REPORT

Effects of anakinra on clinical and radiological outcomes in rheumatoid arthritis

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Interleukin 1 (IL1) plays a central part in the pathophysiology of rheumatoid arthritis (RA).[1 2] The IL1 gene family includes IL1α, IL1β, and IL1 receptor antagonist (IL1Ra). IL1α and IL1β are both agonist molecules. There are two distinct IL1 receptors, designated type I (IL1RI) and type II (IL1RII). IL1 binding to IL1RI results in signal transduction and cell activation. IL1Ra is the third member of the IL1 gene family. The agonistic effects of IL1 are partially blocked by the interaction between IL1Ra and IL1RI. When IL1Ra binds to IL1RI, it blocks the binding of IL1α and IL1β and inhibits signal transduction. Recombinant human IL1Ra, anakinra, has been approved for the treatment of patients with rheumatoid arthritis (RA).

CLINICAL EFFICACY

Conventional response criteria

Five randomised, placebo controlled clinical trials of anakinra in RA have been completed (table 1). A total of 2932 patients were recruited. In four studies, the primary end points were related to clinical efficacy. The primary outcome measures in the fifth were related to safety. Both the European monotherapy and the methotrexate (MTX) combination therapy studies have been published.[3 4] A treatment effect was not observed in the low dose monotherapy study. Radiographic analyses are being completed in the confirmatory efficacy study.

In the European monotherapy study, the onset of action was early in the three treatment groups, and a clinical effect was seen as early as two weeks (fig 1). The clinical effect continued to increase throughout the study, and an American College of Rheumatology (ACR) 20% response[5] was observed in 43% of the 116 patients who were randomised to receive 150 mg/day anakinra, compared with 27% of the 121 patients who received placebo (p=0.014). Significant improvements were observed in each of the individual components of the ACR response in the patients who received 150 mg/day anakinra.[3] The clinical improvements observed in the 30 and 75 mg/day anakinra treatment groups did not reach statistical significance (p=0.054 and 0.258, respectively).

The rapid onset of action was also observed in the MTX combination therapy study.[4] At 24 weeks, 42% of the patients receiving 1 mg/kg/day anakinra achieved an ACR20 response, 24% an ACR50 response, and 10% an ACR70 response (fig 2). The improvements in the individual components of the ACR response were most clearly seen in the patient centred outcomes, such as the patient pain score, the Health Assessment Questionnaire (HAQ),[6] and the patient assessment of disease (fig 3A). Thus, in each of these three outcome measures, the improvements in patients who received 2 mg/kg/day anakinra were highly significant, compared with placebo (p>0.001). In the physician centred outcomes, such as the tender and swollen joint counts and the physician assessment of disease, the placebo responses were greater and the separation between the placebo and the optimal therapeutic responses were less (fig 3B). The improvement in the tender joint count in patients receiving anakinra failed to reach statistical significance, compared with placebo, although the improvements in the swollen joint count and physician assessment of disease were significant in the patients who received 2 mg/kg/day anakinra (p>0.05).

The confirmatory efficacy study evaluated 501 patients who demonstrated an inadequate clinical response to therapeutic doses of MTX and were randomised to receive either placebo or a fixed dose 100 mg/day anakinra in combination with maintainence MTX. At four weeks, significantly more patients receiving anakinra had achieved an ACR20 response (p<0.01). At 24 weeks, 38% of the treatment group achieved an ACR20 response, compared with 22% of the placebo group (p<0.001). Consistent with the previous MTX combination therapy study, the improvements in the individual components of the ACR response were most evident in the patient centred outcomes (data not shown).

