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Tacrolimus in Rheumatoid Arthritis Patients Receiving Concomitant Methotrexate

A Six-Month, Open-Label Study

Joel M. Kremer,[1] Joseph S. Habros,[2] Karen S. Kolba,[3] Jeffrey L. Kaine,[4] Mary Ann Borton,[5] Laurel J. Mengle-Gaw,[6] Benjamin D. Schwartz,[6] Wayne Wisemandle,[5] and Qais A. Mekki,[5] for the Tacrolimus-Methotrexate Rheumatoid Arthritis Study Group

Objective. **To assess the safety of tacrolimus used in combination with oral methotrexate (MTX) to control the signs and symptoms of rheumatoid arthritis (RA) in patients whose disease remains active despite treatment with MTX.**

Methods. **This was a multicenter open-label study conducted at 13 US sites. Eighty patients who at baseline had active RA (mean tender/painful joint count 29.4, mean swollen joint count 17.4, mean erythrocyte sedimentation rate 25.1 mm/hour) despite treatment for ≥1 month with a stable, maximally tolerated dosage of oral MTX (≤20 mg/week, median dosage 15 mg/week, range 5–20 mg/week) were enrolled and received 3 mg/day tacrolimus as a single oral dose once per day for 6 months while continuing to receive MTX at the existing stable dosage. All other disease-modifying antirheumatic drugs were discontinued; stable dosage of nonsteroidal antiinflammatory drugs and oral corticosteroids (≤10 mg/day prednisone or its equivalent) were allowed. All 80 patients received at least one dose of the study drug and were included in the primary safety and efficacy analyses. Seventy-five patients had at least one postbaseline efficacy assessment, and 63 patients (78.8%) completed the study. The primary clinical response criterion was the American College of Rheumatology definition of 20% improvement (ACR20) at the end of treatment.**

Results. **Seven patients (12.5%) withdrew from the study because of adverse events possibly or probably related to treatment with tacrolimus, and 4 (5.0%) withdrew due to lack of efficacy. One serious adverse event (pancreatitis) was possibly related to tacrolimus treatment. The mean (±SD) creatinine (Cr) level increased from 0.74 ± 0.16 mg/dl at baseline to 0.81 ± 0.22 mg/dl ($P < 0.001$) at the end of treatment. Twenty-three patients (28.8%) had a ≥30% maximum increase in the Cr level from baseline during the study, with the Cr level in 3 patients (3.8%) exceeding the range considered normal for their age and sex. The maximum Cr level during the study was 1.8 mg/dl. The ACR20 clinical response rate at the end of treatment was 52.5% (95% confidence interval 41.6–63.4%).**

Conclusion. **In patients whose active RA persists despite treatment with MTX, tacrolimus in combination with MTX is safe and well-tolerated and provides clinical benefit.**

Rheumatoid arthritis (RA) is a chronic, progressive disease that requires early diagnosis and aggressive treatment to minimize morbidity (1). Disease-modifying antirheumatic drugs (DMARDs) are used to reduce inflammation and to decrease the progression of articular damage. A prominent feature of several newer DMARDs is their immunosuppressive properties (1). Methotrexate (MTX) is the most widely used DMARD because of its favorable efficacy and safety profile, its

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[1]Joel M. Kremer, MD: Center for Rheumatology, Albany, New York; [2]Joseph S. Habros, MD: Radiant Research, Scottsdale, Arizona; [3]Karen S. Kolba, MD: Pacific Arthritis Center, Santa Maria, California; [4]Jeffrey L. Kaine, MD: Sarasota Arthritis Center, Sarasota, Florida; [5]Mary Ann Borton, BS, RN, Wayne Wisemandle, MA, Qais A. Mekki, MD, PhD: Fujisawa Healthcare, Deerfield, Illinois; [6]Laurel J. Mengle-Gaw, PhD, Benjamin D. Schwartz, MD, PhD: The Camden Group, St. Louis, Missouri.

Address correspondence and reprint requests to Joel M. Kremer, MD, The Center for Rheumatology, 1367 Washington Avenue, Suite 101, Albany, NY 12206. E-mail: jkremer@joint-docs.com.

