CONCISE REPORTS

Treatment of refractory juvenile chronic arthritis by monoclonal CD4 antibodies: a pilot study in two children

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Abstract

Objective—To study the effect of anti-CD4 treatment in patients suffering from refractory systemic onset juvenile chronic arthritis (JCA).

Methods—Two children were treated with the mouse CD4 antibody MAX.16H5. The effects on numbers of circulating CD4 T cells, clinical symptoms and C reactive protein (CRP) level were studied and the appearance of human antimouse immunoglobulin antibodies investigated.

Results—In patient one, disappearance of fever and malaise and a reduction of arthritic activity were observed together with a reduction in CRP. When disease activity returned eight weeks later, a second successful course of treatment was administered. It was possible to reduce the corticosteroid dosage permanently. In the other child, a first treatment cycle did not alter disease activity. A marked reduction in clinical and laboratory disease activity markers was observed after the second course. Only transient and mild side effects were observed. One patient exhibited a short lasting febrile reaction with chills, the other an urticarial rash. In both patients, human antibodies to mouse immunoglobulin became detectable. The decrease in the number of CD4 T cells in the peripheral blood was only short lasting and numbers returned to normal values within one to eight weeks, even after the second course of antibody treatment and under concomitant immunosuppressive treatment. No sustained clinical remissions could be achieved.

Conclusions—These preliminary observations support the evidence of positive effects of CD4 antibody treatment in refractory systemic onset JCA. Long term efficacy, however, remains to be established.

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CD4 positive T cells are thought to play an important part in the pathogenesis of rheumatoid arthritis (RA).¹ Use of monoclonal antibodies to CD4 therefore seemed promising, and more than 100 adult RA patients have been treated to date.^{2–7} Twelve

RA patients with refractory disease were treated with the CD4 antibody MAX.16H5, resulting in significant improvement in clinical and laboratory parameters (reported previously,³ and unpublished observations). Major side effects have yet to be observed. Concomitant immunological investigations demonstrated only transient depletion of CD4 T cells and monocytes.⁸ A possible mechanism of action of the CD4 antibody is the inhibition of T cell activation by blocking interactions between CD4 molecules on T cells and major histocompatibility complex (MHC) class II molecules on antigen presenting cells, thereby interrupting the physical association of T cell receptor and CD4 which is critical for T cell activation. This may lead to modulation of cytokine secretion, and indirectly also to modulation of antibody production. Furthermore, CD4 antibodies might reduce monocyte-macrophage activation, with a decreased secretion of proinflammatory cytokines.⁸ The results of the studies with MAX.16H5 in adult RA patients prompted us to use MAX.16H5 to treat two children with severe and active systemic onset juvenile chronic arthritis (JCA) in whom conventional treatments had failed.

Patients and methods

The study was approved by the ethics committee of the University of Düsseldorf. Written informed consent was obtained from both patients and their parents. The mouse monoclonal CD4 antibody MAX.16H5 (IgG1 isotype) had been prepared according to the procedures of the European Community Committee for Proprietary Medicinal Products⁹ and had been used previously in adults.³ It was diluted in a human albumin solution (0.2 mg/ml) and administered intravenously in a dosage of approximately 0.3 mg/kg body weight over a period of four to six hours every morning on seven consecutive days. As our experience with repeat treatment after six to eight weeks had given promising results in adult RA patients, the treatment was repeated eight weeks later in the two children.

Ritchie index¹⁰ and joint swelling were used to evaluate clinical response. The patients were questioned as to the duration of morning stiffness, and their global assessment of their condition was recorded by a 10 cm visual analogue scale (10 = bad ... 0 = good). All

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clinical examinations were performed between 09:00 and 10:00, by the same physician (UD). Routine laboratory tests included leucocyte counts and differential leucocyte counts, erythrocyte sedimentation rate, haemoglobin, biochemistry, immunoglobulins, C reactive protein, complement components, and urine analysis. For cellular immunological investigations, peripheral blood mononuclear cells were separated by standard Ficoll-Hypaque centrifugation methods.¹¹ Surface marker analysis of lymphocyte subsets was performed by direct or indirect immunofluorescence by flow cytometry using a Becton-Dickinson FACS-Scan. Human antimouse antibody activity was measured as described previously.¹²

