evaluating upadacitinib (a JAK1 inhibitor) is ongoing (NCT03725202).

The JAK/STAT pathway has been found to play an important role in the pathogenesis of TAK (32), and JAK inhibitors are emerging as a treatment option. A prospective, observational study compared the efficacy and safety of tofacitinib (a JAK1/JAK3 inhibitor) and MTX in 53 patients with treatment-naïve and refractory TAK (85). At the end of 12 months, 88% in the tofacitinib group had complete remission compared to 57% treated with MTX (85).

In another prospective, observational study (86), 67 patients with TAK were treated with tofacitinib and GC ($n = 32$) or LEF and GC ($n = 35$). The response rates were similar in both groups at 6 months (88% tofacitinib, 89% LEF) and 12 months (72% tofacitinib, 71% LEF). Radiographic improvement was observed in more patients in the tofacitinib group (25%) compared to LEF (6%) ($p = 0.04$). More patients in the tofacitinib group were in remission and on a dose of $\leq$7.5 mg GC after 12 months of treatment (46.88% versus 17.14%, $p = 0.02$) (86). A small series of two patients treated with barcitinib has also been published (32). There are ongoing trials of tofacitinib (NCT04299971) and upadacitinib (NCT04161898) for TAK.

SUMMARY

Over the past decade, numerous advances have been made in the treatment of GCA and TAK, including the first FDA-approved medication for GCA and the conduct of the first two RCTs in TAK. These steps, along with a better understanding of the pathogenesis of both conditions, have paved the way for additional studies evaluating targeted approaches, as evidenced by the numerous RCTs currently ongoing. Ongoing challenges include the lack of standardized outcome measures for use in clinical trials. International collaborative efforts to address these are underway (5). In GCA, it is unclear whether certain subsets (e.g., extracranial disease) would benefit from earlier initiation of adjunctive therapies. The impact of medications like TCZ on severe complications, including development of aortic aneurysms, is unclear. Despite treatment, relapses occur, and a significant proportion of patients with TAK ultimately require revascularization procedures to repair vascular damage (2). Clinical trials in GCA and TAK do not regularly incorporate imaging studies, and much uncertainty exists about the optimal modalities and interpretation of imaging findings such as persistent vessel wall edema. Imaging may be an important outcome measure in patients with LVV and, in the future, may help determine optimal duration of therapy. Cost and access to biologic medications are also important considerations in routine clinical practice. Studies to address the optimal combination of therapeutics, duration of treatment, long-term impact on quality of life, and vascular damage are needed. Regardless, the therapeutic landscape in these two forms of vasculitis is rapidly changing, with many promising new alternatives to address the unmet needs.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

