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Case Report

Humanized Monoclonal Antibody Treatment in Rheumatoid Arthritis

VALERIE KYLE, JANET RODDY, GEOFFREY HALE, BRIAN L. HAZLEMAN, and HERMAN WALDMANN

Abstract. **A 41-year-old woman with active, seropositive erosive rheumatoid arthritis was treated with the humanized monoclonal antibody Campath 1H. She had not responded or developed side effects to myocrisin, sulfasalazine and penicillamine, and had not responded to inpatient bedrest and physiotherapy. There was a rapid clinical improvement within 24 hours of infusion, which was maintained for about 12–14 weeks after the infusion. The lymphocyte count was suppressed for 7 months after treatment. There were no significant side effects during or after treatment. No anti-Campath 1H response was detected. This preliminary study suggests humanized monoclonal antibody therapy may be of value in the treatment of rheumatoid arthritis. (*J Rheumatol 1991;*18:1737–8)**

Key Indexing Terms:
RHEUMATOID ARTHRITIS THERAPEUTICS
HUMANIZED MONOCLONAL ANTIBODIES

Monoclonal antibody (Mab) therapy in rheumatoid arthritis (RA) allows the targeting of specific cells or effector mechanisms believed to be important in the pathogenesis. Initial pilot studies using rat[1,2] and mouse[3] Mab have shown some benefit, though there has been concern that the development of human antimouse Mab may prevent retreatment[3-5]. This concern has been due to the risk of sensitization, and evidence suggests repeat infusions may be less effective. The development of humanized Mab[6] should minimize this risk. We report the beneficial effect of Campath 1H, a humanized Mab, against surface antigen CDW52 in a patient with RA.

Campath 1H is the humanized form of the rat Mab produced by fusion of the Y3 rat myeloma line with a spleen from a rat immunized with human T lymphocytes. The hypervariable regions of this rat antibody are then transplanted into normal human immunoglobulin (Ig) genes.

The Campath 1 antigen is present on the majority of, if not all, lymphocytes and monocytes[7].

CASE REPORT

A 41-year-old woman with active erosive RA for 6 years was admitted for treatment with Campath 1H. Written consent and ethical approval were obtained. She had not responded or had developed side effects to sulfasalazine, gold or penicillamine, and was taking naproxen only. At the time of the study she had persistent synovitis affecting most joints, with morning stiffness for 2 h, and had failed to improve after a period of inpatient bedrest and physiotherapy.

Twelve infusions of 2 mg Campath 1H in 500 ml normal saline were given over 4 h on Days 1 through 12. Pulse, blood pressure and temperature were recorded at 15-min intervals during the infusion, then every 2 h for 4 h afterwards. Her functional score was derived from the pain scores, sense of wellbeing and ability to cope with daily activities. These were all measured using a visual analog scale, 0 being normal and 10 maximal discomfort. Ritchie index, grip strength, and thermal index derived from themography were recorded daily during infusions and every 2–4 weeks for 4 months afterwards. The following laboratory tests were performed before treatment, daily during infusions and regularly in followup: full blood count including differential white cell count, erythrocyte sedimentation rate (ESR) (Westergren), C-reactive protein (CRP) (nephelometry) and rheumatoid factor (RF) (nephelometry). Ig, CD4 and CD8 levels, urea and electrolytes were measured and liver tests administered before and after treatment.

There were no significant side effects. There were no febrile episodes or cardiovascular effects during the Campath 1H infusion or over the subsequent 4 h. There was rapid clinical improvement, with a fall in Ritchie index from 26 to 9, a fall in functional score from 19.5 to 5.25, and a rise in grip strength (Figure 1). Morning stiffness decreased to 30 min and the thermal index fell. Functionally she was able to knit, walk more than 1 mile and sleep comfortably in any position for the first time in over a year. This improvement in function was maintained for about 12–14 weeks. Her symptoms were controlled with naproxen alone during this time. Laboratory data showed that the total lymphocyte count became undetectable after the second infusion. At 6 months posttreatment the lymphocyte count was still slightly below normal (1.05×10^9/l) and the suppression involved all T cell subsets, but the B lymphocyte count was normal. The total lymphocyte count returned to normal 7 months after treatment. During this time there was no clinical evidence of immunosuppression. The monocyte count had fallen from normal (0.415×10^9/l) to zero 2 days into treatment. One month after the final infusion it had returned to normal. RF fell within 2 days to ⅓ of the initial value and rose after 8 weeks to baseline levels. There was no significant change in ESR or CRP (Figures 2a and 2b).