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record of safety, and its ability to maintain a prolonged response (2–4). However, use of MTX as monotherapy most often induces a partial response, and therefore patients are commonly given a combination of MTX and other DMARDs (5–8). Combination therapy with MTX is beneficial for patients in whom the maximally tolerated dose of MTX does not provide adequate disease control (6,8).

Tacrolimus (Prograf, FK506), a macrolide immunosuppressant, has been approved in the US, Europe, and Japan to prevent allograft rejection in liver and kidney transplantation. Similar to cyclosporin A (CsA), it suppresses the activation and proliferation of antigen-specific T cells; however, tacrolimus is more potent than CsA (9,10). A recent double-blind, placebo-controlled, phase II study demonstrated the usefulness of tacrolimus as monotherapy for the treatment of RA in patients who have shown a lack of response to MTX therapy (11). We undertook the present study to determine whether tacrolimus, combined with a therapeutic dosage of MTX, is safe and effective for relief of the signs and symptoms of the disease in patients who attain only a partial clinical response to MTX therapy alone.

PATIENTS AND METHODS

Patients. Eighty patients who were ≥16 years of age, who met the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 revised criteria for RA (12), whose disease was ≥6 months in duration, and who had active RA (≥5 tender/painful joints and ≥3 swollen joints) at baseline were enrolled at 13 US centers for this 6-month, open-label study. Eligible patients had been receiving oral MTX (≤20 mg/week) at a stable dosage for ≥1 month prior to study entry, and were to continue on the same dosage of MTX throughout the study. All other DMARDs were discontinued ≥2 weeks prior to study entry. Patients were allowed to receive stable dosages of nonsteroidal antiinflammatory drugs (NSAIDs) and oral corticosteroids (≤10 mg/day of prednisone or its equivalent) from 2 weeks and 4 weeks, respectively, prior to study entry. Intra- and/or periarticular steroid injections were allowed during the study, but the injected joint was excluded from subsequent efficacy assessments. Exclusion criteria included pregnancy or lactation, liver disease (defined by levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, or total bilirubin >2 times the upper limit of normal), serum creatinine (Cr) levels outside the normal range for the patients' age and sex, hemoglobin concentration <9.0 mg/dl, white blood cell count <3,000/mm^3, platelet count <100,000/mm^3, or an ACR RA functional classification of IV. The study protocol was approved by each institution's review board. All patients gave their written informed consent.

Treatment. Patients were treated with 3 mg of tacrolimus (three 1-mg capsules; Fujisawa Ireland, Killorglin, County Kerry, Republic of Ireland), which was administered orally, once daily, in addition to each patient's current prescribed oral MTX dosage (highest tolerated MTX dosage ≤20 mg/week). The MTX dosage could be lowered only if the patient experienced an adverse event (AE) that may have been related to the MTX treatment. All patients received stable folate supplementation (1 mg/day).

Assessment. Clinical and laboratory assessments were performed at baseline, week 2, and months 1–6. Safety was evaluated by physical examinations, monitoring of vital signs and treatment-emergent AEs, and routine clinical laboratory testing (with emphasis on parameters that had previously shown elevations among transplantation patients who were treated with tacrolimus; i.e., serum Cr, blood urea nitrogen [BUN], glucose, and hemoglobin A_{1c} [HgbA_{1c}]). Patients who had ongoing treatment-emergent AEs at the end of treatment were monitored until the event resolved or stabilized. The serum Cr level was measured at baseline, week 2, and months 1–6, or at the end of treatment. Patients who had an increase in the serum Cr level of ≥40% from baseline or ≥30% from the previous visit, which was considered clinically significant, had the test repeated in 1 week. If the Cr level remained elevated, treatment with tacrolimus was withheld. If the elevation persisted, the patient was withdrawn from the study. If, in the investigator's opinion, the serum Cr level decreased to a sufficient extent after the tacrolimus was withheld, then the treatment could be reinstated within 2 weeks, and the patient was allowed to remain in the study. Cr levels were not routinely monitored after the end of the study.

