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”1. 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—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 reported raised contralateral 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 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.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.

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,4 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.

W P Docken
Brigham and Women’s Hospital, Boston, MA 02115, USA

Correspondence to: Dr W P Docken, 850 Boylston St, Chestnut Hill, MA 02467, USA; wpdocken@partners.org

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 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, constitutional 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 oral prednisolone and corticosteroids, 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, 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 (above 100) 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.

Fenofibrate and losartan

The leader by Professor Bardin 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.5–6 However, the mechanisms involved are not clear cut; we speculate that atorvastatin can increase renal blood flow and decrease serum creatinine levels.7 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) diabetes.8 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, diflunisal has been reported to have a uricosuric effect, although the inhibition of xanthine oxidase activity has also been proposed.9 Azapropazone (not used as a first-line option) has been shown to lower serum urate levels.10 Indomethacin may have uricosuric properties.11 Tiaprofenic acid

www.annrheumdis.com
is another NSAID with hypouricaemic effect.”

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.11

The clinical significance of these “addi-
tional” 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.

S S Daskalopoulou, D P Mikhailidis
Department of Clinical Biochemistry (Vascular Disease Prevention Clinic), Royal Free Hospital, Royal Free and University College Medical School, London, UK

V G Athyros, A A Papageorgiou
Atherosclerosis Unit, 2nd Propedeutic Department of Internal Medicine, Aristotelian University, Hippocratie Hospital, Thessaloniki, Greece

M Eliaf
Department of Internal Medicine, Medical School, University of Ioannina, Greece

Correspondence to: D P Mikhailidis, Department of Clinical Biochemistry (Vascular Disease Prevention Clinic), Royal Free Hospital, Royal Free and University College Medical School, Pond street, London NW3 2QG, UK; mikhailidis@bath.com

References

NOTIFICATION AND CORRECTION

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


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

Does long term treatment with azathio-


doi: 10.1136/ard.2002.005371cor1

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

2. Moll JMH. Drug therapy (3): “specific” drugs. In: Management of rheumatic dis-


4. Sutcliffe N, Smith C, Speight PM, Isenberg DA. Mucosa-associated lymphoid tissue lymphomas in two patients with rheumatoid arthritis on sec-


INTERNATIONAL CONGRESS ON SLE AND RELATED CONDITIONS

9–13 May 2004; New York, New York, USA
Contact: The Oakley Group, 2014 Broadway, Suite 250, Nashville, Tennessee 37203, USA
Tel: +1 615 322 2785 Fax: +1 615 322 2784
Email: Lupus2004@theoakleygroup.com
Website: http://www.lupus2004.org

10th World Congress on Osteoporosis
14–18 May 2004; Rio de Janeiro, Brazil
IOF awards are available for scientists:
IOF Claus Christiansen Research Fellowship: 45 000
IOF Servier Young Investigator Fellowship: 40 000
Contact: Congress Secretariat at info@
 osteofound.org
Website: www.osteofound.org

INTERNATIONAL SOCIETY FOR THE STUDY OF THE LUMBAR SPINE

31 May–5 June 2004; Porto, Portugal
Contact: International Society for the Study of the Lumbar Spine, 2075 Bayview Avenue, Room MG 323, Toronto, Ontario, Canada M4N 3M5
Tel: 00 1 416 480 4830 Fax: 00 1 416 480 6055
Email: shirley.fitgerald@sw.ca

8th EULAR Sonography Course
7–9 June 2004; Berlin, Germany
Organising Committee: Marina Backhaus, Wolfgang Schmidt
Contact: Congress Organisation: Gede1 Congress Service
Tel: +49-30-22488390 Fax: +49-30-22488389
Email: gedel.cm@t-online.de
Website: www.eular.org

First European Course: Capillaroscopy and Rheumatic Diseases
10–12 September 2004; Genova, Italy
Contact: Scientific Secretariat: Professor Maurizio Cutolo, Division of Rheumatology, DIMI, University of Genova, Italy
Email: mcutolo@unige.it
Organising Secretariat: Michela Civelli, EDRA spa, Viale Monza , 133 – 20125, Milan, Italy
Tel: +39 02 281 72300 Fax: +39 02 281 72399
Email: edracongress@dsmedigroup.com

XIIth International Conference on Behcet’s Disease
27–31 October 2004; Antalya, Turkey
Contact: Congress Secretariat, Figur Congress and Organization Services Ltd. STI, Ayazmaderesi Cad. Karadut Sok. No: 7 80888 Dikilitas, Istanbul, Turkey
Tel: +90 (0212) 258 6020 Fax: +90 (0212) 258 6078
Email: behcet2004@figur.net
Website: www.behcet2004.org

www.annrheumdis.com