LETTERS

Management of treatment resistant inflammation of acute on chronic tophaceous gout with anakinra

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We report a 74-year-old man with acute on chronic tophaceous gout in whom conventional treatments failed but who responded to treatment with the interleukin-1 receptor antagonist, anakinra. The patient presented in February 2004 with a severe flare of gout. Multiple joints were swollen, including the right fifth proximal interphalangeal (PIP), the left fourth PIP, and the first metatarsophalangeal (MTP) joints bilaterally. Apart from chronic tophaceous gout, he also had a history of membranous glomerulonephritis (for which he was on prednisolone 5 mg/day), hypertension, and ischaemic heart disease. Allopurinol had previously induced a severe anaphylactic reaction and his renal impairment was exacerbated by non-steroidal anti-inflammatory drugs.

On examination, the above mentioned joints were swollen with associated tenderness and erythema, and there were multiple tophi. Investigations revealed a raised C reactive protein (CRP) of 72 mg/l (normal <10 mg/l), a raised urate of 0.6 mmol/l (0.20–0.42 mmol/l), urea of 13.9 mmol/l, and creatinine of 155 μmol/l, with creatinine clearance reduced to 54 ml/min. The patient could only tolerate colchicine 0.5 mg daily and probenicid 1 g daily, both of which were continued throughout anakinra therapy. A prednisolone dose of up to 40 mg daily was used but his symptoms worsened whenever steroids were tapered. This inadequate control resulted in foot deformities with dropping of the right metatarsal arch, associated with radiographic osteopenia and erosions of the left first interphalangeal joint. Febuxostat, benzbromarone, and uricase inhibition were considered but were not used because of lack of availability or concerns about toxicity.[1–3] However, recent data show that uric acid activates the NALP3 inflammasome, leading to release of interleukin-1 (IL-1β), which provides a novel theoretical basis for anti-IL-1β treatment.[4–9]

The patient was prescribed anakinra 100 mg daily subcutaneously, and outcomes were assessed regularly thereafter. The joints involved were photographed before and after therapy (fig 1) with the patient's consent. Pre-therapy, the total swollen joint count (SJC) was 14 and the tender joint count (TJC) 24. The CRP and erythrocyte sedimentation rate (ESR) were normal pre-therapy (<1 mg/l and 13 mm/h, respectively), probably reflecting the effect of the steroid treatment. The patient improved within two weeks, with the global assessment score falling from 65 mm to 20 mm on a visual analogue scale (VAS 0–100 mm), and SJC improving from 14 to 3. The physician global assessment score fell from 80 mm to 50 mm. The patient received a continuous daily dose of anakinra during the follow up as he had residual joint tenderness, and maintained the benefit from this treatment at six months. Prednisolone 5 mg daily was continued for the glomerulonephritis. We plan to wean the patient off anakinra if symptoms resolve.

There is surprisingly little information about the management of ''intractable'' gout, and treatment options remain empirical. So *et al* have recently shown the efficacy of anakinra in resistant gout in a small pilot study.[9] In contrast to other reports, our patient was at the most severe end of the disease spectrum but nevertheless improved significantly. There has been one report on the successful use of anti-tumour necrosis factor in severe gout.[10] It remains to be determined whether anakinra is especially effective in gout or whether antagonism of other key cytokine pathways is also effective.

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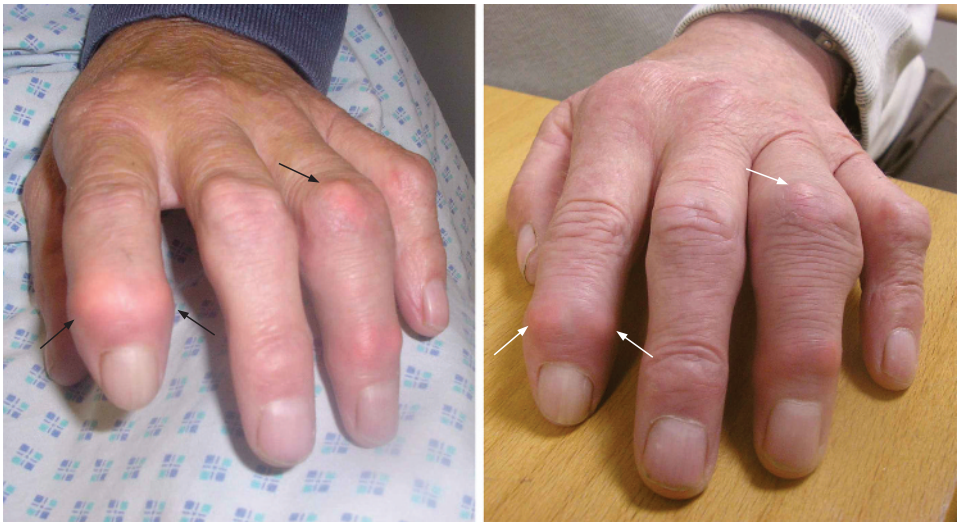

