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Efficacy and Safety of Tacrolimus in Patients With Rheumatoid Arthritis

A Double-Blind Trial

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Objective. **To evaluate the efficacy and safety of tacrolimus as monotherapy in controlling the signs and symptoms of patients with rheumatoid arthritis (RA).**

Methods. **This was a 6-month, phase III, double-blind, multicenter study. Patients with active RA who had discontinued all disease-modifying antirheumatic drugs (DMARDs) for an appropriate washout period (at least 1 month) and who, after the washout period, had a stable joint count (at least 10 tender/painful joints and 7 swollen joints) were stratified according to DMARD intolerance or DMARD resistance, and randomized to receive a single daily oral dose of placebo, tacrolimus 2 mg, or tacrolimus 3 mg.**

Results. **A total of 464 patients received at least 1 dose of study drug. Baseline characteristics were similar among the 3 treatment groups. American College of Rheumatology 20% improvement (ACR20) success (defined as completion of 6 months of treatment and an ACR20 response at the month 6 visit) for the placebo, tacrolimus 2 mg, and tacrolimus 3 mg groups was 10.2%, 18.8% ($P < 0.05$ versus placebo), and 26.8% ($P < 0.0005$ versus placebo), respectively. At the end of treatment, the ACR20 and ACR50 response rates in the 3-mg group were 32.0% ($P < 0.005$ versus placebo) and 11.8% ($P < 0.05$ versus placebo), respectively. DMARD-intolerant patients had better ACR response rates than did DMARD-resistant patients. Although serum creatinine levels increased by ≥40% from baseline at some time during the trial in 20% and 29% of patients receiving tacrolimus 2 mg/day and 3 mg/day, respectively, the serum creatinine level remained within the normal range throughout the trial in ~90% of patients.**

Conclusion. **Tacrolimus, at dosages of both 2 mg/day and 3 mg/day, is efficacious and safe as monotherapy for patients with active RA, but treatment with the 3-mg dose of tacrolimus resulted in generally better ACR response rates.**

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that requires early diagnosis and aggressive treatment to minimize the morbidity associated with its progression (1,2). Disease-modifying antirheumatic drugs (DMARDs) and biologic modifiers have been used to accomplish these objectives (3–23). A common prominent feature of these agents is their immunosuppressive properties.

Tacrolimus (Prograf, FK506), an orally available macrolide calcineurin inhibitor, is an immunomodulatory and antiinflammatory agent (24–31). It diminishes the ability of calcineurin to dephosphorylate and translocate the nuclear factor of activated T cells that initiates gene transcription for the synthesis of inflammatory cytokines such as tumor necrosis factor α, interleukin-2,

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and interferon-γ. Because of these properties, tacrolimus is used to prevent organ transplant rejection and has been studied as a treatment in RA. Recently, tacrolimus was shown to be efficacious in a phase II trial of RA patients who were either resistant to or intolerant of methotrexate therapy (32). Tacrolimus has a lower molecular weight and is 100-fold more potent in inhibiting T cell proliferation than is cyclosporine, another calcineurin inhibitor with documented efficacy in treating patients with RA (6,31).

The double-blind study reported here was undertaken to determine the efficacy and safety of tacrolimus as monotherapy in the treatment of RA in patients who are either resistant to or intolerant of 1 or more DMARDs. Results of 2 companion trials in patients with RA, 1 open-label long-term safety trial of tacrolimus as monotherapy, and 1 open-label trial of tacrolimus and methotrexate as combination therapy, are being reported elsewhere (33,34).

PATIENTS AND METHODS

Patients. This 6-month, phase III, double-blind, randomized, placebo-controlled study began July 15, 1999, and ended May 15, 2001. A total of 465 patients were enrolled at 54 sites in the US. Eligible patients were at least 16 years of age, had RA according to American College of Rheumatology (ACR; formerly, American Rheumatism Association) criteria (35) for at least 6 months, were ACR functional class I–III as defined by the revised criteria (36), had demonstrated, in the opinion of the investigator, either resistance to or intolerance of 1 or more DMARDs, had not received any DMARDs for at least 4–12 weeks (dependent on the DMARD), and, following the DMARD washout period (at study entry), had at least 10 of 68 joints assessed as tender or painful and at least 7 of 66 joints assessed as swollen, with no more than a 30% variation in the tender/painful joint count as assessed 1 week prior to study entry. DMARD resistance was defined as continued active RA despite receiving a therapeutic dosage of a specific DMARD for a duration of time typically sufficient to elicit a therapeutic response. DMARD intolerance was defined as the inability or unwillingness of the patient to continue therapy due to an adverse drug experience.

Concomitant therapy with nonsteroidal antiinflammatory drugs (NSAIDs) and oral corticosteroids (≤10 mg/day of prednisone or its equivalent) was permitted, provided that NSAID dosages were stable for at least 2 weeks, and oral corticosteroid dosages were stable for at least 4 weeks prior to study entry, and that these dosages were continued throughout the study. Patients with moderate or severe liver disease, a creatinine level >1.5-fold the upper limit of normal, a hemoglobin value of <9.0 mg/dl, a white blood cell count of <3,000 cells/mm^3, or a platelet count of <100,000 platelets/mm^3 were excluded.

