

# Giant cell arteritis

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Giant cell arteritis (GCA), the most common form of systemic vasculitis in adults, preferentially involves large and medium-sized arteries in patients over the age of 50. The classic manifestations are headache, jaw claudication, polymyalgia rheumatica (PMR), and visual symptoms, but 40% of patients present with a wide range of occult manifestations. Early diagnosis and treatment with prednisone can prevent blindness, the most feared complication of GCA. The pathogenesis of GCA is T-cell dependent and antigen driven. Clinical subsets of GCA appear to result from variable cytokine expression. The risk of developing thoracic aortic aneurysm is increased more than 17-fold in patients with GCA. GCA can also involve large arteries, especially the subclavian and axillary arteries. Color Doppler ultrasound, magnetic resonance imaging, and positron-emission tomography scanning are providing insights into the extent and pathogenesis of the disease but have not replaced temporal artery biopsy as the gold standard for securing the diagnosis. Two recently completed double-blind, placebo-controlled trials concerning whether methotrexate plus prednisone is more effective than prednisone alone reached conflicting conclusions. *Curr Opin Rheumatol* 2002, 14:3–10 © 2002 Lippincott Williams & Wilkins, Inc.

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## Abbreviations

<b>ESR</b>	erythrocyte sedimentation rate
<b>GCA</b>	giant cell arteritis
<b>IFN</b>	interferon
<b>IL</b>	interleukin
<b>MRI</b>	magnetic resonance imaging
<b>PAN</b>	polyarteritis nodosa
<b>PET</b>	positron-emission tomography
<b>PMR</b>	polymyalgia rheumatica

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In the decade since giant cell arteritis (GCA) was last reviewed in this journal, a cornucopia of research studies have greatly expanded what we know about this remarkable disease. So many of the insights or advances have come in the last year or so, the time focus of this review, that we thought it advisable to orient the reader to some of the topics we will cover. We begin by reviewing the expanding knowledge of the epidemiology of GCA. We then summarize myriad basic science studies suggesting that GCA is a T cell-dependent disorder, that the key inflammatory cells are T cells and macrophages, that local factors determine how these cells organize themselves from the intima to the adventitia, and that GCA is not a single disease but a group of clinical subsets caused by differential expression of various cytokines. New information also abounds in the clinical arena, where investigators have at last pinpointed the sites of inflammation in polymyalgia rheumatica (PMR). Other reports have expanded our appreciation for the extraordinary range of occult manifestations that can occur in GCA and challenge the diagnostic skills of even the most masterful clinician. In particular, we highlight the importance of large artery involvement in GCA. We then review the new imaging modalities that are challenging, weakly we believe, the time-honored practice of relying on temporal artery biopsy for diagnosis. We conclude by trying to make sense of the conflicting new data on methotrexate as a corticosteroid-sparing agent and the role of interleukin (IL)-6 levels in monitoring the course of the disease.

## Epidemiology

The single greatest risk factor for the development of GCA is aging; the disease rarely occurs before age 50 and its incidence climbs steadily thereafter. A new study from Spain emphasized this point, showing that the overall annual incidence of GCA in people over the age of 50 was 10.24/100,000, but rose from 1.54/100,000 in the sixth decade to 20.7/100,000 in the eighth decade [1]. The second most important risk factor appears to be latitude; in Europe, GCA is twice as prevalent in Sweden as it is in Spain or Italy [1–4]. Race or ethnic origin also seems to be important, inasmuch as the disease is most prevalent in Scandinavians or in Americans who emigrated from Scandinavia [1,2]. GCA has been infrequently reported in African Americans. This decreased prevalence may be explained by the low frequency of the HLA-*DRB1-04* gene in that population. This allele has been identified as a risk factor for the development of GCA [5]. Studies suggest that the annual incidence of GCA has risen 10% from 1981 to 1998 [1]. PMR occurs three times more commonly than GCA [2,6].

