Mod Rheumatol (2008) 18:345–353
DOI 10.1007/s10165-008-0058-8

ORIGINAL ARTICLE

Safety of long-term tacrolimus therapy for rheumatoid arthritis: an open-label, uncontrolled study in non-elderly patients

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Received: 5 November 2007 / Accepted: 9 February 2008 / Published online: 22 April 2008

Abstract In this study we focused on the safety of long-term tacrolimus therapy in non-elderly patients with rheumatoid arthritis who were treated with tacrolimus or mizoribine in a previous double-blind study. The patients received oral tacrolimus at a dose ≤3 mg once daily for 76 weeks. The safety analysis population included 115 patients aged 20–64 years. Adverse drug reactions presented as symptomatic events in 39 patients (33.9%), laboratory abnormalities in 38 patients (33.0%), and infections in 19 patients (16.5%). The major reactions were gastrointestinal disorders and hypertension as symptomatic events, increases of creatinine, urinary *N*-acetyl-β-D-glucosamidase and hemoglobin A_{1C} as laboratory abnormalities, and the common cold syndrome as infections. After 76 weeks of tacrolimus treatment, the ACR20 response rates of patients who had also received tacrolimus during the preceding double-blind study was 61.5% (compared with the status at baseline in the preceding study). The corresponding response rate for patients who had previously received mizoribine was 66.0%. The mean blood concentration of tacrolimus was 3.8–4.8 ng/mL. In conclusion, safety profiles of tacrolimus treatment for long-term seems to be similar to those of previous studies in patients with rheumatoid arthritis.

Keywords Long-term open study · Rheumatoid arthritis · Safety · Tacrolimus

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Introduction

Tacrolimus is an immunosuppressive agent with a macrolide skeleton that was discovered as a metabolite of *Streptomyces tsukubaensis*. In Japan, oral and parenteral formulations have been approved for use in patients with transplantation or autoimmune diseases, while tacrolimus ointment has been approved for the treatment of atopic dermatitis. The pathogenesis of rheumatoid arthritis (RA) has been reported to be related to immunocompetent T cells [1], and the T cell-selective immunosuppressant cyclosporine has shown efficacy for this disease [2].

The mechanism of action of tacrolimus differs from those of conventional disease-modifying antirheumatic drugs (DMARDs). Tacrolimus inhibits T cell activation and thereby suppresses the production of tumor necrosis factor-α and other inflammatory cytokines involved in the development of RA [3]. This drug has shown efficacy in animal models of RA, such as rats with collagen-induced arthritis and adjuvant-induced arthritis [4–6]. An early phase II study of tacrolimus in patients with RA demonstrated its usefulness as a new DMARD at doses of 1.5 and 3 mg/day [7]. A late phase II study [8] and phase III studies [9, 10] conducted in non-elderly

patients aged 20–64 years and elderly patients aged 65 years or older demonstrated the efficacy and safety of tacrolimus therapy for RA in both age groups. Based on these findings, tacrolimus was approved in 2005 for the treatment of RA with an insufficient response to existing therapy in Japan.

However, the maximum duration of treatment in these clinical studies was 28 weeks. The safety of long-term tacrolimus therapy has been investigated by a 12-month open study in the United States [11], but there have been no long-term studies in Japanese patients. Accordingly, we performed an open-label, uncontrolled study to focus on the safety of long-term tacrolimus treatment in non-elderly Japanese patients who had previously been enrolled in a phase III double-blind controlled trial [10].

Patients and methods

Patients

This study was conducted from May 2001 to December 2003 at 25 institutions. The subjects comprised RA patients who had participated in a previous double-blind controlled study of tacrolimus (the preceding study) [10] and had completed 28 weeks of treatment with tacrolimus or the control drug (mizoribine), or else had discontinued therapy due to lack of symptomatic improvement despite at least 12 weeks of treatment. All of the patients wished to receive long-term treatment with tacrolimus and were judged to be eligible for this study by their investigators.

The patients entering the present study had all met the following inclusion criteria at the time of their enrollment in the preceding study: (1) a diagnosis of RA according to the American College of Rheumatology (ACR) criteria (revised in 1987) [12]; (2) a disease duration of at least 6 months; (3) an age between 20 and 64 years at the time of giving informed consent; (4) an insufficient response to treatment with at least one DMARD other than tacrolimus or mizoribine before entering the study; (5) active disease (which was defined by a C-reactive protein level $\geq$1.0 mg/dL or an erythrocyte sedimentation rate $\geq$30 mm/h, at least six tender joints, and at least three swollen joints).

