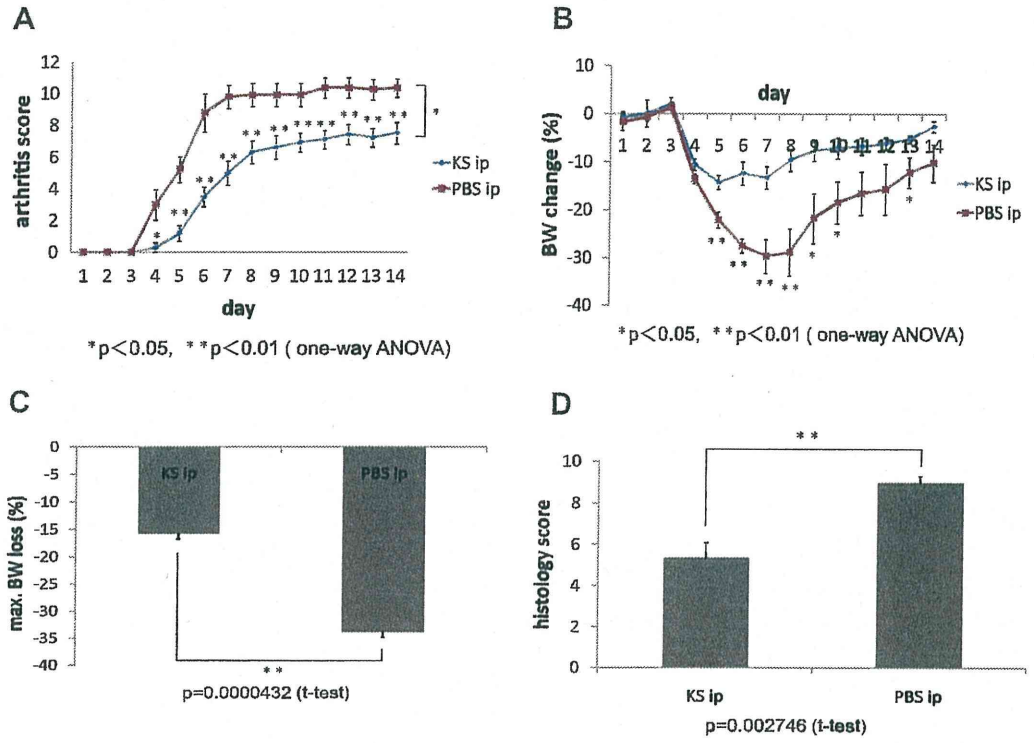

Fig. 3. Suppression of antibody-induced arthritis by KS administration in GlcNAc6ST-1$^{-/-}$ mice. (A) Time course for arthritis development in GlcNAc6ST-1$^{-/-}$ mice treated with and without KS (n = 10/group). (B) Time course for changes in body weight (n = 10/group). (C) Maximum body weight loss (n = 10/group). (D) Histologic scores on day 7 (n = 6/group).

(33.85 ± 2.76 vs. 15.79 ± 1.45) (Fig. 3C). Histologic analysis also revealed that cartilage degradation was more severe in mice not administered KS than in mice administered KS (8.99 ± 0.31 vs. 5.39 ± 0.71) (Fig. 3D). Thus, the intraperitoneal injection of KS ameliorated arthritis in GlcNAc6ST-1$^{-/-}$ mice. Thus, KS significantly suppressed arthritis, and that suppressive effect was much greater in GlcNAc6ST-1$^{-/-}$ mice than in the WT DBA/1J mice that we examined previously [9].

4. Discussion

The inflammatory cytokines TNF-α and IL-1 in articular cartilage are believed to play important roles in the degradation of the cartilage matrix in patients with osteoarthritis (OA) [16]. Anti-TNF-α inhibitors are used clinically as anti-arthritic drugs for RA patients. Whether these drugs provide chondroprotection directly remains unclear. The loss of proteoglycan aggrecan is the principal feature in damage to the articular cartilage in both OA and RA [17]. IL-1 can induce resorption of proteoglycans [18], and in mature bovine articular cartilage, inhibitors of matrix metalloproteinase (MMP)-8 and MMP-13 may protect against proteoglycan reduction in IL-1α–induced arthritis [19]. In an experiment with mature meniscal tissue explants, aggrecanases were responsible for IL-1–stimulated GAG release [20]. In bovine cartilage, collagen fibrils interact with the KS-rich regions of several aggrecan monomers aligned within a proteoglycan aggregate and serve as a backbone [21].

From our previous study, we proved that aggrecan release induced by IL-1α is greater in cartilage explants of WT DBA/1J mice not administered KS than in those administered KS [9]. In this second report we showed that the release of GAGs induced by IL-1α is greater in the cartilage explants of GlcNAc6ST-1$^{-/-}$ mice than in the explants of WT mice. But in this *in vitro* study we did not use exogenous KS, and the difference between those 2 types of cartilage was only whether they had GlcNAc6ST-1 in their genes. That being the case, why is the release of GAGs induced by IL-1α greater in the cartilage explants of GlcNAc6ST-1$^{-/-}$ mice than it is in the explants of WT mice in this experiment? Vestigial KS chains or altered glycosylation may exist in the articular cartilage of mice, unlike thought previously, and have the ability to protect against cartilage degradation in IL-1α–induced arthritis. Molecular fragments of cartilage are themselves antigenic and can stimulate an arthritic response [22]. Therefore, if KS provides chondroprotection *in vitro*, its ability may be related to the suppressive effects of arthritis *in vivo*.

Aggrecan cleavage is reported to be the first step in cartilage destruction in inflammatory joints, followed by the breakdown of type II collagen [23]. An increasing body of evidence now supports the idea that an aggrecanase (aggrecanase-2: ADAMTS-5), rather than MMPs, is primarily responsible for the catabolism and loss of aggrecan from articular cartilages in the early stages of arthritic joint diseases [24–29]. Consistent with these findings, ADAMTS-5-deficient mice exhibit less severe OA and antigen-induced arthritis than WT mice [30,31]. Mice carrying a mutation at the specific site of aggrecanase cleavage show resistance to cartilage erosion [32]. Articular cartilage explants from these mice show less GAG releases after IL-1α stimulation compared with the explants from WT mice [32]. GAG release from cartilage explants on IL-1α stimulation is associated with an increased expression of aggrecanases and an increase in the release of aggrecan fragments cleaved with aggrecanases [28]. In this context, it is noteworthy that the aggrecans released from mice without KS administration was greater than those released from mice with KS administration [9], and that the GAG release observed in cartilage explants of KS-deficient (GlcNAc6ST-1$^{-/-}$) mice was significantly greater than that of WT mice. Our data therefore may suggest that KS deficiency potentiates the susceptibility of aggrecan to aggrecanase-mediated cleavage.

Our *in vivo* study demonstrated that arthritis was more severe in GlcNAc6ST-1$^{-/-}$ mice than in their littermate WT mice and that KS administration ameliorated arthritis in GlcNAc6ST-1$^{-/-}$ mice efficiently. These *in vivo* observations were complimented by an *ex vivo* study of cartilage explants in which the release of GAGs induced by IL-1α was greater in the cartilage explants from GlcNAc6ST-1$^{-/-}$ mice than in the explants from WT mice. In contrast, the infiltration of neutrophils or lymphocytes was not affected by the GlcNAc6ST-1 deficiency. Our results collectively, however, suggest that KS plays an indispensable role in the pathogenesis of antibody-induced arthritis.

Sialyl 6-sulfo Le^X is another product of GlcNAc6ST-1 [10,33,34]. Because sialyl 6-sulfo Le^X is a determinant for L-selectin, GlcNAc6ST-1$^{-/-}$ mice show less lymphocyte homing, and GlcNAc6ST-1 and GlcNAc6ST-2 double-deficient mice suppress lymphocyte homing by 75% [10,34]. Therefore, we used acute antibody-induced arthritis model in this study to exclude the effects of lymphocyte participation, and the role of KS alone in the cartilage degradation associated with arthritis could be examined. We interpreted our results from the point of view that GlcNAc6ST-1$^{-/-}$ mice were different from their WT littermates solely with regard to the lack of KS biosynthesis. Our present study has verified that GlcNAc6ST-1 is also crucial in chondroprotection in articular cartilages. This study modeled early onset antibody-induced arthritis that is characterized by the infiltration of neutrophils only, which, in turn, triggers cartilage destruction involving induction of TNF-α and IL-1β [35]. Because L-selectin is less important in neutrophil infiltration associated with early onset, the amelioration of arthritis by exogenous KS and increased GAG release observed in the cartilage explants of either WT or GlcNAc6ST-1$^{-/-}$ mice provide evidence in support of the idea that KS, rather than sialyl 6-sulfo Le^X, is important in the joint damage associated with the arthritis in mice.

In summary, our results collectively suggest that KS-deficient mice cartilage is more fragile than WT mice cartilage, antibody-induced arthritis is exacerbated in KS-deficient mice compared with WT mice, and exogenous KS can suppress arthritis induction in KS-deficient mice. It may be possible that vestigial KS chain or altered glycosylation in articular cartilage in mice is protective against arthritis and associated cartilage damage. Phosphate prodrugs derived from GlcNAc have provided chondroprotection in *in vitro* bovine articular cartilage cultures [36]. Our studies indicate that administration of therapeutic KS may provide a novel strategy for the treatment of human inflammatory diseases such as RA and may be of value in OA.

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Safety and Efficacy of Various Dosages of Ocrelizumab in Japanese Patients with Rheumatoid Arthritis with an Inadequate Response to Methotrexate Therapy: A Placebo-controlled Double-blind Parallel-group Study

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ABSTRACT. ***Objective.*** To evaluate the safety and efficacy of ocrelizumab (OCR) in Japanese patients with rheumatoid arthritis (RA) with an inadequate response to methotrexate (MTX).

Methods. RA patients with an inadequate response to MTX 6–8 mg/week received an infusion of 50, 200, or 500 mg OCR or placebo on Days 1 and 15 and were observed for 24 weeks. The double-blind period was prematurely terminated because of a possible risk for serious infection from OCR.