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Some studies have found seasonal variation and periodicity (with peaks every 7 years) in the incidence of GCA [2], but others have not [1,3,4]. Smoking increases the risk of GCA in women sixfold [7]. Interestingly, in women, diabetes appears to cut in half the risk of developing GCA [7].

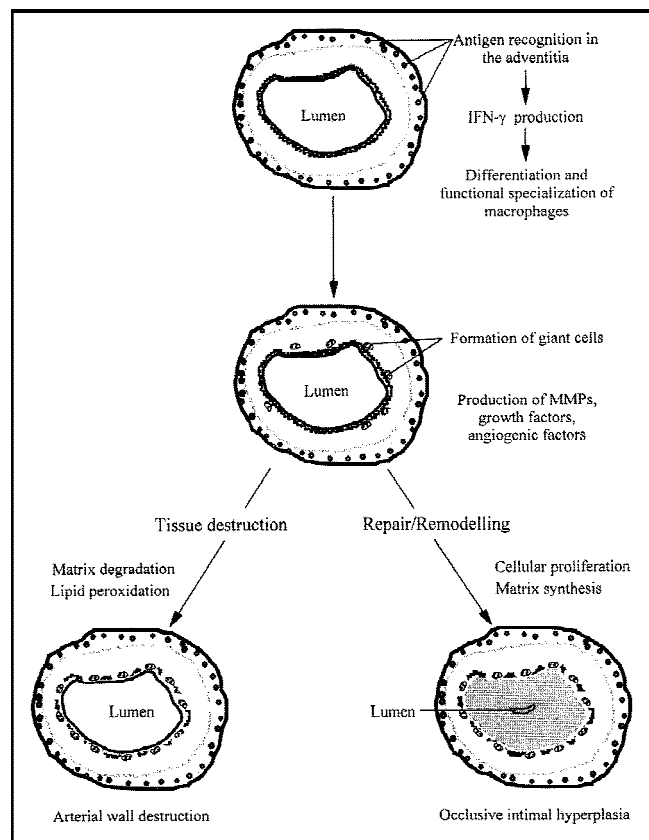
#### Pathogenesis and etiology

The pathologic lesion in GCA consists of a granulomatous inflammatory reaction concentrated in the medial layer of medium- to large-sized muscular arteries. The infiltrate is largely mononuclear, and is associated with marked disruption of the internal elastic lamina. A number of new studies have begun to shed light on the underlying pathogenesis of GCA [8–19]. Evidence suggests that the inflammatory lesion observed in GCA is an antigen-driven process. The inflammatory infiltrate is largely composed of CD4<sup>+</sup> T-cells and macrophages, and approximately 50% of lesions contain multinucleated giant cells clustered near the disrupted internal elastic lamina. B cells are distinctly rare in these lesions [9]. There are conflicting data on the role of CD8<sup>+</sup> T-cells in the pathogenesis of GCA [20].

There is growing evidence that local factors in the arterial wall guide the inflammatory reaction in GCA. Structural changes are not homogeneous throughout the arterial wall, and cell type and cytokine expression is layer-specific as well. Interferon (IFN)- $\gamma$  secreting T-cells are almost exclusively found in the adventitial layer, suggesting that initial antigen contact and recognition occurs here [9]. Studies on tissue-infiltrating macrophages reveal the presence of at least three functionally distinct subsets in these lesions [9,12]. Macrophages in the adventitia produce the proinflammatory cytokines IL-1 and IL-6, macrophages in the arterial media secrete matrix metalloproteinase 2, and those in the intima produce nitric oxide synthetase. Additionally, lesional T cells produced IL-2 and IFN- $\gamma$ , consistent with a Th1, cell-mediated process. The T-cell infiltrate in GCA appears to be polyclonal, whereas a small subset of cells appears to be clonally expanded [18].

