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Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011
Evento : 379
Actuación : 467

Referencia : Expediente No. 05109276
Asunto : Solicitud de patente para: **MÉTODOS PARA TRATAR
ENFERMEDADES RELACIONADAS CON INTERLEUKIN-6**
Solicitante : CHUGAI SEIYAKU KABUSHIKI KAISHA
Clase : A61K 039/395, A61K 039/505, A61P 037/000
Fecha solicitud: 26 de Octubre de 2005

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al Oficio No. 12204 notificado por fijación en lista del 26 de Septiembre de 2008, y atentamente presento junto con este escrito los siguientes documentos:

- Choy et al, Arthritis and Rheumatism, Vol. 46 No. 12, 2002, pp 3143-3150.
- Nishimoto et al, Arthritis and Rheumatism, Vo. 44, No. S9-191, 2002, página S84.

2. Puesto que se han atendido a cabalidad las peticiones hechas por su Despacho sobre la presente solicitud de patente, atentamente solicito que se continúe su tramitación.

Señora Jefe,

EMILIO FERRERO

T.P.A. No. 31.929

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Therapeutic Benefit of Blocking Interleukin-6 Activity With an Anti-Interleukin-6 Receptor Monoclonal Antibody in Rheumatoid Arthritis

A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Trial

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Objective. To investigate the safety and efficacy of MRA, a recombinant human anti-interleukin-6 (anti-IL-6) receptor monoclonal antibody of the IgG1 subclass that inhibits the function of IL-6, in patients with established rheumatoid arthritis (RA).

Methods. A randomized, double-blind, placebo-controlled, dose-escalation trial was conducted in 45 patients with active RA, as defined by the American College of Rheumatology (ACR) revised criteria. Patients were sequentially allocated to receive a single

intravenous dose of either 0.1, 1, 5, or 10 mg/kg of MRA or placebo. The primary efficacy end point was meeting the ACR 20% response criteria at week 2 after treatment.

Results. Demographic features were similar between treatment groups. At week 2, a significant treatment difference was observed between the 5 mg/kg of MRA and placebo, with 5 patients (55.6%) in the MRA cohort and none in the placebo cohort achieving ACR 20% improvement. There was no statistically significant difference in the ACR 20% response between the other 3 MRA cohorts and placebo at week 2. The mean disease activity score at week 2 in those who received 5 mg/kg and 10 mg/kg of MRA was 4.8 and 4.7 ($P < 0.001$ and $P < 0.001$ by analysis of variance), respectively. These mean scores were statistically significantly lower than those in the 0.1- and 1-mg/kg MRA and the placebo cohorts (6.4, 6.2, and 7.0, respectively). The erythrocyte sedimentation rate and C-reactive protein values fell significantly in the 5- and 10-mg/kg MRA cohorts and normalized 2 weeks after treatment. Seventeen patients (5, 4, 6, 2, and 0 patients in the placebo, 0.1-, 1-, 5-, and 10-mg/kg MRA cohorts, respectively) required corticosteroid or disease-modifying antirheumatic drug treatment because of active disease before study end. They were regarded as nonresponders from the time they received these treatments. Diarrhea was the most common adverse event, occurring in 8% of patients. Seven patients (15.6%) reported a severe adverse event (3, 1, 2, and 2 patients in the placebo, 0.1-, 1-, and 10-mg/kg

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Chugai Pharmaceutical Company, Ltd. supplied the humanized anti-interleukin-6 receptor antibody used in this study. Drs. Yoshizaki and Nishimoto have received consulting fees and a research grant for other projects from Chugai Pharmaceutical. Dr. Choy has received honoraria from Chugai Pharmaceutical for lectures and for consulting on protocol design.

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MRA cohorts). There were no serious adverse events that were thought to be related to the study drug.

Conclusion. This is the first randomized controlled trial showing that inhibition of IL-6 significantly improved the signs and symptoms of RA and normalized the acute-phase reactants. Further research with multiple dosing is necessary to define the most appropriate therapeutic regimen of MRA in RA.