Results. A total of 152 patients were randomized into the study. The incidence of infection was 37.7% (43/114) in the OCR groups combined, compared to 18.9% (7/37) in the placebo group. Serious infections occurred in 7 patients in the OCR groups combined; there were no serious infections in the placebo group. Among the serious infections, *Pneumocystis jirovecii* pneumonia occurred in 2 patients in the OCR 200 mg group. The American College of Rheumatology 20% response rates at Week 24 (the primary endpoint) of the OCR 50, 200, and 500 mg groups were 54.1% ($p = 0.0080$), 55.6% ($p = 0.0056$), and 47.2% ($p = 0.044$), respectively, all significantly higher than that of the placebo group (25.0%).

Conclusion. These results suggest inappropriate benefit-risk balance of OCR in this patient population. Because rituximab is not approved for treatment of RA in Japan, it will be necessary to investigate safety and efficacy of other anti-B cell therapies in Japanese patients with RA. (ClinicalTrials.gov NCT00779220). (J Rheumatol First Release Jan 15 2012; doi:10.3899/jrheum.110994)

Key Indexing Terms:
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The possible involvement of B cells in the pathogenesis and progression of RA, including autoantibody production, autoantigen presentation, T cell activation, and production of proinflammatory cytokines and chemokines, has been suggested[1,2,3,4,5,6]. Based on these reports, clinical trials of rituximab (RTX), a chimeric anti-CD20 monoclonal antibody (mAb) targeting CD20 molecules, were conducted in patients with rheumatoid arthritis (RA)[7,8]. Subsequently, RTX was approved for treatment of RA in Europe and the United States.

Ocrelizumab (OCR) is a humanized mAb that also targets CD20[9,10] and eliminates B cells by inducing antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis. While the epitopes recognized by OCR and RTX on the extracellular domain of the CD20 molecule partially overlap, OCR offers some advantages over RTX. First, OCR is expected to be better tolerated over repeated and longterm administration because OCR induced higher ADCC activity and lower CDC activity than RTX *in vitro*; this has clinical relevance

because CDC activation has been associated with the incidence and severity of infusion-related reactions (IRR)[11]. Second, as a humanized mAb, OCR may have lower immunogenicity than RTX, a chimeric mAb.

A 6-month, double-blind, phase I/II study of OCR (the ACTION study) was undertaken in the United States, enrolling patients with RA with an inadequate response to disease-modifying antirheumatic drugs (DMARD). The results of the ACTION study confirmed the clinical usefulness of OCR in combination with methotrexate (MTX)[12]. To investigate the dose-responsive effects of OCR in Japanese patients with RA, we conducted a 24-week, placebo-controlled, double-blind, phase II study of OCR with concomitant MTX treatment in Japanese patients with RA whose response to MTX had proved inadequate.

MATERIALS AND METHODS

Patients. Our study was conducted at 37 sites in Japan with approval from the Institutional Review Board at each participating site. Written informed consent was obtained from each patient participating in the trial. Our study was conducted in accord with the Declaration of Helsinki and the Good Clinical Practice guidelines, and was registered at ClinicalTrials.gov, NCT00779220.

Patients selected were ≥ 20 years old, fulfilled the American College of Rheumatology (ACR) 1987 revised criteria for RA[13], were rheumatoid factor (RF)-positive (> 20 IU/ml), showed an inadequate response to MTX at a dosage of 6–8 mg/week (maximum approved dose in Japan at that time: 8 mg/wk) for at least 12 weeks with a stable dose for the last 4 weeks before study treatment, had not used tocilizumab, infliximab, adalimumab, or leflunomide for at least 8 weeks before study treatment, and had used no other DMARD except MTX for at least 4 weeks before study treatment. Active disease was defined as swollen joint count ≥ 8 (66-joint count), tender joint count ≥ 8 (68-joint count), and either serum C-reactive protein (CRP) ≥ 1.5 mg/dl or erythrocyte sedimentation rate (ESR) ≥ 28 mm/h. Key exclusion criteria were additional autoimmune disorders, previous treatment with cell-depleting agents, neutrophil count < 1500/μl, platelet count < 100,000/μl, IgG or IgM less than the lower limit of normal (LLN), or hemoglobin < 8.5 g/dl.

Study design. This was a placebo-controlled, double-blind, multicenter, phase II study. The overall study design is illustrated in Figure 1. The subjects were randomly allocated into 4 groups, the OCR 50, 200, or 500 mg group, or the placebo group, in equal numbers and then given an infusion of their assigned investigational product on Days 1 and 15. Methylprednisolone 100 mg was given intravenously as premedication 30 min before administration of each investigational product. The use of oral antihistamine and acetaminophen 30 to 60 min before administration of investigational product was also permitted. Patients who were withdrawn from the double-blind period entered the safety followup period and were followed for at least 48 weeks from the first infusion of investigational product. This report includes the initial 24-week results.

All patients received uninterrupted stable dosages of MTX (6–8 mg/wk) and folate (≥ 5 mg/wk) from at least 4 weeks before the initiation of study treatment to the end of the study period. Concomitant use of a stable dosage of oral corticosteroid (prednisolone equivalent dose ≤ 10 mg/day) was permitted if the dosage was unchanged in the last 4 weeks before the study, and the concomitant use of nonsteroidal antiinflammatory drugs was also permitted if the dosage had not been changed within the last 2 weeks. Concomitant use of biological or nonbiological DMARD other than MTX was prohibited. The following rescue treatments were allowed from Week 8 at the investigator's discretion if control of disease activity was judged inadequate: increased MTX up to 8 mg/week, use of nonbiological DMARD, increase of oral corticosteroid, intraarticular administration of corticosteroid, intraarticular administration of hyaluronic acid preparation, and the use of 1 biological DMARD (excluding RTX).

Evaluation. Safety and efficacy were evaluated on Days 1 and 15, and every 4 weeks thereafter from Week 4 to Week 24 in the double-blind treatment period. During the safety followup period, safety and efficacy were evaluated every 12 weeks. The primary efficacy endpoint was the ACR 20% (ACR20) response rate at Week 24[14]. The ACR50 and ACR70 response rates and a reduction in the Disease Activity Score (DAS28-ESR) values[15] and European League Against Rheumatism (EULAR) response rates[16] over time up to Week 24 were calculated as secondary endpoints. The percentage of patients achieving DAS28-ESR remission (DAS28-ESR < 2.6) by Week 24 was investigated as exploratory analyses.

To evaluate safety, all adverse events (AE) that occurred during the study were recorded; their severity was judged using the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Version 3.0. Serious AE (SAE) were defined using criteria from the International Conference on Harmonization. Serious infections (SI), defined as SAE infections or infections requiring intravenous antibiotic injection, were tabulated. Human anti-human antibody (HAHA) and serum immunoglobulin (IgG, IgM, and

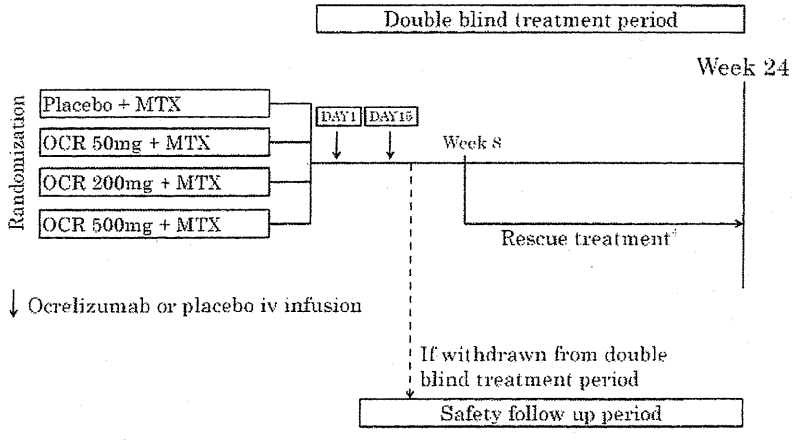

Figure 1. The study design. †Use of additional treatments for RA was permitted after Week 8 if control of disease activity was inadequate, at the discretion of the investigators or subinvestigators. OCR: ocrelizumab; MTX: methotrexate.

IgA) concentrations were also measured. To evaluate pharmacokinetics, OCR concentration in serum was measured, and the number of CD19-positive cells in peripheral blood was measured using flow cytometry.

Statistical analyses. The target sample size was calculated based on the ACR20 response rate in the ACTION study. Using an allocation ratio of 1:2 (placebo vs combined OCR 200 and 500 mg groups), the ACR20 response rate in the combined OCR group of 48.7% and the placebo group of 24.3%, a 2-tailed significance level of 5%, and a power of 80%, the required sample size was calculated by the chi-square test to be 46 patients per group. Allowing for untreated patients, the target group size was set at 50 patients, giving a total target sample size of 200 patients. Calculation of the sample size was performed using nQuery Advisor Version 5.0 (Statistical Solutions Ltd., Farmer's Cross, Ireland).

While our study was in progress, an increased incidence of SI, including opportunistic infections, was reported in multinational clinical trials of OCR that were being conducted at the same time. Based on these safety reports, the enrollment of new patients and the administration of the investigational product in our study were halted, resulting in administration of investigational product to only 151 patients. The double-blind period was prematurely terminated in January 2010 and all patients entered a safety followup period.

The analysis of efficacy was performed using 145 patients (36 patients in the placebo group, 37 in the OCR 50 mg, 36 in the OCR 200 mg, and 36 in the OCR 500 mg), excluding 1 patient in the placebo group, 2 in the OCR 50 mg, and 3 in the OCR 200 mg group who did not receive the second infusion of investigational product because the study was stopped. We recalculated the statistical power and confirmed that it decreased from 80% to 69% with the same assumptions except for the number of patients. The analysis of safety was performed using 151 patients who received investigational products at least once. Safety data were evaluated up to 24 weeks from the first infusion of investigational product regardless of whether patients completed the double-blind period.

The ACR20 response rate at Week 24 (primary endpoint) and ACR50 and ACR70 response rates at Week 24 (secondary endpoints) in each OCR group were compared with the placebo group using the Cochran-Mantel-Haenszel test, accepting a 2-sided significance level of 5%. Based on the predefined analysis plan, descriptive statistics were calculated for the remaining endpoints, but no intergroup comparisons were performed. Adjusted mean changes in DAS28-ESR were based on the analysis of covariance using the baseline value as a covariate.

Efficacy data obtained after the day of rescue treatment or after the day when the decision to withdraw was made were handled as follows: categorical data (ACR responses, EULAR response rates, DAS28-ESR remission) were treated as "no response," continuous data (DAS28-ESR) as "missing data," and the last observation was carried forward.

