Update on the Epidemiology and Treatment of Giant Cell Arteritis

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Published online: 11 April 2016

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This article is part of the Topical Collection on *Vasculitis*

Keywords Giant cell arteritis · Epidemiology · Treatment · Immunosuppression · Glucocorticoids · Biologic agents

Opinion statement

Giant cell arteritis is the most common form of primary systemic vasculitis in people over the age of 50 years. This disease affects the aorta and its branches, and complications may include vision loss, arterial stenosis, and aortic aneurysm. Early recognition and treatment of giant cell arteritis is important to mitigate long-term damage. While glucocorticoids remain the mainstay of treatment, relapses are common and morbidity related to treatment frequently occurs. There is an unmet need for immunosuppressive therapies that are able to induce long-term remission while avoiding the adverse effects of glucocorticoids. Of available conventional immunosuppressive treatments, methotrexate is generally considered a first-line steroid-sparing agent for patients with disease refractory to glucocorticoids and in those at high risk for glucocorticoid-associated toxicity. Advances in understanding of disease pathogenesis continue to identify potential therapeutic targets, and several biologic agents are currently under investigation. Preliminary reports from controlled studies demonstrate potential efficacy of tocilizumab and abatacept in both newly diagnosed and relapsing patients; however, use of these agents should not yet be considered standard therapy. The role of anti-platelet therapy in prevention of ischemic complications is controversial, but low-dose aspirin is considered reasonable in this population. Statin medications have little role in the management of giant cell arteritis (GCA) and should be reserved for those with clinical indications for lipid reduction. Correction of arterial stenosis with surgical revascularization is uncommonly required for patients with refractory ischemic symptoms. Intervention should be performed in patients

with quiescent disease. Monitoring for late-onset complications, particularly thoracic aortic aneurysm, should take place though the frequency of screening and the optimal timing of intervention is not established.

Introduction

Giant cell arteritis (GCA) is a chronic, granulomatous, large-vessel vasculitis that selectively affects the aorta and its primary and secondary branches [1•]. The most common presenting symptom of GCA is headache, which is reported in two thirds of patients [2••]. Vision loss from ischemia of the optic nerve may occur in 20 % patients and is considered an ophthalmologic emergency [2••, 3]. While GCA was previously known as “temporal arteritis,” it is a systemic vasculitis whose clinical manifestations include ischemia from large-artery stenosis/occlusion and aortic manifestations including aneurysm formation and dissection [4•]. Timely diagnosis and initiation of therapy is therefore essential to mitigate the morbidity and mortality associated with both the acute presentation and long-term complications of this disease.

Glucocorticoids (GCs) have remained the mainstay of treatment induction and maintenance of remission for the past 50 years, and attempts at identifying beneficial steroid-sparing agents have been disappointing. Nevertheless, there continues to be an unmet need as treatment-associated morbidity from GC is observed in 73–100 % of patients [5•, 6].

Recent advances in genetic analyses have provided a greater understanding of the epidemiology and pathogenesis of this disease, resulting in potential targets for therapeutic intervention. This review will focus on these epidemiologic updates as well as the advances in both conventional and targeted therapeutics in the management of GCA (Fig. 1).

Epidemiology

Nearly all of the studies evaluating the incidence of GCA are from Europe and USA which may reflect the demographic that is most frequently affected by GCA. Majority of the available studies evaluating the epidemiology of GCA in the literature are over two decades old. Caution must be used in interpreting the results since in these studies, the GCA diagnosis is often based on cranial manifestations of GCA or 1990 American College of Rheumatology (ACR) classification criteria. Therefore, these studies do not capture the subset of patients who present with large-artery manifestation who often do not meet ACR classification criteria [7••]. In one study from Olmsted County, Minnesota which did include patients with large-vessel confirmation, no change was noted in the overall incidence of GCA even after inclusion of these patients [9].

Age, ethnicity, and sex are consistent risk factors for GCA based on currently available epidemiology studies [10]. In nearly all published studies of patients with GCA, women are affected two to four times more often than men.

