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Modified Release Tacrolimus

M. Roy First and William E. Fitzsimmons

Fujisawa Healthcare Inc., Three Parkway North, Deerfield, IL 60015-2548, USA.

Modified Release (MR) tacrolimus is an extended release formulation of tacrolimus (Prograf®) administered once daily in the morning. In healthy volunteers, the MR tacrolimus formulation given qd AM and Prograf administered twice daily (bid) have a similar exposure (AUC) and trough levels (Cmin), with a reduced peak level (Cmax). Subsequently, pharmacokinetic studies were performed in stable kidney and liver transplant recipients converted from Prograf bid to MR tacrolimus qd AM. The steady-state tacrolimus exposure and target trough level range of MR tacrolimus were equivalent to Prograf after a mg-for-mg daily dose conversion in these two groups of patients, and there is a high correlation of exposure to trough levels for both Prograf and MR tacrolimus, as well as significantly less intra-subject variability in exposure after conversion to MR tacrolimus. These results indicate that stable kidney and liver transplant recipients can be safely converted from standard Prograf twice daily dosing to the same mg-for-mg daily dose of MR tacrolimus once daily in the morning. Hopefully a once daily dosing regimen of tacrolimus can improve patient compliance while maintaining effective immunosuppression.

Key Words: Immunosuppression, tacrolimus, kidney transplantation

INTRODUCTION

The introduction of more potent immunosuppressive agents over the last two decades has resulted in a progressive improvement in 1-year graft survival rates after solid organ transplantation. While long-term graft survival has followed a similar trend,[1] graft loss after the first year post-transplantation continues at an annual rate of 3-5%.[2]

Successful avoidance of acute rejection in the first year post-transplant with modern immunosuppression has translated into a steady improvement in long-term allograft survival. Tacrolimus, a calcineurin inhibitor, is approved for the prevention of acute rejection following kidney and liver transplantation. In a number of studies, tacrolimus-based immunosuppression has been associated with a more favorable cardiovascular risk profile and superior long-term renal function when compared with another calcineurin inhibitor, cyclosporine.[3-9] In the U.S in 2003, 67% of new kidney transplant recipients and 89% of new liver transplant recipients were discharged on tacrolimus. Despite this improvement in outcomes, medication compliance remains a serious problem after transplantation;[10,11] a once daily tacrolimus regimen could potentially improve compliance while the maintaining the established safety and efficacy of the drug.

This report details the development to date of a modified release formulation of tacrolimus by Fujisawa.

MODIFIED-RELEASE TACROLIMUS (MR-4)

Tacrolimus (Prograf®) was approved in the U.S. for prophylaxis of rejection in recipients of liver and kidney transplants in 1994 and 1997, respectively. In 2003, 89% of new liver transplant recipients, and 67% of new kidney transplant recipients and were discharged on tacrolimus.[12] The oral dosage forms of Prograf currently available are 0.5, 1, and 5 mg hard gelatin capsules which are administered in a twice-daily (bid) regimen. The safety and efficacy of Prograf in solid renal trans-

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Reprint address: requests to Dr. M. Roy First, Senior Medical Director, Research & Development, Fujisawa Healthcare, Inc., Three Parkway North, Deerfield, IL 60015-2548, USA. Tel: 847-317-8812, Fax: 847-317-8861, E-mail: roy_first@fujisawa.com

plants is well established.[4,13-15] Prograf is administered in two divided doses per day at dosages sufficient to maintain whole blood trough concentrations generally within the range of 5-15 ng/mL in order to prevent rejection. The modified-release oral dosage form of tacrolimus (MR-4) is being developed for once daily (qd) administration.[16]

The potential for developing an acceptable modified release formulation of tacrolimus was established by a biopharmaceutical study of four formulations designated MR-1, MR-2, MR-3, and MR-4 relative to Prograf.[17] As MR-4 had a similar extent of absorption (mean ratios of MR-4 to Prograf for AUC (0-t) and AUC (0-inf) were 93.7% and 97.3%, respectively), but a substantially reduced Cmax relative to Prograf, it was chosen for further evaluation.[18] MR-4 has been administered to over 100 healthy human volunteers in five Phase I pharmacokinetic studies.[19-23] Three single-dose studies were conducted in the United States[19-21] and two repeat-dose studies were conducted in Europe.[22,23]

The three U.S. single-dose studies were designed to compare MR-4 and Prograf at three different doses using three distinct capsule strengths (3×0.5 mg, 3×1 mg and 1×5 mg). Taken together, results from the three U.S. single-dose studies yielded a lower Cmax, after dosing with MR-4 than after dosing with Prograf, and similar geometric mean AUC (0-inf) for both formulations. The MR-4 formulation was well tolerated in all three studies with a safety profile consistent with Prograf.