Results

The table summarises details of the first patient—a 13 year old boy. JCA (known as juvenile rheumatoid arthritis (JRA) in the USA) was diagnosed according to the criteria of the JRA subcommittee of the American College of Rheumatology (ACR).¹³ He suffered from unremitting systemic onset JCA for two years. Perimyocarditis had occurred in the first year of the disease. Intermittent high grade fever, rash, and polyarthritis with marked synovitis could not be controlled by several immunosuppressive agents which had been given at commonly recommended doses for several months. Before receiving anti-CD4 treatment, the patient had intermittent increases in body temperature to 38°C while receiving 2 × 100 mg cyclosporin (5 mg/kg body weight) and 15 mg prednisolone (0.35 mg/kg) per day, which could not be reduced without provoking reappearance of high grade fever. After anti-CD4 treatment, the increased temperatures disappeared, as did the resting joint pain. A 50% reduction in the Ritchie index and disappearance of morning stiffness were noted at the end of the one week course of treatment. All clinical response criteria demonstrated clear benefit from the treatment and he tolerated prednisone 10 mg per day (0.23 mg/kg). When disease activity flared again eight weeks later, cyclosporin A was concluded to be totally ineffective and discontinued. A second anti-CD4 treatment was performed with an even better response compared with the first treatment (figure). Symptoms of systemic illness such as fever and

rash did not return during the next two months. CRP levels decreased from 157 mg/l to 37 mg/l in parallel with the response to the first treatment and increased again to 144 mg/l just before the second treatment, after which no significant change in CRP was observed.

The second patient was an 11 year old girl in whom systemic onset JCA began at the age of 30 months and proved resistant to conventional treatment (table). Because of recurrent fever, prednisone 0.3 mg/kg was introduced. Anti-CD4 treatment was added to a drug regimen that had included weekly methotrexate (15 mg/m²) for the past two years. Although a first treatment cycle had failed to improve her condition, a second course of anti-CD4 treatment was successful. A marked reduction of synovitis and joint tenderness, and an 80% decrease in Ritchie index were observed. Morning stiffness totally disappeared (figure). The steroid dosage was reduced a little (to prednisone 0.2 mg/kg daily). CRP levels decreased only moderately from 136 mg/l to 115 mg/l in response to treatment one and from 148 mg/l to 100 mg/l in response to treatment two.

After the first infusion of MAX.16H5, the number of CD4 T cells decreased markedly, from 1312/μl to 62/μl in the boy and from 1164/μl to 71/μl in the girl. Labelling of CD4 epitopes *in vivo* by the therapeutic antibody was demonstrated by staining with fluorescein isothiocyanate conjugated goat antimouse serum (data not shown). One day after the full treatment cycle had been completed the number of CD4 T cells was moderately decreased in the boy (720/μl), and low in the girl (96 cells/μl). Both the number of CD4 cells and the CD4:CD8 ratio returned to normal values (1155/μl and 1229/μl, respectively) within eight weeks. When the second course of treatment was given, again, there was a decrease in the number of CD4 positive cells with a return to normal values over a period of four to eight weeks. All changes were similar to those described in adults.³

Both first treatment courses were tolerated without side effects. After the first infusion of the second treatment course, the boy developed an urticarial rash, but further infusions were tolerated well. The girl had a sharp flare of fever up to 39.5°C with chills after the first antibody infusion of the second course of treatment, but tolerated

Details of two young patients with JCA, treated with CD4 antibody

	Patient 1	Patient 2
Age (years)/Sex/Weight (kg)	13/M/42	11/F/32
Duration of disease (years)	2	8
Disease presentation	Pericarditis, rash, intermittent fever, polyarthritis	Rash, intermittent fever, polyarthritis
Rheumatoid factor	Negative	Negative
Antinuclear antibodies	Negative	Negative
Previous DMARD treatment	Gold (weekly up to 1 mg/kg im), azathioprine (daily 3 mg/kg), methotrexate (weekly up to 15 mg/m ²), cyclosporin (daily 5–6 mg/kg), iv immunoglobulins (2 g/kg every four weeks)	Pulse steroids (iv 20 mg/kg on three consecutive days every four weeks), azathioprine (daily 3 mg/kg), methotrexate (up to 20 mg/m ² weekly), iv immunoglobulins (2 g/kg every four weeks)
Concomitant treatment	Diclofenac 3 × 25 mg, prednisone 15 mg (reduced to 10 mg§), cyclosporine 2 × 100 mg†	Naproxen 2 × 250 mg, prednisone 10 mg (reduced to 7.5 mg§), methotrexate 17.5 mg

DMARD = Disease modifying antirheumatic drug.