Improvements in function

In each of the three anakinra studies that evaluated therapeutically effective doses, clinically meaningful improvements in the HAQ scores (a reduction of greater than 0.22) were observed (fig 4). In the European monotherapy study, patients receiving each of the anakinra doses demonstrated reductions in the HAQ scores at 24 weeks that were significantly better than placebo, and the improvement observed in the patients who received 150 mg/day anakinra was clinically meaningful.[3] Similarly, in both the MTX combination and the confirmatory efficacy studies, patients receiving anakinra doses 1 or 2 mg/kg/day, or the fixed dose of 100mg/day, demonstrated reductions in HAQ scores that were clinically meaningful and significantly better than placebo.[4]

A second validated measure of function, the Economic Resource Survey, was used in the European monotherapy

Table 1 Randomised, placebo controlled trials of anakinra		
Study	**Daily doses of anakinra**	**N**
European Monotherapy Study	0, 30, 75, 150 mg	472
Low Dose Monotherapy Study	0, 2.5, 10, 30 mg	141
MTX Combination Therapy Study	0, 0.04, 0.1, 0.4, 1.0, 2.0 mg/kg	419
Confirmatory Efficacy Study	0, 100 mg	501
Safety Study	0, 100 mg	1399
Total		2932
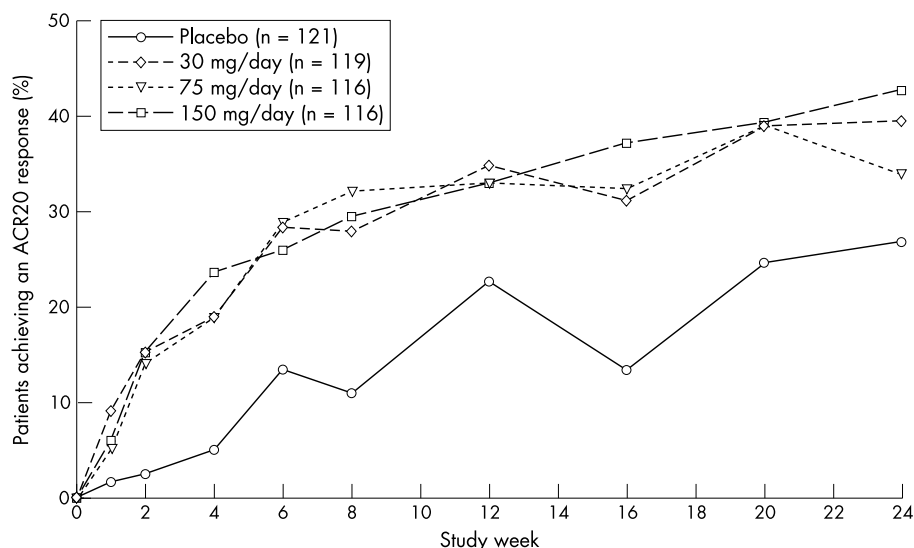
Figure 1 American College of Rheumatology 20% response (ACR20) after treatment with anakinra administered as monotherapy, compared with placebo, in patients with rheumatoid arthritis. The early onset of action is demonstrated.

study to evaluate patient and caregiver days of missed work or domestic activity in successive four week periods.[7] There were rapid gains in the number of days at work or domestic activity in the treated patients (data not shown). The increases in productivity were dose related with a total of 15.7 days gained over 24 weeks in patients receiving 150 mg/day anakinra, compared with 3.6 in the placebo group (p=0.026). Moreover, the percentage of patients receiving 150 mg/day anakinra with at least one missed day of work or domestic activity decreased by 20%, from 48% at baseline to 28% at 24 weeks. In the placebo group, the decrease was only 6%.

After completing the 24 week placebo controlled phase of the study, all patients were offered the option of continuing treatment in a double blind, 24 week extension study. Patients receiving placebo were randomised to one of the three anakinra doses, and patients receiving anakinra continued to receive the same dose. At 48 weeks, patients who received anakinra for the entire duration of the study demonstrated greater benefit during the second 24 week treatment period than the first.[7] For example, the patients who received 150 mg/day anakinra for 48 weeks demonstrated a mean gain of 22.36 days productivity during the second 24 week period, compared with 13.98 during the first. Patients who received

any dose of anakinra for 48 weeks demonstrated a mean gain of 16.98 days productivity during the second 24 weeks, compared with 12.24 during the first (data not shown).

Finally, the Nottingham Health Profile is a validated instrument that provides indications of patients' perceived health problems. The scale contains 38 items that can be grouped into six sections: mobility (eight items), pain (eight items), sleep (eight items), social isolation (eight items), emotional reactions (nine items), and energy (three items). In the patients who received anakinra in the European monotherapy study, there were significant improvements in four of the six sections after 24 weeks, compared with the placebo group[8] (data not shown).