LITERATURE CITED

1. Jennette JC, Falk RJ, Bacon PA, et al. 2013. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheumatol.* 65:1–11
2. Pugh D, Karabayas M, Basu N, et al. 2022. Large-vessel vasculitis. *Nat. Rev. Dis. Primers* 7:93
3. Grayson PC, Ponte C, Suppiah R, et al. 2022. 2022 American College of Rheumatology/EULAR classification criteria for Takayasu arteritis. *Ann. Rheum. Dis.* 81:1654–60
4. Ponte C, Grayson PC, Robson JC, et al. 2022. 2022 American College of Rheumatology/EULAR classification criteria for giant cell arteritis. *Ann. Rheum. Dis.* 81:1647–53
5. Aydin SZ, Robson JC, Sreih AG, et al. 2019. Update on outcome measure development in large-vessel vasculitis: report from OMERACT 2018. *J. Rheumatol.* 46:1198–201
6. Boleto G, Berti A, Merkel PA, et al. 2022. Measurement properties of outcome instruments for large-vessel vasculitis: a systematic literature review. *J. Rheumatol.* 50:789–98
7. Agueda AF, Monti S, Luqmani RA, et al. 2019. Management of Takayasu arteritis: a systematic literature review informing the 2018 update of the EULAR recommendation for the management of large vessel vasculitis. *RMD Open* 5:e001020
8. Monti S, Agueda AF, Luqmani RA, et al. 2019. Systematic literature review informing the 2018 update of the EULAR recommendation for the management of large vessel vasculitis: focus on giant cell arteritis. *RMD Open* 5:e001003
9. Langford CA, Cuthbertson D, Ytterberg SR, et al. 2017. A randomized, double-blind trial of abatacept (CTLA-4Ig) for the treatment of giant cell arteritis. *Arthritis Rheumatol.* 69:837–45
10. Langford CA, Cuthbertson D, Ytterberg SR, et al. 2017. A randomized, double-blind trial of abatacept (CTLA-4Ig) for the treatment of Takayasu arteritis. *Arthritis Rheumatol.* 69:846–53
11. Stone JH, Tuckwell K, Dimonaco S, et al. 2017. Trial of tocilizumab in giant-cell arteritis. *N. Engl. J. Med.* 377:317–28
12. Nakaoka Y, Isobe M, Takei S, et al. 2018. Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomised, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study). *Ann. Rheum. Dis.* 77:348–54
13. Hellmich B, Agueda A, Monti S, et al. 2020. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. *Ann. Rheum. Dis.* 79:19–30
14. Maz M, Chung SA, Abril A, et al. 2021. 2021 American College of Rheumatology/Vasculitis Foundation guideline for the management of giant cell arteritis and Takayasu arteritis. *Arthritis Rheumatol.* 73:1349–65
15. Carmona FD, Coit P, Saruhan-Direskeneli G, et al. 2017. Analysis of the common genetic component of large-vessel vasculitides through a meta-Immunochip strategy. *Sci. Rep.* 7:43953
16. Carmona FD, Mackie SL, Martin JE, et al. 2015. A large-scale genetic analysis reveals a strong contribution of the HLA class II region to giant cell arteritis susceptibility. *Am. J. Hum. Genet.* 96:565–80
17. Ortiz-Fernandez L, Saruhan-Direskeneli G, Alibaz-Oner F, et al. 2021. Identification of susceptibility loci for Takayasu arteritis through a large multi-ancestral genome-wide association study. *Am. J. Hum. Genet.* 108:84–99
18. Terao C, Yoshifuji H, Kimura A, et al. 2013. Two susceptibility loci to Takayasu arteritis reveal a synergistic role of the IL12B and HLA-B regions in a Japanese population. *Am. J. Hum. Genet.* 93:289–97
19. Wen X, Chen S, Li P, et al. 2017. Single nucleotide polymorphisms of IL12B are associated with Takayasu arteritis in Chinese Han population. *Rheumatol. Int.* 37:547–55
20. Teng MW, Bowman EP, McElwee JJ, et al. 2015. IL-12 and IL-23 cytokines: from discovery to targeted therapies for immune-mediated inflammatory diseases. *Nat. Med.* 21:719–29
21. Ma-Krupa W, Jeon MS, Spoerl S, et al. 2004. Activation of arterial wall dendritic cells and breakdown of self-tolerance in giant cell arteritis. *J. Exp. Med.* 199:173–83
22. Weyand CM, Goronzy JJ. 2023. Immunology of giant cell arteritis. *Circ. Res.* 132:238–50