The Institutional Review Board at each study site approved the protocol, and all patients gave written informed consent prior to any study-related procedures.

Study protocol. Patients participating in the study were stratified according to DMARD resistance or DMARD intolerance prior to being randomized to receive a single daily oral dose of placebo, tacrolimus 2 mg, or tacrolimus 3 mg for 6 months, in a 1:1:1 allocation. Efficacy was assessed at each monthly visit using the ACR definitions of improvement (ACR20, ACR50, and ACR70 response) (37). ACR20, ACR50, and ACR70 responses were defined as ≥20%, ≥50%, and ≥70% improvement, respectively, in the tender/painful and swollen joint counts plus ≥20%, ≥50%, or ≥70% improvement, respectively, in 3 of the following 5 parameters: patient's assessment of pain on a 100-mm visual analog scale (VAS), patient's global assessment of disease activity on a 100-mm VAS, physician's global assessment of disease activity on a 100-mm VAS, patient's assessment of physical function (based on the modified Health Assessment Questionnaire [38]), and acute-phase reactant levels (erythrocyte sedimentation rate [ESR] by the Westergren method or C-reactive protein [CRP]).

Safety was evaluated at week 2 and at each monthly visit and was based on physical examinations, the incidence of treatment-emergent adverse events, and the results of clinical laboratory tests (with an emphasis on creatinine, blood urea nitrogen, glucose, and hemoglobin A_{1C} because of the previous experience in transplant patients in which tacrolimus use was associated with changes in these laboratory values). In patients who exhibited an increase in the serum creatinine level of ≥40% from the baseline visit, or an increase of ≥30% from the previous visit that was clinically significant in the investigator's opinion, the test was repeated in 1 week; if the elevation persisted, the study drug was withheld for up to 14 days. If the test value remained elevated after the study drug was withheld, the patient was withdrawn from the study. A Data Safety Monitoring Board monitored the study for issues that could impact the study or safety of patients.

Tacrolimus levels and modification of treatment. Although trough levels of tacrolimus were monitored during the study, they were not used to determine patient management. Tacrolimus was either withheld or discontinued based on treatment-emergent adverse events or a rise in creatinine levels.

Statistical analysis. The primary efficacy end point was the incidence of ACR20 success, defined as completion of 6 months of treatment and an ACR20 response at the month 6 visit. The primary analysis was between the placebo group and the combined 2-mg and 3-mg tacrolimus groups. The primary analysis method was based on logistic regression, with DMARD strata and treatment as the main effects in the model.

Secondary end points included the ACR20, ACR50, and ACR70 response rates (37) at month 1 through month 6 and at the end of treatment, and the percent change from baseline for the various individual ACR component scores at the end of treatment.

The efficacy and safety analyses for this study were performed on the full analysis set (i.e., all patients who received at least 1 dose of study drug). Patients who had both a baseline visit and at least 1 posttreatment efficacy visit were analyzed using the last observation carried forward method.

Table 1. Demographics and baseline characteristics*

Characteristic	Placebo (n = 157)	Tacrolimus groups 2 mg (n = 154)	Tacrolimus groups 3 mg (n = 153)
Female sex	119 (75.8)	117 (76.0)	120 (78.4)
Race			
White	138 (87.9)	137 (89.0)	146 (95.4)
African American	8 (5.1)	13 (8.4)	4 (2.6)
Asian	8 (5.1)	2 (1.3)	1 (0.7)
American Indian	2 (1.3)	2 (1.3)	2 (1.3)
Indian	1 (0.6)		
Age, mean years	55.8	55.9	55.8
DMARD stratum			
Resistant	98 (62.4)	100 (64.9)	95 (62.1)
Intolerant	59 (37.6)	54 (35.1)	58 (37.9)
ACR functional class			
I	16 (10.2)	11 (7.1)	12 (7.8)
II	91 (58.0)	98 (63.6)	94 (61.4)
III	50 (31.8)	45 (29.2)	47 (30.7)
Rheumatoid factor positive†	99 (63.1)	116 (75.3)	100 (65.4)
Duration of RA, mean ± SD years	11.8 ± 9.01	11.4 ± 9.12	11.3 ± 8.99
Tender or painful joint count, mean ± SD (0–68 joints)	26.3 ± 13.48	28.1 ± 13.06	26.6 ± 13.69
Swollen joint count, mean ± SD (0–66 joints)	18.2 ± 9.08	19.9 ± 10.09	19.0 ± 10.03
ESR, mean ± SD mm/hour	39.2 ± 30.40	39.1 ± 30.16	40.0 ± 30.04
CRP level, mean ± SD mg/dl‡	2.1 ± 2.63	2.3 ± 2.63	2.2 ± 2.75
Drugs used in previous 2 years			
Corticosteroids	86 (54.8)	96 (62.3)	87 (56.9)
NSAIDs	131 (83.4)	126 (81.8)	120 (78.4)
DMARDs	134 (85.4)	138 (89.6)	138 (90.2)
No. of DMARDs previously used			
0	23 (14.6)	16 (10.4)	15 (9.8)
1	61 (38.9)	54 (35.1)	63 (41.2)
2	40 (25.5)	38 (24.7)	46 (30.1)
≥3	33 (21.0)	46 (29.9)	29 (19.0)

* Except where indicated otherwise, values are the number (%). DMARD = disease-modifying antirheumatic drug; ACR = American College of Rheumatology; RA = rheumatoid arthritis; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; NSAIDs = nonsteroidal antiinflammatory drugs.
† Positivity defined as ≥80 IU/ml.
‡ CRP levels below the lower limit of quantitation (<0.4 mg/dl) were set to 0.2 mg/dl for the calculation of descriptive statistics.