These observations have led Weyand *et al.* [9] to propose a model of the pathogenesis of GCA (Fig. 1). Antigen is initially encountered in the adventitia; T cells enter the artery via the vasa vasorum confined to this layer, are activated, and secrete IFN- $\gamma$ . This results in macrophage differentiation and migration, and the formation of giant cells. Further production of metalloproteinase and other growth factors, including platelet-derived growth factor secreted by multinucleated giant cells [3,13] leads to both tissue destruction and remodeling. These changes ultimately result in degradation of the internal elastic lamina and occlusive luminal hyperplasia [9]. Although the target antigen remains unknown, the observation that multinucleated giant cells cluster near the internal elastic lamina has raised the possibility that the initial

Figure 1. A proposed model for the pathogenesis of giant cell arteritis



IFN- $\gamma$ , Interferon- $\gamma$ ; MMP's, matrix metalloproteinases. Published with permission [19].

lesion might represent a foreign body reaction to age-related calcifications in the lamina [3,4]. Other potential targets include viral epitopes, elastin, and other extracellular matrix elements [11].

#### Immunogenetic risk factors

In a study of patients with biopsy-proven GCA, 60% of patients were found to share specific HLA-DR4 haplotype variants (\*0401, \*0404/8) [19]. More recent studies in different patient populations show a similar pattern of HLA-DR expression [21–23]. Patients with GCA with these haplotypes share a common sequence motif in the third hypervariable region of the  $\beta$ 1 molecule distinct from that found in patients with rheumatoid arthritis [16]. Additionally, Matthey *et al.* [24] have described the correlation of GCA with certain polymorphisms in the tumor necrosis factor- $\alpha$  locus. This association appears to be independent of *HLA-DR $\beta$ 1*, and was found in 37.5% of patients with GCA versus 19.2% of controls [24]. These findings further support the concept that GCA is an antigen-driven process.

#### Cytokine-defined subsets of giant cell arteritis

An increasing number of studies suggest that GCA is not one disease but consists of clinical subsets that are

**Table 1. Classic symptoms and findings in giant cell arteritis**

Symptoms	Initial	Ever
Headache	86	90
Jaw claudication	64	67
Polymyalgia rheumatica	21	50
Visual symptoms	35	40
Findings		
Fever	19	21
Abnormal temporal artery	40	50

Data from Hellmann [36], and Huston [72]. Adapted with permission.

caused by variable expression of different cytokines [25]. For example, patients who have ischemic events demonstrate upregulation of IL-1 and IFN- $\gamma$  in the temporal artery, whereas those with PMR show up-regulation of IL-2 mRNA [19,25]. Patients with large artery involvement also appear to be defined, at least in part, by their cytokine pattern. If these findings stand the test of time, cytokine patterns could be used to define patients at risk of ischemic events and might be used to direct therapy.

### Viruses and bacteria

The potential role of microbial pathogens in the pathogenesis of GCA has come under increasing scrutiny. One study of 50 patients presenting for temporal artery biopsy, found parvovirus B19 DNA by polymerase chain reaction analysis in 54% of positive lesions [26]. Elling *et al.* [27] evaluated the correlation between positive temporal artery biopsy and parvovirus infection during a viral epidemic, and found a synchronous increase in the number of positive temporal artery biopsy during the epidemic period. Human parainfluenza virus type 1 infection has also been correlated with GCA [28]. Additionally, two reports of patients developing GCA after influenza vaccination have recently been published [29,30], including one case of GCA-related cavernous sinus thrombosis. Bacterial pathogens have been implicated in the pathogenesis of GCA as well. *Chlamydia pneumoniae* DNA was found in temporal artery specimens of 8 of 9 patients with GCA, and was localized to the adventitial layer with significant numbers of dendritic cells [31]. Seroepidemiologic studies have revealed a rise in the incidence of new cases of GCA during a *C. pneumoniae* epidemic [32] and a recent case report describes the development of GCA after acute *C. pneumoniae* infection [33].

