Peer reviewed article

Inhibition of the TNF pathway: use of infliximab and etanercept as remission-inducing agents in cases of therapy-resistant chronic inflammatory disorders

Daniel Aeberli, Stefan Oertle, Heribert Mauron, Stephan Reichenbach, Beat Jordi, Peter M. Villiger

Department of Rheumatology and Clinical Immunology/Allergology
University Hospital (Inselspital), Bern, Switzerland

Summary

Objective: To examine the potential of the two tumour necrosis factor (TNF) inhibitors infliximab and etanercept as remission-inducing agents in chronic therapy-resistant inflammatory disorders of immune or non-immune pathogenesis.

Methods: 14 patients with adult Still's disease/macrophage activation syndrome (4), Wegener's disease (3), Behçet's disease (3), keratoscleritis (1), lymphomatous tracheo-bronchitis (1) Cogan's syndrome (1), and rapidly destructive crystal arthropathy (1) were treated with infliximab (n = 10) and etanercept (n = 4). All patients showed organ-threatening progression of their diseases with resistance to conventional immunosuppressive medication. Therapeutic benefit was assessed clinically and by documenting organ-specific functional and morphological alterations. Side effects were compared with the data of our clinic's rheumatoid arthritis (RA) patients treated by TNF inhibitors.

Results: A rapid and dramatic beneficial effect was documented in 9 patients and a moderate one in 5. Best responses (clinical and laboratory parameters) were seen in patients with macrophage activation syndrome/adult Still's disease and Behçet's disease, while the results were less impressive in those with Wegener's disease, Cogan's syndrome, idiopathic cerato-scleritis and lymphomatous tracheobronchitis. In all cases immunosuppressive agents and systemic glucocorticoids could be reduced or discontinued.

Conclusions: TNF inhibition may be highly effective in patients with severe, therapy-resistant chronic inflammatory disorders.

Key words: tumour necrosis factor; vasculitis; macrophage activation syndrome; rheumatoid arthritis; Wegener's disease; Behçet's disease; Cogan syndrome; infliximab; etanercept

Introduction

Tumour necrosis factor alpha (TNF alpha) plays a central role in inflammation [1]. It initiates production and secretion of a cascade of inflammatory mediators such as cytokines and adhesion molecules. This, in turn, generates fever, loss of appetite, elevation of CRP, anaemia and other typical signs of inflammation [2]. Inhibition of TNF alpha results in a decrease in adhesion molecules and pro-inflammatory cytokines, as well as regulation of chemokines. [3–8]. Today two compounds are available to neutralise the biological action of TNF alpha, a monoclonal antibody (infliximab) and a soluble TNF receptor (etanercept). Both molecules are effective in treating rheumatoid arthritis (RA) [9–13], but only infliximab induces remission in Crohn's disease [14–16]. TNF inhibition using either compound results in full recovery in approximately 15% of the RA patients. 15% of patients do not respond and the remaining 70% are partial responders. These data clearly show that TNF alpha plays a central and non-redundant role in a sixth of RA patients, while other biological pathways appear to be important or even central in the remaining cases [1, 17, 18]. More recent studies have demonstrated that TNF blockade using infliximab not only ameliorates acute signs of inflammation but also inhibits joint destruction over a period of at least three years [9]. Taken together the available data clearly demonstrate the potential of TNF-

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neutralising agents in inducing and maintaining remission of RA.

Current knowledge of the effect of the TNF blockers in other diseases than RA and, more recently, spondylarthropathies [19, 20] is limited. There are some published case reports and clinical trials in patients with Wegener's disease [21], Behçet's disease [22–27] and Still's disease [28–31]. Evidence exists that TNF inhibition may be helpful in therapy-resistant arteritis temporalis [32, 33]. Some authors believe that connective tissue disorders such as scleroderma [34], Sjögren's syndrome and polymyositis may benefit from TNF blockers [24, 35]. We have so far failed to find any reports on the influence of TNF antagonists on destructive metabolic arthropathy or Cogan's syndrome.

Despite the convincing clinical benefit of the TNF-blocking agents in RA, several questions remain unanswered. Reports of severe and potentially fatal mycobacterial infections point to compromised intracellular killing of bacteria [26, 37]. Cases with common bacterial infections illustrate the fact that – due to the action of TNF blocking agents – inflammatory signs are less impressive. The well-documented finding of autoantibody formation (production of antinuclear antibodies or antibodies against ds-DNA) in patients treated with TNF blockers may be regarded as dysregulation of B lymphocyte function [9]. Cases which develop systemic lupus erythematosus [38, 39] clearly show that functions of the adaptive immune system are not simply suppressed but rather dysregulated and possibly even induced by disrupted feedback loops of the immuno-inflammatory network. Such aspects must be considered if TNF-blocking agents are used "off-label" in therapy-resistant systemic autoimmune disorders of varying pathogenesis.