Age

GCA almost never occurs in individuals below the age of 50 years [11]. In a systematic literature review, only 2 out of 1435 subjects (0.1 %) from 26 studies were younger than 50 years of age [11]. In most studies, the mean age at diagnosis of GCA is in the eighth decade of life [10]. Further strengthening the association between age and risk of GCA are several studies where the incidence of GCA

Fig. 1. Treatment recommendations for giant cell arteritis.

increases with each increase in decade of age [9, 12, 13, 14•, 15]. Three studies have found that the mean age at diagnosis of GCA has increased in recent years, and this is not explained by demographic changes in the populations [16–18].

Geographic variation

Europe

The highest incidence rates for GCA are from the Scandinavian countries. The highest estimated incidence reported is from Ribe County, Denmark with an annual incidence of 76.6 per 100,000 people ≥ 50 years [19]. Rates of between 14 and 32.8 per 100,000 people ≥ 50 years have been reported from other Scandinavian countries [13, 20–25]. Much lower incidence rates of between 2.2 to 10 per 100,000 people ≥ 50 years have been reported from other European countries [15, 26–30]. The higher incidence of GCA in countries in Northern Europe suggests that latitude may affect risk. However, a study evaluating geographic variation in incidence of GCA within the UK showed higher incidence for areas in the south of the UK compared to the north [30].

The Americas

The estimated incidence of GCA in population-based studies from Olmsted County, Minnesota is similar to that observed in Scandinavian countries (18.9 per 100,000 people ≥ 50 years) perhaps reflecting the Scandinavian background

of the population in this region [9]. Few other studies have evaluated the epidemiology of GCA in North America. In a study from Shelby County, Tennessee, the estimated annual incidence of GCA was 2.4 per 100,000 people ≥ 50 years in Whites [31]. A study from Saskatoon, Canada estimated the incidence of GCA at 9.4 per 100,000 people > 50 years [32]. GCA appears to be rare among non-Caucasian populations in North America. The estimated annual incidence in African Americans was 0.36 per people ≥ 50 years [31] and 1 per 100,000 people ≥ 50 years in Alaska Natives [33].

The incidence of GCA in other ethnic groups in the Americas is not well studied. In the study from Saskatoon, only 2 of the 35 patients (5.7 %) with GCA were of Aboriginal descent [32]. In a study, from University of California San Francisco, only 1 of 38 patients (2.6 %) with positive temporal artery biopsy was Asian [34].

Likewise, the incidence of GCA for the Hispanic population is not well known. Most of this data is based on small series reported from different centers. This includes a small case series of 11 patients from Puerto Rico [35]. In another series, 257 patients who had undergone temporal artery biopsy at a tertiary care center were contacted for information on their race [36]. No differences were observed between the rates of temporal artery biopsy positivity among those who identified themselves as Hispanic (20 %) compared to non-Hispanic patients (28 %) [36]. Majority of the Hispanic population from this study was Cuban-American [36]. Likewise, estimates of the incidence of GCA in South America are also not available with only one published case series of 22 patients from a center in Mexico (Mestizo population) [37].

Australia and New Zealand

Two studies are available evaluating the epidemiology of GCA in this region. Both studies evaluated only subjects who underwent temporal artery biopsies, and the incidence of biopsy-positive GCA was estimated [14•, 38•]. In the study from Otago, New Zealand, the estimated annual incidence of GCA as 12.7 per 100,000 patients ≥ 50 years of age [38•], while the study from South Australia reported a lower incidence rate of 3.2 per 100,000 people > 50 years [14•].

Other reports

The estimated incidence of GCA in Israel is 11.3 per 100,000 people ≥ 50 years [39]. Significantly lower incidences have been reported from Turkey (1.13 per 100,000 people ≥ 50 years) [40] and Japan (1.47 per 100,000 ≥ 50 years) [41]. Case reports have been published from Mumbai, India [42] and Riyadh, Saudi Arabia [43], Tunisia [44].

Genetic factors

Given the demographic of patients who are most commonly affected by GCA, genetic factors likely play an important role in susceptibility. Not unexpectedly, the strongest genetic association is with the major histocompatibility complex (MHC) genes and with genes involved in regulation of the immune system [45••]. The strongest and most consistent genetic association of GCA is with MHC class II alleles, especially HLA DRB1*04 allele [7••, 45••]. In a large-scale genetic analysis, which included patients with GCA from Europe and North America, non-MHC associations (not reaching genome-wide significance) were

observed including PTPN22 (a central negative regulator of T and B cells which has also been associated with various autoimmune diseases [46•]), REL (encodes a member of the nuclear factor- κ B family of transcription factors), and LRRC32 (encodes a protein that is expressed in activated T regulatory cells) [7••]. Likewise, polymorphisms in interleukin 33 [47•], interleukin 17 [47•], toll-like receptors, other cytokines, and molecules involved in endothelial function have been evaluated, but the sample sizes and lack of replication limit the ability to draw any conclusions at this time [45••].

