

LETTERS

Safety and efficacy of TNF α blockade in relapsing vasculitis

A D Booth, H J Jefferson, W Ayliffe, P A Andrews, D R Jayne

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Blockade of tumour necrosis factor alpha (TNF α) using infliximab, a chimeric monoclonal antibody against TNF α , is an effective treatment in rheumatoid arthritis and Crohn's disease.^{1,2} Sifkakis reported success using infliximab in sight threatening Behçet's disease.³ A preliminary study has also reported clinical improvements in the primary systemic vasculitis, Wegener's granulomatosis, with the soluble TNF α receptor etanercept.⁴ The benefit of lenercept, a soluble p55 TNF α receptor fusion protein, on digital vasculitis in rheumatoid arthritis has also been reported.⁵

We report the compassionate treatment of six patients with refractory vasculitis using infliximab. Diagnoses were Wegener's granulomatosis in three and microscopic polyangiitis in three. Three patients were positive for proteinase-3 antineutrophil cytoplasmic antibodies (PR3-ANCA) and one for myeloperoxidase (MPO)-ANCA. Four were female, with a mean age of 58 years (range 23–77) and mean disease duration of 3.5 years. All had had at least three clinical relapses and had received prolonged treatment with corticosteroids and at least four immunosuppressive drugs. At the time of infliximab treatment the eyes were affected in four patients and the lung in three; in addition, five had profound constitutional symptoms. The mean prednisolone dose was 17 mg.

Three intravenous doses of infliximab 200 mg were given at monthly intervals for three months. One patient complained of fatigue, myalgia, and blurred vision 24 hours after the first infusion, which did not recur on rechallenge. Infliximab was otherwise well tolerated. Five patients had remission of their disease, four within two weeks of treatment. This allowed steroid withdrawal in three and reduction by more than 50% in two. Disease activity assessed by the Birmingham Vasculitis Activity Scores (BVAS) improved from a mean of 6.3 to 0.8 at three months (fig 1).⁶ One patient receiving continued infliximab for six months relapsed when the treatment interval was extended to two months. Mean falls in erythrocyte sedimentation rate and C reactive protein were 17 mm/1st h and 13 mg/l, respectively. The ANCA status was unchanged.

Anti-TNF α treatment heralds a new wave of specifically targeted biological interventions of potential value in the treatment of vasculitis. It offers the hope of improved therapeutic efficacy over current agents and the possibility of reducing exposure to steroids and immunosuppressive drugs. Further studies are warranted to confirm these observations and explore the role of infliximab as a component of initial protocols.

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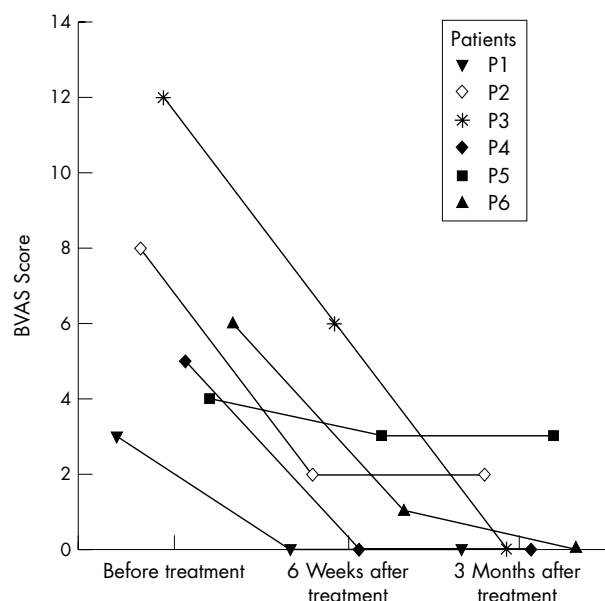


Figure 1 BVAS scores for the six patients treated with infliximab.

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Anti-tumour necrosis factor monoclonal antibody treatment for ocular Behçet's disease

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Ocular involvement is a common and serious component of Behçet's disease (BD). This manifestation worsens without treatment, and loss of vision occurs an average of 3.3 years after the onset of eye symptoms.¹ High levels of tumour necrosis factor (TNF) α have been found in the serum of patients with BD together with other proinflammatory cytokines.^{2,3} Many studies indicate a strong polarised Th1 immune response as in rheumatoid arthritis and Crohn's disease.⁴

High affinity monoclonal anti-TNF α antibody treatment has been recently introduced for patients with Crohn's disease or rheumatoid arthritis who were resistant to standard treatment. We describe the use of the anti-TNF α chimeric monoclonal antibody, infliximab (Remicade; Centocor Inc, Malvern, PA; Schering Plough SpA, Italy) in a patient with BD who exhibited a severe ocular involvement refractory to standard treatment.

CASE REPORT

An 18 year old man with BD was admitted in January 2001. He had been diagnosed with BD four years earlier in view of his presentation of recurrent oral and genital aphthous ulcers, polyarthritis, erythema nodosum, and superficial thrombophlebitis. The onset of the ocular disease was in 1999, when the patient was treated with steroids and cyclosporin for bilateral posterior uveitis. In the course of cyclosporin treatment he had several attacks of uveitis in both the eyes.

Cyclophosphamide was introduced without a satisfactory control of disease symptoms and of the ocular manifestations.

A new relapse of severe neuroretinitis occurred in October 2000. He was treated with intravenous methylprednisolone, followed by oral prednisone (50 mg/day), topical steroids, and mydriatic agents. Tapering of the prednisone dose resulted in November in a new acute attack of neuroretinitis in the left eye. Intravenous methylprednisolone was reintroduced, followed by 75 mg of oral prednisone and by local peribulbar injection of methylprednisolone every 15 days. Recovery was slow and less evident and, the visual acuity being 20/30, optic disc oedema and retinal vasculitis were still present. The patient received prednisone maintenance treatment (15 mg /day) for approximately four weeks before receiving an infliximab infusion.

At admission, fluorescein angiography (fig 1A) showed a hyperfluorescent optic disc in both eyes, and diffuse irregular mottled retinal hyperfluorescence and haemorrhagic hypofluorescence in the left eye. Oral and genital ulcerations were present together with erythema nodosum, thrombophlebitis, and arthritis. An infusion protocol was designed and approved by the Department of Internal Medicine Institutional Board and informed consent for treatment was obtained from the patient.