Trough whole-blood tacrolimus concentrations were determined at baseline, and at months 1, 3, and 6, or at the end of treatment. The latter results were not used to modify or discontinue the tacrolimus dosing. Clinical response was determined by the proportion of patients who achieved the ACR 20% response level of improvement (ACR20) at end of treatment. Secondary clinical end points were the ACR 50% (ACR50) and ACR 70% (ACR70) improvement levels at the end of treatment (13).

All patients received at least one dose of study drug and were included in the safety and efficacy analyses. Patient data were analyzed according to baseline MTX dosage (5–12.5 mg/week for the low-dose group and 15–20 mg/week for the high-dose group), to evaluate the safety of tacrolimus in combination with a low dose of MTX versus a high dose of MTX. The last observation carried forward method was used to handle missing data for calculation of the ACR response at the end of treatment. Patients who were not evaluated for treatment efficacy while receiving the study drug were considered failures in terms of ACR composite scores. The 95% confidence intervals (95% CIs) were constructed for the ACR response rates at the end of treatment, assuming a normal approximation to the binomial parameter.

RESULTS

Patient characteristics. Of the 80 patients enrolled in the study, 63 (78.8%) completed 6 months of treatment (Figure 1). The patients were predominantly white (93%) and female (74%), with a mean age of 55 years and mean duration of RA of 9 years. Forty percent

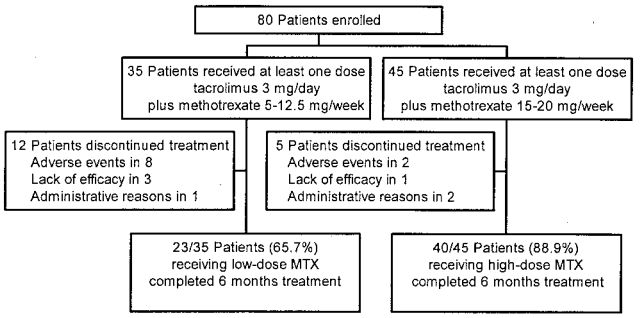

Figure 1. Schematic diagram showing, by baseline methotrexate (MTX) dosage, the number of rheumatoid arthritis patients enrolled, reasons for discontinuing treatment with tacrolimus, and number of patients who completed the study. Administrative reasons for withdrawal were protocol noncompliance, discovery of preexisting protocol violation, and investigator discretion.

of patients had received at least one DMARD other than MTX during the 2 years prior to enrollment. The majority of patients were in ACR functional class II (76%) and were rheumatoid factor positive (64%), and all had active disease at baseline. Seventy-three percent of patients had received MTX at a stable dosage for ≥90 days prior to enrollment. Two patients had their MTX dosage reduced from 12.5 mg/week to 10 mg/week during the study, due to gastric distress. Among the 80 patients, 68% and 54% received concomitant NSAIDs and glucocorticoids, respectively. Patient demographics and baseline disease characteristics were similar between the 2 MTX dose subgroups.

Adverse events. Sixty-nine patients (86.3%) experienced ≥1 AE during the study (Table 1). The overall incidence of AEs was generally similar between the low-dose and high-dose MTX subgroups. Seven patients reported developing tremors during the study; for 5 of these patients (4 in the low-dose MTX subgroup and 1 in the high-dose MTX subgroup), the tremor was possibly or probably related to the effects of the study drug. For all reports, the median time to onset of tremor was 30 days. The overall incidence of treatment-emergent AEs was similar for patients <65 years of age (87.7%) and for patients ≥65 years of age (82.6%). In general, patients with underlying diseases such as hypertension, hyperlipidemia, and diabetes had AEs that were similar to those in patients without these conditions.

Eight patients in the low-dose MTX subgroup and 2 patients in the high-dose MTX subgroup discontinued the study due to AEs (Figure 1). The more common AEs leading to discontinuation were tremor (3 patients) and nausea (2 patients), all occurring in the low-dose MTX subgroup. Other AEs leading to discontinuation for 1 patient each were anxiety, cerebrovascular accident, migraine, and herpes zoster in the low-dose MTX subgroup, and arterial anomaly and urinary urgency in the high-dose MTX subgroup. Of note, no patient withdrew early due to hypertension or increased levels of serum Cr.

