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

Infliximab is highly effective and relatively safe for the treatment of patients with rheumatoid arthritis (RA) in clinical trials. 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 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. 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.

There is evidence that a higher risk for infections occurs with a higher RA activity. 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

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>3 mg/kg infliximab (n = 132)</th>
<th>3–7.5 mg/kg infliximab (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events/ patient/year</td>
<td>Events/ patient/year</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>122 (73)</td>
<td>208</td>
</tr>
<tr>
<td>All infections*</td>
<td>96 (57)</td>
<td>153</td>
</tr>
<tr>
<td>Clinical infections†</td>
<td>72 (43)</td>
<td>93</td>
</tr>
<tr>
<td>Clinically important infections‡</td>
<td>60 (36)</td>
<td>85</td>
</tr>
<tr>
<td>Antibiotics (go)</td>
<td>50 (30)</td>
<td>74</td>
</tr>
<tr>
<td>Serious infections§</td>
<td>10 (6)</td>
<td>11</td>
</tr>
</tbody>
</table>

*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, bacteriemia/sepsis, 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 pneumonias); †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.

References


Authors’ affiliations

A E Voskuyl, B A C Dijkmans, Department of Rheumatology, VU University Medical Centre, Amsterdam, The Netherlands

M T Nurmohamed, University Medical Centre, Amsterdam, The Netherlands

N Neven, M Vis, G J Wolbink, W F Lems, Department of Rheumatology, Slotervaart Hospital, Amsterdam, The Netherlands

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

Accepted 18 August 2004

For personal use. Only reproduce with permission from BMJ Publishing Group Ltd

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 Köttér

Wegener’s granulomatosis is a systemic vasculitis mainly affecting the lungs, nasal sinuses, and kidneys. Treatment usually consists of cyclophosphamide (Cy) and steroids.1 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.2

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/m² 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 cyclosporin 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/m² 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 4 g/m², followed by granulocyte-colony stimulating factor 5 µg/kg days 1–4 and ATG 5 mg/kg days 1–4, followed by retransfusion of 2.82 x 10⁹ CD34+ cells/kg body weight was given. The conditioning regimen was chosen according to the protocol for aplastic anaemia.3 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.
Refractory adult onset Still’s disease successfully treated with anakinra

F M Vasques Godinho, M J Parreira Santos, J Canas da Silva

Proinflammatory cytokines like tumour necrosis factor α (TNFα), interleukin (IL) 6, IL18, and IL1 have been implicated in the pathogenesis of several chronic rheumatic inflammatory diseases, including juvenile idiopathic arthritis and adult onset Still’s disease (AOSD). The treatment of these diseases includes non-steroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids and, in resistant cases, methotrexate (MTX), cyclophosphamide, sulfasalazine, and ciclosporin A have been used. Over the past years, several cases of successful treatment with infliximab and etanercept in AOSD, refractory to conventional drugs, have been published.

CASE REPORT
We report a favourable response to anakinra in a patient unresponsive to several disease modifying antirheumatic drugs (DMARDs) and TNFα blockers, requiring chronic high doses of steroids. The patient is a 32 year old woman diagnosed at the age 18 with AOSD, defined by the criteria of Yamaguchi et al. She was treated with NSAIDs, systemic immunosuppression and autologous stem cell support. Five cases (including this one) are registered in the European Group for Blood and Bone Marrow Transplantation database. Intensive T cell depletion bears an increased risk of opportunistic infections as seen in our patient with an unusual course of an EBV infection. The increase of the PR3-ANCA titre during EBV infection fits the hypothesis that Wegener’s granulomatosis may be triggered by infectious agents and is supported by the findings of Mayet et al., who found cANCA production after transforming B cells in vitro with EBV.

**REFERENCES**


**Authors’ affiliations**

T Daikeler, C Amberger, H Einsele, L Kanz, I Kötter, Department of Rheumatology, Haematology, Immunology and Oncology, University Hospital Tübingen, Germany

C Erley, Department of Nephrology, University Hospital Tübingen, Germany

M Mohren, Department of Haematology, University Hospital Magdeburg, Germany

The first and last authors contributed equally to this work.