On the hypothesis that TNF neutralisation exerts a beneficial effect in cases with systemic or organ-specific inflammation, we treated patients with therapy-resistant Wegener's disease, Behçet's disease, adult Still's disease/macrophage activation syndrome, Cogan's syndrome and, to include a non-immune disease, one case with rapidly destructive arthropathy. The patients were closely monitored to detect potential complications early, and side effects were compared with the side effects of our RA patients. To date this is the most diverse cohort of patients treated "off-label" with TNF blocking agents and monitored clinically using organ-specific functional and morphologic tests.

Patients and methods

Between May 2001 and March 2002 14 off-label patients were started on anti-TNF alpha therapy. The cohort of the off-label treated patients is presented in table 1. The clinical situation and therapeutic options were discussed thoroughly with each patient and informed consent was obtained. As described in the results section, some patients were switched from etanercept to infliximab or vice versa in view of inefficacy or side effects.

No validated tools are available by which to judge the effect of TNF-blocking agents in the off-label treated patients. We therefore used disease- and organ-specific functional tests (e.g. lung function tests) and imaging methods (e.g. magnetic resonance imaging) as well as conventional laboratory parameters of inflammation (e.g. C-reactive protein) and diagnosis-specific parameters of disease actvity (e.g. c-ANCA) to measure the efficacy of TNF-blockers. In addition, subjective and clinical parameters were applied such as dyspnoea, physical activity and ability to go back to work. Finally, the use of other anti-inflammatory and immunosuppressive drugs (e.g. methotrexate, cyclophosphamide, prednisone) was monitored.

Side effects were monitored and compared with our RA patients. In March 2002 all available sera were tested for the presence of antinuclear antibodies, rheumatoid factor and antibodies to extractable nuclear antigens.

Between October 1999 and March 2002 a total of 103 patients (1042 patient months) were treated for RA with etanercept (62 patients, 680 treatment months) or with remicade (44 patients, 362 treatment months) in the Clinic of Rheumatology and Clinical Immunology of the University Hospital of Bern. In 33 cases the use of TNF blockers was discussed but not initiated because of active infections, risk of recurrent infections, history of tuberculosis or malignancy or, in patients with RA, because the indication of the international consensus conference was not present [40].

Patients with RA were monitored using the Swiss Clinical Quality Management (SCQM) program, which consists of validated assessment tools for disease activity and disease damage [41].

To learn about clinical benefit or discontinuation of therapy, as well as side effects, all patients or their family doctors were interviewed by phone in March 2002.

Table 1

Diagnoses of the patients treated with etanercept (Enbrel®) or infliximab (Remicade®).

	Etanercept	Infliximab
Off-label number (patient months)	7 (57)	12 (60)
Still's disease	4 (31)	4 (15)
Wegener's disease	0	3 (12)
Behçet's disease	1 (4)	2 (19)
Cogan's syndrome	0	1 (4)
Idiopathic keratoscleritis	0	1 (4)
Lymphomatous tracheobronchitis	1 (16)	1 (6)
Rapidly destructive (crystal) arthropathy	1 (6)	0

Results

Adult Still's disease: Therapy with infliximab and etanercept resulted in rapid and sustained improvement of articular and systemic parameters. Three of four patients are currently free of symptoms and back to work full-time. Prednisone could be tapered and methotrexate lowered to a weekly dose of 15 mg. Two patients were initially treated with infliximab but had to be switched to etanercept due to allergic reactions. Due to systemic bacterial infection TNF inhibition with etanercept was discontinued in one patient but could be readministered four months later with infliximab. One person started with etanercept but then stopped because of financial and social problems. In one case infliximab was combined with butazolidin, also resulting in sustained remission.

Behçet's disease (see also case 1): In a 46-year-old patient with a recurrent form of haemophagocytosis with spontaneous perforation of the small intestine, treatment with ciclosporin, methotrexate and butazolidin had to be discontinued because of side effects or inefficacy. In the course of the disease multiple oral, genital and cutaneous ulcers developed, suggesting Behçet's disease. Treatment with thalidomide was successful but had to be withdrawn due to neuropathy. Infliximab (3 mg/kg bodyweight, administered every 8 weeks) combined with low-dose methotrexate (12.5 mg per week) has resulted in complete and sustained remission since May 2001. Another patient was treated with methotrexate, ciclosporin and prednisone. She was hospitalised for *Pneumocystis carinii* pneumonia. After completion of antibiotic treatment, TNF inhibition was started using etanercept, which allowed tapering of prednisone and discontinuation of methotrexate and ciclosporin.

