Figure 2 Changes to inflammatory markers and eosinophil count with rituximab (indicated by arrows)

precursors will abrogate ANCA production. However, we need to be aware of the concurrent risks of robust immunosuppression and predisposition to serious infections. Further research is warranted into the maintenance of remission and the long term safety with rituximab use.

Authors' affiliations

V V Kaushik, H V Reddy, R C Bucknall, Department of Rheumatology, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK
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Correspondence to: Dr V V Kaushik, vvkaushik@hotmail.com

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Successful treatment of refractory adult onset Still's disease with rituximab

K Ahmadi-Simab, P Lamprecht, C Jankowiak, W L Gross

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We read with interest the article by Aarntzen *et al*¹ reporting the inefficacy of anti-tumour necrosis factor (TNF) α inhibitor treatment with etanercept in adult onset Still's disease (AOSD).

We found that etanercept and also infliximab were ineffective in two patients with AOSD. Both patients were subsequently successfully treated with the monoclonal anti-CD20 antibody rituximab, targeting B cells. In both cases AOSD was diagnosed according to American College of Rheumatology criteria. Major symptoms were polyarthritis, fever, and typical skin lesions. Despite successive treatment

with prednisolone and methotrexate (MTX), ciclosporin, leflunomide, cyclophosphamide po, and intravenous immunoglobulin, the patients' AOSD remained active, with recurrent febrile episodes, rash, synovitis, a serum ferritin level of 6400 $\mu\text{g/l}$ (normal ≤ 200), and a mean C reactive protein level of 82 mg/l (normal < 8). Use of the TNF α inhibitors etanercept and infliximab (5 mg/kg intravenously (IV)) in one patient and etanercept in the other was also ineffective after treatment in combination with MTX for an adequate time. The average dosage of concomitant prednisolone required was > 30 mg daily.

Two weeks after stopping this immunosuppression we applied the monoclonal anti-CD20 antibody rituximab. Two rituximab infusions (375 mg/m² IV) plus a single additive dose of 100 mg prednisolone IV at 4-week intervals induced remission of polyarthritis and other symptoms in both cases. The concomitant oral steroid dose could be tapered from 50 mg to 5 mg oral prednisolone/day. FACS analysis of lymphocytes showed depletion of circulating B cells. The patients have remained in remission receiving either MTX or ciclosporin after a follow up period of 6 months.

AOSD is a rare systemic inflammatory disorder of unknown origin. The treatment of AOSD is often difficult. Non-steroidal anti-inflammatory drugs, steroids, and disease modifying antirheumatic drugs have been shown to be effective in the treatment of AOSD. Recently, two case studies reported the successful induction of remission with the interleukin 1 receptor antagonist anakinra in refractory AOSD.^{1,2} In addition to the patient reported by Aarntzen *et al*,¹ two of the six patients reported on by Fitzgerald *et al*² had been resistant to etanercept treatment. Anakinra rapidly induced remission in these three patients,^{1,2} whereas rituximab was effective in both of our TNF α inhibitor (etanercept and infliximab) resistant patients. Concomitant oral prednisolone dosages could be tapered to 5 mg/day and remission maintained with MTX and ciclosporin, respectively during follow up.

The report of Aarntzen *et al*¹ suggests that interleukin 1 rather than TNF α is important in the pathogenesis of AOSD. However, the range of disease manifestations and courses suggests considerable heterogeneity of the disease entity and its pathogenetic background.^{3,4} Lymphadenopathy is seen in 65% of patients. Lymph node lesions display distinct patterns. Paracortical hyperplasia may be combined with vascular proliferation, histiocytosis, diffuse T cell infiltration, plasma cells, and B immunoblasts.⁵ Lymph node lesions may be reminiscent of malignant T cell lymphoma.⁶ However, transition to malignant B cell lymphoma has also been reported.⁷ Therefore, B cells might represent another target of successful treatment in AOSD.

Our report suggests that B cell depletion with the monoclonal, chimeric, humanised mouse antibody rituximab may be another possible treatment for refractory AOSD. Our patients did not have any severe adverse events, especially no infections. Edwards *et al*⁸ reported a low rate of infections in their trial on rituximab treatment in MTX resistant

rheumatoid arthritis. Anakinra treatment has also been reported to be complicated by a low rate of infections (but with apparently less efficacy in rheumatoid arthritis than with TNF α inhibitors). However, some reports of serious infectious complications, such as septicæmia with anakinra treatment, have appeared.⁹ To our knowledge this is the first report of the successful induction of remission with rituximab in AOSD. Further studies are needed to determine the place of B cell depletion in AOSD.

Authors' affiliations

K Ahmadi-Simab, P Lamprecht, C Jankowiak, W L Gross, Department of Rheumatology, University Hospital of Schleswig-Holstein, Campus Luebeck, and Rheumaklinik Bad Bramstedt, Ratzeburger Allee 160, 23538 Luebeck, Germany

Correspondence to: Dr K Ahmadi-Simab, Germany; ahmadi@r-on-klinik.de

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Protective effect of pravastatin on vascular endothelium in patients with systemic sclerosis: a pilot study

S Furukawa, S Yasuda, O Amengual, T Horita, T Atsumi, T Koike

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In patients with systemic sclerosis (SSc), endothelial cell activation or damage in small vessels is followed by intimal hyperplasia and peripheral ischaemia.¹ Raised levels of plasma von Willebrand factor (vWF), thrombomodulin (TM), and other endothelial/thrombotic markers have been found in patients with SSc²⁻⁵; vWF is increased in plasma from patients with SSc with diffuse skin involvement and with severe disease, presumably correlating with disease activity.³

Besides a cholesterol lowering effect, statins exert non-lipid related mechanisms, so-called "pleiotropic effects", which may contribute to reducing risks of cardiovascular events. In this study the effect of a low dose pravastatin on markers of endothelial cell activation/injury and coagulation was investigated in patients with SSc.

This clinical trial was approved by the ethical committee of Hokkaido University Graduate School of Medicine, and all