Patients were excluded from the present study for the following reasons: (1) study drug-related adverse events had occurred during the preceding study and the potential risks of long-term tacrolimus therapy were expected to outweigh the potential benefits, (2) surgery had been performed and the effects of surgical invasion were persistent, or (3) they had renal dysfunction, pancreatitis/glucose intolerance, hyperkalemia, severe liver dysfunction, heart disease (e.g., ischemic heart disease, arrhythmias requiring treatment, and heart failure), malignancy, severe infections, or severe drug hypersensitivity.

Methods

Prior to the present study, the Institutional Review Board at each participating institution approved the study protocol. All of the patients involved gave written informed consent. A multicenter open-label design was employed without a control drug.

There was an off-treatment interval in all patients between the end of the preceding study and the start of tacrolimus therapy in the present study. During the interval, blinding for the preceding study was maintained and the treatment of RA was not specified.

Tacrolimus was initiated at a dose of 3 mg orally once a day after the evening meal, which was the dosage for tacrolimus group in the preceding study. Dose reduction was possible (i.e., 3 mg/day was the maximum dose) depending on the patient's symptoms or adverse drug reactions at the discretion of the investigator. The duration of treatment in the present study was scheduled to be 76 weeks. The nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids that were used prior to the study could be continued, but commencement of these drugs was prohibited. Use of two or more NSAIDs was avoided whenever possible, and dose reduction was allowed for NSAIDs and steroids during the study period. Concomitant use of other DMARDs (including gold salts, D-penicillamine, bucillamine, salazosulfapyridine, lobenzarit, actarit, cyclosporine, methotrexate, and mizoribine) was prohibited. Administration of any drug (e.g., astemizole or terfenadine) that could influence the blood level of tacrolimus was also prohibited.

Safety evaluation

Blood pressure and body weight were measured at the start of treatment (baseline), after 4 weeks of treatment, at 12-week intervals thereafter, and at the completion or discontinuation of treatment (the end of treatment). Laboratory investigations included hematology tests (red cell count, hemoglobin, hematocrit, platelet count, leukocyte count, and differential leukocyte count), biochemistry tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), γ-glutamyl transpeptidase (γ-GTP), total bilirubin, cholesterol, triglycerides, amylase, glucose, hemoglobin A_{1c} (HbA_{1c}), β_2-microglobulin, blood urea nitrogen (BUN), serum creatinine, uric acid, and serum electrolytes [Na, K, Cl, Ca, and Mg]), urinalysis (tests for protein, glucose, urobilinogen, and *N*-acetyl-β-D-glucosamidase (NAG)), and electrocardiography at baseline, after 2 and 4 weeks of treatment, at 4-week intervals thereafter (12-week intervals for electrocardiography), and at the end of treatment.

The blood level of tacrolimus was measured after 2 and 4 weeks of treatment, at 4-week intervals thereafter, and at the end of treatment by high performance liquid chromatography-tandem mass spectrometry using whole blood samples collected at 12 ± 4 h after drug administration. All adverse events were examined and those for which a causal relationship to tacrolimus could not be ruled out by the investigator were classified as adverse drug reactions. Adverse events other than laboratory abnormalities and infections were classified as symptomatic events to distinguish these from the other events.

Efficacy evaluation

Disease activity was assessed by determining the tender joint count (based on evaluation of 48 joints, including temporomandibular ($n = 2$), sternoclavicular ($n = 2$), shoulder ($n = 2$), elbow ($n = 2$), wrist ($n = 2$), metacarpophalangeal ($n = 10$), interphalangeal of thumb ($n = 2$), proximal interphalangeal ($n = 8$), hip ($n = 2$), knee ($n = 2$), ankle mortise ($n = 2$), ankle tarsal ($n = 2$), and ten complete sets of toe joints (each set was counted as one joint)) and the swollen joint count (based on evaluation of 46 joints, excluding the hips from those assessed for tenderness), with modification of the number of joints recommended by ACR [13], the C-reactive protein level, and the 1-h erythrocyte sedimentation rate (Westergren method) at baseline, at 4-week intervals thereafter, and at the end of treatment. At the same times, global assessment of disease activity by the investigator, global assessment of disease activity by the patient, and assessment of joint tenderness by the patient were also performed. At the end of treatment, clinical improvement was assessed according to both ACR response criteria (ACR20%/50%/70% responses) [14].

Statistical analysis

For the ACR20, ACR50, and ACR70 responses, last observation carried forward (LOCF) analysis was performed using the last observation recorded while patients were receiving the study drug. LOCF analysis was also used for DAS28. Wilcoxon signed rank test was used for comparison between baseline values and those at each time point. Statistical tests were two sided and $p < 0.05$ was taken as statistically significant unless otherwise specified.