The purpose of the two repeat-dose studies conducted in Europe was to compare the biopharmaceutics of MR-4 and Prograf at the same total daily dose. In the first repeat-dose study, fourteen healthy volunteers were randomized to receive 1 mg Prograf twice daily or 2 mg MR-4 once daily for 10 consecutive days. After a 14-day washout period, subjects received the opposite formulation for 10 consecutive days. On Days 1 and 10, the AUC (0-24) geometric means for MR-4 and Prograf were similar, as was Cmin at Day 10. There was no difference in elimination of absorbed tacrolimus between MR-4 and Prograf on Day 10 as the mean terminal T1/2 was approximately the same for both formulations (41 hours in one study, 38 hours in the other). Both tacrolimus formulations were safe and well tolerated. In the second repeat-dose study, 25 healthy volunteers were randomized to receive a higher total daily dose of tacrolimus of 4 mg (2 mg Prograf bid, 4 mg MR-4 qd) in two treatment groups as above. As in the first repeat-dose study, AUC (0-24) geometric means for MR-4 and Prograf were similar on Days 1 and 10. Cmax for MR-4 was lower than Prograf. For both MR-4 and Prograf, Cmin and AUC (0-24) were highly correlated. Although not statistically significant, the correlation coefficient was numerically higher for MR, suggesting that Cmin measurements may be a more reliable indicator of exposure for the MR-4 formulation. Both MR-4 and Prograf were well tolerated and the incidence and type of adverse events were similar for the two formulations. The results from the two repeat-dose studies demonstrated that the AUC (0-24) for MR-4 at Day 1 was approximately equal to the sum of the AM and PM AUC12 for Prograf. At Day 10 in both studies, the AUC (0-24) ratio of geometric means for MR-4 and Prograf were similar, as the 90% confidence intervals (CIs) around the geometric mean ratios (MR-4/Prograf) for the area under the concentration-time curve AUC0-24 after the first day of dosing and at steady state were contained within the bioequivalence range (80% to 125%) recommended by the Food and Drug Administration.[24,25]

These data from the healthy volunteer studies indicate that the modified release formulation and Prograf have a similar AUC and that MR-4 has similar, or stronger, correlation between AUC and Cmin (trough). The trough concentrations in the repeat-dose studies were similar between Prograf and MR-4 and, in the second study, approached levels used clinically. Therefore, the same target concentration range was decided upon for both Prograf and MR-4 in clinical studies.

To date two clinical studies in transplant patients with MR-4 have been completed in the U.S. The first was a pharmacokinetic (PK) study to evaluate tacrolimus exposure and trough levels in stable kidney transplant recipients converted from Prograf to MR-4.[26] Seventy stable kidney transplant recipients were enrolled in this open label, multicenter study. Eligible patients were 18 to 65 years who had received a renal transplant at least 6

months prior to enrollment, on stable doses of Prograf for more than 2 weeks prior to enrollment, and with stable renal function (serum creatinine < 3.0 mg/dL and variation < 0.5 mg/dL for 2 levels at least 6 days apart) prior to enrollment. Patients receiving any drug interfering with tacrolimus metabolism, or any patient with a rejection episode requiring antibody therapy in the last 6 months were excluded. Patients continued Prograf bid through Day 7. 24 hour PK profiles were obtained on Days 1 and 7. Patients were converted to the same mg-for-mg daily dose to MR qd in the morning on Day 8. 24 hour PK profiles were obtained for MR on Days 8, 14 and 21. Day 8 PK data were not included in the comparative analyses, since steady-state had not been reached. The PK of tacrolimus (Cmin and AUC0-24) were comparable for Prograf (Days 1 and 7) and MR (Days 14 and 21) within the equivalence range of 80-125% supporting the 1:1 conversion from Prograf bid to MR-4 qd. 90% confidence intervals (CI) comparing MR and Prograf (Days 14 and 21 vs. Days 1 and 7) were 0.91-0.99 for AUC0-24, and 0.82-0.91 for Cmin. MR was well tolerated with a safety profile comparable to Prograf. AUC0-24/Cmin correlation for Prograf was (Day 1 r=0.81; Day 7 r=0.87) and for MR was (Day 14 r=0.93, Day 21 r=0.88). This correlation is illustrated in Fig. 1. Serum creatinine levels remained stable after conversion to MR; 67/70 patients completed all five PK profiles; no patients experienced acute rejection or discontinued for treatment failure. The steady-state pharmacokinetics and the target whole blood trough concentration range of MR in this study were equivalent to Prograf after a mg -for- mg conversion in stable kidney transplant recipients, supporting a safe 1 : 1 conversion from Prograf bid to MR qd.