RESULTS

Baseline characteristics and patient distribution. The mean RA disease duration of the patients in each group was 6.7–10.0 years. The patients had high RA disease activity with a mean DAS28-ESR of 6.3–6.5, a mean serum CRP level of 1.8–3.0 mg/dl, a mean ESR of 53.1–57.0 mm/h, and functional disabilities shown by a mean J-HAQ of 1.3–1.4. The mean MTX dosage was 7.3–7.6 mg/week. In each group, 25.6%–38.9% of the patients had previously received a biological DMARD (Table 1).

Including withdrawals because of the halt in administration of the investigational product, the patients who withdrew from the study before Week 24 numbered 6 in the placebo group, 10 in the OCR 50 mg, 11 in the OCR 200 mg, and 6 in the OCR 500 mg groups. The number of patients who withdrew because of insufficient response was 3 in the placebo group and none in the OCR groups. The proportion of patients receiving rescue treatments up to Week 24 was 32.4% in the placebo group, but lower in the

Table 1. Rheumatoid arthritis (RA) patient demographics and baseline disease characteristics (n = 151).

	Placebo, n = 37	OCR 50 mg, n = 39	OCR 200 mg, n = 39	OCR 500 mg, n = 36
Age, mean (SD), yrs	55.0 (12.1)	54.3 (10.9)	53.1 (10.9)	53.4 (10.3)
No. female (%)	27 (73.0)	30 (76.9)	33 (84.6)	29 (80.6)
RA duration, mean (SD), yrs	8.9 (7.8)	6.7 (7.1)	9.7 (8.1)	10.0 (9.3)
Steinbrocker stage, I/II/III/IV	5/8/9/15	3/15/10/11	3/10/4/22	6/6/13/11
Swollen joint counts (66 joints), mean (SD)	15.2 (6.1)	18.2 (9.7)	15.6 (8.8)	17.4 (9.7)
Tender joint counts (68 joints), mean (SD)	22.2 (11.6)	21.5 (12.3)	19.8 (9.7)	19.0 (9.9)
J-HAQ score, mean (SD)	1.4 (0.6)	1.4 (0.7)	1.3 (0.6)	1.3 (0.7)
CRP, mg/dl, mean (SD)	2.7 (2.7)	2.4 (2.7)	1.8 (1.5)	3.0 (2.8)
ESR, mm/h, mean (SD)	53.1 (29.0)	57.0 (29.0)	54.0 (26.6)	54.7 (31.3)
DAS28-ESR, mean (SD)	6.3 (0.9)	6.5 (0.8)	6.3 (0.8)	6.4 (0.9)
Anti-CCP antibody-positive, no. (%)	35 (94.6)	34 (87.2)	37 (94.9)	32 (88.9)
RF-positive, no. (%)	37 (100)	39 (100)	39 (100)	36 (100)
Corticosteroid use, no. (%)	23 (62.2)	23 (60.0)	28 (71.8)	18 (50.0)
Corticosteroid dose, mg/day, mean (SD)	5.4 (2.2)	5.1 (2.8)	5.2 (2.2)	6.3 (2.4)
MTX dose, mg/wk, mean (SD)	7.4 (0.9)	7.6 (0.8)	7.3 (1.0)	7.6 (0.8)
Previous use of biologics, no. (%)	11 (29.7)	10 (25.6)	11 (28.2)	14 (38.9)
Anti-TNF agent	10 (27.0)	10 (25.6)	10 (25.6)	13 (36.1)
Tocilizumab	2 (5.4)	0 (0.0)	1 (2.6)	3 (8.3)
Abatacept	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)
Previous nonbiological DMARD (except for MTX), mean (SD)	1.8 (1.4)	1.4 (1.1)	1.8 (1.6)	1.7 (1.7)

OCR: ocrelizumab; RA: rheumatoid arthritis; TNF: tumor necrosis factor; DMARD: disease-modifying antirheumatic drug; J-HAQ: Japanese version of the Health Assessment Questionnaire; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS28: Disease Activity Score (28 joint count); CCP: cyclic citrullinated protein; RF: rheumatoid factor; MTX: methotrexate.

OCR groups: 12.8% in the OCR 50 mg, 7.7% in the OCR 200 mg, and 16.7% in the OCR 500 mg groups (Figure 2).

Safety. During the 24-week observation period, the incidence of AE was 59.5% in the placebo group and 79.5% in the OCR 50 mg, 79.5% in the OCR 200 mg, and 61.1% in the OCR 500 mg groups (Table 2). The majority of AE were infections and IRR. An IRR was defined as an AE occurring during or within 24 hours after administration of investigational product.

The proportion of subjects experiencing at least 1 infection was 18.9% (7/37) in the placebo group and 37.7% (43/114) in the OCR groups combined. There were no patients with SI in the placebo group and 7 in the OCR groups combined. There were 4 SI in 2 patients in the OCR 50 mg group, consisting of 1 incident each of herpes zoster, pneumonia, sepsis, and septic shock. Six SI occurred in 4 patients in the OCR 200 mg group, 2 incidents of *Pneumocystis jirovecii* pneumonia (PCP), and 1 each of sepsis, herpes simplex, bacterial pneumonia, and febrile neutropenia. There was 1 SI (epididymitis) in 1 patient in the OCR 500 mg group.

Two incidents of malignant tumors (uterine cancer and ovarian cancer) in 1 patient in the OCR 500 mg group were reported, which were diagnosed 153 days after the first infusion of OCR. There were no intergroup differences in the incidences of other AE.

There were 2 deaths during our study. One was a 61-year-old man who had concurrent depression and hypertension, and a history of cerebral infarction and cerebral hemorrhage. He developed pneumonia and sepsis 67 days after administration of OCR 500 mg followed by septic shock, disseminated intravascular coagulation, and multiorgan failure and died the following day. The other death was a 64-year-old man in the placebo group; he died of acute respiratory failure after withdrawal from the study because of insufficient response. No definitive diagnosis was made and an autopsy was not performed.

The increase in incidences of IRR following the first administration (Day 1) of investigational product was dose-dependent: 0% in the placebo group and 15.4% in the OCR 50 mg, 20.5% in the OCR 200 mg, and 25.0% in the OCR 500 mg groups. Following the second administration (Day 15) of investigational product, the incidence of IRR was markedly decreased in all 3 OCR groups (Table 2, Figure 3), 2.9% in the OCR 50 mg, 6.1% in the OCR 200 mg and 8.8% in the OCR 500 mg groups. All patients, except for 1 in the OCR 500 mg group, who experienced an IRR at the second administration also had an IRR at the first administration. Of the 26 IRR, 4 were moderate (NCI CTC Grade 2) and 22 were mild (NCI CTC Grade 1). One patient in each of the OCR 200 mg and the OCR 500 mg groups withdrew from the study because of IRR.

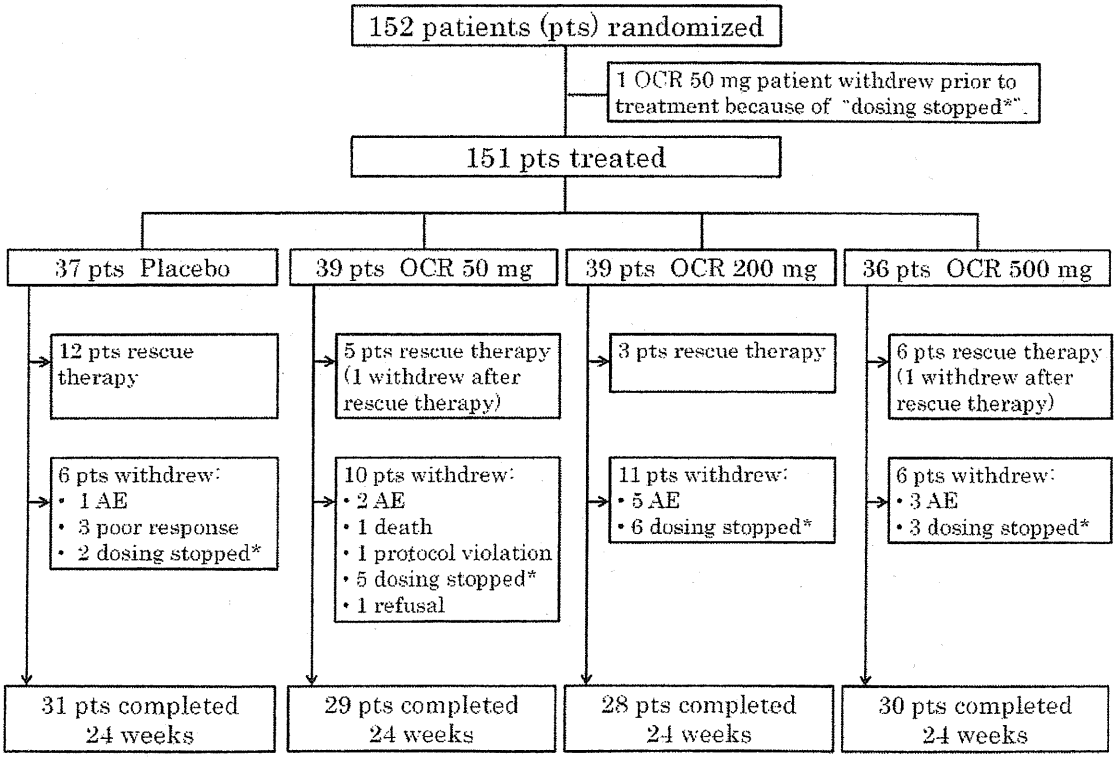

Figure 2. Disposition of patients with RA at Week 24. *Dosing of investigational product was stopped, patients were withdrawn from the study, and enrollment of new patients was halted because of the increased incidence of serious infections, including opportunistic infections, reported in other multinational clinical studies of ocrelizumab (OCR). AE: adverse event.

Table 2. Summary of adverse events (AE) in the safety analysis population of patients with rheumatoid arthritis (n = 151) during the 24-week observation period. Values are the number (%) of patients.

