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ABSTRACT

Objective: To assess anti-tumour necrosis factor (anti-TNF) agents in patients with refractory systemic rheumatoid vasculitis (SRV).

Methods: 1200 rheumatologists and internists were asked to provide medical files for patients with anti-TNF agents given as a second-line treatment for active SRV refractory to cyclophosphamide and glucocorticoids.

Results: We identified nine cases in which anti-TNF drugs were given for active SRV, despite previous treatment with a mean cumulative dose of 8.4 g of cyclophosphamide in association with high-dose glucocorticoids. The mean prednisone dose before anti-TNF therapy was 29.6 mg/day. After 6 months, six patients were in remission (complete in five, partial in one). The treatment failed in one patient and two patients stopped taking the anti-TNF treatment due to side-effects. Mean prednisone dose was reduced to 11.2 mg/day. Severe infection occurred in three patients. Relapses were observed in two patients. Remission was re-established by reintroducing anti-TNF therapy in one case and increasing the dose in the other.

Conclusions: This study provides evidence of efficacy of anti-TNF therapy in adjunct to glucocorticoids for treating active refractory SRV. Remission was achieved in two-thirds of patients, with a significant decrease in prednisone dose, although there was a high rate of infection in these severely ill patients.

Rheumatoid vasculitis in an inflammatory condition of the small- and medium-sized vessels that affects a subset of patients with rheumatoid arthritis (RA). The treatment of systemic rheumatoid vasculitis (SRV) is poorly codified. Five-year mortality rates remain high, at 33–43%, depending on the study considered, with significant morbidity.[1–3]

There is mounting evidence to suggest that tumour necrosis factor (TNF) plays a central role in the pathophysiology of SRV.[4 5] Encouraging results with TNF inhibitors have been reported in a total of 10 patients with SRV,[6–12] with anti-TNF agents used as a second-line therapy in eight of these patients.[6 8–11]

The efficacy of anti-TNF drugs in RA, the involvement of TNF as a key mediator in the pathogenesis of rheumatoid vasculitis and encouraging results reported in case reports led us to evaluate the possible therapeutic benefits of anti-TNF drugs for treating SRV. In this study, we assessed the value of anti-TNF agents as a second-line treatment in patients with SRV resistant to conventional therapy.

PATIENTS AND METHODS

Patient selection

We carried out a retrospective survey to identify cases of SRV treated with anti-TNF drugs. Twelve hundred rheumatologists and internists were asked to supply medical records for any patients with SRV who had been treated with an anti-TNF agent. Patients were included in this study if they had: (1) RA according to the American College of Rheumatology classification criteria;[13] (2) SRV according to the criteria published by Scott and Bacon;[14] (3) active SRV, either persistent or relapsing, at the time of initiation of anti-TNF therapy; and (4) second-line treatment with anti-TNF agents after the failure of cyclophosphamide and glucocorticoids.

Assessment of rheumatoid arthritis, vasculitis and anti-tumour necrosis factor treatment

A standard file was completed and the medical records of all patients were reviewed. A database was created with RA characteristics and description of vasculitis and treatment. Tolerance and adverse events were recorded.

The Birmingham Vasculitis Activity Score (BVAS) is a validated instrument that quantifies disease activity as the weighted sum of the defined manifestations, including the item arthralgia/arthritis.[15] Treatment response was evaluated clinically and with the modified BVAS for RA (BVAS/RA), corresponding to the BVAS, excluding the item arthralgia/arthritis. Complete remission of vasculitis was defined as the absence of all symptoms and clinical features of active disease and a BVAS/RA of 0. Partial remission was considered to have occurred if initial vasculitis activity had decreased by at least 50% but remained greater than 0. Active or relapsing disease was considered to be present if the patient displayed new vascular manifestations.