Wegener's disease (see also case 2): One patient had severe visual problems (visibility of hand movement and room orientation with right eye, blind left eye) due to MRI-confirmed N. opticus infiltration by cells (histologically, nasal and ethmoidal granulomas). Infliximab (5 mg/kg body weight) resulted in partial improvement of sight and prednisone could be tapered. In a 22-year-old man pulse cyclophosphamide and prednisone (1 mg/kg bodyweight) did not produce complete remission. Instead of switching to oral cyclophosphamide, infliximab was used alternately with pulses of cyclophosphamide at intervals of 4 weeks. This made it possible to lower daily prednisone and substantially reduce the cumulative dose of toxic cyclophosphamide.

Cogan's syndrome: One patient with Cogan's syndrome was treated by pulse cyclophosphamide. Because of the inadequate effect on scleritis, infliximab was given and resulted in sustained remission of ocular signs of inflammation. In addition, clinical symptoms of systemic inflammation improved but tinnitus persisted.

Recurrent idiopathic keratoscleritis: Under infliximab the pain and visual problems of a patient with recurrent idiopathic keratoscleritis partially improved, and chronic high ocular pressure decreased. Prednisone was spared. However, due to tuberculosepsis two weeks after the last administration of infliximab, the patient had recently to be hospitalised.

To illustrate the potentially beneficial effect of TNF inhibition we present four representative patients with the following diagnoses: Behçet's disease with retinal vasculitis, Wegener's disease, lymphomatous tracheobronchitis (atypical Sjögren syndrome?) and rapidly destructive arthropathy.

Case presentations

Case 1

A 38-year-old female Bosnian refugee has had Behçet's disease since 1997. In addition to recurrent oral and genital ulcers and thrombophlebitis of the left leg, MRI of the brain revealed old vascular lesions presumably representing scars of cerebral vasculitis. Currently the most important manifestation of the disease is eye-threatening bilateral uveitis with remitting macular oedema (fig. 1A).

In addition to colchicine, the immunosuppressive treatment consisted of ciclosporin (5 mg/kg), followed by a combination of ciclosporin, azathioprine and glucocorticoids (prednisone 40–60 mg daily) and finally, in view of inadequate effect, intravenous pulses of cyclophosphamide (900 mg monthly) while continuing glucocorticoid therapy. After two pulses of cyclophosphamide the uveitis deteriorated and the visus fell from 0.3 to 0.125. As a consequence this widowed biologist was unable to read and had difficulty in looking after her 5-year-old son.

At this point we started treatment with infliximab (5 mg/kg bodyweight). The effect was striking. The visus recovered to 0.3 within days and prednisone could be reduced to 10 mg for the first time in two years. Methotrexate is comedicated in a dose of 10 mg per week to suppress formation of antibodies against infliximab. The treatment with infliximab is being continued at intervals of 8 weeks. Fig. 1B shows the retina 6 weeks after the last infliximab infusion.

Case 2

At the age of 33 this 53-year-old Italian woman had developed antibiotic-resistant maxillar and ethmoidal sinusitis. She was admitted for diagnostic workup. CT scan and bronchoscopy showed inflammation of sinuses, large airways and both lungs. Biopsy specimens of nose and sinuses revealed a granulomatous inflammation but no vasculitis. C-ANCA were negative and there were no signs of kidney involvement. Wegener's granulomatosis was diagnosed and immunosuppressive treatment was initiated.

