Bringing the clinical experience with anakinra to the patient

S. B. Cohen and A. Rubbert

The recombinant interleukin-1 receptor antagonist, anakinra (Kineret®, Amgen Inc., Thousand Oaks, CA), has been approved by the US Food and Drug Administration and the European Commission for the treatment of patients with active rheumatoid arthritis (RA). Approval was granted following the extensive evaluation of anakinra in five pivotal clinical trials that assessed its efficacy and safety in RA patients. These studies have indicated that anakinra has a favourable risk–benefit profile, producing rapid and sustained reductions in the signs and symptoms of RA, as measured by improvements in the American College of Rheumatology response criteria, particularly in patient-reported indicators of function and disability. The data from these trials suggest that anakinra is likely to provide a useful therapeutic option to clinicians and also meet the treatment expectations of patients with RA; however, further studies are underway to investigate additional benefits that anakinra may offer, particularly in patients with existing co-morbidities.

KEY WORDS: Anakinra, Clinical experience, Compliance, IL-1 receptor antagonist, Patient expectation, Patient-reported outcomes, Rheumatoid arthritis.
the registration of anakinra for the treatment of patients with RA in the USA and Europe [1–5]. Three of these trials have investigated the efficacy of anakinra at clinically relevant dosages.

The first trial was conducted in Europe in patients with active RA and demonstrated that anakinra monotherapy was more effective than placebo in improving signs and symptoms of RA and retarding radiographic progression over a 24 week treatment period [1, 6]. Patients (n = 472) met American College of Rheumatology (ACR) criteria for RA, had experienced disease symptoms for between 6 months and 8 years and had typical features of active disease. Disease-modifying anti-rheumatic drugs (DMARDs) were discontinued at least 6 weeks prior to enrolment. Patients were randomized to receive anakinra 30, 75, or 150 mg or placebo, administered by daily s.c. injection. At 24 weeks, 43% of anakinra 150 mg recipients achieved the primary endpoint of a 20% improvement in ACR response criteria (ACR20), compared with 27% of placebo recipients (P = 0.014). Furthermore, anakinra 150 mg produced statistically significant improvements vs placebo for all individual ACR clinical parameters assessed. When radiographic progression was evaluated by Genant-modified Sharp score in patients completing at least 20 weeks of treatment, there was a statistically significant reduction in progression of erosions (38%, P = 0.0097), joint space narrowing (58%, P = 0.0003) and total score (47%, P = 0.0004) with anakinra at all dosages compared with placebo. Such improvements continued in patients completing 48 weeks of treatment with anakinra. The most frequently observed adverse event in this study was injection-site reactions (ISRs); 5% of patients receiving anakinra 150 mg withdrew from treatment for this reason.

As MTX is the most commonly used DMARD for RA, it was important to determine the efficacy and safety of anakinra as combination therapy in MTX-treated patients. The first MTX combination trial was a 24 week, placebo-controlled, dose-ranging trial evaluating anakinra 0.04–2 mg/kg, administered as a single daily s.c. injection in patients (n = 419) with active RA also receiving MTX 15–25 mg/week [3]. Patients enrolled in this study had a mean disease duration of 7 years, mean baseline tender/painful and swollen joint counts of >20 and a mean HAQ score of 1.4. The primary efficacy endpoint was improvement in the signs and symptoms of RA, measured by the proportion of subjects achieving an ACR20 response at 12 weeks. A dose-dependent improvement in ACR20 response was seen across the five anakinra dosage groups at 12 and 24 weeks (P = 0.001 and P = 0.004, respectively). At 12 weeks, 19% of placebo recipients achieved an ACR20 response compared with 46% (P = 0.001) and 38% (P = 0.007) of those receiving anakinra 1.0 and 2.0 mg/kg, respectively—dosages similar to those used in clinical practice. Similar results were seen when assessing ACR20 response at week 24. Anakinra was well tolerated, with the most common adverse event reported being ISRs. This led to study withdrawal in 3.5% of anakinra-treated patients and 2.7% of placebo-treated patients.