Correspondence to: Dr I Kötter, Department of Internal Medicine II, University Hospital, Offried-Müller-Str 10, D-72076 Tübingen, Germany; ina.koetter@med.uni-tuebingen.de

Accepted 18 September 2004

**FIGURES**

**Figure 1** PR3-ANCA titre and the number of EBV DNA copies before stem cell mobilisation May 1999, before stem cell transplantation (STX) September 1999, and during EBV infection.

The PR3-ANCA titre fell in parallel with the EBV viral load in plasma (fig 1). The patient remains in remission of Wegener's granulomatosis now 5 years after transplantation continuing treatment with low dose CSA (3 mg/kg body weight) and, later, mycophenolate mofetil (2 g) for host versus graft reaction prophylaxis. The CD3+, CD4+ T helper cells are still slightly lowered at 664 × 10⁶ cells/l and the CD4/CD8 ratio is reduced to 0.63. PR3-ANCA titres vary between 0 and 1/280, but have not consistently been negative (fig 1).

**DISCUSSION**

High dose immunosuppression with in vitro and in vivo T cell purging followed by autologous stem cell support was effective in our patient with severe, refractory Wegener's granulomatosis. It remains to be seen if disease remission continues after complete immune reconstitution. To our knowledge, this is the first reported case of refractory Wegener’s granulomatosis successfully treated with high dose immunosuppression and autologous stem cell support.
steroids, and several DMARDs (MTX, sulfasalazine, and ciclosporin A) over a period of 10 years, but she had sustained disease with frequent flares requiring high doses of steroids (up to 1 mg/kg/day).

At the age of 28, she was referred to our rheumatology unit with persistent fever, arthritis, anaemia, leucocytosis, and raised serum level of C reactive protein, erythrocyte sedimentation rate (ESR), and ferritin despite treatment with prednisolone 30 mg/day, naproxen 1 g/day, and MTX 20 mg/week. At examination she had six tender and six swollen joints and reduced range of motion of the neck, wrists, and hips. Screening tests for infection were negative. She was treated with intravenous immunoglobulin (2 g/kg) and prednisolone, and MTX was increased up to 25 mg/week subcutaneously (SC), but only showed a partial response. At 2 months’ follow up the patient reported difficulty in walking, with increased hip pain. A pelvic x-ray examination disclosed bilateral aseptic necrosis of the femoral heads and was admitted for total bilateral hip arthroplasty.

In October 2000 infliximab was added to her treatment, initially at a dose of 3 mg/kg and increased to 5 mg/kg. Six months later she continued to have fever, arthritis (19 tender and two swollen joints) and a raised ESR (117 mm/1st h); infliximab was discontinued. Treatment was changed to etanercept, 25 mg SC, twice a week for 54 weeks, with little clinical response. Throughout this period she continued to have intermittent fever, arthritis, and raised serological inflammatory markers.

In October 2002 it was decided to attempt anakinra 100 mg/day SC in addition to MTX 25 mg/week SC, prednisolone 20 mg/day, and naproxen. An impressive improvement of the systemic features and joint disease occurred over the first weeks of treatment and the acute phase reactants returned to normal. Steroids could be reduced and discontinued. Anakinra was well tolerated and no adverse effects were seen. After 18 months of follow up the patient remains in full clinical remission, without steroids or NSAIDs (table 1).

This is, to our knowledge, the first reported case of successful treatment of AOSD with anakinra.

**DISCUSSION**

Although TNFα antagonists have revolutionised the treatment of refractory AOSD, some patients do not respond to this treatment. The dramatic response to anakinra in this case of AOSD refractory to conventional treatments and to anti-TNFα blockers, suggests that the inhibition of IL1 may be an important therapeutic target in some patients.