RESULTS

We collected a total of nine cases (five men and four women). The baseline demographic and clinical characteristics of the patients are shown in table 1. All patients presented refractory SRV. Necrotising vasculitis of the medium-sized arteries was documented in five patients and cutaneous

Table 1 Demographic and clinical characteristics of patients with systemic rheumatoid vasculitis refractory to conventional therapy and treated with anti-TNF drugs

Before anti-TNF treatment											After anti-TNF treatment						Last follow-up	
			Duration				At initiation of anti-TNF											
Patient	Sex	Age	RA (years)	Vasculitis (months)	Clinical manifestations	Past treatment for vasculitis	Clinical manifestations	Pred. mg/day	Other*	TNF agent initial dose	Outcome	Pred. mg/day	Other	No. of wk of anti-TNF therapy	Relapse (time to relapse)	Adverse events	Pred. mg/day	Duration of anti-TNF therapy
1	M	70	19	22	Bilateral necrotic leg ulcers; purpura; livedo; digital ischaemia; Several relapses; nerve: NV	Pred. 30 mg/day CYC IV 15 g in 10 mo Ilomedine	Uncontrolled second relapse of vasculitis: leg ulcers; mononeuritis multiplex	40	AZT	INF 3 mg/kg every 8 wk after S0, S2, S6	Complete remission	10	MMF	43	None	Oesophageal candidiasis†	8	Ongoing; follow-up of 15 mo
2	F	38	5	6	Mononeuritis multiplex; digital ischaemia; purpura; haematuria; Muscle: NV	Methylpred. 1 g ×3 days Pred. 75 mg/day CYC IV 5 g in 3 mo	Uncontrolled vasculitis: persistent neuropathy, haematuria; distal ischaemia	65	MTX	INF 5 mg/kg every 8 wk after S0, S2, S6	Complete remission	10	MTX	26	None	None	5	17 mo; follow-up of 49 mo
3	F	65	39	7	Necrotic leg ulcers; livedo; Skin: necrotic LV	Pred. 20 mg/day CYC IV 7 g in 6 mo	Uncontrolled vasculitis: New necrotic cutaneous ulcers	20	AZT	INF 5 mg/kg every 8 wk after S0, S2, S6	Complete remission	8	AZT	26	First at 8 mo: INF increased to 5 mg/kg/4 wks: remission in 2 mo; Second 3 mo after INF withdrawal: remission in 3 mo with INF resumption; Third under INF 5 mg/kg/6 wks	None	10	Ongoing; follow-up of 55 mo
4	F	47	3	12	Mononeuritis multiplex; weight loss	Methylpred. 0.5 g ×3 days Pred. 60 mg/day CYC IV 6.3 g in 6 mo AZT	Incomplete vasculitis remission	20	MTX	INF 5 mg/kg S0, S2	Not evaluable	10	MTX	2	None	Diffuse cutaneous reaction during INF‡	20	2 wk; follow-up of 5 mo
5	M	54	20	23	Deep leg ulcers; Skin: NV	Methylpred. 0.5 g ×3 days Pred. 60 mg/day CYC IV 4 g in 3 mo	Uncontrolled cutaneous vasculitis relapse: worsening necrotic ulcers	20	None	ETA 25 mg twice a wk	Failure to achieve remission	20	None	17	None	None	2	ongoing; follow-up of 13 mo
6	M	61	14	102	Chronic bilateral leg ulcers; polyneuropathy; Skin: NV	Methylpred. 1 g ×6 days CYC IV 12 g in 10 mo CSA; AZT; MTX; LEF	Uncontrolled vasculitis: persistent ulcers	20	None	INF 5 mg/kg every 8 wk after S0, S2, S6	Incomplete remission: ulcers almost healed	10	None	39	13 mo: aggravation of ulcers	None	7.5	15 mo; follow-up of 27 mo
7	M	60	36	5	Mononeuritis multiplex; uveitis	Pred. 60 mg/day CYC IV 5 g in 4 mo	Uncontrolled vasculitis: no improvement	40	CYC IV 9 g in 9 mo	ETA 25 mg twice a wk	Complete remission	15	None	30	None	Cutaneous staphylococcaemia†	5	Ongoing; follow-up of 64 mo