The second MTX combination trial evaluated 906 patients on stable dosages of MTX who were randomized to anakinra 100 mg/day or placebo in a 1:1 ratio [2, 4]. An initial analysis was performed of the first 501 patients entering the trial who completed 24 weeks of treatment to assess improvement in signs and symptoms of RA with anakinra, measured by ACR response criteria. Patients enrolled in the study had active RA despite receiving at least 6 months of treatment with MTX 10–25 mg/week and had radiographic evidence of at least one bone erosion. At baseline, all patients demonstrated active disease, with mean duration of 10–11 years and a mean HAQ score of 1.34. After 24 weeks of treatment, significantly more patients receiving anakinra achieved an ACR20 response than those receiving placebo (38 vs 22%, respectively, P < 0.001). Higher ACR50 and ACR70 response rates were also achieved in the anakinra group compared with the placebo group (17 vs 8%, P = 0.001 and 6 vs 2%, P = 0.024, respectively). ISRs were the most frequently reported adverse event, leading to premature study withdrawal in 8.4% of patients receiving anakinra and 0.8% of those receiving placebo. The frequency of serious infectious events was similar in both groups and no opportunistic infections were noted.

The value of patient-reported vs physician-reported outcomes

Previous evaluation of clinical trial data sets has demonstrated that patient-reported outcomes may be more reflective of an accurate treatment effect and less susceptible to placebo effect than physician-reported outcomes [7]. For example, placebo data from a trial comparing leflunomide, MTX and placebo [8] were analysed to determine the placebo effect for various measures of RA [7]. Patients receiving placebo demonstrated a greater magnitude of improvement in physician-reported outcomes such as tender joint count, swollen joint count and physician global assessment of disease activity than was seen with patient-reported parameters such as modified HAQ, HAQ disease index, patient global assessment of disease activity, or SF-36 physical component. A similar pattern was observed when the dataset for placebo response was examined for a trial comparing leflunomide, sulphasalazine and placebo [7, 9].

The impact of anakinra on patient-reported outcomes was evaluated in a meta-analysis of the three large anakinra clinical trials using standard effect size [10]. Effect size is a standardized measure of the difference from baseline between two study groups and provides a measure of the magnitude of the overall treatment effect. The effect sizes for the ACR20 and the physician- and patient-reported subcomponents of the ACR score were calculated by standardizing the differences between the
anakinra and placebo groups using the following formula:

\[
\frac{X_t - X_c}{\text{S.D.}}
\]

where \(X_t\) is the mean change from baseline for active treatment and \(X_c\) is the mean change from baseline for the placebo response, divided by the standard deviation (S.D.) of the change [11]. Patient-reported measures (i.e. HAQ, patient global assessment of disease activity and patient assessment of pain) and physician-reported measures (i.e. swollen joint count, tender/painful joint count and physician global assessment of disease activity) were pooled within each study comparison.

The effect size was greater for the composite patient-reported outcomes than for the physician-reported outcomes in all three studies and was nearly double in the MTX combination therapy study (Fig. 1). The effect size for the acute phase reactants was also significant; this was not unexpected in view of the biological response of the inflammatory markers erythrocyte sedimentation rate and C-reactive protein to interleukin-1 (IL-1) inhibition. This suggests that either anakinra is more effective at improving patient-reported indicators of pain, physical function and disability compared with physician-reported elements, or that there is a greater placebo response associated with physician-reported outcomes that decreases the effect size of these measurements. Further analyses of these observations are in progress.

**Anakinra in clinical practice**

In clinical practice, anecdotal reports indicate that anakinra has a positive impact on various aspects of patients’ daily lifestyle, including their HRQOL. Improvements in energy and mobility and a reduction of pain have been reported by patients, with a resulting improvement in the ability to undertake personal activities, such as dressing, maintaining hygiene and facilitating social contact. This improvement in ability to perform activities of daily living was formally evaluated in patients enrolled in the European Monotherapy Study [12]. When compared with placebo recipients, the patients in the anakinra group also experienced significant improvements in physical mobility (\(P < 0.01\)), energy level (\(P = 0.01\)), pain (\(P = 0.02\)) and emotional reactions (\(P = 0.01\)), and an improvement in sleeping ability and social contact, as measured by the Nottingham Health Profile. Furthermore, patients have indicated their ability to work on a more regular basis when treated with anakinra, with less days lost from work or domestic activity. In the European Monotherapy Study, patients who received anakinra 150 mg/day for 24 weeks demonstrated a mean gain of 15.66 days of work or domestic activity (2.33 days during weeks 20–24) compared with 3.55 days in the placebo group (\(P < 0.05\); 0.02 days during weeks 20–24) [13]. Furthermore, at 24 weeks, 14% of anakinra recipients reported that they had not missed any days of work compared with 6% of those receiving placebo. When assessed at 48 weeks, patients who received anakinra at any dosage for the entire study period had a greater benefit during the second 24 weeks compared with the first 24 weeks (2.49 vs 2.04 days per month) [14]. Patients who received placebo during the first phase of the study and were then switched to anakinra also demonstrated greater gains in productivity days during the latter 24 weeks (2.04 vs 0.02 days per month).

