Rheumatology 2002;41:1126–1132

Efficacy of the anti-TNF-α antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients

P. Bartolucci, J. Ramanoelina, P. Cohen, A. Mahr, P. Godmer, C. Le Hello and L. Guillevin

Department of Internal Medicine, French Vasculitis Study Group, UPRES 'Recherche Clinique et Thérapeutique', Hôpital Avicenne, Assistance Publique Hôpitaux de Paris, 125 route de Stalingrad, 93000 Bobigny, France

Abstract

Objective. Evidence indicates that tumour necrosis factor (TNF) is a major agent in the pathogenesis of vasculitis. We studied the short-term effect of anti-TNF-α antibody in systemic vasculitis patients refractory to steroids and immunosuppressive agents.

Methods. Ten patients refractory to corticosteroids and at least one immunosuppressant and who had persistently active disease or a new flare were included. Seven had Wegener's granulomatosis, two had rheumatoid arthritis-associated vasculitis and one had cryoglobulinaemia with mean duration of 9.1, 21.5 and 17 yr. They received infliximab (5 mg/kg) on days 1, 14, 42 and then every 8 weeks. Immunosuppressants were stopped between days 0 and 42 for eight patients, while the steroid dose was maintained or lowered. The treatment response was evaluated clinically with the Birmingham Vasculitis Activity Score 2000 (BVAS).

Results. Complete or partial remission was observed in all patients. The mean BVAS at entry was 9.1 (range 4–15) and had declined to 1.9 (range 0–4) by day 42 and 1.3 (range 0–4) at 6 months; BVAS of 0 was recorded for four patients on day 42 and for five at 6 months. The only adverse effect was cutaneous eruption in two patients.

Conclusion. Anti-TNF-α successfully induced prompt symptomatic responses in patients with systemic vasculitis not responding to conventional treatment. Infliximab was well tolerated during the short-term follow-up.

The treatment of systemic vasculitides is based, for most patients, on the combination of corticosteroids (CS) with immunosuppressants. Despite the improvement obtained with this strategy, relapses and failure are frequent, occurring in 49% of Wegener's granulomatosis (WG) patients [1], 7.9% of patients with HBV-related polyarteritis nodosa (PAN), 19.4% with non-HBV-related PAN, 20.3% with Churg–Strauss syndrome and 34.5% with microscopic polyangiitis [2]. Relapses need to be treated by intensification of the CS dose or with new immunosuppressants. Some patients can also be refractory to all treatments, even those prescribed at optimal dose and for sufficient duration. We enrolled 10 such patients in an open pilot study to assess the efficacy of anti-tumour necrosis factor α antibody (anti-TNF-α Ab) (infliximab; Schering-Plough, Kenilworth, NJ, USA).

Submitted 6 December 2001; revised version accepted 5 April 2002.

Correspondence to: L. Guillevin.

Materials and methods

Patients

The 10 patients participating in the trial had been referred to our specialized centre for vasculitis between 1986 and 2000 for different types of vasculitides refractory to conventional treatments. The trial was organized by the French Vasculitis Study Group.

Vasculitides met the American College of Rheumatology criteria for WG [3] and rheumatoid arthritis (RA)-associated vasculitis or were biopsy-proven. Patients also satisfied the criteria for vasculitides according to the Chapel Hill nomenclature [4]. At the time when anti-TNF-α Ab therapy was initiated, all the patients had persistent active vasculitis or were experiencing a new flare.

Study protocol

Patient inclusion criteria were: (i) failure to respond to CS and at least one immunosuppressant [cyclophosphamide (CYC), azathioprine (AZA), methotrexate

(MTX) or mycophenolate mofetil (MMF)] or (ii) CYC had to have been discontinued because of side-effects. Another patient with mixed cryoglobulinaemia (MC)-associated vasculitis was enrolled because poor venous access contraindicated the continuation of plasma exchanges (PE), which had previously been effective.

To evaluate the efficacy of anti-TNF-α Ab in combination with CS (dose range 5–65 mg/day), immunosuppressants were stopped at day 0, except for two patients with severe disease who received CYC (patient 8) or MTX and MMF (patient 9). The CS dose was maintained or lowered when possible. Patients received anti-TNF-α Ab intravenously at 5 mg/kg on days 0, 14 and 42 and then every 8 weeks. Immunosuppressants were reintroduced on day 42. The choice of immunosuppressant was based on the prior responses (ineffective, toxic) to the drugs administered previously. For example, when a patient had relapsed under MTX, we subsequently chose another immunosuppressant, e.g. AZA. Treatment with anti-TNF-α Ab could be discontinued during the following weeks if the flare was controlled by the first three infusions. Patients were seen on days 0, 14 and 42, and at 2 and 6 months or more often if necessary.

