Treatment of rheumatoid arthritis with interleukin 1 receptor antagonist

Barry Bresnihan

Rheumatoid arthritis (RA) is characterised by chronic synovial inflammation of multiple large and small joints in the upper and lower limbs. The pathogenesis of RA is complex and involves the activation of several synovial cell populations and the production of many proinflammatory and destructive mediators including cytokines, prostaglandins and proteases. Many investigators have suggested that tumour necrosis factor (TNF) and interleukin 1 (IL1) play a critical part in the pathogenesis of RA. The IL1 family includes IL1α, IL1β and IL1 receptor antagonist (IL1Ra). IL1α and IL1β are both agonist molecules that can influence the functions of most cell types by binding to the IL1 receptor (IL1R). In experimental models of arthritis IL1β causes exacerbation of disease, stimulates cartilage and bone resorption and inhibits the synthesis of articular collagen and proteoglycan. IL1Ra is responsible for the regulation of IL1α and IL1β by competitively binding with high avidity to IL1R. Thus, the level of target cell activation may depend on the balance between the agonistic effect of IL1α and IL1β and the inhibitory effect of IL1Ra, each competing for the same cell surface receptor.

IL1Ra has been given therapeutically in several experimental models of arthritis with dramatic effects. For example, IL1Ra was administered intraperitoneally by continuous infusion to male DBA/1 mice with collagen induced arthritis (CIA). This resulted in clear suppression of established arthritis. Histological analysis demonstrated markedly reduced cartilage destruction. Moreover, the synthetic function of articular cartilage chondrocytes fully recovered. Further studies of IL1 inhibition in experimental arthritis have confirmed the dominant role of IL1 in cartilage destruction and have established the hypothesis that optimal IL1 blockade will result in reduced joint inflammation and the prevention of progressive joint damage.

Further insights into the potential merits of IL1Ra treatment have been provided by studies of gene therapy. Thus, using the murine CIA model, fibroblasts transfected with the IL1Ra gene were transplanted into the knee joint cavity before the onset of arthritis. Arthritis was almost completely prevented in the joints containing IL1Ra producing cells. In contrast, joints containing normal cells demonstrated severe inflammation and cartilage destruction. Moreover, the onset of arthritis in the ipsilateral paws of the IL1Ra gene bearing knee joint was also prevented.

Interleukin 1 blockade in rheumatoid arthritis

SOLUBLE IL1 RECEPTOR

Both IL1α and IL1β mediate their biological activity through two specific membrane receptors, designated type I and type II. Soluble forms of both receptors have been detected in human body fluids. A recombinant soluble human form of type I IL1R (rHuIL1RI) was produced. Quantitative binding studies demonstrated that the affinity of rHuIL1RI was equivalent to the full length membrane bound IL1RI.

Twenty three patients were enrolled into a randomised dose ranging, double blind, placebo controlled study of rHuIL1RI, administered subcutaneously for 28 consecutive days. The doses were 125, 250, 500 or 1000 mg/m²/day. Treatment with rHuIL1RI resulted in a reduction of monocyte cell surface IL1α, which indicated that the doses used were functional. However, only one patient, who received the highest concentration of rHuIL1RI, demonstrated clinically relevant improvement, and dose limiting toxicity was observed in two. Further studies of treatment with soluble IL1R have not been reported.

IL1RA

Dose range study

One hundred and seventy five patients with active RA were enrolled in a randomised, double blind trial of recombinant human IL1Ra administered by subcutaneous injection. The study was divided into two phases. During the initial three week treatment phase, patients received IL1Ra 20, 70 or 200 mg once, three times or on several days per week. A second four week maintenance phase followed immediately when patients received their treatment phase dose once weekly. Treatment was generally well tolerated. Injection site reactions were the most frequently reported adverse event observed in 62% of patients. Only 5% withdrew prematurely because of an injection site reaction. Six per cent withdrew because of unsatisfactory therapeutic response. Dropout rates were similar across dose levels and dosing frequencies. Infections thought to be of bacterial origin were observed in 8% of patients who received IL1Ra 20 mg/day, 11% receiving 70 mg/day and 13% receiving 200 mg/day.

Because of the lack of a placebo arm and the multiple small treatment groups, a definitive statement regarding the efficacy of IL1Ra was not possible. However, at the end of the three week treatment phase daily dosing appeared more effective than weekly dosing when assessed by the number of swollen joints (p=0.0001, investigator (p=0.0002) and pa-
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Satisfied the Paulus criteria for a 20% four per cent of the IL1Ra 150 mg/day group significantly higher at 43% (p=0.014). Forty response in the IL1Ra 150 mg/day group was relatively high at 27%. However, the activity (p=0.012), pain VAS (p=0.001), HAQ (p=0.0006) and patient assessment of disease activity were similar in the treatment groups and were consistent with active and severe RA: mean number of swollen joints 25.6 to 26.6, number of tender joints 32.8 to 35.7, erythrocyte sedimentation rate (ESR) 46.8 to 53.2 mm 1st h, CRP 4.0 to 4.2 mg/dl. In each treatment group, between 69.0 and 76.5% of patients had radiographic erosions.

