Effect of Anakinra on Functional Status in Patients with Active Rheumatoid Arthritis Receiving Concomitant Therapy with Traditional Disease Modifying Antirheumatic Drugs: Evidence from the OMEGA Trial

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ABSTRACT. ***Objective.*** To assess changes in functional status in patients with rheumatoid arthritis (RA) receiving the interleukin-1 receptor antagonist anakinra in addition to a disease modifying antirheumatic drug (DMARD).

Methods. In this large, multicenter, open-label, single-arm study, adult patients with RA receiving methotrexate, sulfasalazine, or hydroxychloroquine for ≥ 3 months were given anakinra 100 mg once daily for up to 36 weeks. The primary objective was to evaluate changes from baseline to week 36 in the Health Assessment Questionnaire (HAQ) disability index and subscales. Changes in the 28-joint Disease Activity Score (DAS28), proportion of patients meeting European League Against Rheumatism (EULAR) response criteria, and the safety of each combination regimen were also assessed.

Results. A total of 1207 patients were enrolled, received ≥ 1 dose of anakinra, and were included in the efficacy and safety analyses. A statistically significant change in the HAQ disability index was observed ($p = 0.0001$); no significant differences were seen among the 3 DMARD groups. A clinically meaningful improvement in HAQ (> 0.22) was observed in 51% of patients. Mean improvement in DAS28 was 1.5 ($p < 0.0001$), and 64% of patients achieved a good or moderate EULAR response score. Injection site reaction was the most frequently (62%) reported adverse event. The incidence of infections (24%), most commonly respiratory infection, was similar across treatment groups. No notable changes were observed in laboratory findings and vital signs.

Conclusion. These findings indicate that anakinra 100 mg/day in combination with DMARD therapy safely improved functional status in patients with active RA. (First Release July 15 2008; J Rheumatol 2008;35:1538–44)

Key Indexing Terms:
INTERLEUKIN-1 RECEPTOR ANTAGONIST RHEUMATOID ARTHRITIS
QUALITY OF LIFE TREATMENT OUTCOME QUESTIONNAIRES

Rheumatoid arthritis (RA) is a chronic disease characterized by persistent joint inflammation that results in progressive destruction of bone and cartilage. Although the cause of RA remains uncertain, a greater understanding of its underlying pathophysiology has facilitated the development of new disease targets. Proinflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-1, play key roles in synovial inflammation and progressive joint damage[1,2]. The consequences of joint damage in RA include pain, loss of function, and difficulty engaging in daily activities, such as dressing, grooming, and walking[3-5]. Diminished function has also been shown to be a strong predictor of mortality in patients with RA[6].

Therapy for patients with moderate to severe RA usually includes disease modifying antirheumatic drugs (DMARD). DMARD treatment has been shown to improve the signs and symptoms of RA but does not completely control disease progression[7]. Biologic agents that directly target inflammatory cytokines involved in the pathogenesis of RA have demonstrated improved efficacy in the treatment of

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these patients compared with traditional DMARD therapy[8,9]. Addition of a biologic agent to DMARD therapy has been shown to significantly reduce disease activity and inhibit radiographic progression compared with DMARD therapy alone[10]. These clinical benefits of combination therapy have also been associated with improvements in patient function[11,12].

Anakinra is the first biologic agent developed specifically as an exogenous IL-1 receptor antagonist (IL-1Ra). The imbalance between endogenous IL-1Ra and IL-1 plays an important role in the pathogenesis of RA[13,14]. Mononuclear cell cultures from patients with RA have been shown to produce less IL-1Ra than necessary to inhibit IL-1 activity. In addition, increased ratios of IL-1Ra to IL-1 have been shown to be associated with decreased disease activity, improving the prognosis in patients with RA[15,16].

