Concomitant Medication Use in a Large, International, Multicenter, Placebo Controlled Trial of Anakinra, a Recombinant Interleukin 1 Receptor Antagonist, in Patients with Rheumatoid Arthritis

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ABSTRACT. Objective. To examine the safety of anakinra when added to a background of standard rheumatoid arthritis (RA) medications in patients with RA with active disease.

Methods. This analysis further evaluates data from the first 6 months of a blinded, placebo controlled safety trial that had a subsequent 30 month, open label portion (not reported here). Patients with RA with a wide range of comorbid conditions, disease activity, and background medications were randomly assigned in a 4:1 allocation ratio to treatment with anakinra 100 mg or placebo administered daily by injection. Safety was assessed by comparing adverse event profiles between anakinra and placebo patients according to concomitant medications received.

Results. Anakinra patients (n = 1116) showed no difference in the incidence of upper respiratory infections or overall serious adverse events compared with placebo patients (n = 283). The anakinra group had more injection site reactions (72.6% vs 32.9% in placebo) and a small increase in serious infections (2.1% vs 0.4% in placebo). Anakinra’s safety profile did not differ in patients receiving antihypertensive, antidiabetic, or statin drugs.

Conclusion. This study indicates that anakinra has a good safety profile in patients typically seen in a rheumatology practice who are considered candidates for therapy with agents that are immunomodulatory and disease modifying. Except for injection site reactions and a nonstatistically although potentially clinically significant increase in serious infections in the anakinra versus the placebo groups, the addition of anakinra to a stable background regimen of RA medications introduced no other important safety risk in patients with RA. (J Rheumatol 2004;31:649–54)

Key Indexing Terms:
INTERLEUKIN 1 RECEPTOR ANTAGONIST ANAKINRA CONCOMITANT MEDICATION

Today a variety of treatment options are available for patients with rheumatoid arthritis (RA), each providing some degree of efficacy, although also potentially limited by their toxicity. Nonsteroidal antiinflammatory drugs (NSAID) such as ibuprofen and the newer selective inhibitors of the cyclooxygenase enzyme (COX-2) provide relief from joint pain and swelling and are widely used by patients with RA. Corticosteroids are very effective in treating RA, and provide some degree of disease control, although their side effects limit their utility as a treatment option for many patients. Traditional disease modifying antirheumatic drugs (DMARD) can control pain and swelling to a fair extent. Some, such as methotrexate (MTX), sulfasalazine, and leflunomide, have shown an ability to inhibit the progressive joint destruction that develops in patients with RA. However, despite the available therapies, for many patients the goal of longterm control of their disease with an adequate degree of safety remains elusive. Research to develop new, safe, and effective treatments for RA continues.

The pathophysiology of RA is thought to involve the production of proinflammatory cytokines by antigen-activated T cells and autoreactive B cells. These cytokines further promote the activities that lead to the chronic inflammation and joint destruction characteristic of RA. The cytokines tumor necrosis factor (TNF) and interleukin 1 (IL-1) appear to play key roles in this process.

Recently developed biological treatments for RA were aimed at decreasing the concentrations of endogenous TNF or blocking the activity of IL-1. The ability to inhibit these
cytokines offers a novel and effective approach to suppressing inflammation and preventing joint damage caused by RA. Anakinra, a recombinant IL-1 receptor antagonist, is a competitive antagonist of IL-1 that blocks the actions of IL-1 without detectable agonist activity. Anakinra has shown activity in numerous experimental animal models of arthritis. Anakinra, a recombinant form of human IL-1Ra (r-metHuIL-1ra) or Kinerey is a recombinant form of human IL-1ra. In controlled clinical trials, treatment with anakinra improved the signs and symptoms and slowed the radiographic progression of RA.

The primary safety analysis from the group of patients discussed here has been reported. In this report, we examined in further detail the safety of anakinra in combination with other treatments by analyzing subgroups of patients based on their use of background RA medications and other concomitant medications. This analysis was performed to assess any significant differences between the anakinra and placebo treated patients based on their concomitant medications. Data were drawn from a large and diverse database and represent current practices in the use of DMARD, NSAID, and corticosteroid treatments, either alone or in combination, in the general RA patient population. This population includes patients with comorbid conditions, these data provide an accurate assessment of the safety of anakinra in a community practice setting.

