Clinical and radiological effects of anakinra in patients with rheumatoid arthritis

B. Bresnihan and M. Cobby

Interleukin-1 (IL-1) is a proinflammatory cytokine that plays a pivotal role in the pathophysiology of rheumatoid arthritis (RA). Inhibiting the activities of IL-1 at the receptor level with the recombinant human IL-1 receptor antagonist anakinra (Kineret®, Amgen Inc., Thousand Oaks, CA) is a new therapeutic option for the management of patients with RA. Randomized, placebo-controlled trials have demonstrated that anakinra, alone and in combination with methotrexate, improves the signs and symptoms of RA. Anakinra also produces improvements in patient functionality and health-related quality of life, as measured by the Health Assessment Questionnaire and the Nottingham Health Profile, and reduces the number of productivity days missed due to illness. Furthermore, an initial study indicates that anakinra retards the progression of radiographic joint damage. Such clinical findings suggest that anakinra is an important addition to the rheumatology treatment armamentarium.

**Key Words:** Anakinra, Efficacy, Functionality, Health-related quality of life, Interleukin-1 receptor antagonist, Radiographic progression, Rheumatoid arthritis.
Clinical efficacy of anakinra

Five randomized, placebo-controlled clinical trials of anakinra have been completed in a total of 2932 patients with RA: the European Monotherapy Study [14]; the Low-dose Monotherapy Study [15]; the Methotrexate (MTX) Combination Study [16]; the Confirmatory Efficacy Study [17]; and the Safety Study [18] (Table 1). The primary end-points of the first four studies were related to clinical efficacy, while primary outcome measures in the fifth study were safety-related. The European Monotherapy Study and the MTX Combination Study have both been published and, along with the Confirmatory Efficacy Study, demonstrate that anakinra improves the signs and symptoms of RA. A treatment effect was not observed in the Low-dose Monotherapy Study.

The mean duration of RA across the five studies ranged from 3.5 to 10.8 yr. Mean baseline tender joint count ranged from 22.6 to 34.3 joints (out of a maximum of 68) and swollen joint count ranged from 18.3 to 26.1 joints (out of a maximum of 66). 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% of patients were receiving non-steroidal anti-inflammatory drugs (NSAIDs) at baseline [15].

Improvements in the American College of Rheumatology response criteria

In the European Monotherapy Study, patients (n = 472) were randomized to anakinra 30, 75, or 150 mg/day or placebo. At 24 weeks, 43% of patients receiving anakinra 150 mg/day achieved a 20% response according to the American College of Rheumatology (ACR) criteria (ACR20) [19], compared with 27% in the placebo group (P = 0.014) [14]. An early onset of action was observed in the active treatment groups, with a clinical effect observed as early as 2 weeks following initiation of therapy (Fig. 2) [15, 20]. Significantly greater improvements were observed at 24 weeks in each of the individual components of the ACR response criteria in the patients who were receiving the highest dosage of anakinra (150 mg/day) compared with those receiving placebo: the number of swollen and tender joints (P = 0.009 and P = 0.0009, respectively); physician and patient global assessments of disease activity (P = 0.0006 and P = 0.012, respectively); patient pain scores (P = 0.001); Health Assessment Questionnaire (HAQ) disease index (P = 0.0007); and both ESR and CRP values (P < 0.0001 and P = 0.0017, respectively) [14].

A rapid onset of action was also observed with anakinra in the MTX Combination Study (Fig. 3) [16, 20]. Patients (n = 419) were randomized to anakinra at dosages ranging from 0.04 to 2.0 mg/kg/day. The overall magnitude of clinical response was assessed according to ACR20, ACR50 and ACR70 response at 12 and 24 weeks. At 12 weeks, anakinra 1.0 mg/kg/day was associated with an ACR20 response of 46%, an ACR50 response of 19%, and an ACR70 response of 5%. Corresponding response rates with anakinra 2.0 mg/kg/day were 38, 24 and 11%, compared with 19, 4, and 0% with placebo. The overall dose response was highly statistically significant (P = 0.001). At 24 weeks, there was also a significant dose response when the percentages of patients achieving an ACR20, ACR50 and ACR70 response were considered (P = 0.003). In the anakinra 1.0 mg/kg/day treatment group, the ACR20, ACR50 and ACR70 response rates were 42, 24 and 10%, respectively, compared with 23, 4 and 0% with placebo. Corresponding rates with anakinra 2.0 mg/kg/day were 35, 17 and 7%. Improvements in the individual components of the ACR response were seen most clearly in the