The patient was infused with infliximab, 5 mg/kg, by a two hour infusion, at weeks 0, 2, 4, and 8, and the patient observed for a further two hours without adverse effects. An improvement in symptoms was noticed within 24 hours after

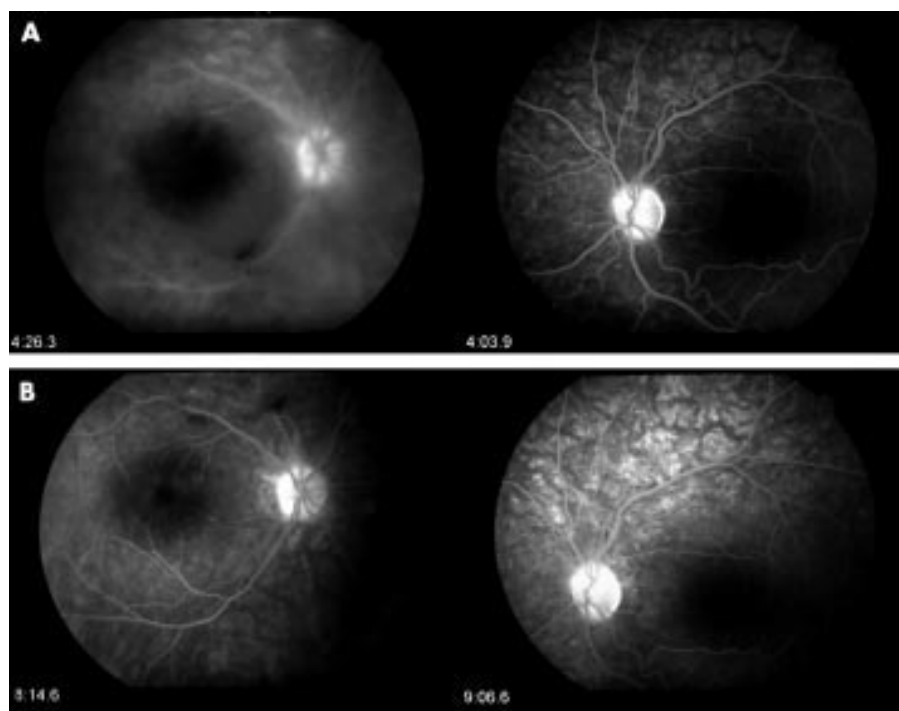


Figure 1 (A) Fluorescein angiography obtained at admission, showing a hyperfluorescent optic disc in both eyes, diffuse irregular mottled retinal hyperfluorescence, and haemorrhagic hypofluorescence in the left eye. (B) Fluorescein angiography obtained before the third infusion, showing a normal optic disc aspect, improvement of macular oedema in the right eye and still in the mottled aspect of retinal capillary filling.

receiving the first infusion. At the time of the second infusion he had a complete remission of all signs and symptoms. A new fluorescein angiography was performed just before the third infusion. At that time there was a normal optic disc aspect, improvement of macular oedema in the right eye and still in the mottled aspect of retinal capillary filling (fig 1B). Before the first infusion the erythrocyte sedimentation rate was 35 mm/1st h and the C reactive protein level was 34 mg/l. They decreased to 22 mm/1st h and 6 mg/l (normal <10 mg/l), respectively, by week 2 and remained within the normal range for the duration of the study.

DISCUSSION

This is the first report, to our knowledge, of the treatment of ocular BD with anticytokine specific treatment. Treatment with infliximab led, in our patient, to a complete remission of all disease manifestations and there was no recurrence after steroid tapering.

Three interesting points can be made. Firstly, the drug had a profound effect on ocular BD as well as on the other manifestations of disease. This effect on global diseases seems to be remarkable, as standard treatments had failed in our patient. Secondly, the onset of improvement was fast. Thirdly, when a loading dose regimen of four infusions (weeks 0, 2, 6, and 8) was used, remission continued for up to eight weeks. Further confirmation of the beneficial effects of TNF α blockade in randomised, controlled, double blind studies is necessary.

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Is hirudin a potential therapeutic agent for arthritis?

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A recent pilot study by Michalsen *et al* showed that a single brief treatment with medicinal leeches (*Hirudo medicinalis*) can give relatively long term relief from pain in osteoarthritic joints. A number of leech salivary components are known, which may contribute to this effect.¹ Although there was no evidence for any therapeutic outcomes, other than pain relief, the extended timescale suggests that one or more leech components may exert more than an anaesthetic or analgesic effect. Independent evidence indicates that the leech anticoagulant protein, hirudin, may make a significant contribution to this phenomenon.

A synovial stimulatory protein (SSP), acting as an autoantigen to which T lymphocytes from patients with rheumatoid arthritis respond, has been identified in synovial fluid.² A smaller protein, derived from human fibroblasts, and identifiable from its amino acid sequence as a fragment of the SSP, has been found to bind to a hirudin-agarose affinity chromatography matrix.³ More recently, we have shown that both the SSP and its smaller derivative, now known as the DING protein, are found in synovial fluid samples and synovial fibroblasts from normal subjects, and from patients with a range of arthritic conditions, including rheumatoid and osteoarthritis. The proteins act as autocrine growth stimulators for normal and arthritic synovial fibroblasts.⁴ The presence of hirudin can inhibit this stimulation.³ Given that hyperproliferation of synovial fibroblasts is believed to contribute to the formation of the destructive pannus that is characteristic of some arthritic joints,⁵ the SSP and DING protein may act to promote this process, and hirudin may have the potential to retard it. Hirudin might thus have value in treating arthritis. Recombinant hirudin has already been used in a range of therapeutic anticoagulant applications,⁶⁻⁸ so patient safety and other clinical data have been collected and evaluated. A trial of hirudin in an antiarthritis role may now be appropriate.

The first DING protein isolates displayed proteolytic activity, and its inhibition was believed to be the basis of the action of hirudin, but subsequent DING preparations have had little or no proteolytic activity.^{3, 4} The basis of the inhibitory action of hirudin is thus not known. Peptides derived from hirudin such as hirulog (bivalirudin), which are effective anticoagulants by virtue of thrombin inhibition,^{9, 10} may not possess the ability to bind and inhibit the SSP or DING proteins.

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Steroid induced psychosis in systemic lupus erythematosus: a possible role of serum albumin level

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Steroids may have diverse and sometimes severe adverse effects in the short and long term.¹ We present three patients with systemic lupus erythematosus (SLE)² and steroid induced psychosis (table 1), emphasising the importance that serum albumin levels may have on the development of this complication.

CASE REPORTS

Case 1

Patient No 1 is a 20 year old woman with SLE diagnosed five years ago, in whom a serum albumin level of 24 g/l and proteinuria of 3.2 g/l were detected in routine tests. Diffuse proliferative lupus nephritis was diagnosed by renal biopsy and she was treated with one pulse of cyclophosphamide (500 mg) and oral prednisone (60 mg/day). Three days later she developed anxiety, insomnia, euphoria, verbosity, grandiosity, and megalomaniac ideas. She was treated with oral risperidone (2 mg/12 h), oral clonazepam (0.5 mg/12 h), and the prednisone dosage was progressively tapered. Over the next 15 days she experienced a fluctuating but progressive improvement until she became psychiatrically asymptomatic. Five years previously, when she was first diagnosed as having SLE, she had been treated with oral prednisone (60 mg/day) but had not had any psychiatric symptoms. At that time, however, she had serum albumin levels of 33 g/l without proteinuria.

Case 2

Patient No 2, a 21 year old woman who was diagnosed as having SLE, with cutaneous, articular and renal involvement, started treatment with oral prednisone (30 mg/day). At that time she had a serum albumin level of 30.2 g/l and proteinuria of 2.37 g/day. Renal biopsy was refused by the patient.

Over the following days and in a progressive manner, she developed mania, with euphoria, disinhibition as well as ideas of grandiosity. All these manifestations disappeared under psychiatric supervision and when steroids were discontinued.

