SUPPRESSION OF FEVER AND THE ACUTE-PHASE RESPONSE IN A PATIENT WITH JUVENILE CHRONIC ARTHRITIS TREATED WITH MONOCLONAL ANTIBODY TO TUMOUR NECROSIS FACTOR-\(\alpha\) (cA2)

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SUMMARY

Juvenile chronic arthritis (JCA) is the most common chronic rheumatic disorder of childhood. Although conventional therapy of JCA continues to improve, many patients experience long-term ill health as a result of their disease or treatment. In adult rheumatoid arthritis (RA), similar concerns have led to the development of therapies designed to interfere in key disease processes. One such therapy is cA2, a chimeric neutralizing monoclonal antibody to the inflammatory cytokine, tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)). The administration of cA2 in adult RA has led to impressive short-term suppression of disease, with a good safety profile. Here, we report the first use of cA2 in childhood arthritis, choosing a patient with severe systemic-onset JCA, resistant to conventional therapies. The patient received two i.v. infusions of cA2, each at a dose of 10 mg/kg, separated by 1 week. The treatment was well tolerated and induced rapid control of fever, anorexia and serositis, together with downregulation of interleukin (IL)-6, soluble TNF receptors (sTNFR) and IL-1ra, and the acute-phase proteins C-reactive protein (CRP) and serum amyloid A (SAA). In contrast, we saw no significant improvement in joint pain or tenderness. Our findings suggest that TNF-\(\alpha\) is a mediator of fever and other systemic aspects of disease in systemic JCA. TNF-\(\alpha\) blockade as a treatment modality in JCA deserves further study.

KEY WORDS: Tumour necrosis factor, Juvenile chronic arthritis, Monoclonal antibody.

JUVENILE chronic arthritis (JCA) is the most common chronic rheumatic disorder of childhood. Although the prognosis for the young-onset pauciarticular subgroup is generally good, persistent destructive arthritis occurs in many patients with polyarticular or systemic-onset disease [1]. In these patients, there is a high risk of growth retardation and osteoporosis [2, 3], and children with a continuing high-level acute-phase response are at risk from secondary amyloidosis, with its associated morbidity and mortality [4].

Useful treatment modalities in systemic JCA include non-steroidal anti-inflammatory drugs (NSAIDs), which help in the management of articular disease and in the control of fever, and intra-articular and systemic corticosteroids, which are useful in the short-term treatment of arthritis and severe systemic disease episodes [3, 5]. Methotrexate is effective in suppressing polyarthritis in children [6] and may be efficacious in combination with pulse corticosteroids and cyclophosphamide in systemic disease [7]. Other ‘disease-modifying’ drugs which have been tested in controlled trials have been no more effective than placebo [3]. More effective and less toxic therapies for childhood arthritis need to be found.

In adult rheumatoid arthritis (RA), similar concerns about the success (or lack of) of standard therapy have led to the development of new therapeutic agents, designed to interfere in key disease processes. We have a particular interest in an inflammatory cytokine, tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)), and its role in the development and perpetuation of RA [8]. Using a chimeric (human/mouse) high-affinity neutralizing monoclonal antibody to TNF-\(\alpha\) (cA2) [9], we showed that in vivo blockade of TNF-\(\alpha\) was highly effective compared with placebo in suppressing joint disease [10, 11]. Although arthritis returned some weeks (or months) after single-dose treatment with cA2, we showed that repeated dosing led to repeated clinical responses, highlighting the potential for long-term disease suppression with this agent [12].

The role of TNF-\(\alpha\) in the pathogenesis of JCA is less well defined than in adult arthritis, but recent studies have started to address this question. Elevated circulating TNF-\(\alpha\) is seen occasionally in JCA [13, 14], but levels are higher in synovial fluid [13] and the cytokine is expressed in synovial fluid mononuclear cells [15]. Recently, one of us demonstrated elevations in circulating cytokines, including interleukin (IL)-1, IL-6 and TNF-\(\alpha\), in patients with systemic episodes of disease, with a rise and fall in circulating TNF-\(\alpha\) out of phase with the fever [16]. Soluble TNF receptors (sTNFR) have also been studied: p55 and p75 sTNFR were significantly elevated in serum samples from all JCA subgroups, particularly in those with systemic-onset disease, and levels correlated with disease activity [17, 18]. Taken together, these data indicate that TNF-\(\alpha\) is involved in the disease process in JCA, but

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provide little indication of its importance relative to the other cytokines and inflammatory mediators which have been studied.

