

Immunosuppressive Therapy in Giant Cell Arteritis: Do Steroids Still Reign Supreme?

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Giant cell arteritis (GCA) is the most common vasculitis in adults, and patients with GCA often present with vision loss that may progress to permanent blindness. For this reason, empirical treatment with corticosteroids is initiated when there is reasonable suspicion of GCA. Corticosteroids have remained the mainstay of treatment for GCA for the past 70 years due to their profound immunosuppressive effects. However, not all patients tolerate or respond adequately to corticosteroids, and prolonged dosages increase the risk for adverse side effects. There have also been recent advances and investigations into alternative immunosuppressive therapies for GCA; specifically, interleukin 6 inhibitors and other alternatives have been approved by the American College of Rheumatology and European League Against Rheumatism for adjunctive use with corticosteroids or for refractory GCA. However, it is unclear whether current immunosuppressive alternatives can conclusively replace corticosteroids in the treatment of GCA and prevention of vision loss. This article reviews the robust immunosuppressive mechanisms of corticosteroids and summarizes clinical investigations of alternative therapies for GCA.

Keywords

Corticosteroids, giant cell arteritis, immunosuppressive therapies, methotrexate, tocilizumab

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Giant cell arteritis (GCA) is a medium-to-large vessel vasculitis that affects branches of the thoracic aorta, including the carotid artery.¹⁻⁴ The most feared ophthalmic complication is blindness (seen in up to ~25% of cases) due to arteritic ischaemic optic neuropathy involving ophthalmic artery circulation (e.g. retinal, choroidal or optic nerve). GCA may also lead to serious non-ocular vascular complications (e.g. extremity claudication, aortic aneurysm).

The mainstay of treatment for GCA over the past 70 years has been corticosteroids (e.g. prednisone, prednisolone, methylprednisolone).⁵⁻⁷ Corticosteroids, especially high-dose oral or intravenous (IV) corticosteroids, are typically successful in preventing blindness as well as other ischaemic complications and in improving inflammatory symptoms of GCA; however, corticosteroid therapy is associated with significant adverse side effects.^{1,8,9}

As our understanding of the pathophysiology of GCA has advanced, the immunosuppressive therapies for GCA have also progressed.^{6,9} This review aims to: a) describe the underlying mechanisms of corticosteroids to illuminate their profound immunosuppressive capacity; b) outline several novel therapeutic options (especially interleukin 6 [IL-6] inhibitors) for GCA with available clinical data; and c) determine whether alternative therapies can conclusively replace corticosteroids in the treatment of GCA and in cases with high risk for permanent vision loss.

PubMed and the Texas Medical Center Library were searched for peer-reviewed literature on treatment of GCA. Search criteria included keywords such as 'GCA immunosuppressive treatment', 'alternative immunosuppression in GCA' and 'corticosteroids mechanism'. A focus was placed on randomized controlled trials (RCTs) within the past 10 years if available. The following discussion describes the current treatments available, including some therapies that are not currently approved by the US Food and Drug Administration and have been used off-label for the treatment of GCA.

Corticosteroids

The success of corticosteroid treatment is achieved through powerful anti-inflammatory and immunosuppressive effects on leukocytes and immune cells.¹⁰ The mechanisms of action of corticosteroids can be grouped into genomic and non-genomic pathways.

Genomic pathway

Corticosteroids are lipophilic compounds and can readily cross cell membranes and bind to the ligand-binding domain of the cytosolic glucocorticoid receptor (cGR).^{11,12} This binding results

in activation of cGR.¹³ The corticosteroid–cGR complex alters genomic activity across innate and adaptive immune cells. Two underlying pathways – transrepression and transactivation pathways – can be described.