Despite therapy a saddle-nose deformity developed

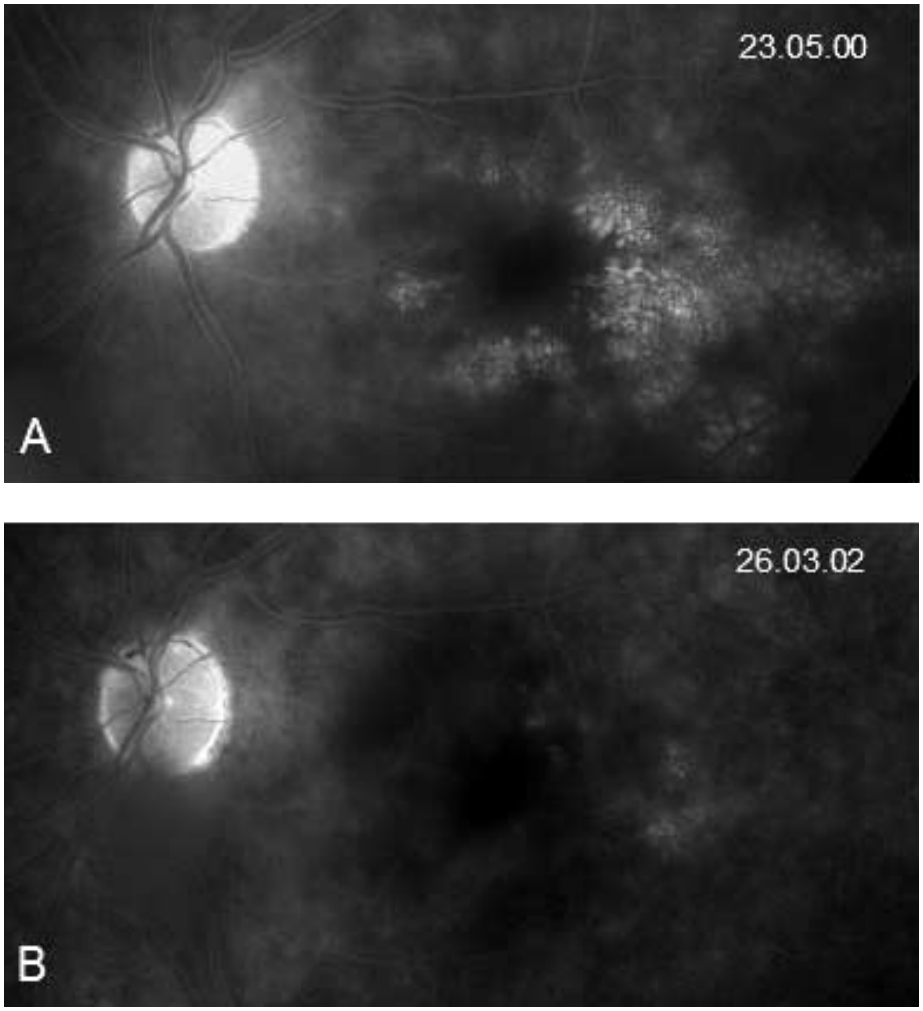

Figure 1

Behçet's disease: Amount of retinal inflammatory fluorescein leakage.
A before, B after treatment with infliximab (5 mg/kg bodyweight). Pictures were taken 8.6 min and 9.0 min after intravenous fluorescein injection (late phase angiography).

and obstruction of the large airways progressed. In 1998 intravenous cyclophosphamide pulse therapy and high-dose glucocorticoids failed to alter the disease course and finally total atelectasis of the right lung was diagnosed in autumn 1999. In 2001 the situation worsened and the patient became severely dyspnoeic (fig. 2A). The remaining therapeutic options were discussed, and despite chronic infection in the destroyed left sinus maxillaris we decided to use infliximab with the aim of suppressing acute inflammation. Within 10 days the patient experienced clinical signs of systemic infection with high fever, leucocytosis and an increase in CRP to a maximum of 204 mg/l. Unexpectedly, x-rays of the lung taken 4 weeks after infusion showed partial reventilation of the right lung, indicating reopening of the airways two years after complete airway obstruction (fig. 2B, C).

Case 3

A 52-year-old Caucasian woman was admitted with a suspected connective tissue disorder. Having been healthy and physically very active until a few weeks previously, she complained of therapy-resistant hoarseness, dyspnoea NYHA class II and dryness of eyes and mouth. Clinical examination showed no abnormalities except for in- and expiratory stridor. Laboratory tests confirmed an elevated ANA antibody titre (1:160), but specific antinuclear antibodies including SS-A and SS-B antibodies were negative. The complement components were within normal limits, as were all other laboratory findings. MRI showed a diffuse subglottic thickening of the trachea without enlarged lymph nodes. Histologic examination of several biopsy specimens revealed signs of chronic inflammation with some eosinophils and fibrotic areas in the mucosa of the bronchial system, subglottic lymphocytic sialadenitis and normal findings in a lip biopsy. No granuloma formation, amyloid deposits, inflammatory cartilage destruction or neoplastic tissue was found in any of the locations. The symptoms disappeared under oral glucocorticoids but recurred within days of drug discontinuation.

The patient decided to try homoeopathic medicine but came back several months later with severe dyspnoea. She had increased her daily dose of prednisone to 50 mg and was just able to walk slowly. CT scan showed comparable results to MRI, with diffuse thickening of the wall of the large airways (fig. 3A). Bronchoscopy documented diffuse narrowing of the large airways, the lumen being an estimated 30–50% of the normal value at several sites. Pulmonary function studies showed a fixed upper airway obstruction. In an attempt to spare glucocorticoids and as an immunosuppressive agent, azathioprine was introduced but had to be discontinued because of side effects. With a combination of leflunomide and prednisone the situation remained stable, but the glucocorticoid dose could not be reduced. In an attempt to induce remission and to spare glucocorticoids, we finally proposed treatment with infliximab. A few days after infusion of 5 mg/kg body weight the symptoms markedly improved. With monthly infusions of infliximab it was possible to taper and finally discontinue glucocorticoids. Due to granulocytopenia, leflunomide was discontinued after the third infusion of infliximab. Pulmonary function studies improved and CT scan showed normalisation of the tracheal wall (fig. 3B).

