

## LETTERS

# Adverse events in patients with rheumatoid arthritis treated with infliximab in daily clinical practice

N Neven, M Vis, A E Voskuyl, G J Wolbink, M T Nurmohamed, B A C Dijkmans, W F Lems

*Ann Rheum Dis* 2005;64:645–646. doi: 10.1136/ard.2004.028597

Infliximab is highly effective and relatively safe for the treatment of patients with rheumatoid arthritis (RA) in clinical trials.<sup>1–5</sup> This prospective cohort study was undertaken to determine adverse events, in particular, infections in patients with RA treated with infliximab in daily clinical practice.

## METHODS AND RESULTS

We treated 168 patients with RA between 1 April 2000 and 1 October 2002, 82% female, with a median disease duration of 10 years (range 1–49). Inclusion criteria were 28 joint count Disease Activity Score (DAS28) of >3.5 and failure of two disease modifying antirheumatic drugs, including methotrexate. Patients with heart failure or with a malignancy 5 years before screening were excluded. After the alert about tuberculosis,<sup>6</sup> patients starting with infliximab treatment were screened for that disease.

All patients were treated with an initial infliximab dose of 3 mg/kg (weeks 0, 2, 6, and subsequently, every 8 weeks). When the response was insufficient—that is, a decrease in DAS28 <1.2 compared with baseline on two subsequent occasions, the dose could be increased to 7.5 mg/kg. The median duration of treatment was 0.86 years (range 0–2.5); the median number of infusions used was 7 (range 1–18). Methotrexate and prednisone were used by 92% and 50% of the patients, respectively.

Patients were systematically asked about events and, explicitly, about infections at each visit. All events occurring during the infliximab treatment period were interpreted as adverse events.

The most common mild adverse event was short lived headache. Early allergic reactions were seen in 12 patients (0.08/patient-year), but none developed severe cardiopulmonary problems. Some cases of heart failure (n = 2), neuropathy (n = 1), and malignancy (n = 2) were observed. Two patients died during the study, one of a cerebrovascular accident and one of unknown cause.

Patients frequently (43–57%, depending on the definition used) had infections, most commonly from the upper respiratory tract and the lower urinary tract (table 1). One case of tuberculosis was seen. The number of clinically important infections was 0.59/patient-year, whereas serious infections were found in 0.08/patient-year.

Compared with patients receiving low dose infliximab, significantly (p < 0.05) more patients with the increased dose had clinically important infections (including serious infections), but other adverse events, demographic characteristics, and drug use between the groups were comparable. After correction for treatment duration with infliximab, the rate of clinical infections was significantly higher in the group receiving the increased dose. However, after correction for treatment duration, clinically important infections were not significantly more common in the group receiving the increased dose.

## DISCUSSION

Our study has shown that infection is the most common adverse event of infliximab treatment in daily practice. Clinical infections and clinically important infections were found more frequently in patients receiving high dose infliximab, without proven causality.

The occurrence of infections in our study is in the same range as that described in (randomised) clinical trials of infliximab.<sup>1 3 5 7</sup> However, the incidence of infection in our study was much higher than those described in a population based study of patients with RA not treated with infliximab, 64 versus 32 events per patient per year.<sup>8</sup>

There is evidence that a higher risk for infections occurs with a higher RA activity.<sup>9</sup> It is reasonable to suppose that patients with a dose increase had greater disease activity than those treated with only low dose infliximab. We are unable to comment on whether the higher incidence of infections is associated with a high disease activity or with the strong immunosuppressive action of infliximab, or both.

**Table 1** Occurrence of adverse events in 168 patients with RA treated with infliximab

Adverse events	3 mg/kg infliximab (n = 132)			3→7.5 mg/kg infliximab (n = 36)		
	No (%)	Events	Events/patient/year	No (%)	Events	Events/patient/year
Any adverse event	122 (73)	208	1.44	89 (67)	152	1.40
All infections*	96 (57)	153	1.06	69 (52)	109	1.01
Clinical infections†	72 (43)	93	0.64	50 (38)¶	65	0.41¶
Clinically important infections‡	60 (36)	85	0.59	42 (32)¶	59	0.55
Antibiotics (po)	50 (30)	74	0.51	35 (27)¶	51	0.47
Serious infections§	10 (6)	11	0.08	7 (5)	8	0.07

\*All infections defined as: objective and non-objective infections as reported by patient, clinical physician, or general physician, including unconfirmed upper respiratory tract infection and unconfirmed lower urinary tract infection; †clinical infections as considered present by a physician—that is, sinusitis, upper respiratory tract infection, pneumonia, pyelonephritis, bacteraemia/septicaemia, lower urinary tract infection, gastroenteritis, skin and soft tissue infections with relevant findings of physician; ‡clinically important infections as defined by objective infection, eventually requiring oral antibiotic treatment; §serious infection as defined by admission to hospital and/or requiring IV antibiotic treatment (in majority pneumoniae); ¶difference significant, p value < 0.05.

In conclusion, infliximab can be used safely in daily clinical practice, but both doctors and patients should be aware of the (infection) risks, especially in patients receiving a higher dose (>3 mg/kg) of infliximab, in order to anticipate and minimise these risks.

