Letters to the Editor

Rheumatology 2004;43:243–244

doi:10.1093/rheumatology/keg454

Long-term treatment of rheumatoid arthritis with tumour necrosis factor α blockade: outcome of ceasing and restarting biologicals

Sir, Infliximab, a chimeric monoclonal antibody, has demonstrated effective suppression of disease and prevention of the progression of structural damage in rheumatoid arthritis (RA) in its phase III randomized study (ATTRACT study) [1, 2]. Two anti-tumour-necrosis factor α (TNF-α) drugs, infliximab and etanercept, have recently been approved by the National Institute of Clinical Excellence [3].

With a large number of patients at a single centre for the ATTRACT study [1], the follow-up of our patients represents a special cohort of patients with RA who have received 2 yr of TNF-α blockade. Consequently, several questions arose regarding their long-term management, the most important being whether they would flare when anti-TNF-α treatment ceased and, if so, did the maintenance of response depend on the previous dose and response? Finally, the practical question of whether the drug could be restarted safely and effectively was addressed. This is of particular relevance because of concerns regarding the development of human anti-chimeric antibodies when infliximab treatment is interrupted. This study provides new insights into the strategy of long-term therapy with infliximab. This observational study was in accordance with our local ethics committee guidelines.

In the ATTRACT study, patients on methotrexate were randomized to placebo or one of four active treatment infliximab regimens (either 3 mg/kg every 4 or 8 weeks or 10 mg/kg every 4 or 8 weeks). Fifty to sixty per cent of patients on infliximab achieved the primary end-point of an ACR (American College of Rheumatology) 20 response. On completion of the ATTRACT study after 24 months, patients were continued on methotrexate alone. Subsequent relapse was defined as a 20% or greater deterioration in swollen and tender joint count and three out of the five other ACR criteria (composite score). On relapse, patients were recommenced on infliximab at the licensed dose of 3 mg/kg at weeks 0, 2 and 6, and then 8-weekly. The outcome was assessed 9 months after re-induction. Details of baseline disease activity before the ATTRACT study and at 2 yr on infliximab were collected to calculate ACRn (i.e. the ACRn response at the end of 2 yr). The 9-month ACRn after re-introduction of infliximab was assessed.

Of 24 patients who received infliximab as part of the ATTRACT study in Leeds, six dropped out on medical grounds or due to lack of efficacy, one died and 17 entered the 2-yr extension phase. All 17 flared after therapy was ceased at 2 yr. Mean time to flare varied between 13.5 and 15 weeks for the four treatment groups. Patients on the 10 mg/kg dose flared later than those in the 3 mg/kg group (not significant) (Fig. 1A). There was no relationship between time taken to flare and the degree of previous response.

Of the 17 patients, 15 were re-infused with commercially supplied drug and two chose alternative treatments. No infusion reactions or toxicity were observed with re-exposure to infliximab. The mean ACRn at 2 yr of the ATTRACT study and 9 months after re-introduction (on stable therapy) is summarized in Fig. 1B. Fifteen of the 17 patients were re-established on infliximab therapy at 3 mg/kg every 8 weeks (one patient’s results are not included as treatment stopped due to attempted pregnancy). On re-establishing therapy, the ACR response on infliximab was comparable in 12/14 patients and worse in only two. No adverse reactions were observed.

This study primarily addressed the question of whether anti-TNF treatment for RA needs to be continued in the long term in a group of patients with established RA. A special group of responding patients had received 2 yr of infliximab therapy, three-quarters of them receiving a dose (maximum 10 mg/kg 4-weekly) higher than that licensed. These patients should have had the best chance of a profound modification of the underlying inflammatory disease. In the event, all relapsed, albeit with a slight delay in those who had previously received a higher dose of drug. According to infliximab’s pharmacokinetic profile, this would be approximately 6 weeks after clearance of the drug.

Other questions were answered by the study namely despite concerns regarding intermittent therapy, all those patients resuming therapy after a prolonged gap did so without adverse reactions. Furthermore, the response was comparable, although these patients were started with an induction regime, which gives a higher dose for the first 6 months. For this reason the assessments were made at 9 months in the stable phase.