Patients with no on-treatment efficacy examination were considered failures for the ACR20, ACR50, and ACR70 responses, and for these patients individual ACR components were categorized as missing. Determination of the change or percent change from baseline was performed for the patient's last observation carried forward at the end of treatment. The analysis of change from baseline for the mean was completed using a general linear model, with treatment group and DMARD strata included. The analysis of percent change from baseline for the median was completed using a stratified Wilcoxon's rank sum test (the stratification variable was DMARD status [resistance or intolerance]). This nonparametric test assesses whether there is a shift in the location parameter (i.e., median) between the groups. Primary and secondary efficacy parameters were also analyzed by DMARD strata.

The sample size for this study was based on estimates of ACR20 success taken from the phase II study of tacrolimus in RA (32). The ACR20 success rate for the combined tacrolimus group was estimated at 24.8%. With a sample size of 150 per group, the study had >80% power to detect a difference between the combined tacrolimus group and the placebo group for a placebo response rate up to 13.6% using a significance level of $P < 0.05$ (2-sided). If the primary end point in the combined tacrolimus treatment group was statistically significantly different from that in the placebo group, pairwise comparisons between the individual treatment groups and the placebo group were to be performed at the 0.05 level of significance.

RESULTS

Demographics, baseline characteristics, and disposition. Four hundred sixty-five patients were enrolled, but 1 patient randomized to the 2-mg tacrolimus group never received study drug. Thus, 464 patients received at least 1 dose of study drug and are included in all of the efficacy and safety analyses. The demographics, baseline characteristics, and measures of disease activity were similar in the 3 treatment groups (Table 1). However, the proportion of white patients was slightly greater in the 3-mg tacrolimus group (95.4%) than in the 2-mg tacrolimus group (89.0%) and the placebo group (87.9%). The proportion of African-American patients in the 2-mg tacrolimus group (8.4%) was greater than that in the placebo group (5.1%) and the 3-mg tacrolimus group (2.6%). These disparate proportions led to a statistically significant difference ($P = 0.044$) for race across the 2-mg tacrolimus, the 3-mg tacrolimus, and the placebo groups.

Two hundred ninety-three patients were DMARD resistant, and 171 were DMARD intolerant. In this study, lack of efficacy was rigorously predefined in the protocol as follows: the patient completed the safety and efficacy assessments through the month 3 visit; the patient had <20% improvement in both the tender/painful and swollen joint counts at the time of withdrawal; and both the patient and investigator believed that the patient's RA was not being controlled. Thus, of the 307 patients who received tacrolimus, 144 (46.9%) completed the 6-month double-blind study, 41 (13.4%) withdrew because of an adverse event, 61 (19.9%) withdrew because of lack of efficacy, and 61

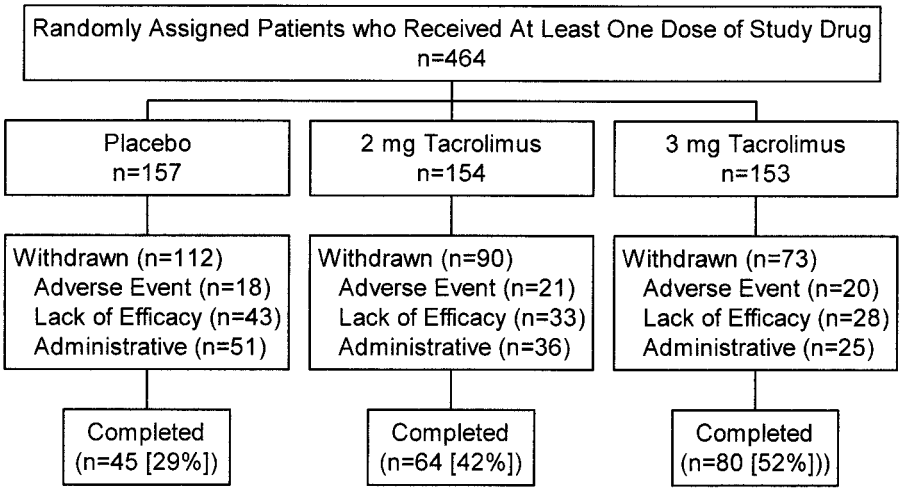

Figure 1. Disposition of patients.

(19.9%) withdrew for administrative reasons. Of the 157 patients who received placebo, 45 (28.7%) completed the study, 18 (11.5%) withdrew because of an adverse event, 43 (27.4%) withdrew because of lack of efficacy, and 51 (32.5%) withdrew for administrative reasons (Figure 1).