Continued

Table 1 Continued

Patient	Sex	Age	Duration RA (years)	Vasculitis (months)	Clinical manifestations	Past treatment for vasculitis	At initiation of anti-TNF: Clinical manifestations	Pred. mg/day	Other*	TNF agent initial dose	Outcome	After anti-TNF treatment: Pred. mg/day	Other	No. of wk of anti-TNF therapy	Relapse (time to relapse)	Adverse events	Last follow-up: Pred. mg/day	Duration of anti-TNF therapy
Before anti-TNF treatment																		
8	M	54	3	13	Mononeuritis multiplex; deep cutaneous ulcers (elbow, legs); toes ischaemia; livedo; Nerve: NV	Methylpred. 0.25 g ×2 days Pred. 70 mg/day CYC IV 6 g in 4 mo LEF	Uncontrolled vasculitis: new onset of mononeuritis; persistent deep ulcers; digital ischaemia; livedo	25	AZT	INF 3 mg/kg/8 wk until incomplete remission (5 mo); increased to 5 mg/kg/6 wk thereafter	Complete remission	8	AZT	52	None	None	3	ongoing; follow-up of 56 mo
9	F	64	6	77	Mononeuritis multiplex; purpura; periungueal vasculitis; fever; weight loss; Skin: LV	Methylpred. 1 g ×3 days Pred. 60 mg/day CYC IV 15 g in 10 mo AZT γ-globulins	Uncontrolled vasculitis: severe and persistent neurological and constitutional signs and symptoms; cutaneous vasculitis	16	AZT	INF 3 mg/kg every 8 wk after S0, S2, S6	Failure to achieve remission	10	AZT	22	None	Septicaemia (Listeria); severe sepsis (Staphylococcus) infectious pneumopathy‡ (Klebsiella, candida) with positive staining for PCP	12	5 mo; follow-up of 9 mo death due to severe physical and psychological distress after severe vasculitis and side effects

INF, infliximab; ETA, etanercept; CYC, cyclophosphamide; AZT, azathioprine; MMF, mycophenolate mofetil; MTX, methotrexate; Methylpred., methylprednisolone; Pred., prednisone; CSA, cyclosporin A; LEF, leflunomide; NV, necrotic vasculitis of the medium-sized arteries; LV, leucocytoclatic vasculitis; PCP, *Pneumocystis jiroveci* (ex *carinii*); TNF, tumour necrosis factor; IV, intravenously; mo, months; wk, weeks.
*In no case was another new agent added at the initiation of anti-TNF treatment. †Leading to a 2-month interruption of anti-TNF therapy. ‡Leading to the withdrawal of anti-TNF therapy.

leucocytoclastic vasculitis was reported in another two patients. Complete vasculitis remission had never been achieved in seven patients and the other two patients had experienced several relapses of vasculitis. The patients had received a mean of 1.8 immunosuppressants (range 1–5) for vasculitis, including cyclophosphamide and azathioprine. All patients presented progressive active vasculitis with mononeuritis multiplex (n = 7) and/or severe cutaneous vasculitis lesions (n = 6) despite treatment with a mean cumulative dose of 8.4 g (range 4–15) of intravenous cyclophosphamide over a mean of 6.2 months (median 6, range 3–10) and a mean initial daily prednisone dose of 50.6 mg (median 60, range 20–75).

Treatment with etanercept or infliximab was introduced as a second-line treatment. Etanercept was administered subcutaneously at a dose of 25 mg twice per week in two patients. The other seven patients received infliximab, at a starting dose of 3 mg/kg (n = 3) or 5 mg/kg (n = 4) intravenously, followed by infusions at weeks 0, 2, 6 and every 8 weeks thereafter. In only one patient was cyclophosphamide treatment continued once anti-TNF therapy had begun. No other disease modifying anti-rheumatic drug was associated. At the start of anti-TNF therapy, the mean BVAS/RA was 7.2 (median 5; range 3–15) and mean daily dose of prednisone was 29.6 mg (median 20; range 16–65) (fig 1).

