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Prospective Study of TNFα Blockade with Infliximab in Anti-Neutrophil Cytoplasmic Antibody-Associated Systemic Vasculitis

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Abstract. Tumor necrosis factor α (TNFα) plays an important role in the pathogenesis of anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. TNFα blockade is a potential therapy for these disorders. Methods: An open-label, multi-center, prospective clinical trial in two subgroups was performed. Study I examined acute disease, either first presentation or relapse (Birmingham Vasculitis Activity Score [BVAS] $\geq$ 10; n = 16); study II examined persistent disease (BVAS $\geq$ 4; n = 16). Patients received infliximab (5 mg/kg) at 0, 2, 6, and 10 wk. Concomitant therapy in study I included prednisolone and cyclophosphamide. Study II patients continued their existing treatment regimens, with prednisolone tapered according to clinical status. Results: Mean age was 52.4 yr, 53% of the patients were female, and follow-up was 16.8 mo. Twenty-eight patients (88%) achieved remission (14 per study group). BVAS decreased from 12.3 (confidence interval [CI] = 10.5 to 14.0) at entry to 0.3 (CI = 0.2 to 0.9) at wk 14 ($P < 0.001$). C-reactive protein (mg/L) decreased from 29.4 (CI = 16.8 to 42.0) at entry to 7.0 (CI = 3.3 to 10.9) by wk 14 (P = 0.001). Mean prednisolone dose (mg/d) in study II decreased from 23.8 (CI = 15.0 to 32.5) at entry to 8.8 (CI = 5.9 to 11.7) at wk 14 (P = 0.002). There were two deaths and seven serious infections. Relapse occurred in five patients (three in study II) after a mean of 27 wk. Conclusion: TNFα blockade with infliximab was effective at inducing remission in 88% of patients with antibody-associated systemic vasculitis and permitted reduction in steroid doses. Severe infections were seen in 21% of patients, and despite continued infliximab, 20% of initial responders experienced disease flares. Infliximab is a promising new therapy for vasculitis both as a component of initial therapy and in the management of refractory disease. These results need confirmation in larger randomized trials.

The primary systemic necrotizing vasculitides are a group of life-threatening diseases that, untreated, have an 85% 2-yr mortality. The best defined and most studied subgroup of these diseases are the anti-neutrophil cytoplasmic antibody (ANCA)-related small vessel vasculitides (AASV), which are characterized by a pauci-immune microscopic vasculitis and focal, necrotizing glomerulonephritis (1).

The introduction of steroids and cyclophosphamide results in disease remission in 80% of patients by 3 mo and in 95% by 6 mo (15). However, there is considerable morbidity related to current regimens, on which at least 25% of patients experience severe drug-related adverse effects. Furthermore, 50% of patients experience disease relapse, resulting in accumulating damage from disease scars and treatment (2,3,16). The addition of plasma exchange or pulsed methylprednisolone improves rates of renal recovery but increases the risk of side effects. There is a clear need to achieve more effective remission induction and to reduce therapy-related toxicity in AASV.

Evidence suggests that tumor necrosis factor α (TNFα) plays a central role in the pathogenesis of AASV in which ANCA activates neutrophils, leading to endothelial and vascular damage. TNFα facilitates damage by priming neutrophil and endothelial cells (4). There is both increased expression of TNFα at sites of vasculitic injury (5) and circulating levels of both TNFα and TNFα receptors during disease activity that normalize with disease remission (6,7). Furthermore, treatment with anti-TNFα therapy abrogates inflammation in an animal model of human renal vasculitis *in vivo* (8). Compassionate-use studies have reported improvements in disease activity in AASV using both the anti-TNFα monoclonal antibody infliximab (9–11) and the soluble p75 receptor etanercept. However, one short prospective study of etanercept in localized Wegener's granulomatosis (12) initially

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reported success in remission induction but was subsequently associated with relapse in 75% of patients.

We studied the safety and efficacy of TNFα inhibition with infliximab in the therapy of AASV for the control of disease flares (study I) and in the longer-term control of vasculitis in patients with persistent disease activity despite conventional therapy (study II).

Materials and Methods

Patients

This open-label, multi-center trial recruited patients from three centers in the United Kingdom. Eligible patients were those aged 18 to 85 yr with ANCA-associated small vessel vasculitis established according to the Chapel Hill definitions (13) and included patients with Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA). The Birmingham Vasculitis Activity Score (BVAS), a validated scoring index, was used to assess the degree of active vasculitis (14).