Case 3

Patient No 3 is a 36 year old woman who had been diagnosed as having SLE with diffuse proliferative lupus nephritis seven years before. She had started oral prednisone (60 mg/day), without adverse psychiatric effects. At that time, she had serum total protein level of 66 g/l and a serum albumin level of 43 g/l. She currently presented with an articular "flare" of her lupus, and started treatment with oral prednisone (30 mg/day). Her total protein level was 59 g/l, the serum albumin level fell to 29 g/l with proteinuria of 1.2 g/l. Seven days later, she developed anxiety, insomnia, and hyperactivity that disappeared over the following few days after reduction of the dose of prednisone to 2.5 mg/day.

DISCUSSION

Steroid induced psychiatric disturbances appear in 3-6% of the patients who are treated with these drugs.³⁻⁶ The differential diagnosis with lupus psychosis⁷ is difficult. In case of doubt, some authors advocate increasing the dose of steroids and awaiting a clinical response over the next days. Others advocate rapid tapering and stopping steroids in order to eliminate a drug induced adverse event.

Our three patients developed psychiatric symptoms while receiving steroids for lupus nephritis with hypoalbuminaemia and significant proteinuria. Moreover, it seems relevant that

Table 1 Main clinical features of three patients with SLE and steroid induced psychosis

	Patient 1	Patient 2	Patient 3
Sex	Female	Female	Female
Age	20	21	36
Years after SLE diagnosis	5	Present diagnosis	7
Treatment at SLE diagnosis	Prednisone 60 mg/day	See present diagnosis	Prednisone 60 mg/day
Serum albumin at SLE diagnosis (g/l)	33	See present diagnosis	43
Psychiatric manifestations at SLE diagnosis	No	See present diagnosis	No
Present diagnosis	Lupus nephritis	Lupus nephritis	Articular and cutaneous flare
Serum albumin at present diagnosis (g/l)	24	30	29
Proteinuria at present diagnosis (g/day)	3.2	2.37	1.2
Treatment of present diagnosis	Prednisone 60 mg/day	Prednisone 30 mg/day	Prednisone 30 mg/day
Psychiatric manifestations at present diagnosis	Yes	Yes	Yes

two of them (patients 1 and 3) had not developed psychiatric manifestations when they had previously been receiving similar doses of steroids, but had higher serum albumin levels at that time. Lewis *et al* found a 37% incidence of adverse effects of steroids in those patients with serum albumin <25 g/l but of only 15% in those with higher serum albumin.⁸ The explanation for these findings may be that corticosteroid binding globulin does not bind to synthetic steroids, whose transport depends on serum albumin which, by contrast, presents low affinity but a great capacity to transport the steroids because of its high plasma concentration. Steroids are biologically inactive when bound to albumin. Therefore, the free (and active) fraction of steroids is higher in patients with low plasma albumin levels, and this will expose the patient to more adverse effects.

Interestingly, there is a lower incidence of psychosis in other groups of patients treated with steroids (for example, those with chronic obstructive pulmonary disease).⁹ Therefore, those patients whose disease causes low levels of serum proteins (as in those with SLE) will be more predisposed to have adverse effects of steroids.

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Autoantibodies against C1q: view on association between systemic lupus erythematosus disease manifestation and C1q autoantibodies

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Activation of the complement system is the first step in the prevention of damage by immune complexes. Systemic lupus erythematosus (SLE) is the prototype of immune complex diseases. The classical pathway of the complement system is considered to be the most important pathway in immune complex clearance. This pathway may be activated by IgM- and IgG-containing immune complexes after binding to C1q.¹

In 1984 autoantibodies to C1q (C1qAb) were reported to be present in serum of patients with SLE.² The recognition that C1q may serve as a non-organ-specific autoantigen has attracted a growing number of investigators.³

We studied 42 patients (38 female, four male, aged 19-64) with SLE. Twenty eight (67%) had proven renal biopsy lupus nephritis (two patients had WHO class II lesions, four had WHO class III, 18 had WHO class IV, four had WHO class V), 14 (33%) patients had evidence of lupus pneumonitis, and 11 (26%) central nervous system disease (table 1).

All patients were tested by both basic and subclass enzyme linked immunosorbent assays (ELISAs) for C1qAb using a modification of the method of Wisniewski and Jones.⁴ Whole C1q was purified from human plasma by the method of Tenner *et al*.⁵ Raised C1qAb titres were found in 18 (43%) patients. Of the patients with C1qAb, 12 had renal manifestations of SLE (10 (83%) of them had focal or diffuse proliferative

glomerulonephritis), six central nervous system disease, and five lupus pneumonitis. Patients with raised C1qAb titres were younger, seven of them were positive for antibodies to dsDNA. The magnitude of proteinuria was positively associated with the presence of C1qAb.

Selective complete C1q deficiency was established in seven of our patients (Nos 6, 11, 16, 18, 28, 32, 33); in two of them (Nos 18, 28), clinical data showed the presence of SLE in the family.

Available serum samples testing positive for IgG C1qAb were analysed for C1qAb IgG subclass distribution. Six (33%) of the 18 patients had IgG2 C1qAb only, 3/18 (17%) patients had IgG1 C1qAb only, and 9/18 (50%) had both IgG1 and IgG2 C1qAb. Therefore, IgG2 C1qAb was present in 15/18 (83%) patients. The subset of sera from patients with IgG1 or IgG2 C1qAb was assayed for total serum IgG1 and IgG2 levels by radial immunodiffusion. The mean total serum IgG1 was 7.9 (4.5) mg/ml, the mean total serum IgG2 was 2.6 (1.4) mg/ml. The mean ratio of IgG1/IgG2 (3.4 (2.1)) was similar to that reported in the literature for disease free subjects.⁶ The percentage of IgG2 C1qAb relative to total IgG2 was significantly greater than the percentage of IgG1 C1qAb relative to total IgG1 (0.03 (0.06)% *v* 0.01 (0.02)% respectively, *p*<0.005, *t* test). Thus in our patient group the IgG2 component of the autoantibody response to C1q was disproportionately enriched relative to the overall IgG

Table 1 Basic clinicolaboratory parameters in study patients

No/sex/age (years)	C1qAb	Anti-dsDNA	ANA	Lupus nephritis/WHO class/proteinuria (g/24 h (SD))	Pneumonitis	Central nervous system involvement
1/F/28	+			+ WHO class IV (6.8 (2.4))	+	
2/F/19	+	+	+	+ WHO class IV (8.7 (3.1))		+
3/F/36					+	
4/F/25	+		+	+ WHO class V (5.4 (0.5))		+
5/F/34						
6/M/33				+ WHO class II (2.1 (0.9))	+	+
7/F/41						
8/F/27	+	+	+	+ WHO class IV (7.2 (3.4))		
9/F/34	+					+
10/F/50				+ WHO class IV (3.5 (1.4))		
11/F/44			+	+ WHO class IV (4.1 (1.5))		+
12/F/26	+	+		+ WHO class IV (4.4 (2.3))		
13/F/30	+			+ WHO class V (7.1 (1.2))	+	+
14/F/64			+	+ WHO class IV (2.5 (0.9))	+	
15/F/24	+	+	+	+ WHO class IV (3.4 (1.7))		
16/F/38					+	+
17/F/40				+ WHO class IV (1.2 (0.7))		
18/F/47		+	+	+ WHO class IV (2.4 (0.8))	+	+
19/F/29	+			+ WHO class IV (4.2 (1.3))	+	
20/F/22	+	+	+			
21/F/34	+			+ WHO class IIIB (3.8 (1.7))		
22/F/31	+					
23/F/28	+	+		+ WHO class IV (5.3 (2.0))	+	
24/F/42						
25/M/36	+	+	+	+ WHO class IIIB (4.8 (1.4))		
26/F/32	+					+
27/F/25	+					
28/F/31		+	+	+ WHO class IV (3.1 (1.7))	+	
29/F/36					+	+
30/F/27			+			
31/F/23	+					
32/M/24		+	+	+ WHO class V (4.0 (1.1))	+	
33/F/34				+ WHO class IIIA (2.3 (0.8))	+	
34/F/41	+			+ WHO class IV (4.2 (2.3))		+
35/F/28		+	+	+ WHO class IV (3.0 (0.6))		
36/F/23						
37/M/31		+	+	+ WHO class IV (2.4 (0.3))		
38/F/36				+ WHO class V (1.7 (0.3))		
39/F/25				+ WHO class IV (1.7 (0.5))		
40/F/34				+ WHO class IIIB (2.1 (0.4))		
41/F/27		+	+	+ WHO class IV (5.2 (2.6))		
42/F/20				+ WHO class II (0.9 (0.3))		