How might medium and large elastic containing arteries become preferentially infected? Dal Canto *et al.* [15] have developed a murine model of large vessel vasculitis caused by herpesvirus that has recently provided possible answers. These investigators have demonstrated that the arterial media (at least in the mouse) serves as an immunoprivileged site that allows for persistent disease propagation. They found that infection of the arterial media persisted despite clearance from other tissues and

organs. They argue that this persistent infection, or persistent antigen in the case of GCA, leads to IFN- $\gamma$ -dependent chronic vessel inflammation [15].

## Clinical features

### Classic manifestations

The classic manifestations of GCA are headache, jaw claudication, PMR, visual symptoms, fever, and an abnormal temporal artery (Table 1) [34–37]. However, the range of presenting features is enormous and 40% of patients do not present with classic features [38–44]. Recently published studies have delineated the source of inflammation in PMR, better described some of the occult manifestations of GCA, and emphasized the importance of aortic and large artery involvement.

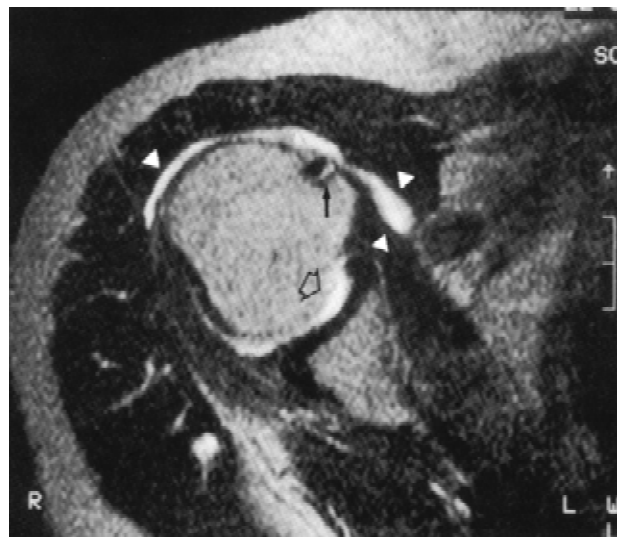
### Source of inflammation in polymyalgia rheumatica

When asked to pinpoint the site of discomfort in PMR, patients usually localize the discomfort to “tissues” more than to joints. New studies using magnetic resonance imaging (MRI) and other techniques prove that patients are right: subacromial/subdeltoid bursitis is much more striking than glenohumeral synovitis [45] (Fig. 2). In an Italian study of 18 patients, 17 of 18 had evidence of bilateral, proximal shoulder bursitis on MRI or ultrasound, whereas only 6 of 18 had bilateral glenohumeral synovitis [45]. Biceps tenosynovitis was present in 9 of 18.

### Occult manifestations of giant cell arteritis

Table 2 lists the occult manifestations of GCA. A review of 83 patients identified 17 cases of GCA presenting as a tumorlike lesion [46]. Only a minority of these patients

**Figure 2. Magnetic resonance image of the shoulder in a patient with PMR demonstrating bursitis**



Axial T2-weighted image shows fluid in the subdeltoid and subacromial bursa (white arrowheads), fluid in the glenohumeral joint (open arrowhead), and synovitis of the biceps tendon (black arrow). Published with permission [45].

**Table 2. Occult manifestations of giant cell arteritis**


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Fever of unknown origin
Respiratory symptoms (especially cough)
Otologic manifestations
Glossitis
Lingual infarction
Tongue infarction
Throat pain
Large artery disease
Aortic aneurysm
Aortic dissection
Limb claudication
Raynaud phenomenon
Neurologic manifestations
Peripheral neuropathy
TIA/stroke
Dementia
Myocardial infarction
Tumorlike lesions
Breast mass
Ovarian and uterine mass
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Microangiopathic hemolytic anemia

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Adapted with permission [36].

exhibited any of the classic features of GCA, and all initially presented with either a breast or ovarian mass. The only other form of vasculitis to affect the breast was Wegener granulomatosis, and the only other arteritis to affect the ovary was polyarteritis nodosa [46].

