PostScript

MATTERS ARISING

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, which was ascribed to ''arteritis (sic)''. An insufficiency fracture ensued. As the erythrocyte sedimentation rate and C reactive protein were persistently raised, 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[2]—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 in fact a unilateral 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%.[3 4]

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 sundry 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.[5] The patient described by Tan *et al* had left arm weakness, almost surely attributable to ischaemia of the middle cerebral artery, thus effectively ruling out GCA as the cause for the TIA.

I therefore submit that this patient did not have ''resistant giant cell arteritis''; rather, he represents a case of the successful treatment by tumour necrosis factor α (TNFα) blockade of symptoms and signs referable to PMR.

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,[6] 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 blockade.

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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 how 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 as having GCA (in addition to PMR) based on his headaches, reported visual abnormalities, temporal tenderness, and resistance to 15 mg of prednisolone a day. We know that the disease was resistant because his symptoms and laboratory abnormalities persisted despite continued use of relatively high dose steroids, and there was clinical deterioration mirrored by an increase of the acute phase response.

Of course it is entirely possible that his transient ischaemic attack was related to atheroma, even in the face of very active GCA, but a rare arteritic related event could not be excluded in the clinical circumstances. The adverse effect of high dose steroids on blood pressure and lipid profiles and their association with atheromatous related disease was an additional concern about their continued use. We agree that it would be folly to treat patients on the basis of a raised erythrocyte sedimentation rate (ESR) alone but an extremely high ESR, as in this case, invariably signifies disease flare. Activation of the inflammatory cascade has a pivotal role in the pathogenesis of GCA so it seems logical that anti-tumour necrosis factor treatment could abrogate this regardless of the other cytokine mediators of disease.

Fifteen months after the original case report the clinical diagnosis remains the same and the patient continues to experience flares in disease with tapering of the steroid dose below 5 mg/day.

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Fenofibrate and losartan

The leader by Professor Bardin[1] 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.[2–4] However, the mechanisms involved are not clear cut; we speculate that atorvastatin can increase renal blood flow and decrease serum creatinine levels.[2–4] 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.[5] This effect on GFR would almost certainly influence urate excretion. These statin mediated effects are relevant because, as Professor Bardin[1] 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, diflunisal has been reported to have a uricosuric effect, although the inhibition of xanthine oxidase activity has also been proposed.[6 7] Azapropazone (not used as a first line option) has been shown to lower serum urate levels.[7 8] Indometacin may have uricosuric properties.[7] Tiaprofenic acid

is another NSAID with hypouricaemic effect.[9]

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.[10] 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.[10]

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 high doses of NSAIDs. It could be useful to have NSAIDs with uricosuric properties as well as the analgesic and anti-inflammatory effect.

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NOTIFICATION AND CORRECTION

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

Intra-articular rheumatoid nodules and triggering of the knee joint (Tak-Diamant Z, Hooning van Duyvenbode FJ, Eulderink F, Janssen M. *Ann Rheum Dis* 1992;**51**:533–5.)

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

Does long term treatment with azathioprine predispose to malignancy and death in patients with systemic lupus erythematosus? (Nero P, Rahman A, Isenberg DA. *Ann Rheum Dis* 2004;**63**:325–6.)

doi: 10.1136/ard.2002.005371corr1

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

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NOTICE

8th EULAR Postgraduate Course in Rheumatology

28 November–3 December 2004; Prague, Czech Republic

The course will cover clinical aspects of rheumatic disease concentrating on outcome, assessment, and evidence based management and will include the scientific basis of rheumatology. The course is aimed at junior rheumatologists at the end of their training but is open to all rheumatologists.

The registration fee of €600 will include tuition, accommodation for seven nights and all meals.

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EULAR will consider granting bursaries to young rheumatologists from countries where there is a real educational need. More information will be available on the EULAR website from 1 April 2004.

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