Results

Patient characteristics

Among 204 patients who were treated during the preceding study, 103 were assigned to receive tacrolimus and 101 were given mizoribine. Tacrolimus was discontinued by 39 patients and mizoribine was discontinued by 68 patients. The main reasons for discontinuation of treatment were adverse events (12 patients in the tacrolimus group and 10 patients in the mizoribine group) and no response or worsening of RA (19 patients in the tacrolimus group and 52 patients in the mizoribine group) [10].

A total of 115 patients were enrolled in the present study. Among them, 65 patients had already been treated with tacrolimus in the preceding study and 50 patients had been treated with mizoribine. All of the patients received tacrolimus therapy in this study. There was an off-treatment interval for each patient ranging from 13 to 307 days. During this interval, the patients received other therapy for RA that did not include tacrolimus.

Treatment with tacrolimus for 76 weeks was completed by 67.8% of the subjects (78/115 patients), while tacrolimus was discontinued in 32.2% of them (37/115 patients) (Fig. 1). All 115 patients were included in the safety and efficacy analyses. The main reasons for discontinuation of treatment were adverse events in 15.7% (18/115 patients) and lack of improvement/worsening of RA in 13.0% (15/115 patients). Discontinuation due to an increase of creatinine occurred in 3.5% (4/115) of all patients. The mean age (±standard deviation) of the patients was 49.8±8.7 years at enrollment in the preceding study, and 66.1% (76/115 patients) had stage III or IV RA at that time (Table 1).

Treatment period and dose of tacrolimus

The median duration of treatment in the present study (including any period of suspension during the study) was 532.0 days. A dose of 3 mg/day was received by 91.0% (91/100) of the patients remaining on treatment after 6 months (28 weeks), 83.0% (73/88) of the remaining patients after 1 year (52 weeks), and 80.8% (63/78) of the remaining patients at completion (76 weeks), showing a gradual decrease. Thus, most of the on-study patients were receiving 3 mg/day during the study period, and most of the other patients were receiving 2.0 or 2.5 mg/day.

Safety

The incidence of adverse events was 88.7% (102/115 patients) and that of adverse events with a possible relationship to tacrolimus, defined as adverse drug reactions, was 58.3% (67/115 patients). During the study period, no deaths occurred. Serious adverse events occurred in ten patients, including 12 serious adverse drug reactions in six patients (diverticulitis of the colon, cerebral infarction, bronchopneumonia, multiple gastric ulcers, perforated duodenal ulcer, acute renal failure, pyelonephritis,

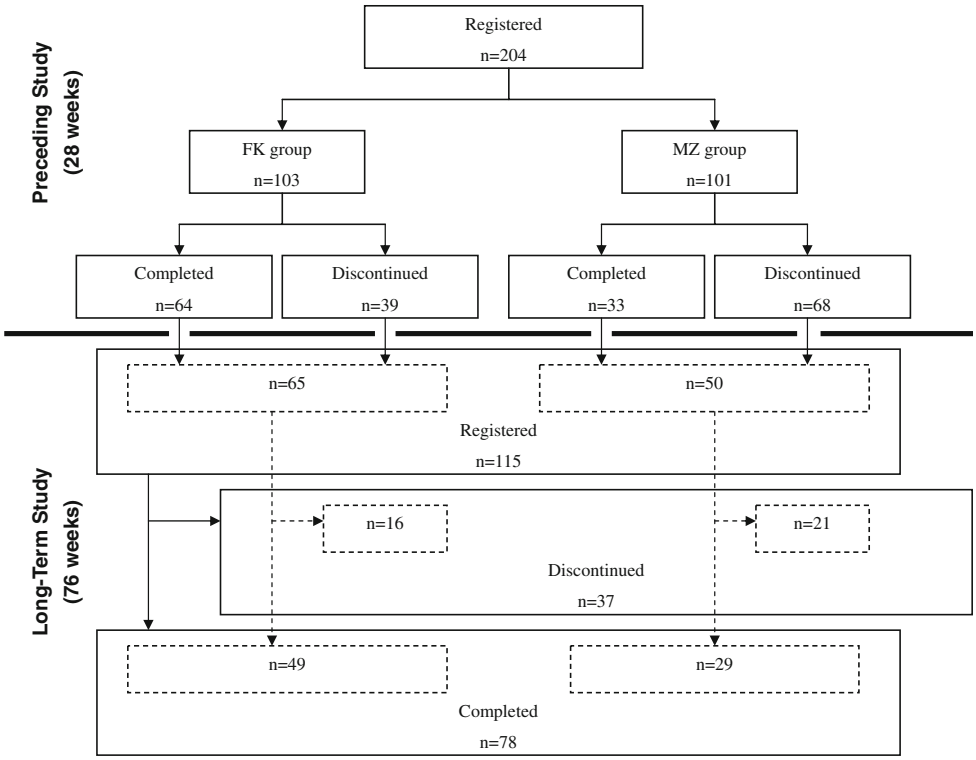

Fig. 1 Disposition of the patients. Patients enrolled in the preceding study were randomized to receive tacrolimus (*FK*) or mizoribine (*MZ*). Patients who completed 28 weeks of treatment with *FK* or *MZ*, or else discontinued therapy due to lack of symptomatic improvement despite at least 12 weeks of treatment, and who were judged to be eligible for long-term treatment with tacrolimus were enrolled in the present study. *n* total number of patients in each group, *FK* tacrolimus; *MZ* mizoribine