Transrepression

In the transrepression pathway, the function of pro-inflammatory transcription factors is inhibited either directly or indirectly by corticosteroids. In the direct pathway, the corticosteroid–cGR complex translocates from the cytosol to the nucleus, where it dimerizes with another corticosteroid–cGR complex. This homodimer binds to DNA at promoter regions of certain glucocorticoid response elements to regulate gene transcription; this results in the down-regulation of expression of pro-inflammatory proteins (e.g. IL-1, IL-2, IL-6, cyclooxygenase-2, interferon-gamma, prostaglandins).^{10,14,15}

In the indirect pathway, corticosteroid–cGR complexes interact with DNA by binding to certain transcription factors and competing with pro-inflammatory transcription factors (e.g. nuclear factor κ B) for nuclear activation.^{11,12} This competition results in decreased expression of pro-inflammatory proteins.^{11,12}

Transactivation

In the transactivation pathway, corticosteroid–cGR complexes alter gene regulation to increase expression of anti-inflammatory proteins (e.g. IL-10) and immunoregulatory proteins (e.g. tyrosine aminotransferase).^{11,12} These are believed to precipitate adverse effects of corticosteroids.¹¹

Genomic effects are also present even at low doses, but they become more pronounced with larger doses of corticosteroids.¹¹ However, it is important to note that such genomic alterations take time; in fact, the effects of the genomic pathway may take up to days to manifest systemically.¹¹ This can be problematic in the treatment of GCA, in which irreversible vision loss may occur rapidly.¹⁶ The potential solution for this delay may be found in the non-genomic pathway of corticosteroid treatment.

Non-genomic pathway

Although the genomic pathway offers robust targets for immunotherapy, there are certain observed anti-inflammatory and immunosuppressive effects of corticosteroids that manifest too rapidly to be explained by the genomic pathway.^{15,17} These effects are thought to be part of the ‘non-genomic pathway’ and are prominent when corticosteroids are administered intravenously.¹¹ The non-genomic pathway is believed to be mediated through three mechanisms: 1) non-specific interactions with cell membranes; 2) non-genomic effects of the corticosteroid–cGR complex; and 3) specific interactions between corticosteroids and membrane-bound glucocorticoid receptors (mGR).

Non-specific interactions with cell membranes

Corticosteroids have been shown to change the physicochemical properties of cell and mitochondrial membranes.^{17,18} Specifically, corticosteroids intercalate into plasma membranes and alter the function of membrane-bound proteins and membrane permeability.^{17,18} In immune cells, this interaction between plasma membranes and corticosteroids causes a prompt reduction of calcium and sodium cation cycling across the membrane.^{17,18} This is thought to decrease inflammation and contribute to immunosuppression.^{17,18} Moreover, corticosteroids decrease adenosine triphosphate (ATP) production via inhibition of oxidative phosphorylation and increasing proton leakage in mitochondria.¹¹ The lack of ATP in immune cells may blunt cytokine synthesis, phagocytosis, antigen processing and other immune functions,^{11,19} thus resulting in a notable decrease in inflammation.

Non-genomic effects of the corticosteroid–cytosolic glucocorticoid receptor complex

Corticosteroids may exert non-genomic effects through binding of the cGR. Once corticosteroids bind the cGR, several proteins (e.g. Src) are released from the cGR–multiprotein complex and may mediate rapid effects of corticosteroids.²⁰ Moreover, activation of the cGR has been shown to inhibit the release of arachidonic acid, a key source of inflammatory mediators.²⁰

Specific interactions between corticosteroids and membrane-bound glucocorticoid receptors

Binding of corticosteroids to mGR has been shown to inhibit T-cell receptor signalling (e.g. lymphocyte-specific tyrosine kinase, Fyn) via mediation through an mGR–multiprotein complex.^{21,22} This, in turn, down-regulates cytokine synthesis and lymphocyte activation and proliferation.^{21,22}

As the non-genomic pathway bypasses the process of gene transcription, non-genomic effects occur rapidly and could manifest within minutes, particularly after IV administration.¹⁰ Moreover, it is important to note that the non-genomic effects can only be stimulated to a discernible degree with high doses of corticosteroids.²³

