Recurrent uveitis in a patient with juvenile spondyloarthropathy associated with tumour necrosis factor α inhibitors

O Kaipiainen-Seppänen, M Leino

Ann Rheum Dis 2003;**62**:88–89

Tumour necrosis factor α (TNFα) antagonists have been shown to be effective in controlling symptoms in patients with rheumatoid arthritis (RA)[1 2] and juvenile RA (JRA).[1] The most common adverse events associated with etanercept are injection site reactions and infections, and with infliximab, headache, infections and, occasionally, infusion related reactions.[2] Cutaneous vasculitis associated with etanercept has been described in three patients, and one of them also had a similar skin manifestation secondary to the treatment with infliximab.[3] The possible association of a demyelinating syndrome with the use of anti-TNF agents in inflammatory arthritides needs further surveillance.[4]

CASE REPORT

A 31 year old female patient has had juvenile rheumatic disease since the age of 10. She has had a polyarticular disease in her peripheral joints with inflammatory manifestations both in the cervical spine and sacroiliac joints. She is HLA-B27 positive. At the time of diagnosis she was treated with aurothiomalate and hydroxychloroquine, but they were withdrawn because of side effects. During treatment with D-penicillamine remission was achieved. This drug was discontinued after treatment of 2.5 years. Between 1984 and 1989 she was in remission. Thereafter she was treated with D-penicillamine, azathioprine, podophyllotoxin, auranofin, chlorambucil, cyclosporin, and methotrexate, either each drug alone or in the 1990s with a combination of two drugs. Most often the combinations included methotrexate, which she has used continuously since May 1995. Many of the aforementioned drugs were withdrawn because of side effects, but some of them owing to lack of efficacy. Her joint disease was continuously active.

In July 1999, etanercept 25 mg twice weekly was started and methotrexate was continued with a small dose reduction from 25 mg to 20 mg/week. Her joint disease responded well to this combination treatment; within three months she gained remission. Her haemoglobin rose from 91 to 124 g/l, the erythrocyte sedimentation rate (ESR) decreased from 60 to 8 mm/1st h, and C reactive protein (CRP) from 44 to 5 mg/l. In March 2000, for the first time during her longlasting disease, she had acute anterior uveitis, which ran a chronic course. From June to August 2000 the dose of etanercept was reduced to 25 mg/week and it was discontinued at the end of August 2000. Inflammation in her eye was temporarily depressed, but it was reactivated again in December 2000 and March 2001. Between September 2000 and May 2001 she was treated with a combination of prednisolone, methotrexate, and leflunomide, but the joint disease flared. Leflunomide was discontinued and infliximab infusions were started in May 2001. Corticosteroid treatment was withdrawn after the first infusion. Uveitis in her right eye relapsed in March 2002, but it responded to topical corticosteroids in two weeks. At that time her joint disease was in remission, the ESR was 7 mm/1st h and CRP <5 mg/l.

DISCUSSION

Chronic uveitis is an important complication of JRA. Uveitis is usually asymptomatic and often bilateral. It becomes manifest usually within seven years from the onset of arthritis.[5] In epidemiological studies the incidence of uveitis has varied from 4 to 16% among patients with JRA in population based series.[6 7] Up to 27% of patients with juvenile onset ankylosing spondylitis have one or more attacks of non-granulomatous acute uveitis.[8]

Among 16 patients who had inflammatory eye disease (uveitis or scleritis), 13/16 also having an associated joint disease, and who were treated with etanercept or infliximab, the joint disease responded excellently to treatment, but the eye disease improved in only 6/16 patients (38%).[9] Five patients developed an inflammatory eye disease for the first time while taking a TNF inhibitor. Among 10 children with uveitis refractory to long term treatment, 3/14 (21%) eyes achieved remission, 5/14 (36%) eyes improved, 5/14 eyes (36%) remained unchanged, and one eye (7%) worsened during etanercept treatment.[10] In endotoxin induced uveitis in mice, both pretreatment with TNFα or with anti-TNFα antibody caused the ocular inflammation to worsen significantly.[11] Thus, TNFα blockade may also stimulate certain aspects of immune defence, exacerbating immune reaction in the tissues which TNF inhibitors do not effectively penetrate, such as the central nervous system,[4] or the eye. The peripheral joint disease responded well to both TNF inhibitors in our patient. Although a disease associated manifestation cannot be excluded, recurrences of uveitis, when the joint disease was in remission, may be secondary to TNF inhibition. Both etanercept and infliximab induced similar cutaneous vasculitis in a susceptible patient, which might be due to anti-drug antibody production or perturbation in the TNF/TNF receptor system in the target organ.[3] It was recently shown that peripheral T cell reactivity was increased after four and eight weeks of etanercept treatment among patients with RA.[12] Surveillance of large patient groups is needed to reveal the magnitude of immune reactions associated with TNFα blockade.