Table 1 Characteristics of the patients at enrollment in the preceding study

No. of patients analyzed	FK→FK, $n = 65$	MZ→FK, $n = 50$	Total, $n = 115$
Sex (no., female (%))	58 (89.2)	46 (92.0)	104 (90.4)
Age (years, mean ± SD)	49.6 ± 8.9	50.1 ± 8.5	49.8 ± 8.7
Body weight (kg, mean ± SD)	53.1 ± 7.2	53.9 ± 8.1	53.4 ± 7.6
Steinbrocker stage (no. (%))			
I	7 (10.8)	3 (6.0)	10 (8.7)
II	19 (29.2)	10 (20.0)	29 (25.2)
III	19 (29.2)	15 (30.0)	34 (29.6)
IV	20 (30.8)	22 (44.0)	42 (36.5)
Steinbrocker class (no. (%))			
1	10 (15.4)	5 (10.0)	15 (13.0)
2	48 (73.8)	35 (70.0)	83 (72.2)
3	7 (10.8)	10 (20.0)	17 (14.8)
4	0 (0.0)	0 (0.0)	0 (0.0)
Duration of RA (months, mean ± SD)	108.6 ± 98.3	131.4 ± 103.9	118.5 ± 100.9
Tender joint count (mean ± SD)	13.6 ± 7.3	13.6 ± 7.1	13.6 ± 7.2
Swollen joint count (mean ± SD)	10.5 ± 6.8	9.5 ± 4.3	10.1 ± 5.8
Erythrocyte sedimentation rate (mm/h, mean ± SD)	63.0 ± 28.5	57.0 ± 25.1	60.4 ± 27.1
C-reactive protein level (mg/dL, mean ± SD)	3.46 ± 2.85	3.75 ± 2.44	3.58 ± 2.67

proteinuria, increased creatinine, increased BUN, increased uric acid, and increased β_2-microglobulin). Cerebral infarction resulted in mildly remaining neurological deficits, but the other events resolved.

Symptomatic events occurred in 85 patients (73.9%), and were defined as adverse drug reactions in 39 patients (33.9%). The major reactions were hypertension, stomach ache, gastric ulcer, diarrhea, nausea, stomach discomfort, gastritis, pollakiuria, and alopecia, so there was a predominance of gastrointestinal disorders (Table 2). Most of these adverse reactions resolved or were alleviated. Treatment with tacrolimus was continued (including dose

Table 2 Symptomatic events

No. of patients analyzed	115
Adverse events: no. of patients (%); no. of events	85 patients (73.9%); 211 events
Adverse drug reactions: no. of patients (%); no. of events	39 patients (33.9%); 60 events
Withdrawals due to adverse drug reactions (%)	6 patients (5.2%)
Adverse drug reactions stratified by body system	**No. of patients (%)**
Central and peripheral nervous system disorders	
Tremor	1 (0.9)
Numbness of lips	1 (0.9)
Migraine	1 (0.9)
Dizziness	1[a] (0.9)
Respiratory system disorders	
Rhinitis (allergic)	1 (0.9)
Cardiovascular disorders (general)	
ST segment depression	1[a] (0.9)
Cardiomegaly	1 (0.9)
Increased blood pressure	1 (0.9)
Hypertension	4[a] (3.5)
Aggravated hypertension	1 (0.9)
Heart rate and rhythm disorders	
Extrasystoles	1 (0.9)
Vascular (extracardiac) disorders	
Cerebral infarction	1[a] (0.9)
Gastrointestinal system disorders	
Gingivitis	1 (0.9)
Stomatitis	1 (0.9)
Oesophagitis	1 (0.9)
Anorexia	1 (0.9)
Heartburn	1 (0.9)
Retching	1 (0.9)
Nausea	2 (1.7)
Vomiting	1 (0.9)
Stomach heaviness	1 (0.9)
Stomach discomfort	2 (1.7)
Stomach ache	3 (2.6)
Stomach pain	1 (0.9)
Gastritis	2 (1.7)
Gastric ulcer	3 (2.6)
Duodenal ulcer	1 (0.9)
Duodenal ulcer (perforated)	1[a] (0.9)
Diarrhea	3 (2.6)
Irritable bowel syndrome	1 (0.9)
Metabolic and nutritional disorders	
Abnormal glucose tolerance	1 (0.9)
Urinary system disorders	
Pollakiuria	2 (1.7)
Renal failure (acute)	1[a] (0.9)
Reproductive disorders (female)	
Menstrual irregularity	1 (0.9)
Visual disorders	
Conjunctivitis (allergic)	1 (0.9)
Disorders of other special senses	
Dysosmia	1 (0.9)
Skin and appendageal disorders	
Pruritus	1 (0.9)
Pruritus cutaneous	1 (0.9)
Urticaria	1 (0.9)
Erythema	1 (0.9)
Alopecia	2 (1.7)
Body as a whole-general disorders	
Hot flushes	1 (0.9)
Fever	1 (0.9)
Oedema of lower extremities	1 (0.9)
Fatigability	1 (0.9)
Weakness	1 (0.9)