Rheumatoid arthritis (RA) is a common, severe disorder whose distinctive features include a persistent and symmetric peripheral inflammatory arthritis as well as extraarticular manifestations. The disease is associated with significant morbidity and mortality (1). The exact cause of RA is not known, but it is now clear that immunogenetic predisposition to the disease is a contributing factor.

Since the exact cause of RA is unknown, therapies have been directed against the various components of the chronic inflammatory response (2). Interleukin-6 (IL-6) is produced by lymphocytes, monocytes, fibroblasts (3), synoviocytes (4), and endothelial cells, leading to local production in RA joints (5). Higher levels of IL-6 and soluble IL-6 receptor (sIL-6R) have been found in the sera of RA patients compared with controls, and in synovial fluid compared with serum, reflecting local production by the rheumatoid synovium (5-7).

The precise pathogenic role of IL-6 in RA is a subject of controversy, since it has proinflammatory and antiinflammatory properties in vitro. The proinflammatory actions of IL-6 include stimulating hepatocytes to produce acute-phase reactants, leukocyte chemotaxis, and T and B cell proliferation and differentiation (8). In contrast, IL-6 can abrogate inflammation by suppressing IL-1 and tumor necrosis factor α (TNF α) production and by inducing the release of IL-1 receptor antagonist and soluble TNF α receptor in vitro (8). In patients with RA, levels of serum IL-6 and sIL-6R have been shown to correlate with disease activity (9) and radiologic joint damage (10). Disease improvement noted after treatment with disease-modifying antirheumatic drugs (DMARDs) is also accompanied by a reduction in serum IL-6 levels (9,11). RA synovial fluid containing high levels of IL-6 and sIL-6R was shown to promote osteoclast cell formation when added to cocultures of osteoblasts and bone marrow cells (10). Given these observations, trials of anti-IL-6 therapies in RA are clearly warranted.

These observations suggest that inhibition of the activity of IL-6 in patients with RA may be of clinical benefit. In an open-label study, Wendling et al (12)

treated 5 RA patients with a murine monoclonal anti-IL-6 antibody (B-E8; IgG1) given intravenously (10 mg/day) for 10 consecutive days. No side effects were noted, although an unexpected rise in serum IL-6 levels was seen in 4 of the 5 patients. Clinical improvement appeared rapidly during the treatment period, with improvement in the degree of pain, the duration of morning stiffness, the number of tender and swollen joints, and the Ritchie Articular Index. The improvement was associated with a reduction in C-reactive protein (CRP) levels and lasted 2 months.

MRA is a humanized anti-IL-6R monoclonal antibody of the IgG1 subclass that was developed by Chugai Pharmaceutical Company using recombinant DNA technology. The antibody was humanized by the technique of complementarity-determining region grafting from a mouse anti-human IL-6R monoclonal antibody. MRA has been shown to compete for both the membrane-bound and the soluble forms of human IL-6R and to inhibit the function of IL-6. MRA has also been shown to reduce joint inflammation and destruction in cynomolgus monkeys with collagen-induced arthritis (13). Infusions of MRA in healthy adult men were found to be well tolerated. The present study was a phase I/II randomized, double-blind, placebo-controlled, dose-escalation trial to investigate the safety, tolerability, antigenicity, pharmacokinetics, and efficacy of MRA in patients with established and active RA.

PATIENTS AND METHODS

Patient population. Patients who were ages 18-75 years and had RA, according to the 1987 American College of Rheumatology (ACR; formerly, the American Rheumatism Association) diagnostic criteria (14), were recruited from outpatient clinics. All patients had clinically active disease, as defined by the presence of at least 3 of the 4 following features: ≥ 3 swollen joints, ≥ 6 painful or tender joints, duration of early morning stiffness ≥ 45 minutes, and erythrocyte sedimentation rate (ESR) ≥ 28 mm/hour. They must have failed treatment with at least 1 DMARD. DMARD therapy must have been discontinued for at least 1 month before administration of the study medication. Concomitant oral steroid treatment was permitted if the dosage was ≤ 7.5 mg of prednisolone daily and remained unchanged throughout the study. Use of parenteral and/or intraarticular steroids, immunosuppressants, investigational drugs, and oral anticoagulant drugs within 4 weeks before administration of the study medication was not permitted.