The second study was a PK study to evaluate tacrolimus exposure in 70 stable liver transplant recipients converted from Prograf to MR in a single sequence, four period crossover study design.[27] This was an open label, multi-center study. Eligible patients were 18 to 65 years who had received a liver transplant at least six months prior to enrollment, who were receiving stable doses of Prograf for more than 2 weeks prior to enrollment and who had stable renal function (defined by serum creatinine < 2.0 mg/dL) prior to enrollment. Patients receiving any drug interfering with tacrolimus metabolism, or experiencing abnormal liver function (defined as AST or ALT >2x the upper limit of normal) or any patient experiencing rejection episodes requiring antibody therapy in the last six months were excluded from this study. Patients received Prograf bid on Days 1-14 and Days 29-42. Patients were converted to the same mg for mg daily dose of MR-4 qd on Days 15-28 and Days 43-56. Twenty-four hour PK profiles were obtained on Days 14, 28, 42 and 56. Laboratory and safety parameters were also evaluated. The AUC0 -24 of tacrolimus was comparable for Prograf (Days 14 and 42) and MR-4 (Days 28 and 56) within the

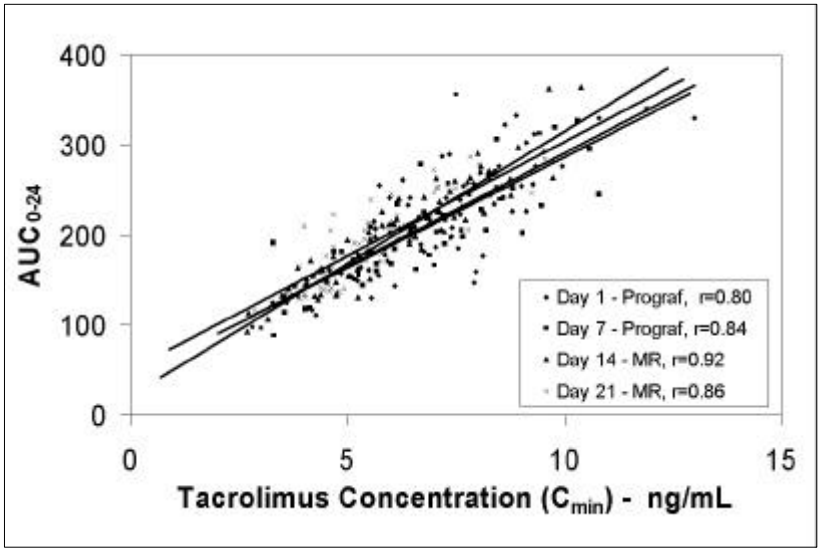

Fig. 1. AUC_{0-24}/Cmin correlation for Prograf (Days 1 and 7) and for MR (Days 14 and 21).

equivalence range of 80-125%. The 90% CI for the MR versus Prograf comparison at steady state (Days 28 and 56 vs. Days 14 and 42) was 0.85 to 0.92 for AUC0-24. MR was well tolerated, with a safety profile comparable to that of Prograf. AUC0-24 was highly correlated to Cmin for Prograf (Day 14 r=0.93; Day 42 r=0.89) and MR-4 (Day 28 r=0.93, Day 56 r=0.92). Renal and liver function remained stable throughout the study; one patient experienced biopsy confirmed acute rejection, and 62/70 patients completed all four PK profiles. This study, like that in the kidney transplant recipients, indicates that the steady-state tacrolimus exposure of MR is equivalent to Prograf after a mg-for-mg conversion in stable liver transplant recipients.

Currently, a large phase III clinical trial is underway in the U.S. in de novo kidney transplant recipients. This is a three-arm study comparing the safety and efficacy of MR-4/mycophenolate mofetil (MMF)/steroids with Prograf/MMF/steroids and Neoral®/MMF/steroids. Similar conversion and de novo studies are also ongoing in Europe and Japan in kidney, liver, heart, and bone marrow transplant recipients.

CONCLUSION

Currently the most commonly prescribed immunosuppressive regimen after kidney transplantation in the U.S. is tacrolimus combined with MMF. Studies conducted thus far indicate that renal and hepatic transplant recipients can be converted safely and effectively from a standard Prograf twice daily dosing to the same daily dose of MR tacrolimus once daily in the morning. Hopefully this will improve patient adherence to their medication regimen, and improve long-term outcome.