Disease assessment

At each visit, we collected data on clinical symptoms, response to therapy and possible side-effects. Biological analyses and radiological examinations were performed according to each patient's clinical symptoms. The treatment response was evaluated clinically and with the Birmingham Vasculitis Activity Score 2000 (BVAS) determined on day 42 and at 6 months [5]. Because of the diversity of the vasculitides included in this pilot trial, we used the BVAS 2000 and not the modified BVAS for WG [6]. Responses were defined as follows: complete remission (CR) when no clinical and biological signs of activity were present at 6 months with BVAS = 0; partial remission (PR) when the clinical and biological responses were incomplete with BVAS >0 but inferior to the entry score; sequelae were defined as clinical manifestations that persisted and remained stable and for which no further improvement was expected.

Results

Baseline patient characteristics

Ten patients—four women and six men with mean age 51.5 yr (median 55.5 yr, range 30–65 yr)—were included in the study: eight for prior treatment failure, one for CYC toxicity and one with poor venous access (Table 1). Seven had WG, two had RA-associated vasculitis and one had hepatitis C virus-related type II MC. The mean duration of vasculitis before anti-TNF-α Ab initiation was 9.1 yr (median 5 yr, range 0–19 yr) in the WG patients; in the two RA patients it was 5 months (3 and 7 months in the two individuals). In the two patients with RA, the RA had lasted 4 and 39 yr before anti-TNF-α Ab treatment was started. The mean number of flares before anti-TNF-α Ab therapy was 6.5 (range 1–11). For patients 1, 2 and 8, anti-TNF-α Ab was instigated for the first flare occurring under CS and the optimal CYC dose.

At the time of anti-TNF-α Ab prescription, five patients were receiving CYC and one was taking AZA; patient 3 was taking MMF after 4 months on AZA and patient 9 was taking MMF and MTX. Immunosuppressants were combined with CS for all except patient 10, who had been receiving CS and PE for MC-associated vasculitis. Patients 7 and 9 had CYC-induced haemorrhagic cystitis (present at the time of inclusion in patient 7).

Prior immunosuppressant treatments prescribed before anti-TNF-α Ab were CYC in nine patients, MTX in six, AZA in three, MMF in two and immunoglobulins in three. Patient 1 had also received D-penicillamine and cyclosporin for severe RA, patient 3 had also taken sulphasalazine and mesalazine for WG with colon involvement, and patient 10 had also received interferon α for MC-associated vasculitis. Patients 7 and 10 also underwent PE for refractory WG and MC-associated vasculitis respectively. The baseline data and outcome are detailed in Table 1.

Clinical manifestations of vasculitides present at the time of anti-TNF-α Ab initiation were: inflammatory syndrome ($n=5$); upper respiratory tract involvement ($n=4$); lung involvement ($n=4$); eye involvement ($n=3$); arthritis ($n=2$); skin ulcers ($n=2$); glomerulonephritis with hypertension, proteinuria, renal insufficiency and microscopic haematuria without biopsy ($n=1$); colitis due to WG proven histologically ($n=1$); stroke ($n=1$); dura mater infiltration with hypophyseal involvement, revealed by diabetes insipidus ($n=1$); worsening mononeuritis multiplex ($n=1$); worsening pyoderma gangrenosum ($n=1$ WG patient). The mean BVAS at entry was 9.1 (median 8, range 4–15).

Immunosuppressants were reintroduced after day 42: AZA for six patients; MMF for three; MTX for two; and left unchanged for patient 9, who received a combination of CYC, MMF and MTX (Table 1).

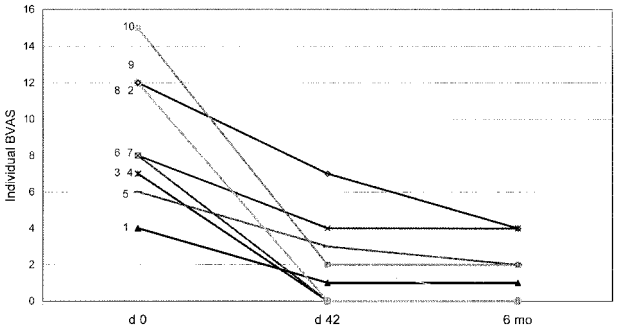

FIG. 1. Individual BVAS on days 0 and 42 and at 6 months.