ANA, antinuclear antibodies; C1qAb, autoantibodies to C1q; Anti-dsDNA, anti-double stranded DNA antibodies; F, female; M, male.

subclasses distribution, as no alteration in IgG subclass distribution was noted. The C1qAb in our group were predominantly of IgG2 and IgG1 subclasses. This distribution is consistent with that found by Wisniewski and Jones in a study characterising C1qAb in patients with SLE and hypocomplementaemic urticarial vasculitis,³ but contrasts with the IgG3 and IgG2 predominance reported by Coremans *et al* in patients with SLE.⁷

The mechanisms mediating autoantibody pathogenicity remain unclear. It has been proposed that C1qAb may act systemically by up regulating activation of classical complement pathway.⁸ Alternatively, C1qAb may act locally within the renal glomerulus to enhance tissue injury initiated by immune complex deposition. The association of C1qAb with proliferative lupus nephritis is now well established,² but the significance of C1qAb for lupus pneumonitis and cerebrovasculitis should be a target for future investigations.

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Silent thyroiditis associated with etanercept in rheumatoid arthritis

E Andrès, F-X Limbach, B Goichot, J Sibilia

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In recent years, monoclonal antibodies (infliximab) and a recombinant human tumour necrosis factor receptor (p75)-Fc fusion protein (TNFR:Fc) (etanercept) have been successfully used to treat rheumatoid arthritis (RA).¹ These TNF blocking agents are now widely employed in patients with treatment resistant RA. TNF inhibitors are generally well tolerated with <0.5% of patients developing a drug induced lupus syndrome, although 4–16% may develop antibodies to double stranded DNA (dsDNA). Apart from two patients presenting autoimmune skin diseases associated with etanercept (discoid lupus and necrotising vasculitis),² there are no other reports of well documented autoimmune disease. In this paper we describe the first case of silent autoimmune thyroiditis during TNFR:Fc treatment for severe RA.

CASE REPORT

A 43 year old woman followed up since 1991 for erosive RA had been successively treated with various disease modifying antirheumatic drugs (Allochrysin, D-penicillamine, and methotrexate) combined with low dose corticosteroids. In March 1998 she reported an important flare up despite corticosteroids (10 mg/day) and methotrexate (15 mg/week). Methotrexate was replaced by etanercept (25 mg twice a week), which led to a dramatic improvement after one month of treatment. The evaluation before TNFR:Fc treatment disclosed no evidence of thyroid disorders: the patient had no clinical features, serum thyroid stimulating hormone (TSH) and free thyroid hormones were normal, and thyroid antibodies were negative. No other autoantibody (anti-dsDNA, anticardiolipin, anti-extractable nuclear antigen (ENA)) was present except a high titre of IgM rheumatoid factor. In January 2000 the patient developed a non-tender moderate goitre. Thyroid evaluation disclosed modest hypothyroidism: serum TSH 6.3 mU/ml (normal <4.5) and serum free thyroxine (T4) 11 pmol/l (normal 11–23) (Elecsys assay). Titres of native antimicrosomal and antithyroglobulin antibodies were raised at 820 IU/ml (normal <60) and 230 IU/ml (normal <60), respectively (radioimmunoassay, Brahms). Anti-TSH receptor antibodies were negative (<5 IU/l, normal <11) (Radio Receptor Assay, Brahms) and no other autoantibodies (anti-dsDNA, anticardiolipin, anti-ENA) were found except an IgM rheumatoid factor. A technetium-99m pertechnetate thyroid scintigraphic scan showed reduced uptake.

In the absence of other known cause, the diagnosis was silent thyroiditis induced by TNFR:Fc. Etanercept treatment was completed four months after the onset of hypothyroidism, and there was no aggravation of the thyroid disorder without hormonal substitution after a year and a half of follow up.

DISCUSSION

This report describes a case of silent autoimmune thyroiditis which developed during TNFR:Fc treatment in a patient with RA without evidence of previous thyroid disorders. Thyroiditis has not to our knowledge been described as a side effect of TNFR:Fc treatment and a causal relationship cannot formally be established in our case report. However, cytokines like interferon γ or interleukin 2 often induce thyroiditis in patients with pre-existing autoimmune thyroid disease. T cell (Th1) depletion with monoclonal antibodies (Campath-1) can also lead to the development of antibody mediated thyroid autoimmunity.³ The mechanism of this effect of TNF blocking agents is not well understood, but modulation of the homing of Th1 and Th2 cells may explain the induction of autoimmune thyroiditis.^{4,5} In our opinion, TNFR:Fc treatment should be considered as a potential cause of drug induced autoimmune thyroiditis. Nevertheless, further studies are needed to estimate the incidence and the mechanism of this side effect.

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Synovial T cell proliferation to the *Yersinia enterocolitica* 19 kDa antigen differentiates yersinia triggered reactive arthritis (ReA) from ReA triggered by other enterobacteria

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Reactive arthritis (ReA) mostly presents as an asymmetrical oligoarthritis, usually affecting the leg joints.¹ It is a T cell dependent inflammatory disease following infections with various enteropathic bacteria—for example, *Yersinia enterocolitica* 0:3, *Salmonella enteritidis*, *Shigella flexneri*, or microbes pathogenic for the urogenital tract such as *Chlamydia trachomatis*.² Identification of the structure of antigens of triggering microbes which drive immune responses in the synovial fluid would be of great interest.

We recently described two major antigens, the Ye 19 kDa and the Ye HSP60 inducing synovial T cell proliferation in patients with Ye triggered ReA.^{3–7} They seemed to overcome the specificity problem of proliferation assays with T cells cultured from the site of inflammation to ReA triggering bacteria, because the local immune response to whole bacteria is accompanied by a restricted specificity probably due to cross reactivity with common epitopes.⁸ Since Ye is the only known ReA triggering bacteria expressing the Ye 19 kDa protein from the β subunit of urease,⁶ we investigated the possibility that synovial T cell proliferation to this protein might help to differentiate Ye triggered arthritis from arthritides caused by other bacteria.

In view of this specificity problem it was not unexpected to find a large number of patients in our clinic who showed clinical features of ReA and had synovial T cell proliferation to two or more enteropathic bacteria.

