Anakinra as a new therapeutic option in rheumatoid arthritis: Clinical results and perspectives

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ABSTRACT

Interleukin-1 receptor antagonist (IL-1Ra) is a member of the IL-1 gene family, which blocks IL-1-mediated signal transduction. In rheumatoid arthritis (RA), recombinant human IL-1Ra (anakinra) has been evaluated in 5 randomized, placebo-controlled clinical trials. In the European monotherapy study, 43% of patients receiving 150 mg/day anakinra achieved a 20% response according to the American College of Rheumatology criteria (ACR 20), compared to 27% in the placebo group. In the methotrexate combination therapy study, 42% of the patients receiving 1 mg/kg/day anakinra achieved an ACR20 response, 24% an ACR50 response, and 10% an ACR70 response. In each study, clinically meaningful improvements in the Health Assessment Questionnaire scores were observed. The Economic Resource Survey was employed in the European monotherapy study to evaluate patient and caregiver days of missed work or domestic activity in successive 4-week periods. There were rapid gains in the number of days at work or domestic activity in the treated patients, and the increases in productivity were dose-related. The mean change in the total modified Sharp score of patients who completed treatment with anakinra was significantly less than in the patients who received placebo. Anakinra, a new biologic approach to the treatment of RA, results in significant improvements in the signs and symptoms, has beneficial effects on functional status, and on the rate of progressive structural joint damage.

Introduction

Interleukin-1 (IL-1) plays a central role in the pathophysiology of rheumatoid arthritis (RA) (1). The IL-1 gene family includes IL-1 , IL-1 and IL-1 receptor antagonist (IL-1Ra) (2). IL-1 and IL-1 are both agonist molecules. Activated monocytes and macrophages are the principal source of IL-1 and IL-1 . There are two distinct IL-1 receptors, designated type I (IL-1RI) and type II (IL-1RII) (3). IL-1 binding to IL-1RI results in signal transduction and cell activation. IL-1RII is a 'decoy' receptor that functions by scavenging IL-1 and IL-1 , but does not have a role in cell signaling (4). Binding of IL-1 to IL-1RI produces many effects that are central to the pathogenesis of RA (3). The agonistic effects of IL-1 include the stimulation of matrix metalloproteinase (MMP) release by fibroblast-like synoviocytes (5). IL-1Ra is the third member of the IL-1 gene family (2,3,6). IL-1Ra is also produced by activated monocytes and tissue macrophages. The agonistic effects of IL-1 are partially blocked by the interaction between IL-1Ra and IL-1RI. When IL-1Ra binds to IL-1RI, it blocks the binding of IL-1 and IL-1 and inhibits signal transduction.

IL-1 and IL-1 are abundantly produced by synovial tissue macrophages in RA. In a study of patients with early RA, it was observed that synovial tissue samples selected from areas adjacent to the cartilage-pannus junction contained IL-1 -producing cells that occupied up to 58.6% (mean 14.9%) of the total tissue area (7). This contrasted with TNF-producing cells, which occupied up to 11.7% (mean 6.7%) of the total tissue area. Moreover, IL-1 - and IL-1 -producing cells were demonstrated in the majority of patients with long-standing disease (6 to 29 years after the onset). Therefore, by administering recombinant IL-1Ra to block IL-1 binding to IL-1RI, clinical benefits should be anticipated at all stages of RA.

Clinical efficacy

Improvements in the American College of Rheumatology response criteria

Five randomized, placebo-controlled

Table I. 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

clinical trials of anakinra in RA have been completed (Table I). A total of 2,932 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 (8, 9). A treatment effect was not observed in the low dose monotherapy study. Radiographic analyses are being completed in the confirmatory efficacy study.

The mean duration of RA across the five studies ranged between 3.5 and 10.8 years. The baseline tender and swollen joint counts were up to 34.3 and 26.1, respectively; the mean baseline erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values were between 36.7 and 49.5 mm/h, and 1.91 and 4.14 mg/dL, respectively. Up to 64.2% and 87.0% of patients were receiving corticosteroids and NSAIDs, respectively.