A French group has reported follow-up on 8 cases of GCA with lower extremity involvement [47]. This experience emphasized that the acute onset of bilateral and rapidly progressive lower extremity claudication and other symptoms of lower extremity arterial insufficiency can be the first manifestation of GCA. More typical GCA symptoms occur infrequently in this group: only 3 of 8 patients experienced headache [47]. Diagnosis was aided by arteriography that revealed multiple, bilateral, long and smooth stenoses [47]. Although corticosteroid therapy usually halted disease progression, 3 of 8 required revascularization.

#### **Aortic and large artery involvement**

Much recent work has focused on GCA involvement of large arteries, especially the aorta. A study of 238 patients published in 1975 demonstrated large artery involvement in 34 (14%) [48], but the vast majority of these cases concerned symptoms caused by carotid, vertebral, and subclavian arteries. Aortic involvement was thought to be less common. However, a retrospective, population-based study from the Mayo clinic in 1995 showed that 14 of 96 (15%) patients with GCA had an aortic aneurysm (9 thoracic and 5 abdominal) [49]. Thus, patients with GCA were found to be 17.3 times more likely to have thoracic aortic aneurysm and 2.4 times more likely to develop abdominal aortic aneurysm than age-related controls [49]. Aneurysms may have been present at the time of diagnosis, but on average they became evident nearly 6 years after GCA had been diagnosed

[49]. The incidence of thoracic aortic aneurysm and GCA was 999/100,000 person years [49]. Of patients with thoracic aortic aneurysms, 44% died suddenly of dissection and 33% developed aortic regurgitation [49]. The finding that 2 of 3 aortic specimens available for review demonstrated aortitis suggests that giant cell arteritis was the cause of the aneurysms. No other risk factor for developing thoracic aortic aneurysm was identified. Thus, patients with GCA have a greatly increased risk of developing thoracic aortic aneurysm, usually as a late complication of GCA.

A review of 1204 surgical aortic specimens from the Cleveland Clinic also suggests that vasculitis generally is an important cause of thoracic aortic aneurysm [50]. Among 383 thoracic aneurysms 12% demonstrated aortitis. Although most these cases were described as "idiopathic," a form fruste of GCA is also possible.

Studies with positron-emission tomography (PET) scanning suggest that aortic inflammation may occur in most patients with GCA. For example, PET scans demonstrated activities suggestive of inflammation in the aorta in 7/13 (54%) of patients with GCA [51]. Therefore, subclinical aortic inflammation may be the rule rather than the exception in giant cell arteritis.

There has also been growing evidence that the patients who have large artery involvement defined by subclavian and axillary disease may constitute a separate subset of GCA. Clinically these patients are distinctive for their low prevalence of positive temporal artery biopsies: only 33% are positive [25]. Diagnosis is often made by angiography. Patients with subclavian and axillary disease also demonstrate distinct cytokine patterns, characterized by higher concentrations of IL-2 gene transcripts in arterial samples [25]. A final difference noted in these patients with large artery disease is the overrepresentation of the *HLA-DRB1\*0404* allele compared with patients with other manifestations of GCA [25].

#### **Laboratory findings**

##### **Giant cell arteritis with normal erythrocyte sedimentation rate**

Although an erythrocyte sedimentation rate (ESR) > 50 is such a common feature of GCA that it constitutes 1 of the 5 American College of Rheumatology criteria for the classification of the disease, the prevalence of low or normal ESRs at diagnosis has reported to vary from 0% to 22.5% [52–55]. A study of 167 patients with GCA living in Olmsted County, Minnesota found that 18 of 167 (10.8%) had an ESR <50, 9 of 167 (5.4%) <40, and 6 of 167 (3.6%) <30 [52]. GCA patients with low ESRs closely resembled those with high ESRs in clinical features and in response to therapy. The low ESR group differed only in having less frequent systemic manifestations (*ie*, fever, fatigue, and malaise) and in having a higher hematocrit [52].