**REFERENCES**


**Table 1 Clinical evolution of the patient**

<table>
<thead>
<tr>
<th></th>
<th>Infliximab</th>
<th>Etanercept</th>
<th>Anakinra</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (mg/l)</td>
<td>89 88 94</td>
<td>87 92 92</td>
<td>12.4</td>
</tr>
<tr>
<td>Leucocytes (×10³/μl)</td>
<td>18.3 26.3 26.0</td>
<td>17.1 23.6 23.6</td>
<td>8.1</td>
</tr>
<tr>
<td>ESR (mm/1st h)</td>
<td>112 120 117</td>
<td>120 107 112</td>
<td>13</td>
</tr>
<tr>
<td>Platelets (×10³/μl)</td>
<td>591 777 703</td>
<td>689 748 748</td>
<td>387</td>
</tr>
<tr>
<td>Fever</td>
<td>Yes Yes Yes</td>
<td>Yes Yes Yes</td>
<td>No</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Yes Yes Yes</td>
<td>Yes Yes Yes</td>
<td>No</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>Yes Yes Yes</td>
<td>Yes Yes Yes</td>
<td>No</td>
</tr>
<tr>
<td>PDN doses (mg/day)</td>
<td>40 30 30</td>
<td>15 20 20</td>
<td>0</td>
</tr>
</tbody>
</table>
Neuropathy associated with leflunomide: a case series

K Martin, F Bentaberry, C Dumoulin, M Longy-Boursier, F Lifermann, F Haramburu, J Dehais, T Schaeverbeke, B Bégaud, N Moore

Leflunomide is a new disease modifying drug (DMARD) recently licensed for treatment of rheumatoid arthritis. This isoxazole derivative is a prodrug for the active metabolite A77 1726, which has immunosuppressive properties. Leflunomide is now part of the therapeutic arsenal presently available for rheumatic disease, and its safety profile has been assessed by clinical trials and extended clinical trials. Among adverse peripheral nervous events, only paraesthesia has been reported. Nevertheless, 14 cases of peripheral neuropathy occurring during leflunomide treatment for rheumatoid arthritis have been reported to the regional pharmacovigilance centre in Bordeaux (table 1).

The cases include seven men and seven women. Mean age at the start of treatment with leflunomide was 69 years (range 57–78). Median duration of treatment at the onset of neuropathy was 7.5 months (range 3 weeks–29 months). Median duration of disease at treatment onset was 8.2 years (range 1–20). All patients had previously received a 100 mg loading dose of leflunomide for 3 days and were treated with a 20 mg daily dose. All patients presented with paraesthesia. A nerve conduction study demonstrated either motor or sensory axonal neuropathy in four cases and sensory axonal neuropathy in 10 cases.

All the patients were concomitantly receiving several drugs. Four patients were diabetic. In two cases, retinal angiography did not disclose any diabetic macroangiopathy. In two patients (Nos 5 and 10), aspecific vasculitis was diagnosed by neuromuscular biopsy when the neuropathy was explored. No biopsy was performed for the others patient. In three patients (Nos 1, 5, and 12) the pANCA were positive. None of these cases were treated concomitantly with other neurotoxic DMARDs. One patient (No 12) was concomitantly treated with infliximab. Two patients (Nos 6 and 10) concomitantly received a statin for a long period. Another patient (No 6) was treated concomitantly with almitrine, a known neurotoxic drug. Nevertheless, the neuropathy did not resolve after almitrine was discontinued but improved after leflunomide was stopped. The condition of patient No 12, whose neuropathy was related to previous use of thalidomide, worsened as soon as leflunomide was prescribed. In two patients (Nos 5 and 8) a previous diagnosis of neuropathy was present. Nevertheless, the peripheral nervous system event also worsened as soon as the DMARD was started, with a much shorter delay of onset than in the other cases. Other possible causes of neuropathy (metabolic or immune disorders, vitamin deficiency, neoplasia, viral and bacterial serology, etc) were ruled out in all cases. In half of the patients, the neuropathy improved after 3–6 months when leflunomide was discontinued (no nerve conduction study was performed). In the other patients, the neuropathy did not worsen.