From the Rheumatology Research Unit and Division of Rheumatology Addenbrooke's Hospital, Cambridge, United Kingdom.

V. Kyle, MD, MRCP, Lecturer in Rheumatology; J. Roddy, MD, FRCP, Clinical Research Fellow in Rheumatology, Rheumatology Research Unit; G. Hale, PhD, Director of Therapeutic Antibody Unit; B.L. Hazleman, MB, FRCP, Consultant Rheumatologist, Rheumatology Research Unit, Addenbrooke's Hospital; H. Waldmann, PhD, MRCP, Professor of Therapeutic Immunology, Department of Pathology.

Address reprints requests to Dr. B.L. Hazleman, Rheumatology Research Unit, Addenbrooke's Hospital, Cambridge, United Kingdom.

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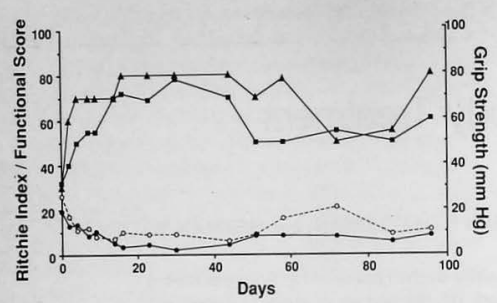

Fig. 1. Clinical course in patient receiving Campath 1H. Infusions were given on Days 1–12. The Ritchie index is used to assess joint inflammation. Grip strength R▲, L ■; functional score ●; Ritchie index ○.

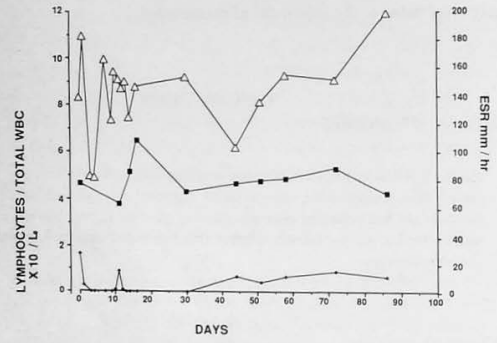

Fig. 2a. Laboratory variables in patient receiving Campath 1H. Total white blood cell count △, lymphocytes ◇, ESR ■.

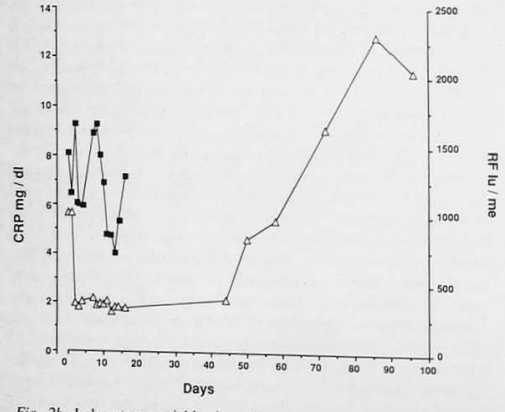

Fig. 2b. Laboratory variables in patient receiving Campath 1H. CRP ■, RF △.

No anti-Campath 1H response was detected. Ig levels before and after treatment were unchanged, with a polyclonal increase in IgA and IgG but normal IgM.

DISCUSSION

Earlier studies using lymphopheresis or T cell irradiation resulted in short term benefit in patients with RA. More recently, studies have shown benefit from treatment with Mab[8,9]. Campath 1H infusions caused destruction or removal of T lymphocytes from peripheral blood and were followed by sustained clinical benefit for 3 months. The fall in RF probably reflects loss of T cell cooperation in stimulating B cell production of RF. It is interesting that neither ESR nor CRP fell significantly despite the marked clinical improvement; this may have been due to established inflammation that was unaffected by T cell removal.

The development of humanized Mab such as Campath 1H should allow repeated infusions without the risk of sensitization or decreasing efficacy. No antibodies to Campath 1H were detected. There were no serious side effects following Campath 1H in our study or reported during treatment of patients with lymphatic malignancies[10]. Although lymphopenia can predispose to viral or fungal infections, this was not a problem in our patient.

Further studies of humanized Mab are warranted.

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