Case 4

This 60-year-old man was admitted for workup of a rapidly destructive arthropathy. He showed symmetrical

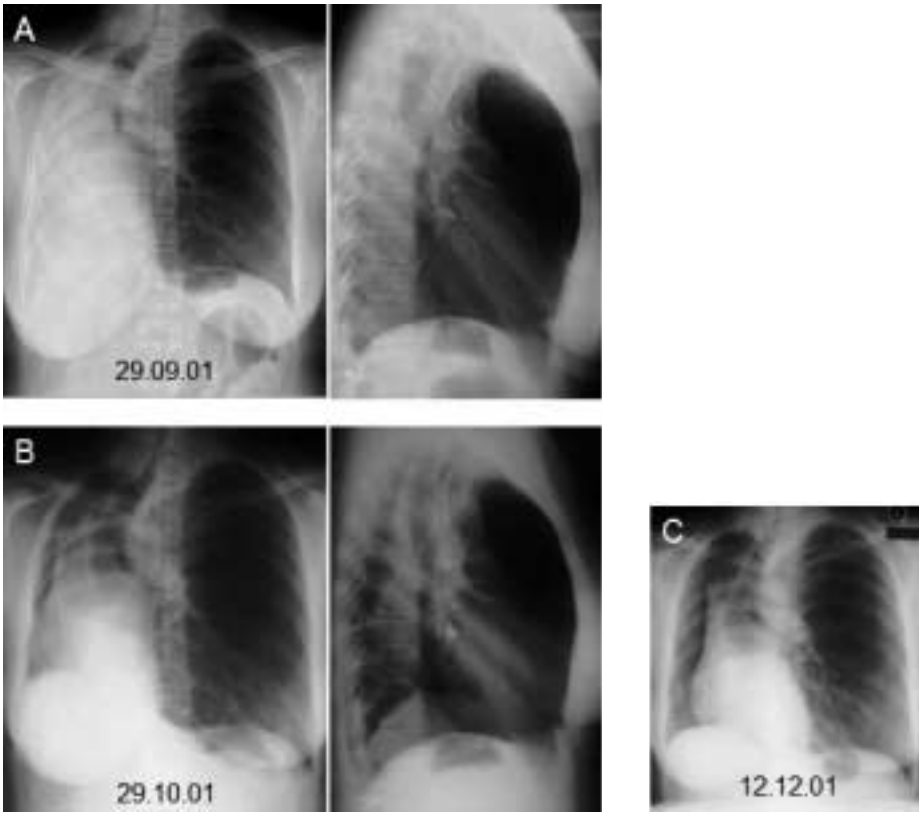

Figure 2

Wegener's disease: A: In autumn 2001 the large airways of the right side occluded with shrinking of the lung and traction of the trachea to the right. As a consequence only the left diaphragm is visible on lateral exposure. B: Four weeks after infusion of infliximab (3 mg/kg bodyweight) the right lung was re-ventilated. On lateral exposure both diaphragms are visible. Addition of prednisone (50 mg per day) further improved ventilation (2C).