	Placebo, n = 37	OCR 50 mg, n = 39	OCR 200 mg, n = 39	OCR 500 mg, n = 36
Any AE	22 (59.5)	31 (79.5)	31 (79.5)	22 (61.1)
Serious AE	3 (8.1)	2 (5.1)	7 (17.9)	5 (13.9)
AE leading to withdrawal	1 (2.7)	2 (5.1)	5 (12.8)	3 (8.3)
Infection	7 (18.9)	16 (41.0)	16 (41.0)	11 (30.6)
Serious infection	—	2 (5.1)	4 (10.3)	1 (2.8)
Infusion-related reactions	2 (5.4)	6 (15.4)	8 (20.5)	10 (27.8)
Serious infusion-related reactions	—	—	—	1 (2.8)
All AEs affecting ≥ 5% of patients				
Pharyngitis	1 (2.7)	3 (7.7)	1 (2.6)	1 (2.8)
Nasopharyngitis	2 (5.4)	1 (2.6)	3 (7.7)	0
Bronchitis	0	2 (5.1)	3 (7.7)	0
Upper respiratory tract infection	0	1 (2.6)	2 (5.1)	1 (2.8)
Herpes zoster	0	2 (5.1)	1 (2.6)	1 (2.8)
Cystitis	0	0	2 (5.1)	1 (2.8)
P. jirovecii pneumonia	0	0	2 (5.1)	0
Infusion-related reaction	2 (5.4)	6 (15.4)	8 (20.5)	10 (27.8)
Pyrexia	1 (2.7)	2 (5.1)	0	0
Hepatic function abnormal	1 (2.7)	2 (5.1)	2 (5.1)	4 (11.1)
Constipation	1 (2.7)	2 (5.1)	1 (2.6)	0
Stomatitis	2 (5.4)	0	0	0
Upper abdominal pain	0	0	0	2 (5.6)
Urticaria	0	2 (5.1)	0	1 (2.8)
Drug eruption	0	0	2 (5.1)	0
Headache	0	0	1 (2.6)	3 (8.3)
Conjunctivitis	0	2 (5.1)	0	0

OCR: ocrelizumab.

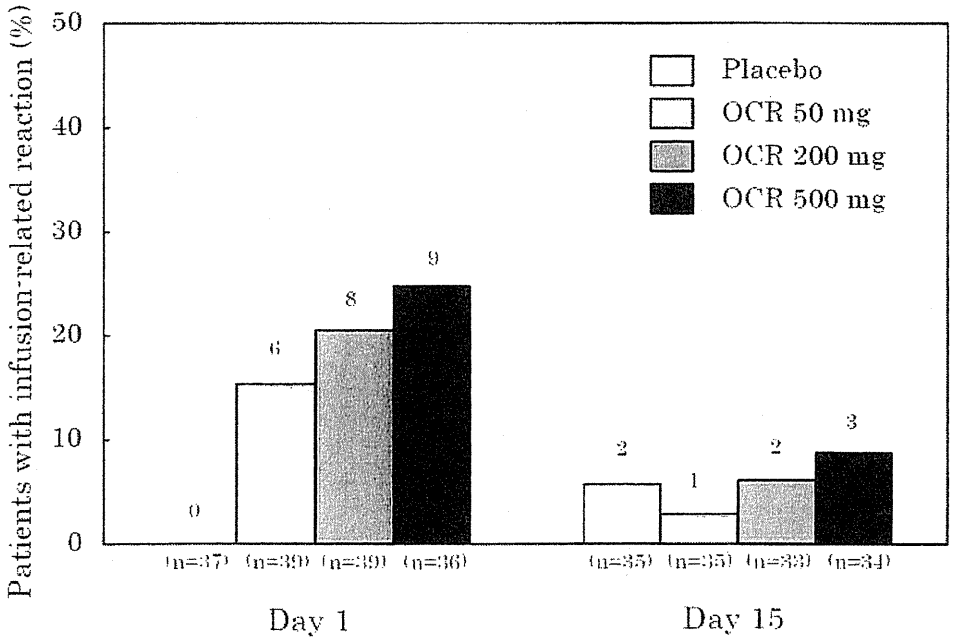

Figure 3. Incidence of infusion-related reactions at Days 1 and 15. Patient numbers shown here represent patients in each group at Days 1 and 15. OCR: ocrelizumab.

No placebo group patients became HAHA-positive during the study, but 2 patients in the OCR 50 mg group and 1 each in the OCR 200 mg and OCR 500 mg groups were HAHA-positive. An IRR occurred in 1 of the 4 patients who became HAHA-positive; this patient developed the IRR at the first administration prior to the expression of HAHA. No serious AE occurred in any HAHA-positive patient. Two of the 4 HAHA-positive patients achieved ACR20 at Week 24, and 1 achieved ACR70. A comparison of HAHA-positive and HAHA-negative patients showed no consistent difference in serum OCR concentration during the study period. The presence of HAHA did not appear to influence either efficacy or safety outcomes.

Efficacy. The ACR20 response rates at Week 24, the primary endpoint, in the OCR groups were significantly higher than the 25.0% of the placebo group [OCR 50 mg: 54.1% ($p = 0.0080$), OCR 200 mg: 55.6% ($p = 0.0056$), OCR 500 mg: 47.2% ($p = 0.044$)]. The ACR50 responses at Week 24 were 16.7% for the placebo group, 37.8% for the OCR 50 mg, 38.9% for the OCR 200 mg, and 30.6% for the OCR 500 mg groups. The ACR50 response rates in the OCR 50 mg and OCR 200 mg groups were significantly higher than those in the placebo group ($p = 0.038$, $p = 0.031$, respectively). The ACR20, ACR50, and ACR70 response rates over time are shown in Figure 4 A-C. The adjusted means (± SE) of the ΔDAS28-ESR, the good responses rates using the EULAR response criteria, and the DAS28-ESR clinical remission rates (DAS28-ESR < 2.6) of the OCR groups at Week 24 were better than those of the placebo groups (Figure 4D, 4E).

Pharmacodynamics. Although the number of CD19-positive cells increased transiently in the placebo group following intravenous administration of methylprednisolone as premedication on Days 1 and 15, the number remained stable through Week 24. In all 3 OCR-treated groups, the number of CD19-positive cells in peripheral blood decreased rapidly after the first administration of OCR; that effect was maintained throughout the 24-week study period (Figure 5). The proportion of patients in whom the number of CD19-positive cells had recovered to at least LLN (80 cells/μl) or the baseline value, whichever was lower, by Week 24 was 80.6% in the placebo group and 6.9% in the OCR 50 mg, 3.4% in the OCR 200 mg, and 0% in the OCR 500 mg groups.

DISCUSSION

Our double-blind placebo-controlled study demonstrated the safety profile of OCR in Japanese patients with RA. The OCR clinical development program in patients with RA was terminated because the risk of SI outweighed the clinical benefits observed in patients with RA, based on the data from our trial and multinational clinical trials of OCR.

In our study, the majority of AE were IRR and infections, and the incidence of IRR was consistent with results reported for anti-CD20 antibodies[7,8,12]. Characteristic IRR symptoms in the OCR group were hypertension in 7 patients (6.1%), headache in 5 (4.4%), pyrexia in 4 (3.5%), and pruritus in 4 (3.5%); these results did not differ from previous studies of OCR or RTX.

By Week 24, SI had occurred only in the OCR group. In the OCR groups combined, the 7 patients who developed SI and the 107 patients who did not develop SI had comparable baseline white blood cell (WBC), neutrophil, and lymphocyte counts and immunoglobulin (IgG, IgM, and IgA) levels. The WBC, neutrophil, and immunoglobulin levels did not fall below LLN [WBC < 3900/μl; neutrophils < 1500/μl; IgG < 870 mg/dl; IgM < 33 mg/dl (males), < 46 mg/dl (females); IgA < 10 mg/dl] in any of the 7 patients with SI during our study, but the lymphocyte count did fall below 500/μl during the study period in 2 patients with SI. In the OCR groups combined, 2 of the 9 patients (22%) whose lymphocyte counts fell below 500/μl developed SI, while 5 of the 105 patients (4.8%) with lymphocyte count > 500/μl developed SI. Among the SI, PCP occurred in 2 patients in the OCR 200 mg group. At the onset of PCP, both patients exhibited pyrexia, hypoxemia, pulmonary ground-glass opacity, and increased serum ß-D-glucan levels, and 1 patient was positive on the polymerase chain reaction test for *P. jirovecii*. Both patients recovered with methylprednisolone pulse therapy and trimethoprim-sulfamethoxazole. Advanced age, concurrent lung disease, and concomitant corticosteroid use have been reported as risk factors for bacterial pneumonia or SI including PCP during treatment of Japanese RA patients with tumor necrosis factor (TNF) inhibitors[17,18,19,20,21]. In our study, 6 of the 7 patients with SI were using prednisolone concomitantly, but only 3 of the 7 patients with SI were over 60 years of age (3 were in their 40s and 1 in her 20s) and none had concurrent lung disease. Similarly, both patients who developed PCP in our study were taking 7.5 mg/day oral prednisolone, but both were 42 years old and did not have concurrent lung disease. Further, their lymphocyte counts at onset of PCP were decreased to 651 and 890/μl, respectively. These results suggest that risk factors for SI, including PCP, during OCR treatment may differ from those during treatment with TNF inhibitors.

Although there were differences of sample size, patient background, and observation period, the incidence of SI in our study (6.1%) was comparable to the results of other Japanese clinical trials of biologic agents: 7.6% in a 52-week study of tocilizumab in patients with inadequate response to DMARD (SAMURAI study)[22]; 3.3% in a 24-week study of tocilizumab in patients with inadequate response to MTX (SATORI)[23]; 5.2% in a 54-week study of infliximab in patients with inadequate response to MTX (RISING)[24]; and 4.9% in a 24-week study of adalimumab in patients with inadequate response to DMARD (CHANGE)[25]. PCP was observed in 2 patients (1.75%) in our study, but in the SAMURAI, SATORI, and CHANGE studies, no PCP was observed. Further, the incidence of PCP in our study was

