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 excluded. After the alert about trexate, Patients with heart failure or with a malignancy disease modifying antirheumatic drugs, including methotrexate. Patients with RA treated with infliximab in daily clinical practice. All 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 = 3), and malignancy (n = 1) 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>
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</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) 208 1.44</td>
<td>96 (57) 153 1.06</td>
</tr>
<tr>
<td>Any infections*</td>
<td>96 (57) 153 1.06</td>
<td>69 (52) 109 1.01</td>
</tr>
<tr>
<td>Clinical infections†</td>
<td>72 (43) 93 0.64</td>
<td>50 (38) 65 0.41‡</td>
</tr>
<tr>
<td>Clinically important infections‡</td>
<td>42 (27) 59 0.59</td>
<td>42 (27) 59 0.59</td>
</tr>
<tr>
<td>Antibiotics (po)</td>
<td>50 (30) 74 0.51</td>
<td>35 (27) 51 0.47§</td>
</tr>
<tr>
<td>Serious infections§</td>
<td>10 (6) 11 0.08</td>
<td>7 (5) 8 0.07</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; †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**


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 50 mg/kg days 1–4 and ATG 5 mg/kg days 1–4, followed by retransfusion of 2.82 × 10⁸ CD34+ cells/kg body weight was given. The conditioning regimen was chosen according to the protocol for aplastic anaemia. 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.

**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

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

**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/d) because of persistent disease activity with relapsing pulmonary infiltrations. The transplanted kidney remained unaffected.
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 dose 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.

**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. 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**


**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 infliximab and etanercept in AOSD, refractory to conventional drugs, have been published.

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**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 x 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).
steroids, and several DMARDS (MTX, sulfasalazine, and ciclosporin A) over a period of 10 years, but she had sustained 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.

**Table 1 Clinical evolution of the patient**

<table>
<thead>
<tr>
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<th>Infliximab</th>
<th>Etaanercept</th>
<th>Anakinra</th>
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</thead>
<tbody>
<tr>
<td>Haemoglobin (mg/l)</td>
<td>89</td>
<td>88</td>
<td>94</td>
</tr>
<tr>
<td>Leucocytes (×10^9/l)</td>
<td>18.3</td>
<td>26.3</td>
<td>26.0</td>
</tr>
<tr>
<td>ESR (mm/1st h)</td>
<td>112</td>
<td>120</td>
<td>117</td>
</tr>
<tr>
<td>Platelets (×10^9/l)</td>
<td>591</td>
<td>777</td>
<td>703</td>
</tr>
<tr>
<td>Fever</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>PON (doses mg/day)</td>
<td>40</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

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 she 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 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**

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

<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>
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<tr>
<td>Age at onset</td>
<td>64</td>
<td>64</td>
<td>67</td>
<td>59</td>
<td>61</td>
<td>57</td>
<td>69</td>
<td>73</td>
<td>61</td>
<td>70</td>
<td>72</td>
<td>69</td>
<td>75</td>
<td>59</td>
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<td>Sex</td>
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<td>F</td>
<td>M</td>
<td>F</td>
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<td>F</td>
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<td>F</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>F</td>
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<tr>
<td>Duration of disease</td>
<td>3</td>
<td>5</td>
<td>10</td>
<td>3</td>
<td>10</td>
<td>15</td>
<td>3</td>
<td>5</td>
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<td>11</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Neurological status</td>
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<td>Normal</td>
<td>Normal</td>
<td>Dysaesthesia</td>
<td>Normal</td>
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<td>Normal</td>
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<td>Normal</td>
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<td>Normal</td>
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<tr>
<td>Neurotoxic DMARDs</td>
<td>CNS SAN MSAN SAN MSAN MSAN SAN SAN MSAN SAN SAN SAN SAN SAN SAN</td>
<td></td>
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<tr>
<td>Diabetic</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>No previous or concomitant neurotoxic drug</td>
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<tr>
<td>Outcome after stopping drug</td>
<td>Improvement</td>
<td>Improvement</td>
<td>Stabilisation</td>
<td>Stabilisation</td>
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<td>Improvement</td>
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</tr>
</tbody>
</table>

* M, male; F, female; MSAN, motor and sensory axonal neuropathy; SAN, sensory axonal neuropathy; CNS, central nervous system; MSAN, motor and sensory axonal neuropathy; SAN, sensory axonal neuropathy; DMARD, disease modifying drug; pANCA, perinuclear antineutrophil cytoplasmic antibodies; WASHOUT, washout, 10 days cholestyramine after stopping leflunomide; Un, unknown; major concomitant drug: 1, corticosteroids; 2, non-steroidal anti-inflammatory drugs; 3, analgesics; 4, antiulcer drugs; 5, antihypertensive drugs; 6, antidiabetic drugs; 7, anticoagulant drugs; 8, vitamin D substances.
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.\(^1\) However, they decrease resistance to infection, including unusual infections such as tuberculosis,\(^2,3\) and in an experimental setting have been shown to impair wound healing.\(^4\) Previous studies have shown that TNFα antagonists do not increase the risk of postoperative surgical complications in patients with Crohn’s disease who undergo restorative bowel surgery,\(^5,6\) 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; and minor day case procedures.