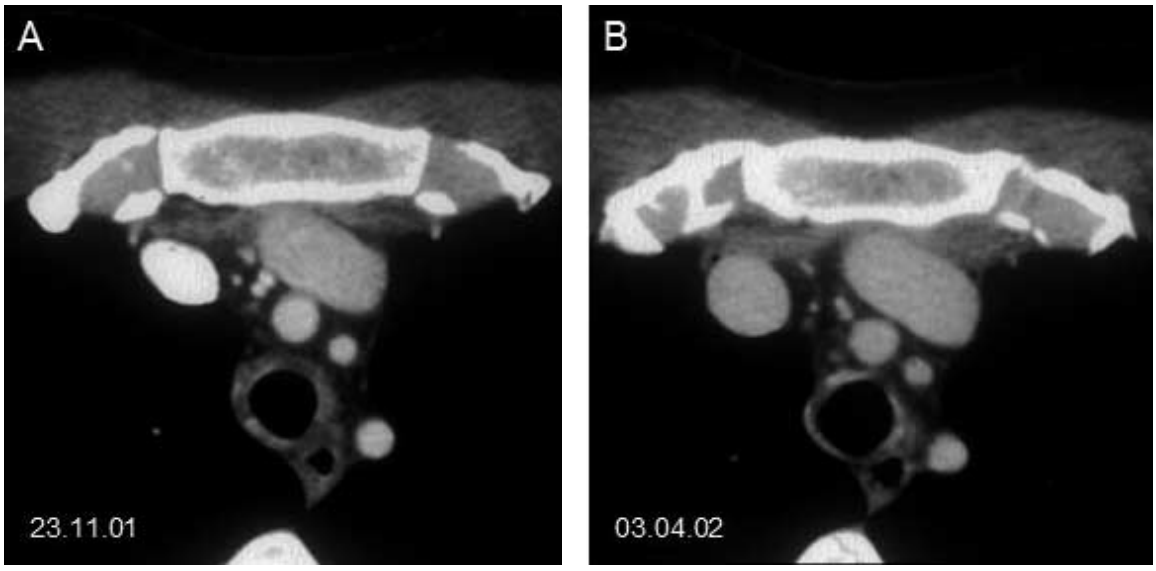

Figure 3

Lymphomatous tracheobronchitis: A: The tracheal wall shows diffuse thickening due to lymphomatous inflammation. The cartilage is not affected and the geometry of the trachea remains intact. B: After administration of infliximab (5 mg/kg bodyweight) the tracheal wall appears normal.

polyarthritis affecting small and large joints of the upper and lower extremities. With the diagnosis of atypical RA he had been treated with sulfasalazine, then with methotrexate and finally with a combination of both drugs, all regimens being ineffective. He had undergone multiple surgical interventions, such as synovectomy of both knees and of the right glenohumeral joint, and finally arthroplasty of both knees and the left elbow. Synovial biopsy specimens analysed on several occasions between 1993 and 1997 showed signs of inflammation but no typical features of RA. Disease relapses were usually accompanied by impressive increases in erythrocyte sedimentation rate and CRP.

X-rays documented rapid destruction of large joints (e.g. glenohumeral joint, fig. 3C and D). Rheumatoid factors, ANA and HLA B27 were negative, but calcium hydroxyapatite crystals were readily found in the synovial fluid of both knees and the left elbow. In the light of the rapid therapy-resistant destruction of the joints, the impressive clinical and laboratory signs of systemic and local inflammation and the patient's suffering, we finally proposed treatment with etanercept. The clinical response was rapid and impressive. Three months after the start of therapy there were no symptoms of systemic inflammation and synovitis had improved, as had anaemia and laboratory signs of inflammation.

In summary, disease activity was markedly suppressed in all off-label treated patients. Complete and sustained remissions were documented in Behçet's disease, in adult Still's disease and in a case with macrophage activation syndrome/Behçet's disease. Marked improvements were

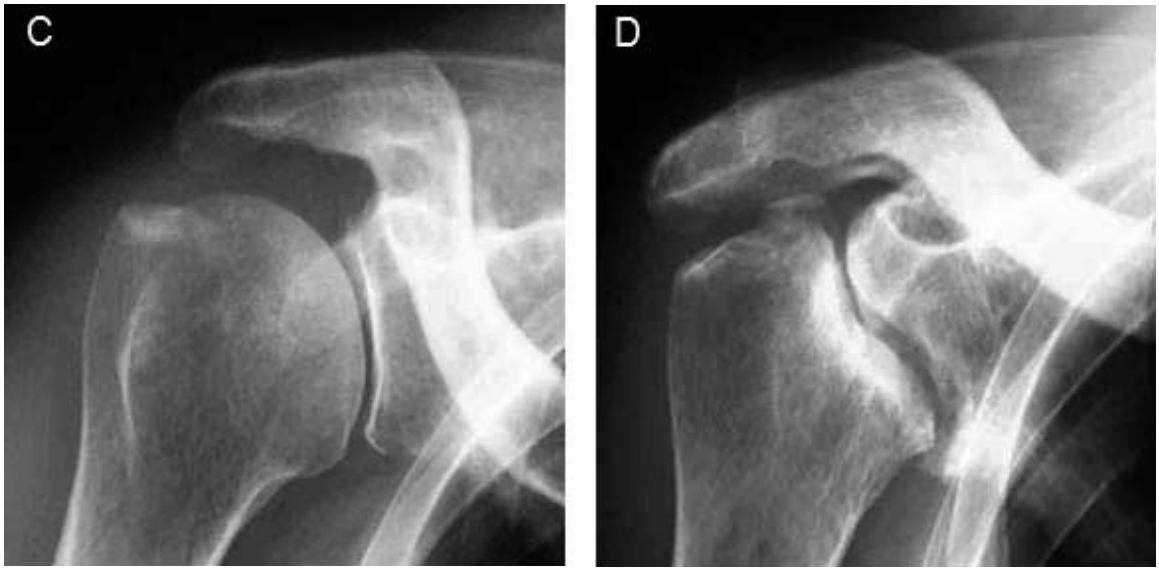

Figure 4

Rapidly destructive arthropathy: C and D illustrate rapid destruction of the right shoulder, presumably due to apatite-induced inflammation.

recorded in other immune-mediated and inflammatory diseases. As an indirect measure of efficacy the use of immunosuppressive treatment, including prednisone, was recorded. In all patients it was possible to reduce immunosuppressive treatment and prednisone could be tapered or even discontinued.