Against this background, we were interested in testing the use of cA2 in chronic arthritis in children. Here we report the repeated administration of cA2 in a patient with severe, long-standing, systemic-onset JCA who was experiencing a prolonged systemic flare, unresponsive to high-dose corticosteroids.

CASE REPORT

The patient was a 16-yr-old Asian female with a 12 yr history of systemic-onset JCA. She presented in 1981 with arthralgia, an evanescent cutaneous rash and quotidian fever. Investigations revealed a mild anaemia, high serum IgM and a markedly elevated erythrocyte sedimentation rate (ESR). She was negative for rheumatoid factor. The patient was treated with aspirin and other NSAIDs, and subsequently with prednisolone with good effect. Further systemic episodes of disease in 1983 and 1984, with associated laboratory abnormalities, were successfully treated with short courses of prednisolone. Since 1984, the patient suffered with a chronic erosive polyarthritis affecting large and small joints, anaemia and abnormal liver function tests. Treatment included D-penicillamine, intra-articular corticosteroids, physical therapy and surgical procedures, including release of flexion contractures and bilateral total hip replacement.

Her current illness began in early 1994 while in hospital for physical therapy. She developed pharyngitis, cervical lymphadenopathy, an unproductive cough and features of a left basal pleuritis, together with myalgia, arthralgia, abdominal pain and fever. Investigations included a normal chest X-ray and white cell count, increased platelet count, but no other features of note. With the exception of a modest elevation of mycoplasma IgM antibody (1:80) early in the course of the illness, an extensive infection screen was negative. The patient was treated with i.v. benzyl-penicillin, then cefotaxime and finally oral erythromycin, with improvement in the upper respiratory symptoms.

Over the subsequent month, the clinical picture evolved to that of a systemic episode of JCA, with regular evening fever to 40°C, rash, marked anorexia with weight loss of ~20% of admission body weight, malaise, myalgia and arthralgia with prominent joint stiffness and features of serositis, including left basal pleuritis, pericarditis with typical electrocardiogram features and a small effusion on echocardiogram and abdominal pain, all showing evening exacerbation. Associated laboratory abnormalities included marked elevation of the acute-phase response and of liver function tests, anaemia, leucocytosis and thrombocytosis.

The patient was treated with high-dose oral prednisolone (up to 1.5 mg/kg/day) and i.v. methylprednisolone (two pulses of 25 mg/kg), NSAIDs including ibuprofen and diclofenac, i.v. immunoglobulin and nutritional support by nasogastric tube. These measures resulted in some improvement in the abnormal laboratory tests, but no significant clinical change in the systemic or articular disease over a period of several weeks.

In view of the severity of her disease and the failure of conventional management, the patient was considered on compassionate grounds for a trial of therapy with cA2. Approval was granted from the local research ethics committee. On transfer to the clinical trials centre, the patient was markedly unwell with polyarthritiis, polymyalgia, polyserositis, hepatitis, cachexia and quotidian fever to 41°C (Fig. 1). Her weight was 38.8 kg. The following abnormal laboratory tests were recorded: haemoglobin 8.8 g/dl (normal range 12–16); total white cell count 14 × 10³/l (4–11); neutrophil count 10.9 × 10³/l (1.8–7.7); ESR > 100 mm/h (15); C-reactive protein (CRP) 88 mg/l (10); serum IgM 4.2 g/l (0.5–1.9); albumin 19 g/l (33–47); alanine transferse 123 U/l (40). Rheumatoid factor, antinuclear antibody and antibodies to extractable nuclear antigens were negative; the 24 h urinary protein excretion was < 1 g; the HLA tissue type was DR3, 8, DRw52. Medication consisted of prednisolone 60 mg/day in two divided doses, dihydrocodeine 60 mg twice daily, ranitidine 150 mg twice daily, ferrous sulphate 200 mg three times a day, and vitamin and mineral supplements.

The patient was administered 10 mg/kg cA2 on day 0 and again on day 7. The antibody was diluted in 300 ml of normal saline and administered by a peripheral vein over 2 h. Changes and additions to other baseline medications are indicated in Fig. 1, and included the introduction of ibuprofen from day 6 and a reduction in the prednisolone dose from day 8.