Recommendations and advantages of corticosteroid use

In a study by Kanakamedala et al., more than 70% of surveyed neuro-ophthalmologists reported that they would prescribe oral prednisone 1.0–1.5 mg/kg daily for patients with GCA without vision loss.²⁴ The same study reported that more than 70% would prescribe IV methylprednisolone 500–1000 mg daily for patients with vision loss. Salvarani et al. recommended IV methylprednisolone 1000 mg daily for 3 days for patients with GCA and recent vision loss.^{24,25}

In 2018, the European League Against Rheumatism (EULAR) updated the recommendations for immunosuppressive treatment of GCA. Prednisone 40–60 mg daily is suggested for the treatment of acute GCA without visual symptoms.²⁶ However, in cases with transient or sustained loss of vision, high-dose IV methylprednisolone 250–1000 mg daily is recommended for up to 3 days before transitioning to oral prednisone at 1 mg/kg.²⁶ Once remission is achieved, the EULAR criteria recommend corticosteroids to be tapered to 15–20 mg/day within 2–3 months, and then to ≤ 5 mg/day after 1 year.²⁶

In 2021, the American College of Rheumatology (ACR) published updated guidelines for the immunosuppressive treatment of GCA. Oral prednisone 1 mg/kg (up to 80 mg) daily is advised for active GCA without visual symptoms; the ACR also suggests adjunctive therapy with tocilizumab with corticosteroids in these cases.²⁷ Adjunctive therapy with methotrexate or use of corticosteroids alone may be recommended for some patients.²⁷ For patients with active GCA and visual symptoms or loss, IV methylprednisolone 500–1000 mg daily for 3–5 days is recommended.²⁷ Following IV methylprednisolone, oral prednisone 1 mg/kg (up to 80 mg) daily is recommended; if clinical remission is achieved, a taper of daily oral corticosteroids is recommended over weeks to months.²⁷

Thus, high-dose IV corticosteroids are recommended in both the rheumatology and neuro-ophthalmology literature as initial treatment for patients with high risk for permanent vision loss (e.g. monocular patients, bilateral involvement, severe visual loss, transient visual loss). This may be because IV steroids are potentially more effective in offering rapid disease control for the following reasons.

1. A higher dose and IV route allow for greater bioavailability of administered corticosteroids.²⁸
2. Higher doses may stimulate the non-genomic pathways of corticosteroid therapy. This allows for rapid contributions to the therapeutic efficacy of corticosteroids, which is especially important for patients at high risk for vision loss.^{11,12}
3. Higher doses allow for more cGRs to be recruited and the genomic effects to be more intense.^{17,23}

Disadvantages of corticosteroid use

Despite the efficacy of corticosteroid therapy, use of these drugs carries certain risks. The common ocular side effects include cataracts, glaucoma and central serous chorioretinopathy.²⁹⁻³¹ Worrisome systemic side effects include increased risk for osteoporosis, hypertension, infections, atherosclerosis, weight gain, Cushing's syndrome, cardiovascular events, adrenal insufficiency, psychosis, hyperglycaemia and diabetes.³¹⁻³⁵ It is recommended that patients undergoing corticosteroid treatment be treated with calcium and vitamin D supplementation, with bisphosphonate potentially, for bone protection.³¹ Moreover, multiple studies have shown that ~40% of patients with GCA suffer one or more relapses of GCA during or after initial treatment.³⁶ GCA relapses tend to occur at prednisone doses below 20 mg/day; this is particularly apparent during the first year of treatment.³⁶

In summary, IV corticosteroids allow for not only a large range and magnitude of therapeutic effects, but also rapid onset of response. Thus, despite well-known side effects, corticosteroids may offer the highest efficacy of currently available treatments in preventing vision loss in GCA, as well as rapid disease control of active GCA.

Conventional synthetic disease-modifying anti-rheumatic drugs

Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) are a group of pharmacotherapies that are commonly used to treat auto-immune disorders, including GCA. csDMARDs non-selectively target the immune system, unlike their biological counterparts. In this section, we offer a short description of the mechanism of prominent csDMARDs, and summarize the available clinical data on their potential in treating GCA and preventing blindness.