Figure 1 Left hand of the patient before treatment with anakinra, and three months after starting anakinra. Acute inflammatory tophi can be seen on the index finger distal interphalangeal joint and the proximal interphalangeal (PIP) joint of the ring finger (black arrows) pre-therapy. These erythematous and swollen joints improved following treatment with anakinra (white arrows). Note that the angle of the photograph highlights the joint deformity in the PIP joint of the ring finger in the post-anakinra image, but joint diameters were unchanged from before treatment with anakinra. Images reproduced with the patient's consent.

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Tumour necrosis factor receptor 2 (TNFRSF1B) association study in Sjögren's syndrome

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Primary Sjögren's syndrome (pSS) is a complex disease involving both genetic and environmental factors. Among the genetic susceptibility factors, *HLA-DRB1* has been extensively studied as a strong candidate gene and the association of *HLA-DRB1*0301* (DR3) with pSS has been frequently reported among Caucasians.[1 2] As the Tumour Necrosis Factor α (*TNFα*) gene is located within the *HLA* region, its contribution to disease susceptibility has also been studied. We have previously reported a significant association of *TNF-308A* allele with pSS, in strong linkage disequilibrium with *HLA-DRB1*03*.[3] This association was restricted to patients with anti-SSB antibodies. TNF exerts its action through two cell surface receptors, TNF receptors 1 and 2 (TNFR1 and TNFR2, 55 and 75 kDa respectively). Due to the functional interaction between TNF and TNFR2, we considered this receptor (also named TNFRSF1B) as another interesting candidate gene for the genetic susceptibility to pSS. *TNFR2 T676G* polymorphism replacing a methionine by an arginine (TNFR2 196 M/R) is functional as the cytotoxic activity induced by TNFR2 196R (*TNFR2 696 G* allele) is increased.[4] Moreover, *TNFR2 T676G* polymorphism has been previously associated with the genetic susceptibility to other autoimmune diseases: familial, but not sporadic, rheumatoid arthritis (RA)[5] and systemic lupus erythematosus (SLE).[6]

We carried out a case–control association study of *TNFR2 T676G* polymorphism among 119 unrelated patients with pSS according to European–American consensus group (46 patients without autoantibodies (Ab), 33 patients with anti-SSA Ab only, 40 patients with anti-SSA and anti-SSB Ab) and 95 healthy controls. Both patients and controls were of Caucasian origin. *TNFR2 T676G* polymorphism was genotyped by polymerase chain reaction–restriction fragment length polymorphism analysis (*Nla* III).

No significant differences in allele and genotype frequencies of *TNFR2 T676G* polymorphism were detected between patients with pSS and controls (Table 1). *TNFR2 T676G* polymorphism was not involved in the genetic predisposition to a specific pattern of autoantibody secretion ($p = 0.61$). No association was found with extraglandular involvement ($p = 0.34$). Interestingly, there was a trend in favour of an association with joint involvement (arthritis and arthralgia) ($p = 0.06$). An epistatic effect between *TNF -308A/G* and *TNFR2 T676G* polymorphisms was then looked for, but not evidenced, among 55 pSS patients.

Table 1 Allelic and genotypic frequencies of *TNFR2 T676G* polymorphism in 119 patients with pSS and 95 controls

TNFR2 T676G **Allele frequencies**	**pSS n = 238**	**Controls n = 190**	**p**	**Odds ratio (95% CI) pSS versus controls**
676T (%)	191 (80.3)	149 (78.4)	NS	1.12 (0.7 to 1.79)
676G (%)	47 (19.7)	41 (21.6)		
Genotype frequencies	**n = 119**	**n = 95**		
TT	72 (60.5)	56 (58.9)	NS	0.85 (0.62 to 1.15)
TG	47 (39.5)	37 (38.9)	NS	1.17 (0.86 to 1.60)
GG	0	2 (2.2)		

pSS, primary Sjögren's syndrome; CI, confidence interval; NS, not significant.