[a] Tacrolimus treatment was discontinued in these patients

reduction or retreatment after withdrawal) in seven patients with persistent adverse reactions (migraine, aggravated hypertension, gastric ulcer, abnormal glucose tolerance, menstrual irregularity, dysosmia, and alopecia). Treatment was discontinued due to adverse drug reactions in six patients (dizziness, ST segment depression, hypertension, cerebral infarction, perforated duodenal ulcer, and acute renal failure), and these abnormalities resolved or were alleviated after discontinuation.

Abnormal changes in laboratory values were observed in 47 patients (40.9%), and were classified as adverse drug reactions in 38 patients (33.0%). The major reactions were increases of creatinine, urinary NAG, HbA_{1c}, BUN, and ALP, as well as a decrease of magnesium, showing a predominance of abnormal renal function and abnormal glucose tolerance (Table 3). Most of these adverse reactions resolved. Tacrolimus treatment was continued (including dose reduction) in most of eight patients with 18 persistent events [increased ALP (4), increased γGTP (2), increased uric acid (2), increased triglycerides, increased HbA_{1c}, increased total bilirubin, increased creatinine, increased BUN, increased urinary NAG, increased red cell count, increased hemoglobin, increased hematocrit, and decreased magnesium]. Treatment was discontinued in seven patients with ten events [increased creatinine (4), increased glucose (2), increased HbA_{1c} (2), increased

Table 3 Abnormal laboratory findings

No. of patients analyzed	115
Adverse events: no. of patients (%); no. of events	47 patients (40.9%); 103 events
Adverse drug reactions: no. of patients (%); no. of events	38 patients (33.0%); 78 events
Withdrawals due to adverse drug reactions (%)	7 patients (6.1%)

Adverse drug reactions	No. of patients (%)
Red cell count increased	1 (0.9)
Hemoglobin increased	1 (0.9)
Hemoglobin decreased	1 (0.9)
Hematocrit increased	1 (0.9)
Leukocytosis	1 (0.9)
Neutrophilia	1 (0.9)
Lymphopenia	1 (0.9)
Alkaline phosphatase increased	6 (5.2)
γ-glutamyl transpeptidase increased	4 (3.5)
Total bilirubin increased	1 (0.9)
Creatinine increased	14^{1-4} (12.2)
Blood urea nitrogen increased	7^{5} (6.1)
Uric acid increased	3 (2.6)
β_2-microglobulin increased	2 (1.7)
Amylase increased	1 (0.9)
Blood sugar increased	$3^{6,7}$ (2.6)
Hemoglobin A_{1C} increased	$8^{6,7}$ (7.0)
Triglycerides increased	2 (1.7)
Potassium increased	1 (0.9)
Magnesium decreased	6 (5.2)
Urinary sugar	2^{6} (1.7)
Urinary protein	2 (1.7)
Urinary *N*-acetyl-β-D-glucosamidase increased	9 (7.8)

[1–7] Tacrolimus treatment was discontinued in these patients (reactions bearing the same number occurred in the same individual)

BUN, or urinary sugar], and these laboratory abnormalities all resolved or improved after discontinuation.

Infections occurred in 70 patients (60.9%), and were classified as adverse drug reactions in 19 patients (16.5%). The major infections considered to be adverse drug reactions were common cold syndrome, pneumonia, and Candida esophagitis (Table 4). All of these adverse infections resolved or were alleviated, but treatment was discontinued due to infections (bronchitis, bronchopneumonia, pneumonia, diverticulitis, and pyelonephritis) in five patients.

Blood level of tacrolimus

The mean whole blood concentration of tacrolimus was 3.8–4.8 ng/mL, with a median value of 3.6–4.5 ng/mL. One patient had a blood level greater than 20 ng/mL (21.19 ng/mL at 14 h and 40 min after taking 3 mg of tacrolimus on study day 449), but this patient's blood levels ranged between 4.67 and 7.12 ng/mL at the other times of assessment (8–16 h after administration) and no adverse drug reactions occurred throughout the study.