### Prevention of structural damage

Radiographs of the hands and wrists were obtained at weeks 0, 24, and 48 and scored according to Genant's modification of Sharp's method.[9] Erosions, including new erosions and extensions of old ones, were quantified at 14 joints in each hand and wrist. Each of the joints was scored on an eight point scale of 0 to 3.5, giving a maximum erosion score of 49 per hand and wrist, or 98 per patient. The maximum erosion score was normalised to 100. Thirteen joints were examined for joint space narrowing and each joint was scored on a nine point scale of 0 to 4.0, giving a maximum joint space narrowing score of 52 per hand and wrist, or 104 per patient. The maximum joint space narrowing score was normalised to 100, giving a maximum total damage score of 200 per patient.

The mean change in the total modified Sharp score of 178 patients who completed 48 weeks treatment with anakinra was 2.12, significantly less than 3.81 observed in 58 patients who received placebo for 24 weeks and anakinra for 24 weeks (p=0.015) (data not shown). The mean change in the erosion score of patients who received anakinra treatment was 1.15, which was significantly less than 2.03 observed in the patients who received placebo for 24 weeks and anakinra treatment for 24 weeks (p=0.006). A significant reduction in the erosion score was observed with each of the three doses. The mean change in the joint space narrowing score was 1.53 in placebo treated patients, compared with 0.89 in anakinra treated patients (p=0.084).

Changes in the rate of joint damage during the two 24 week treatment periods were compared (data not shown). In the 58 patients who received placebo during the first 24 weeks, a significant reduction of the median change in the total modified
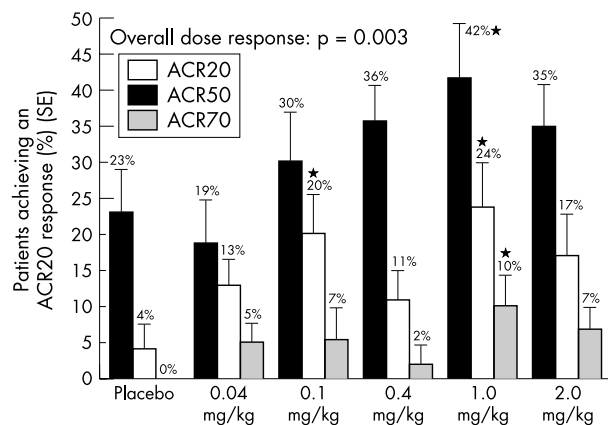
Figure 2 Magnitude of the American College of Rheumatology clinical responses after treatment with anakinra administered in combination with methotrexate in patients with rheumatoid arthritis (*p<0.05 v placebo).
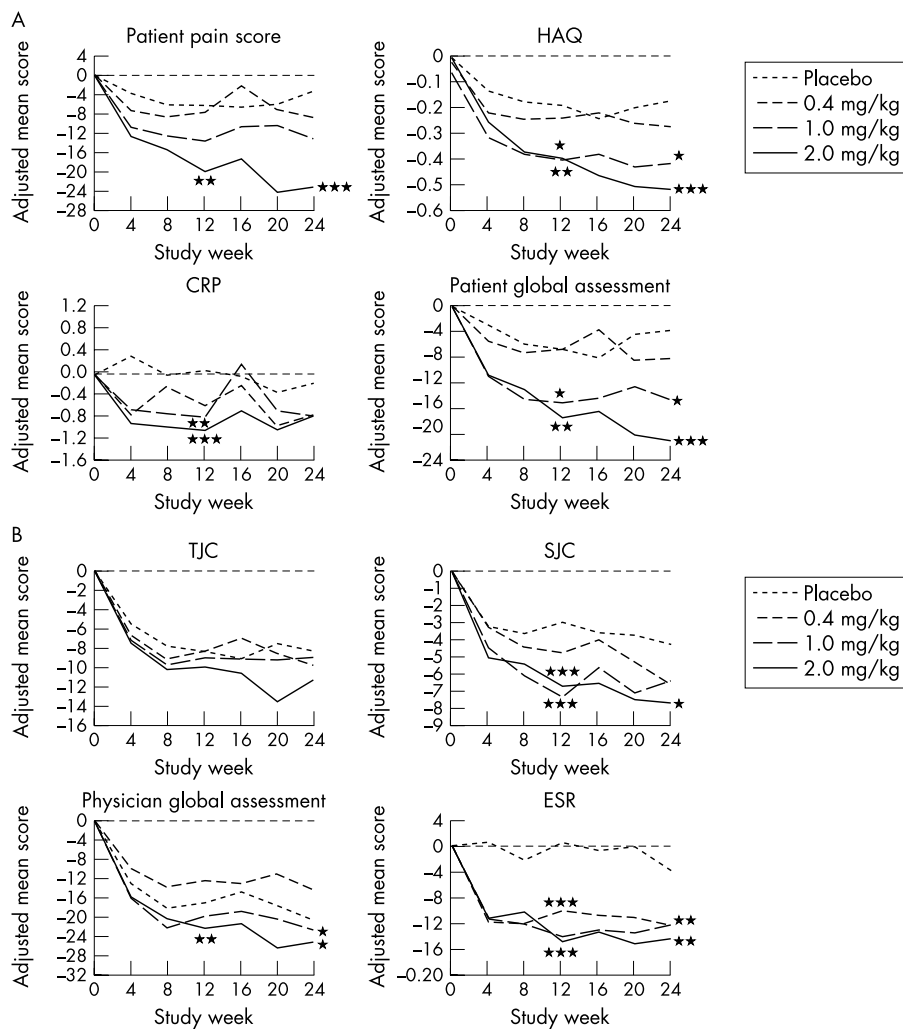
Figure 3 Improvements in individual American College of Rheumatology criteria components after treatment with anakinra administered in combination with methotrexate. Patient centred outcomes are included in panel A; physician centred outcomes are included in panel B (*p<0.05; **p<0.01; ***p<0.001 v placebo).