Efficacy. The signs and symptoms of RA improved in more patients in both tacrolimus groups than in the placebo group (Table 2 and Figure 2), as judged by the ACR20 success rate. The ACR20 success rate for the placebo, 2-mg tacrolimus, and 3-mg tacrolimus groups was 10.2%, 18.8% ($P < 0.05$ versus placebo), and 26.8% ($P < 0.0005$ versus placebo), respectively. In addition, at the end of treatment, compared with patients receiving placebo, patients receiving tacrolimus 2 mg had statistically significantly superior ACR50 and ACR70 response rates, and patients receiving tacrolimus 3 mg had statistically significantly superior ACR20 and ACR50 response rates (32.0% [$P < 0.005$] and 11.8% [$P < 0.05$], respectively) (Table 3 and Figure 2).

Additional analysis indicated that DMARD-intolerant patients had somewhat better ACR response rates than did DMARD-resistant patients. Thus, among DMARD-intolerant patients, the ACR20 success rate and the ACR20 and ACR50 response rates for both the 2-mg and 3-mg tacrolimus groups were statistically superior to those for the placebo group, while among DMARD-resistant patients, the ACR20 success rate and ACR20 response rate for only the 3-mg tacrolimus group were statistically superior to those for the placebo group (Figure 2). Results for patients who were methotrexate intolerant or methotrexate resistant (data not shown) were similar to results for the DMARD-intolerant and DMARD-resistant groups as a whole.

Figure 3 shows the percentage of patients achieving an ACR20 response over the course of the 6-month study, by treatment group. The ACR20 response rate increased over time for the 2-mg and 3-mg tacrolimus groups. Table 4 shows the mean absolute change and median percent change from baseline in the individual components of the ACR criteria for improvement. In the 3-mg tacrolimus group, a statistically significant mean absolute change and median percent improvement from baseline in all individual components was observed, and the median percent improvement was 30% in both tender/painful and swollen joints. In contrast, in the 2-mg tacrolimus group, a statistically significant mean absolute change and median percent improvement from baseline was seen in all individual components except for the tender/painful joint count.

Safety. Tacrolimus was generally well tolerated over the 6-month treatment period. The median trough tacrolimus levels were ~2–3 ng/ml, and tacrolimus did not accumulate over the duration of the study. Adverse events were common in all groups, including the placebo

Table 2. ACR20 success*

Treatment group	No. (%)	*P*
Placebo (n = 157)	16 (10.2)	–
Tacrolimus 2 mg (n = 154)	29 (18.8)	0.0318
Tacrolimus 3 mg (n = 153)	41 (26.8)	0.0003

* ACR20 = American College of Rheumatology 20% improvement. ACR20 success was defined as completion of 6 months of treatment and an ACR20 response at the month 6 visit. *P* values are versus placebo. See Patients and Methods for an explanation of the rating scale and methods used for statistical analysis.