Methotrexate

Methotrexate induces multiple immunosuppressive and anti-inflammatory mechanisms. Some of the most prominent effects include: 1) inhibiting the enzyme dihydrofolate reductase, which is involved in pyrimidine synthesis;³⁷ 2) inhibiting the Janus kinase-signal transducer and activator of transcription proteins (JAK/STAT) signalling;^{37,38} 3) inhibiting translocation of nuclear factor- κ B to the nucleus.³⁷

One of the variables that has been especially studied is whether the combination of methotrexate and corticosteroids leads to fewer relapses in patients with GCA compared with patients receiving corticosteroids alone. These studies have produced largely conflicting results, with some showing that patients on methotrexate and corticosteroids had a reduced number of relapses than those on corticosteroids alone,^{6,39,40} and others finding that there was no significant difference in number of relapses between the two groups.⁴¹⁻⁴³ However, it is important to mention that the RCTs were underpowered because of small sample sizes. Furthermore, a meta-analysis by Mahr et al. showed that adjunctive methotrexate offers a moderate role in decreasing the number of relapses, lowering the cumulative corticosteroid dose and providing a higher probability of corticosteroid-free remission of GCA for at least 6 months.⁴⁴

The 2021 ACR guideline states that methotrexate may offer benefit in treating cases of active GCA refractory to corticosteroids. A combination of methotrexate and corticosteroids may be indicated in active GCA with or without visual symptoms if there is limited access to other alternatives (e.g. tocilizumab) due to cost or history of gastrointestinal perforation, diverticulitis, etc.²⁷ The 2018 EULAR guideline indicates that methotrexate can be directly used in conjunction with corticosteroids in active GCA with concern for corticosteroid side effects. Methotrexate with corticosteroids can also be considered in cases of refractory GCA or relapses.²⁶

Thus, more research may be necessary to further discern the exact efficacy of methotrexate in the treatment of GCA. In the meantime, methotrexate may be most useful in refractory cases or in certain cases as an adjunctive therapy with corticosteroids to help reduce the side effects and cumulative dose of corticosteroids.

Cyclophosphamide

Cyclophosphamide provides an anti-inflammatory action mediated by its active metabolites acrolein and phosphoramidate. These compounds are potent DNA alkylating agents and induce apoptosis in affected cells.⁴⁵ When used in low doses, cyclophosphamide selectively inhibits the function of regulatory T cells and enhances that of effector T cells.^{46,47}

Few RCTs have been conducted to evaluate cyclophosphamide in the treatment of GCA. One retrospective analysis by Loock et al. showed that 90.3% of patients with refractory GCA or who were dependent on high maintenance corticosteroid dosage had significant improvement in disease condition and a decrease in maintenance corticosteroid dosage.⁴⁸ In another retrospective analysis by Quartuccio et al., the efficacy of cyclophosphamide was demonstrated in 78.9% of patients for whom high-dose oral corticosteroids had failed or who relapsed with medium-to-high oral corticosteroids.⁴⁹ However, it is important to note that both studies had small sample sizes and may be underpowered.

A case series and review by de Boysson et al. examined cyclophosphamide use in patients with GCA according to corticosteroid maintenance dosages. In the case series, the authors found that use of cyclophosphamide had a corticosteroid-sparing effect in all 15 patients, with five patients discontinuing corticosteroids long term.⁵⁰ In the review, the authors determined that 84% of patients with refractory GCA or who were dependent on high maintenance dosage of corticosteroids had a favourable response to cyclophosphamide.⁵⁰ However, all studies reviewed were either case reports or limited case series that may have focused on positive outcomes. Furthermore, cyclophosphamide has multiple well-known toxic side effects, some of which are life threatening. These include syndrome of inappropriate antidiuretic hormone secretion, haemorrhagic cystitis, transitional cell carcinoma of the bladder and myelosuppression (particularly B-cell depletion).