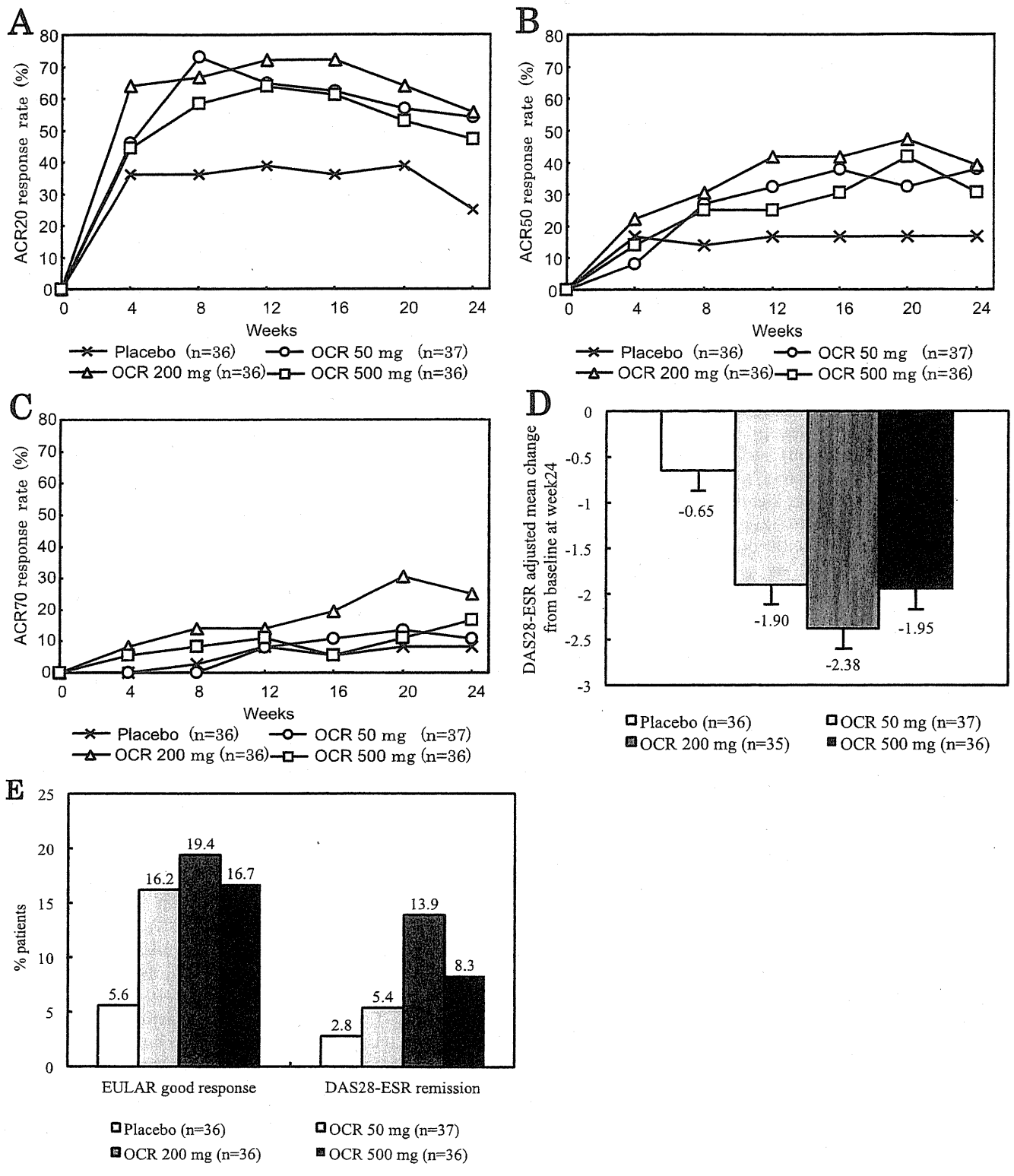

Figure 4. Clinical efficacy of ocrelizumab (OCR). A. ACR20 response rate over time. B. ACR50 response rate over time. C. ACR70 response rate over time. Patients receiving rescue therapy or withdrawing from the study were classified as nonresponders. D. DAS28-ESR mean changes from baseline at Week 24. Error bars represent standard error of the mean. E. The proportion of patients achieving a good response according to the EULAR criteria and remission according to DAS28-ESR. ACR: American College of Rheumatology; DAS28: Disease Activity Score (28 joint count); ESR: erythrocyte sedimentation rate; EULAR: European League Against Rheumatism.

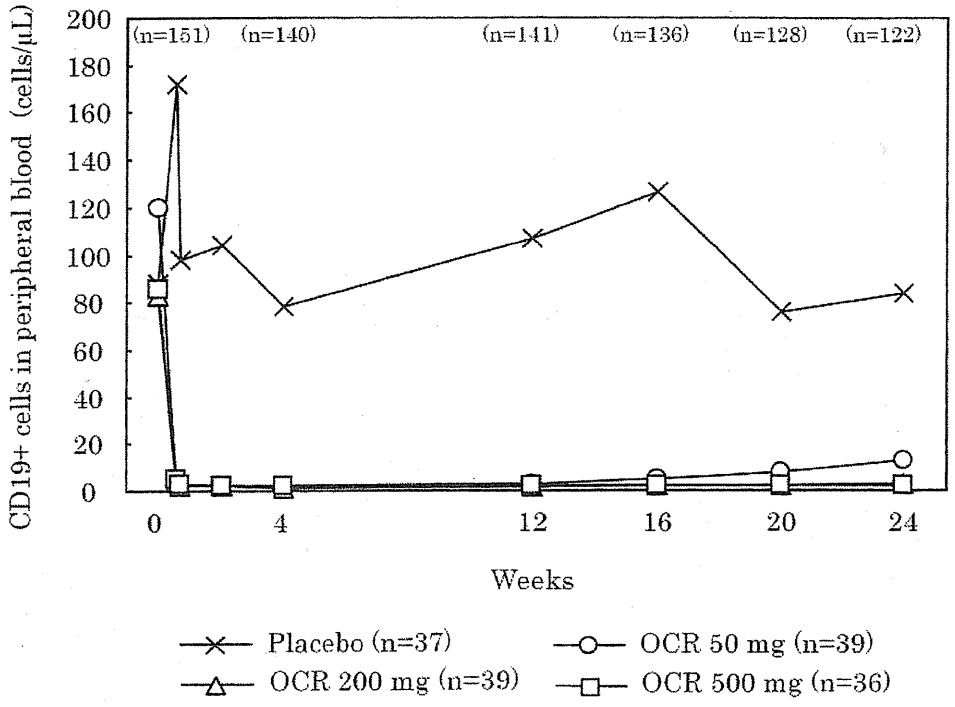

Figure 5. Median peripheral blood CD19-positive B cell counts over time. The lower limit of normal (LLN) was 80 cells/μl. The patient numbers shown with each investigational group represent the number of patients in that group at Time 0. Numbers shown above the different timepoints represent total number of patients in the study at that timepoint. OCR: ocrelizumab.

higher than those in the Japanese postmarketing surveillance data of biologic agents (tocilizumab, infliximab, and etanercept), that is, 0.2% to 0.4%[17,18,19,26]. These results suggest that treatment with OCR in Japanese patients with RA may have higher risk for PCP than treatment with the other biologic agents.

A possible association of efficacy with B cell depletion was reported in patients with RA treated with OCR in the ACTION study[12], which ascertained that B cell depletion was maintained until Week 24 in groups that received ≥ 200 mg OCR, but was not maintained in groups with lower dosages. Significant improvements of signs and symptoms of RA shown by relatively stringent response criteria, including ACR70 response, DAS28-ESR clinical remission, and EULAR good response, were also obtained only in groups that received ≥ 200 mg OCR[12]. The clinical response to RTX has been reported to be determined by the level of B cell depletion rather than by the dose of the drug[27]. In our study, the percentages of patients with peripheral blood B cell count at Week 24 that was above LLN or baseline values were 6.9%, 3.4%, and 0% in the OCR 50, 200, and 500 mg groups, respectively. The OCR 200 mg group showed higher clinical responses than the other 2 OCR groups in every efficacy criterion used in our study. In addition, the peripheral B cell count recovered to at least the LLN (80 cells/μl) or the baseline value in 4 patients in the OCR groups combined, but these patients showed sustained efficacy through Week 24. It is difficult to draw firm conclusions because of the small number of patients with B cell recovery and the limited study period (24 weeks), but these results suggest that peripheral B cell count alone may not account for maintenance of efficacy in patients with RA treated with OCR.

As a limitation of our study, we note the dosage of MTX. The mean MTX dosage in each group was 7.3–7.6 mg/week, which was lower compared to clinical trials of OCR for RA conducted in some Western countries. The approved maximum dose of MTX was 8 mg/week in Japan when this trial was implemented and we had to design the trial under this restriction. This should be taken into account when interpreting our results.

Serious infections, including PCP, occurred only in the combined OCR groups in our study, possibly indicating an elevated risk for SI from OCR use in Japanese patients with RA. Treatment with OCR resulted in better clinical responses than treatment with the placebo in Japanese RA patients with an inadequate response to MTX, about 30% of whom had been previously treated with a biological DMARD. Although we should take into account the small sample size and the premature termination of the study, these results would suggest an inappropriate benefit-risk balance for OCR in this patient population. Because of the lack of

approval for RTX for RA in Japan and the recommended use of the drug for patients with RA who have failed TNF inhibitor therapy in Western countries, it will be necessary to investigate the safety and efficacy of other anti-B cell therapies in Japanese patients with RA.

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APPENDIX

List of study collaborators. Primary investigators of the JA21963 study group: Kazuhide Tanimura (Hokkaido Medical Center for Rheumatic Diseases), Hiroki Takahashi (Sapporo Medical University), Yukitomo Urata (Seihoku Central Hospital), Yasuhiko Hirabayashi (Hikarigaoka Spellman Hospital), Tomonori Ishii, Hiroshi Fujii (Tohoku University Hospital), Takayuki Sumida (Tsukuba University Hospital), Chihiro Terai (Jichi Medical University Saitama Medical Center), Ryutaro Matsumura (National Hospital Organization Chiba-East Hospital), Makoto Sueishi (National Hospital Organization Shimoshizu Hospital), Kazuhiko Yamamoto (The University of Tokyo Hospital), Akio Yamada, Daitaro Kurosaka (Jikei University School of Medicine), Akio Mimori (International Medical Center of Japan), Yusuke Miwa (Showa University Hospital), Masataka Kuwana (Keio University Hospital), Shinichi Kawai (Toho University Omori Medical Center), Yoshiaki Ishigatsubo (Yokohama City University Hospital), Kazunori Sugimoto (Fukui General Clinic), Noriyoshi Ogawa (Hamamatsu University School of Medicine), Toshiaki Miyamoto (Seirei Hamamatsu General Hospital), Shigenori Tamaki, Motokazu Kai (National Hospital Organization Mie Chuou Medical Center), Daisuke Kawabata (Kyoto University Hospital), Toshio Tanaka (Osaka University Hospital), Masaaki Inaba (Osaka City University Hospital), Shunichi Kumagai, Akio Morinobu, Yasushi Miura (Kobe University Hospital), Hajime Sano (Hyogo College of Medicine), Naoki Kashihara, Yoshitaka Morita (Kawasaki Medical School Hospital), Kazuhiko Ezawa (Kurashiki Kosai Hospital), Yuji Yamanishi, Masanori Kawashima (Hiroshima City Hospital), Seizo Yamana, Mitsuhiro Iwahashi (Higashihiroshima Memorial Hospital), Hiroaki Dobashi (Kagawa University), Kiyoshi Takasugi (Dohgo Spa Hospital), Takahiko Horiuchi (Kyusyu University Hospital), Eiichi Suematsu (National Hospital Organization Kyushu Medical Center), Takaaki Fukuda (Kurume University Medical Center), Katsumi Eguchi, Atsushi Kawakami (Nagasaki University Hospital).