Although paraesthesia is mentioned in the drug’s summary of product characteristics, we report here the first (as far as we know) case series of adverse peripheral nerve effects during leflunomide treatment. Although these neuropathies may be multifactorial, the individual cases (delay of onset of the neuropathy and improvement after the DMARD was stopped) seem to suggest that this drug may be neurotoxic.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (years)</td>
<td>64</td>
<td>64</td>
<td>66</td>
<td>68</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>72</td>
<td>72</td>
<td>72</td>
<td>74</td>
<td>74</td>
<td>75</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Duration of treatment before neuropathy onset (months)</td>
<td>5</td>
<td>1</td>
<td>10</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Diabetic mellitus</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>pANCA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Concomitant drugs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Improvement after stopping drug</td>
<td>Stabilisation</td>
<td>Stabilisation</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Stabilisation</td>
<td>Stabilisation</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Stabilisation</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Stabilisation</td>
<td>Improvement</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Characteristics of patients with suspected leflunomide associated peripheral neuropathy

*Letters 649

Characteristics 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Age at onset 64 64 66 68 70 70 70 70 72 72 72 74 74 75
Sex M F M M M M M M M M M M M
Duration of disease 3 5 5 7 7 7 7 7 7 10 10 10 10 10
Duration of treatment before neuropathy onset 5 1 10 15 15 15 15 15 15 15 15 15 15 15
Diabetic mellitus Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes
pANCA Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes
Concomitant drugs - - - - - - - - - - - - -
Outcome after stopping drug Stabilisation Improvement Improvement Stabilisation Improvement Improvement Stabilisation Improvement Improvement Stabilisation Improvement Improvement

www.annrheumdis.com
A report of only one other case has been published previously.10 To date, five other cases have been reported to the French pharmacovigilance system9 over a period of 2 years.

Carulli and Davies suggested that the neuropathy might be due to a neurological vasculitis induced by leflunomide.8 In the absence of a neuromuscular biopsy, this hypothesis could not be confirmed, but it is supported by a case report of cutaneous vasculitis induced by leflunomide without any neurological disorder.10 Moreover, two cases in this case series presented with aspecific vasculitis diagnosed by neuromuscular biopsy when the actiology of the neuropathy was explored.

Clearly, clinicians should be aware of the possibility of peripheral neuropathy in patients treated with leflunomide, especially when other risk factors are present. This does not detract from the usefulness of this drug in the treatment of rheumatoid arthritis.

**Authors’ affiliations**

K Martin, F Haramburu, Inserm U 657, Bordeaux, France; Centre Régional de Pharmacovigilance, Département de Pharmacologie, CHU de Bordeaux, 33076 Bordeaux, France  
F Bentaberry, C Dumoulin, J Dehais, T Schaeverbeke, Service de Rhumatologie, CHU, Bordeaux, France  
M Longy-Boursier, Service de Médecine Interne, CHU, Bordeaux, France  
F Lifermann, Service de Médecine Interne, CHG Dax, France  
K Martin, F Haramburu, B Bégaud, N Moore, Inserm U 657, Bordeaux, France; Département de Pharmacologie, IFR99, Université Victor Segalen, 33076 Bordeaux, France  
Correspondence to: Dr K Martin, Inserm U 657, IFR 99; MP2S, Département de Pharmacologie, Zone Nord, Bâtiment 1A, Université Victor Segalen – CHU, 33076 Bordeaux cedex, France; karin.martin@pharmaco.u-bordeaux2.fr

**References**


---

**Tumour necrosis factor α antagonists and early postoperative complications in patients with inflammatory joint disease undergoing elective orthopaedic surgery**

**S C Talwalkar, D M Grennan, J Gray, P Johnson, M J Hayton**

Tumour necrosis factor α (TNFα) antagonists are now established as therapeutic agents for active rheumatoid arthritis (RA) resistant to conventional drug treatment. However, they decrease resistance to infection, including unusual infections such as tuberculosis, and in an experimental setting have been shown to impair wound healing. Previous studies have shown that TNFα antagonists do not increase the risk of postoperative surgical complications in patients with Crohn’s disease who undergo resective bowel surgery, but the safety of these drugs in patients with RA who undergo elective orthopaedic surgery has not yet been established.

As over 10% of patients with RA at our institution receiving antirheumatic drugs still require some form of elective orthopaedic surgical intervention we carried out a retrospective study of patients who received anti-TNF drug treatment before elective orthopaedic surgery.