Pregnant women, nursing women, and women of child-bearing potential who were not using an effective method of contraception were excluded. Patients were excluded if they had severe disability (Steinbrocker class IV), significant hepatic or renal impairment, active intercurrent infection, previous therapy with murine, chimeric, or human monoclonal

antibodies or other xenogeneic proteins, history of cancer (excluding cervical or basal cell carcinoma), known infection with the human immunodeficiency virus, weight >100 kg, or significant surgery within 4 weeks prior to inclusion.

Written informed consent was obtained from each patient before enrollment. The study was approved by a multicenter research ethics committee and local ethics committees. Patients were indemnified by the sponsor of the study, Chugai Pharmaceutical Company, Ltd. (Tokyo, Japan).

Treatment schedule. Four cohorts of 12 subjects were sequentially allocated to a single intravenous dose of MRA or placebo. The dose levels studied were 0.1, 1, 5, and 10 mg/kg. Within each cohort, 9 subjects received MRA and 3 subjects received placebo. Both active drug and placebo were allocated randomly by a predetermined computer-generated randomization schedule. Escalation to the next dose level was permitted only if the previous dose level was satisfactory in terms of safety and tolerability, as determined by an independent safety reviewer. Patients, assessors, and local investigators were all blinded to the nature of treatment. MRA or placebo was administered by slow intravenous infusion over 1 hour. Patients were observed and monitored for another 8 hours after treatment.

Assessment of efficacy. Efficacy of treatment was based on the World Health Organization/International League of Associations for Rheumatology Outcome Measures in RA Clinical Trials core data set (15). These included tender and swollen joint counts, a pain score, patient's and physician's global assessments of disease activity, the modified Health Assessment Questionnaire, and the ESR and CRP values. Assessments were performed at baseline and at 1, 2, 3, 4, 6, and 8 weeks after treatment. The primary end point of the study was achievement of an ACR 20% response (16) at week 2. Secondary efficacy parameters included an ACR 20% response at weeks 4, 6, and 8; an ACR 50% response at weeks 2, 4, 6, and 8; and the Disease Activity Score in 28 swollen and 28 tender joints (17) at weeks 2, 4, 6, and 8.

Assessment of safety. A physical examination, including a 12-lead electrocardiogram, measurement of vital signs (supine blood pressure and pulse rate), respiratory rate, oral body temperature, height, and weight, were performed at regular intervals throughout the clinical study. Hematologic and biochemical analyses, urinalysis, and the assay for the presence of antibody to MRA were performed on blood and urine samples collected at the screening visit, baseline, and at weeks 1, 2, 3, 4, 6, and 8 of study.

Statistical analysis. The study was analyzed on an intent-to-treat basis with the last observation carried forward method. All analyses included pairwise comparisons between each dose group and the combined placebo group. Categorical data were analyzed using the Cochran-Mantel-Haenszel test. Where transformed or untransformed continuous data fulfilled the normality assumptions, analysis of variance was used. Normality assumptions were checked by review of residual plots. If the data did not fulfill the assumptions, then they were analyzed using Wilcoxon's rank sum test for nonparametric data. Fisher's exact test was used for the ACR response data. Analysis of variance models included the baseline value of the variable to ensure that change was included in the analysis. The null hypothesis for the overall analysis was that there was no difference in the means of the treatment groups; the null