Sharp score from 1.95 to 0 after randomisation to anakinra treatment was demonstrated (p<0.001). The 178 patients with a complete set of radiographs who completed 48 weeks anakinra treatment demonstrated a significant reduction in the median total modified Sharp score from 0.51 after the first treatment phase and 0 after the second.

CONCLUSIONS

Anakinra, a recombinant human IL1Ra, is the first treatment for RA that neutralises IL1 activity. Treatment with anakinra results in significant improvements in the signs and symptoms, and has a beneficial effect on functional status. The therapeutic effects occur early and are sustained
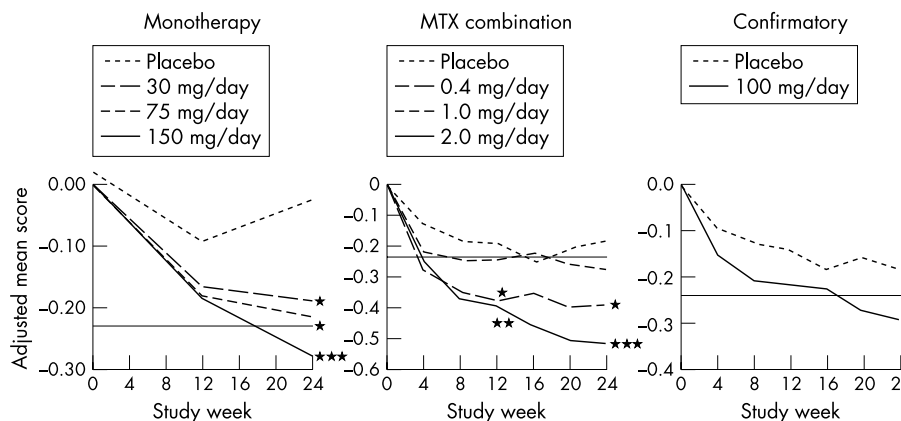
Figure 4 Improvements in the Health Assessment Questionnaire (HAQ) disease index from the three efficacy studies of anakinra. Clinically relevant improvements (>−0.22) were observed in all.

throughout treatment. Anakinra delays the rate of structural joint damage.

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