#### Authors' affiliations

**N Neven, M Vis, G J Wolbink, W F Lems**, Department of Rheumatology, Slotervaart Hospital, Amsterdam, The Netherlands  
**A E Voskuyl, B A C Dijkmans**, Department of Rheumatology, VU University Medical Centre, Amsterdam, The Netherlands  
**M T Nurmohamed**, Department of Rheumatology, Jan van Breemen Institute, Amsterdam, The Netherlands

Correspondence to: Dr A E Voskuyl, Department of Rheumatology 4A42, VU University Medical Centre, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands; ae.voskuyl@vumc.nl

Accepted 18 August 2004

#### REFERENCES

- 1 **Maini R**, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, *et al*. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999;**354**:1932–9.
- 2 **Lipsky PE**, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, *et al*. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000;**343**:1594–602.
- 3 **Elliott MJ**, Maini RN, Feldmann M, Kalden JR, Antoni C, Smolen JS, *et al*. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. *Lancet* 1994;**344**:1105–10.
- 4 **Harriman G**, Harper LK, Schaible TF. Summary of clinical trials in rheumatoid arthritis using infliximab, an anti-TNFalpha treatment. *Ann Rheum Dis* 1999;**58**(Suppl 1):i61–4.
- 5 **Kroesen S**, Widmer AF, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. *Rheumatology (Oxford)* 2003;**42**:617–21.
- 6 **Keane J**, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, *et al*. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001;**345**:1098–104.
- 7 **Fitzcharles MA**, Clayton D, Menard HA. The use of infliximab in academic rheumatology practice: an audit of early clinical experience. *J Rheumatol* 2002;**29**:2525–30.
- 8 **Doran MF**, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. *Arthritis Rheum* 2002;**46**:2287–93.
- 9 **Doran MF**, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. *Arthritis Rheum* 2002;**46**:2294–300.

## Fever and increasing cANCA titre after kidney and autologous stem cell transplantation for Wegener's granulomatosis

**T Daikeler, C Erley, M Mohren, C Amberger, H Einsele, L Kanz, I Kötter**

*Ann Rheum Dis* 2005;**64**:646–647. doi: 10.1136/ard.2004.029009

**W**egener's granulomatosis is a systemic vasculitis mainly affecting the lungs, nasal sinuses, and kidneys. Treatment usually consists of cyclophosphamide (Cy) and steroids.<sup>1</sup> High dose Cy with autologous stem cell support could be an alternative treatment for patients resistant to conventional treatment or requiring long term immunosuppression with the risk of secondary malignancy.<sup>2</sup>

#### CASE REPORT

We report on a 33 year old woman with chronic relapsing sinusitis, pulmonary granuloma, and proteinuria with progressive renal insufficiency since 1988. Renal biopsy showed necrotising glomerulonephritis, and biopsy of the nasal sinus showed granuloma with necrotising vasculitis. Proteinase-3-antineutrophil cytoplasmic antibodies (PR3-ANCA) were detectable with a titre of 1/280. Despite treatment with Cy (750 mg/m<sup>2</sup> every 3 weeks, later 100 mg/day orally) and steroids renal function deteriorated, and she underwent dialysis from April 1995 to December 1998. Live kidney transplantation from the patient's sister matched for HLA was performed in December 1998. Irrespective of ciclosporin A (CSA), which was given as prophylaxis for host versus graft reaction, she continuously needed immunosuppression with Cy (orally, 100 mg/day) because of persistent disease activity with relapsing pulmonary infiltrations. The transplanted kidney remained unaffected.

A cumulative Cy dose of over 100 g was reached and in view of the relapsing pulmonary granuloma and increasing PR3-ANCA titres, which in our patient correlated well with disease activity, stem cell mobilisation was performed in May 1999 with Cy 4 g/m<sup>2</sup> followed by granulocyte-colony stimulating factor 5 µg/kg for 10 days. Stem cell apheresis and selection of CD34+ stem cells was performed using the CliniMacs device on day 10. When PR3-ANCA titres increased from 1/128 to 1/500 after 4 months, high dose immunosuppression with Cy 50 mg/kg days 1–4 and ATG 5 mg/kg days 1–4, followed by retransfusion of 2.82 × 10<sup>6</sup> CD34+ cells/kg body weight was given. The conditioning regimen was chosen according to the protocol for aplastic anaemia.<sup>3</sup> Marked clinical improvement was seen with a regression of pulmonary infiltrates on chest x ray examination. Complete haematological reconstitution was achieved on day 12 after stem cell retransfusion. CSA was continued for renal graft protection.

Five months after high dose Cy, the patient was admitted with malaise, high grade fever, and pancytopenia. The PR3-ANCA titre was 1/1000, but computed tomography scans of the lungs and nasal sinuses were normal. An active Epstein-Barr virus (EBV) infection was diagnosed by serology (IgG and IgM). Polymerase chain reaction disclosed a high plasmatic viral load with 1 270 000 EBV transcripts per 100 ng genomic DNA. Treatment with intravenous ganciclovir and immunoglobulins led to resolution of all symptoms.