The efficacy of anakinra alone or in combination with methotrexate (MTX) and the safety of anakinra alone or in combination with other DMARD have been evaluated in 4 randomized, double-blind, placebo-controlled trials as well as in observational studies of adult patients with RA[17-22]. Anakinra produced statistically significant and clinically meaningful improvements in disease activity, radiographic progression, and patient-reported outcomes, which included assessments of pain reduction and functional disability as measured by the Health Assessment Questionnaire (HAQ). Maintaining functional capacity is an important therapeutic goal in RA, and the HAQ has been shown to be highly predictive of the response to treatment with biologic therapies and DMARD in clinical trials[23]. The Outcome Measures Generated by Anakinra (OMEGA) is a multicenter, open-label, single-arm trial. It included a large, diverse population of patients with RA who are representative of those seen in a clinical practice setting (e.g., women, mean age 55.2 yrs, mean duration of RA 9.5 yrs, taking commonly prescribed DMARD). The objective of our study was to further elucidate the functional improvements using HAQ in patients treated with anakinra in addition to traditional DMARD therapy. In particular, the study was designed to compare the efficacy and safety of anakinra in combination with either MTX, hydroxychloroquine (HCQ), or sulfasalazine (SSZ).

MATERIALS AND METHODS

Patients. Eligible patients were men and women (aged ≥ 18 yrs) with a diagnosis of RA as determined by American College of Rheumatology criteria and European League Against Rheumatism (EULAR) criteria [28-joint Disease Activity Score (DAS28) ≥ 3.8]. Before screening, patients were to have been receiving a stable dose (defined as the same dose for ≥ 4 wks) of a single DMARD (MTX, SSZ, or HCQ) for ≥ 3 months. Doses of nonsteroidal antiinflammatory drugs and oral corticosteroids were allowed, up to 10 mg/day of prednisone or equivalent, provided the dose was stable for ≥ 4 weeks before screening.

Major exclusion criteria included use of DMARD other than MTX, SSZ, or HCQ; use of intraarticular injections (e.g., corticosteroids, hyaluronate preparations) or systemic corticosteroid injections within 4 weeks of screening; known allergy to *Escherichia coli*–derived products; neutropenia or thrombocytopenia; abnormal liver or impaired renal function; diagnosis with Felty's syndrome, any uncontrolled clinically significant systemic disease, or an autoimmune disease other than RA; history of recurrent or chronic infections; malignancy other than basal cell carcinoma of the skin or *in situ* carcinoma of the cervix within the past 5 years; or pregnancy. The Institutional Review Boards/Independent Ethics Committees at each site approved the study. All patients provided informed written consent, and the study was conducted in accordance with the International Conference on Harmonisation and Good Clinical Practice regulations and guidelines.

Study design. This multicenter, open-label, single-arm study was designed to evaluate changes in functional status, as assessed by HAQ, from baseline to week 36 in patients with active RA receiving anakinra in combination with an established dose of a single DMARD therapy (MTX, SSZ, or HCQ) chosen by the investigator. The study was conducted at 144 sites in 12 countries: Austria, Belgium, Denmark, Finland, France, Germany, Italy, the Netherlands, Norway, Portugal, Spain, and Sweden. After a 2- to 4-week screening period, patients were eligible for study entry. Patients received a fixed dose of anakinra 100 mg, given as a daily subcutaneous injection from a prefilled syringe, for up to 36 weeks in addition to their established DMARD therapy. No additional DMARD therapies were permitted. Study assessments were performed at screening; baseline; and weeks 2, 4, 12, 24, and 36 (end of study). Patients who withdrew from the study were not replaced.

Clinical measurements. The primary measure of efficacy was the change in the HAQ disability index from baseline to week 36. The HAQ is a validated, self-administered questionnaire that measures functional status (i.e., dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities) and has been widely used in the RA population[6,23,24]. HAQ scores range from 0 to 3, with lower scores indicating better functional status. A change in HAQ of between –0.19 and –0.22 is considered to be clinically relevant[25,26]. Exploratory measures included assessments of DAS at screening, baseline, and weeks 4, 12, 24, and 36. DAS28 incorporates 4 core set measures: 28-joint count for tenderness and swelling, patient global assessment of disease scored on a visual analog scale, and erythrocyte sedimentation rate (ESR). Further, the proportion of patients meeting EULAR response criteria (good, moderate, or none) at week 36 was assessed.