**Compliance with anakinra treatment**

Anakinra has a relatively short half-life (4–6 h) [15]. Consequently, prior to the initiation of the clinical trials, there was concern over patients’ compliance with a regimen requiring them to self-inject daily. However, treatment compliance in anakinra trials was high, with

### Table 1. Patient compliance with anakinra and placebo treatment in the large randomized controlled safety study [5]

<table>
<thead>
<tr>
<th>Compliance</th>
<th>Placebo ((n = 283))</th>
<th>Anakinra ((n = 1116))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of patients who completed the 6 month blinded phase</td>
<td>230 (81.3%)</td>
<td>875 (78.4%)</td>
</tr>
<tr>
<td>Percentage compliance on study drug for patients who completed the 6 month blinded phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90–100%</td>
<td>212 (92.2%)</td>
<td>814 (93.0%)</td>
</tr>
<tr>
<td>80–89%</td>
<td>11 (4.8%)</td>
<td>48 (5.5%)</td>
</tr>
<tr>
<td>70–79%</td>
<td>3 (1.3%)</td>
<td>6 (0.7%)</td>
</tr>
<tr>
<td>&lt;70%</td>
<td>4 (1.7%)</td>
<td>7 (0.8%)</td>
</tr>
</tbody>
</table>

Compliance was calculated as the percentage of total doses taken when compared with the total intended doses during the 6 months of treatment and was assessed by drug accountability and patient diaries.
93% of anakinra-treated patients receiving >90% of their injections and 43.8% of patients administering 100% of the injections in a large 6 month study (Table I) [5]. This suggests that patients’ compliance with anakinra treatment is high if they are continuing to derive benefit from the treatment. The daily s.c. injection regimen described should not, therefore, represent an issue in terms of patient management.

As noted previously, the most frequently reported adverse events seen in the randomized clinical trials with anakinra were ISRs. Similar to other injectable biological response modifiers, these ISRs generally occurred early in the treatment course and were rated by 95% of the patients as mild-to-moderate in severity [2]. The ISRs tended to resolve with continued therapy and rarely occurred after the first 4 weeks of treatment. From all anakinra clinical trials, 5.6% of anakinra-treated patients discontinued treatment owing to ISRs compared with 1.3% of placebo-treated patients [2].

As most anakinra-associated ISRs resolve within the first few weeks of therapy [2], appropriate patient instruction concerning these events is likely to lead to a lower dropout rate in clinical practice. Therefore, it may be advisable to inform the patient about the likelihood of an ISR and advise them to alternate injection sites as a preventative measure. In the eventuality that an ISR develops, the associated bruising and swelling at the injection site can be reduced by the application of a cold pack immediately after the injection. Itching is usually relieved by the application of a topical steroid.

**Patient selection for anakinra treatment**

Randomized, controlled-trial data support the use of anakinra as monotherapy in patients with moderate-to-severe RA or as combination therapy in patients with active disease despite DMARD treatment. To date, anakinra has primarily been used in patients receiving concurrent DMARD therapy with ongoing active disease.

There are further indications that anakinra may offer treatment benefits in patients with conditions co-morbid to RA [5]. An ongoing, randomized, controlled trial evaluating anakinra in patients with multiple sclerosis will help to determine the safety of this treatment in patients with RA and co-morbid demyelinating diseases. The short half-life of anakinra may also be a potential advantage for patients with co-morbidities that predispose them to infection and post-marketing surveillance will determine if this hypothesis is confirmed. Finally, we await the results of studies directly comparing lance will determine if this hypothesis is confirmed.

**Summary**

Anakinra is a novel drug approved for the treatment of RA and is the first IL-1 inhibitor currently indicated for patients with this condition. Extensive clinical studies of anakinra suggest that anakinra has a favourable risk–benefit profile, producing early and sustained reductions in RA signs and symptoms, measured by improvements in ACR response, and important effects on patient-reported indicators of function and disability. Accordingly, the introduction of anakinra provides clinicians with a useful new tool in the treatment of RA and offers patients another option for improving symptoms of this debilitating condition.

**References**


13. Bresnihan B, Chan WW, Woooley JM. Anakinra increases days of work and domestic activity in patients with rheuma-