Four patients each had a single serious AE during the study, comprising cerebrovascular accident and skin carcinoma in the low-dose MTX subgroup, and

Table 1. Incidence of treatment-emergent adverse events reported by ≥5% of patients who received at least one dose of the study drug*

Adverse event	Tacrolimus 3 mg + MTX 5–12.5 mg/week (n = 35)	Tacrolimus 3 mg + MTX 15–20 mg/week (n = 45)	Total (n = 80)
Any adverse event	30 (85.7)	39 (86.7)	69 (86.3)
Any serious adverse event†	2 (5.7)	2 (4.4)	4 (5.0)
Specific event			
Diarrhea	9 (25.7)	9 (20.0)	18 (22.5)
Flu syndrome	8 (22.9)	10 (22.0)	18 (22.5)
Headache	5 (14.3)	5 (11.1)	10 (12.5)
Abdominal pain	2 (5.7)	6 (13.3)	8 (10.0)
Accidental injury	1 (2.9)	7 (15.6)	8 (10.0)
Dyspepsia	4 (11.4)	4 (8.9)	8 (10.0)
Nausea	5 (14.3)	3 (6.7)	8 (10.0)
Tremor	5 (14.3)	2 (4.4)	7 (8.8)
Vomiting	5 (14.3)	1 (2.2)	6 (7.5)
Asthenia	1 (2.9)	3 (6.7)	4 (5.0)
Back pain	2 (5.7)	2 (4.4)	4 (5.0)

* Values are the number (percentage) of patients.
† Serious adverse events were classified according to the World Health Organization adverse reaction terminology.

Table 2. Incidence of increase in serum creatinine (Cr) among patients who received at least one dose of study drug and for whom a baseline and at least one on-treatment Cr measurement were available*

Serum Cr	Tacrolimus 3 mg + MTX 5–12.5 mg/week (n = 35)	Tacrolimus 3 mg + MTX 15–20 mg/week (n = 45)	Total (n = 80)
% increase from baseline			
≥30% to <40%			
Maximum†	4 (11.4)	5 (11.1)	9 (11.3)
End of treatment	2 (5.7)	4 (8.9)	6 (7.5)
≥40%			
Maximum†	7 (20)	7 (15.6)	14 (17.5)
End of treatment	3 (8.6)	3 (6.7)	6 (7.5)
Maximum on-treatment value			
≥0.5 mg/dl to ≤1.4 mg/dl‡	34 (97.1)	43 (95.6)	77 (96.3)
>1.4 mg/dl to ≤1.8 mg/dl	1 (2.9)	2 (4.4)	3 (3.7)
>1.8 mg/dl	0	0	0

* Values are the number (percentage) of patients.
† Maximum increase during treatment, from baseline.
‡ Normal range.

arterial anomaly and pancreatitis in the high-dose MTX subgroup. All of these serious events resolved within several days and the patients recovered without residual effects, with the exception of the patient diagnosed as having skin carcinoma. Only the pancreatitis was possibly related to treatment with tacrolimus.

Renal effects. The mean (±SD) Cr level in all patients increased, from 0.74 ± 0.16 mg/dl at baseline to 0.81 ± 0.22 mg/dl at the end of treatment ($P < 0.001$). The mean baseline level of Cr and changes from baseline were similar between the 2 MTX dose subgroups. A maximum increase in Cr of ≥30% from baseline occurred in 23 patients (28.8%) during treatment and in 12 patients (15%) at the end of treatment (Table 2). Three patients (3.8%) had Cr levels >1.4 mg/dl at some time during treatment. The maximum Cr level observed was 1.8 mg/dl in 1 patient, a 71-year-old man in the low-dose MTX subgroup (12.5 mg/week). The other 2 patients with maximum Cr values above the normal limit had maximum on-treatment Cr values of 1.7 mg/dl and 1.6 mg/dl, accompanied by elevated BUN levels of 46 mg/dl and 27 mg/dl (upper limit of normal 25 mg/dl), respectively, with both the Cr and BUN values returning to within normal limits in the respective patients within 17 days and 6 days of the initially observed elevation.