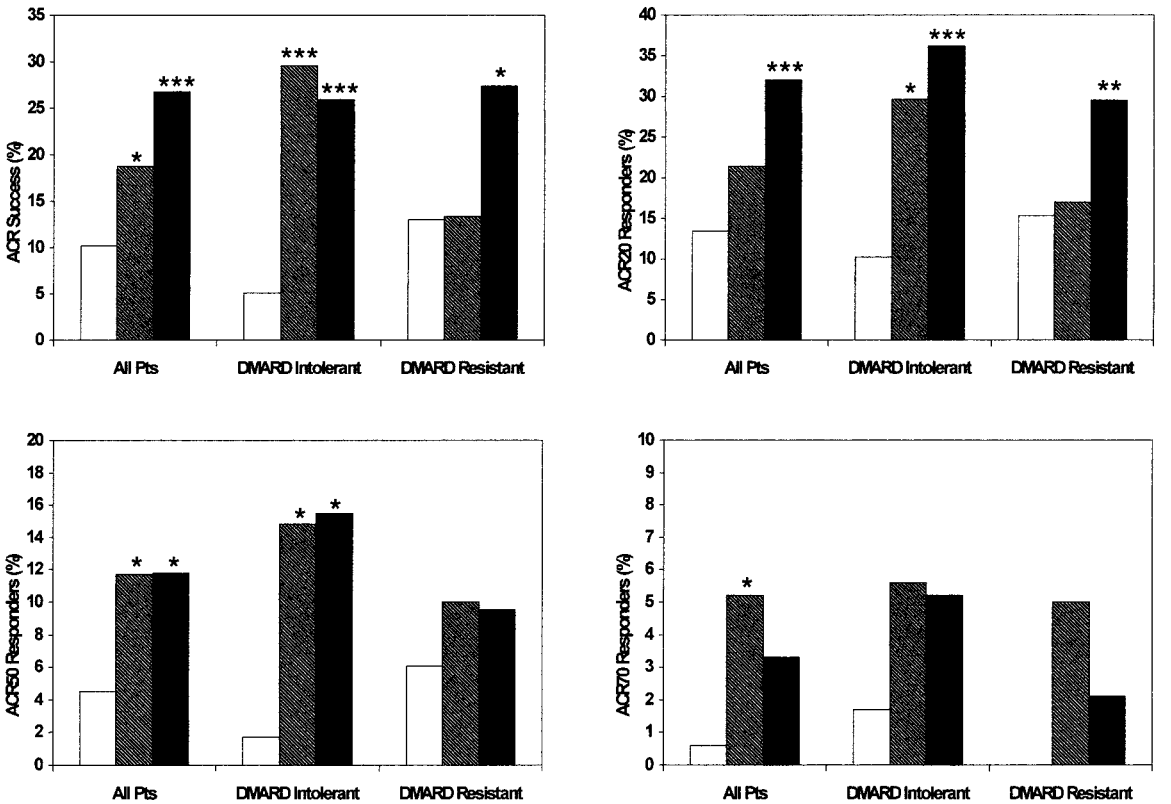

Figure 2. American College of Rheumatology 20% improvement (ACR20) success rate and ACR20, ACR50, and ACR70 responder rates at end of treatment for patients (Pts) receiving placebo (□), tacrolimus 2 mg (▨) or tacrolimus 3 mg (■). ACR success was defined as completion of 6 months of treatment and an ACR20 response at the month 6 visit. Determination of the percentage of ACR responders was based on the last observation carried forward method. Patients with no on-treatment efficacy evaluation were considered failures for ACR response rates at all visits. * = $P < 0.05$ versus placebo; ** = $P < 0.01$ versus placebo; *** = $P < 0.005$ versus placebo, by logistic regression, with treatment and disease-modifying antirheumatic drug (DMARD) strata as the main effects.

Table 3. ACR response rates at end of treatment*

Treatment group	Response rate					
	ACR20		ACR50		ACR70	
	No. (%)	*P*	No. (%)	*P*	No. (%)	*P*
Placebo (n = 157)	21 (13.4)	–	7 (4.5)	–	1 (0.6)	–
Tacrolimus 2 mg (n = 154)	33 (21.4)	0.0595	18 (11.7)	0.0228	8 (5.2)	0.0425
Tacrolimus 3 mg (n = 153)	49 (32.0)	0.0001	18 (11.8)	0.0228	5 (3.3)	0.1314

* Calculations were based on the last observation carried forward method. Patients with no on-treatment efficacy visits were considered failures for American College of Rheumatology (ACR) response rates at all visits. *P* values are versus placebo, and were determined by logistic regression, with treatment and disease-modifying antirheumatic drug strata as the main effects. See Patients and Methods for an explanation of the rating scale.

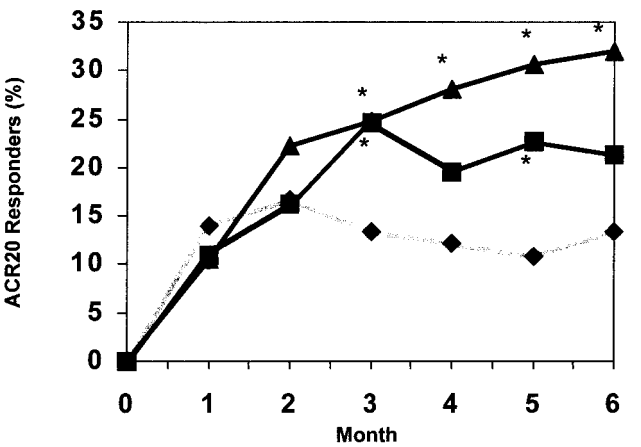

Figure 3. American College of Rheumatology 20% improvement (ACR20) responder rates over time in patients receiving placebo (◆), tacrolimus 2 mg (■), or tacrolimus 3 mg (▲), based on the last observation carried forward method. Patients with no on-treatment efficacy evaluation were considered failures for calculating ACR response rates at all visits. * = $P \leq 0.05$ versus placebo.

Table 4. Change and percent change from baseline to end of treatment for individual ACR component scores*

	Placebo (n = 157)			Tacrolimus					
				2 mg (n = 154)			3 mg (n = 153)		
ACR component	No.	Mean ± SEM absolute change	Median % change (10th, 90th percentiles)	No.	Mean ± SEM absolute change	Median % change (10th, 90th percentiles)	No.	Mean ± SEM absolute change	Median % change (10th, 90th percentiles)
Tender/painful joint count (0–68 joints)	155	−1.86 ± 1.09	−2.2 (−70.6, 66.7)	143	−3.09 ± 1.14	−10.5 (−85.0, 61.3)	149	−7.25 ± 1.11†	−30.0 (−90.9, 33.3)†
Swollen joint count (0–66 joints)	155	−1.47 ± 0.73	−5.9 (−62.5, 61.5)	143	−4.02 ± 0.76‡	−16.7 (−80.0, 37.5)§	149	−5.30 ± 0.74†	−30.0 (−80.0, 40.0)†
Patient's assessment of pain (0–100 scale)	154	−2.13 ± 2.17	0.0 (−58.9, 51.1)	142	−11.28 ± 2.28¶	−9.5 (−74.4, 50.7)‡	147	−10.62 ± 2.23§	−13.8 (−65.4, 60.6)¶
Patient's global assessment of disease activity (0–100 scale)	154	2.48 ± 2.16	1.4 (−52.2, 127.9)	142	−7.25 ± 2.26¶	−10.5 (−63.8, 73.8)†	147	−6.55 ± 2.21¶	−13.6 (−71.8, 113.0)§
Physician's global assessment of disease activity (0–100 scale)	155	−8.98 ± 2.21	−8.3 (−76.5, 33.4)	142	−15.84 ± 2.32‡	−21.4 (−80.0, 30.5)§	148	−18.19 ± 2.26¶	−37.7 (−81.9, 30.6)†
Modified HAQ (0–3 scale)	155	0.09 ± 0.04	6.7 (−45.5, 100.0)	143	−0.13 ± 0.04†	−10.6 (−75.0, 88.9)†	149	−0.04 ± 0.04‡	0.0 (−66.7, 100.0)§
ESR, mm/hour	143	2.64 ± 1.89	4.4 (−50.0, 150.0)	135	−4.31 ± 1.94§	−12.2 (−60.0, 84.6)¶	144	−8.59 ± 1.89†	−17.4 (−71.4, 66.7)†
C-reactive protein level, mg/dl (normal <0.8)	150	−0.05 ± 0.18	0.0 (−71.9, 247.5)	140	−0.75 ± 0.18§	−23.7 (−80.4, 115.5)†	140	−0.64 ± 0.18‡	−8.3 (−82.8, 105.0)†