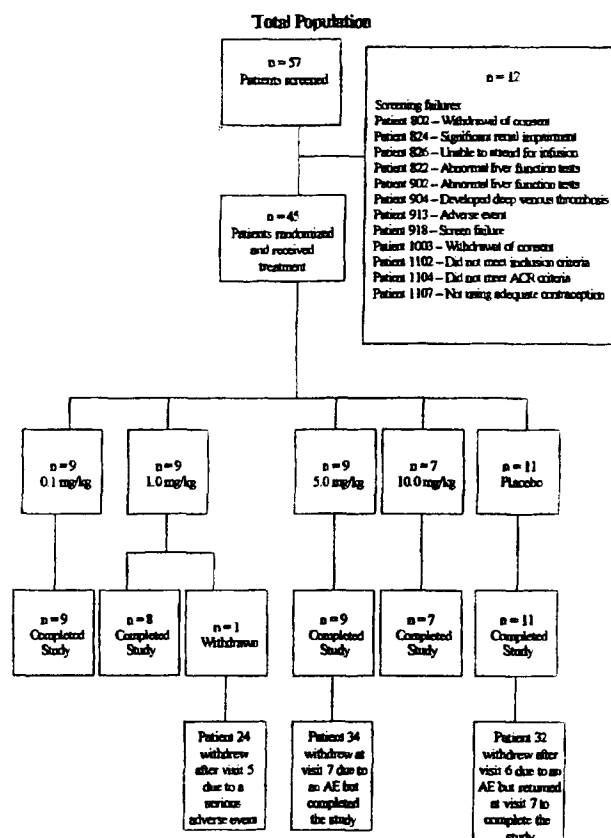


Figure 1. Flowchart showing randomization of the total population of rheumatoid arthritis patients who were initially screened for study inclusion. ACR = American College of Rheumatology; AE = adverse event.

hypothesis for each comparison of Dunnett's test was that there was no difference in the means, while the overall significance level was maintained. For all analyses, a 5% significance level was used. No adjustments were made for multiple testing, other than the use of Dunnett's test.

RESULTS

A total of 57 patients were screened for entry into the clinical study (Figure 1). Nine patients failed to satisfy the inclusion and exclusion criteria. Three patients did not give their consent. The remaining 45 patients were randomized and received treatment. Demographic data for the randomized patients are given in Table 1.

Eleven patients (24.4%) were randomized to the placebo group, 9 patients (20.0%) were randomized to each of the 0.1-, 1-, and 5-mg/kg MRA groups, and 7

Table 1. Demographics of the study patients*

	Placebo group (n = 11)	MRA group (n = 34)			
		0.1 mg/kg (n = 9)	1.0 mg/kg (n = 9)	5.0 mg/kg (n = 9)	10.0 mg/kg (n = 7)
Age, mean $\pm$ SD years	61.8 $\pm$ 10.6	54.6 $\pm$ 10.0	55.7 $\pm$ 9.0	57.2 $\pm$ 12.1	61.5 $\pm$ 7.8
Sex, no. of males:no. of females	6:5	3:6	2:7	2:7	2:5
Disease duration, mean $\pm$ SD years	14 $\pm$ 10	17 $\pm$ 15	6 $\pm$ 4	14 $\pm$ 12	13 $\pm$ 11
No. of failed DMARDs, mean $\pm$ SD	4 $\pm$ 2	3 $\pm$ 2	3 $\pm$ 2	2 $\pm$ 1	3 $\pm$ 2
No. positive for rheumatoid factor	7	6	4	6	6
Race, no. (%)					
White	9 (81.8)	7 (77.8)	5 (55.6)	6 (66.7)	6 (85.7)
Asian	1 (9.1)	2 (22.2)	1 (11.1)	—	1 (14.3)
Black	1 (9.1)	—	3 (33.3)	3 (33.3)	—

* MRA is a recombinant human anti-interleukin-6 receptor monoclonal antibody of the IgG1 subclass; it inhibits the function of interleukin-6. DMARDs = disease-modifying antirheumatic drugs.

patients (15.6%) were randomized to the 10-mg/kg MRA group. All patients who received treatment were included in the analyses. Only 1 patient (in the 1-mg/kg cohort) did not attend the final visit at week 8. This patient withdrew because of an adverse event and subsequently died. A further 2 patients withdrew during the clinical study because of adverse events but attended the week 8 visit. Seventeen patients (5, 4, 6, 2, and 0 patients in the placebo and the 0.1-, 1-, 5-, and 10-mg/kg MRA groups, respectively) required treatment with corticosteroids or DMARDs because of active disease before the end of the trial. They were regarded as nonresponders from the time they received these treatments.