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ORIGINAL ARTICLE

Postmarketing surveillance of safety and effectiveness of etanercept in Japanese patients with rheumatoid arthritis

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Abstract Our aim was to evaluate real-world safety and effectiveness in a 6-month postmarketing surveillance study covering all Japanese patients with rheumatoid arthritis (RA) who received etanercept during a 2-year period. Data for 13,894 patients (1334 sites) enrolled between March 2005 and April 2007 were collected. Adverse events (AEs) and serious adverse events (SAEs) were reported in 4336 (31.2%) and 857 (6.2%) patients, respectively. The most frequent AEs were injection site reactions ($n = 610$, 4.4%) and rash ($n = 339$, 2.4%), whereas pneumonia ($n = 116$, 0.8%) and interstitial lung disease ($n = 77$, 0.6%) were the most frequent SAEs. Significant improvement in the proportion of patients with a good European League Against Rheumatism (EULAR) response was observed from week 4 (17.6%) to week 24 (31.6%) ($p < 0.001$); 84.3% of patients had good or moderate EULAR responses at week 24. The percentage of patients achieving remission increased significantly from week 4 (9.3%) to week 24 (18.9%) ($p < 0.001$). Patients with early moderate RA were less likely to experience SAEs and were more likely to achieve remission compared with patients with more severe disease. The safety and effectiveness of etanercept was demonstrated in Japanese patients in one of the largest observational trials conducted thus far in RA patients treated with biologics.

Keywords DAS28 · Etanercept · Postmarketing surveillance study · Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA), a chronic inflammatory disease affecting joints and extra-articular tissues, is associated

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with increased pain, deterioration of physical function, and decreased life expectancy [1, 2]. Achievement of disease remission is considered a realistic and crucial goal for patients with RA, as reflected by current treatment guidelines and recommendations of the European League Against Rheumatism (EULAR), the American College of Rheumatology (ACR), and others [3–5]. The modified disease activity score (DAS28) [6] is a validated 28-joint instrument that measures joint tenderness and/or swelling and can accurately evaluate the status of disease activity and the efficacy of treatment. Because of its reliability in monitoring and defining disease activity and remission, the DAS28 is commonly used in RA trials; it has also been endorsed by the EULAR working group recommendations for management of RA [5, 7].

Recent randomized clinical trials have demonstrated the efficacy and safety profile of RA treatments that function as antagonists of tumor necrosis factor alpha (TNF-α), either as monotherapy or combined with methotrexate [7–12]. In general, these treatment regimens were effective at reducing disease activity, achieving remission, and preventing joint destruction in patients with RA. However, most of the data describing efficacy and safety for RA treatments come from late-phase clinical trials or national databases. Inclusion criteria for the studies are not always reflective of treatment in a real-world environment. Large well-designed phase 3 trials generally provide useful patient outcomes data, but these studies may not adequately define the true safety and effectiveness of a drug outside the clinical research setting.

As one of the conditions of approval of etanercept in Japan, the Pharmaceutical and Medical Device Agency (PMDA) requested that Wyeth (now integrated into Pfizer as of October 2009) conduct surveillance to confirm the safety and effectiveness of etanercept in Japanese patients in the clinical setting after the drug was marketed. To comply with this request, we performed a postmarketing surveillance (PMS) study that registered all Japanese RA patients treated with etanercept at the participating study sites for the survey period. Etanercept is a fully human soluble TNF-α receptor fusion protein with demonstrated efficacy against RA in patients not adequately responding to disease-modifying antirheumatic drugs (DMARDs) such as methotrexate [13, 14]. Etanercept has shown superior efficacy to methotrexate in patients with RA [15], and the combination of etanercept plus methotrexate was superior to either monotherapy alone [16]. The goal of this PMS study was to evaluate the real-world safety and effectiveness of etanercept for a large Japanese patient population receiving etanercept for the treatment of RA. A previous interim analysis comprising data for 7091 of the registered patients reported that etanercept was effective with no new safety signals [17]. This report covers nearly 14,000 Japanese patients with RA registered to the PMS study from 2005 to 2007.

Patients, materials, and methods

Patients

Between March 2005 and April 2007, all Japanese patients with RA from 1334 sites were enrolled in a 6-month PMS study of etanercept use (NCT00503503). Patient eligibility for treatment with etanercept was based on the Japan College of Rheumatology treatment guidelines [18]. Briefly, etanercept was indicated for patients with RA who were previously treated with DMARDs (e.g., methotrexate, salazosulfapyridine, or bucillamine) for >3 months, and had ≥6 tender joints, ≥6 swollen joints, and erythrocyte sedimentation rate (ESR) ≥28 mm/h or C-reactive protein (CRP) levels ≥2.0 mg/dL [17]. Patients had a low risk for opportunistic infections, defined as white blood count ≥4000/mm^3, peripheral blood lymphocyte count ≥1000/mm^3, and negative serum β-D-glucan. Mandatory chest radiographs and tuberculin tests were conducted before initiation of treatment. Information on age, sex, comorbidity, Steinbrocker radiographic stage [19], Steinbrocker functional class [19], duration of RA, smoking history, previous and concomitant use of glucocorticoids, and concomitant use of DMARDs (including methotrexate) was collected. Also, ESR and CRP levels were assessed. Etanercept 10 or 25 mg was administered subcutaneously twice weekly, with the dose determined by the prescribing physician. After an initial 1-month training period, patients were allowed to self-inject etanercept.

The PMS protocol was reviewed and approved by the Japanese Ministry of Health, Labor, and Welfare. Registration was conducted centrally at the time of treatment initiation. Data collection was performed through an electronic data capture system, the Internet, or hardcopy case report forms, and medical representative staff members from Wyeth and Takeda Pharmaceutical Company visited sites periodically to collect additional data as required.

Assessments

All patients were assessed for safety every 2 weeks. Safety evaluations included all events occurring ≤24 weeks after the first etanercept dose and ≤30 days after the last dose. All adverse events (AEs) were reported. Safety data were coded with preferred terms from the Medical Dictionary for Regulatory Activities [20]. All AEs, serious AEs (SAEs), adverse drug reactions (ADRs; noxious and unintended responses deemed to be related to the treatment), and serious ADRs, including infection, were defined

based on the International Conference on Harmonisation tripartite harmonised guideline [21]. Particular attention was paid to the occurrence of infections, especially tuberculosis, pneumonia, *Pneumocystis jiroveci* pneumonia, cytomegalovirus infection, and sepsis and to specific important ADRs that included malignant neoplasm, demyelination, congestive heart failure, injection site reaction, and lupus. Safety information was independently evaluated by the Japan College of Rheumatology PMS committee.

Treatment effectiveness was measured monthly using the EULAR response criteria [22] and the DAS28 [6]. The DAS28 is divided into 4 categories: remission (DAS28 <2.6), low disease activity (DAS28 ≥2.6 and ≤3.2), moderate disease activity (DAS28 >3.2 and ≤5.1), and high disease activity (DAS28 >5.1). A good response was defined as a DAS28 improvement from baseline of >1.2 and a DAS28 of ≤3.2 during follow-up. Patients with score improvements of ≤0.6 or those with improvements between 0.6 and 1.2 plus a DAS28 of >5.1 during follow-up were defined as nonresponders. Moderate responders were those with DAS28 improvements from baseline between 0.6 and 1.2 plus a DAS28 of ≤5.1 during follow-up. Treatment was considered to be effective in patients with moderate or good DAS28 responses. General health status was measured using a patients' visual analog scale (100 being the worst they can imagine, 0 being the best they can imagine), and duration of morning stiffness was also assessed.

Statistical analysis

Missing data were processed using the last-observation-carried-forward method, except for baseline values, which were not carried forward. The χ^2 or *t*-test was used to compare differences in baseline values between men and women. The *t*-test was used to compare DAS28 differences between baseline and weeks 4 and 24; χ^2tests were used to compare differences in EULAR response rates, and Cochran-Armitage tests were used to examine evidence of trends in response rates. Cox proportional hazard models were used to estimate the influence of multiple variables on the occurrence of serious infections (AEs). These variables included the confounders assessed at baseline: age, sex, concomitant methotrexate use, concomitant glucocorticoid use, history of infectious disease, history of tuberculosis, presence of any comorbidities, Steinbrocker functional class, and duration of RA. A total of 1274 patients with missing data [duration of RA ($n = 1267$) and other ($n = 7$)] were excluded from the Cox proportional hazard models. We also used multiple logistic regression models to estimate the effect of variables on the likelihood of achieving remission. Patients who had missing DAS28 data at either baseline or at 24 weeks, a DAS28 value of <2.6 at baseline, or missing data for other adjustment factors were excluded from these models. Furthermore, we used Cox proportional hazard models and multiple logistic regression models to examine the combined effects of multiple risk factors on the occurrence of serious infections and the likelihood of achieving remission, respectively. The hazard ratio or odds ratio and the 95% confidence interval (CI) for each of the combined factors after adjustment for major confounders and the combined effect relations with numbers of factors were further explored by trend tests. All statistical analyses were performed using SAS® software version 8.2 (SAS Institute, Cary, NC, USA). Two-sided *P* values of < 0.05 were considered statistically significant.