Table 4 Infections

No. of patients analyzed	115
Adverse events: no. of patients (%); no. of events	70 patients (60.9%); 105 events
Adverse drug reactions: no. of patients (%); no. of events	19 patients (16.5%); 23 events
Withdrawals due to adverse drug reactions (%)	5 patients (4.3%)

Adverse drug reactions	No. of patients (%)
Sinusitis	1 (0.9)
Sore throat	1 (0.9)
Upper respiratory tract infection	1 (0.9)
Common cold syndrome	6 (5.2)
Coughing	1 (0.9)
Bronchitis	1[a] (0.9)
Bronchopneumonia	1[a] (0.9)
Pneumonia	2[a] (1.7)
Candida esophagitis	2 (1.7)
Diverticulitis	1[a] (0.9)
Pyelonephritis	1[a] (0.9)
Tinea	1 (0.9)
Rash (acneiform)	1 (0.9)
Dermatitis	1 (0.9)
Herpes zoster	1 (0.9)
Purulence	1 (0.9)

[a] Tacrolimus treatment was discontinued in these patients

Efficacy

Compared with their status at baseline of the preceding study, the patients who received tacrolimus during both studies (FK→FK group) had an ACR20 response rate (number of responders/number of patients evaluated) of 64.6% (42/65) and 61.5% (40/65), respectively, at the end of the preceding and present studies, and the two response rates were similar. The corresponding ACR20 response rates of the patients who received mizoribine during the preceding study (MZ→FK group) were 12.0% (6/50) and 66.0% (33/50), respectively, with a better response at the end of the present study. Changes of the ACR50 and 70 response rates in the two groups were similar to those of the ACR20 (Fig. 2).

The median DAS28 value showed a significant decrease ($p < 0.001$) throughout the study from 8 weeks onward in the FK→FK group and from 4 weeks onward in the

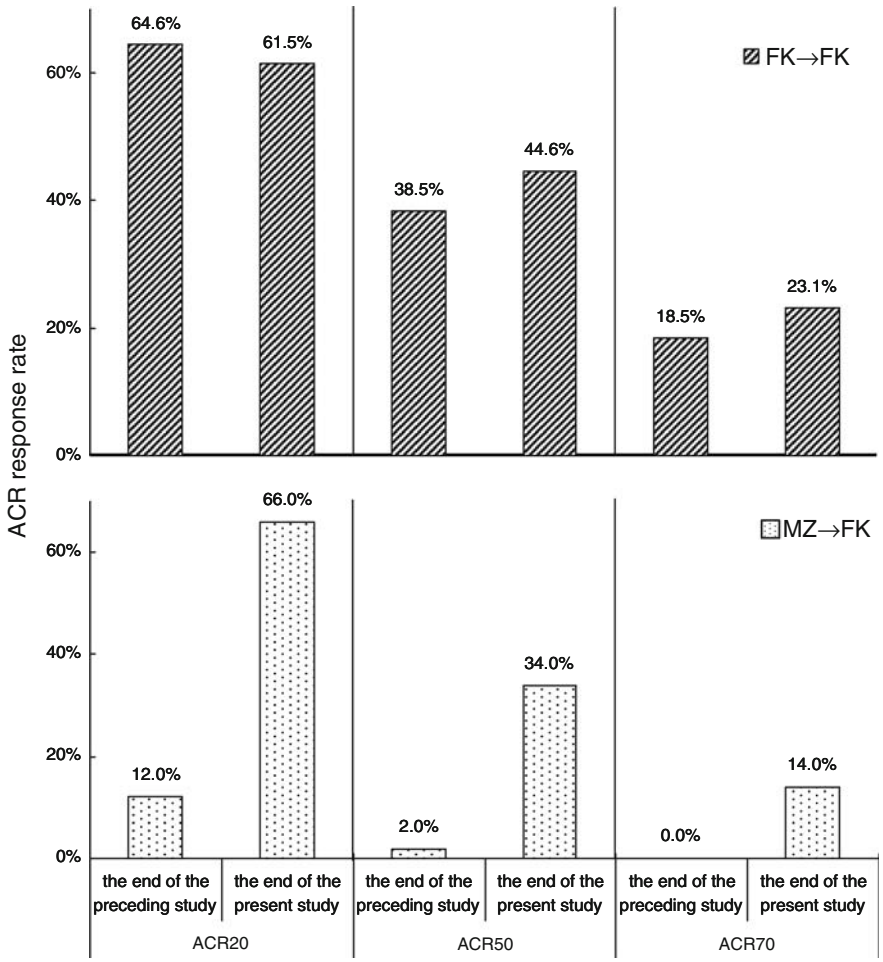

Fig. 2 Clinical improvement measured by the ACR20/50/70 responses. Response rates were calculated relative to the status at enrollment in the preceding study. *FK→FK*: patients receiving tacrolimus during both the preceding and present studies. *MZ→FK* patients receiving mizoribine during the preceding study and FK in the present study

MZ→FK group compared with that at baseline of the present study (Fig. 3).

