Infliximab in patients with systemic vasculitis that is difficult to treat: poor outcome and significant adverse effects

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The traditional treatment of systemic vasculitides with long-term oral cyclophosphamide (CPM) and high-dose corticosteroids has given way to more conservative approaches with shorter induction with CPM, followed by maintenance treatment with azathioprine or methotrexate.¹ Despite this, 30–50% of patients relapse by 12 months. Endothelial dysfunction and tumour necrosis factor (TNF) α play a major part in pathogenesis.² Raised TNF levels are associated with vascular damage and correlate with disease activity.

We describe an open-label uncontrolled prospective study of anti-TNF α (infliximab), in the management of patients with systemic vasculitides who failed to maintain remission on conventional immunosuppressive treatment.

We prospectively recruited nine patients with systemic vasculitides: three with Wegener's granulomatosis, two with Behçet's disease, and one each with Churg Strauss vasculitis, adult onset still's disease, Henoch Schonlein purpura and relapsing polychondritis. All failed to respond to one or more immunosuppressives (cyclophosphamide, methotrexate, azathioprine or mycophenolate mofetil) and required >15 mg/day prednisolone (range 15–80 mg).

All patients were scheduled to receive five infusions of infliximab (5 mg/kg) over a period of 6 months. The study was approved by the Guy's and St Thomas' Hospital Research Ethics Committee, and informed consent was obtained from patients before entering the study.

The median age of the patients was 46 years (range 34–62 years) and disease duration was 6 years (range 3–8 years).^{3–8} Only five patients completed five infusions of infliximab; in four, infliximab was discontinued because of adverse effects (table 1).

We found no improvement in the median Birmingham Vasculitis Activity Score, Vascular Damage Index and SF-36

scores. Four patients developed new autoantibodies (table 1), which became negative 3 months after discontinuation of infliximab. Four patients required admission for a severe flare of symptoms and lupus-like reaction, and rescue with methyl prednisolone (500 mg) pulses and intravenous immunoglobulins (table 1). One patient with adult-onset still's disease died after 6 months secondary to cardiac failure. Her inflammatory markers remained grossly abnormal throughout (table 1). The relationship with the infliximab infusions was not clear, but a postmortem examination did not show coronary artery disease, thrombosis or valvular abnormality. The study was terminated prematurely on safety grounds, and relevant authorities were informed.

Previously, several reports have suggested that anti-TNF α is effective in patients with systemic vasculitides.^{3–4} Booth *et al*⁵ described improvement in endothelial function after anti-TNF α treatment in patients with systemic vasculitides. Our findings do not support previous observations that infliximab helps to achieve remission in patients with systemic vasculitides that is difficult to treat.

A recent study (Wegener's Granulomatosis Etanercept Trial) failed to show any additional advantage when etanercept was added to conventional treatment. Solid malignancies were noted in the etanercept arm, giving rise to serious safety concerns.⁶

In summary, the adverse effects and lack of benefit experienced in our series raises concerns about the role of anti-TNF α in patients with systemic vasculitides. Other biological treatments such as B cell depletion⁷ and/or intravenous immunoglobulin in antineutrophil cytoplasmic antibodies associated vasculitides may be more fruitful.⁸

Abbreviations: CPM, cyclophosphamide; TNF, tumour necrosis factor

Table 1 Adverse effects/flares after infliximab infusions

Diagnosis	Number of infusions	New autoantibodies	Adverse events/flares	Hospital admission	Treatment for flares/adverse reaction	Deaths
Wegener's granulomatosis	5	Nil	Hearing and vision deterioration	No	CPM+M pred	No
Wegener's granulomatosis	5	ANA, DNA	Hearing loss and lupus-like reaction	No	Prednisolone+CPM	No
Wegener's granulomatosis	3	Nil	Leucopenia and anaemia	No	Blood transfusion	No
Churg strauss disease	2	Nil	Brain stem event and lupus-like reaction	Yes	M pred +IVIG	No
Behçet's disease	5	Nil	Severe lupus-like syndrome and flare	Yes	M pred and IVIG	No
Behçet's disease	5	ANA, DNA	Scleritis, nodular vasculitis	No	Prednisolone 80 mg/day	No
Henoch Schonlein purpura	1	Nil	Severe lupus-like reaction	Yes	M pred+IVIG	No
Relapsing polychondritis	3	ANA, DNA and lupus anticoagulant	Tired and progressive tracheal stenosis	No	Prednisolone 20 mg/day	No
Adult-onset Still's disease	5	ANA, DNA and smooth muscle	Severe flare (serum ferritin >14 000, CRP >300 and ESR 110)	Yes	M pred+IVIG	Yes, after 6 months

ANA, antinuclear antibodies; CPM, intravenous cyclophosphamide; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IVIG, intravenous immunoglobulins; M pred, intravenous methyl prednisolone.