MATERIALS AND METHODS

Study design. This analysis evaluates data from a randomized, multicenter safety study. The study was designed to be placebo controlled and double blinded for the first 6 months to assess any significant differences that might occur between patients receiving active drug and placebo. This analysis focuses on comparison of adverse event profiles between anakinra and placebo patients based on their concomitant medications. Patients completing the 6 month blinded phase were eligible for a 2.5 year extension phase in which all patients received active drug to assess any late and rare safety issues in a controlled setting (those results are not reported here). This study represents the largest known double blind, long-term safety trial in rheumatology to date.

The patients with RA were representative of those seen in the usual community practice setting. Patients with RA of varying severity, with various comorbid conditions and background RA medications, were included.

Patients. The protocol was approved by the study centers’ institutional review boards or institutional ethics committees, and all patients provided written informed consent, before any study procedures. Enrollment occurred during the period from September 1999 to January 2002. Eligible patients were at least 18 years old with a diagnosis of RA based on the American College of Rheumatology (ACR) 1987 diagnostic criteria, and had RA for at least 3 months. Patients were required to have active disease at baseline, defined as at least 3 swollen joints and 3 tender/painful joints, or 45 minutes of morning stiffness. Patients receiving NSAID and/or oral corticosteroids (up to 10 mg/day prednisone or equivalent) were required to be taking stable doses for at least 1 month before randomization, and those receiving DMARD were required to be taking stable doses for at least 2 months before randomization. While on study, patients were permitted to receive NSAID, corticosteroids, and DMARD, either alone or in any combination, and changes could be made in these medications during the course of the study if clinically indicated by the treating physician. Patients were not allowed to be taking biologic TNF inhibitors at entry or during the course of the study.

The study was designed to include patients with comorbid conditions and excluded as few patients as possible. However, patients were excluded if they had uncontrolled medical conditions (e.g., diabetes with HbA1c > 8%), a malignancy other than basal cell carcinoma of the skin or in situ carcinoma of the cervix within the previous 5 years, Felty’s syndrome, white blood cell count < 2.0 × 10^9/l, neutrophil count < 1.0 × 10^9/l, platelet count < 100 × 10^9/l, AST or ALT ≥ 1.5 times the upper limit of normal, or they were known to be positive for hepatitis B or C or human immunodeficiency virus. Women who were pregnant or breastfeeding were also excluded.

Study drug. Anakinra (Amgen Inc., Thousand Oaks, CA, USA) was supplied in vials as a clear, colorless, sterile solution containing 100 mg r-metHuIL-1ra. Placebo consisting of the vehicle used in the preparation of anakinra was provided in similar vials. Both anakinra and placebo were self-administered daily as a 1.0 mg subcutaneous injection. Patients, healthcare providers, and the sponsor were blinded to the identity of the drug being administered. Treatment compliance was assessed by drug accountability and patient diaries.

Analysis endpoints. The analyses presented here assess the safety of anakinra by summarizing the incidence of upper respiratory infections; serious adverse events, including infections; and injection site reactions during the first 6 months of treatment. A serious adverse event was defined as any event that suggested a significant hazard or side effect, regardless of the investigator’s or sponsor’s opinion on the relationship to study medication. By regulatory definition, serious adverse events included any event that was fatal or life-threatening, resulted in a persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or those that required or prolonged inpatient hospitalization. Information on infectious episodes was collected separately from other adverse events on a case report-form page specific for that purpose. Serious infections were defined as the subset of serious adverse events that were also included in the category of infections. Adverse events were grouped by body system and by preferred term within the body system, according to a modified World Health Organization adverse reaction term dictionary.

Statistical analysis. During the 6 month blinded phase, the probability of observing at least 1 serious event/infectious episode at a 1.0% incidence rate was estimated to be 87% for the placebo group and greater than 99% for the anakinra group, with the planned sample size.