* Calculations were based on the last observation carried forward method. Data for patients with no on-treatment efficacy evaluation were considered missing. The mean absolute change from baseline was calculated using least square means. Statistical analyses were performed using treatment group and disease-modifying antirheumatic drug strata. ACR = American College of Rheumatology; HAQ = Health Assessment Questionnaire (part 1, questions A–H); ESR = erythrocyte sedimentation rate.
† $P < 0.001$ versus placebo.
‡ $P < 0.05$ versus placebo.
§ $P < 0.01$ versus placebo.
¶ $P < 0.005$ versus placebo.

group, and were reported at least once in >80% of tacrolimus-treated patients compared with 72% of placebo-treated patients ($P < 0.05$). The 5 most common adverse events occurring in all patients receiving tacrolimus were flu syndrome, diarrhea (the prevalence was statistically significantly different from that in the placebo group), nausea, dyspepsia, and headache. The overall incidence of adverse events for each treatment group was similar between patients younger than age 65 years and those ages 65 years and older.

A total of 27 patients (5.8%) experienced 31 treatment-emergent serious adverse events (6 patients [3.8%] who received placebo, 10 patients [6.5%] who received 2 mg of tacrolimus, and 11 patients [7.2%] who received 3 mg of tacrolimus). Twenty-eight of the 31 serious adverse events were considered to have no relationship to the study drug. One patient in the 2-mg tacrolimus group and 2 patients in the 3-mg tacrolimus group had treatment-emergent serious adverse events considered to have a possible relationship to study drug; each of these events (infection, convulsion, and increased creatinine level) resolved without residual effects. Two deaths were reported, both in patients receiving placebo.

The mean (±SD) creatinine levels at baseline and at the end of treatment were 0.74 ± 0.21 mg/dl and 0.76 ± 0.24 mg/dl, respectively, for placebo-treated patients; 0.72 ± 0.19 mg/dl and 0.78 ± 0.27 mg/dl, respectively, for patients treated with 2 mg/day of tacrolimus; and 0.72 ± 0.21 mg/dl and 0.80 ± 0.28 mg/dl, respectively, for patients treated with 3 mg/day of tacrolimus. Maximum increases in the baseline creatinine level of ≥30% to <40% or ≥40% at any time during treatment, and increases in the baseline creatinine level

Table 5. Creatinine level increases from baseline at any time during treatment, and absolute values*

Treatment group	Creatinine level increase from baseline		Absolute creatinine value, mg/dl	
	≥30% to <40%	≥40%	>1.4 to ≤1.9	>1.9
Placebo (n = 155)				
Maximum	10 (6.5)	15 (9.7)	7 (4.5)	0 (0.0)
End of treatment	6 (3.9)	9 (5.8)	4 (2.5)	0 (0.0)
Tacrolimus 2 mg (n = 149)				
Maximum	8 (5.4)	30 (20.1)	3 (2.0)	1 (0.7)
End of treatment	4 (2.7)	19 (12.8)	1 (0.7)	1 (0.7)
Tacrolimus 3 mg (n = 151)				
Maximum	7 (4.6)	44 (29.1)	10 (6.6)	1 (0.7)
End of treatment	6 (4.0)	19 (12.6)	6 (4.0)	1 (0.7)

* Values are the number (%) of patients. The patient base is all patients who received at least 1 dose of study drug and for whom a baseline and at least 1 on-treatment creatinine value were available. Maximum = maximum percent increase from baseline or maximum absolute creatinine value during treatment.

of ≥30% to <40% or ≥40% at the end of treatment are shown in Table 5. Among patients who experienced an increase in the baseline creatinine level of ≥30% and in whom study drug may have been continued, interrupted, or discontinued, 12 (46.2%) of 26 patients in the placebo group, 20 (52.6%) of 38 patients in the 2-mg tacrolimus group, and 27 (50.9%) of 53 patients in the 3-mg tacrolimus group experienced a documented subsequent return to baseline creatinine values (mean time to return to baseline level 29.3 days, 34.6 days, and 39.0 days, respectively). (Although creatinine values may have returned to baseline levels in additional patients, this was not documented.)