TABLE 1. Patient characteristics and outcome

Patient	Sex	Age (yr)	Vasculitis	Symptoms at disease onset	Clinical manifestations at time of relapse and anti-TNF-α initiation	Disease duration before anti-TNF-α	Previous immuno-suppressants	Trial inclusion criteria	Immuno-suppressants reintroduced after day 42	6-month status: outcome
1	F	65	RA	Cutaneous ulcers, livedo, inflammatory syndrome	Necrotizing cutaneous ulcers	7 months	MTX, CYC, cyclosporin	Failure of CS + 6 CYC pulses	AZA	PR: ulcer healing, pain relieved within 2 months
2	F	37	RA	Mononeuritis multiplex, Raynaud's phenomenon, microscopic haematuria, inflammatory syndrome[a]	Worsening of mononeuritis multiplex, Raynaud's phenomenon (ischaemia), arthritis, inflammatory syndrome	3 months	MTX CYC	Failure of CS + 5 CYC pulses	MTX	CR: mononeuritis multiplex attenuation, arthritis regression within 1 week, Raynaud's phenomenon regression within 2 weeks, inflammatory parameters regressed
3	M	61	WG	Fever, fatigue, rhinitis, sinus involvement, cough, inflammatory colitis, cANCA, inflammatory syndrome	Cough relapse and dyspnoea, basal lung infiltrate, bloody diarrhoea with granuloma in colon biopsy	12 yr	AZA CYC MMF	Failure of CS + AZA for 4 months, replaced by MMF for 2.5 months	MTX stopped at 3 months (GI intolerance), replaced by AZA	CR: cough disappearance within 2 months, rectorrhagia and granuloma regression within 1 week
4	M	63	WG	Rhinitis, granulomatous sinusitis, episcleritis, iridocyclitis, cough and haemoptysis, bronchial granulomatous obstruction, cANCA, inflammatory syndrome	Nasal crusting, sinus involvement, persistent dyspnoea with bronchial stenosis, inflammatory syndrome	4 yr	MTX, CYC, AZA, Ig IV	Failure of CS + AZA for 2 yr	MMF	CR: nasal and sinus improvement within 2 months, persistent dyspnoea, inflammatory parameters regressed
5	M	30	WG	Purpura, orchitis, otitis, Raynaud's phenomenon, abdominal pain, arthralgia, myalgia, cANCA, inflammatory syndrome	Exophthalmos, otitis cough	5 yr	CYC	High cumulative CYC dose (50 g) with GI intolerance	AZA	PR: cough regression within 2 months, exophthalmos decreased within 2 months
6	F	50	WG	Weight loss, arthralgia conjunctivitis, purpura, cutaneous and mouth ulcers, nasal crusting with granuloma, cANCA, inflammatory syndrome	Sinus involvement and nasal crusting, dura mater infiltration with hypophyseal involvement (diabetes insipidus), blepharitis and choroiditis, inflammatory syndrome	4 yr	MTX CYC	Failure of CS + CYC for 2 yr, high cumulative CYC dose (140 g)	AZA	CR: choroiditis and sinusitis regressed within 2 months, persistent hypophyseal involvement

Table 1. Continued

7	M	42	WG	Fever, asthenia, nasal obstruction, granulomatous sinusitis, pulmonary nodules, cANCA	Exophthalmos with blurred vision, corneal perforation, bloody nasal discharge	19 yr	MTX CYC PE Ig IV	Failure of CS + 12 CYC pulses, high cumulative CYC dose (200 g), haemorrhagic cystitis	MMF	PR: exophthalmos attenuated within 2 months, persistent bloody nasal discharge
8	M	63	WG	Weight loss, fever, fatigue, myalgia, livedo, mononeuritis multiplex, abdominal pain proteinuria, haematuria, cANCA, inflammatory syndrome	Weight loss, persistent fatigue, stroke, inflammatory syndrome	7 months	CYC	Failure of CS + 4 CYC pulses	8 CYC pulses then AZA	CR: neurological improvement, weight gain, fatigue abated within 2 months, inflammatory parameters regressed
9	M	42	WG	Nasal crusting, pansinusitis, pulmonary nodules, proteinuria, leucocyturia, cANCA	Nasal crusting, nasal obstruction, hearing loss, sinus involvement, pulmonary nodule reappeared, pyoderma gangrenosum, arthritis	9 yr	MTX MMF AZA CYC Ig IV	Failure of CS + MMF for 20 months + MTX for 4 months	MMF, MTX	PR: pyoderma gangrenosum healing, persistent nasal obstruction, dyspnoea arthritis attenuation, seizure and nasal crusting at 4 months
10	F	62	MC (HCV)	Purpura, polyneuropathy, haematuria, positive Rose–Waaler and latex agglutination test	Fatigue, painful cutaneous ulcers, purpura, glomerulonephritis relapse, hypertension, inflammatory syndrome	13 yr	PE, interferon	Poor venous access preventing continuation of effective PE	MMF stopped at 1 month (toxicodermia) then AZA	PR: ulcers attenuation within 2 weeks, neurological pain disappeared within 2 months, mild ulcer and purpura relapse at 4 months

[a]Elevated CRP and ESR.