All patients who were randomized and received at least 1 dose of study drug were included in the statistical analyses. Mean values (± SD) for continuous measures and numbers (%) for categorical measures were used to summarize baseline demographic and disease characteristics including background medication use. The numbers (%) of patients experiencing at least 1 adverse event were summarized by preferred term and treatment group.

RESULTS

Patients. This report presents results from the initial 6 month, placebo controlled phase of the study. A total of 1414 patients were enrolled at 169 centers in the US, Canada, Europe, and Australia, and 1399 patients received at least 1 dose of study drug (1116 anakinra and 283 placebo). The 2 treatment groups were well balanced at baseline with respect to demographics and baseline disease status. Most patients were white women. In both treatment groups, the mean age was mid-fifties, the duration of RA was about 10 years, and C-reactive protein (CRP) concentrations were 2.7 (± 3.3) mg/dl. The mean number of tender/painful joints was 22.6 (± 14.5) in the placebo and 22.6 (± 14.7) in the anakinra
treatment group; the mean number of swollen joints was 18.3 (± 11.7) and 18.8 (± 11.9), respectively.

Use of RA medications at baseline. Patients were permitted to use DMARD, NSAID, and corticosteroids, either alone or in any combination, while on study. The use of these medications was balanced across the 2 treatment groups at baseline. Overall, 1090 of the 1399 enrolled patients (77.9%) were receiving 1 or more DMARD at the time of study entry (Figure 1). About half of all patients (747, 53%) were receiving MTX, which was the only DMARD administered in 31.9% of patients. Following trends in clinical practice, the use of multiple DMARD was common in this population, with 21.5% of patients receiving MTX in combination with 1 or more other DMARD. Of the patients who were not taking MTX, 19.2% of patients were taking another single DMARD and 5.3% were taking multiple other DMARD. Leflunomide monotherapy was taken by 5.4% of patients, hydroxychloroquine monotherapy by 4.9%, and gold or azathioprine monotherapy was taken by up to 2.0%.

The use of non-DMARD RA medications at baseline is presented in Table 1. NSAID and corticosteroids were used extensively, with 87.0% of all patients taking at least 1 NSAID and 57.8% receiving a corticosteroid. COX-2 inhibitors, introduced shortly before the initiation of this study, were used by 9.1% of patients.

A total of 318 (22.7%) patients were receiving at least 1 medication from all 3 categories (DMARD, NSAID, and corticosteroids). The use of these medications was similar across the 2 treatment groups.

Safety of anakinra with background RA medications. Safety was assessed by comparing the incidence of infections, particularly upper respiratory infections and serious infections; adverse events; and injection site reactions in patients taking anakinra and placebo. For the overall population of 1399 patients, no differences between the placebo and anakinra groups were seen in the incidence of upper respiratory infections (19.1% placebo, 14.3% anakinra) or overall serious adverse events (7.8% placebo, 7.7% anakinra) (Table 2). Injection site reactions, the most common side effect of treatment with anakinra, occurred in 72.6% of anakinra patients and 32.9% of placebo patients. These injection site reactions were generally transient and mild or moderate in severity. These observations are consistent with previously reported clinical experience with anakinra.

The incidence of serious infectious events was greater in the anakinra group (23 patients, 2.1%) compared with the placebo group (1 patient, 0.4%), although the increase was not statistically significant (p = 0.068, Fisher exact test). However, this difference in the rate of serious infections may be clinically significant. These infections consisted primarily of pneumonia and cellulitis in patients already at risk for infection (i.e., those with underlying pulmonary disease or history of pneumonia at study entry in 8 of the 10 patients with pneumonia, and diabetes or toe ulcer at study entry in all 3 patients with cellulitis). No serious infectious event was fatal. All but 2 of the patients with infections (1 with appendicitis and 1 with gastroenteritis) were treated with antibiotics, and all but 6 resumed anakinra therapy once their infection resolved.

Overall, infections (including those not considered to be serious) occurred at a similar incidence in the 2 groups: 43.5% of placebo patients and 41.2% of anakinra patients (Table 3).