Discussion

Common problems encountered with DMARDs are: (1) a slow onset of action and sometimes an insufficient response or no response; (2) an occasional decline of efficacy over time after a response is initially obtained; (3) unsuitability for some patients due to various adverse effects (specific to each drug); and (4) difficulty in continuing long-term therapy. These problems are currently handled by switching DMARDs or by concomitant use of other DMARDs/non-DMARDs. Thus, it is worthwhile to develop drugs with a new mechanism of action or greater efficacy to expand the available treatment options. Tacrolimus inhibits T cell activation and thereby suppresses the production of inflammatory cytokines, including tumor necrosis factor-α responsible for the occurrence of RA [3]. Therefore, this drug was investigated as a new DMARD with a different mechanism of action from those of the standard drugs, and it was approved for the treatment of RA in 2005 in Japan.

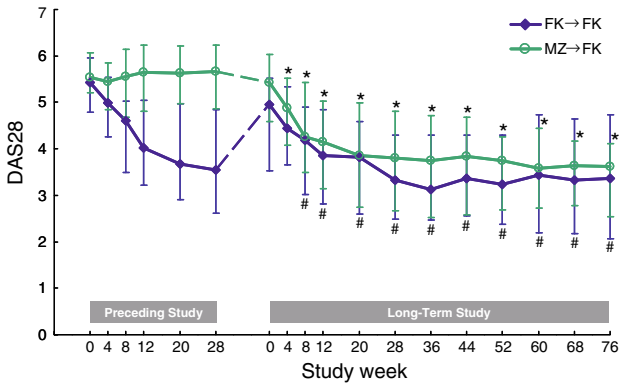

Fig. 3 Changes of DAS28 (median and the 1st–3rd quartiles). *Asterisks* and *sharps* indicate significant differences ($p < 0.05$) between baseline and each time point within the groups. *FK→FK* patients receiving tacrolimus during both the preceding and present studies. *MZ→FK* patients receiving mizoribine during the preceding study and FK in the present study

The present open-label uncontrolled study was performed to focus on the safety of long-term tacrolimus therapy, and the results suggested that this drug may be safe for long-term use in non-elderly Japanese patients with RA.

The present study was conducted following the preceding study, but a period of 13–307 days elapsed between the end of treatment in the preceding study and the start of treatment in the present study, with the interval being more than 4 weeks in 70.4% (81/115) of the patients. Since therapy for RA was not specified during the interval, the patients received various medications. Thus, this study was not actually an extension of the previous double-blind study, so we analyzed it as an open-label uncontrolled study that involved patients from the earlier study.

Safety was evaluated by assessing the adverse drug reactions that occurred during long-term treatment with tacrolimus. The main adverse drug reactions were gastrointestinal disorders, abnormal renal function (increased creatinine and increased BUN), and abnormal glucose tolerance (increased glucose and increased HbA_{1c}). These are all known adverse reactions of tacrolimus and no events specifically related to long-term therapy were detected. Most of the adverse reactions resolved or improved, while most of those that persisted were mild enough to allow the continuation of treatment.

Concomitant NSAID and/or steroid therapy as well as advanced age are common features in patients with RA. Thus, patients who are treated with tacrolimus should be assessed for the presence of renal dysfunction and abnormal glucose tolerance, and they should be monitored carefully during administration. If such abnormalities are detected, adequate measures such as dose reduction/suspension or discontinuation of tacrolimus therapy should be taken according to the patient's condition. In the present study, hypertension and cardiac dysfunction ascribable to tacrolimus therapy were also observed. Since RA itself has been reported to be a risk factor for cardiovascular disease [15–17], careful attention should be paid to the development of cardiovascular complications during tacrolimus therapy. Severe central nervous system disorders such as encephalopathy have been encountered in patients treated with tacrolimus after transplantation [18], but central nervous system disorders were relatively infrequent during the present study and there were no serious events.

The standard dose of tacrolimus for RA is 3 mg/day, which is lower than that for transplantation patients, so there is a lower incidence of adverse drug reactions and most events are mild. Use of tacrolimus after transplantation is determined by weighing the potential risks and benefits in each patient, while safety is given a higher priority in the case of RA patients. Most of the adverse drug reactions encountered during the present study resolved or improved with appropriate management, and 67.8% (78/115) of the patients were able to complete 76 weeks of tacrolimus therapy. Of the 78 patients who completed treatment, 55 (70.5%) had also completed tacrolimus therapy during the preceding study, so these patients tolerated long-term tacrolimus therapy very well.