Environmental factors

Few studies have found cyclic pattern or seasonal variations (increased incidence summer months in majority of studies) suggesting environmental triggers for GCA, but these remain poorly understood [12, 14•, 25, 38•, 39, 48, 49]. Recent studies from one group have reported the presence of varicella zoster virus in biopsies of patients with GCA, but these findings need to be replicated [50•]. Socioeconomic status was associated with increased risk of ischemic events in one study from the UK [51] but not in another study from Sweden [52]. In one study, a higher prevalence of GCA was noted in urban populations [29].

Treatment

Glucocorticoids

Prompt initiation of high-dose glucocorticoids (GCs) remains the cornerstone of remission induction treatment for GCA. The guidelines for use of GC are based on decades of clinical experience and expert consensus opinion. Initial dose and tapering regimens, however, have never been formally studied with prospective randomized trials. For patients with severe ischemic manifestations, particularly evolving visual loss, some experts recommend pulse-dose treatment with intravenous methylprednisolone (0.5–1.0 g, daily for three consecutive days) prior to high-dose oral GC in attempts to mitigate further visual compromise [53]. In the absence of acute visual ischemic complications, high-dose oral prednisone (or equivalent) is advocated by both the European League Against Rheumatism (EULAR) [1 mg/kg/day, up to maximum 60 mg/day] [54] and the British Society for Rheumatology (BSR) [40–60 mg/day] [53]. Continuation of high-dose GC until symptoms and laboratory abnormalities resolve, usually 3–4 weeks, is suggested prior to initiating a gradual taper [53, 54]. The duration of GC treatment is highly variable and depends on the individual patient's disease course and propensity to relapse. Furthermore, the presence of extracranial large-vessel involvement (LV-GCA) portends the likelihood of a higher GC cumulative dose, longer GC treatment duration, and more frequent use of additional immunosuppressive therapies [2••]. In clinical practice, patients frequently require long-term GC therapy with up to 46 % of patients remaining on GC at 5 years after initial diagnosis [5•].

In an attempt to limit cumulative GC exposure and reduce the frequency of GC-associated adverse events (GC-AEs), various GC regimens have been investigated. While alternate-day dosing has proven less effective than daily dosing [55], the long-term GC-sparing effect of induction with pulse-dose steroids in non-complicated GCA has shown conflicting results [56, 57]. Investigators have also proposed that lower initial GC doses may be as effective as high-dose

regimens for GCA [58–60]. A retrospective study performed by Les et al. evaluated patients receiving initial daily treatment with medium-dose (≤ 30 mg) or high-dose (> 30 mg) prednisone [61]. The primary endpoint of clinical and biological remission (on a prednisone maintenance dose of ≤ 7.5 mg/day) was reached in a shorter time among those started on a medium-dose compared to those on a high-dose regimen (median 186 vs. 236 days), without an increase in GCA complications. The mean cumulative prednisone dose at 6 months was 1.4 g greater in the high-dose cohort, and GC-AE were more frequent (medium dose 43 %, high dose 66 %). However, differences between the two groups, including a higher percentage of baseline ocular ischemic manifestations in the high-dose cohort as well as more frequent use of methotrexate and methylprednisolone pulses in the medium-dose group, limit interpretation of these results.

In contrast, the benefit of initial high-dose oral GC was observed by Labarca and Koster et al. in a large retrospective study evaluating prednisone use and associated outcomes [5•]. Among the 286 patients with biopsy-proven GCA followed for a median of 5 years, patients receiving an initial oral prednisone dose > 40 mg/day (mean 60.2 mg/day; 0.9 ± 0.2 mg/kg) were able to reach a dose of < 5 mg/day [hazard ratio (HR) 1.46 (95 % CI 1.09, 1.96)] and discontinue prednisone [HR 1.56 (95 % CI 1.09, 2.23)] sooner than patients receiving ≤ 40 mg/day (mean 36.3 mg/day; 0.6 ± 0.2 mg/kg) without an increase in observed GC-AE.