Based on a review of laboratory values, adverse events, and background RA use, no evidence of any nephrotoxicity associated with anakinra use was observed in this study.

The adverse event profiles were similar between patients who were or were not taking concomitant antihypertensive, antidiabetic, or statin drugs (Table 4). The safety profile
observed in the overall patient population remained consistent when patients were subdivided and analyzed based on their concurrent RA medications. Table 2 presents this analysis for various individual DMARD and combinations of DMARD used by patients in the study. These DMARD represent the typical second-line agents used in practice today. Compared with the addition of placebo, anakinra added to a background of MTX monotherapy resulted in no increased incidence of upper respiratory infections (placebo, 23.0%; anakinra, 14.5%) or serious adverse events (placebo, 7.0%; anakinra, 6.9%). The same was true for patients receiving combination therapy with 1 or more other DMARD in addition to MTX: upper respiratory infections occurred in 25.0% of placebo patients and 15.5% of anakinra patients; serious adverse events arose in 8.8% of placebo and 5.2% of anakinra patients.

As in the overall study population, the incidence of injection site reactions in the DMARD subgroups was higher in anakinra patients than placebo patients: reactions occurred in 28.0% in placebo patients and 74.3% in anakinra patients receiving MTX as their only DMARD, and 39.7% in placebo patients and 79.4% in anakinra patients receiving MTX plus 1 or more other DMARD. Of note, the incidence of injection site reactions among anakinra patients was somewhat lower (63.3%) in the subgroup of patients who were not receiving any DMARD on study. Serious infectious events were not observed in any of the placebo patients in the MTX monotherapy and MTX plus other DMARD group, but did arise (2.3% and 2.1%, respectively) in the corresponding anakinra patient groups. The azathioprine group is notable for its serious infection rate of 8.3% (n = 2) in patients receiving anakinra in addition to this immunosuppressive agent. However, the numbers of patients in all subgroups of patients receiving DMARD other than MTX are too small to draw any definitive conclusion.

Table 3 presents the incidence of adverse events in the non-DMARD RA medication subgroups. A similar pattern was seen in patients taking NSAID or corticosteroids to that seen for the DMARD subgroups and the overall study population.
The most significant safety concern in these patients is serious infections. Given the immunosuppressive effects of certain therapies used in the treatment of RA, such as corticosteroids and some DMARD, adding an agent that suppresses IL-1 might further diminish the immune response and allow events such as serious infections to occur. In this study the incidence of serious infections among patients receiving anakinra was 2.1% overall, and 3.0% for anakinra patients receiving corticosteroids. No opportunistic infections were observed.

Although corticosteroid use may be a risk factor, the interpretation of these rates is somewhat complicated by the unusually low rate of serious infections among the patients receiving placebo in this study. Only 1 patient in the placebo group experienced a serious infection, which gave a rate of 0.4% for all patients in the placebo group or 0.6% for placebo patients receiving corticosteroids. The rate of serious infections in anakinra patients is consistent with previous reports in similar RA populations. It is also consistent with that seen in another large anakinra study, where the placebo and anakinra rates were similar.

Microbiologic data from the patients with serious infections were limited, but the available data revealed only the presence of common organisms such as Streptococcus pneumoniae in patients with pneumonia and Staphylococcus aureus in patients with bone and joint infections. No case of tuberculosis, histoplasmosis, listeriosis, or aspergillosis (observed in some patients receiving RA treatments targeting TNF) was reported.

Patients with serious infections resumed their anakinra treatment once their infection resolved most of the time: of the 23 patients who experienced a serious infection in this study, only 6 permanently discontinued anakinra as a result. Upper respiratory infections did not increase in patients assigned anakinra in this study (19.1% placebo, 14.3% anakinra). No trends were observed among the medication subgroups. In patients receiving MTX, either alone or with other DMARD, the incidence of upper respiratory infections actually appeared to be lower in the anakinra patients (14.5% and 15.5%) than the placebo patients (23.0% and 25.0%).