Eligible patients were entered into one of two studies. Study I (as adjuvant therapy for remission induction) examined patients with acute flares of AASV disease that were not immediately life-threatening (BVAS $\geq$ 10), either initial disease presentation or relapse. Typical clinical features associated with a positive ANCA or histopathological evidence of active necrotizing vasculitis had to be present. Study II (as additional therapy in persistent disease) examined patients with active AASV (BVAS $\geq$ 4) who had received at least 3 mo of combination therapy with prednisolone and either cyclophosphamide, azathioprine, or methotrexate before enrollment and had not achieved remission.

Exclusion criteria were as follows:(*1*) immediately life-threatening pulmonary manifestations of vasculitis; (*2*) untreated infection or previous tuberculosis; (*3*) cardiac failure; (*4*) pregnancy; or (*5*) leukopenia (white cell count $<$ 4000/μl). Patients were followed for 18 mo.

The local research ethics committee gave approval for the study, and informed, written consent was obtained from each participant. The investigations conformed to the principles outlined in the Declaration of Helsinki.

Treatment Protocol

Patients in both study subgroups initially received infliximab (5 mg/kg) intravenously at 0, 2, 6, and 10 wk. Study II patients achieving remission were invited to continue receiving infliximab at six weekly intervals for 1 yr. Concomitant therapy in study I was oral cyclophosphamide (2 mg/kg per d) for 14 wk and a reducing course of oral prednisolone. Patients in remission were then switched to a remission maintenance regimen of azathioprine (2 mg/kg) and prednisolone, unless intolerance or failure of azathioprine had been demonstrated, in which case mycophenolate mofetil was substituted. Azathioprine was tapered to 1.5 mg/kg at 1 yr. Antibiotic prophylaxis against both *Pneumocystis carinii* pneumonia (sulfamethoxazole/trimethoprim 480 mg three times per week) and fungal infection (oral fluconazole, nystatin, or amphotericin) was continued for 14 wk in patients receiving cyclophosphamide. In study II, patients continued their existing regimens with prednisolone tapered according to clinical status.

Assessment of Disease Activity

The definitions for refractory disease, remission, and relapse as well as the use of BVAS were adopted from the criteria used in therapeutic trials of the European Vasculitis Study Group (15). The primary end points of the study were (*1*) induction of remission (BVAS $\leq$ 1); (*2*) time taken to achieve remission; and (*3*) safety and tolerability measured in terms of the incidence of infusion reactions, infections, and other reactions during the study period.

Biochemical Markers

Baseline demographic characteristics were recorded for each patient, and at each visit, venous blood was immediately centrifuged and the supernatant stored at −80°C for subsequent analysis. Highly sensitive C-reactive protein (CRP) was determined. In addition, serum creatinine, ANCA indirect immunofluorescence, and ANCA levels were also determined.

Statistical Analyses

All results are expressed as means ± 95% confidence intervals (95%CI). Data were analyzed using the SPSS PC statistical package (version 11). Group comparisons of continuous variables were made using *t* tests, and BVAS values were compared with the use of the Mann-Whitney *U* test. A *P* value of $<$0.05 was considered significant.

Results

Treated Patients

Thirty-two patients were enrolled, 16 in each study group. Disease subgroups included WG (n = 19) and MPA (n = 13). There was histologic confirmation of the diagnosis in 32 patients, and 31 (97%) had ANCA-positive immunofluorescence. Mean age at study entry was 52.4 yr (95%CI = 46.3 to 58.6), and 17 patients (53%) were female. Mean follow-up was 16.8 mo.

Study I (n = 16). Diagnoses included WG (n = 7) and MPA (n = 9). Mean age was 58.1 yr (95%CI = 49.1 to 67.0), and 63% of the patients were female. ANCA was positive in all 16 patients: c-ANCA/PR3 in 7 and p-ANCA/myeloperoxidase (p-ANCA/MPO) in 9. Eight patients were newly diagnosed, and 8 had an acute disease relapse; for the latter group, the mean disease duration was 7.0 yr (95%CI = 4.1 to 9.9). Previous treatment included prednisolone (n = 8) with a mean cumulative dose of 11.9 g (95%CI = 2.6 to 26.4), cyclophosphamide (n = 7) with a mean dose of 20.7 g (95%CI = 2.6 to 38.7), azathioprine (n = 4), and methotrexate (n = 1). Organ involvement at presentation included biopsy-proven renal disease (n = 13; mean creatinine 337 μmol/L [95%CI = 233 to 440]), pancreas (n = 1), lung (n = 3), and upper respiratory tract (ear, nose, and throat [ENT]) (n = 3). The concomitant cyclophosphamide dose was 114.3 mg/d (95% CI = 91.1 to 137.4) until 14 wk before substitution with azathioprine (n = 10) or mycophenolate mofetil (n = 3). The mean BVAS and CRP (mg/L) at entry were 17.1 (95%CI = 14.5 to 19.6) and 44.5 (95%CI = 24.4 to 64.5), respectively.