METHODS

We tested the synovial T cells of 66 patients with arthritis of one or more joints. Ye triggered ReA was diagnosed based on a typical history of previous symptomatic gastrointestinal infection or significant agglutinin titre. *Chlamydia trachomatis* triggered ReA was diagnosed in patients with arthritis and positive urogenital swabs or chlamydia-specific antibodies and a recent history of symptomatic urethritis or cervicitis. Synovial fluid mononuclear cells were cultured in the presence of heat inactivated bacterial antigens such as *Yersinia enterocolitica*, *Salmonella enteritidis*, *Shigella flexneri*, *Campylobacter jejuni*, and *Chlamydia trachomatis*. For stimulation with Ye 19 kDa we used 1 μ g/ml recombinant protein, which was expressed as described previously.⁴ Stimulation indices were calculated in comparison with background activity by T cell medium. A stimulation index (SI) of >5 was classified as positive.

RESULTS

We identified 11 (28%) subjects among the 40 patients with T cell proliferation to Ye (mean (SD) SI 39.88 (30.22)) and at least to one more enterobacterium (SI 36.87 (34.62)), who responded also to Ye 19 kDa (SI 38.34 (32.97)) (group 1a), whereas 29 patients (Ye: SI 21.06 (16.71), other enterobacteria: SI 21.81 (20.23)) had no cellular immune response to Ye 19 kDa (SI 1.77 (1.27)) (group 1b, fig 1). We performed the same

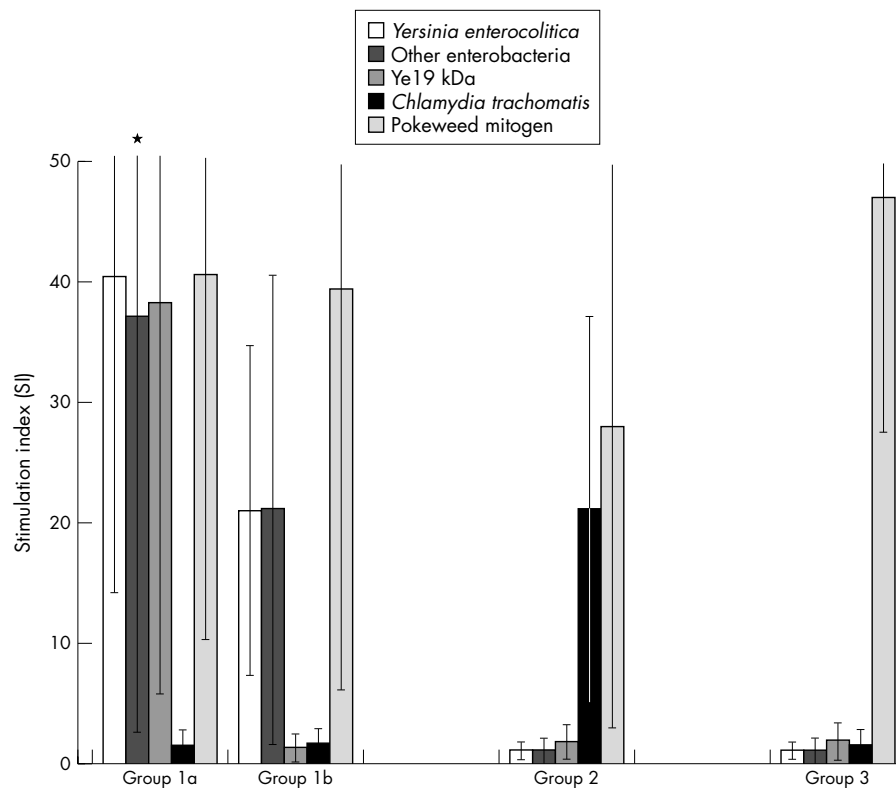


Figure 1 Synovial T cell response to whole *Yersinia enterocolitica* (Ye) and recombinant Ye 19 kDa helps to differentiate yersinia triggered reactive arthritis (ReA) from ReA triggered by other bacteria. The synovial T cell proliferation to Ye 19 kDa protein was analysed in 66 patients with ReA. *Highest value for any enterobacterium other than yersinia.

experiment with synovial T cells from 11 patients with chlamydia triggered ReA (SI 20.8 (15.51)) (group 2). In this case none of the patients had a T cell proliferation to Ye 19 kDa (SI 1.72 (1.5)) (fig 1). In 15 patients with the clinical diagnosis of ReA or undifferentiated oligoarthritis synovial T cells proliferated to mitogen, but not to any of the ReA triggering bacteria or Ye 19 kDa (SI 1.78 (1.25)) (group 3, fig 1).

Because the Ye 19 kDa as the β subunit of urease⁶ is a yersinia antigen not shared by other ReA triggering enterobacteria we believe that we have identified the cause of disease of a substantial number of patients with ReA in clinical practice which would not have been known by other means. We assume that Ye 19 kDa used in synovial T cell proliferation assays is a useful antigen to specify Ye as the disease triggering bacteria and might be of diagnostic value in ReA.

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Leflunomide and hypertension

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Leflunomide is a new isoxazole drug with disease modifying properties for the treatment of rheumatoid arthritis (RA). Hypertension has been mentioned as a common side effect of the treatment. It was found in up to 10.6% of patients receiving 25 mg leflunomide in a phase II study.¹ New onset hypertension occurred in 3.7% of patients in a phase III European study,² and in 2.1% of patients, with a mean increase in systolic and diastolic blood pressure of 2.2 and 1.9 mm Hg, respectively, in an American phase III study.³ There was no evidence that hypertension was related to an impairment of renal function or proteinuria. The changes in blood pressure during leflunomide treatment have not been studied in detail.

PATIENTS AND METHODS

Thirty consecutive patients fulfilling the American Rheumatism Association criteria for RA were recruited into a prospective study and treated with standard doses of leflunomide. Other enrolment criteria included stable treatment with non-steroidal anti-inflammatory drugs up to the maximum recommended dose and/or corticosteroid treatment up to 10 mg/day for at least three months before starting treatment with leflunomide. The patients were followed up at two week intervals. A trained nurse according to the Slovenian and WHO/ISH hypertension guidelines measured blood pressure.⁴ Automatic oscillometric monitors (Spacelabs 90209) were used for ambulatory blood pressure monitoring (ABPM).⁵ Seventeen patients finished the study according to the protocol with 6.5 (1) months between the two ABPM procedures.

RESULTS

A statistically significant increase in conventional blood pressure measurements of both systolic and diastolic blood pressure was seen (table 1). The rise in systolic blood pressure was seen relatively early—in 2-4 weeks (from 127.03 (20.2) mm Hg to 134.1 (24.3) mm Hg, $p=0.034$). On the contrary, the rise in diastolic blood pressure was not significant after 2-4 and 6-8 weeks, respectively. In 7/17 patients, the initially normal blood pressure values exceeded the systolic and/or diastolic blood pressure values of 140/90 mm Hg in the follow up measurements. Moreover, in four patients the systolic blood pressure was, at least once in the follow up period, more than 40 mm Hg and diastolic blood pressure more than 20 mm Hg above the initial values. According to the ambulatory blood pressure monitoring (ABPM) measurements the overall trend after the start of leflunomide treatment was an increase in both systolic and diastolic blood pressure and heart rate, which was highly statistically significant (table 1). Figure 1 shows individual changes in blood pressure and heart frequency.