Depending on the complexity, operations were divided into major surgery, including joint replacement surgery and lower limb arthrodeses; minor cases, including day case surgery; drug stopped before surgery (days)  
- Drug restarted after surgery (days)  

**Figure 1** Time at which drug treatment was stopped and restarted.

---

Table 1 Complications

<table>
<thead>
<tr>
<th>Group</th>
<th>Complications</th>
<th>Type of surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n = 4)</td>
<td>2</td>
<td>Reflex sympathetic dystrophy</td>
</tr>
<tr>
<td>B (n = 12)</td>
<td>1</td>
<td>Medial malleolar fracture</td>
</tr>
<tr>
<td>B (n = 12)</td>
<td>1</td>
<td>Hip dislocation</td>
</tr>
</tbody>
</table>

and the remaining procedures, which were in an intermediate group.

Patient records were used to identify which anti-TNF antagonist was used. We reviewed 16 operations in 11 patients who had received an anti-TNF drug in the perioperative period. Patients comprised six women and five men with a mean age of 57.8 years (range 33–75). Of the patients studied, 10 had RA and one patient had psoriatic arthritis. The average disease duration from diagnosis was 17.6 years (range 6–27).

Two groups of patients were identified. Group A represented patients in whom anti-TNF drug treatment was continued in the postoperative period, whereas group B comprised patients for whom the drug was stopped before surgery and restarted after the procedure. In group A, infliximab was used in one operation, the patient receiving the injection 3 days before surgery while etanercept (Enbrel) was used in three patients. All the patients in group A underwent joint replacement surgery. Figure 1 shows when the different drugs were stopped and started with reference to surgery in group B. Infliximab, owing to its long half life and different administration schedule, was stopped at 2 weeks. The timings for restarting the drug were variable and depended on the preference of individual consultants.

Three patients had complications (table 1). The patient who underwent hip replacement surgery required revision surgery to correct the femoral stem and had an inpatient stay of 55 days. In the remaining patients who underwent major surgery the duration of stay was between 6 and 13 days, with an average of 10.6 days.

There was no serious wound or systemic infections in any of the patients on follow up. Postoperatively, one flare up occurred in a patient receiving etanercept in group B, who underwent a triple arthrodesis of the ankle. The flare up developed during the postoperative period and was well controlled once the drug was restarted.

In a previous similar study by the authors, the overall rate of complications and infections in the perioperative period was found to be 10% in 388 patients.7 In the present study none of the patients being treated with an anti-TNF antagonist developed infections. Although two of the three complications were in group A, these were not thought to be drug related. Therefore in this small study there is no evidence that anti-TNF drug treatment, whether discontinued or continued, increased either the rate of infection or the complication rate.

Authors’ affiliations
S C Talwalkar, M J Hayton, Department of Upper Limb Surgery, Wrightington Hospital, Manchester, UK
D M Grennan, Department of Rheumatology, Wrightington Hospital, Manchester, UK
J Gray, P Johnson, Clinical Trials Unit, Wrightington Hospital, Manchester, UK
Correspondence to: Mr S C Talwalkar, 508 Imperial Point, The Quoys, Manchester M50 3RA UK; stalwalkar@aol.com

Accepted 18 September 2004

REFERENCES


Cutaneous vasculitis developed in a patient with breast cancer undergoing aromatase inhibitor treatment

H Shoda, S Inokuma, N Yajima, Y Tanaka, K Setoguchi

Aromatase inhibitors are used in a newly introduced hormonal regimen for breast cancer. They reduce endogenous oestrogen production, and control the progression of oestrogen receptor positive breast cancer. Among aromatase inhibitors, anastrozole is a newly developed inhibitor. We treated a patient with cutaneous vasculitis

that developed during a therapeutic course of anastrozole for her breast cancer, in whom anastrozole was suspected to have had a role in inducing the vasculitis.

**CASE REPORT**

A 78 year old Japanese woman noticed a nodule in her left breast in November 2002. She had been taking a hydrogen blocker and antihypertensive drugs for many years. Breast cancer was cytologically diagnosed by aspiration biopsy, and her left breast was totally resected by the Auchincloss procedure in January 2003. No metastatic lesions were seen. The tumour cells were shown to be oestrogen receptor positive, and 1 mg of anastrozole daily was prescribed immediately after the operation.