Because the response to treatment of patients enrolled in the present study may have been affected by the drug (tacrolimus or mizoribine) administered in the preceding study, we assessed efficacy separately divided into the treatment group in the preceding study. Compared with the status at baseline of the preceding study, the ACR20 response rate of the FK→FK group was 64.6% (42/65 patients) at the end of the preceding study and 61.5% (40/65 patients) at the end of the present study, so the two response rates were similar. The corresponding ACR20 response rates for the MZ→FK group at the end of the present study was 66.0% (33/50 patients). Changes of the ACR50 and ACR70 response rates in the two groups were similar to those for ACR20. The DAS28 showed significant improvement from 8 weeks after the start of the present study in the FK→FK group and from 4 weeks in the MZ→FK group, when compared with that at baseline of this study, and the improvement persisted throughout the study period.

Both the FK→FK and MZ→FK groups included patients who showed various responses to tacrolimus and the latter group included patients refractory to mizoribine, but the present study demonstrated that tacrolimus did not lose efficacy during long-term treatment for up to 76 weeks.

However, the present study may have suffered from selection bias due to enrollment of patients who were likely to have tolerated and responded to tacrolimus in the preceding study, as well as evaluation bias related to its unblinded and uncontrolled design. In addition, the off-treatment interval between the preceding and present studies as well as the unspecified drugs used during the interval may have influenced the results of the present study. Because this study was conducted with a suboptimal design, patients and methods, there is an obvious need for caution when interpreting the results. Despite such considerations, the present study still confirmed the absence of new adverse drug reactions or any loss of efficacy during long-term treatment with tacrolimus for 76 weeks.

In conclusion, safety profiles of tacrolimus treatment for long-term seem to be similar to those of previous studies [8–11] in non-elderly patients with rheumatoid arthritis. Careful note should be taken of any fresh information obtained by post-marketing surveillance or other studies.

Acknowledgments We wish to thank the following investigators and institutions for participating in this study: Koji Taneichi, MD (Kitami Red Cross Hospital, Hokkaido); Takashi Murayama, MD and Satoshi Nakazaki, MD (Kanazawa Rehabilitation Hospital, Ishikawa); Seigaku Hayashi, MD (Fukui General Hospital); Takashi Kanno, MD, PhD (Ohta Nishinouchi Hospital, Fukushima); Yuichi Nishioka, MD, PhD (Yamanashi Prefectural Central Hospital, Yamanashi); Makoto Nishinarita, MD, PhD and Shuji Ohta, MD (Taga General Hospital, Ibaraki); Takayuki Sumida, MD, PhD (Tsukuba University Hospital, Ibaraki); Hitoaki Okazaki, MD, PhD (Jichi Medical School Hospital,

Tochigi); Shoji Kumaki, MD, PhD (Hokushin General Hospital, Nagano); Kimihiro Suzuki, MD, PhD (National Defense Medical College Hospital, Saitama); Tsutomu Takeuchi, MD, PhD (Saitama Medical Center,Saitama Medical University, Saitama); Fumihiko Imai, MD, PhD (Imai Medical Clinic, Saitama); Naoya Takashina, MD (Takashina Clinic, Tokyo); Shigeru Hosaka, MD (Hosaka Clinic, Tokyo); Shigeto Tohma, MD (Sagamihara National Hospital, National Hospital Organization, Kanagawa); Hirobumi, Kondo, MD, PhD (Kitasato University School of Medicine, Kanagawa); Tadao Mitsui, MD, PhD (Aichi Medical University Hospital, Aichi); Katsuji Shimizu, MD, DMSc (Gifu University School of Medicine and Gifu University Hospital, Gifu); Norikazu Murata, MD, PhD and Osamu Saiki, MD, PhD (National Hospital Organization, Osaka Minami Medical Center, Osaka); Tsukasa Matsubara, MD, PhD (Matsubara Clinic, Hyogo); Keisuke Hashimoto, MD, PhD and Yoshinobu Koyama, MD, PhD (Matsubara Mayflower Hospital, Hyogo); Eisuke Shono, MD, PhD (Fukuoka University Hospital, Fukuoka); Masakazu Kondo, MD (Kondo Clinic of Rheumatology and Orthopaedics, Fukuoka); Hideyuki Ikematsu, MD (Hara-doi Hospital, Fukuoka); and Ryuji Nagamine, MD, PhD (Kyushu Rosai Hospital, Fukuoka). This study was funded by a grant from Astellas Pharma Inc. (Tokyo, Japan). All authors participated as a medical consultant or members of the safety committee of Astellas Pharma Inc. They have received consultant fees from this company.

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