Safety was assessed by adverse events (AE), which were recorded throughout the study regardless of relationship to study drug as assessed by the investigator. In addition, blood and urine samples were collected for laboratory analysis (chemistry, hematology, and urinalysis) at all visits except that at week 2. Electrocardiogram and chest radiograph were measured at screening only, with examination and vital signs assessed at screening and week 36. Concomitant medications were recorded at all visits.

Statistical analyses. A sample size of 1200 patients was selected. This was calculated to provide 90% power to detect a change of at least 0.19 in the HAQ disability index with alpha = 0.05 and assuming a standard deviation (SD) of 0.63. Efficacy analyses were performed for the intent-to-treat (ITT) population, which included all patients who were enrolled and received at least 1 dose of anakinra and had at least 1 postbaseline dose efficacy assessment. Last observation carried forward was used in the ITT analyses for handling missing data. Analysis of variance (ANOVA) was performed for the change from baseline in HAQ and DAS28 (including individual core components), adjusting for country and DMARD groups. Analysis of covariance adjusting for baseline covariates was also performed for the change from baseline in HAQ and DAS28. An additional analysis determined the proportion of patients who achieved a clinically meaningful HAQ response. The proportion of patients achieving EULAR response criteria at week 36 was analyzed using a stratified chi-square test adjusting for country. Safety data (AE, serious AE, events related to treatment, events leading to withdrawal, laboratory findings, vital signs, and concomitant medications) were assessed for all enrolled patients who received at least 1 dose of anakinra. Descriptive statistics were used to summarize all efficacy

and safety data, including 2-sided 95% confidence intervals (CI) for changes from baseline.

RESULTS

Patient disposition and demographics. The ITT population comprised 1207 patients who enrolled, received at least 1 dose of anakinra, and completed at least 1 postbaseline assessment. Patient disposition is shown in Figure 1. A total of 21 patients (1.7%) included in the ITT population analysis received medication in violation of the protocol: cyclophosphamide, etanercept, glucosamine, infliximab, or leflunomide, or they received MTX, SSZ, or HCQ in addition to their established DMARD. Similar proportions of patients in each DMARD group withdrew from the study. The most common primary reason for discontinuation was the occurrence of an AE; 155 of 1207 (12.8%) patients withdrew because of an AE. The majority (67%) of these patients reported injection site reactions as the reason.

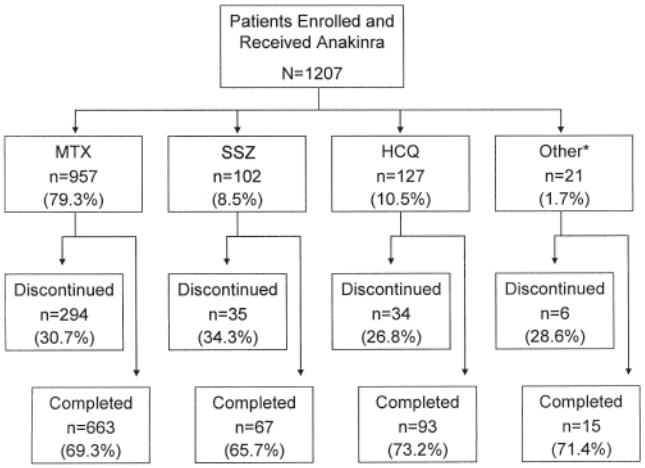

Figure 1. Patient disposition. HCQ: hydroxychloroquine; MTX: methotrexate; SSZ: sulfasalazine. *Patients using other DMARD in violation of the protocol.