Table 1. Randomized, placebo-controlled trials of anakinra

<table>
<thead>
<tr>
<th>Study</th>
<th>Daily dosages of anakinra</th>
<th>n°</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Monotherapy Study</td>
<td>0, 30, 75, 150 mg</td>
<td>472</td>
</tr>
<tr>
<td>Low-dose Monotherapy Study</td>
<td>0, 2.5, 10, 30 mg</td>
<td>141</td>
</tr>
<tr>
<td>Methotrexate Combination</td>
<td>0, 0.04, 0.1, 0.4, 1.0,</td>
<td>419</td>
</tr>
<tr>
<td>Therapy Study</td>
<td>2.0 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Confirmatory Efficacy Study</td>
<td>0, 100 mg</td>
<td>501</td>
</tr>
<tr>
<td>Safety Study</td>
<td>0, 100 mg</td>
<td>1399</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>2932</td>
</tr>
</tbody>
</table>

\*Number of patients who received at least one dose of the study drug.

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patients were positive for TNFα. Further analyses of synovial explants indicated that there is an imbalance between IL-1 and IL-1Ra in the rheumatoid synovium, in favour of elevated IL-1 [12, 13]. Therefore, administration of exogenous IL-1Ra to block binding of IL-1 to IL-1RI should translate into clinical benefits at all stages of RA. Anakinra (Kinereft®; Amgen Inc., Thousand Oaks, CA) is a recombinant form of human IL-1Ra produced in an Escherichia coli expression system. This review will discuss the clinical and radiological effects of anakinra in patients with RA.
In each of the three studies that evaluated therapeutically effective dosages of anakinra, clinically meaningful improvements in the HAQ scores (a reduction >0.22 from baseline) [24] were observed with active treatment (Fig. 5). In the European Monotherapy Study, patients receiving each of the anakinra dosages demonstrated reductions in HAQ scores at 24 weeks that were significantly better than the placebo group \( (P = 0.011, P = 0.048 \text{ and } P = 0.0007 \text{ with } 30, 75 \text{ and } 150 \text{ mg/day, respectively}) \) [14]. Similarly, in the MTX Combination and the Confirmatory Efficacy studies, reductions in HAQ scores that were clinically meaningful and significantly better than placebo were observed in patients receiving anakinra 1.0 or 2.0 mg/kg/day \( (P = 0.036 \text{ and } P = 0.0005, \text{ respectively}) \) [16] or 100 mg/day \( (P = 0.017) \) [15].

The effects of anakinra on patient functionality and health-related quality of life were also assessed with the Nottingham Health Profile (NHP) in the European Monotherapy Study [25]. The NHP is a validated instrument that provides indications of patients' perceived health problems, with a scale comprising 38 items that can be grouped into six subscales: mobility (five items), pain (eight items), sleep (five items), social isolation (five items), emotional reactions (nine items) and energy (three items) [26]. In the patients who received anakinra, there were significant improvements in the energy \( (P = 0.01) \), pain \( (P = 0.02) \), emotional reactions \( (P = 0.01) \) and physical mobility \( (P < 0.01) \) subscales at 24 weeks, compared with the placebo group.

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 [27]. There were rapid gains over time in the number of days at work or domestic activity in the patients treated with anakinra. Increases in productivity were dose-related, with a mean total of 15.66 days gained over 24 weeks in patients receiving the highest dosage of anakinra compared with 3.55 days in the placebo group \( (P < 0.05) \). The mean total number of days gained across all three anakinra dosages was 13.37 \( (P < 0.05 \text{ vs placebo}) \). Moreover, an additional 14% of anakinra recipients did not miss any days of work or domestic activity over the course of the study. The corresponding decrease with placebo was only 6%.

After completing the 24-week placebo-controlled phase of the European Monotherapy Study, patients were given the option of continuing therapy in a 24-week double-blind extension phase. Patients receiving placebo during the first 24 weeks were randomized to one of the three anakinra dosages for the second 24 weeks, while patients originally randomized to anakinra continued to receive the same dosage during the extension phase. Patients who had received anakinra for the entire study period demonstrated a greater gain in productivity days during the second 24-week period compared with the first 24-week phase [28]. For example, the patients who received anakinra 150 mg/day for 48 weeks demonstrated a mean gain of 22.58 days during the second 24-week period, compared with 13.98 days during the first.

**Effect of anakinra on measures of patient functionality**

Functional decline in RA is a consequence of both disease activity and structural joint damage and translates into impaired health-related quality of life and work disability [22, 23]. The effects of a therapeutic agent on measures of patient functionality are an important consideration when assessing treatment options for RA.

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**Fig. 3.** ACR20 response rate over time following treatment with anakinra administered in combination with MTX, compared with placebo plus MTX, in patients with RA \( (**P < 0.05, ***P = 0.001, \text{ vs placebo; intent-to-treat with non-responder imputation}) \) [15, 16]. (Modified from Arthritis and Rheumatism) [16].