23. Piggott K, Deng J, Warrington K, et al. 2011. Blocking the NOTCH pathway inhibits vascular inflammation in large-vessel vasculitis. *Circulation* 123:309–18
24. Zhang H, Watanabe R, Berry GJ, et al. 2017. Immunoinhibitory checkpoint deficiency in medium and large vessel vasculitis. *PNAS* 114:E970–79
25. Deng J, Younge BR, Olshen RA, et al. 2010. Th17 and Th1 T-cell responses in giant cell arteritis. *Circulation* 121:906–15
26. Corbera-Bellalta M, Alba-Rovira R, Muralidharan S, et al. 2022. Blocking GM-CSF receptor alpha with mavrilimumab reduces infiltrating cells, pro-inflammatory markers and neoangiogenesis in ex vivo cultured arteries from patients with giant cell arteritis. *Ann. Rheum. Dis.* 81:524–36
27. Graver JC, Boots AMH, Haacke EA, et al. 2019. Massive B-cell infiltration and organization into artery tertiary lymphoid organs in the aorta of large vessel giant cell arteritis. *Front. Immunol.* 10:83
28. Ciccia F, Rizzo A, Maugeri R, et al. 2017. Ectopic expression of CXCL13, BAFF, APRIL and LT-β is associated with artery tertiary lymphoid organs in giant cell arteritis. *Ann. Rheum. Dis.* 76:235–43
29. Jiang W, Sun M, Wang Y, et al. 2022. Critical role of Notch-1 in mechanistic target of rapamycin hyperactivity and vascular inflammation in patients with Takayasu arteritis. *Arthritis Rheumatol.* 74:1235–44
30. Saadoun D, Garrido M, Comarmond C, et al. 2015. Th1 and Th17 cytokines drive inflammation in Takayasu arteritis. *Arthritis Rheumatol.* 67:1353–60
31. Watanabe R, Berry GJ, Liang DH, et al. 2020. Pathogenesis of giant cell arteritis and Takayasu arteritis—similarities and differences. *Curr. Rheumatol. Rep.* 22:68
32. Regnier P, Le Joncour A, Maciejewski-Duval A, et al. 2020. Targeting JAK/STAT pathway in Takayasu's arteritis. *Ann. Rheum. Dis.* 79:951–59
33. Hoyer BF, Mumtaz IM, Loddenkemper K, et al. 2012. Takayasu arteritis is characterised by disturbances of B cell homeostasis and responds to B cell depletion therapy with rituximab. *Ann. Rheum. Dis.* 71:75–79
34. Sima D, Thiele B, Turowski A, et al. 1994. Anti-endothelial antibodies in Takayasu arteritis. *Arthritis Rheum.* 37:441–43
35. Strehl C, Ehlers L, Gaber T, Buttgereit F. 2019. Glucocorticoids—all-rounders tackling the versatile players of the immune system. *Front. Immunol.* 10:1744
36. Birkhead NC, Wagener HP, Shick RM. 1957. Treatment of temporal arteritis with adrenal corticosteroids; results in fifty-five cases in which lesion was proved at biopsy. *JAMA* 163:821–27
37. Christ L, Seitz L, Scholz G, et al. 2021. Tocilizumab monotherapy after ultra-short glucocorticoid administration in giant cell arteritis: a single-arm, open-label, proof-of-concept study. *Lancet Rheumatol.* 3:E619–26
38. Fraga A, Mintz G, Valle L, Flores-Izquierdo G. 1972. Takayasu's arteritis: frequency of systemic manifestations (study of 22 patients) and favorable response to maintenance steroid therapy with adrenocorticosteroids (12 patients). *Arthritis Rheumatol.* 15:617–24
39. de Boysson H, Barakat C, Dumont A, et al. 2022. Tolerance of glucocorticoids in giant cell arteritis: a study of patient-reported adverse events. *Rheumatology* 61:3567–75
40. Misra DP, Rathore U, Patro P, et al. 2021. Corticosteroid monotherapy for the management of Takayasu arteritis—a systematic review and meta-analysis. *Rheumatol. Int.* 41:1729–42
41. Mainbourg S, Addario A, Samson M, et al. 2020. Prevalence of giant cell arteritis relapse in patients treated with glucocorticoids: a meta-analysis. *Arthritis Care Res.* 72:838–49
42. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. 2007. Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients. *Arthritis Rheumatol.* 56:1000–9
43. Mutoh T, Shirai T, Fujii H, et al. 2020. Insufficient use of corticosteroids without immunosuppressants results in higher relapse rates in Takayasu arteritis. *J. Rheumatol.* 47:255–63
44. Hoffman GS, Cid MC, Hellmann DB, et al. 2002. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. *Arthritis Rheumatol.* 46:1309–18
45. Jover JA, Hernandez-Garcia C, Morado IC, et al. 2001. Combined treatment of giant-cell arteritis with methotrexate and prednisone: a randomized, double-blind, placebo-controlled trial. *Ann. Intern. Med.* 134:106–14