Baseline demographics and disease characteristics were generally similar among the treatment groups (Table 1). Most patients were women (80%) and white (98%) and ranged in age from 20 to 86 years. At baseline in the ITT population, 127 (10.5%) patients were taking HCQ, 102 (8.5%) were taking SSZ, and 957 (79.3%) were taking MTX [median daily doses of 400.0 mg, 2000.0 mg, and 2.1 mg (or 14.7 mg/wk), respectively]. Overall, 20.3% of patients had been treated with > 1 DMARD. Patients in the anakinra + HCQ group had a slightly longer duration of RA compared with the other 2 groups (median, 9 yrs vs 7 yrs and 6 yrs in the MTX and SSZ groups, respectively) but a much shorter duration of DMARD use (median, 239 days vs 351 and 304 days). Most patients were receiving corticosteroids at baseline (72.9%), and few patients increased or decreased their dose throughout the study (< 4% of patients receiving any given corticosteroid).

Efficacy evaluations. Anakinra produced statistically significant improvements from baseline in the HAQ disability index for all DMARD groups (Figure 2). Overall, the mean ± SD improvement in the HAQ disability index was 0.2 ± 0.55 (95% CI 0.2–0.3), with the greatest improvement observed in the MTX group (0.3; 95% CI 0.2–0.3). The mean percentage improvement overall (Figure 3) was 13.4%

Table 1. Baseline demographics and disease characteristics (ITT population).

	Anakinra + MTX (n = 957)	Anakinra + SSZ (n = 102)	Anakinra + HCQ (n = 127)	Total (n = 1207*)
Women, n (%)	757 (79.1)	79 (77.5)	113 (89.0)	965 (80.0)
White, n (%)	934 (97.6)	98 (96.1)	126 (99.2)	1179 (97.7)
Age, median (range), yrs	56 (20–86)	57 (23–80)	57 (24–80)	56 (20–86)
Body weight, median (range), kg	68 (40–151)	69 (40–128)	65 (43–122)	68 (40–151)
RA duration, median (range), yrs	7.3 (0.0–50.5)	6.1 (0.4–48.6)	9.0 (0.0–51.9)	7.4 (0.0–51.9)
Total daily DMARD dose, median (range), mg	2.1† (0.2–6.4)	2000.0 (480–8000)	400.0 (57–800)	—
DMARD duration, median (range), days	351.0 (1–7392)	304.5 (6–4680)	239.0 (44–4324)	328.0 (1–7392)
Number of DMARD used, n (%)				
1	769 (80.4)	80 (78.4)	100 (78.7)	962 (79.7)
2	166 (17.3)	17 (16.7)	20 (15.7)	210 (17.4)
3	20 (2.1)	5 (4.9)	5 (3.9)	31 (2.6)
≥ 4	2 (0.2)	0 (0)	2 (1.6)	4 (0.3)
HAQ score, mean (SD)	1.6 (0.64)	1.5 (0.67)	1.6 (0.63)	1.6 (0.64)
DAS28 score, mean (SD)	6.1 (1.0)	5.9 (1.1)	5.9 (1.1)	6.0 (1.0)

* Includes 21 patients who received other DMARD in violation of the protocol. † Median 14.7 mg/wk. DAS28: 28-joint Disease Activity Score; DMARD: disease modifying antirheumatic drug; HAQ: Health Assessment Questionnaire; HCQ: hydroxychloroquine; mITT: modified intent to treat; MTX: methotrexate; RA: rheumatoid arthritis; SD: standard deviation; SSZ: sulfasalazine.