The treatment and outcome measures of patients are summarised in table 2. After a mean of 28.6 weeks, remission was obtained in six cases (complete in five, incomplete in one). A failure to achieve remission was observed in one patient. Two patients withdrew from anti-TNF treatment due to side-effects. A diffuse cutaneous reaction occurred during the second infliximab infusion in one patient. Another patient presented *Listeria* septicaemia with *Staphylococcus* sepsis and bronchopneumonia caused by *Klebsiella*, *Pneumocystis jiroveci* and *Candida*. This led to the withdrawal of anti-TNF treatment. The patient died 4 months later whereas the vasculitis was not controlled. Two other infections occurred. Digestive candidiasis and cutaneous staphylococci led to the temporary suspension of anti-TNF treatment in one case each. At the 30-week evaluation, mean BVAS/RA was 2.6 (median 0; range 0–5) and mean prednisone dose was 11.2 mg/day (median 10, range 8–20), corresponding to a mean decrease of 18.3 mg/day (median 18; range 0–55) (fig 1).

Four cutaneous relapses were observed in two patients. Three relapses occurred during anti-TNF treatment and the fourth occurred 3 months after the withdrawal of anti-TNF treatment for complete vasculitis remission. Remission was obtained again within 3 months of the reintroduction of anti-TNF treatment in this case and within 2 months of increasing the frequency of

Figure 1 Individual Birmingham Vasculitis Activity Score for rheumatoid arthritis (BVAS/RA) and mean glucocorticoid dose before and after anti-tumour necrosis factor therapy.

Table 2 Treatment and outcome measures of patients with systemic rheumatoid vasculitis treated with anti-TNF agents as second-line therapy

Initial treatment for vasculitis	
Intravenous methylprednisolone (% of patients)	66
mean cumulative dose(g)	1.7 (median 1.5; range 0–6)
Prednisone (% of patients)	100
mean dose (mg/day)	50.6 (median 60; range 20–75)
Intravenous cyclophosphamide (% of patients)	100
mean cumulative dose (g)	8.4 (median 6.3; range 4–15)
mean duration (months)	6.2 (median 6; range 3–10)
Mean duration of vasculitis before anti-TNF therapy (months)	29.7 (median 13; range 5–102)
Mean total number of immunosuppressants before anti-TNF therapy	1.8 (median 1; range 1–5)*
Mean BVAS/RA at initiation of anti-TNF therapy	7.2 (median 5; range 3–15)
Mean prednisone at initiation of anti-TNF therapy (mg/day)	29.6 (median 20; range 16–65)
Anti-TNF therapy	
Infliximab (number of patients)	7
Etanercept (number of patients)	2
Mean duration of anti-TNF therapy at evaluation (weeks)	28.6 (median 32.5 ; range 2.2–52)
Outcome at evaluation (number of patients)	
Complete remission	5
Incomplete remission	1
Failure to achieve remission and/or side effects	3
Mean BVAS/RA score at evaluation after anti-TNF therapy	2.6 (median 0; range 0–13)
Mean prednisone dose at evaluation after anti-TNF therapy (mg/day)	11.2 (median 10; range 8–20)
Mean decrease in prednisone dose at evaluation after anti-TNF therapy (mg/day)	18.3 (median 18; range 0–55)
Mean total follow-up period (months)	32.6 (median 27; range 5–64)
Number of patients still being treated with the initial anti-TNF agent at final evaluation	5
Mean total duration of anti-TNF therapy at last follow-up (months)	26.7 (median 15; range 0.5–64)
Causes of anti-TNF therapy withdrawal (number of patients)	4
Complete vasculitis and articular remission	1
Vasculitis relapse while on anti-TNF therapy	1
Adverse events	2
Mean prednisone dose at last follow-up (mg/day)	8.1 (median 5; range 2–20)

TNF, tumour necrosis factor; BVAS/RA, Birmingham Vasculitis Activity Score for rheumatoid arthritis.
*In addition, one patient received intravenous immunoglobulins and another intravenous ilomedine.

infliximab infusions from 5 mg/kg every 8 weeks to 5 mg/kg every 4 weeks in another case.

After a mean total follow-up period of 32.6 months, eight of the patients are still alive and five are still being treated with the initial anti-TNF agent. Their mean prednisone dose is currently 8.1 mg/day (median 5, range 2–20) (table 2).