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**Table 3.** ACR20 response rate over time following treatment with anakinra administered in combination with MTX, compared with placebo plus MTX, in patients with RA \( (**P < 0.05, ***P = 0.001, \text{ vs placebo; intent-to-treat with non-responder imputation}) \) [15, 16]. (Modified from Arthritis and Rheumatism) [16].
Patients who received anakinra at any dosage for 48 weeks demonstrated a mean gain of 2.82 productivity days per month during the second 24 weeks, compared with 2.04 days per month during the first.

**Prevention of structural damage with anakinra**

Joint damage occurs early in the course of RA with >50% of patients showing radiological erosions within the first 2 yr of disease onset [29]. The degree of joint damage...
assessed by radiographic imaging represents a key outcome in RA and can be used to evaluate the effectiveness of an interventional therapy. Structural progression was selected as a secondary end-point in the first phase of the European Monotherapy Study and as a primary end-point for the extension phase of this study [14, 30].

Measuring radiographic disease progression

The Larsen score [31] and Genant-modified Sharp score [32] were used to assess structural progression in the European Monotherapy Study [14, 30]. These scoring methods assess erosions and cartilage destruction in slightly different ways, but each can provide a single composite measure of overall joint damage for each subject after scoring individual joints of the hand and wrist. The Larsen scoring method has a relatively narrow reading scale, providing a conservative estimate of progression and combining joint space narrowing and joint erosion into a single global score. Films are read independently, with more emphasis placed on erosive damage. In contrast, the Genant-modified Sharp scoring method provides separate scores for joint space narrowing and erosion, which can then be combined to provide a total modified Sharp score. In this method, the examinations are read as a blinded set, i.e. with pre- and post-treatment radiographs available to the reader in blinded order. The modified Sharp scoring method has a comparatively extended scoring range and, therefore, potentially allows for more subtle radiographic changes to be detected and measured than the Larsen score.

Effects of anakinra on radiographic progression

In the European Monotherapy Study, radiographs were initially evaluated using the Larsen score alone. However, during recent years in Europe and for some time in North America, various modifications of the Sharp scoring method have been used to measure radiographic progression in different trials. For this reason, radiographs were reassessed using the Genant-modified Sharp score.

When radiographs were scored with the Genant-modified Sharp method, anakinra significantly inhibited the progression of structural damage at all dosages tested (Fig. 6). At 24 weeks, there was a 47% reduction in the rate of progression for the combined treatment group compared with placebo ($P = 0.0004$) [30]. The pattern was similar when the radiographs were evaluated using erosion and joint space narrowing subscales of the Genant-modified Sharp score, with 38% ($P = 0.0097$) and 58% ($P = 0.0003$) reductions in progression observed, respectively, compared with placebo (data not shown).

Introduction of anakinra in the extension phase of the European Monotherapy Study to patients initially randomized to placebo resulted in a slowing of disease progression at 48 weeks by up to half of that seen in the first phase [30]. Significantly less progression of structural damage was observed in patients who received anakinra for the entire 48-week treatment period compared with those receiving the active treatment in the second phase of the study only ($P = 0.0005$ and $P = 0.0001$ for the Genant-modified Sharp total score and erosion score, respectively).

The sustained effects of anakinra on structural damage were further evident when the median change in
Genant-modified Sharp total score over time was calculated. In patients who received anakinra for the entire 48-week study period, the median change in score was 0.6 during the first 24 weeks of treatment and <0.1 during the second 24 weeks \((P < 0.001)\) [33]. In patients who received placebo for the first phase of the trial and who were then switched to anakinra during the second phase, the median change in score was 2.2 and 0.1 for the first and second phases, respectively \((P < 0.001; \text{Fig. 7})\).

Patients who received active treatment during both phases of the trial experienced sustained benefit, in terms of structural progression. Analysis of the Genant-modified Sharp score subscales indicates that anakinra may exert its effects in dual fashion, with early and maintained protection of cartilage and an accelerated erosion benefit in the extension of the study. These findings suggest that anakinra has a role in the treatment of both early and established RA as it protects patients from the formation of erosions and preserves hyaline cartilage.

**Conclusions**

Anakinra, a recombinant human IL-1Ra, specifically inhibits the proinflammatory and destructive pathophysiological effects of IL-1. Results from large efficacy studies indicate that treatment with anakinra results in significant improvements in the signs and symptoms of RA and has beneficial effects on functional status. The therapeutic effects occur early and are sustained throughout treatment. In addition, randomized clinical trials indicate that treatment with anakinra retards the rate of structural joint damage in RA and is beneficial in preserving and protecting bone and cartilage.

**References**

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