DISCUSSION

Using standardised conditions of blood pressure measuring (not the case in phase II and phase III clinical trials) and ABPM, we confirmed the blood pressure rises during treatment with leflunomide. Adding to the knowledge from previous studies, we showed that a statistically significant rise in systolic blood pressure was apparent already after

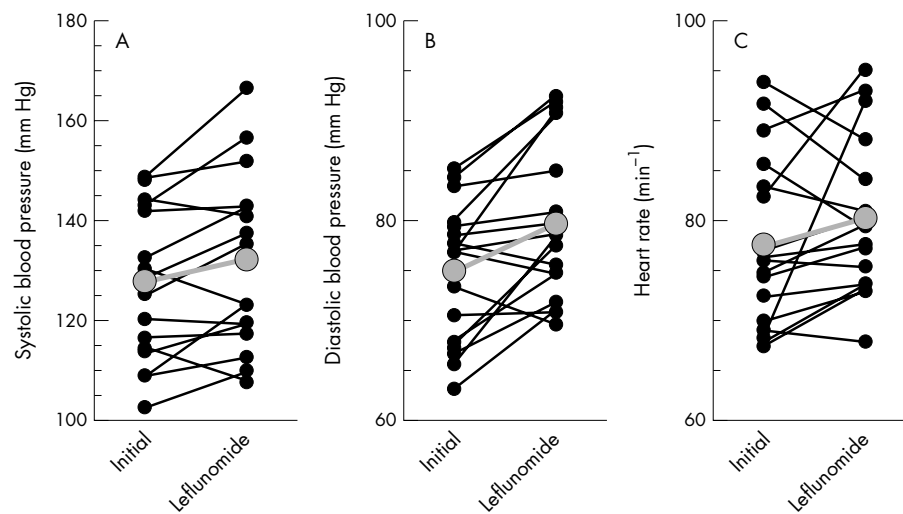


Figure 1 Changes in (A) systolic blood pressure, (B) diastolic blood pressure, and (C) heart rate in 17 patients with RA treated with leflunomide. Twenty four hour averages of individual patients during ABPM performed during and after 6.5 (1) months of treatment with leflunomide are shown. The overall trends in individual variables are shown by the grey line.

2–4 weeks of the treatment, thus pointing to the need for early blood pressure monitoring. By contrast, the rise in diastolic blood pressure appeared later. Hypertensive values in individual patients suggest that regular measuring of blood pressure is required during treatment with leflunomide.

Employing ABPM, we confirmed the significant rise in blood pressure during the leflunomide treatment, thus making the role of the “white coat” phenomenon unlikely. It should be mentioned that it has been confirmed that non-invasive ABPM has no effect on blood pressure because of discomfort during cuff inflation. We are also not aware of any

special device developed to measure blood pressure in patients with painful limbs. However, as a clinically relevant (>5 joints) improvement in tender and swollen joint count was seen in 14 (83%) of the 17 patients analysed, the degree of pain imposed by blood pressure measurements and its effect on blood pressure were expected to decrease rather than rise during the study.

The results do not allow us to speculate on the mechanism of the blood pressure increase associated with the leflunomide treatment. As the heart rate also rises during leflunomide treatment, it has been assumed that hypertension may be caused by an increased sympathetic drive.

Table 1 Conventional systolic and diastolic blood pressure measurements, 24 hour averages of blood pressure, and heart frequency before (initial ABPM) and after treatment with leflunomide (final ABPM) in 17 patients with rheumatoid arthritis. Twenty four hour, day time (6 00 am to 10 00 pm), and night time (10 00 pm to 6 00 am) mean values and standard deviations are shown. Statistical significance of differences was tested with Student’s *t* test. *p* Values of ≤ 0.05 were considered significant

	Initial measurement	Final measurement	<i>t</i> Test	Significance (<i>p</i>)
Conventional measurements (mean)				
Systolic blood pressure (mm Hg)	127.3 (20.2)	140.7 (20.1)	3.55	0.003
Diastolic blood pressure (mm Hg)	76.7 (9.3)	84.0 (8.6)	3.08	0.007
ABPM (mean)				
Systolic blood pressure (mm Hg)	127.8 (19.7)	132.1 (21.4)	3.01	0.003
Diastolic blood pressure (mm Hg)	74.9 (12.4)	79.7 (13.0)	5.43	0.000
Mean arterial pressure (mm Hg)	93.6 (14.8)	98.7 (15.8)	4.76	0.000
Pulse pressure (mm Hg)	52.9 (14.0)	52.4 (15.5)	0.46	NS
Heart frequency (min ⁻¹)	77.6 (13.7)	80.2 (13.5)	2.71	0.007
Day time (6 00 am to 10 00 pm)				
Systolic blood pressure (mm Hg)	130.2 (18.2)	135.2 (19.6)	5.18	0.000
Diastolic blood pressure (mm Hg)	77.8 (11.4)	83.1 (11.7)	9.04	0.000
Mean arterial pressure (mm Hg)	96.1 (13.4)	83.1 (11.7)	7.86	0.000
Pulse pressure (mm Hg)	52.5 (14.2)	52.1 (15.4)	0.44	NS
Heart frequency (min ⁻¹)	81.8 (13.7)	83.7 (13.3)	2.83	0.005
Night time (10 00 pm to 6 00 am)				
Systolic blood pressure (mm Hg)	121.9 (20.6)	124.1 (20.6)	1.20	NS
Diastolic blood pressure (mm Hg)	69.1 (12.2)	72.3 (11.8)	3.07	0.002
Mean arterial pressure (mm Hg)	87.8 (15.5)	91.5 (14.6)	2.77	0.006
Pulse pressure (mm Hg)	52.8 (13.3)	51.7 (15.0)	0.86	NS
Heart frequency (min ⁻¹)	68.7 (9.2)	72.9 (10.9)	4.78	0.000

This hypothesis remains to be tested. The changes in the raised blood pressure after six months of leflunomide treatment will be clarified after the final report of all extended studies.

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Adhesion molecule expression in the synovial membrane of psoriatic arthritis

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Endothelium may play a part in the pathogenesis of long-standing psoriatic arthritis (PsA),¹ whereas a higher vascularisation and a less intense adhesion molecule expression have been found in PsA synovial membrane compared with rheumatoid arthritis.² Some proinflammatory molecules, such as tumour necrosis factors (TNFs), can induce synovial endothelial cells and fibroblast-like synoviocytes to express adhesion molecules.^{3,4}

PATIENTS AND METHODS

In two groups of patients with PsA—eight patients with synovitis of <1 year and six patients with synovitis >1 year—we studied the expression and pattern of the synovial distribution of endothelial leucocyte adhesion molecule-1 (ELAM-1 or E-selectin) (CD62E), intercellular adhesion molecule-1 (ICAM-1) (CD54), vascular cell adhesion molecule-1

(VCAM-1) (CD106) (Immunotech, Marseille, France), and of TNF α and TNF β cytokines (Chemicon International, Temecula, CA, USA) using a standard three stage immunoperoxidase labelling technique (LAB VISION, Fremont, CA, USA).⁵ The lining layer, the infiltrating elements, and the endothelial cells were evaluated for the number of positive cells per high power field ($\times 40$).⁶

RESULTS

Table 1 summarises the main clinical and laboratory data of the two groups; no significant clinical or laboratory differences were seen.