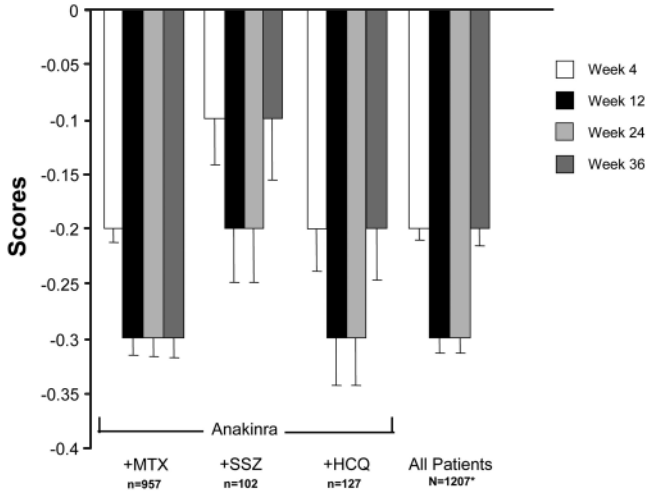

Figure 2. Mean changes (± standard error of the mean) in Health Assessment Questionnaire scores from baseline to week 36 by disease modifying antirheumatic drug (DMARD) cohort (intent-to-treat population, last observation carried forward imputation). HCQ: hydroxychloroquine; MTX: methotrexate; SSZ: sulfasalazine. All changes from baseline $p < 0.05$. *Includes 21 patients using other DMARD in violation of the protocol.

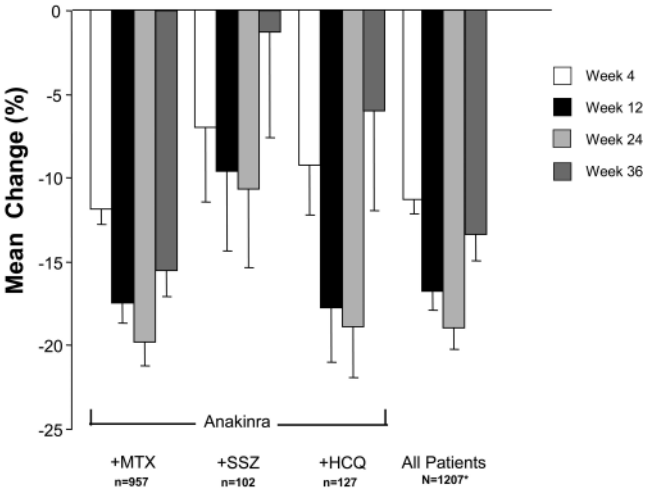

Figure 3. Mean percentage change (± standard error of the mean) in Health Assessment Questionnaire scores from baseline to week 36 by disease modifying antirheumatic drug (DMARD) cohort (intent-to-treat population, last observation carried forward imputation). HCQ: hydroxychloroquine; MTX: methotrexate; SSZ: sulfasalazine. *Includes 21 patients using other DMARD in violation of the protocol.

(95% CI 10.4–16.4). A total of 51.2% of all patients enrolled had a clinically relevant improvement > 0.22 in the HAQ disability index from baseline, with a similar percentage of patients across DMARD cohorts (Figure 4). The changes from baseline to week 36 in the HAQ disability index subscales were similar to the overall HAQ index. The greatest improvements were seen in dressing and grooming (0.3 ± 0.83), eating (0.3 ± 0.88), reach (0.3 ± 0.88), and grip (0.3 ± 0.84).

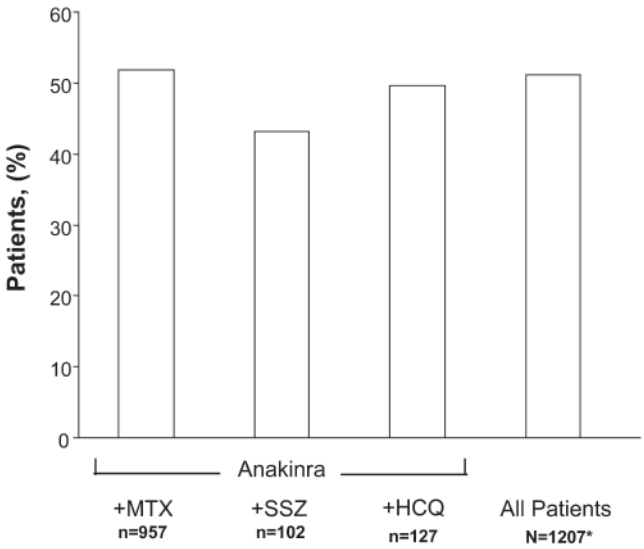

Figure 4. Percentage of patients with clinically relevant improvement > 0.22 in Health Assessment Questionnaire at week 36 relative to baseline (intent-to-treat population, last observation carried forward imputation). HCQ: hydroxychloroquine; MTX: methotrexate; SSZ: sulfasalazine. *Includes 21 patients using other DMARD in violation of the protocol.