Study II (n = 16). Diagnoses included WG (12) and MPA (4). Mean age was 46.8 yr (95%CI = 38.3 to 55.3), and 50% of the patients were female. At entry, ANCA was positive in 13 patients (81%): c-ANCA/PR3 in 11 and p-ANCA/MPO in 2. Mean disease duration (years) and number of relapses were 10.0 (95%CI = 6.2 to 13.7) and 3.5 (95%CI = 2.0 to 4.9), respectively. Organ involvement at presentation included ENT (n = 10), eye (n = 4; retro-orbital granuloma [n = 3]), joint (n = 5), skin (n = 1), and neuropathy (n = 1). Concomitant therapy was continued at unchanged dosage with methotrexate (n = 4), azathioprine (n = 2), mycophenolate mofetil (n = 9), and co-

trimoxazole ($n = 7$). Previous disease-related treatment included prednisolone with a mean cumulative dose of 26.9 g (95%CI = 4.3 to 39.6), cyclophosphamide ($n = 15$) with a mean dose of 21.0 g (95%CI = 11.5 to 31), azathioprine ($n = 14$), methotrexate ($n = 8$), mycophenolate mofetil ($n = 9$), and anti-CD52 antibody (CAMPATH-1H) ($n = 7$). Fourteen patients (88%) continued infliximab at 6-wk intervals for 1 yr. At entry, mean BVAS, CRP (mg/L), and serum creatinine (μmol/L) levels were 10.3 (95%CI = 7.6 to 13.0), 14.3 (95%CI = 0.9 to 27.7), and 102 (95%CI = 82 to 122), respectively.

Efficacy

Remission. Twenty-eight patients (88%, 14 in each study) achieved remission (BVAS ≤ 1) at a mean time of 6.4 wk (95%CI = 5.9 to 6.8). BVAS decreased from 12.3 (95%CI = 10.5 to 14.0) at entry to 0.3 (95%CI = −0.2 to 0.9) at wk 14 ($P = 0.001$) (Figure 1A). Four patients failed to achieve remission. In study I, one patient died and one failed to respond to infliximab but is now in remission after CAMPATH-1H therapy. There were two treatment failures in study II; subsequently, one patient responded to rituximab and the other had a partial response to leflunomide.

Steroid Dose. The mean prednisolone dose (mg/d) decreased from 44.8 (95%CI = 34.3 to 55.2) to 12.9 (95%CI = 9.7 to 16.1) ($n = 14$) at wk 14 in study I ($P = 0.002$), and the total steroid dose received in the first 12 wk was 2.2 g (95%CI = 1.9 to 2.6). The steroid dose in 75% of study II patients was stable for 1 mo before enrollment and decreased from 23.8 (95%CI = 15.0 to 32.5) to 8.8 (95%CI = 5.9 to 11.7) ($n = 14$) at wk 14 ($P = 0.002$).

Laboratory Markers. CRP decreased from 29.4 mg/L (95%CI = 16.8 to 42.0) at entry to 7.0 (95%CI = 3.3 to 10.9) by wk 14 ($P < 0.001$) (Figure 1B). Mean creatinine (μmol/L) at entry in patients with renal involvement in study I ($n = 13$) was 337 (95%CI = 233 to 440) and decreased to 194 (95%CI = 143 to 246) at wk 14 ($P = 0.04$) and 193 (95%CI = 134 to 252) at 18 mo ($P = 0.05$).

Relapse. Of the 28 patients achieving remission, 5 (18%) experienced relapse of disease (2 in study I [16%] and 3 in study II [21%]) requiring a change in medication. Organ involvement in study II at the time of relapse included ENT ($n = 2$) at wk 8 and 28 and joint disease ($n = 1$) at wk 30.