HCV, hepatitis C virus; MMF, mycophenolate mofetil; Ig IV, intravenous immunoglobulin; PE, plasma exchange; GI, gastrointestinal; cANCA, cytoplasmic labelling pattern of antineutrophil cytoplasmic antibodies.

TABLE 2. BVAS on days 0 and 42 and at 6 months

	Day 0		Day 42		6 months	
Category	Persistent	New/worse	Persistent	New/worse	Persistent	New/worse
General	1	5	2	0	0	0
Cutaneous	0	16	4	4	3	0
Eyes	0	12	4	0	4	0
ENT	2	18	3	0	2	4
Chest	2	6	2	0	0	0
Cardiovascular	0	0	0	0	0	0
Abdominal	0	3	0	0	0	0
Renal	0	8	0	0	0	0
Nervous system	0	18	0	0	0	0
Mean BVAS	0.5	8.6	1.5	0.4	0.9	0.4

ENT, ear, nose and throat.

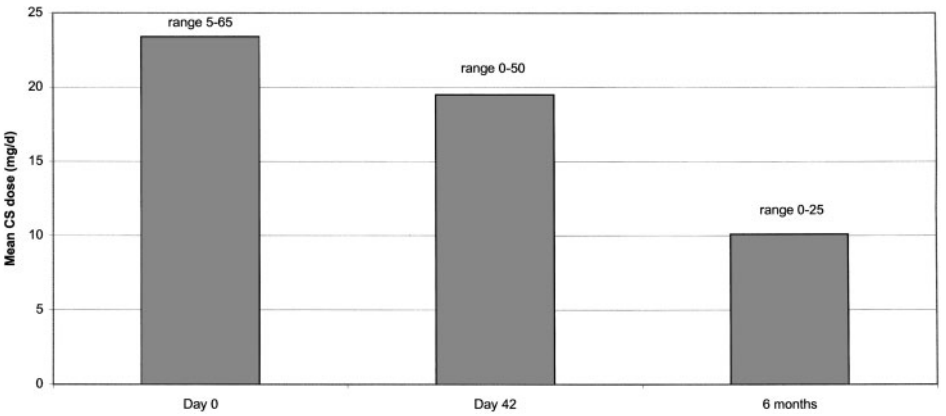

FIG. 2. Prednisone doses on days 0 and 42 and at 6 months.

Outcome and response to treatment

All patients had improved on day 42 and improvement persisted at 6 months. For 4/10 patients, symptom attenuation was obtained within 2 weeks (Table 1).

The mean BVAS (Table 2 and Fig. 1) had declined to 1.9 (median 1.5, range 0–4) on day 42 (79% decrease) and 1.3 (median 0.5 range 0–4) at 6 months (85% decrease). Anti-TNF-α Ab could be stopped in four patients (patients 4, 5, 6 and 8), because of good efficacy; their mean BVAS was 8.25 (median 8, range 6–12) on day 0, 0.75 (median 0, range 0–3) on day 42 (90% decrease) and 0.5 (median 0, range 0–2) at 6 months (93% decrease).

A BVAS of 0 was recorded for four patients (patients 3, 4, 6 and 8) on day 42 and five (2, 3, 4, 6 and 8) at 6 months (three discontinued anti-TNF-α Ab).

The CS dose was lowered for five patients, maintained for three, stopped for one on day 42, and increased for patient 10, who developed purpura and skin ulcers. CS were decreased for five patients, maintained for three and stopped for two at 6 months, and were not increased. Mean prednisone doses (mg) on day 0, day 42 and at 6 months were respectively 23.4 (range 5–65), 19.5 (0–50) and 10.1 (0–25) (Fig. 2). Three of five patients who decreased and 3/3 patients who maintained their CS dose at 6 months were receiving anti-TNF-α Ab. Patients 4 and 5, who stopped CS, were also able to discontinue anti-TNF-α Ab.