Of the 23 patients whose Cr level increased by ≥30% (n = 9) and ≥40% (n = 14) from baseline while receiving tacrolimus treatment, 4 of 9 patients (44%) and 6 of 14 patients (43%), respectively, had Cr levels that returned to baseline values by the end of the study, with a mean time to return of 30.6 days and 24.6 days, respectively. The patients whose Cr levels returned to baseline levels included both those patients whose dosing was interrupted and those whose dosing was uninterrupted. The remaining 13 patients either exhibited the first ≥30% elevation in the Cr level at the final study visit, which was not monitored for return to baseline levels after the study (4 patients with an end-of-treatment Cr level of 0.8–1.3 mg/dl) or had a Cr level that did not return to within 0.1 mg/dl of the baseline value by the final study visit (4 patients with an end-of-treatment Cr level of 0.7–0.8 mg/dl, 2 patients with a value of 1.3 mg/dl, and 1 patient each with values of 1.1 mg/dl, 1.2 mg/dl, and 1.6 mg/dl, respectively). For all patients, the mean (±SD) change in BUN levels from baseline to end of treatment was an increase of 1.3 ± 4.0 mg/dl. The baseline BUN value and mean changes from baseline to end of treatment were similar between the 2 MTX dose subgroups.

Hypertension was reported as an AE in 3 patients (3.8%) in the high-dose MTX subgroup during the study. Two of these patients reported a history of hypertension. For all patients, the mean (±SD) diastolic blood pressure decreased from 80.3 ± 9.0 mm Hg at baseline to 80.0 ± 8.2 mm Hg at the end of treatment. The mean (±SD) systolic blood pressure decreased from 130.4 ± 17.8 mm Hg at baseline to 129.0 ± 15.4 mm Hg at end of treatment. The mean baseline diastolic and systolic blood pressures and changes from baseline were similar between the 2 MTX dose subgroups.

Hyperglycemia. Clinically relevant fasting blood glucose levels (>150 mg/dl) were observed in 2 patients with a history of diabetes. Five additional patients had fasting blood glucose levels between 125 mg/dl and 150 mg/dl at some time during the study. All other patients had fasting blood glucose levels that remained within the

normal range. For all patients, the maximum increase from baseline $HgbA_{1c}$ level was <30%. Four patients in the high-dose MTX subgroup had elevated levels of $HgbA_{1c}$ (>6.5%). One of these patients had a history of diabetes. Three other patients entered the study with $HgbA_{1c}$ levels of 6.3%, 6.5%, and 6.6%, respectively, which increased to 6.7% in all 3 patients at month 3, and remained high in the first 2 patients (7.1% and 6.7%, respectively) at the end of treatment.

Tacrolimus blood concentrations. Trough levels of tacrolimus in whole blood showed mean (±SD) concentrations of 2.9 ± 1.14 ng/ml and 2.6 ± 7.45 ng/ml at the end of treatment for patients in the low-dose and high-dose MTX subgroups, respectively. These levels are similar to those observed in patients receiving tacrolimus 3 mg/day as monotherapy for RA (Fujisawa Ireland: unpublished data).

Clinical response. At the end of treatment, the ACR20 response rate was 52.5% (95% CI 41.6–63.4%), the ACR50 response rate was 28.8% (95% CI 18.8–38.7%), and the ACR70 response rate was 13.8% (95% CI 6.2–21.3%). Among the treated patients, 67.5% experienced ≥50% improvement in the number of tender/painful joints, and 60% of patients had ≥50% improvement in the number of swollen joints. The rates and distributions of clinical improvement were similar between the 2 MTX dose subgroups.

DISCUSSION

This multicenter open-label study assessed the safety and efficacy of tacrolimus in combination with oral MTX for the treatment of RA. All patients whose disease remained active despite treatment with their highest tolerated dosage of MTX were enrolled.