DISCUSSION

We report here the first series of patients with refractory SRV and the first study of anti-TNF treatment in these patients. Our results suggest that anti-TNF drugs may be effective in SRV after the failure of conventional therapy. This study is unique as it includes only patients with very severe disease in whom a previous course of cyclophosphamide and high-dose glucocorticoids had failed to induce remission in seven patients and had not led to sustained remission in another two patients. Despite the activity and severity of the vasculitis at the start of anti-TNF drug treatment, remission was achieved in two-thirds of patients, together with a significant and clinically relevant lowering of dose of glucocorticoids administered. Furthermore, remission was restored within 3 months of the reintroduction of infliximab in one patient who had a flare-up of vasculitis after the withdrawal of infliximab treatment and within 2 months of an increase in infliximab dose in another patient.

In this study, we used a modified activity score BVAS/RA, which appears to be an appropriate and simple tool to assess vasculitis activity in RA. We recommend using it in further SRV trials.

Our study has several limitations. The flaws inherent to retrospective studies include a lack of exhaustivity and of uniformity in record keeping and data acquisition. Given the low incidence of SRV and the rarity of refractory forms, it would have been difficult to conduct a prospective study. Most, if not all of the cases of SRV treated with anti-TNF drugs in France were included. The inclusion of patients with SRV refractory to cyclophosphamide and glucocorticoids gave a homogeneous group of patients, but it remains unclear whether the risk–benefit ratio would be similar if anti-TNF drugs were administered as a first-line treatment. However, for patients with severe refractory SRV, no alternative treatment has yet been validated and the prognosis remains very poor. In a study of 32 patients with SRV, five (16%) patients were found to have a vasculitis refractory to corticosteroids.[2] After the initiation of cyclophosphamide treatment, a transient remission was induced in two of these patients but all five died within 3 years. The small number of patients included in our study may also be seen as a limitation. However, this study includes more patients than previously reported in all case reports of SRV patients treated with anti-TNF agents. Our patients also constitute the first series of patients with SRV refractory to conventional therapy to be studied. The high rate of response to TNF inhibitors was remarkable in these patients suffering from the most severe forms of SRV.

Anti-TNF treatment is known to have toxic side-effects. One patient presented a diffuse cutaneous reaction at the second infusion. Three developed infection leading to the definitive withdrawal of anti-TNF treatment in one case. It is unclear whether these infections would have occurred in the absence of anti-TNF treatment. As many patients with SRV who might potentially benefit from anti-TNF therapy receive concomitant glucocorticoid treatment or other immunosuppressive therapy, caution is required and the treating clinicians should remain vigilant so that any infections are rapidly detected and treated.

There is mounting evidence to suggest that TNF plays a central role in the pathophysiology of SRV. Anti-TNF agents have been shown to decrease cellularity and the expression of adhesion molecules, to deactivate the vascular endothelium and to modulate angiogenic vascular endothelial growth factor levels. Patients with SRV have been shown to have higher serum concentrations of TNF-α than patients with RA without vasculitis. Expression of TNF-α is increased in endothelial cells and perivascular cellular infiltrates in patients with SRV.[4] Furthermore, TNF-α is known to be a potent inducer of fractalkine (CX3CL1) in endothelial cells, which acts as an adhesion molecule. Serum levels of soluble fractalkine are significantly higher in patients with SRV than in patients with RA without vasculitis, and are correlated with vasculitis activity.[5]

In conclusion, because any randomised trial would be difficult to implement due to the rarity of this complication, the only way to come up with any conclusions on treatment with anti-TNF is by this sort of retrospective approach. This study provides

evidence of efficacy of anti-TNF therapy in adjunct to glucocorticoids for treating active refractory SRV after the failure of conventional therapy, including cyclophosphamide and high-dose glucocorticoids, although there is a high risk of infection in these severely ill patients.

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Competing interests: XM, XP and SS have been investigators of studies evaluating the role of anti-tumour necrosis factor therapy in rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis, which were partially funded by Immunex, Amgen and Abbott. XM, XP and SS have also been investigators of a study evaluating anti-tumour necrosis factor therapy in Sjögren syndrome, which was partially funded by Schering Plough.

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