No statistically significant difference was observed in the HAQ change from baseline to week 36 between the 3 DMARD groups ($p = 0.0762$); however, there was a trend favoring the MTX group compared with the other DMARD groups. After a rapid initial improvement in all DMARD groups between baseline and week 4, and a further improvement at week 12, the HAQ disability index scores remained consistent for most groups over the study period (Figure 2).

A repeated measures analysis was performed on the HAQ index data collected over all 5 visits as a sensitivity analysis, which incorporated baseline HAQ, country, and background DMARD use as factors. In the ITT analysis, a statistically significant improvement from baseline to week 36 was observed at the 5% level ($p < 0.0001$). The adjusted mean (standard error) improvement in the HAQ observed was 0.24 (0.015), which is consistent with the results found in the ANOVA analysis.

The mean improvement in DAS28 from baseline was 1.5 (95% CI 1.4–1.6; $p < 0.0001$), and the mean percentage improvement was 24.7% (95% CI 23.4%–26.0%). Improvements were seen in all DMARD groups for all 4 core components of the DAS28 (tender/painful joint score, swollen joint score, ESR, and patient global assessment). Further, 64.0% of patients (n = 773) received a good or moderate EULAR response score at week 36 (65.8% in the MTX group, 53.9% in the SSZ group, and 59.1% in the HCQ group).

Safety evaluations. Treatment groups were similar with respect to incidence of AE (Table 2). A total of 1030 patients (85.3%) reported 1 or more AE, and 224 (18.6%) patients experienced severe, life-threatening, or fatal AE. AE leading

Table 2. Overall incidence of adverse events (AE).

	Anakinra + MTX n (%) n = 957	Anakinra + SSZ n (%) n = 102	Anakinra + HCQ n (%) n = 127	Total n (%) n = 1207*
All AE	816 (85.3)	92 (90.2)	106 (83.5)	1030 (85.3)
Severe AE†	186 (19.4)	15 (14.7)	22 (17.3)	224 (18.6)
Serious AE	82 (8.6)	6 (5.9)	6 (4.7)	95 (7.9)
All treatment-related AE	715 (74.7)	80 (78.4)	97 (76.4)	904 (74.9)
Serious treatment-related AE	17 (1.8)	0 (0.0)	1 (0.8)	18 (1.5)
Discontinuations due to AE (excluding death)	136 (14.2)	14 (13.7)	16 (12.6)	167 (13.8)
Death‡	6 (0.6)	0 (0.0)	0 (0.0)	6 (0.5)

* Includes 21 patients who received other DMARD in violation of the protocol. † Includes severe, life-threatening, or fatal events. ‡ Also included with serious AE. DMARD: disease modifying antirheumatic drug; HCQ: hydroxychloroquine; MTX: methotrexate; SSZ: sulfasalazine.

to study withdrawal occurred in 167 patients (13.8%). Similar proportions of patients in the 3 DMARD groups withdrew because of AE: 136 patients (14.2%) in the MTX group, 14 patients (13.7%) in the SSZ group, and 16 patients (12.6%) in the HCQ group. Injection site reaction was the most common AE leading to study withdrawal (9.5%, 5.9%, and 7.9% of the MTX, SSZ, and HCQ groups, respectively).

