Treatment of resistant giant cell arteritis with etanercept

Tan et al recently described a case of “resistant giant cell arteritis” successfully treated with etanercept.1 Their patient, who had classical symptoms of polymyalgia rheumatica (PMR), developed headaches while receiving low dose steroids. Biopsy of a temporal artery showed no arteritis. Because giant cell arteritis (GCA) was suspected on clinical grounds, high dose steroids were instituted. Six months later, despite continued steroid treatment, a transient ischaemic attack (TIA) involving right arm weakness occurred. A diagnosis of GCA resistant to treatment was made, and etanercept was given. The acute phase reactants normalised, and the symptoms referable to PMR resolved completely.

I am not persuaded that the patient in question had GCA.

Firstly, the temporal artery biopsy was negative. Definitive criteria for the entity of so-called biopsy negative GCA are lacking, and, in my opinion, this concept remains a problematic one. Negative temporal artery (TA) biopsies do occur in certain subsets of GCA—for example, upwards of 50% of patients with so-called large artery involvement have such negative biopsies—but the extent to which TA biopsies are negative in bona fide cases of cranial arteritis in GCA is unclear. Two recent papers have suggested that at least 14% of ipsilateral TA biopsy negative for arteritis markedly reduces the probability of the diagnosis of GCA, because the yield of a positive contralateral biopsy is no more than 1–3%.2

The issue of what constitutes a flare in GCA (and PMR) is also problematic. It has been my experience over the years that many cases of alleged flares of both conditions involve little more than asymptomatic rises in the acute phase reactants, and that the pursuit of such rises with increased doses of steroids not uncommonly results in unduly untoward complications—notably, steroid induced osteoporosis and associated fractures.

The patient under discussion is a case in point. The acute phase reactants were raised coincident with the occurrence of a TIA, but it is unlikely that this latter episode was caused by GCA. Though GCA is occasionally complicated by stroke, such an event nearly always involves the territory of the vertebral-basilar circulation, and rarely occurs in the distribution of the internal carotid artery. The explanation for this fact may result from the specific exclusion of the intracranial arteries from involvement by GCA, possibly because these arteries lack an internal elastic lamina, which plays a pivotal part in the pathogenesis of GCA. The internal elastic lamina is said to be maintained for a few millimetres after the vertebral arteries pierce the dura, thus accounting for the strokes referable to the vertebral-basilar circulation.3

The patient described by Tan et al of relatively high dose weakness, almost surely attributable to ischaemia of the middle cerebral artery, thus effectively ruling out GCA as the cause for the TIA.4 I therefore submit that this patient did not have “resistant giant cell arteritis”;

On one final caveat: although further study may show that TNFα blockade does successfully reduce the levels of cytokines that drive the acute phase response in GCA, thus ameliorating constitutional symptoms and signs, this treatment may not mitigate the disease’s most feared consequence—namely, ischaemia leading to visual loss. As demonstrated by elegant work over the past decade by Weyand and Goronzy,5 ischaemia in GCA results from an array of other cytokines with pathogenic potential—for example, platelet derived growth factor and vascular endothelial growth factor, which would be unaffected by TNFα’s blockade.

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References


Authors’ reply

We thank Dr Dockens for his comments on the difficulty in the diagnosis, treatment, and classification of polymyalgia rheumatica (PMR) and giant cell arteritis (GCA). However, the sole purpose of our case report was to show that etanercept might have a role in the treatment of resistant disease of the PMR/GCA spectrum. From a clinical standpoint we are happy to label our patient a case of the successful treatment of resistant giant cell arteritis with etanercept.6

Our comments were directed at cases where the clinical presentation, laboratory abnormalities, and medical treatment of resistant PMR or GCA fail to improve. This study was conducted as a case report to document the potential benefit of etanercept in resistant disease. Further studies are warranted to determine the role of etanercept in resistant disease.

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Fenofibrate and losartan

The leader by Professor Bardin7 makes an excellent point. We could benefit from the hypouricaemic action of drugs that are not licensed for this use (for example, losartan and fenofibrate).

Other drugs in common use may also have a uricosuric effect. For example, atorvastatin can reduce serum uric acid concentrations in patients with peripheral arterial disease or hyperlipidaemia.8,9 However, the mechanisms involved are not clear cut; we speculate that atorvastatin can increase renal blood flow and decrease serum creatinine levels.10 Thus, the Medical Research Council/British Heart Foundation Heart Protection Study (HPS) showed that simvastatin decreased the deterioration of the glomerular filtration rate (GFR) over a period of 4.6 years in high risk patients with (n = 5963) or without (n = 14 573) diabetes.11 This effect on GFR would almost certainly influence urate excretion. These statin mediated effects are relevant because, as Professor Bardin points out, patients with hyperuricaemia may also be dyslipidaemic.

Closer to the interests of rheumatologists are the non-steroidal anti-inflammatory drugs (NSAIDs). Some NSAIDs may exert a favourable effect on urate excretion. For example, difluinusal has been reported to have a uricosuric effect, although the inhibition of xanthine oxidase activity has also been proposed.12 Azapropazone (not used as a first line option) has been shown to lower serum urate levels.13 Indomethacin may have uricosuric properties.14 Tiaprofenic acid

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is another NSAID with hypouricaemic effect.\textsuperscript{10} Aspirin has a bimodal effect on the renal handling of uric acid. High doses (>3 g/day) are uricosuric, while lower doses (1–2 g/day) cause urate retention.\textsuperscript{11} At the lowest dose (75 mg/day) aspirin caused a 15% decrease in urate excretion with a slight but significant increase in serum urate levels.\textsuperscript{12} The clinical significance of these “additional” uricosuric effects remains to be established. There is also a need to assess the value of using combinations of these drugs (for example, losartan and fenofibrate together with an NSAID with beneficial effects on urate excretion).

The search for NSAIDs that do not exert renal toxicity may well be worthwhile because of their widespread use. Acute attacks of gout are usually treated with their widespread use. Acute attacks of gout are usually treated with:

- The name of the first author of this paper has changed from Tak-Diamant Z to Diamant Z.

We regret that the references for this letter were omitted. They are given below.


**NOTIFICATION AND CORRECTION**

Corrections printed in the journal also appear on the Annals website www.annrheumdis.com and are linked to the original publication.

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