E-selectin was present more often at endothelial, cellular infiltrate, and lining layer levels in 7/8 (88%) patients with a disease duration <1 year, where only 3/6 patients (50%) with disease duration >1 year were positive. ICAM-1 was

Table 1 Main clinical and demographic features of 14 patients with PsA with a disease duration of less (group 1) or more (group 2) than one year

Patient number	Sex	Age (years)	Duration of arthritis (years)	Duration of psoriasis (years)	PASI	Ritchie index	Subgroup	CRP (mg/l)	ESR (mm/1st h)	Treatment
Group 1										
1	F	60	<1	1	3.2	17	Polyarthritis	5	14	NSAIDs
2	F	28	<1	1	4.5	11	Polyarthritis	4	28	NSAIDs
3	F	48	<1	<1	0.3	3	Oligoarthritis	35	52	Steroids
4	M	37	<1	4	0.9	18	Polyarthritis	6	8	NSAIDs
5	M	31	<1	2	0.3	9	Polyarthritis	12	24	None
6	F	35	<1	1	9.0	20	Polyarthritis	24	66	NSAIDs
7	F	25	<1	19	2.1	5	Oligoarthritis	6	16	HCG/NSAIDs
8	F	35	<1	18	0.9	15	Polyarthritis	6	23	HCG/NSAIDs
Group 2										
1	M	35	2	10	3.1	9	Polyarthritis	21	38	NSAIDs
2	M	36	5	13	6.6	10	Polyarthritis	80	86	MTX/steroids
3	M	53	3	37	8.9	21	Polyarthritis	6	3	NSAIDs
4	M	39	3	2	1.2	9	Polyarthritis	25	11	SSZ
5	M	43	5	30	4.2	6	Oligoarthritis	6	8	NSAIDs
6	M	50	10	25	9.0	15	Polyarthritis	6	10	NSAIDs

PASI, Psoriasis Areas Severity Index; CRP, C reactive protein; ESR, erythrocyte sedimentation rate (Westergren); NSAIDs, non-steroidal anti-inflammatory drugs; HCG, hydroxychloroquine; MTX, methotrexate; SSZ, sulfasalazine.

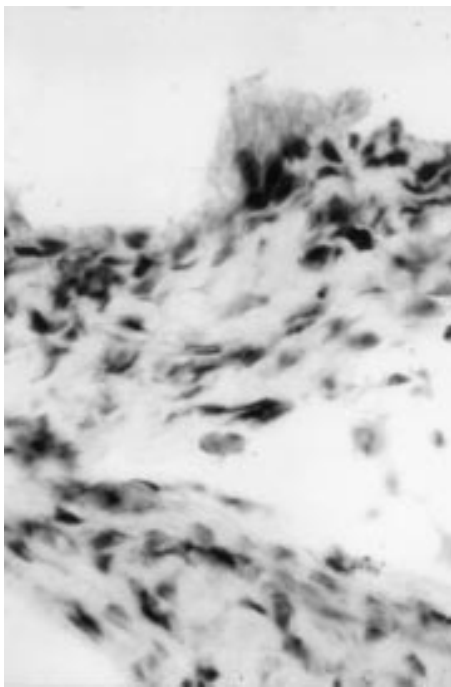


Figure 1 Representative specimen from the synovial membrane of a patient with psoriatic arthritis of <1 year; staining with ICAM-1 using monoclonal antibody CD54. Antigen positive cells are present throughout the entire specimen (original magnification $\times 250$).

overexpressed in the lining layer of the early synovitic specimens compared with the longstanding samples (100% v 33%; $p < 0.001$) (fig 1). On the contrary, VCAM-1 positivity was more commonly found in patients with longstanding PsA (5/5 (100%) v 4/7 (57%)). Cells containing TNF α and TNF β were consistently found in the synovial lining layer, in the infiltrates, and in the blood vessels, with no appreciable difference between the two groups.

DISCUSSION

Our results show that longstanding psoriatic synovitis may reduce the E-selectin expression, as already found in different forms of synovitis,⁷ and confirms the presence of ICAM-1 and VCAM-1 positivity in PsA, as already described.² As ICAM-1 was present in vessel walls in all tissue samples, this supports the view that this adhesion molecule is not only constitutively expressed on endothelial cells but is also increased during activation and is the most important adhesion molecule for cell binding to endothelium in inflamed tissue.⁷ VCAM-1 expression, generally absent on normal synovium, is found on activated endothelium and its up regulation has been recently implicated in various pathological conditions.⁸

The different expression of these adhesion molecules seems to be connected to the disease duration. A more frequent positivity for E-selectin, and partly for ICAM-1, in earlier synovitis compared with longstanding disease, where VCAM-1 expression was constantly found, shows for the first time how these molecules may separately participate in the synovitic process in the different phases of PsA, with a changing involvement as the disease evolves.

The presence of TNF α and TNF β , together with E-selectin, ICAM-1, and VCAM-1 positivity in the same samples, confirms the ability of TNFs to induce the expression of such adhesion molecules.³ Their localisation on the endothelial cells also suggests that these cells can produce TNFs, indicating the involvement of TNFs in the regulation of cell adhesion before migration into diseased joints. Our findings gain more importance in view of a recent immunohistochemical study, which showed a convincing effect of anti-TNF treatment on synovium in spondyloarthritis, suggesting immunomodulatory mechanisms involving adhesion molecule expression.⁹

In conclusion, the variations in the presence of some adhesion molecules and TNFs shown in our study, partly related to disease duration, indicate their relative importance in mediating the succeeding mechanisms of psoriatic synovitis. This should be taken into account in the assessment of disease progression and in developing possible new therapeutic approaches.

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Headache as the initial presentation of Wegener's granulomatosis

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In Wegener's granulomatosis (WG), neurological involvement is rare at onset. We present an unusual case where headache was the initial, dominant presentation of WG.

CASE REPORT

A 34 year old white man presented with a three month history of headache. The headaches were migratory, throbbing, and were accentuated with head movement. Physical examination was normal. Computed tomography (CT) of the sinuses was normal. The patient was diagnosed with non-specific vascular headaches, and was prescribed pizotifen, which alleviated his headaches.

One month later, the patient developed a red right eye. Bilateral papilloedema was noted. He was now unable to work because of the headache. Magnetic resonance imaging (MRI) of the brain disclosed a normal ventricular system, but pronounced gadolinium enhancement of the meninges around the entire left hemisphere, most of the parieto-occipital region on the right, as well as the tentorium bilaterally (fig 1). Lumbar puncture disclosed a high cerebrospinal fluid (CSF) opening pressure of 27 cm (13–18 cm). A CSF examination was entirely normal and cultures were negative. The headache was partially relieved by CSF drainage, and acetazolamide was started.

One week later, the patient developed a red left eye and left knee arthritis. Over the course of the next week, his condition progressed rapidly with purpuric lesions appearing on his hands and feet, followed by pericarditis and pulmonary haemorrhage. Biopsy of the purpura disclosed leucocytoclastic vasculitis. Antineutrophil cytoplasmic antibody (cANCA) taken at the time that he complained of the red left eye was positive at a titre of 1/80, with specificity for proteinase-3. A week later, repeat testing showed that cANCA had risen to

1/320. There was also a mild normochromic, normocytic anaemia, and raised inflammatory markers. Urine analysis disclosed microscopic haematuria and mild proteinuria. No casts were identified. A CSF examination was again normal, but the opening pressure had risen to 36 cm. WG was diagnosed.