46. Spiera RF, Mitnick HJ, Kupersmith M, et al. 2001. A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). *Clin. Exp. Rheumatol.* 19:495–501
47. Mahr A, Hachulla E, de Boysson H, et al. 2021. Presentation and real-world management of giant cell arteritis (Artemis study). *Front. Med.* 8:732934
48. Kramaric J, Rotar Z, Tomsic M, Hocevar A. 2022. Performance of leflunomide as a steroid-sparing agent in giant cell arteritis: a single-center, open-label study. *Front. Med.* 9:1069013
49. Hoffman GS, Leavitt RY, Kerr GS, et al. 1994. Treatment of glucocorticoid-resistant or relapsing Takayasu arteritis with methotrexate. *Arthritis Rheumatol.* 37:578–82
50. Wu C, Sun Y, Cui X, et al. 2020. Effectiveness and safety of methotrexate versus leflunomide in 12-month treatment for Takayasu arteritis. *Ther. Adv. Chronic Dis.* 11:2040622320975233
51. Dai D, Wang Y, Jin H, et al. 2017. The efficacy of mycophenolate mofetil in treating Takayasu arteritis: a systematic review and meta-analysis. *Rheumatol. Int.* 37:1083–88
52. Valsakumar AK, Valappil UC, Jorapur V, et al. 2003. Role of immunosuppressive therapy on clinical, immunological, and angiographic outcome in active Takayasu's arteritis. *J. Rheumatol.* 30:1793–98
53. Hoffman GS, Cid MC, Rendt-Zagar KE, et al. 2007. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. *Ann. Intern. Med.* 146:621–30
54. Martinez-Taboada VM, Rodriguez-Valverde V, Carreno L, et al. 2008. A double-blind placebo controlled trial of etanercept in patients with giant cell arteritis and corticosteroid side effects. *Ann. Rheum. Dis.* 67:625–30
55. Seror R, Baron G, Hachulla E, et al. 2014. Adalimumab for steroid sparing in patients with giant-cell arteritis: results of a multicentre randomised controlled trial. *Ann. Rheum. Dis.* 73:2074–81
56. Osman M, Pagnoux C, Dryden DM, et al. 2014. The role of biological agents in the management of large vessel vasculitis (LVV): a systematic review and meta-analysis. *PLOS ONE* 9:e115026
57. Misra DP, Rathore U, Patro P, et al. 2021. Disease-modifying anti-rheumatic drugs for the management of Takayasu arteritis—a systematic review and meta-analysis. *Clin. Rheumatol.* 40:4391–416
58. Gudbrandsson B, Molberg O, Garen T, Palm O. 2017. Prevalence, incidence, and disease characteristics of takayasu arteritis by ethnic background: data from a large, population-based cohort resident in southern Norway. *Arthritis Care Res.* 69:278–85
59. Schmidt J, Kermani TA, Bacani AK, et al. 2012. Tumor necrosis factor inhibitors in patients with Takayasu arteritis: experience from a referral center with long-term followup. *Arthritis Care Res.* 64:1079–83
60. Hoffman GS, Merkel PA, Brasington RD, et al. 2004. Anti-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. *Arthritis Rheumatol.* 50:2296–304
61. Molloy ES, Langford CA, Clark TM, et al. 2008. Anti-tumour necrosis factor therapy in patients with refractory Takayasu arteritis: long-term follow-up. *Ann. Rheum. Dis.* 67:1567–69
62. Mertz P, Kleinmann JF, Lambert M, et al. 2020. Infliximab is an effective glucocorticoid-sparing treatment for Takayasu arteritis: results of a multicenter open-label prospective study. *Autoimmun. Rev.* 19:102634
63. Villiger PM, Adler S, Kuchen S, et al. 2016. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* 387:1921–27
64. Schmidt WA, Dasgupta B, Luqmani R, et al. 2020. A multicentre, randomised, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of sirukumab in the treatment of giant cell arteritis. *Rheumatol. Ther.* 7:793–810
65. Stone JH, Han J, Arlinger M, et al. 2021. Long-term effect of tocilizumab in patients with giant cell arteritis: open-label extension phase of the Giant Cell Arteritis Actemra (GiACTA) trial. *Lancet Rheumatol.* 3:E328–36
66. Alibaz-Oner F, Kaymaz-Tahra S, Bayindir O, et al. 2021. Biologic treatments in Takayasu's arteritis: a comparative study of tumor necrosis factor inhibitors and tocilizumab. *Semin. Arthritis Rheum.* 51:1224–29
67. Mekinian A, Biard L, Dagna L, et al. 2022. Efficacy and safety of TNF-α antagonists and tocilizumab in Takayasu arteritis: multicentre retrospective study of 209 patients. *Rheumatology* 61:1376–84
68. Misra DP, Singh K, Rathore U, et al. 2023. The effectiveness of tocilizumab and its comparison with tumor necrosis factor alpha inhibitors for Takayasu arteritis: a systematic review and meta-analysis. *Autoimmun. Rev.* 22:103275