In contrast to what had been previously reported in a Spanish study [56], this Minnesota study found no increased risk of visual loss or other cranial ischemic events in patients with low ESRs [52]. Follow-up revealed that 5 of the 9 patients with low ESRs were never able to mount a high ESR during other episodes of inflammation caused by pneumonia or abdominal abscess, suggesting these patients may have a genetically determined blunted cytokine response to inflammation [52].

### Temporal artery biopsy interpretation

Although it has been known for decades that many different forms of systemic necrotizing vasculitis can inflame the temporal artery, the significance of small vessel vasculitis surrounding a spared temporal artery had not been studied until this year. In a review of 28 patients with this finding, Cid *et al.* [56] found that GCA was still the most common diagnosis, present in 12 of the 28. However, at least 3 of the 28 patients had a systemic necrotizing vasculitis of the polyarteritis nodosa (PAN) type. The other 13 patients either could not be classified or did not undergo sufficiently extensive evaluation to make a diagnosis. Inflammation of the vasa vasorum occurred in 10 of 12 of the GCA patients but in none of those with PAN ( $P = 0.022$ ). Conversely, fibrinoid necrosis was found in all of those with PAN but in none of those with GCA ( $P = 0.0022$ ) [57].

### New imaging modalities in the diagnosis of giant cell arteritis

Temporal artery biopsy is the gold standard for the diagnosis of GCA. However, the invasive nature of the test, and potential for sampling error in patients with noncontiguous lesions make it less than ideal in routine situations. Angiography, although relatively sensitive for large artery disease, is invasive as well, requires contrast material, and fails to detect early arteriopathic changes such as vessel wall edema and early wall thickening [58]. As a result, there has been much interest in recent years in noninvasive modalities for the diagnosis of GCA.

### Ultrasound

In a prospective series of 30 patients with the clinical diagnosis of GCA, Schmidt *et al.* [59] studied the diagnostic performance of duplex ultrasonography versus temporal artery biopsy. Ultrasonography changes, including the presence of a dark halo around the arterial lumen, stenoses, or occlusions, were present in 93% of patients. Subsequent follow-up has found the presence of a luminal halo to be 100% specific for mural inflammation, not being found in the lesions of atherosclerotic vascular disease [60]. Although ultrasonography is inexpensive, readily available at most centers, and is noninvasive, the test remains operator-dependent, and evidence is lacking that general radiology departments can reproduce the high sensitivity and specificity obtained at a few research centers. Until the accuracy of ultrasonography is proven,

the authors believe temporal artery biopsy should remain the gold standard for establishing the diagnosis of GCA.

Magnetic resonance imaging techniques have found wide application in a variety of inflammatory vascular diseases in recent years [61]. Mitomo *et al.* [62] first described the use of MRI in a patient with histologically proven GCA, showing diffuse narrowing in the affected vessel proximal to the biopsy site. Magnetic resonance imaging techniques are promising because they enable detection of both early and late arterial inflammatory changes, as well as more global anatomic detail. However, until the value of MRI is better established, the current authors believe MRI should be reserved for patients who are suspected of having large artery involvement.

### Positron-emission tomography scanning

A number of recent reports have described the use of fludeoxyglucose F18 PET in the diagnosis of GCA. In a study of 25 patients diagnosed with PMR or GCA, PET scanning had a sensitivity of 56%, a specificity of 98%, and a negative predictive value of 80% [51]. PET scanning has also been employed to diagnose GCA in two cases of patients with fevers of unknown origin [63,64]. In one case, repeat PET scanning after 6 weeks of corticosteroid treatment demonstrated decreased uptake in both the major thoracic vessels and the spleen that paralleled clinical improvement. Clearly, these tantalizing results will need to be verified in larger studies before we will know the value of PET scanning in clinical practice.