The percentage and range of side effects was comparable in the off-label cohort and the RA patients (table 2). In one of the 14 off-label patients, TNF blocking therapy had to be discontinued due to systemic mycobacterial infection. In two other cases infections prompted temporary discontinuation of TNF-blocking agents. Regarding all the patients treated with TNF blockers in our institution, the incidence of side effects was in agreement with the data of the Food and Drug Administration (www.fda.gov), i.e. the most frequent side effects were skin reactions. Serious infections involving interruption or definitive discontinuation of TNF blockers occurred in 6 cases. No death was reported.

11 sera of the off-label cohort were analysed for the presence and titre of autoantibodies. Three sera became positive for ANA, but no case of positive RF or antibodies to ENA was identified. No significant increase or decrease in autoantibody titre was measured under treatment with TNF blockers in the off-label cohort.

Table 2

Adverse effects of the patients treated with etanercept (Enbrel®) or infliximab (Remicade®).

Adverse effects (n)	Etanercept			Infliximab		
	Off-label (2)	RA (12)		Off-label (3)	RA (2)	
Pulmonary	0	2 (coughing)	1.8%*	0	0	0.47%*
Gastrointestinal	0	1 (diarrhoea)	2.4%*	0	0	0.38%*
Dermatological	0	2 (vasculitis allergic reaction)	3.2%*	2 (pseudo-allergy)	0	0.35%*
General and administrion site	0	5 (erythema)	8,2%*	0	0	
Infection	2	2	4.1%*	1	2	0.4%*
• Bacterial	1 (Staph aureus)	0		0	1 (PcP)	
• Fungal	1 (Candida oesophagitis)	0		0	1 (Candida oesophagitis)	
• Viral	0	2 (Zoster, tracheitis)		0	0	
• Tuberculous	0	0		1	0	0.05%**
• Sepsis	0	0		0	0	0.04%**
ICU admission	0	0		0	0	
Death	0	0		0	0	0.08%**

* Reported cases (FDA) between 10/98–2/01 (www.fda.gov)

** Data from Essex Switzerland

Discussion

The clinical and laboratory results of this patient cohort clearly confirm that neutralisation of the cytokine TNF may be a powerful means of braking treatment resistance and/or inducing remission in cases of organ- or even life-threatening inflammatory diseases. This includes patients with autoimmune syndromes such as vasculitides, disorders characterised by activation of macrophages and, finally, one patient with a rapidly destructive arthropathy possibly due to crystal-induced inflammation. TNF inhibition resulted in rapid amelioration of signs and symptoms of inflammation, as exemplified by the rapid and substantial fall in the acute phase protein CRP and the possibility of cutting down (additional) immunosuppressive treatment and of tapering or even discontinuing systemic glucocorticoids.

Treatment response was often seen very rapidly. In contrast to the effect of conventional immunosuppressive agents such as azathioprine and cyclophosphamide, which becomes clinically apparent after several weeks of treatment, TNF blockade produces clinical improvement within a few days and sometimes even within hours. This resembles the very rapid healing of mucocutaneous ulcers in Behçet's disease under treatment with thalidomide, a drug which is known to interfere with the TNF pathway [42, 43]. This very rapid kinetics speaks in favour of using TNF-blocking agents in acute, therapy-resistant situations.

The four cases presented in this paper were chosen to illustrate that TNF blockade may be clinically effective in diseases with varying pathogenesis. Regarding immunological features and cytokine pattern, Behçet's disease is considered a classical Th1-driven disease [44]. The fact that systemic levels of soluble TNF receptors correlate with disease activity indicates that the TNF pathway may play a role in the expression of disease features [44]. It remains to be shown whether TNF-blocking strategies are more successful than treatment with interferons. However, TNF-blocking agents are definitely better tolerated by patients than interferons.

In the second case, the indication for the use of infliximab was not an acute disease exacerbation but slowly progressive obliteration of the bronchial system, a typical complication of Wegener's disease. An unintended and surprising finding was re-ventilation of the right lung. The fact that high doses of i.v. glucocorticoids in combination with cyclophosphamide and local injections of glucocorticoids did not affect inflammation of large airways but a single dose of infliximab resulted in re-ventilation, as documented by x-rays, suggests significant differences in the biological action and/or kinetics of these therapeutic regimens. It appears likely that the long-lasting effect of infliximab caused a more profound effect on bronchial inflammation. It is conceivable that infliximab led to apoptosis of inflammatory cells in the bronchial wall, resulting in resetting of inflammatory mechanisms comparable to effects seen in synovial tissue of RA patients [8]. Furthermore, it is noteworthy that inflammation of large airways with complete closure of the lumen did not result in fibrosis and that the lung conserved its potential to reventilate two years after complete airway obstruction.