69. Nakaoka Y, Isobe M, Tanaka Y, et al. 2020. Long-term efficacy and safety of tocilizumab in refractory Takayasu arteritis: final results of the randomized controlled phase 3 TAKT study. *Rheumatology* 59:2427–34
70. Harigai M, Miyamae T, Hashimoto H, et al. 2022. A multicentre, large-scale, observational study of tocilizumab in patients with Takayasu arteritis in Japan: the ACT-Bridge study. *Mod. Rheumatol.* 2022:roac099
71. Sanchez-Alvarez C, Koster M, Duarte-Garcia A, Warrington KJ. 2020. Disease progression of Takayasu arteritis in two patients treated with tocilizumab. *Ann. Rheum. Dis.* 79:e21
72. Nakaoka Y, Yanagawa M, Hata A, et al. 2022. Vascular imaging of patients with refractory Takayasu arteritis treated with tocilizumab: post hoc analysis of a randomized controlled trial. *Rheumatology* 61:2360–68
73. Pazzola G, Muratore F, Pipitone N, et al. 2018. Rituximab therapy for Takayasu arteritis: a seven patients experience and a review of the literature. *Rheumatology* 57:1151–55
74. Nakagomi D, Kronbichler A, Witte T, et al. 2018. Comment on: Rituximab therapy for Takayasu arteritis: a seven patients experience and a review of the literature. *Rheumatology* 57:1309–10
75. Mutoh T, Ishii T, Shirai T, et al. 2019. Refractory Takayasu arteritis successfully treated with rituximab: case-based review. *Rheumatol. Int.* 39:1989–94
76. Deshayes S, Ly KH, Rieu V, et al. 2021. Steroid-sparing effect of anakinra in giant-cell arteritis: a case series with clinical, biological and iconographic long-term assessments. *Rheumatology* 61:400–6
77. Campochiaro C, Tomelleri A, Sartorelli S, et al. 2020. Drug retention and discontinuation reasons between seven biologics in patients with Takayasu arteritis. *Semin. Arthritis Rheum.* 50:509–14
78. Conway R, O'Neill L, Gallagher P, et al. 2018. Ustekinumab for refractory giant cell arteritis: a prospective 52-week trial. *Semin. Arthritis Rheum.* 48:523–28
79. Matza MA, Fernandes AD, Stone JH, Unizony SH. 2021. Ustekinumab for the treatment of giant cell arteritis. *Arthritis Care Res.* 73:893–97
80. Terao C, Yoshifuji H, Nakajima T, et al. 2016. Ustekinumab as a therapeutic option for Takayasu arteritis: from genetic findings to clinical application. *Scand. J. Rheumatol.* 45:80–82
81. Venhoff N, Schmidt WA, Lamprecht P, et al. 2021. Efficacy and safety of secukinumab in patients with giant cell arteritis: study protocol for a randomized, parallel group, double-blind, placebo-controlled phase II trial. *Trials* 22:543
82. Tian X, Li M, Jiang N, et al. 2023. Comparative efficacy of secukinumab versus tumor necrosis factor inhibitors for the treatment of Takayasu arteritis. *Arthritis Rheumatol.* 75:1415–23
83. Cid MC, Unizony SH, Blockmans D, et al. 2022. Efficacy and safety of mavrilimumab in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. *Ann. Rheum. Dis.* 81:653–61
84. Koster MJ, Crowson CS, Giblon RE, et al. 2022. Baricitinib for relapsing giant cell arteritis: a prospective open-label 52-week pilot study. *Ann. Rheum. Dis.* 81:861–67
85. Kong X, Sun Y, Dai X, et al. 2022. Treatment efficacy and safety of tofacitinib versus methotrexate in Takayasu arteritis: a prospective observational study. *Ann. Rheum. Dis.* 81:117–23
86. Wang J, Dai X, Ma L, et al. 2022. Efficacy and safety of tofacitinib versus leflunomide with glucocorticoids treatment in Takayasu arteritis: a prospective study. *Semin. Arthritis Rheum.* 55:152018