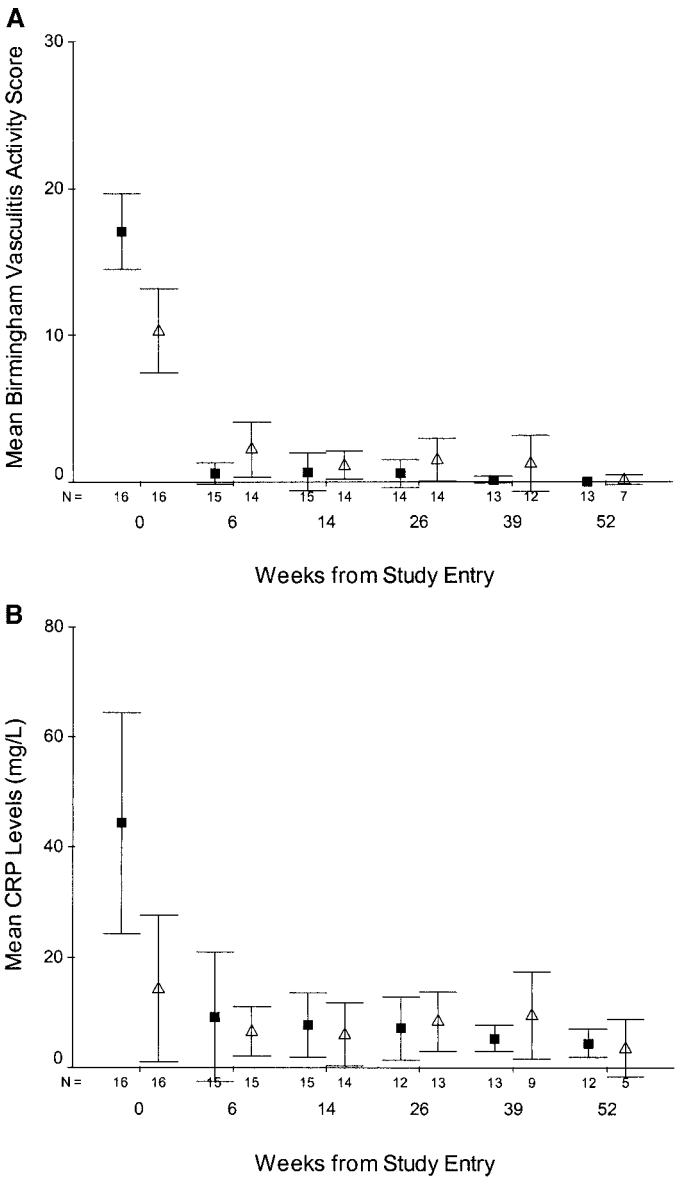

Figure 1. (A) Sequential Birmingham Vasculitis Activity Scores for study I (■) and study II (△) patients. Values are expressed as means ± 95% confidence intervals. (B) Sequential C-reactive protein (CRP) levels in study I (■) and study II (△) patients. Values are expressed as means ± 95% confidence intervals.

Safety

Reported adverse events are listed in Table 1. There were two deaths (6.7%), both among study I patients with ANCA/MPO-associated renal vasculitis: one caused by diffuse pulmonary hemorrhage attributed to pulmonary vasculitis, the other caused by bronchopneumonia associated with cyclophosphamide-induced leukopenia. Two patients in study I had infections requiring hospital admission: *Haemophilus influenzae* pneumonia on two occasions at wk 10 and 30, and recurrent *Klebsiella* urinary tract infections. Four patients in study II developed infections: recurrent *Staphylococcus aureus* skin abscesses ($n = 2$), an uncharacterized diarrheal illness ($n = 1$), and *Nocardia* endophthalmitis ($n = 1$) requiring evisceration of the eye. All four patients were receiving prednisolone (7.5 mg/d) and mycophenolate mofetil (1500 mg/d), and three had received cyclophosphamide (39 g) and CAMPATH-1H in the past. Lymphoma was diagnosed at wk 6 in one patient with relapsing WG in whom previous treatment included cyclophosphamide (26 g), azathioprine, mycophenolate mofetil, and methotrexate. This patient responded to standard chemotherapy, and both ANCA levels and inflammatory parameters normalized during treatment. Two thrombotic episodes were reported: an axillary vein thrombosis at study entry and a pulmonary embolus at wk 6.

Discussion

This study was designed to evaluate the safety and efficacy of infliximab as adjuvant therapy in both acute flares (study I)

Table 1. Reported adverse events

Study	Infliximab Doses (*n*)	Adverse Event		Comment/Treatment
		Time (wk)	Nature	
I	2	6	Death (pulmonary hemorrhage)	No infection discovered
I	4	18	Death (bronchopneumonia)	Leukopenia (white blood cell count 3.6/L)
I	4	10 and 30	Bronchopneumonia	Known bronchiectasis (*Haemophilus influenzae*)
I	4	10	Urinary tract sepsis	*Klebsiella* (creatinine 425 μmol/L)
II	8	39	Leg abcess	Surgical drainage required, (*MRSA* isolated)
II	7	30	Endophthalmitis	Evisceration of the eye (*Nocardia farcinica*)
II	8	39	Skin ulcer/urinary tract infection	*Staphylococcus aureus/Escherichia coli*
II	8	37	Diarrheal illness	Continued therapy
II	2	6	B cell lymphoma	Chemotherapy
I	2	6	Pulmonary embolus	Warfarin
I	1	0	Axillary vein thrombosis	Warfarin