Overall, injection site reactions were the most frequently reported AE. In total, 747 patients (61.9%) developed at least 1 injection site reaction during the study. The median time to initial injection site reaction was 17 days, with a similar profile observed among DMARD groups. The incidence of all AE occurring in ≥ 3% of patients in any DMARD group (not including injection site reactions) is shown in Table 3; common AE included headache (5.2%), erythema (5.2%), and pruritus (4.6%). The most frequent treatment-related AE, other than injection site reaction, that were determined by the investigator to have at least a possible relationship to treatment and occurring in ≥ 3% of any group included erythema (4.2%), pruritus (3.9%), headache (2.6%), and nausea (1.3%).

Most reports of serious AE were single incidents, and none occurred in more than 1% of patients. A total of 95 patients (7.9%) reported at least 1 serious AE: 82 (8.6%) in the MTX group, 6 (5.9%) in the SSZ group, 6 (4.7%) in the HCQ group, and 1 (4.8%) patient in the "other DMARD" group. The most common serious AE were fracture (11 patients, 0.9%), exacerbation of RA (6 patients, 0.5%), and abdominal pain and herniated disc (both in 5 patients, each 0.4%). One patient in the MTX group developed lymphoma

Table 3. Adverse events occurring in ≥ 3% of any DMARD group (not including injection site reactions).

	Anakinra + MTX n (%) n = 957	Anakinra + SSZ n (%) n = 102	Anakinra + HCQ n (%) n = 127	Total n (%) n = 1207*
Headache	45 (4.7)	8 (7.8)	9 (7.1)	63 (5.2)
Erythema	45 (4.7)	7 (6.9)	10 (7.9)	63 (5.2)
Pruritus	40 (4.2)	9 (8.8)	3 (2.4)	55 (4.6)
Rheumatoid arthritis flare	43 (4.5)	5 (4.9)	7 (5.5)	55 (4.6)
Upper respiratory infection	40 (4.2)	7 (6.9)	2 (1.6)	50 (4.1)
Bronchitis	37 (3.9)	5 (4.9)	1 (0.8)	43 (3.6)
Back pain	37 (3.9)	3 (2.9)	3 (2.4)	43 (3.6)
Urinary tract infection	35 (3.7)	1 (1.0)	5 (3.9)	42 (3.5)
Abdominal pain	34 (3.6)	2 (2.0)	6 (4.7)	43 (3.6)
Arthralgia	31 (3.2)	7 (6.9)	4 (3.1)	43 (3.6)
Fever	31 (3.2)	2 (2.0)	3 (2.4)	38 (3.1)
Nausea	29 (3.0)	1 (1.0)	8 (6.3)	38 (3.1)
Influenza-like symptoms	24 (2.5)	5 (4.9)	3 (2.4)	33 (2.7)
Hypertension	23 (2.4)	6 (5.9)	5 (3.9)	36 (3.0)
Vertigo	13 (1.4)	4 (3.9)	3 (2.4)	22 (1.8)

* Includes 21 patients who received other DMARD in violation of the protocol. DMARD: disease modifying antirheumatic drug; HCQ: hydroxychloroquine; MTX: methotrexate; SSZ: sulfasalazine.

on day 185, which was judged by the investigator to be possibly related to anakinra. The patient was withdrawn, and the event was continuing at the last observation. Six deaths occurred in the anakinra + MTX group (incidence, 0.6%) during the study or followup period, which was 1 month after the last dose (including 1 death reported as an off-study event). In general, deaths appeared to result from comorbid conditions that were consistent with this patient population.

Across all treatment groups, 289 patients (23.9%) developed at least 1 infectious episode (IE) during the study. The most common IE in all treatment groups was respiratory infection (12.3%). Seventeen patients in the MTX group developed a serious IE during the study (1.4% of all patients enrolled, 1.8% of the MTX group). A case of nondisseminated pulmonary tuberculosis was reported in 1 patient after 8 months of therapy with anakinra; it was determined that this patient was a miner with an abnormal chest radiograph and a history of occupational lung fibrosis (pneumonoconiosis), which is associated with an increased risk of developing pulmonary tuberculosis. To date, this is the only case of tuberculosis infection reported in clinical trials in RA with anakinra.