Cyclophosphamide may offer some benefit to patients with GCA who are refractory to not only corticosteroids but also other immunosuppressive alternatives (e.g. methotrexate), but more clinical data are necessary to verify the efficacy and safety of cyclophosphamide use in GCA. However, given the relative contraindication for chronic use of cyclophosphamide, it does not appear to be a legitimate corticosteroid-sparing option in the treatment of GCA or in the prevention of vision loss. As such, if cyclophosphamide is chosen for treatment, a major aim should be to help patients discontinue this drug as quickly and safely as possible, and to potentially replace the drug with a safer alternative.⁵¹

Leflunomide

Leflunomide has immunosuppressive effects by inhibiting dihydroorotate dehydrogenase, which is a key enzyme involved in nucleic acid synthesis. By inhibiting this enzyme, leflunomide inhibits the progression of the cell cycle, especially in T cells.⁵²

An open-label study by Hočevár et al. ascertained a statistically significant conclusion that adjunctive therapy with leflunomide added to corticosteroid tapers was able to decrease cumulative corticosteroid dosage compared with corticosteroids alone in patients with GCA.⁵³ The authors also found that adjunctive leflunomide led to a significantly lower rate of relapse compared with corticosteroids alone.⁵³ A 2-year prospective observational study by Das et al. found that all patients treated with leflunomide and a corticosteroid taper exhibited a clinical improvement and 77% could stop corticosteroids completely.⁵⁴ In fact, a recent retrospective study investigating 10 years' worth of medical records of patients with GCA from the United Kingdom found that patients who received leflunomide adjunctive therapy had better clinical outcomes than those who received corticosteroids alone.⁵⁵

Thus, leflunomide has shown potential as an adjunctive therapy in GCA, but RCTs are necessary to further assess and confirm the efficacy of leflunomide as a corticosteroid-sparing agent in GCA.

Azathioprine

Azathioprine is a pro-drug that is metabolized into the purine analog 6-mercaptopurine; this acts to inhibit purine synthesis, especially in leukocytes, and results in significant immunosuppression.

A retrospective study by Boureau et al. found that 64% of patients treated with azathioprine had a sustained improvement in GCA and were asymptomatic with successful reduction in corticosteroid dosage.⁵⁶ The authors concluded that azathioprine may have benefit in patients with GCA who are dependent on high maintenance dosages of corticosteroids or are experiencing significant side effects from corticosteroids.⁵⁶ However, the sample size of this study was small. The results of a recent systematic review by Muratore et al. in 2017 indicated that azathioprine should only be considered as adjunctive therapy in GCA in the rare case that methotrexate is contraindicated or not tolerated.⁵⁷ The authors cite studies such as that of De Silva et al., which showed that azathioprine did have some efficacy in reducing corticosteroid dosage in the treatment of GCA, but this became significant only after 52 weeks.⁵⁸

Thus, azathioprine may have some benefit in GCA cases with high dosage or severe side effects from corticosteroids; otherwise, azathioprine does not appear to be efficacious as the initial treatment of GCA or in treating visual symptoms.

Biological disease-modifying anti-rheumatic drugs

Biological DMARDs (bDMARDs) are biological agents that target specific components of inflammatory pathways of the immune system. They are often used to inhibit major mediators in autoimmune disorders. In this section, we describe the pertinence of certain inflammatory components (namely IL-6) in GCA, and use available clinical data to describe the potential of bDMARDs in the treatment of GCA and prevention of blindness.

Interleukin 6-inhibiting antibodies

Effects of interleukin 6

The systemic inflammatory response induced by IL-6 is a major component of the pathogenesis of GCA. IL-6 is a multi-functional

cytokine and can be used to induce one of two pathways: 1) the classic signalling pathway to induce an anti-inflammatory cascade; or 2) the trans-signalling pathway to induce an inflammatory response.