Authors' affiliations
O Kaipiainen-Seppänen, Department of Medicine, Kuopio University Hospital, Kuopio, Finland
M Leino, Department of Ophthalmology, Kuopio University Hospital, Kuopio, Finland

Correspondence to: Dr O Kaipiainen-Seppänen, Department of Medicine, Kuopio University Hospital, PO Box 1777, 70211 Kuopio, Finland; Oili.Kaipiainen-Seppanen@kuh.fi

Accepted 17 May 2002

REFERENCES

1 **Garrison L**, McDonnell ND. Etanercept: therapeutic use in patients with rheumatoid arthritis. Ann Rheum Dis 1999;58:(suppl I):i165–9.
2 **Maini R**, St Clair EW, Furst D, Kalden J, Weisman M, Smolen J, *et al.* Infliximab (chimeric anti-tumor necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. Lancet 1999;354:1932–9.
3 **McCain ME**, Quinet RJ, Davis WE. Entanercept and infliximab associated with cutaneous vasculitis. Rheumatology (Oxford) 2002;41:116–17.
4 **Mohan N**, Edwards ET, Cupps TR, Oliverio PJ, Sandberg G, Crayton H, *et al.* Demyelination occurring during anti-tumor necrosis factor α therapy for inflammatory arthritides. Arthritis Rheum 2001;44:2862–9.
5 **Kanski JJ**. Juvenile arthritis and uveitis. Surv Ophthalmol 1990;34:253–67.

6 **Towner SR**, Michet CJ Jr, O'Fallon WM, Nelson AM. The epidemiology of juvenile arthritis in Rochester, Minnesota 1960–1979. Arthritis Rheum 1983;26:1208–13.
7 **Kotaniemi K**, Kaipiainen-Seppänen O, Savolainen A, Karma A. A population-based study on uveitis in juvenile rheumatoid arthritis. Clin Exp Rheumatol 1999;17:119–22.
8 **Burgos-Vargas R**, Pacheco-Tena C, Vázquez-Mellado J. Juvenile-onset spondyloarthropathies. Rheum Dis Clin North Am 1997;23:569–98.
9 **Reiff A**, Takei S, Sadeghi S, Stout A, Shaham B, Bernstein B, *et al*. Etanercept therapy in children with treatment-resistant uveitis. Arthritis Rheum 2001;44:1411–15.
10 **Smith RJ**, Levinson RD, Holland GN, Jabs DA, Robinson MR, Whitcup SM, *et al*. Differential efficacy of tumor necrosis factor inhibition in the management of inflammatory eye disease and associated rheumatic disease. Arthritis Care Res 2001;45:252–7.
11 **Kasner L**, Chan CC, Whitcup SM, Gery I. The paradoxical effect of tumor necrosis factor alpha (TNF-α) in endotoxin-induced uveitis. Invest Ophthalmol Vis Sci 1993;34:2911–17.
12 **Berg L**, Lampa J, Rogberg S, van Vollenhoven R, Klareskog L. Increased peripheral T cell reactivity to microbial antigens and collagen type II in rheumatoid arthritis after treatment with soluble TNFα receptors. Ann Rheum Dis 2001;60:133–9.