Two patients relapsed while still receiving anti-TNF-α Ab. Patient 10 developed mild cutaneous ulcers and purpura. Patient 9 relapsed twice, first at 3 months with a new flare of pyoderma gangrenosum, for which we decided to infuse anti-TNF-α Ab every 4 weeks, and again at 4 months, with nasal crusting and his sixth seizure since 1988 (with normal magnetic resonance imaging), possibly related to WG.

At 6 months, five patients were in CR and five in PR. Six patients had sequelae: mononeuritis multiplex (patients 2, 8 and 10); residual effects of a stroke (patient 8); persistent dyspnoea due to bronchial stenosis (patient 4); sinus osseous destruction (patient 9); and hypophysitis with diabetes insipidus (patient 6).

Side-effects

No major side-effects were observed. A mild transient cutaneous eruption was observed only after the first anti-TNF-α Ab infusion in patient 4 and only at 6 months in patient 10, for whom anti-TNF-α Ab was discontinued. No infection was noted.

Discussion

Anti-TNF-α antibody is now widely used to treat RA [7, 8] and Crohn's disease [9, 10]. New indications have been proposed progressively, e.g. refractory ankylosing spondylarthritis [11]. The pathogenetic mechanisms of systemic vasculitides, especially those associated with antineutrophil cytoplasmic antibodies (ANCA), might be susceptible to anti-TNF-α Ab, as TNF-α participates in the cytokine cascade leading to vascular damage.

There is some evidence that could explain the efficacy of anti-TNF-α in vasculitis, particularly WG. TNF-α is a major proinflammatory cytokine. Plasma TNF-α is elevated in patients with active WG [12]. During activation of polymorphonuclear neutrophils (PMN) by TNF-α, intracellular proteinase 3 (PR3) is transported to the cell surface, where it can bind circulating ANCA [13].

Phagocytosis of PR3–ANCA-opsonized PMN by macrophages leads to the release of TNF-α and other proinflammatory mediators and could contribute to the priming and recruitment of more PMN, leading to self-perpetuating inflammation [14].

This open pilot study, lasting 6 months, demonstrated that anti-TNF-α Ab therapy provided clinical benefit for patients who had active vasculitis (including WG and RA) and did not respond to immunosuppressants and CS. Responses to anti-TNF-α Ab were obtained within 2 months and were often observed after the first month. The beneficial effects persisted at 6 months in 8/9 patients. The patient with MC improved markedly after the first infusion but relapsed at 4 months with mild cutaneous ulcers and purpura. This outcome is not surprising in this long-standing multi-relapsing disease.

The BVAS had decreased by 79% from the baseline on day 42 and by 85% at 6 months. In parallel, it was possible to taper CS by 16.6% on day 42 and by 56.8% at 6 months. Under CS and anti-TNF-α Ab therapy, symptoms became attenuated or disappeared (Table 1) in all patients.

The following symptoms were considered sequelae: mononeuritis multiplex, stroke, hypophyseal involvement and dyspnoea due to bronchial stenosis. However, it is sometimes difficult to differentiate between persistent signs of active vasculitis and their definitive residual consequences, both clinically and for the determination of BVAS. The latter requires the retrospective assessment of the patient's disease course from entry onwards in order to distinguish between PR and sequelae. In addition, patient 9's seizure at 4 months was not considered in the 6-month BVAS because it had not occurred during the previous 28 days. Patients who discontinued anti-TNF-α Ab had a lower BVAS at baseline (mean BVAS 8.25 *vs* 9.1), whereas patients 9 and 10, who relapsed, had a higher BVAS at baseline (12 and 15 respectively). Patient 9 had infusions every 4 weeks because of the severity of his disease, but his BVAS at 6 months improved under this regimen (BVAS 4 *vs* 12).

For 8/10 patients, because immunosuppressants were not prescribed during the first 42 days, the reported improvements could be attributed to anti-TNF-α Ab and CS. Nevertheless, immunosuppressants reintroduced after day 42 could have contributed to the beneficial effects seen at 6 months. The combination of immunosuppressant and infliximab is, however, recommended in order to prevent the synthesis of anti-chimeric antibodies.

In the present study, we observed only a minor and transitory effect during the first 2 months of treatment. A tolerance study conducted on WG patients showed good acceptance of anti-TNF-α combined with therapies other than MTX [15].

We attempted to evaluate the effect of short-term infliximab in this study. At present we do not know if this anti-TNF-α Ab can be considered a maintenance treatment or should be prescribed only to treat flares. Further studies are needed to answer this question.

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