### Treatment

There are at least three compelling reasons to search for alternatives to corticosteroids, the only established therapy for giant cell arteritis. First, successful treatment of GCA requires starting with high doses, with most authorities recommending beginning with 40 to 60 mg/d of prednisone or with higher intravenous doses for patients who have experienced an acute visual loss [5,64]. Second, although corticosteroids can control the disease and prevent blindness, relapses occur in more than 60% of patients during corticosteroid tapering [8,66], and at least half of the patients require treatment for more than 1.8 years [26]. And third, corticosteroid therapy for PMR/GCA causes important side effects. In one study of PMR, which requires only 5 to 20 mg/d of prednisone as initial therapy, patients were 2 to 5 times more likely than age-matched controls to develop diabetes, vertebral compression fracture, and hip fracture [26].

Past efforts to find alternative therapies has been largely unsuccessful. Alternate day corticosteroids have fewer side effects, but unfortunately do not work as initial therapy for GCA [67], and are less effective than daily therapy for maintenance [68]. Providing a pulse of intravenous methylprednisolone at the commencement of

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treatment has been recently shown to offer no advantage [69]. Although azathioprine has been reported to reduce the need for corticosteroids, that conclusion must be considered tenuous because it rests on a small study that focused on mixture of patients with PMR and GCA [70]. Cyclosporin has not been effective [64]. Until the last year, the studies on methotrexate could not be interpreted with confidence because the studies were small, uncontrolled, or subject to various forms of bias [65].

### Methotrexate

Given this background, it is remarkable that this year witnessed the presentation of two double-blind, placebo-controlled studies on the efficacy of methotrexate for GCA. Unfortunately, the studies reached opposing conclusions. The first study, and the only one to be published in full-length, comes from Italy, where 42 patients with GCA were randomized to prednisone (60 mg/d to start) plus placebo or to prednisone plus methotrexate (10 mg/week orally) [66]. The methotrexate group experienced significantly fewer relapses (45% *vs* 84%) and received significantly smaller total dose of prednisone, averaging about 2 mg/d less over 24 months than the group treated with prednisone alone. Although prednisone-related side effects tended to be less frequent in the methotrexate group, none of the differences reached statistical significance in this small study. And methotrexate was not entirely benign: three (15%) of the patients on methotrexate had to stop the drug because of cytopenia or mouth ulcers.

The second study is a multicentered study from the United States that to date has been published only in abstract form [71]. (Fairness requires disclosure that we participated in this study.) The American study, which enrolled approximately 80 patients, found no difference in relapse rates between patients treated with prednisone alone or with prednisone and methotrexate. The design of the American study differed from the Italian one in that the American study called for prednisone to be tapered to an every-other-day dose. This difference could explain the conflicting results of the two studies.

Taken together, the two studies should constrain enthusiastic use of methotrexate as a steroid-sparing agent in GCA. Although one study suggests methotrexate reduces the relapse rate, no study yet has demonstrated that using methotrexate reduces the use of prednisone sufficiently to lower the frequency of corticosteroid side effects.

### Monitoring therapy

Traditionally physicians have used the patient's symptoms, physical examination findings, and laboratory measures of inflammation such as ESR and C-reactive protein to monitor the course of GCA. The potential advantage of using other biologic markers to monitor dis-

ease activity was suggested by a new study showing that blood levels of IL-6 are more sensitive than the ESR in detecting flares [8]. The investigators followed 25 patients with biopsy proven GCA and found that 89% of flares were associated with an elevated level of IL-6, whereas the ESR was abnormal during only 58% of flares [8]. Although these data are intriguing, they will need to stand the test of time with much larger patient groups before monitoring IL-6 levels can be recommended for clinical practice.

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