In the European monotherapy study, 43% of patients receiving 150 mg/day anakinra achieved a 20% response according to the American College of Rheumatology (ACR) criteria (10), compared to 27% in the placebo group ($p = 0.014$) (8). The onset of action was early in the treatment groups, and a clinical effect was seen at two weeks. Significant improvements were observed at 24 weeks in each of the individual components of the ACR response in the patients who were receiving 150 mg/day anakinra. Thus, compared to placebo, patients receiving the optimal therapeutic dose demonstrated improvements in the number of swollen and tender joints ($p = 0.009$ and 0.0009, respectively), physician and patient assessments of disease activity ($p = 0.0006$ and 0.012, respectively), patient pain scores ($p = 0.001$), Health Assessment Questionnaire (HAQ) ($p = 0.0007$), and both ESR and CRP values ($p < 0.0001$ and 0.0017, respectively) (8).

The rapid onset of action was also observed in the MTX combination therapy study (9). 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. The improvements in the individual components of the ACR response were most clearly seen in the patient-centered outcomes, such as the patient pain score, the HAQ, and the patient assessment of disease. In the physician-centered 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. A sustained response to anakinra, defined as an ACR20 response at 4 or more of the 4-weekly assessments and including either the 12- or 24-week assessment, was observed in 35% of patients who received 2 mg/kg/day anakinra, compared to 15% of the placebo group ($p = 0.013$).

The confirmatory efficacy study evaluated 501 patients who demonstrated an inadequate clinical response to therapeutic doses of MTX and were randomized to receive either placebo or a fixed dose 100 mg/day anakinra in combination with maintainence MTX. At 4 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 to 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-centered outcomes (data not shown).

Improvements in function

In each of the 3 anakinra studies that evaluated therapeutically effective dosages, clinically meaningful improvements in the HAQ scores (a reduction greater than 0.22) were observed (11). In the European monotherapy study, patients receiving each of the anakinra dosages demonstrated reductions in the HAQ scores at 24 weeks that were significantly better than placebo. Similarly, in both the MTX combination and the confirmatory efficacy studies, patients receiving anakinra dosages 1 or 2 mg/kg/day, or the fixed dose of 100 mg/day, demonstrated reductions in HAQ scores that were clinically meaningful and significantly better than placebo.

The Economic Resource Survey was employed in the European monotherapy study to evaluate patient and caregiver days of missed work or domestic activity in successive 4-week periods (12). There were rapid gains in the number of days at work or domestic activity in the treated patients. 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 to 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 therapy in a double-blind, 24-week extension study. Patients receiving placebo were randomized to one of the three anakinra dosages, and patients receiving anakinra continued to receive the same dosage (13). At 48 weeks, patients who received anakinra for 48 weeks demonstrated greater benefit during the second 24-week period. 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 to 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 to 12.24 during the first.

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 6 sections: mobility (8 items), pain (8 items), sleep (5 items), social isolation (5 items), emotional reactions (9 items), and energy (3 items). In the patients who received anakinra in the European monotherapy study, there were significant improvements in 4 of the 6 sections after 24 weeks, compared to the placebo group.

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 (14). Erosions, including new erosions and extensions of old ones, were quantified at fourteen 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 normalized 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 normalized 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 ($p= 0.015$). 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 dosages. The mean change in the joint space narrowing score was 1.53 in placebo-treated patients, compared to 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. In the 58 patients who received placebo during the first 24 weeks, a significant reduction of the median change in the total modified Sharp score from 1.95 to 0 after randomization 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 following the second.

Conclusions

Anakinra, a recombinant human IL-1Ra, is the first treatment for RA that neutralizes IL-1 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 throughout treatment. Anakinra delays the rate of structural joint damage.

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