She noticed a small patch of slightly oedematous itchy purpura in both her pretibial areas in April 2003. After scratching the purpura, an ulceration developed on her right leg in July 2003. Fibroblast growth factor spray was ineffective, and the ulceration increased to a diameter of 2 cm, with severe leg oedema; the purpuric lesion also progressed (fig 1A). A biopsy specimen obtained from her left pretibial purpuric lesion in September 2003 disclosed the infiltration of inflammatory cells, including lymphocytes and plasma cells, and karyorrhexis around small blood vessels in the dermis. Fluorescent antibody staining demonstrated IgA, IgM, and complements at the basement membrane of small blood vessels. No necrotising lesions were found (fig 1B).

After anastrozole treatment was stopped, purpuric papules, ulceration, and oedema all disappeared within 2 weeks without any additional treatment. The involvement of other organs, such as peripheral nerves, kidneys, and lungs, was not seen. Antinuclear antibody, antineutrophil cytoplasmic antibody, rheumatoid factor, and cryoglobulin were not detected. Sicca syndrome was ruled out owing to normal salivary and lachrymal secretions.

**DISCUSSION**

As far as we know, this is the first report that aromatase inhibitors may induce vasculitis. There have been some reports that hormonal drugs induce vasculitis. Tamoxifen, an oestrogen receptor antagonist, was reported to be a possible cause of cutaneous purpuric vasculitis. This past report suggested that inhibition of the oestrogen effect, which is the prevention of the pathogenesis of vasculitis, may in fact induce vasculitis. A case of frequent recurrences of Henoch-Schönlein purpura was reported when the contraceptive was discontinued and the authors suggested that inflammatory activity might be modulated by sex steroids. These three cases including our present case may be examples of endocrinal modulation of vasculitis. Vasculitis, in general, affects the elderly, also indicating hormonal involvement. This observation may be a clue to clarifying the pathogenesis and endocrinal modulation of vasculitis.

Because aromatase inhibitors are commonly used drugs, and vasculitis can be severe, clinicians should be aware of their association.

**Authors’ affiliations**

H Shoda, S Inokuma, N Yajima, Y Tanaka, K Setoguchi, Department of Allergy and Immunological Diseases, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

**Correspondence to:** Dr H Shoda, shoda-tky@umin.ac.jp

Accepted 25 August 2004

**REFERENCES**


Letters 653

Serositis (47% of patients with SLE from this area). We found that patients with RA have a higher prevalence and patients with SLE have a lower prevalence of β thalassaemia than a control group (19.8% and 9.8% vs 13.1%, respectively).

In this study we describe the clinical characteristics and laboratory findings of our patients with SLE with β thalassaemia and compare them with those of patients with SLE without β thalassaemia.

PATIENTS, METHODS, AND RESULTS

Among 177 consecutive patients with SLE (145 female, 32 male, mean age 54 years, range 20–89) born in the Ferrara and Rovigo areas and attending our institution between January 1998 and June 2003 we found 17 subjects with β thalassaemia (all female, mean age 53 years, range 20–88). Clinical and serological characteristics of these subjects were compared with those of 70 patients with SLE without β thalassaemia matched for sex, age, and disease duration coming from the same area.

Tables 1 and 2 show the demographic and clinical findings for patients with SLE with and without β thalassaemia.

The most remarkable findings were a greater prevalence in β thalassaemia patients of an associated Sjögren’s syndrome (SS) (71% vs 16%, p<0.0001) and a greater prevalence of central nervous system involvement (59% vs 21%, p<0.005), serositis (47% vs 17%, p<0.05), and renal disease (18% vs 4%, p<0.05). The laboratory data showed a greater prevalence of extractable nuclear antigen SSA antibodies in patients with β thalassaemia (71% vs 23%, p<0.0001) and persistently reduced (at least three consecutive determinations) C3 and/or C4 complement fractions (59% vs 27%, p<0.05).

DISCUSSION

The association between SLE and haemoglobinopathies has been poorly explored to date.

Sixteen cases have been reported describing the coexistence of sickle cell disease and SLE, but only Kaloterakis et al reported a case of sickle cell/β thalassaemia in a patient with SLE.