Both cA2 infusions were well tolerated. Three days after the first infusion, the patient developed mild dysuria and urine culture revealed a growth of >100 000 lactose-fermenting coliforms. A urine specimen taken prior to treatment with cA2 had shown an insignificant growth (10–100 000 organisms) of the same organism. The potentiation of this urinary tract infection was judged to be possibly related to cA2, although high-dose prednisolone therapy and the patient’s relative immobility were probably contributing factors. The infection resolved following a 5 day course of trimethoprim. Six days following the first infusion, the patient developed mild peripheral oedema and 2 kg weight gain. The oedema resolved with elevation of the legs and the event was judged possibly related to cA2, but may also have resulted from the low serum albumin, together with immobility and ankle arthritis. No other adverse events were noted.

The clinical response to treatment with cA2 is illustrated in Fig. 1. The first infusion resulted in rapid and complete control of fever, albeit with a gradual loss of response after several days. Following re-treatment on day 7, the fever was again temporarily controlled, but by day 10 the pre-therapy fever pattern was re-established. Other clinical systemic features showing
improvement over this time included anorexia, chest and abdominal pain. In contrast to these findings, the tender joint count showed no significant change over the treatment period (Fig. 1). Other formal assessments of articular disease, including the severity of joint stiffness, joint pain, fatigue, the patient’s and physician’s assessment of global response (all measured on a 10 cm visual analogue scale), the patient’s and physician’s assessment of disease severity (assessed on a 5-point scale) and the grip strength, showed no significant change. In addition, the juvenile arthritis functional assessment report for children (JAFAR-C; [19]) showed no change over the treatment period (data not shown).

Blood samples for measurement of haematological and cytokine parameters were drawn on days –4, 0, 3, 7, 10, 14 and 17. The ESR fell from > 100 mm/h on day 0 to a nadir of 70 mm/h on day 3 (normal range <15). By day 14, the ESR was 76 mm/h. Changes in circulating CRP (measured by fluorescent polarization immunoassay; Abbot Diagnostics, Maidenhead) and serum amyloid A (SAA; measured by solid-phase ELISA; Biosource International, Camerillo, CA, USA) following treatment with cA2 are illustrated in Fig. 2A. The CRP showed a marked decrease following cA2, with a nadir of 16 mg/l (normal range <10) by day 7, but gradual loss of control thereafter. The SAA showed a similar reduction (nadir at day 7 of 145 mg/L, normal <10) although pre-treatment values had varied. By the end of week 3, the acute-phase parameters had reverted to pre-treatment levels.

Changes in circulating cytokines are illustrated in Fig. 2B. Immunoreactive TNF-α (measured by ELISA; Medgenix Diagnostics, Brussels, Belgium) was present at very low levels pre-treatment, but showed a marked increase following administration of cA2, with peak levels observed 7 days following each of the two infusions. In contrast, circulating IL-6 (measured by

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**Fig. 1.** Temperature chart and tender joint count (range 0–59) in a patient with a systemic episode of JCA. The timings of the two infusions of cA2 are indicated by the broken vertical lines. Changes in conventional anti-inflammatory treatments over the course of the study are shown beneath the figure.

**Fig. 2.** (A) Circulating CRP (normal range <10 mg/l) and SAA (normal range <10 mg/ml) in a patient with a current systemic episode of JCA. (B) Circulating TNF-α (normal range <10 pg/ml) and IL-6 (normal range <10 pg/ml) in the same patient. (C) Circulating sTNFR p55 (normal range <1000 pg/ml), sTNFR p75 (normal range <2000 pg/ml) and IL-1ra (normal range <375 pg/ml) in the same patient. The timings of administration of cA2 are indicated by the broken vertical lines.
ELISA; Medgenix Diagnostics) was high pre-treatment and showed a rapid decrease following the first infusion of cA2, with maintenance of the response thereafter.

Changes in circulating cytokine inhibitors are illustrated in Fig. 2C. p55 and p75 sTNFR (measured by ELISA; Medgenix Diagnostics) showed high values pre-treatment and marked decreases following the first infusion of cA2, maximal by day 10. A similar pattern was seen for IL-1ra. Other laboratory measures showing improvement following treatment included the circulating total white cell count and neutrophil count, which normalized by day 10, and serum alanine transferase which fell from 123 U/l at day 0 to 50 U/l by day 12 (normal range <40 U/l).

The subsequent clinical course was one of continuing disease activity. Weekly oral methotrexate at a dose of 15 mg/m² and subsequently 20 mg/m² was without effect after 3 months. A short course of the TNF antagonist oxypentiphylline was ineffective. The patient was therefore commenced on chlorambucil and improvement in her disease was seen after 6 months treatment at a dose of 7 mg/day. Eighteen months later, the patient is receiving chlorambucil 5 mg/day and prednisolone 80 mg/day, and is ambulant, but with residual ankle and knee synovitis.