Results

Patients

A total of 13,894 patients treated with etanercept completed the 24-week study (Table 1). The majority of patients were women ($n = 11,314$; 81.4%). Mean ± SD patient age was 58.1 ± 13.1 years; most patients (78.3%) were aged >50 years (more than one half were aged >60 years), and the mean ± SD patient weight was 53.2 ± 10.1 kg. About 40% of patients had a disease duration of >10 years. Concomitant use of DMARDs/biologics was 74.0% ($n = 10,276$) and that of methotrexate was 55.9% ($n = 7768$). The most commonly used etanercept dose regimen (76.1%; $n = 10,578$) was 50 mg per week (i.e., 25 mg twice weekly). Previous use of glucocorticoid was 83.4% ($n = 11587$) and previous use of infliximab was 13.5% ($n = 1878$). Additionally, 57.1% of patients had comorbidities, including 877 patients (6.3%) with a medical history of tuberculosis. Significant differences were observed between men and women in most demographic characteristics, including age, weight, disease duration, Steinbrocker stage and class, history of concomitant medical conditions, comorbidities, concomitant use of methotrexate, and prior glucocorticoid use (Table 1). A total of 11,615 (83.6%) patients completed 24 weeks of therapy, with 2309 patients (16.6%) discontinuing during the 24-week period. Reasons for stopping treatment were AEs (7.6%, $n = 1049$), lack of treatment effectiveness (2.6%, $n = 368$), refusal of treatment for economic reasons (1.5%, $n = 212$), moved to another hospital (1.6%, $n = 222$), and other (3.3%, $n = 458$).

Safety

As shown in Table 2, AEs and SAEs were reported in 4336 (31.2%) and 857 (6.2%) patients, respectively. The most

Table 1 Patient demographics

Characteristic	Male patients (n = 2580)	Female patients (n = 11,314)	p value[a]
Mean (SD) age, years	57.5 (13.2)	60.7 (12.4)	<0.001[b]
Age range [n (%), years]			
<20	11 (0.4)	65 (0.6)	
20–29	52 (2.0)	342 (3.0)	
30–39	124 (4.8)	843 (7.5)	
40–49	198 (7.7)	1382 (12.2)	
50–59	691 (26.8)	3243 (28.7)	
60–69	837 (32.4)	3358 (29.7)	
≥70	667 (25.9)	2081 (18.4)	<0.001
Mean (SD) weight, kg	61.7 (10.4)	51.3 (9.0)	<0.001[b]
Disease duration [n (%), years]			
<2	436 (16.9)	1168 (10.3)	
2–<5	588 (22.8)	1844 (16.3)	
5–<10	589 (22.8)	2386 (21.1)	
10–<15	328 (12.7)	1925 (17.0)	
15–<20	194 (7.5)	1166 (10.3)	
≥20	208 (8.1)	1795 (15.9)	
Unknown (years)	237 (9.2)	1030 (9.1)	<0.001
Steinbrocker stage [n (%)]			
I	241 (9.4)	624 (5.5)	
II	801 (31.1)	2458 (21.7)	
III	928 (36.0)	3998 (35.4)	
IV	606 (23.5)	4225 (37.4)	<0.001
Steinbrocker class [n (%)]			
1	277 (10.8)	946 (8.4)	
2	1536 (59.6)	6526 (57.7)	
3	694 (26.9)	3482 (30.8)	
4	69 (2.7)	351 (3.1)	<0.001
Positive history of concomitant medical conditions [n (%)]	987 (38.8)	3079 (27.6)	<0.001
Tuberculosis	228 (8.8)	649 (5.7)	<0.001
Interstitial pneumonitis	341 (13.2)	693 (6.1)	<0.001
Follicular bronchitis	5 (0.2)	32 (0.3)	
COPD	43 (1.7)	41 (0.4)	<0.001
Total comorbidities [n (%)]	1570 (60.9)	6359 (56.2)	<0.001
Hepatic	155 (6.0)	475 (4.2)	<0.001
Renal	152 (5.9)	395 (3.5)	<0.001
Hematologic	100 (3.9)	698 (6.2)	<0.001
Cardiac	217 (8.4)	569 (5.0)	<0.001
Infectious (nonserious)	56 (2.2)	168 (1.5)	0.013
Diabetes mellitus	340 (13.2)	758 (6.7)	<0.001
Weekly etanercept dose regimen [n (%), mg]			
50	2018 (78.2)	8560 (75.7)	
25	264 (10.2)	1298 (11.5)	
20	2 (0.1)	27 (0.2)	
20–50[c]	296 (11.5)	1429 (12.6)	0.023[d]
Concomitant DMARD/ biologic use [n (%)]	1924 (74.6)	8352 (73.8)	
Prior glucocorticoid use [n (%)][e]	2209 (88.4)	9378 (85.5)	<0.001
Concomitant MTX use [n (%)]	1371 (53.1)	6397 (56.5)	0.002
MTX dose [n (%), mg/week]			
0–<4	39 (2.8)	271 (4.2)	
4–<6	239 (17.4)	1583 (24.7)	
6–<8	448 (32.7)	2157 (33.7)	
8–<10	497 (36.3)	1898 (29.7)	
≥10	148 (10.8)	488 (7.6)	<0.001
Prior infliximab use [n (%)]	366 (14.2)	1512 (13.4)	

COPD chronic obstructive pulmonary disease, *DMARD* disease-modifying antirheumatic drug, *MTX* methotrexate

[a] The p values indicated are for comparisons between male and female patient data, using χ^2tests unless otherwise indicated

[b] Comparisons were made using the t-test

[c] Patients received variable dosing during the observation period

[d] Comparisons were made using Fisher exact test

[e] Unknown patients were omitted from the percentage calculation

frequently observed AEs were injection site reaction (n = 610, 4.4%), rash (n = 339, 2.4%), and abnormal hepatic function (n = 328, 2.4%). Pneumonia was the most frequently reported SAE (n = 116, 0.8%), followed by interstitial lung disease (n = 77, 0.6%), and pyrexia (n = 40, 0.3%). In total, 26.7 and 4.6% of patients reported ADRs and serious ADRs, respectively. Table 2 also lists selected important ADRs; various forms of pneumonia were the most common ADR (n = 174, 1.3%). Tuberculosis was reported as an ADR in 12 patients (0.1%), and interstitial lung disease in 81 patients (0.6%). No cases of demyelinating disease were observed. Lupus-like syndrome and congestive heart failure (including all heart failure) were recorded as ADRs in 5 and 7 patients, respectively. Thirty cases of malignancy were reported (0.2%), and there were 76 deaths (0.6%) during the 24-week study.

Risk factors for the development of serious infections are shown in Table 3. Compared with the respective referent group, female sex and concomitant methotrexate use significantly lowered the risk of infection, whereas older age (≥65 years), history of infectious disease, presence of any comorbidities, Steinbrocker functional class 4, and concomitant glucocorticoid use significantly increased serious infection risk. Prior history of tuberculosis slightly, but not significantly, raised the infection risk compared

Table 2 Incidences of the most commonly reported adverse events, serious adverse events, important adverse drug reactions, and death

Event	*n* (%)
Patients with at least 1 AE,[a] total	4336 (31.2)
Injection site reaction	610 (4.4)
Rash	339 (2.4)
Abnormal hepatic function	328 (2.4)
Nasopharyngitis	288 (2.1)
Pyrexia	261 (1.9)
Upper respiratory tract infection	224 (1.6)
Pruritus	202 (1.5)
Total pneumonia[b]	189 (1.0)
Herpes zoster	115 (0.8)
Erythema	114 (0.8)
Patients with at least 1 SAE,[a] total	857 (6.2)
Total pneumonia[b]	116 (0.8)
Interstitial lung disease	77 (0.6)
Pyrexia	40 (0.3)
Sepsis	27 (0.2)
Herpes zoster	23 (0.2)
Pneumocystis jiroveci pneumonia	24 (0.2)
Urinary tract infection	16 (0.1)
Abnormal hepatic function	15 (0.1)
Bacterial arthritis	13 (0.1)
Bronchitis	13 (0.1)
Patients with at least 1 important ADR[a]	968 (7.0)[c]
Total pneumonia[b]	174 (1.3)
Interstitial lung disease	81 (0.6)
Pneumocystis jiroveci pneumonia	25 (0.2)
Malignancy	30 (0.2)
Tuberculosis[d]	12 (0.1)
Pulmonary	10 (0.1)
Extrapulmonary	3 (<0.1)
Congestive heart failure	7 (0.1)
Lupus-like syndrome	5 (<0.1)
Demyelinating disease	0 (0)
Deaths	76 (0.6)

ADR adverse drug reaction, *AE* adverse event, *SAE* serious adverse event

[a] Patients who had at least 1 AE, SAE, or specifically important ADR, respectively. The 10 most frequently reported AEs, SAEs, and ADRs are listed

[b] Total pneumonia = pneumonia + bacterial pneumonia + bronchopneumonia + *Chlamydia* pneumonia + staphylococcal pneumonia + *Candida pneumonia* + fungal pneumonia; 1 patient developed both pneumonia and bronchopneumonia

[c] 609 patients who had injection site reactions were included

[d] 1 patient had both pulmonary and extrapulmonary tuberculosis

with those without a history of tuberculosis (model 1). Model 2 showed the combined effects of multiple risk factors on the occurrence of serious infections adjusted for the remaining variables included in model 1. Compared with patients without combined risk factors, the hazard ratio of serious infection was 9.91 (95% CI 5.48–17.94; $p < 0.001$) for patients who had 3 risk factors, 4.24 (95% CI 2.83–6.34; $p < 0.001$) for patients who had 2 risk factors, and 1.96 (95% CI 1.30–2.96; $p = 0.001$) for patients who had 1 risk factor. Highly significant linear association ($p < 0.001$) was evident for increasing number of combined risk factors.

Effectiveness

The effectiveness of etanercept treatment as determined by various assessment methods is shown in Table 4. The mean DAS28 decreased significantly (both $p < 0.01$), from 5.9 at baseline to 4.3 at week 4 (27% improvement) and 3.8 at week 24 (36% improvement). The mean duration of morning stiffness also decreased significantly (both $p < 0.01$), from 111.3 min at baseline to 44.2 min at week 4 (60% improvement) and 31.1 min at week 24 (72% improvement). The mean numbers of tender joints (9.2 at baseline, 4.2 at week 4, and 3.0 at week 24) and swollen joints (8.6, 4.1, and 2.8, respectively), and the mean general health status (60.1, 36.6, and 30.7 mm, respectively, by patients' visual analog scale) all showed significant (all $p < 0.01$) improvements from baseline at weeks 4 and 24. The mean ESR improved significantly, from 58.7 mm/h (baseline) to 38.1 mm/h (week 4) and 34.8 mm/h (week 24), representing improvements of 35 and 41%, respectively (both $p < 0.01$). The mean levels of CRP decreased significantly (both $p < 0.01$), from 3.6 mg/dL at baseline to 1.4 mg/dL at week 4 (61% improvement) and 1.2 mg/dL at week 24 (67% improvement).