Although GC use leads to rapid resolution of systemic inflammatory symptoms and reduction in the risk of vision loss, significant limitations of treatment remain. Indeed, chronic subclinical vascular inflammation often persists despite GC therapy. Lymphocytic infiltration in vascular lesions is largely driven by two T cell subsets: T helper type 17 (Th17) and T helper type 1 (Th1) cells [62••]. Acute inflammation, mediated by Th17 cells, is notably sensitive to GC suppression, whereas the Th1 response is refractory to GC and Th1 cells drive chronic vascular inflammation [63]. Indeed, in a unique GCA study in which repeat temporal artery biopsy was performed in patients on GC therapy, active vasculitis was found in the second biopsy in 75 % of patients at 6 months and in 44 % at 12 months [64]. The persistence of subclinical inflammation despite GC treatment and the high frequency of relapses during GC tapering underscores that GCA is a chronic immune-mediated condition requiring long-term treatment and that more effective immunosuppressive agents are needed.

Conventional immunosuppressive agents

In patients at high risk of GC-AE or in those requiring prolonged high-dose GC for disease control, steroid-sparing agents should be considered. Although both EULAR and BSR guidelines [53, 54] provide such recommendations, the optimal timing of initiation, choice of immunosuppressive agent, and preferred dosing remain unknown.

Methotrexate

Of the limited available evidence from clinical trials, methotrexate is the most studied conventional immunosuppressive agent. Nevertheless, three randomized controlled trials evaluating methotrexate (7.5–15 mg/week) in newly diagnosed patients with GCA have provided discordant results [65–67]. A meta-analysis of the combined 84 patients treated with methotrexate compared to the 77 patients receiving placebo found a modest response in reduction of

cumulative GC dose and a higher probability of achieving sustained GC discontinuation. However, a reduction in GC-AE was not observed [68]. Overall, it was estimated that four patients with GCA would need to be treated with methotrexate for up to 48 weeks in order to prevent a first relapse and ten patients to prevent a first cranial relapse. Even though supportive data is sparse, methotrexate currently remains the most frequently considered adjuvant immunosuppressive agent for patients with relapsing GCA or GC-related toxicity.

Cyclophosphamide

Several retrospective studies have evaluated oral and intravenous cyclophosphamide in patients with refractory GCA [69–71, 72•]. De Boysson et al. reviewed 88 previously published cases and described an additional 15 patients with relapsing GCA treated with cyclophosphamide [72•]. Although overall 86 % of patients experienced clinical and laboratory response, the utility of cyclophosphamide is limited by a significant rate of relapse after discontinuation (25 %) and a high frequency of treatment-limiting adverse events (40 % of patients) [72•]. Therefore, routine use of cyclophosphamide is not currently recommended.

Leflunomide

Two small uncontrolled studies have shown that leflunomide may be an effective steroid-sparing agent for patients with GCA that is refractory to GC or methotrexate [73, 74]. Among leflunomide responders, the clinical improvement, laboratory marker reduction, and prednisone decrease were observed within 2–3 months after initiation. These preliminary results, however, are limited by short duration of follow-up among a small number of patients, and prospective trials are needed.

Azathioprine

One randomized, double-blind, placebo-controlled study has evaluated azathioprine in patients with GCA and/or polymyalgia rheumatica [75]. Among the 31 patients enrolled, 16 received 150 mg daily azathioprine in addition to standard GC treatment. A statistically significant reduction in prednisolone dose was observed only after 52 weeks in the treatment group compared to those receiving placebo (1.9 ± 0.8 vs. 4.2 ± 0.6 mg). Data regarding the effect on GC-AE and relapses is not provided. Given the low dose of prednisolone at study entry (8.1 ± 0.4 mg azathioprine group vs. 7.4 ± 0.4 mg placebo group) and the lack of information on baseline disease characteristics, it is uncertain how to incorporate azathioprine in current clinical practice.

Mycophenolate mofetil

Data regarding the use of mycophenolate mofetil in GCA is limited to a single case series. Sciascia et al. [76] reported the use of adjunct mycophenolate (2 g/day) in three patients with new onset GCA and high risk for GC-AE. Clinical response including symptom alleviation, inflammatory marker normalization, and rapid prednisone reduction was observed within 1 month. Additionally, despite the accelerated GC taper, no signs of clinical relapse were observed at a

median follow-up of 22 months. Mycophenolate has also shown preliminary effectiveness in Takayasu arteritis, another major form of large-vessel vasculitis [77]. Therefore, further investigation into the use of this agent for treatment of GCA is warranted.