Pharmacokinetics. The terminal half-life of MRA increased with an increasing dose over the dose range of 1 mg/kg to 10 mg/kg. In the 5- and 10-mg/kg groups, plasma half-life was 136 hours and 158 hours, respectively.

Efficacy. The primary efficacy analysis showed a significant treatment difference in the ACR 20% response criterion at week 2 in the 5-mg/kg MRA group and the placebo group (Figure 2). There was no evidence of a statistically significant difference between the other treatment groups and placebo at week 2 in this analysis, since as a modestly sized study, it does not have the necessary power to exclude small differences.

The analysis of secondary clinical efficacy variables supported the findings of the primary efficacy analysis. In the secondary analysis of the ACR 20% response, the treatment difference between 5 mg/kg of MRA and placebo was maintained until week 8. The 5-mg/kg MRA group demonstrated a consistent treatment difference from placebo across all secondary efficacy variables. A significant increase in the number of patients with a ACR 20% response was also noted in the

10-mg/kg MRA group versus the placebo group at weeks 6 and 8. The 10-mg/kg MRA group also showed a statistically significant improvement in the ACR 50% response at week 8. Furthermore, a difference in the Disease Activity Score and several disease activity measurements at week 2 was observed between the 5- and 10-mg/kg MRA groups and the placebo group (Figure 3). The secondary analysis did not provide any convincing evidence of a statistically significant difference between the lower-dose MRA groups and the placebo group.

A beneficial effect of MRA treatment in the 5-mg/kg MRA group was further suggested by the observation that fewer patients in this group had disease activity that required either corticosteroids or DMARDs

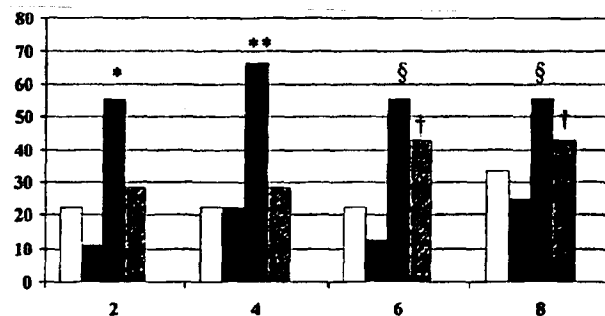


Figure 2. American College of Rheumatology (ACR) 20% response to treatment with 0.1 mg/kg (open bars), 1 mg/kg (darkly shaded bars), 5 mg/kg (solid bars), or 10 mg/kg (hatched bars) of MRA, a recombinant human anti-interleukin-6 receptor monoclonal antibody of the IgG1 subclass that inhibits the function of interleukin-6. * = $P = 0.023$, ** = $P = 0.002$, § = $P = 0.008$, and † = $P = 0.043$ versus placebo, by Fisher's exact test. All other treatment groups were not significantly different from placebo ($P > 0.05$).