§Second course of treatment; †first course of treatment only.

Changes in clinical parameters of disease activity in patient 1 (○) and patient 2 (●), in response to treatment with CD4 antibodies, on seven study days during weeks 1 and 9 (arrows) after treatment. Patients were asked to mark a 10 cm visual analogue scale, between bad (10 cm) and good (0 cm) to indicate their assessment of their condition.

further infusions well. Human antimouse immunoglobulin activity could be detected in both patients after two treatment courses. There were no alterations in organ function, and no infections were observed either during treatment or during a six months follow up observation period.

Discussion

From our observations we conclude that treatment with CD4 antibodies is feasible in children with systemic onset JCA, with limited side effects. It led to a significant but transient reduction in CD4 cell count which lasted from a few days to some weeks but did return to normal values, even after a second course of treatment. There were immediate beneficial clinical effects of treatment in one patient, while in the other marked beneficial effects were achieved only by repeated treatment. These effects could not be attributed to longstanding treatment with immunosuppressants.

Both patients suffered from a highly active disease refractory to all conventional treatments previously applied. Disease activity required continuation of immunosuppression by cyclosporin or methotrexate. It is interesting to note that, even under these difficult conditions, the anti-CD4 treatment provided relief and clinical improvement by reduction in articular pain score, morning stiffness, and joint swelling for a limited period of time. In the first patient (the boy), fever disappeared even though the steroid dosage was reduced after anti-CD4 treatment. CRP levels were

reduced in both patients, indicating a systemic anti-inflammatory effect.³ We studied a third child who had 'adult type' RA and whose data provided a 'disease control' case. This 12 year old girl (data not provided) with primarily seronegative polyarticular JCA, received a single course of anti-CD4 after chloroquine, gold, azathioprine, and methotrexate had failed. This resulted in a decrease in Ritchie index (from 75 to 44), morning stiffness (from 120 to 15 minutes), number of swollen joints (from 23 to 13), and a considerable shift of disease assessment (7.2 to 3.8), comparable to effects observed after anti-CD4 treatment in adult RA patients. CRP levels decreased from 173 to 86 mg/l immediately after the treatment, but increased again four weeks later.

Although the small number of patients investigated does not allow definitive conclusions to be drawn from our study, observations suggest a transient clinical and serological response to the treatment. As our experience in adult RA patients was limited to a single repetition of the CD4 antibody treatment, both these child patients have since received another experimental treatment (cyclophosphamide pulse treatment).

It is important to note that in another study (presented to the ACR Meeting in 1994 by Bredfeld *et al*) using a different and humanised chimeric CD4 antibody in a placebo controlled trial in RA (not JCA) patients, the initial encouraging data could not be confirmed. Unfortunately, the initial anti-CD4 trials were performed with a panel of different CD4 antibodies and differing procedures and cannot easily be compared. However, none of these

observations can be applied to JCA because systemic onset JCA, in particular, is a different disease, which shares only a few similarities with RA.

In common with our previous experiences with anti-CD4 treatment, only occasional and minor side effects were observed which probably resulted from short lived cytokine peaks.¹⁴ Both patients developed small, but detectable amounts of human antibodies to mouse immunoglobulin, and these might have caused urticaria in the first patient. It may be that antimouse immune responses will prevent long term use of the antibody. A multicentre study of RA patients taking methotrexate has reported that treatment with a chimerised CD4 antibody⁷⁻¹⁵ can lead to longlasting depletion of CD4 cells. Further, there are reports on long term depletion of CD4 cells with these antibodies in patients who did not receive additional cytostatic drugs.⁶ The reduction in CD4 counts produced by MAX.16H5 was only transient; the counts returned to normal values even after repeated treatment and under additional medication by immunosuppressive drugs.

These preliminary observations provide supportive evidence of positive effects of anti-CD4 treatment in systemic JCA, but long term efficacy remains to be established.

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