When the effect is anti-inflammatory, IL-6 affects target cells via the classic signalling pathway, in which the cytokine binds to a membrane-bound IL-6 receptor (mIL-6R) that is found on certain cells (e.g. hepatocytes, leukocytes). In the case of hepatocytes, the result is the secretion of acute phase reactants.⁵⁹

For the pro-inflammatory effect, IL-6 affects target cells via the trans-signalling pathway. In this case, rather than binding to a mIL-6R, IL-6 binds to a soluble IL-6 receptor (sIL-6R). This IL-6-sIL-6R complex can induce a pro-inflammatory response by the conversion of CD4+ T-helper (Th) cells to CD4+ Th17 cells and inhibition of their conversion to regulatory T cells.⁶⁰⁻⁶²

IL-6-inhibiting antibodies are currently used in the treatment of multiple immune-mediated disorders (e.g. rheumatoid arthritis, juvenile idiopathic arthritis) as well as in GCA. In the case of GCA, the IL-6-inhibiting antibody that has been most studied is tocilizumab. Tocilizumab is a competitive inhibitor of both mIL-6R and sIL-6R, preventing IL-6 from attaching to its binding sites.⁶³ As such, it blocks the conversion of CD4+ Th cells to pro-inflammatory Th17 cells and instead allows for their differentiation into anti-inflammatory regulatory T cells.⁶⁴

Clinical data on interleukin 6-inhibitors

In the Giant Cell Arteritis Actemra (GIACTA) RCT by Stone et al. and phase II RCT by Villiger et al., the combination of tocilizumab injections and corticosteroid tapers was found to have statistically significant results compared with placebos with corticosteroid tapers.^{65,66} The use of tocilizumab with a corticosteroid taper led to a higher rate of initial disease remission,⁶⁵ a higher rate of sustained disease remission at week 52 of the trials and a decreased cumulative corticosteroid dosage over both trials.^{65,66}

Stone et al. performed a follow-up study to assess the long-term effect of tocilizumab in patients with GCA in the GIACTA RCT. The authors found that 25 of 59 participating patients (42%) who were in clinical remission from adjunctive tocilizumab treatment continued to be in clinical remission for 2 years without further treatment with either tocilizumab or corticosteroids.⁶⁷

The efficacy of another IL-6-inhibiting antibody, sarilumab, in the treatment of GCA was being studied in a phase III RCT that was unfortunately terminated due to the COVID-19 pandemic.⁶⁸ Preliminary results of the study seem to indicate a benefit from sarilumab use in patients with GCA. After 52 weeks, 46.2% of patients who received 200 mg of sarilumab and a 26-week prednisone taper achieved disease remission, compared with only 30% of patients who received a placebo and a 52-week prednisone taper. However, the premature termination of the trial forces us to approach these results with caution. As such, our discussion will primarily focus on the role of tocilizumab in the treatment of GCA.

Recommendations and advantages of interleukin 6-inhibiting antibodies

The clinical data suggest a potential therapeutic role of tocilizumab in the treatment of GCA. In fact, the updated ACR criteria recommend that active GCA without visual symptoms or critical cranial ischaemia

should be treated with high-dose oral corticosteroids with tocilizumab over corticosteroids alone.²⁷ If visual symptoms are also present, the ACR criteria recommend the use of tocilizumab with high-dose oral corticosteroids following an initial pulse of high-dose IV corticosteroids.²⁷ Moreover, the updated EULAR criteria recommend the direct use of tocilizumab with corticosteroids in active GCA with risk or presence of adverse corticosteroid side effects; the EULAR criteria also recommend tocilizumab as adjunctive therapy with corticosteroids in relapses or refractory cases.²⁶

Thus, IL-6 inhibition has been shown to help reduce the duration of treatment and cumulative dose of corticosteroids. This may be especially applicable after patients complete the initial high-dose corticosteroid pulse and are in the tapering phase. Given the elderly epidemiology of GCA, patients may suffer from comorbidities that are contraindications for high-dose or long-term corticosteroid treatment.

Disadvantages of interleukin 6-inhibiting antibodies

Some conflicting evidence exists on the anti-inflammatory effect of tocilizumab.⁶⁹ Prieto-Peña et al. showed that a majority of patients with GCA who were treated solely with tocilizumab continued to show an increase in 18F-fluorodeoxyglucose uptake (i.e. an indication of vascular inflammation) in positron emission tomography-computed tomography scans.⁷⁰ Furthermore, the benchmark RCTs only investigated the effect of tocilizumab on GCA when it was used in conjunction with corticosteroids, not when it was used in isolation.