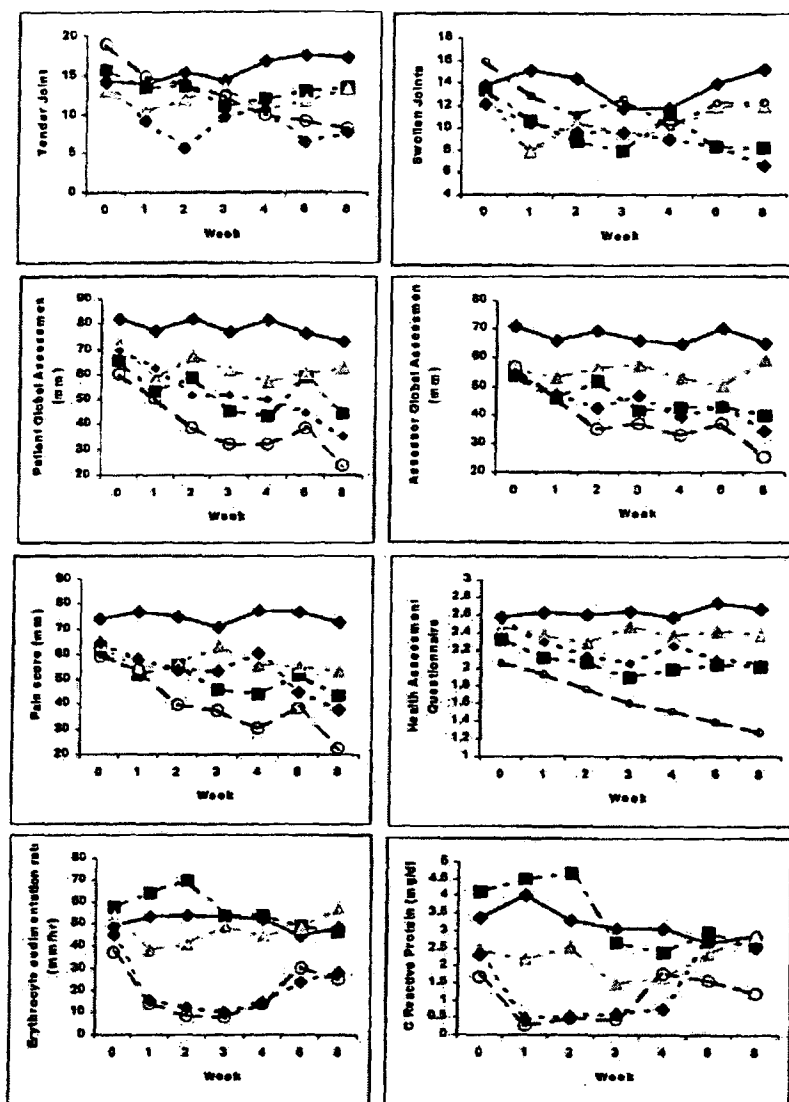


Figure 3. Individual components of the World Health Organization/International League of Associations for Rheumatology core data set in rheumatoid arthritis patients treated with placebo (◆—◆) or with 0.1 mg/kg (■---■), 1 mg/kg (▲---▲), 5 mg/kg (○---○), or 10 mg/kg (◆---◆) of MRA, a recombinant human anti-interleukin-6 receptor monoclonal antibody of the IgG1 subclass that inhibits the function of interleukin-6.

compared with the placebo group. The mean time to initiation of rescue treatments in the 5-mg/kg (24 days; range 5–43) and the 10-mg/kg (41 days; range 6–57) MRA groups compared with the placebo group (11 days; range 0–29) also indicates a reduced need for rescue medication. Efficacy in the 5- and 10-mg/kg MRA groups was further supported by a suppression of the

ESR and CRP values to normal levels compared with the placebo group (Figure 3).

Adverse events. A total of 34 (75.6%) patients reported an adverse event (Table 2). There were no differences in the incidence or type of adverse events between treatment groups. The most common adverse event was diarrhea (8 patients, 17.8%). The incidence of

Table 2. Adverse events occurring in more than 20% of patients in any cohort*

System affected	Placebo group (n = 11)	MRA group (n = 34)				All patients (n = 45)
		0.1 mg/kg (n = 9)	1.0 mg/kg (n = 9)	5.0 mg/kg (n = 9)	10.0 mg/kg (n = 7)	
No. (%) of patients experiencing an adverse event	9 (81.8)	6 (66.7)	6 (66.7)	7 (77.8)	6 (85.7)	34 (75.6)
Blood and lymphatic system	1 (9.1)	2 (22.2)	-	-	1 (14.3)	4 (8.9)
Gastrointestinal tract	7 (63.6)	2 (22.2)	4 (44.4)	4 (44.4)	2 (28.6)	19 (42.2)
General disorders and injection site conditions	4 (36.4)	2 (22.2)	2 (22.2)	2 (22.2)	2 (28.6)	12 (26.7)
Infections and infestations	-	2 (22.2)	1 (11.1)	1 (11.1)	1 (14.3)	5 (11.1)
Musculoskeletal system, connective tissue, and bone	2 (18.2)	2 (22.2)	2 (22.2)	3 (33.3)	4 (57.1)	13 (28.9)
Nervous system	1 (9.1)	-	1 (11.1)	2 (22.2)	1 (14.3)	5 (11.1)
Psychiatric disorders	1 (9.1)	-	1 (11.1)	-	2 (28.6)	4 (8.9)
Respiratory, thoracic, and mediastinal disorders	1 (9.1)	2 (22.2)	-	-	1 (14.3)	4 (8.9)
Skin and subcutaneous tissue	2 (18.2)	1 (11.1)	1 (11.1)	1 (11.1)	2 (28.6)	7 (15.6)
Vascular disorders	2 (18.2)	1 (11.1)	1 (11.1)	2 (22.2)	1 (14.3)	7 (15.6)

