Refractory adult onset Still’s disease and hypersensitivity to non-steroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors: are biological agents the solution?

E H J G Aarntzen, P L C M van Riel, P Barrera


Adult onset Still’s disease (AOSD) is an autoimmune disorder characterised by periodic high fever, arthritis, and typical evanescent rashes. Non-steroidal anti-inflammatory drugs (NSAIDs) are the preferred treatment. In severe cases several disease modifying antirheumatic drugs, thalidomide, and intravenous immunoglobulin have been used. More recently, successful treatment with tumour necrosis factor α (TNFα) blocking agents1 2 and interleukin (IL) 1 neutralisation3 has also been reported.

Hypersensitivity to NSAIDs, often characterised by urticaria, angio-oedema, and asthma, has been well documented, and several studies indicate that anaphylactic reactions are related to the inhibition of cyclo-oxygenase-1 (COX-1) enzyme4–6 and that selective COX-2 inhibitors can be safe in these patients. Here we report a case of AOSD complicated by coexisting hypersensitivity to acetaminophen (paracetamol), aspirin, NSAIDs, and also to selective COX-2 inhibitors. TNFα neutralisation controlled the fever, but not the AOSD related rashes and polyarthritis or the anaphylactic reactions to NSAIDs and COX-2 inhibitors. Treatment with IL1 receptor antagonist led to full remission of the AOSD.

CASE REPORT
A patient, with known AOSD for 22 years, was admitted to our centre with a 3 week history of spiking high fever, chills, skin rash, cough, and a sore throat. Physical examination disclosed a typical AOSD related rash, polyarthritis, and enlarged inguinal lymph nodes without hepatosplenomegaly. Laboratory examination showed an increased acute phase reaction and a normochromic normocytic anaemia; white blood cell count, platelet count, and liver function tests were normal. Serological tests for viral infections, toxoplasma, Bartonella, blood and urine culture rheumatoid factor, and antinuclear antibodies were all negative.

In the past the AOSD had followed a polycyclic course, which had been successfully treated with several NSAIDs alone or in combination with acetaminophen for 10 years. In 1993, she developed an allergic reaction with angio-oedema to naproxen (fig 1), and later also to acetaminophen and sodium salicylate. Methotrexate was used for the next 10 years, but frequently corticosteroids were needed to treat the AOSD exacerbations. To avoid chronic use of corticosteroids, etanercept was started in May 2003 and the corticosteroids were tapered. This led to exacerbations of a mild polyarthritis and worsening of the rash but no fever. Because selective COX-2 inhibitors may be safe in patients with intolerance to NSAIDs4 5 rofecoxib was successfully added to etanercept without intolerance. However, a second challenge with rofecoxib resulted in severe angio-oedema and urticarial rash and the same occurred after challenges with celecoxib and etoricoxib. IL1 receptor antagonist was started in December 2004, leading to a full remission of all AOSD related symptoms despite the withdrawal of long term steroid treatment.

DISCUSSION
Our case illustrates that TNFα blocking agents are only partially effective in the treatment of refractory AOSD. Partial or limited efficacy of these agents has also been also observed in patients with systemic onset juvenile idiopathic arthritis.6 7 Our case and several other reports suggest that it is not TNFα...
but IL1 which has a pivotal role in the pathogenesis of AOSD\(^1\) and systemic onset juvenile idiopathic arthritis.\(^8\) In these diseases and in other rare disorders with a single amino acid mutation in the NALP-3 gene which results in increased IL1 secretion, IL1 blockade seems to be the preferred treatment.\(^10\)

Furthermore, our case suggests that hypersensitivity to NSAIDs is not exclusively mediated by COX-1 blockade, but can also be provoked by selective COX-2 inhibitors that can function as hapitens, resulting in anaphylaxis upon next exposure.\(^9\) Our case shows that these reactions are not mediated by TNF\(_\alpha\) and not altered by TNF\(_\alpha\) neutralisation.

---

**Authors’ affiliations**

E H J G Aarntzen, P L C M van Riel, P Barrera, Department of Rheumatology, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, The Netherlands

Competing interests: none

Correspondence to: Dr P Barrera, p.barrera@reuma.umcn.nl

Accepted 24 June 2005

Published Online First 13 July 2005

---

**Distal degeneration of sensory and autonomic cutaneous nerve fibres in systemic sclerosis**

V Provitera, M Nolano, N Pappone, C di Girolamo, A Stancanelli, F Lullo, C Crisci, L Santoro


W e studied innervation and dermal vasculature in affected and apparently normal skin of sclerodermic patients to evaluate the involvement of different nerve fibre groups and to determine a possible correlation with vascular damage in this disease. Immunohistochemical analysis and confocal microscopic examination of skin biopsy samples were used.

**METHODS AND RESULTS**

We obtained 3 mm punch skin biopsy samples from the distal thigh and distal leg in 11 consecutive 34–70 year old female patients with systemic sclerosis (SSc), identified by the American College of Rheumatology classification criteria.\(^1\) We excluded patients who had been exposed to potentially neurotoxic exogenous or endogenous conditions. The skin appeared sclerotic in 4/11 patients in the leg and in 3/11 in the thigh (table 1). In four patients a further skin sample from fingertip was taken to evaluate myelinated fibres. None of the patients complained of sensory disturbances, and neurological and neurophysiological evaluations were normal except in two patients, in whom a conduction velocity study showed the presence of an entrapment syndrome. Patient morphological findings were compared with data from a group of 16 healthy volunteers (nine male, seven female, age range 34–65 years).

Skin biopsy specimens were processed according to previously published procedures.\(^2\) Floating sections were immunostained using a panel of primary antibodies, including the pan-neuronal marker anti-protein gene product (PGP) 9.5, anti-myelin basic protein for myelinated fibres, anti-vasoactive intestinal peptide (VIP) to mark autonomic nerve fibres, and anti-collagen IV to visualise basement membrane and blood vessels.

We quantified, as previously described, epidermal nerve fibres (ENFs) per linear millimetre,\(^3\) Meissner corpuscles (MCs), and myelinated papillary endings per square millimetre\(^4\) on confocal images using image analysis software (Neurolucida, Microbrightfield Inc, Colchester VT, USA; ScionImage, Scion Corporation, Frederick, MD, USA). On the same images used to quantify ENF density, we measured blood vessel density in \(\mu m^2/100\mu m^2\) of dermal tissue within 250 \(\mu m\) below the basement membrane.

We found a significant loss of ENFs in sclerodermic patients in all the examined sites (table 1) without a distal-proximal gradient, a poor subepidermal neural plexus, and a residual innervation of sweat glands, blood vessels, and arrector pilorum muscles compared with controls. These findings, evident in apparently unaffected areas (figs 1E and 1F), were more severe in clinically involved skin (figs 1C and D compared with 1A and B) and affected both sensory and autonomic unmyelinated nerve fibres as demonstrated by PGP and VIP immunostainings.

The mean (SD) density of blood vessels measured in \(\mu m^2/100\mu m^2\) of dermal tissue, was 6.4 (2.9) and 8.7 (4.7), respectively, in the thigh and leg of patients with SSc. These values significantly correlated with the density of epidermal nerve fibres in both sites \((r^2 = 0.51; p<0.05\) at the thigh and \(r^2 = 0.58; p<0.05\) at the leg). In glabrous skin we found a significant reduction of MC density compared with controls, with a number of intrapapillary myelinated fibres still within the normal range. Moreover, evident structural abnormalities of the surviving mechanoreceptors and degenerative

---

**REFERENCES**