**DISCUSSION**

This is the first report describing the use of a specific cytokine inhibitor in JCA. Administration of cA2 led to rapid and effective control of fever, supporting the notion that TNF-α is a key endogenous pyrogen in systemic JCA. The response to cA2 was of short duration and although the second infusion was associated with a second, brief reduction in fever, the interpretation of this change is rendered difficult by the changes in standard medications which were also made at this time (Fig. 1). TNF-α may be central to the development of fever in conditions other than JCA: the paroxysms of fever associated with *Plasmodium vivax* infection are preceded by peaks of circulating TNF-α [20] and administration of a murine monoclonal antibody to TNF-α (CB0006) in children with cerebral malaria (*Plasmodium falciparum*) resulted in a rapid decline in temperature, which persisted for at least 4 days [21]. The mechanism by which anti-TNF-α acts in either JCA or malaria has not been established: possibilities include a direct effect on TNF-α actions within the hypothalamus, or through inhibition of other pyrogens such as IL-6.

Although more difficult to quantify, the patient reported improvement in other systemic disease features, including pain from serositis and anorexia. The short duration of disease control and the development of fluid retention (see above) precluded meaningful interpretation of the small weight gain recorded. However, TNF-α is a classic mediator of cachexia and it is likely that effective long-term TNF-α blockade would be useful in the correction of malnutrition and growth retardation in JCA [22].

The serial laboratory studies show reduction in the ESR and acute-phase proteins CRP and SAA following the administration of cA2. Although several cytokines contribute to the development of the acute-phase response, IL-6 is of particular importance. Serum IL-6 is elevated in JCA, with most investigators noting a correlation between circulating levels and various indicators of disease activity [13, 14, 17, 23-26], and in systemic disease, levels rise and fall in parallel with the fever [16]. Measurement of circulating IL-6 in our case yielded very high baseline values (during a febrile episode), with rapid and sustained reduction following the first administration of cA2. Interestingly, both fever and the acute-phase response recurred on day 10 despite the continuing suppression of IL-6.

The pattern of change exhibited by TNF-α was the inverse of that for IL-6, with very low pre-treatment values and a rise following infusion of cA2. While the mechanism of this increase in TNF-α is still under investigation, the pattern is similar to that seen in adult RA patients treated with cA2 (Charles *et al.*, in preparation). In these patients, post-cA2 samples positive for TNF-α by ELISA have been consistently negative in TNF-α bioassays. Preliminary evidence suggests that the TNF-α is present in the form of a high-molecular-weight complex, possibly consisting of cA2 complexed to TNF-α or to TNF-α fragments, perhaps with contributions also from sTNFR. The rise in immunoreactive TNF-α in our JCA patient, therefore, is likely to represent trapping of TNF-α within the circulation by cA2.

The reductions in soluble cytokine inhibitors following the administration of cA2 in this patient also mirror those observed in patients with adult RA (Charles *et al.*, in preparation). It is clear that any beneficial effects which cA2 may have in systemic JCA occur in spite of downregulation of these endogenous inhibitors. The findings for IL-1ra are also consistent with previous observations by one of us, where IL-1ra was present at high level during febrile episodes in systemic JCA, and showed a rise and fall in parallel with the fever [16].

Despite transient control of systemic disease features, administration of cA2 did not result in an improvement in this patient’s arthritis. This is in marked contrast to the responses seen in adult RA, where rapid improvement in joint stiffness, pain and swelling is almost universal [10-12]. While the reason for this difference is not known, and while any conclusions drawn from a single case must be considered tentative, the data may indicate that TNF-α is a less important inflammatory mediator in the articular disease of systemic JCA than it is in adult RA. Alternatively, the explanation may lie in matters relating to the dose or scheduling of the cA2. It is noteworthy that even the systemic disease features were controlled for only about 10 days, despite treatment with a relatively high dose of cA2. The patient was catabolic, as evidenced by the significant weight loss she had experienced over the preceding 3 months, and it is possible that the administered cA2 was rapidly degraded as a result of her catabolic state.

This is the first report of the use of specific cytokine
blockade in childhood arthritis. Treatment with cA2 was well tolerated and provided temporary, albeit limited clinical benefit to the patient. Although our scientific conclusions must be considered tentative, the findings support the notion that TNF-z mediates fever and other systemic aspects of disease in JCA. The effective regulation of IL-6 and the acute-phase response by cA2 is of particular interest, and raises the possibility that long-term TNF-z blockade may be useful in the prevention or treatment of secondary amyloidosis.

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