* MRA is a recombinant human anti-interleukin-6 receptor monoclonal antibody of the IgG1 subclass; it inhibits the function of interleukin-6. Values are the number (%) of patients.

diarrhea was comparable between treatment groups. The incidence of nausea was higher in the placebo group (3 patients [27.3%]) compared with all MRA treatment groups (1 patient at 1 mg/kg [11.1%]). The majority of adverse events were of mild or moderate intensity.

Seven patients (15.6%) reported a severe adverse event: 3 patients in the placebo group, 1 patient each in the 0.1-mg/kg and 1-mg/kg MRA groups, and 2 patients in the 10-mg/kg MRA group. One serious adverse event (myocardial ischemia) led to death in a patient in the 1-mg/kg MRA group, but the adverse event was not considered to be related to the MRA. This patient also had evidence of preexisting ischemic heart disease. Two adverse events led to withdrawal from the study: one of the patients experienced a severe aggravation of arthritis and the other had a moderate swelling of the right knee.

There were minor changes in liver enzyme levels, neutrophil counts, and white blood cell counts in the higher dose groups. These changes were not thought to be of clinical significance. Specific antibodies to MRA could not be detected in the serum from patients in any of the treatment groups. There were no between-group differences in electrocardiographic changes or changes in vital signs over time.

DISCUSSION

Our study is the first randomized placebo-controlled trial that has assessed the effect of blocking IL-6 in patients with RA. Although this is a preliminary

study, it suggests that IL-6 blockade may be beneficial in patients with active RA.

In this study, both the primary and secondary efficacy analyses demonstrated a superior effect of 5 mg/kg, and probably of 10 mg/kg, of MRA compared with placebo. The sample size of this study is too small to distinguish any difference in effect between 5 mg/kg and 10 mg/kg of MRA. A recent open-label trial in 15 patients with RA in Japan who were treated with MRA infusions every 2 weeks for 6 months showed an ACR 20% response rate of 60% and 80% after 6 weeks and 6 months, respectively (18). A larger multiple-dose study is currently in progress to define the optimum dose of MRA in the treatment of RA. However, the findings of the present study suggest that IL-6 has a predominantly proinflammatory effect in RA despite some in vitro studies which suggested otherwise (reviewed in the introduction) (8).

Interestingly, levels of the acute-phase reactants ESR and CRP normalized after a single dose of either 5 mg/kg or 10 mg/kg of MRA, and the effects lasted for 4 weeks. This confirms IL-6 as the major cytokine responsible for the production of acute-phase reactants in RA. In studies of other cytokine inhibitors, such as TNF blockers (19,20) and the IL-1 receptor antagonist (21), ESR and CRP levels decreased with treatment but not to normal levels. A further study of MRA treatment in Japan confirms the impressive normalization of the ESR and CRP values in patients with established RA (18).

MRA was well tolerated, with no drug-related serious adverse events. There were, however, a few minor, transient adverse events, with raised transaminase levels and decreased white blood cell counts, which returned to normal at the end of the trial. A long-term study will be needed to confirm the good safety profile.