Observational studies, however, have been conducted to assess the role of tocilizumab alone in patients with refractory GCA. These studies found that patients who were administered tocilizumab showed an improvement in their disease state, but the authors also cautioned that tocilizumab administration introduced a risk of serious infection in patients.^{71,72}

The EULAR and ACR guidelines both indicate high-dose IV corticosteroids (e.g. methylprednisolone) as the initial and first-line therapy in active GCA with visual symptoms and/or vision loss.^{26,27} Tocilizumab is only indicated once high-dose oral corticosteroid therapy is initiated. Thus, tocilizumab may not offer strong efficacy as the initial treatment to prevent blindness in GCA with visual symptoms.

Given the numerous other inflammatory mediators that are involved in the pathogenesis of GCA (e.g. IL-1b, interferon-gamma, IL-17), it is logical that an antibody only targeting IL-6 would not completely control the inflammatory development of the disease. Interestingly, recent observational research has shown that patients with refractory GCA who were administered tocilizumab and a second drug (usually methotrexate) had a longer period of disease remission than those who were administered tocilizumab alone.⁷³ This was also observed in patients with GCA and more extracranial involvement.⁷³

In conclusion, clinical data have shown that the combination of tocilizumab and corticosteroids allows for higher rates of remission from GCA and a lower cumulative corticosteroid dose. A sizeable proportion of patients remain in drug-free clinical remission for 2 years following adjunctive tocilizumab therapy. However, tocilizumab alone may not be effective enough to treat GCA or to conclusively replace corticosteroids. More research is necessary to determine the efficacy of tocilizumab alone in treating GCA and whether tocilizumab has potential in the initial treatment of patients with GCA who present with visual symptoms and/or vision loss.

Inhibition of Janus kinase and the Janus kinase-signal transducer and activator of transcription proteins pathway

The JAK/STAT pathway is an intracellular signalling pathway involved in immune cell signalling via cytokines and ILs; this pathway plays a key role in activating T cells. In fact, both mL-6R and sIL-6R utilize the JAK/STAT signalling cascade to induce either an anti-inflammatory or pro-inflammatory effect. JAK inhibitors are currently being investigated in the treatment of many autoimmune diseases, including Takayasu arteritis, inflammatory bowel diseases and GCA.

There are limited clinical data on the use of JAK/STAT pathway inhibitors in the treatment of GCA. One case report and one case series showed that the use of baricitinib helped to rapidly lower disease activity and had a corticosteroid-sparing effect in patients with GCA refractory to multiple immunosuppressive therapies.^{74,75} Tofacitinib was recently used to successfully treat a case of refractory Takayasu arteritis.⁷⁶

Although a few articles have shown some promise of JAK/STAT inhibitors in the treatment of refractory GCA, more clinical data, especially RCTs, are needed to determine their true efficacy and safety in treating GCA.

Treatments against tumour necrosis factor-alpha

Temporal artery biopsies in patients with GCA have shown increased levels of tumour necrosis factor-alpha (TNF- α).⁷⁷ While the role of TNF- α in the pathogenesis of GCA is unclear, researchers have studied two anti-TNF- α medications as potential therapies: etanercept and adalimumab.⁴⁵ Etanercept is an artificially engineered TNF- α 'decoy' receptor that binds to the cytokine before it can interact with true TNF- α receptors and induce an inflammatory response.⁷⁸ Adalimumab is a humanized monoclonal antibody specific to TNF- α that binds to the cytokine and impedes its ability to interact with TNF- α receptors.⁷⁹

An RCT by Seror et al. found that adding a 10-week course of adalimumab to prednisone treatment did not significantly increase the number of GCA patients in remission.⁷⁹ Another RCT was performed to evaluate infliximab, a chimeric monoclonal anti-TNF- α antibody, in the treatment of polymyalgia rheumatica, a disease that has a high degree of association with GCA. Although the sample size was small, the study nonetheless showed strong evidence of no significant difference in outcomes between patients who received infliximab and prednisone versus placebo and prednisone.⁸¹

Thus, although the data on anti-TNF- α therapy in GCA are limited, the current literature suggests that anti-TNF- α therapy has poor efficacy in treating GCA.