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Adalimumab: a new modality for Behçet's disease?

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Aberrant T cell function,¹ subsequently accompanied by increased tumour necrosis factor α (TNF α) levels, induces inflammatory symptoms in patients with Behçet's disease (BD).² Subsequently, treatment usually involves T cell-directed immunosuppressive or anti-TNF α treatment in patients with severe disease.^{3–7} Administration of the new human monoclonal TNF α antibody adalimumab has only been described in three patients with BD with uveitis.⁸ We analysed

the effects of adalimumab on severe and often chronic disease in six heavily pretreated patients with BD in whom immunosuppressive therapy had failed (table 1).

These patients were treated in the past with infliximab.⁹ Indications for anti-TNF α treatment were uveitis (patients 2 and 4), CNS disease (patients 3 and 5), colitis (patient 6) and severe oral ulcers and arthritis (patient 1), and are further presented in table 1. Symptoms were scored retrospectively

Table 1 Clinical effects in patients treated with infliximab or adalimumab for Behçet's disease

	1		2		3		4		5		6	
Age/gender	43/M		40/M		41/F		36/M		43/F		34/M	
Gifts of infliximab	1		16		9		6		6		10	
Comedication adalimumab*	—		P(15), MTX		D, Cys, Pf		P(10), MP		P(10), A(100)		Cys, Th, P(30), MTX	
Tapering of comedication	—		P(2.5–10)		Cys		P(5)		P(7.5)		Cys, Me, B	
Symptoms and response† before and after anti-TNFα treatment.												
Symptoms and indications for anti-TNFα treatment	I	A	I	A	I	A	I	A	I	A	I	A
	pr	po	pr	po	pr	po	pr	po	pr	po	pr	po
Uveitis	—	—	—	1	1/2	1	1/2	—	—	—	—	—
Oral ulcers	1	0	1	1/2	1	1/2	1	0	1	0	—	—
Genital ulcers	1	0	1	1/2	1	0	1	0	—	—	1	0
Skin	1	0	1	0	1	1/2	1	0	—	—	1	0
Colitis/oesophageal ulcers	—	—	—	—	—	—	—	1	0	—	—	—
CNS involvement	—	—	—	—	—	—	1	0	1	0	—	—
Arthritis or arthralgia	1	0	1	0	1	1/2	1	0	—	—	1	0
Total#	4	0	4	1	5	2	5	0	3	0	2	1/2
Duration (mean 530/427) (days)	30		>327	943	>576	318	>395	259	>405	323	190	808
Rate of relapse (mean 128/–) days57			—	81	—	289	—	201	—	124	270	<30
												>671

—, none; A, adalimumab; B, budesonide; CNS, central nervous system; Cys, ciclosporin; D, dexamethasone; F, female; I, infliximab; M, male; Me, mesalazine; MP, monthly high dose of 1g methylprednisolone; MTX, methotrexate; P, prednisone; Pf, pentoxifylline; po, post; pr, prior; Th, thalidomide; TNF, tumour necrosis factor. Only symptoms preceding anti-TNF α treatment are mentioned. Treatment schedules: infliximab: 3–5 mg/kg every 1–3 months intravenously according to disease intensity and response; adalimumab: 40 mg subcutaneously every 2 weeks.

Relapse rate after cessation of anti-TNF α treatment.

*Immunosuppressive therapy that was combined at the start of adalimumab, dose in milligrams between parentheses.

†Complete response was defined as being free of symptoms. Incomplete response indicates subjective response and reduction in frequency of symptoms. Visual acuity was assessed according to local ophthalmological guidelines. Symptoms before anti-TNF α was indicated were allocated 1; incomplete remission and complete remission were 1/2 and 0, respectively.

#Cumulative score, 1/2 counted as 0.5, complete response as 0.