The EULAR response and DAS28 remission rate were also evaluated. At week 4, 779 patients (17.6%) had achieved a good EULAR response; a trend of significant improvement occurred throughout the observation period, with 2336 patients (31.6%) having a good response by week 24 ($p < 0.001$ for trend; Fig. 1a). At week 4, 77.0% of patients had achieved a good or moderate response; response rates increased from week 4 to 24, with 84.3% of patients achieving a good or moderate response by week 24. A total of 1161 (15.7%) patients had no response to etanercept at week 24 (Fig. 1a). Remission was reported in 1395 patients (18.9%) at week 24, with significant improvement noted during the observation period ($p < 0.001$ for trend; Fig. 1b). Low, moderate, and high disease activity were reported in 1179 (15.9%), 3730 (50.4%), and 1091 (14.8%) patients, respectively, at week 24 (Fig. 1b).

Factors that affected the odds of achieving RA remission are shown in Table 5. Compared with the referent group in model 1, male sex, younger age (<65 years), concomitant methotrexate use, lower baseline DAS28 (moderate

Table 3 Hazard ratios for serious infection (adverse events)

Variable	HR	95% CI	*p* value
Model 1[a]			
Sex (women vs. men)	0.63	0.50–0.81	<0.001
Age (≥65 vs. <65 years of age)	1.66	1.33–2.07	<0.001
History of infectious disease (yes vs. no)	2.26	1.38–3.70	0.001
History of tuberculosis (yes vs. no)	1.24	0.85–1.80	0.274
Presence of any comorbidities (yes vs. no)	2.72	2.02–3.66	<0.001
Steinbrocker functional class (4 vs. 1 + 2 + 3)	2.54	1.73–3.71	<0.001
Duration of RA (years)			
≥5 and <10 vs. <5	1.20	0.89–1.61	0.237
≥10 and <15 vs. <5	1.01	0.72–1.41	0.971
≥15 vs. <5	1.04	0.78–1.40	0.774
Concomitant use of MTX (yes vs. no)	0.59	0.47–0.74	<0.001
Concomitant use of glucocorticoids (yes vs. no)	2.03	1.46–2.84	<0.001
Model 2[b]			
Presence of combined risk factors[c]			
1 vs. 0	1.96	1.30–2.96	0.001
2 vs. 0	4.24	2.83–6.34	<0.001
3 vs. 0	9.91	5.48–17.94	<0.001

HR hazard ratio, *CI* confidence interval, *MTX* methotrexate

[a] Cox proportional hazard model (for all cases, $n = 12{,}620$ and for serious infection cases, $n = 330$)

[b] Results were adjusted for sex, age, history of infectious disease, history of tuberculosis, duration of rheumatoid arthritis (RA), and concomitant use of glucocorticoid

[c] Combined factors: Steinbrocker functional class = 4, concomitant use of MTX = no, any comorbidities = yes; $p < 0.001$ for linear trend using the Wald test

Table 4 Measures of effectiveness

Measure	Baseline, mean (SD)	Patients evaluated at baseline (*n*)	Week 4, mean (SD)[a]	Patients evaluated at week 4 (*n*)	Week 24, mean (SD)[a]	Patients evaluated at week 24 (*n*)
DAS28	5.9 (1.2)	8902	4.3 (1.3)	4754	3.8 (1.3)	8137
Duration of morning stiffness (min)	111.3 (181.3)	5858	44.2 (114.0)	3201	31.1 (90.1)	5058
Tender joints (*n*)	9.2 (7.0)	12727	4.2 (4.8)	7873	3.0 (4.1)	12321
Swollen joints (*n*)	8.6 (6.2)	12727	4.1 (4.3)	7871	2.8 (3.6)	12319
General health status (patient visual analog scale) (mm)	60.1 (22.7)	11535	36.6 (22.5)	6702	30.7 (22.1)	10616
ESR (mm/h)	58.7 (33.0)	9719	38.1 (27.7)	5732	34.8 (27.5)	9484
CRP (mg/dL)	3.6 (3.3)	12693	1.4 (2.1)	8298	1.2 (2.0)	12770

CRP C-reactive protein, *DAS28* modified disease activity score including a 28-joint count, *ESR* erythrocyte sedimentation rate

[a] All comparisons differed significantly ($p < 0.01$ vs. baseline), by *t*-test

disease), and better Steinbrocker functional class (1–3) significantly improved the odds of achieving remission. Shorter duration of RA also significantly improved the chances of achieving remission compared with those with ≥15 years' duration (odds ratio [OR] 1.62; 95% CI 1.36–1.92). Model 2 showed the combined effects of multiple risk factors on the likelihood of achieving remission. Compared with the groups with zero risk factors, the odds ratio of achieving remission was 6.30 (95% CI 4.83–8.21; $p < 0.001$) for patients who had 4 risk factors, 3.20 (95% CI 2.64–3.88; $P < 0.001$) for patients who had 3 risk factors, and 1.87 (95% CI 1.55–2.26; $p < 0.001$) for patients who had 2 risk factors. Highly significant linear association ($p < 0.001$) was evident for increasing number of combined risk factors. When we added 79 patients with lower disease activity (baseline DAS28, ≥2.6 and ≤3.2)

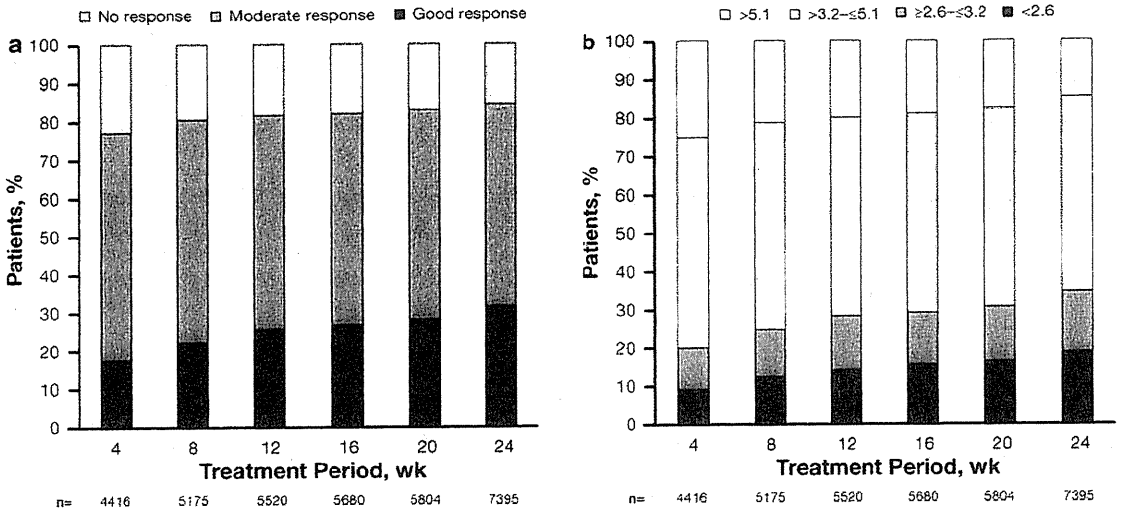

Fig. 1 Time course of **a** EULAR response and **b** DAS28 from week 4 to week 24. *DAS28* modified disease activity score including a 28-joint count, *EULAR* European League Against Rheumatism. Cochran-Armitage tests were used to examine evidence of trends in response rates; trends for good response rate and remission rate were statistically significant ($p < 0.001$). *wk* Week

Table 5 Odds ratios for achieving remission

Variable	OR	95% CI	*p* value
Model 1			
Sex (men vs. women)	1.30	1.10–1.53	0.002
Age (<65 vs. ≥65 years of age)	1.43	1.23–1.65	<0.001
Steinbrocker functional class (1–3 vs. 4)	2.41	1.30–4.49	0.006
Duration of RA (years)			
<5 vs. ≥15	1.62	1.36–1.92	<0.001
5–10 vs. ≥15	1.17	0.97–1.42	0.098
10–15 vs. ≥15	1.04	0.84–1.28	0.733
DAS28 at baseline (moderate vs. high)	2.95	2.59–3.37	<0.001
Concomitant use of MTX			
<8 mg/week vs. none	1.30	1.13–1.49	<0.001
≥8 mg/week vs. none	1.74	1.32–2.28	<0.001
Previous treatment with infliximab (yes vs. no)	0.65	0.53–0.81	<0.001
Model 2[a]			
Presence of combined risk factors[b]			
4 vs. 0–1	6.30	4.83–8.21	<0.001
3 vs. 0–1	3.20	2.64–3.88	<0.001
2 vs. 0–1	1.87	1.55–2.26	<0.001

Multiple logistic regression models [for all cases, $n = 6763$ (79 patients with low disease activity were excluded) and for remission cases, $n = 1234$]

DAS28 modified disease activity score including a 28-joint count, *MTX* methotrexate, *OR* odds ratio, *RA* rheumatoid arthritis

[a] Results were adjusted for sex, age, and previous treatment with infliximab

[b] Combined factors: Steinbrocker functional class = 1–3; MTX = yes; baseline DAS28 = >3.2 and ≤5.1 (moderate disease); duration of RA <5 years; $p < 0.001$ for linear trend using the Wald test

into the lower baseline DAS28 group to examine the odds ratio of achieving remission, a similar pattern was seen (data not shown).

Discussion

The current trial was one of the largest surveillance studies of biologic use in the rheumatology area, with nearly 14,000 patients registered. Mandatory registration for all patients treated with etanercept occurred at participating sites in Japan during the 2-year study period. This PMS study provided a unique opportunity to capture real-world safety and effectiveness data for a large patient population in an Asian country. Although there are published accounts of other PMS studies with RA biologic treatments [23–25], the large number of patients registered in the current study allowed for the safety and effectiveness of etanercept to be documented in a real-world clinical setting in Japan. The advantage of conducting a study like this is a high precision of AE incidence, remission rate, and other important data.

In the current PMS study, AEs and SAEs were reported in 31.2 and 6.2% of patients, respectively. A good or moderate response (i.e., effective treatment) occurred in a very high percentage of patients from week 4 to 24. These data are consistent with those reported in the interim analysis from this study [17]. No new signaling risk factors for serious infection were observed in this PMS study.

Real-world efficacy data were also reported from the Rheumatoid Arthritis DMARD Intervention and Utilization Study (RADIUS), a 5-year, multicenter, observational