Treatments against cytotoxic T-lymphocyte-associated protein 4

GCA is thought to be an antigen-driven disorder. It is believed that antigen-presenting cells (APCs) present antigens to T cells and induce an inflammatory response in GCA. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is a protein receptor that mediates this interaction between APCs and T cells. Abatacept is a modified antibody that targets and inhibits CTLA-4; abatacept essentially helps to inhibit T-cell activation.

An RCT by Langford et al. found that abatacept combined with a prednisone taper yielded a longer median duration of remission as well as a higher relapse-free survival rate at 12 months compared

with placebo with a prednisone taper.⁸² The authors also determined that abatacept with prednisone did not have a higher rate of side effects compared with prednisone alone.⁸² Thus, these positive results warrant further investigation into the efficacy of abatacept in the treatment of GCA. In fact, the new ACR criteria indicate that abatacept may be added or used to replace non-corticosteroid agents when treating GCA (with or without visual symptoms) that is refractory to corticosteroids, tocilizumab and/or methotrexate.²⁷

Treatments against interleukin 17, 12 and 23

IL-12 and IL-23 have been implicated in activating Th1 and Th17 cells, respectively, and their pro-inflammatory roles in the pathophysiology of GCA; furthermore, IL-17 produced by Th17 cells has been shown to mediate downstream pro-inflammatory effects of Th17 cells.^{83–86} There have been recent efforts to investigate whether therapies blocking the actions of these cytokines can prolong the length of GCA remission. Specifically, the use of therapies inhibiting IL-17 or IL-12 and IL-23 is a novel frontier in the realm of GCA treatment research.

A double-blind RCT is currently under way to investigate the benefit of secukinumab, a monoclonal antibody against IL-17, in the treatment of GCA.^{87,88} Patients are randomized to receive either secukinumab and a prednisolone taper or placebo and a prednisolone taper. Preliminary data showed that at 28 weeks, 70.1% of the patients treated with secukinumab were in sustained remission compared with 20.3% in the placebo group. At the 52-week follow-up, 59.3% of the secukinumab-treated group was in sustained remission compared with only 8.0% in the placebo group.^{88,89} Thus, anti-IL-17 therapies show promise in the treatment of GCA. More research is necessary to further determine the efficacy of secukinumab in the treatment of GCA and whether it has any benefit in patients with GCA who present with visual symptoms.

Trials involving the monoclonal antibody ustekinumab, which inhibits both IL-12 and IL-23, have shown mixed results. A prospective open-label trial by Matza et al. found that ustekinumab in combination with prednisone was associated with a high rate of relapses and treatment failure.⁹⁰ However, in a prospective open-label study by Conway et al., the authors found that none of the 25 patients who received ustekinumab relapsed; however, none of the patients achieved complete tapering of corticosteroid therapy.⁹¹ These mixed results perhaps warrant further investigation into ascertaining the efficacy of ustekinumab in the treatment of GCA.⁹¹

Conclusion

Despite recent advances in both the immunology and therapy of GCA, current clinical data do not support the complete replacement of corticosteroids with alternative DMARDs. Alternative therapies are typically recommended to be used in combination with corticosteroids. Thus, corticosteroids remain the predominant treatment for GCA. However, certain therapies, such as methotrexate and especially tocilizumab, may offer benefit in reducing the cumulative dose of corticosteroids. Patients who are non-compliant, intolerant or do not respond well to corticosteroid therapy may receive some benefit from alternative immunosuppressive pharmacotherapy (e.g. tocilizumab or methotrexate). Moreover, novel treatment strategies are constantly being developed and investigated in clinical trials.

IV or high-dose oral corticosteroids remain the primary therapy for patients at risk for permanent loss of vision; the larger dose may stimulate the rapid non-genomic pathways of corticosteroid therapy, induce a larger response from the genomic pathway and allow for greater bioavailability. These effects are ultimately vision saving for many patients with GCA. □

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