Enhancement by iron of interleukin 1 induced granulocyte macrophage colony stimulating factor (GM-CSF) production by human synovial fibroblasts

K Nishiya, H Wang, K Tahara, K Hashimoto

Ann Rheum Dis 2003;**62**:89–90

Iron infusion activates synovium and induced joint inflammation in experimental animals and causes the flaring up of arthritis in patients with rheumatoid arthritis (RA). Marked iron deposition in RA synovia has been reported over the past 30 years and has also recently been demonstrated by quantitative photometric assessment and is correlated with exudative and proliferative histological features.[1] It has been reported that the amount of iron deposition in RA synovial tissue is correlated with disease activity and severity. Iron has an important role in RA synovitis through the formation of radical oxygen species, and the enhancement of collagen synthesis and synovial fibroblast proliferation[2] possibly owing to down regulation of prostaglandin E_2 (PGE_2) production.[3]

Synovial fibroblasts produce a number of inflammatory mediators including cytokines such as interleukin (IL)1, IL6, IL8, fibroblast growth factor, vascular endothelial growth factor, tumour necrosis factor, and granulocyte macrophage colony stimulating factor (GM-CSF). GM-CSF produces the progenitor cells of macrophage lineage stem cells and stimulates mature granulocytes and macrophages. GM-CSF is produced by T cells, macrophages, and fibroblasts and has been found in synovial fluid and tissue from patients with RA. GM-CSF has an important role in type II collagen induced arthritis in rats and in the acute methylated bovine serum albumin induced murine arthritis model. A protective effect against collagen induced arthritis was seen in GM-CSF knockout mice. Using those mice, it has been recently shown that GM-CSF plays a part in the IL1 induced arthritis that follows methylated bovine serum albumin injection.[4] In this study we showed that iron enhanced GM-CSF but did not enhance IL6 or IL8 production by human synovial fibroblasts on stimulation with IL1β in vitro.

Synovial tissues were obtained from 20 patients, 11 with RA and nine with osteoarthritis. The synovial fibroblasts were isolated according to a method described previously.[2] The material containing the synovial fibroblasts during the third to seventh passage was used in the experiments. Synovial fibroblasts were added at a concentration of 1×10^4 cells/well to each well of a 96 well microtitre plate, and cultured for 18, 24, 48, 72, 96, and 120 hours with or without recombinant human IL1β. The cytokines in the culture supernatant were measured with a commercially available enzyme linked immunosorbent assay (ELISA) kit (Amersham Life Science, UK). Ferric citrate was used as an iron salt or sodium citrate as a control. The differences in cytokine production by synovial fibroblasts cultured with ferric citrate compared with sodium citrate or medium alone were analysed by paired Student's *t* test. A level of $p<0.05$ was accepted as significant.

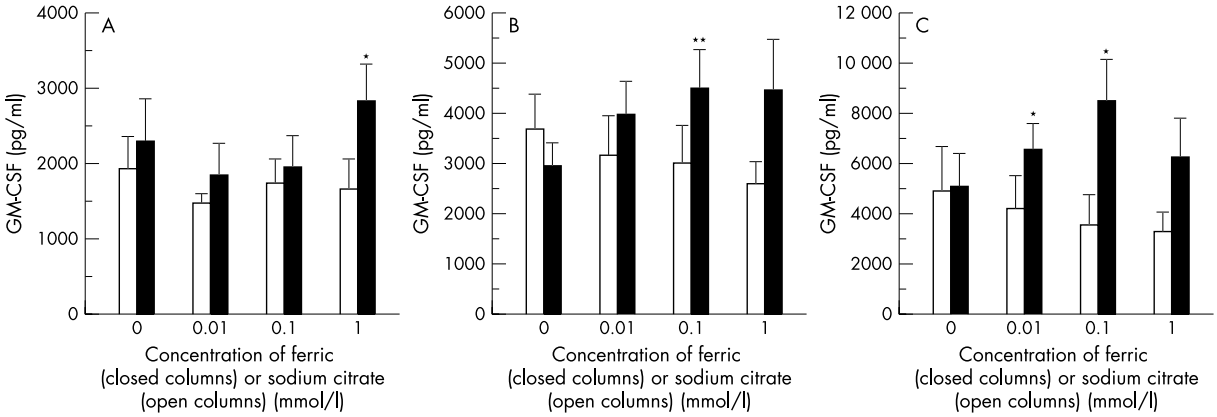

Figure 1 Effects of iron on IL1β induced GM-CSF production by human synovial fibroblasts cultured for 96 hours. Human synovial fibroblasts were stimulated with IL1β in the presence of different concentrations of ferric or sodium citrate. (A) IL1β 1 ng/ml. (Bars represent means (SEM) of six experiments. *p<0.05 *v* medium alone). (B) IL1β 10 ng/ml. (**p<0.01 *v* medium alone; n=6). (C) IL1β 100 ng/ml. (*p<0.05 *v* medium alone; n=6).