Targeted biologic agents

Tumor necrosis factor alpha inhibitors

The role of tumor necrosis factor alpha (TNF- α) in the pathophysiology of GCA is uncertain. Prior reports noted increased expression of TNF- α in the temporal arteries of patients with active GCA [78], but more recent studies have not shown significant elevation of serum TNF- α levels in patients with GCA [79•]. Although TNF- α inhibitors have shown utility in Takayasu arteritis, none of the three randomized controlled trials evaluating TNF- α inhibitors in GCA have shown significant therapeutic efficacy [80–82]. However, the inclusion criteria for these studies focused primarily on patients with cranial symptoms. Therefore, whether patients with predominant LV-GCA features may benefit from these agents is unknown.

Interleukin-6 inhibitors

Because of the central role of interleukin-6 (IL-6) in GCA, biologic agents targeting this cytokine pathway are being actively investigated as therapeutic options. Tocilizumab, a humanized monoclonal IL-6 receptor blocker, has shown promise in several observational studies and is currently being evaluated in randomized controlled trials. The first trial evaluating the efficacy of this medication was reported in abstract form by Adler et al. [83]. Thirty patients with GCA (23 newly diagnosed, 7 relapsing) were randomized 2:1 to treatment or placebo. Among the 20 patients receiving intravenous tocilizumab (8 mg/kg/4 weeks), complete remission at 12 weeks (85 vs. 40 %) and relapse-free survival at 52 weeks (85 vs. 20 %) were higher compared to the placebo group.

A multicenter, randomized, double-blind, placebo-controlled study evaluating subcutaneous tocilizumab (162 mg every 7 or 14 days) in patients with newly diagnosed and relapsing GCA is nearing completion (GiACTA—Clinicaltrials.gov identifier NCT01791153). A total of 241 patients with GCA have been enrolled, making this the largest controlled trial in GCA to date. A randomized controlled trial evaluating sirukumab, a fully human anti-interleukin-6 immunoglobulin G1-kappa with high affinity and specificity for binding the human IL-6 molecule, is also underway (ClinicalTrials.gov identifier NCT02531633).

Abatacept

Activated T cells are present in the vascular lesions of patients with GCA and are considered to play a pivotal role in disease pathogenesis [63]. Abatacept, a fusion protein composed of the Fc region of the immunoglobulin IgG1 fused to the extracellular domain of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), blocks the co-stimulatory signal required for T cell activation. A multicenter, randomized, placebo-controlled trial evaluating the safety and efficacy of

abatacept in GCA (Clinicaltrials.gov identifier NCT00556439) has been completed, and preliminary results are available in abstract form [84]. Following a remission induction phase, 41 patients were randomized to abatacept or placebo. Relapse-free survival at 12 months (48 vs. 31 %) and duration of remission (median 9.9 vs. 3.9 months) were higher in the treatment group compared to placebo. While initial results are promising, complete trial data analysis and further study are needed before determining effectiveness.

Future biologic options

Increased understanding of the cellular mediators and cytokine profiles involved in the pathophysiology of GCA is providing additional molecular targets for possible intervention. Anakinra, an IL-1 type 1 receptor antagonist, has been used in three refractory GCA cases with encouraging results [85]. Further investigation of IL-1 inhibition is underway in a clinical trial evaluating the efficacy of gevokizumab, a monoclonal antibody against IL-1 β (European Clinical Trials Database identifier 2013-002778-38). Ustekinumab, a monoclonal antibody against IL-12/23p40, has shown initial promise in a small open-label study [86]. Although B cells are not considered the primary pathogenic cellular mediator in GCA, rituximab has been used in two patients with noted benefit [87, 88]. Further evaluation of these targeted therapeutics in larger cohorts and prospective trials are necessary prior to consideration for routine usage.