[a] CHOP, chemotherapy, oncology, and pharmacology.

and persistent AASV (study II). The primary objective was the induction of remission, which was achieved in 88% of patients at a mean time of 6.4 wk. Importantly, 14 patients (88%) achieved clinical remission in the study II cohort, a group with persisting disease activity despite dual or triple immunosuppressive therapies. The prednisolone dose in 75% of this group was unchanged for at least 1 mo before enrollment, suggesting that infliximab alone was responsible for the observed remission induction. Furthermore, the clinical response in study II allowed a significant reduction in the prednisolone dose from a mean of 24 mg/d to 7.6 mg/d at 39 wk.

Relapse occurred in 20% of study II patients between 8 and 39 wk, indicating that a proportion of patients will escape from control with TNFα blockade. These patients were mainly c-ANCA-positive with ENT involvement. It is not known whether this is the result of a failure of infliximab to inhibit TNFα-mediated responses or of a switch to other cytokine pathways as drivers of pathogenesis. Infliximab was associated with rapid disease control in study I patients, which permitted early tapering of prednisolone and resulted in a 40% reduction in cumulative prednisolone dose compared with standard regimens (15).

Infliximab was generally well tolerated, with only one moderate infusion-related reaction. Of more concern was the incidence of infection, with seven patients requiring hospital admission (21%) and one infection-related death in a high-risk individual. The incidence of serious infections in the current study is similar to those reported for AASV using prednisolone and cyclophosphamide but higher than that reported for infliximab in rheumatoid arthritis patients (17–19). Previous immunosuppressive exposure was an additional risk factor in this study. Firm conclusions regarding the association of infliximab with infection cannot be made based on our findings. Both *in vitro* evidence and animal studies have suggested the importance of TNFα in the bactericidal activity of immune effector cells against organisms such as *Mycobacterium*, *Nocardia*, *Klebsiella*, and *H. influenzae* (20,21). Infections in study I occurred despite antibiotic prophylaxis; in contrast, all four infective episodes in study II occurred in the absence of antibiotics. Nevertheless, the pattern of organ involvement, the organism type, and the infection rates are consistent with the existing longer-term follow-up in other infliximab-treated autoimmune diseases. The need for increased vigilance for infection and the potential need for antibiotic prophylaxis in patients receiving infliximab are highlighted.

The mechanism by which infliximab is assumed to play a beneficial role in AASV is unclear. *In vitro* studies have shown the importance of TNFα in endothelial activation and neutrophil priming, which facilitates ANCA-mediated amplification of neutrophil-mediated local tissue destruction (5). Both increased circulating and increased tissue TNFα levels have been reported in active disease. For these reasons, blocking the effects of TNFα is of potential benefit in AASV. Furthermore, anti-TNFα antibodies have been shown to abrogate experimentally induced glomerulonephritis *in vivo* (8). Therefore, TNFα is a potential therapeutic target.

The *in vitro* studies suggest that infliximab may be a more effective binding agent to both soluble and membrane-bound TNFα than the soluble fusion protein etanercept (22). Clinical differences in efficacy and side effects of these two therapeutic agents for blocking TNFα exist in other autoimmune diseases such as Crohn's disease (23,24). Furthermore, the use of etanercept in patients with WG was associated with a high relapse rate in a study in which patients with vital organ dysfunction were not included (12). Infliximab has been administered previously to small numbers of patients with persistent or "refractory" disease in both organ-threatening and non-organ-threatening disease (9–11). It is for these reasons that infliximab was chosen in the current study, in which more than 30% of patients had renal involvement.

This preliminary study found that infliximab, in conjunction with prednisolone and an immunosuppressive agent, appears to be effective for remission induction in vasculitis. Its use may permit steroid sparing in both acute and persistent disease. The

possible increased risk of serious infection, especially with prolonged treatment, is of concern and requires careful study. We envisage three potential indications for infliximab in AASV: as a component of induction therapy to achieve more rapid and effective remission and salvage of vital organ function; as a steroid-sparing agent; and in the treatment of refractory vasculitis. Widespread use of infliximab in vasculitis must await support from further study in these areas.

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See related editorial, "Off-Label Use of Approved Drugs: Therapeutic Opportunity and Challenges," on pages 830–831.