It is worth placing this study in the context of other therapies involving the neutralization of cytokines thought to be of relevance to the pathogenesis of RA. There are currently 2 medications that inhibit TNF α , etanercept and infliximab, and both are in clinical use. The findings from clinical trials as well as from clinical practice confirm the concept that TNF α is an important inflammatory mediator in the pathogenesis of RA (22). Clinical trials of IL-1 receptor antagonist therapy suggest that, although it has limited antiinflammatory effects, it may retard radiologic joint destruction (21). The findings of the present study suggest that inhibition of IL-6 also has a beneficial effect on established RA. One potential advantage of IL-6 blockade is the avoidance of secondary amyloidosis, in which accumulation of amyloid A by the liver as a result of chronic inflammation leads to end organ damage. Normalization of the levels of acute-phase reactants may therefore make MRA the treatment of choice in such patients. IL-6 has also recently been implicated in the pathogenesis of osteoporosis (23). Since osteoporosis is more common in RA (24) as a result of chronic inflammation and concomitant steroid usage, IL-6 blockade may provide the additional benefit of reducing bone loss. Hence, IL-6 blockade may improve the signs and symptoms of RA and provide better control of the acute-phase response, protection from osteoporosis, and a lower risk of infection.

Standard treatment with DMARDs improves the signs and symptoms of RA but does not alter the long-term prognosis of this chronic inflammatory disease (25). Recent studies using agents that block proinflammatory cytokines, such as TNF α and IL-1, have shown that this approach is an effective strategy for the treatment of RA (22). Cytokines have been extensively studied in RA synovitis, but how they interact with each other in RA remains unknown. In particular, it remains unclear whether there is a cytokine network or a cytokine hierarchy in RA (26). Our data suggest that IL-6 is an important cytokine for maintaining synovial inflammation and that the interrelationships between cytokines may be more complex than a simple hierarchy. Rather, RA may be thought of as a disease whose activity at any time is maintained by the synergistic and/or additive effects of several cytokines within a network. Such a hypothesis better explains why only a proportion of

patients at any one time respond to inhibition of the action of one cytokine alone, such as TNF α or IL-6. Greater understanding of the cytokine network in RA may help us to develop rational combination therapies that may be more effective than blocking a single cytokine.

In summary, a single dose of MRA was safe and was well tolerated in patients with RA. A larger study with repeated doses of MRA will be necessary to assess the antigenicity and long-term safety and efficacy of MRA as well as its potential to retard or inhibit the development of joint erosions.

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SAFETY AND EFFICACY OF REPETITIVE TREATMENT WITH HUMANIZED ANTI-INTERLEUKIN-6 RECEPTOR ANTIBODY (MRA) IN RHEUMATOID ARTHRITIS (RA). Norihiro Nishimoto, Keiji Maeda, Taro Kuritani, Hitoshi Deguchi, Bunzo Sato, Nobuyuki Imai, Takahiro Kakehi, Masaki Suehara, Tadamitsu Kishimoto, Kazuyuki Yoshizaki Osaka, Hyogo and Tokyo, Japan

Objectives: In an open-label multi-dose trial, 15 RA patients received an intravenous infusion with either 2, 4, or 8 mg/kg of humanized anti-interleukin-6 receptor antibody (MRA) every 2 weeks for 6 months. Safety and efficacy on inflammatory markers including CRP and ESR, and ACR core set were assessed.

Results: The treatment was well tolerated at all doses without any serious adverse reactions and no patients were withdrawn. Increase in serum total cholesterol was detected as a MRA-related reaction in 10/15 (66%). No antinuclear antibody or anti-DNA antibody newly appeared. No anti-MRA antibody was detected.

CRP(7.2 ± 0.7 mg/dl before therapy), ESR(114 ± 3 mm/hr), and serum amyloid A protein (SAA) (604 ± 243 μ g/ml) were completely normalized in 12/15 (80%) after the 3rd dose. The other 3 patients whose blood MRA concentrations were not maintained did not become seronegative for CRP. Increase in serum albumin was also documented for all patients. In addition, decrease in tender or swollen joint counts were also noted. The efficacy assessed by the ACR core set was as shown in the table.

response	at 6 weeks	at 6 months
ACR20	60%	80%
ACR50	6.7%	40%

Conclusion: Repetitive therapy with MRA appeared considerably safe. The improvement of objective markers such as CRP and ESR as well as ACR core set suggests MRA is therapeutically beneficial in RA. At present, a double-blind comparative trial in patients with RA is ongoing.

Keywords: IL-6, IL-6 receptor, humanized antibody, rheumatoid arthritis, safety, CRP, serum amyloid A protein

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