Adjunct medication

Anti-platelet

Preclinical studies using mice engrafted with inflamed human temporal arteries have shown that acetylsalicylic acid (ASA) is an effective inhibitor of cytokine transcription through suppression of interferon-gamma. In these murine studies, the combination of ASA and corticosteroids had synergistic effects on proinflammatory cytokine reduction in the vascular lesions of GCA [89]. Variable results, however, have been observed in retrospective clinical studies evaluating the efficacy of ASA in patients with GCA. While some studies conclude that use of anti-platelet/anti-coagulation therapy prior to GCA diagnosis reduces the risk of visual or cerebrovascular ischemic complications [90, 91], other studies have not replicated these findings [92, 93]. Indeed, in one cohort study, patients on anti-platelet or anti-coagulation therapy had a higher frequency of GCA-related severe cranial ischemic complications [94]. A recent meta-analysis concluded that treatment with anti-platelet/anti-coagulation therapy prior to GCA diagnosis does not protect against the development of severe ischemic complications. However, anti-thrombotic therapy may provide modest protection (odds ratio 0.32; 0.10–0.99) from incident severe ischemic complications in patients with established GCA on GC therapy [95••]. The effect of ASA on disease activity and relapse is poorly understood, and retrospective reviews demonstrate discordant results [5•, 96]. While there is a need for prospective effectiveness trials, at current, both EULAR [54] and BSR [53] guidelines recommend treatment with ASA 75–150 mg/day, unless contraindicated.

Statins

Statin medications, which are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, possess pleiotropic properties including reducing thrombogenicity, improving endothelial dysfunction, as well as providing immunomodulatory and anti-inflammatory effects [97]. Therefore, the potential benefit of these medications in patients with GCA is of clinical interest. Although one population-based study observed that patients treated with statins were less likely to develop GCA [98], these results have not been replicated by other investigators. In a French case-control study, Pugnet et al. observed a modest effect of baseline statin exposure on the likelihood of achieving remission maintenance with low-dose prednisone (HR 1.9), though no difference was seen in the overall cumulative prednisone dose [99]. Nevertheless, the use of statin medications among patients with GCA in additional retrospective studies has not shown a significant clinical impact in decreasing ischemic events or preventing relapses [98, 100, 101]. Consequently, statin medications are not considered requisite adjuncts in the management of GCA and should be reserved for patients with approved clinical indications for lipid-lowering treatment.

Surgical treatment

Extracranial large-vessel involvement in GCA is frequently seen. Autopsy studies [102, 103] have shown that 90–100 % of patients with GCA have arteritis in the aorta, subclavian, or axillary arteries, and recent studies using advanced imaging confirm that radiographic evidence of vascular inflammation can be seen in up to 83 % at diagnosis [8]. Nevertheless, critical limb ischemia from stenotic lesions in GCA is uncommon due to frequent development of adequate collateral circulation. Surgical reconstructive procedures are rarely needed as 89–100 % of patients presenting with upper extremity claudication remain stable or improve with medical management alone [2, 104]. On the other hand, patients with lower extremity involvement are at a higher risk of progression necessitating revascularization, which may be required in 11–26 % of cases [105, 106]. If required, revascularization should take place when arterial inflammation is quiescent [54].

The risk of aortic aneurysm and dissection is also increased in patients with GCA [4]. Although more frequently observed as a late complication, aneurysm/dissection may also be present at diagnosis in a subset of patients. At current, there are no consensus guidelines regarding the method or frequency of aneurysm screening. In the absence of prospective studies in this population, treatment strategies and timing of intervention have been based on management of atherosclerotic aneurysms [107]. The comparative efficacy of endovascular repair to surgical resection has not been studied, but positive outcomes have been seen with both techniques.

Conclusions

Genetic analyses of patients with GCA are providing additional information regarding possible cellular and cytokine-mediated pathways that could be involved in the pathogenesis of this condition. However, due to the relative rarity of this disease, current investigations have been limited by cohort size, highlighting the need for further international collaborative efforts.

Treatment with glucocorticoids remains essential in the management of GCA but is complicated by associated side effects. The benefit of conventional immunosuppression in this condition remains less well understood. Agents showing potential benefit need to be evaluated in well-designed prospective studies to identify efficacy.

Several targeted biologic therapies are currently under investigation. At this time, tocilizumab and abatacept currently show preliminary value in management of both newly diagnosed and refractory GCA. Further information regarding the efficacy of these and other agents is eagerly awaited.

Compliance with Ethical Standards

Conflict of Interest

MJK, KJW, and TAK declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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