In conclusion, in established RA, responding patients require ongoing therapy to maintain their response in the long term. Hence, anti-TNF-α therapy provides immunosuppression rather than immunomodulation. It is noted that the drug can be restarted after an interval of several months without observed problems.

The authors have declared no conflicts of interest.
Anti-CD20 monoclonal antibody (rituximab) for refractory autoimmune thrombocytopenia in a girl with systemic lupus erythematosus

Sir, Childhood-onset systemic lupus erythematosus (SLE) is a disease with considerable morbidity and mortality [1]. Treatment options, depending on the clinical expression of the disease, include non-steroidal anti-inflammatory drugs, hydroxychloroquine, corticosteroids and cytotoxic agents [2]. For immune thrombocytopenia in children corticosteroids, intravenous immunoglobulins, intravenous anti-D immunoglobulin and splenectomy are used [3].

After a 2-yr period with arthritis, lymphadenopathy and mucosal lesions on the hard palate, a 6-yr-old Caucasian girl developed thrombocytopenia and granulocytopenia. Bone marrow investigation showed no malignancy. However, she was found to have autoantibodies against erythrocytes, granulocytes and thrombocytes. Circulating antinuclear antibodies were present, but no antibodies to double-stranded DNA or cardiolipins could be detected. She was therefore diagnosed with systemic lupus erythematosus (SLE) and treated with oral corticosteroids, hydroxychloroquine and naproxen (15 mg/kg/day). Initially, there was a good response but thrombocytopenia persisted. Furthermore, the chronic corticosteroid treatment subsequently led to growth retardation and osteoporosis. A drop in thrombocyte count below 10 x 10^3/1 immediately followed tapering of corticosteroids. Next, monthly intravenous immunoglobulins (IVIG, 2 g/kg in 5 days) in combination with azathioprine (1–2 mg/kg/day) were provided, after which the thrombocyte count normalized.

At the age of 10 yr, magnetic resonance imaging (MRI) of the brain, made because of two generalized seizures, revealed a cerebral lesion. Despite subsequent treatment with oral corticosteroids (prednisone 2 mg/kg/day) and an increased dose of azathioprine (3 mg/kg/day), neurological symptoms recurred, indicating exacerbation of her cerebral SLE, which was confirmed by MRI. A stereotactic biopsy of a lesion showed reactive non-specific inflammation, excluding infection, malignancy and vasculitis. Subsequent treatment consisted of monthly pulses of methylprednisolone (MP) (30 mg/kg) and cyclophosphamide (750 mg/m²) for 6 months, followed by monthly pulses for another year. This was discontinued after 15 months because the next MRI revealed new cerebral lesions. In order to prevent further progression of cerebral lesions, autologous stem-cell transplantation was prepared. This procedure was postponed when a baseline MRI 6 months after cessation of all immunosuppressive therapy revealed clear improvement of nearly all lesions.

However, during the intensive immunosuppressive regimen for cerebral SLE, thrombocytopenia recurred and at the age of 13 yr splenectomy was performed. Reactive thrombocytosis and leucocytosis were observed for 3 months, after which normal counts were measured for 1.5 yr. At the age of 15 yr profuse bleeding from the gums and nose indicated a new episode of thrombocytopenia. Three daily pulses of MP (30 mg/kg) and high-dose IVIG (2 g/kg) had no effect.

As anti-CD20 monoclonal antibody (rituximab) has been reported to be successful in the treatment of autoimmune haemolytic anaemia in a patient with SLE [4] and in patients with chronic refractory idiopathic thrombocytopenic purpura [5], we initiated this treatment in our patient. After informed consent, 375 mg/m² rituximab was administered intravenously once a week for 4 weeks. Clemastine and hydrocortisone were given as premedication. No adverse reactions were observed and the treatment was well tolerated. Monthly IVIG was given at 400 mg/kg. Within 1 month after the first rituximab infusion, thrombocyte counts returned to normal values and remained so for 6 months. Platelet recovery is depicted in Fig. 1.

Rituximab has been used effectively and safely in autoimmune disorders. To our knowledge this is the first patient with juvenile-onset SLE who has been treated successfully with rituximab for refractory thrombocytopenia.

The authors have declared no conflicts of interest. There was no pharmaco-industrial support for the use of anti-CD20.

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Accepted 19 June 2003

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