Tacrolimus was generally safe and well-tolerated by the patients in this study, who were also receiving a full range of concomitant MTX dosages. Overall, the incidence of AEs was similar between the 2 baseline MTX dose subgroups, and was similar to the incidences observed in studies of tacrolimus monotherapy in RA (11). Of note, cotherapy with tacrolimus plus MTX in RA patients did not increase plasma levels of MTX compared with MTX monotherapy (14). This is in contrast to the observed increase in MTX plasma levels when RA patients are treated with MTX plus CsA (15). In addition, the incidence of AEs was not affected by the presence of underlying diseases such as hypertension, hyperlipidemia, and diabetes. In general, the incidence of AEs was similar to or lower than that observed with other combination therapies that are used for the treatment of RA (5–7,16). Finally, there was no indication that the tacrolimus dosage (3 mg/day) administered in this study was diabetogenic.

Some adverse effects on renal function were observed in this study. Moreover, the mean (±SD) changes in the diastolic and systolic blood pressures from baseline to end of treatment were −0.3 ± 8.5 mm Hg and −1.4 ± 12.6 mm Hg, respectively. Because macrolide calcineurin inhibitors have been associated with the development of hypertension, it is noteworthy that 3 patients (3.8%) in the present study reported the AE of hypertension, compared with 16% of patients in a 6-month cyclosporine/MTX study (6), and no patient in this study withdrew early due to hypertension. The mean (±SD) change in serum Cr levels, from baseline to end of treatment, was 0.07 ± 0.14 mg/dl. In contrast, a study of MTX in combination with CsA for the treatment of RA found greater increases in the mean (±SD) Cr level (0.14 ± 0.27 mg/dl) (6), and CsA/MTX combination treatment is associated with a higher incidence of Cr increases of ≥30% compared with those reported herein (55% and 28.8%, respectively) (17). In the present study, although patients were allowed to interrupt their tacrolimus therapy for up to 2 weeks, no dosage adjustments were allowed. Even with these constraints, no patient withdrew from the study due to an increase in the Cr level, and 80% of patients completed the study. The incidence of a ≥30% increase in Cr levels reported herein for patients treated with tacrolimus/MTX is less than that reported in a phase II study in which RA patients were treated with 3 mg/day of tacrolimus as monotherapy, and the time to return to baseline Cr level observed in our combination tacrolimus/MTX study is consistent with that reported in patients receiving tacrolimus monotherapy (11).

Roughly half of the patients showed clinical improvement, as measured by the ACR20, when 3 mg/day of tacrolimus was added to their prescribed stable MTX dosage regimen. Seventy-three percent of patients had been receiving MTX at a stable dosage for ≥3 months prior to enrollment, and although this study was open label, and determination of efficacy was not the primary study objective, the overall ACR20, ACR50, and ACR70 response rates at the end of treatment of 52.5%, 28.8%, and 13.8%, respectively, compare favorably with those observed in placebo-controlled MTX studies in which patients exhibited a partial response to MTX in combination with other therapeutic agents (5–8). Patient satisfaction with the clinical response obtained with the combination therapy given in this

study is evidenced by the low (5%) dropout rate due to lack of efficacy.

The results of this study demonstrate that tacrolimus at an oral dosage of 3 mg/day can be safely used in combination with oral MTX (up to 20 mg/week) for the treatment of RA, and suggest that the combination is an effective alternative for patients who attain only a partial response to MTX.

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APPENDIX A: THE TACROLIMUS-METHOTREXATE RHEUMATOID ARTHRITIS STUDY GROUP

In addition to Drs. Habros, Kolba, and Kaine, members of the Tacrolimus-Methotrexate Rheumatoid Arthritis Study Group include F. Avni, MD (Hill Top Research, West Palm Beach, FL), A. Baldassare, MD (Arthritis Consultants, St. Louis, MO), R. K. Bath, MD (Radiant Research, Cincinnati, OH), B. Bode, MD (Radiant Research, Tucson, AZ), B. Laura, MD (Radiant Research, Evansville, IN), M. Lovy, MD (Radiant Research, Lakewood, WA), D. C. Owens, MD (Radiant Research, Greer, SC), P. A. Saway, MD (Radiant Research, Birmingham, AL), D. G. Stainbrook, Jr., DO (Hill Top Research, Columbus, OH), and M. L. Throne, MD (Atlanta, GA).