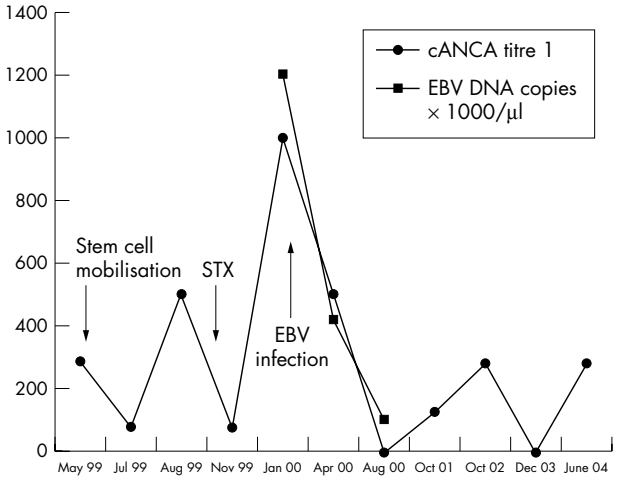

Figure 1 PR3-ANCA titre and the number of EBV DNA copies before stem cell mobilisation May 1999, before stem cell transplantation (STX) September 1999, and during EBV infection.

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 (2×1 g) for host versus graft reaction prophylaxis. The CD3+, CD4+ T helper cells are still slightly lowered at 664×10^6 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. 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[4] and is supported by the findings of Mayet *et al*,[5] who found cANCA production after transforming B cells in vitro with EBV.

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, Otfried-Müller-Str 10, D-72076 Tübingen, Germany; ina.koetter@med.uni-tuebingen.de

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Refractory adult onset Still's disease successfully treated with anakinra

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

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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).[1–5] 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[6–8] 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.[8 9]

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*.[10] She was treated with NSAIDs, systemic

Table 1 Clinical evolution of the patient

		Infliximab		Etanercept		Anakinra	
	Jun 2000	Oct 2000	Jun 2001	Aug 2001	Sept 2002	Oct 2002	Mar 2004
Haemoglobin (mg/l)	89	88	94	87	92	92	12.4
Leucocytes ($\times 10^9$/l)	18.3	26.3	26.0	17.1	23.6	23.6	8.1
ESR (mm/1st h)	112	120	117	120	107	112	13
Platelets ($\times 10^9$/l)	591	777	703	689	748	748	387
Fever	Yes	Yes	Yes	Yes	Yes	Yes	No
Arthritis	Yes	Yes	Yes	Yes	Yes	Yes	No
Arthralgias	Yes	Yes	Yes	Yes	Yes	Yes	No
PDN doses (mg/day)	40	30	30	15	20	20	0

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 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 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.

Authors' affiliations

F M V Godinho, M J P Santos, J C da Silva, Rheumatology Department, Hospital Garcia de Orta, Almada, Portugal

Correspondence to: Dr F M Vasques Godinho, Av Prof Torrado da Silva, Hospital Garcia de Orta, Almada, Portugal; fatima_godinho@hotmail.com

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