No notable changes were observed for any of the laboratory measures from baseline to week 36. Further, there were no clinically relevant mean changes noted in vital signs.

DISCUSSION

In this cohort of patients representative of those seen in typical rheumatology practices, the addition of anakinra to standard DMARD therapy resulted in significant improvements in patient function as measured by the HAQ disability index. Benefits of combination therapy were observed in all treatment groups: anakinra + MTX, SSZ, and HCQ. The magnitude of the improvement in HAQ was similar to that observed in a previous randomized controlled trial (RCT)[18]. In our study, the proportion of patients with a clinically relevant improvement in HAQ at week 36 relative to baseline and the improvement in HAQ score from baseline to week 36 were similar among all 3 groups. Although mean scores appeared to trend in favor of the anakinra + MTX group, and a decrease in mean scores in patients receiving anakinra plus SSZ or HCQ appeared to decline from week 24 to week 36, these differences were not statistically significant. Overall, the mean improvement in HAQ was 0.2 from baseline to week 36, with 51% of patients achieving a clinically relevant improvement > 0.22 at study's end. The results of this patient-reported measure were consistent with physician-reported assessments of DAS28 and EULAR scores. These data are also consistent with observations from a well-controlled trial of anakinra + MTX, which showed improved clinical responses in patients with RA compared with DMARD therapy alone[18].

As therapeutic options advance, rheumatologists are challenged to reexamine their current expectations of attainable goals and to define new standards to measure the outcome of RA treatment. Biologic agents alone or in combination with traditional DMARD offer the potential for better clinical outcomes compared with the use of traditional therapies. Moreover, patient-reported outcomes such as the HAQ have been shown to be sensitive to these improvements with effective treatment. Such measures are important because they reflect the patient's perspective on their disease and how it influences their daily life. In our analysis, anakinra therapy in combination with a DMARD resulted in meaningful changes in patient function, including daily activities such as dressing, grooming, eating, and the ability to reach or grip.

One limitation of the OMEGA study is the open-label study design. Open-label studies, however, can provide information that complements results from RCT. Data from RCT may be difficult to apply to clinical practice because they may exclude patients with comorbid conditions and may enroll patients with more severe disease[27,28]. In the OMEGA trial we evaluated 1207 patients across 144 centers in 12 European countries who had active RA and who were using commonly prescribed DMARD. The findings from our study demonstrate the efficacy of anakinra in patients managed with DMARD monotherapy in typical rheumatology practices and confirm reports from controlled studies[17-19].

Injection site reaction was the most reported AE. Most cases of injection site reaction were considered to be mild and manageable, and less than 10% of patients withdrew from the study because of this event. IE were reported in 24% of patients. Serious infections were rare, and, with the exception of 1 case of tuberculosis, no cases of opportunistic infections were observed. To date, this is the only case of tuberculosis infection reported in a clinical trial with anakinra in patients with RA. The general safety observations in our study are similar to those reported from a large, placebo-controlled, prospective trial that enrolled a diverse population of patients with RA, including those with comorbid conditions and those using multiple combinations of concomitant therapies[20]. As in our study, safety observations also were consistent with those in earlier RCT. The incidence of AE across the 3 treatment groups was similar. However, it should be noted that our study was powered to detect changes in HAQ disability index rather than incidence of AE.

Overall, the findings of OMEGA confirm the reports of earlier RCT of anakinra administered either alone or in combination with MTX, and demonstrate that, in our study, anakinra was similarly efficacious and safe when used in combination with HCQ and SSZ to achieve improved control of the signs and symptoms of RA without increasing AE. Patients in our study population reported rapid and statistically significant improvements in functional status as measured by the HAQ disability index, and treatment benefits occurred in each DMARD group. The patients in this

cohort were representative of those receiving DMARD therapy in rheumatology clinics; therefore, our study results support the use of anakinra as a treatment option, especially when combinations of traditional DMARD or TNF antagonists are not suitable for a given patient.

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