Treatment was started with a 1 g pulse of intravenous methylprednisone, followed by oral daily doses of 1 mg/kg prednisone and 2 mg/kg cyclophosphamide. A few days after the start of treatment, the headaches had resolved and the CSF opening pressure was normal. Six months later, the patient is symptom-free, the papilloedema has resolved, MRI is normal, and the patient has returned to full-time work.

DISCUSSION

It is rare for WG to present with neurological symptoms. Neurological presentations described include ataxia, ocular nerve palsies, seizures, and deteriorating mental status.^{1–4} Shiotani *et al* described a 37 year old man with chronic sinusitis, who presented with fever and headache for 10 days before CT disclosed subdural and paranasal masses with marked thickening of the nasal mucosa.⁵ Our patient presented far more insidiously, with significant headache that persisted and worsened with time. The headache had clear vascular features but, beyond this, was non-specific. It was only four months later that musculoskeletal, cutaneous, ophthalmic, and cardio-respiratory features developed. Although neurological involvement may eventually develop in 33.6% of patients with WG,⁶ meningeal involvement, as gauged by meningeal enhancement on MRI or by biopsy is particularly uncommon, being recorded in only a handful of case reports.^{2–5 7–10} There also seems to be no relation between CSF abnormalities, clinical symptoms, or extent of meningeal involvement on MRI.⁷ A CSF examination may show no abnormality^{3 4 7} or a pleocytosis.^{3 5 8 9} High opening pressures are unusual but have been described.^{9 10}

In conclusion, we have presented a case of WG with extensive meningeal involvement. The exceptional feature in this case is the fact that headache was the sole symptom of the disease over several months, before a dramatic activation of the disorder with more typical features of WG.

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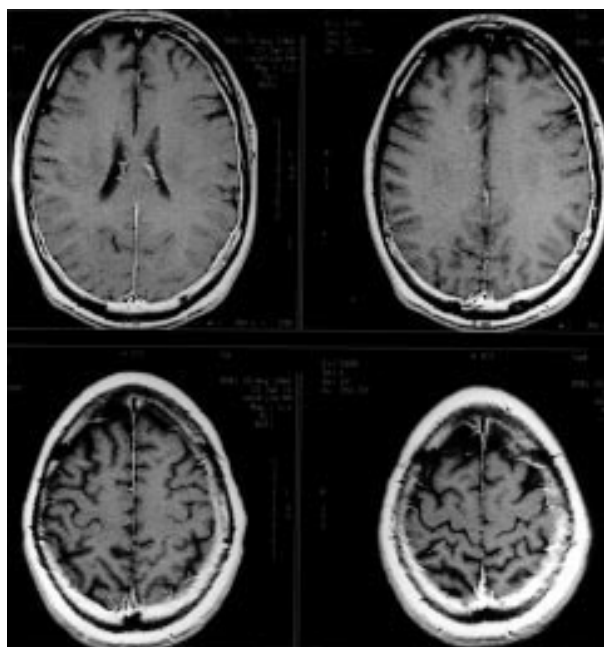


Figure 1 MRI showing diffuse meningeal enhancement.

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Extremely high dose pravastatin may suppress amyloidogenesis in a mouse model

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Pravastatin is a cholesterol lowering agent,¹ recently reported to have anti-inflammatory properties.² It was suggested that the prevention and regression of atherosclerosis by pravastatin is partially related to its anti-inflammatory effect,² probably mediated by inhibition of proinflammatory cytokines.³ Pravastatin's anti-inflammatory effect is associated with, and probably reflected by, reduced levels of the acute phase reactants, C reactive protein and serum amyloid A (SAA).² The N-terminal fragment of the SAA is amyloid A (AA), which is deposited in a fibrillar form in the tissues of up to 30% of patients with a variety of chronic infectious and chronic inflammatory disorders, leading to reactive amyloidosis.⁴

Because prevention and treatment of AA amyloidosis are currently unsatisfactory and reactive amyloidosis is a potentially lethal complication, it is important to find out whether pravastatin affects amyloidogenesis.

The effect of pravastatin on amyloidogenesis was studied in several groups of male Swiss mice 7-17 weeks old, which were subjected to amyloid induction, using intravenous amyloid enhancing factor (1 µg in 0.5 ml phosphate buffered saline on day 0) and subcutaneous AgNO₃ (0.5 ml 2% daily, on days 0, 1, and 2), according to our published protocol.⁵ Two groups of study mice (groups I and II) received intraperitoneal pravastatin 0.4 mg/day in 0.5 ml saline, and two other groups (III and IV) received intraperitoneal pravastatin 10 mg/day. The human oral dose analogous to these regimens is 0.5 mg/kg and 12.5 mg/kg respectively (assuming a 20-fold increase in drug catabolism in mice as compared with man). The experiments lasted for 72 hours (groups I and III) or 96 hours (groups II and IV). The 72 hour interval, during which the amount of amyloid deposits is still low, allows the detection of a mild inhibition. All experiments were controlled by mice of the same strain, sex, and age, which received the same amyloid induction regimen, but 0.5 ml saline intraperitoneally instead of pravastatin. The amount of amyloid deposition in the spleen was studied by the crush and smear technique and a five grade score, estimated by polarised microscopy.⁶ All experiments were repeated two to three times.

Amyloidosis in mice receiving pravastatin was somewhat less abundant and developed in fewer animals than in controls (table 1). This trend was noted only in animals receiving 10 mg/day and only in the short term experiments, but the statistical significance obtained was inconsistent (table 1). No amyloid inhibition by pravastatin was seen in any of the other experiments, either when a lower pravastatin dose (0.4 mg/day) was used or when mice were subjected to a longer (96 hours) amyloidogenic stimulus.

These findings suggest that pravastatin in a very high dose may have a mild amyloid protecting effect and thus increases

Table 1 High dose pravastatin may suppress amyloidogenesis

Group III* experiment number	Type of experiment	Amyloid positive mice per group	Median (range) of amyloid grade	p Value†
1	Study	5/6	2.5 (0-3)	0.24
	Control	6/6	1.5 (1-3)	
2	Study	4/6	0.75 (0-1.5)	0.03
	Control	6/6	2.0 (0.5-3)	
3	Study	2/5	0.5 (0-3)	0.07
	Control	5/6	2.0 (0-2.5)	
Combined	Study	11/17	1.0 (0-3)	0.05
	Control	17/18	2.0 (0-3)	

*Amyloidosis was induced by amyloid enhancing factor and AgNO₃. Study animals received intraperitoneally pravastatin 10 mg/day on days 0, 1, and 2. Control mice received 0.5 ml saline instead. The mice were killed after 72 hours (24 hours after the last pravastatin injection) and the amount of splenic amyloid was estimated by the Crush and Smear technique; †using Fisher's exact probability test.

the spectrum of drugs with a possible tangible amyloid preventive effect. Further studies are warranted to determine underlying mechanisms and to see whether other statins also have anti-amyloidogenic qualities.

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Is hirudin a potential therapeutic agent for arthritis?

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