### Table 5. Adverse events for patients taking other RA medications.

<table>
<thead>
<tr>
<th>Subgroup (Placebo, Anakinra)</th>
<th>Upper Respiratory Infection</th>
<th>Serious Infectious Episode</th>
<th>Serious Adverse Event</th>
<th>Injection Site Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (283, 1116)</td>
<td>PLA, % 19.1</td>
<td>ANA, % 14.3</td>
<td>PLA, % 0.4</td>
<td>ANA, % 2.1</td>
</tr>
<tr>
<td>NSAID (244, 973)</td>
<td>PLA, % 19.3</td>
<td>ANA, % 15.0</td>
<td>PLA, % 0.4</td>
<td>ANA, % 2.0</td>
</tr>
<tr>
<td>COX-2 inhibitor (29, 99)</td>
<td>PLA, % 31.0</td>
<td>ANA, % 15.2</td>
<td>PLA, % 0.0</td>
<td>ANA, % 3.0</td>
</tr>
<tr>
<td>Corticosteroids (172, 636)</td>
<td>PLA, % 19.8</td>
<td>ANA, % 13.2</td>
<td>PLA, % 0.6</td>
<td>ANA, % 3.0</td>
</tr>
<tr>
<td>NSAID, corticosteroids, with no DMARD (24, 112)</td>
<td>PLA, % 8.3</td>
<td>ANA, % 13.4</td>
<td>PLA, % 4.2</td>
<td>ANA, % 4.5</td>
</tr>
</tbody>
</table>

PLA: placebo, ANA: anakinra.

The incidence of injection site reactions in anakinra patients receiving NSAID (72.5%) and in those receiving corticosteroids (71.2%) was essentially the same as the incidence in the overall study population (72.6%).

Patients receiving NSAID and/or corticosteroids but no DMARD had a somewhat different profile. In these patients, the incidence of serious infections was higher for both placebo and anakinra patients (4.2% and 4.5%, respectively) compared with the rates for the overall population (0.4% and 2.1%). Serious adverse events were seen in 12.5% and 16.1% of the placebo and anakinra groups, respectively, compared with 7.8% and 7.7% for the overall population, and injection site reactions occurred at a lower incidence (25.0% and 64.3%) than in the overall population (32.9% and 72.6%).

### DISCUSSION

Although drug treatment options for RA patients have improved dramatically over the past decade, the typical RA patient, until recently, was taking 1 or more arthritis medications and still not obtaining optimal control of disease symptoms or reduction in disease progression. Each addition to the existing regimen of DMARD increases the risk of toxicity. This study was designed to provide information on the safety of introducing a biological therapy targeted at the IL-1 pathway in RA patients typically treated in clinical practice. We studied anakinra, a new biologic therapy for RA that inhibits IL-1, under controlled conditions in a large number of patients already receiving other RA medications.

A preliminary analysis of patients from this study with high-risk comorbid conditions has been published. Patients with 1 or more comorbid conditions had about the same amount of increased risk of infections and serious adverse events whether they were in the placebo or anakinra groups.
In contrast, patients receiving hydroxychloroquine had a higher incidence of upper respiratory tract infections in the anakinra group (17.0%) compared to placebo (6.3%). In summary, no clear pattern emerged.

While these subgroup analyses were not prespecified in the study protocol, they do suggest that anakinra can be safely added when a number of commonly used medications are already present. The only consistent trend is an increased incidence of injection site reactions in patients receiving anakinra. These injection site reactions are known and well characterized effect of anakinra and have been reported frequently in most of the clinical studies. The reactions are generally mild or moderate in severity, consist most often of erythema, pruritus or rash, and are uncommonly a cause for discontinuation of anakinra therapy. In this study, the incidence of injection site reactions among anakinra patients was somewhat lower (63.3%) in the subgroup of patients who were not receiving DMARD (compared with 72.6% overall). Injection site reactions typically occurred during the first month of treatment and were unlikely to occur for the first time after the first month of treatment.

The findings from this large, randomized study, designed to reflect current practices in the use of RA treatment, suggest that patients already receiving 1 or more commonly used RA medications may safely add anakinra to their treatment regimen. However, vigilance for clinically significant infectious episodes needs to be maintained.

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REFERENCES