Figure 1 Time at which drug treatment was stopped and restarted.
Letters 651

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.2 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.3 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.

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REFERENCES
naemia of varying degree is a quite common finding in systemic lupus erythematosus (SLE), but only rarely has an association with concomitant haemoglobinopathies and, in particular, \( \beta \) thalassaemia minor, been studied.

In Ferrara and Rovigo areas (the Po’ delta, in the north east of Italy) the prevalence of \( \beta \) thalassaemia is higher than in other parts of Italy (13.1% v 2.1%). We have previously studied the prevalence of this haemoglobinopathy in patients with rheumatoid arthritis (RA)\(^1\) and, subsequently, in patients with SLE from this area.\(^2\) We found that patients with RA have a higher prevalence and patients with SLE have a lower prevalence of \( \beta \) thalassaemia than a control group (19.8% and 9.8% v 13.1%, respectively).

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

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

DISCUSSION

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

Sixteen cases have been reported describing the co-existence of sickle cell disease\(^3\) and SLE, but only Kaloterakis \( et \ al \) reported a case of sickle cell/\( \beta \) thalassaemia in a patient with SLE.\(^4\)

In this study we found a greater prevalence of an associated SS in patients with SLE and \( \beta \) thalassaemia than in those patients with SLE without \( \beta \) thalassaemia. The same finding has already been reported by Montecucco \( et \ al \) in patients with RA with \( \beta \) thalassaemia.\(^5\) 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 \( \beta \) thalassaemia patients with SLE. It is unclear whether the increased presence of SSA antibodies among those with \( \beta \) thalassaemia may have some role\(^6\) or whether a more severe disease with persistently reduced C3 and C4 levels is typical of patients with \( \beta \) thalassaemia. Both an increased incidence of atherosclerotic events (secondary to the chronic hypercoagulable state\(^7\) or to the homocystinemia\(^8\)) and a reduced ability to bind immune complexes\(^9\) have been described in \( \beta \) 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 \( \beta \) 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 \( \beta \) thalassaemia

<table>
<thead>
<tr>
<th>Patients with SLE</th>
<th>With ( \beta ) thalassaemia</th>
<th>Without ( \beta ) thalassaemia</th>
</tr>
</thead>
<tbody>
<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 \( \beta \) thalassaemia

<table>
<thead>
<tr>
<th>Patients with SLE</th>
<th>With ( \beta ) thalassaemia</th>
<th>Without ( \beta ) thalassaemia</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sjögren’s syndrome</td>
<td>12 (71)</td>
<td>11 (16)</td>
<td>(&lt;0.0001 )</td>
</tr>
<tr>
<td>CNS</td>
<td>10 (59)</td>
<td>15 (21)</td>
<td>(&lt;0.005 )</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>3 (18)</td>
<td>3 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>3 (18)</td>
<td>10 (14)</td>
<td>NS</td>
</tr>
<tr>
<td>Haematological</td>
<td>3 (18)</td>
<td>24 (34)</td>
<td>NS</td>
</tr>
<tr>
<td>Serositis</td>
<td>8 (47)</td>
<td>12 (17)</td>
<td>(&lt;0.05 )</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>7 (41)</td>
<td>23 (33)</td>
<td>NS</td>
</tr>
<tr>
<td>Dyslipidosis</td>
<td>4 (24)</td>
<td>20 (29)</td>
<td>NS</td>
</tr>
</tbody>
</table>

G Castellino, M Govoni, M Padovan, N Rizzo, F Trotta

Authors’ affiliations

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**References**


4. Sjo¨gren’s syndrome 12 (71) 11 (16) <0.0001

5. CNS 10 (59) 15 (21) <0.005

6. Nephropathy 3 (18) 3 (4) NS

7. Thrombosis 3 (18) 10 (14) NS

8. Haematological 3 (18) 24 (34) NS

9. Serositis 8 (47) 12 (17) <0.05

10. Osteoporosis 7 (41) 23 (33) NS

11. Dyslipidosis 4 (24) 20 (29) NS
Feasibility of 1 hour infliximab infusions

R F van Vollenhoven, E Gullström, L Klareskog

Abstract
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 0.9% 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.

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