The primary outcome measure was the ACR 20% response. The response in the placebo group was relatively high at 27%. However, the response in the IL1Ra 150 mg/day group was significantly higher at 43% (p=0.014). Forty per cent of the IL1Ra 150 mg/day group satisfied the Paulus criteria for a 20% improvement (p=0.0003). Overall, those who received IL1Ra 150 mg/day demonstrated the maximal responses compared with placebo at 24 weeks: number of swollen (p=0.0009) and tender joints (p=0.0009), investigator (p=0.0006) and patient assessment of disease activity (p=0.012), pain VAS (p=0.001), HAQ score (p=0.0007), ESR (p=<0.0001) and CRP (p=0.0017). The clinical effect became apparent at approximately four weeks after starting treatment whereas the laboratory effects were evident at one week.

IL1Ra was generally well tolerated during the 24 weeks. As in the dose range study, the most frequent adverse event was an injection site reaction, experienced by 25% of the placebo group and by 50%, 73% and 81% of patients in the IL1Ra 30, 75 and 150 mg/day groups, respectively. The reactions were usually mild and transient. Only 2% of the placebo group withdrew from the study because of injection site reactions, compared with <1%, 3% and 5% of patients in the IL1Ra 30, 75 and 150 mg/day groups, respectively. Other adverse events were encountered infrequently and affected the placebo group as frequently as the IL1Ra groups. Thus, both the efficacy and the safety of IL1Ra was confirmed in a large cohort of patients with active and severe RA.

Randomised clinical trial

After the observations of the dose range study, a total of 472 patients were recruited into a randomised, 24 week, double blind, placebo controlled multicentre study. Patients were randomised into one of the four treatment groups: placebo or a single self administered subcutaneous injection of IL1Ra 30 mg, 75 mg or 150 mg/day. Patients ranged in age from 18 to 75 years and all met the American College of Rheumatology (ACR) criteria for the diagnosis of RA, had symptoms for >6 months and <8 years. The clinical parameters of disease activity were similar in the treatment groups and were consistent with active and severe RA: mean number of swollen joints 25.6 to 26.6, number of tender joints 32.8 to 35.7, erythrocyte sedimentation rate (ESR) 46.8 to 53.2 mm 1st h, CRP 4.0 to 4.2 mg/dl. In each treatment group, between 69% and 76.5% of patients had radiographic erosions.

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Effects on joint damage

Serial hand radiographs obtained immediately and after 24 weeks of treatment were available from 347 of the 472 patients (74%) entering the randomised clinical trial. Radiographs were analysed according to the Larsen method. The mean Larsen score in the placebo group increased by 6.4, from 15.4 at baseline to 21.8 at 24 weeks. In contrast, the mean Larsen score in the patients receiving IL1Ra increased by only 3.8. This represents a 41% reduction in the rate of radiographic joint damage over 24 weeks (p=0.03). The effects on radiographic joint damage was similar in the three treatment groups: 44%, 39% and 37% reduction in the rate of radiographic joint damage compared with placebo in the IL1Ra 30, 75 and 150 mg/day groups, respectively. When radiographic joint damage was measured according to the number of joints with erosions, an increase of 2.6 from 5.0 to 7.6 was observed in the placebo group. In contrast, the mean number of joints with erosions in the IL1Ra treated groups increased by only 1.4 (p=0.004 compared with placebo), representing a reduction of 46%.

A further analysis of radiographic change was performed using the Genant method, which distinguishes two aspects of joint damage: articular erosion, representing direct invasiveness of cartilage and bone by proliferating synovial pannus, and joint space narrowing, which represents diffuse enzymatic destruction of the cartilage surfaces. Radiographs obtained before and after the randomised clinical trial and after the 24 week extension study were analysed. There were strong correlations between the Genant scores and the Larsen scores at each time point. The analyses produced a number of additional interesting observations. Firstly, patients who received IL1Ra during the 0–24 week period demonstrated a 58% reduction in the rate of radiographic joint space narrowing compared with placebo (p=0.003) but only a 38% reduction in the rate of radiographic erosion (p=0.01), suggesting that the predominant early manifestation of blocking IL1 mediated joint damage is a reduction in the rate of cartilage surface loss. Secondly, when patients who received IL1Ra both during the 0–24 week period and the 24–48 week period were analysed it was observed that the mean changes in the measures of joint space narrowing according to the Genant scoring method were identical (0.61) in the two treatment peri-
Effects on synovial tissue

Twelve paired synovial biopsy samples were obtained before and after entering the randomised clinical trial of IL1Ra. There was a notable reduction in intimal layer macrophage accumulation and subintimal macrophage and lymphocyte infiltration after IL1Ra 150 mg/day compared with placebo and IL1Ra 30 mg/day. Down regulation of E selectin, vascular cell adhesion molecule 1 and intercellular adhesion molecule 1 was also associated with IL1Ra 150 mg/day. Apparent total arrest of joint damage was observed in four patients and all had received IL1Ra. The arrest of joint damage was associated with the cessation or reversal of intimal layer macrophage accumulation. These preliminary observations may represent inhibition of several biologically relevant IL1 mediated pathogenic effects.

Conclusion

Experimental studies have demonstrated that IL1 blockade with either anti-IL1 antibodies or IL1Ra produced significant, but often modest, anti-inflammatory effects and potent inhibition of cartilage and bone damage. Maximal effectiveness of IL1Ra in experimental arthritis required continuous infusion. Randomised clinical trials in RA have also demonstrated modest anti-inflammatory effects and significant slowing in the rate of joint damage. The reduced joint damage manifested initially as slowing in the rate of cartilage surface loss and, subsequently, as inhibition of cartilage and bone invasion by proliferating synovial pannus. These effects may be in part attributable to reduced IL1 mediated mononuclear cell infiltration of synovial tissue and protease release by intimal layer synoviocytes and macrophages.

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