The numbers of patients in each treatment group with maximum creatinine levels above the upper limit of normal at any time during the study and with creatinine levels above the upper limit of normal at the end of treatment are also shown in Table 5. Serum creatinine levels increased by ≥40% from baseline at some time during the trial in 20% and 29% of patients receiving tacrolimus 2 mg/day and 3 mg/day, respectively. The maximum creatinine values were 1.8 mg/dl (in 2 patients) in the placebo group, 2.6 mg/dl (in 1 patient) in the 2-mg tacrolimus group (the next highest value was 1.7 mg/dl, in 1 patient), and 2.0 mg/dl (in 1 patient) in the 3-mg tacrolimus group (all other patients in this group had levels ≤1.9 mg/dl). Increased creatinine levels were responsible for withdrawal of 4 patients (2.6%) receiving tacrolimus 3 mg/day. Of note, 89.2% of patients receiving placebo, 90.9% of patients receiving 2 mg of tacrolimus, and 87.6% of patients receiving 3 mg of tacrolimus had creatinine levels below or within the normal range throughout the study.

Hypertension was reported as a treatment-emergent adverse event for 7 (4.5%) of 157 placebo-treated patients (3 with a history of hypertension and 4 with no history of hypertension), 9 (5.8%) of 154 patients treated with 2 mg/day of tacrolimus (3 with a history of hypertension and 6 with no history of hypertension), and 12 (7.8%) of 153 patients treated with 3 mg/day tacrolimus (5 with a history of hypertension and 7 with no history of hypertension). These adverse events were considered to be possibly or probably related to treatment with study drug for 5 placebo-treated patients (3.2%), 5 patients treated with 2 mg/day of tacrolimus (3.2%), and 11 patients treated with 3 mg/day of tacrolimus (7.2%). Hypertension was responsible for withdrawal of 2 patients (1.3%) receiving tacrolimus 3 mg/day. The mean (±SD) change from baseline to the end of treatment for systolic blood pressure was 0.4 ± 14.3 mm Hg among placebo-treated patients, 2.4 ± 15.0 mm Hg among patients treated with tacrolimus 2 mg/day, and −1.0 ± 16.9 mm Hg among patients treated with tacrolimus 3 mg/day. The mean (±SD) change from baseline to the end of treatment for diastolic blood pressure was −0.4 ± 8.8 mm Hg among placebo-treated patients, 2.1 ± 8.5 mm Hg among patients treated with tacrolimus 2 mg/day, and −0.7 ± 9.9 mm Hg among patients treated with tacrolimus 3 mg/day.

Tremor was experienced by 3 patients in the placebo group (1.9%), 7 patients in the 2-mg tacrolimus group (4.5%), and 13 patients in the 3-mg tacrolimus group (8.5%), and was considered to be possibly or probably related to study drug in 2 patients (1.3%), 6 patients (3.9%), and 12 patients (7.8%), in the respective treatment groups. The adverse event of diabetes was reported for 1 patient in the 2-mg tacrolimus group, who had no previous history of diabetes, and for 1 patient in

the 3-mg tacrolimus group, who did have a previous history of diabetes.

DISCUSSION

The results of the 6-month, double-blind, placebo-controlled study reported here demonstrate the efficacy and safety of tacrolimus as monotherapy for RA. Among all patients enrolled in the trial, greater ACR response rates were seen in the group receiving tacrolimus 3 mg/day than in the group receiving tacrolimus 2 mg/day. The ACR20, ACR50, and ACR70 response rates at the end of treatment were 32.0%, 11.8%, and 3.3%, respectively, among patients treated with 3 mg/day tacrolimus, compared with 13.4%, 4.5%, and 0.6%, respectively, in the placebo group. The differences between the 3-mg tacrolimus group and the placebo group for the ACR20 and ACR50 response rates were statistically significant. In addition, it is important to note that compared with patients receiving placebo, patients receiving tacrolimus 3 mg/day had a statistically significant median improvement of 30% in both painful/tender and swollen joints at the end of treatment, and statistically significant differences in mean absolute change from baseline and median percent change from baseline in *all* components of the ACR responder index. These efficacy results for the 3-mg tacrolimus group in this study are consistent with those reported for the 3-mg tacrolimus group in the phase II, placebo-controlled study (32).

Patients enrolled in the trial were stratified prior to randomization according to resistance to or intolerance of at least 1 DMARD. The responses of each group were analyzed separately. Both DMARD-resistant and DMARD-intolerant groups showed a dose–response relationship with respect to ACR response rates. Of note, however, is that DMARD-intolerant patients responded somewhat better to tacrolimus than did DMARD-resistant patients. Thus, among DMARD-intolerant patients, both 2 mg/day and 3 mg/day of tacrolimus were statistically superior to placebo for the ACR20 success rate and the ACR20 and ACR50 response rates at end of treatment. In contrast, among DMARD-resistant patients, only the 3-mg dose of tacrolimus was statistically superior to placebo, and only for the ACR20 success rate and the ACR20 response rate at end of treatment. This observation suggests that resistance to at least 1 DMARD may predict resistance to other DMARDs.