REFERENCES

1. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. N Engl J Med 2000;342:605-12.
2. Pascual M, Theruvath T, Kawai T, Tolkoff-Rubin N, Cosimi AB. Strategies to improve long-term outcomes after renal transplantation. N Engl J Med 2002;346:580-90.
3. Hariharan S, McBride MA, Cherikh WS, Tolleris CB, Bresnahan BA, Johnson CP. Post-transplant renal function in the first year predicts long-term kidney transplant survival. Kidney Int 2002;62:311-8.
4. Vincenti F, Jensik SC, Filo RS, Miller J, Pirsch J. A long-term comparison of tacrolimus (FK506) and cyclosporine in kidney transplantation: evidence for improved allograft survival at five years. Transplantation 2002;73:775-82.
5. Klein IH, Abrahams A, van Ede T, Hene RJ, Koomans HA, Ligtenberg G. Different effects of tacrolimus and cyclosporine on renal hemodynamics and blood pressure in healthy subjects. Transplantation 2002;73:732-6.
6. Margreiter R. for the European Tacrolimus vs Ciclosporin Microemulsion Renal Transplantation Study Group. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomised multicentre study. Lancet 2002;359:741.
7. Mayer AD for the European Tacrolimus Multicentre Renal Study Group. Chronic rejection and graft half-life: five-year follow-up of the European tacrolimus multicenter renal study. Transplant Proc 2002;34:1491-2.
8. First MR. Renal function as a predictor of long-term graft survival in renal transplant patients. Nephrol Dial Transplant 2003;18 (Suppl 1):3-6.
9. Jurewicz WA. Tacrolimus versus ciclosporin immunosuppression: long-term outcome in renal transplantation. Nephrol Dial Transplant 2003;18 (Suppl 1):7-11.
10. Didlake RH, Dreyfus K, Kerman RH, Van Buren CT, Kahan BD. Patient noncompliance: a major cause of late graft failure in cyclosporine-treated renal transplants. Transplant Proc 1988;20 (Suppl 3):63-9.
11. Butler JA, Roderick P, Mullee M, Mason JC, Peveler RC. Frequency and impact of nonadherence to immunosuppressants after transplantation: a systematic review. Transplantation 2004;77:769-76.
12. UNOS Market Share Report, February, 2004.
13. Pirsch JD, Miller J, Deierhoi MH, Vincenti F, Filo RS. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. Transplantation 1997;63:977-83.
14. Mayer AD, Dmitrewski J, Squifflet JP, Besse T, Grabensee B, Klein B, et al. Multicenter randomized trial comparing tacrolimus (FK506) and cyclosporine in the prevention of renal allograft rejection. Transplantation 1997;64:436.
15. Miller J. Tacrolimus and mycophenolate mofetil in renal transplant recipients: one year results of a multicenter, randomized dose ranging trial. Transplant Proc 1999;31:276-7.
16. First MR, Fitzsimmons WE. New drugs to improve transplant outcomes. Transplantation 2004:77:S88.
17. Package insert for tacrolimus (Prograf®) from Fujisawa Healthcare, Inc. Revised July 2001.
18. Data on file. Company Report 98-0-048, Fujisawa

Healthcare, Inc., 2001.
19. Data on file. Company Report 00-0-076, Fujisawa Healthcare, Inc., 2001.
20. Data on file. Company Report 00-0-077, Fujisawa Healthcare, Inc., 2001.
21. Data on file. Company Report 00-0-078, Fujisawa Healthcare, Inc., 2001.
22. Data on file. Company Report FG-506-04-21, Fujisawa Healthcare, Inc., 2001.
23. Data on file. Company Report FG-506-04-25, Fujisawa Healthcare, Inc., 2002.
24. Guidance for Industry. Bioavailability and bioequivalence studies for orally administered drug products-general considerations. US Department of Health, Food and Drug Administration, Center for Drug Evaluation and Research (CDER); July 2002.
25. Guidance for Industry. Bioavailability and bioequivalence studies for orally administered drug products-general considerations. US Department of Health, Food and Drug Administration, Center for Drug Evaluation and Research (CDER); March 2003; BP Revision 1.
26. Alloway R, for the Tacrolimus Modified Release Kidney Conversion Study Group. Conversion of stable kidney transplant recipients from a twice daily Prograf based regimen to a once daily modified release tacrolimus based regimen. Am J Transplant 2004;4 (Suppl 8):230 (Abstract).
26. Florman S, for the Tacrolimus Modified Release Liver Conversion Study Group. Conversion of stable liver transplant recipients from a twice daily Prograf based regimen to a once daily modified release tacrolimus based regimen. Am J Transplant 2004;4 (Suppl 8):268 (Abstract).