In this study we found a greater prevalence of an associated SS in patients with SLE and β thalassaemia than in those patients with SLE without β thalassaemia. The same finding has already been reported by Montecucco et al in patients with RA with β thalassaemia. Reasons for this association are at present unknown. Further studies of patients with different connective tissue disorders should be performed to exclude the possibility that the association is fortuitous.

In addition to SS, all major systemic complications were more prevalent in β thalassaemia patients with SLE. It is unclear whether the increased presence of SSA antibodies among those with β thalassaemia may have some role or whether a more severe disease with persistently reduced C3 and C4 levels is typical of patients with β thalassaemia. Both an increased incidence of atherosclerotic events (secondary to the chronic hypercoagulable state determined by the homocystinemia and a reduced ability to bind immune complexes have been described in β thalassaemia subjects and might be responsible for a more aggressive disease in these subjects.

In conclusion, in contrast with other systemic rheumatic diseases (RA, in particular), the prevalence of β thalassaemia in patients with SLE seems to be lower than in the general population. However, when the two conditions coexist, SLE seems to have a more severe course and to be more frequently associated with SS.

Table 1 Demographic data of patients with SLE with and without β thalassaemia

<table>
<thead>
<tr>
<th>Patients with SLE</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>With</td>
<td>Without</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=17</td>
<td>n=70</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>0/17</td>
<td>0/70</td>
</tr>
<tr>
<td>Age (years), mean (range)</td>
<td>53.4 (20–88)</td>
<td>52.8 (20–81)</td>
</tr>
<tr>
<td>Disease duration (years), mean (range)</td>
<td>9.5 (2–30)</td>
<td>9.2 (2–24)</td>
</tr>
</tbody>
</table>

Table 2 Clinical manifestations in patients with SLE with and without β thalassaemia

<table>
<thead>
<tr>
<th>Patients with SLE</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>With</td>
<td>Without</td>
<td>p Value</td>
</tr>
<tr>
<td></td>
<td>SSA</td>
<td>SSA</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>12 (71)</td>
<td>11 (16)</td>
</tr>
<tr>
<td>CNS</td>
<td>10 (59)</td>
<td>15 (21)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>3 (18)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>3 (18)</td>
<td>10 (14)</td>
</tr>
<tr>
<td>Haematological</td>
<td>3 (18)</td>
<td>24 (34)</td>
</tr>
<tr>
<td>Serositis</td>
<td>8 (47)</td>
<td>12 (17)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>7 (41)</td>
<td>23 (33)</td>
</tr>
<tr>
<td>Dyslipidosis</td>
<td>4 (24)</td>
<td>20 (29)</td>
</tr>
</tbody>
</table>

Authors’ affiliations

G Castellino, M Govoni, M Padovan, N Rizzo, F Trotta, Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Ferrara, Italy

www.annrheumdis.com
Feasibility of 1 hour infliximab infusions

R F van Vollenhoven, E Gullström, L Klareskog

Since 1 January 2003 we have changed our routine clinical practice and now give infliximab over 1 instead of 2 hours to those patients who have had at least three uneventful prior infusions (that is, did not experience infusion related side effects). To date, we have given 440 such infusions to 113 patients. Four infusions (0.9%) occurring in four different patients were associated with an adverse event: general infusion related symptoms rated as mild in two patients, tiredness rated as moderate after the infusion in one patient, and a sense of pressure over the eyes in one patient with prior open angle glaucoma. This last patient was subsequently examined by an ophthalmologist and ocular pressure was documented as normal. The pressure sensation resolved subsequently. The <1% incidence of infusion related adverse events compares favourably with the overall incidence of such events at our institution, which is about 5%; this is of course explained by our selection of patients with prior uneventful infusions.

We conclude that more rapid infliximab infusions over 1 hour, when given to patients who have tolerated at least three previous infliximab infusions without side effects, are tolerated well. Administering infliximab over 1 hour to such patients is a useful saving of time for both the patient and the healthcare provider.

Authors’ affiliations
R F van Vollenhoven, E Gullström, L Klareskog, Department of Rheumatology, D2-1 Karolinska Hospital, Stockholm, Sweden

Correspondence to: Associate Professor R F van Vollenhoven, ronald.vannvollenhoven@ks.se
Accepted 21 October 2003