The efficacy results seen for all patients in the 3-mg tacrolimus group are in the same range of ACR20 responses that have been reported for cyclosporine monotherapy. In four 6-month placebo- and/or active comparator–controlled studies of cyclosporine, 25–35% of patients achieved an ACR20 response at the end of the 6-month study period (39). No data were reported for ACR50 or ACR70 responses for those studies.

Recent monotherapy trials with newer DMARDs and biologic agents have shown somewhat higher ACR response rates than those seen at 6 months in the current efficacy trial (13–17,21). The lower ACR response rates for tacrolimus monotherapy may be explained in part by the differences in patients' background, including disease severity, in different studies. In addition, the lower response rates may in part be explained by a lack of a minimum requirement for the CRP level or the ESR, one of the components of the ACR20, for patients enrolling in the double-blind tacrolimus efficacy study. A total of 21.6% of patients in the double-blind tacrolimus efficacy trial had a CRP level that was below the limit of quantitation at enrollment and therefore could not demonstrate a 20% improvement in this parameter.

Nonetheless, despite a fifth of the patients being precluded from achieving a 20% improvement in this parameter, 32.0%, 11.8%, and 3.3% of RA patients treated with 3 mg/day of tacrolimus achieved an ACR20, ACR50, and ACR70 response, respectively, at the end of treatment, based on the other ACR response parameters. Thus, individual patients in the 3-mg/day group responded well to tacrolimus treatment with respect to most ACR parameters. For this group of responder patients, tacrolimus is an effective treatment of RA.

The adverse events seen in the trial reported here were generally similar in nature to those that had previously been observed in trials of tacrolimus in patients who had received liver or kidney transplants. However, the incidences of adverse events (including hypertension, tremor, diabetes, and increased creatinine level) previously identified as safety concerns with tacrolimus in transplant studies were generally notably lower in the RA patients receiving 3 mg of tacrolimus for 6 months than the incidences seen in transplant patients (7.8% versus 38–50%, 8.5% versus 48–56%, >5% versus 24%, and 6.5% versus 24–45%, respectively). Moreover, several adverse events, including insomnia, paresthesias, oliguria, hyperkalemia, hypokalemia, hyperglycemia, hypomagnesemia, hypophosphatemia, anemia, and peripheral edema, which were seen with an incidence of at least 15% in trials of tacrolimus in liver and/or kidney transplant patients, were seen in <5% of RA patients treated with tacrolimus. The lower incidence of these adverse events in the RA population is consistent with

that seen for the 3 mg/day treatment group in the previous tacrolimus trial (32) and is almost certainly the result of the lower dosage used to treat RA (3 mg/day) than that needed to prevent transplant rejection (0.1–0.2 mg/kg/day). Thus, tacrolimus appears to be generally well tolerated by patients with RA.

A comparison of the incidence of adverse events, including hypertension, tremor, abdominal pain, and hypertrichosis, reported in RA patients treated with macrolide calcineurin inhibitors demonstrates a generally similar or lower incidence in patients treated with 3 mg/day of tacrolimus for up to 6 months in the study reported here (7.8%, 8.5%, 7.8%, and 0%, respectively) compared with patients treated with 2.5–5 mg/day of cyclosporine for up to 6 months in 4 trials (8–25%, 7–13%, 15%, and 15–19%, respectively) (39). A comparison of the incidence of creatinine increases of ≥30% from baseline in populations of RA patients receiving monotherapy with tacrolimus or cyclosporine shows an incidence of 34% for tacrolimus 3 mg/day in both the trial reported here and the tacrolimus trial reported previously (32), compared with 39–48% for cyclosporine (39). For tacrolimus, however, it is important to note that despite the 34% incidence of an increase of ≥30% from the baseline creatinine level, ~90% of patients in the tacrolimus groups maintained creatinine levels below or within the normal range (0.5–1.4 mg/dl) throughout their participation in this study. In addition, a comparison of withdrawal rates indicates that fewer patients receiving tacrolimus than the number receiving cyclosporine had to be withdrawn for hypertension (1.3% versus 5.3%) and increased creatinine levels (2.6–3.2% versus 7%). Thus, as monotherapy in patients with RA, tacrolimus is at least as efficacious as cyclosporine and appears to possess at least as good a safety profile as that of cyclosporine.

In summary, tacrolimus was safe and well tolerated in patients with RA. Tacrolimus was more efficacious than placebo: a dose–response relationship was demonstrated, with a single daily dose of 3 mg being more effective than the lower dose of 2 mg, and tacrolimus was more efficacious in patients who were intolerant of previously administered DMARDs than in patients who were resistant to previous DMARDs. The incidence of known macrolide calcineurin inhibitor–associated adverse events previously identified in trials of tacrolimus for the prophylaxis of transplant rejection also demonstrated a dose–response relationship in the tacrolimus-treated RA patients; however, these adverse events generally occurred at notably lower rates than in the studies of tacrolimus in transplant patients, and at lower rates than in the studies of cyclosporine in RA patients. For patients who respond to it, tacrolimus is an effective and well-tolerated oral therapy for RA.

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APPENDIX A: THE TACROLIMUS RHEUMATOID ARTHRITIS STUDY GROUP

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