The third case did not show features of acute inflammation (as in relapsing polychondritis), nor did we find signs of vasculitis. Histology of biopsy specimens documented lymphocytic inflammation in the bronchial wall and subglottic lymphocytic sialadenitis. At this stage the disorder cannot be classified, but despite negative SS-A and SS-B antibodies and negative histology of the lip biopsy, atypical Sjögren syndrome suggested itself. In this case the indication for the use of infliximab was the disabling character of the local inflammation and the necessity but also the efficacy of high-dose glucocorticoids. Again the clinical effect was striking, but despite normalisation of the bronchial wall – as documented by CT-scan and MRI – complete remission could not be achieved. Nevertheless, this regimen helped to taper and discontinue systemic glucocorticoids.

It can be argued that the fourth patient has seronegative RA and not crystal-induced arthropathy. However, the fact that he was unresponsive to conventional immuno-suppressive treatment and that synovial tissue specimens repeatedly failed to demonstrate typical histological features of immune-driven disease argues against seronegative RA. Furthermore, the rapid kinetics of large joint destruction is a typical feature of crystal (apatite) arthropathy. Taken together the disease course and the findings show a pattern compatible with a non-immune disorder and, again, TNF blockade was clinically highly effective. It remains to be shown whether TNF-blocking strategies have the potential to modify the disease course, i.e. to prevent destruction of joints. Given the fact that there are no convincing disease-modifying agents for crystal-induced joint destruction, the excellent clinical result in this case suggests a new and attractive strategy.

Although all the patients in our cohort responded to TNF inhibition therapy, subjective and objective criteria suggest differences in effectiveness. Most striking results were noted in patients with macrophage activation syndrome, adult Still's disease and Behçet's disease. Common denominators of these diseases were high levels of systemic inflammation, activation of macrophage lineage cells and problems with wound healing (skin, intestine). On the other hand, patients with vasculitides, with B- or T-lymphocyte disorders and with more local inflammation tended to respond with

partial remissions. These findings may suggest different strategies for maintenance therapy. Whereas in the first group of patients TNF blockade may prove sufficient, in the second group combined therapy with immunosuppressive agents would appear reasonable.

Obviously this study did not set out to provide data for the long-term use of TNF-blocking agents in classified (autoimmune) diseases. We thought it interesting to communicate the successful use of these powerful agents in individual clinical situations for the short or medium term. Our results suggest five arguments which in a clinical situation may help to decide in favour of the administration of infliximab or etanercept: first, TNF inhibition may brake therapy resistance and eventually lead to full remission. Second, TNF-blocking agents act rapidly, but – in the case of etanercept – the effect is not long-lasting. Third, TNF inhibition may help to reduce substantially the number and dosage of immuno-suppressive medications. Fourth, TNF blockers qualify as steroid-sparing agents. Finally, as illustrated by the last case, inhibition of TNF's biological action may dramatically lessen the burden of disease in a situation where disease damage is established.

In summary, the results in our cohort of patients show that selective interruption of the TNF pathway may lead to a striking improvement in signs and symptoms in a broad variety of inflammatory diseases.

Correspondence:
Peter M. Villiger, MD
Department of Rheumatology
and Clinical Immunology / Allergology
University Hospital
CH-3010 Bern
E-Mail: Peter.Villiger@Insel.ch

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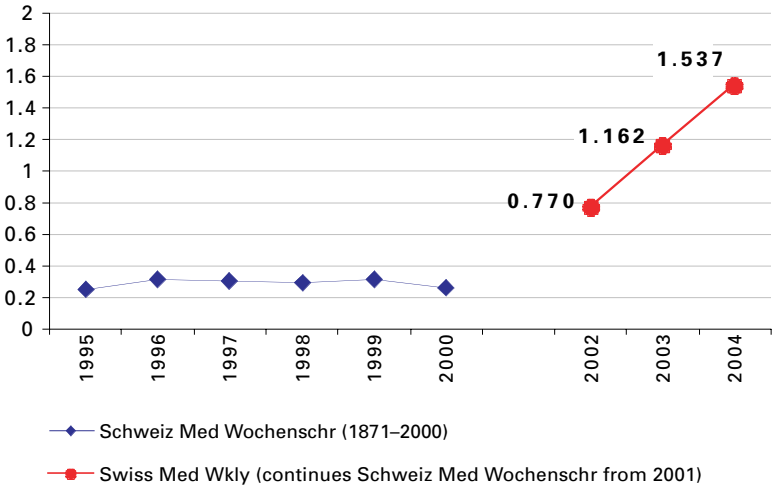

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