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Immunosuppression with Tacrolimus Early after Orthotopic Heart Transplantation: A Comparison of Prograf and Advagraf

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ABSTRACT

Background: We compared trough levels and clinical outcomes in patients who received Prograf or Advagraf (tacrolimus) de novo following heart transplantation surgery.

Methods: Eighty-two patients were included in this follow-up study. Biopsy results were controlled for the first 3 months after orthotopic heart transplantation. Trough levels were monitored for 4 weeks: daily during the first 7 days and once every week thereafter. The lengths of stay in the hospital and in intensive care were compared. The end point of the study was the 1-year mortality rate.

Results: We found significant differences between the groups for both biopsy results and trough levels. Trough levels differed for the first 5 days and then converged on the sixth day. The levels remained comparable throughout the monitoring period. The 1-year mortality rates for Prograf and Advagraf were 20% and 15%, respectively.

Conclusions: Trough levels were comparable after an adjustment period. There were no differences between the 2 groups in their 1-year mortality rates. These results suggest that Advagraf is a safe alternative to Prograf for patients who have undergone heart transplantation.

INTRODUCTION

Calcineurin inhibitors have become an essential element in immunosuppressive regimens for patients undergoing transplantation surgery. The increased use of cyclosporine, however, has led to the discovery of several important adverse effects, such as nephrotoxicity [Sommerer 2002; Nankivell 2004] and an increased incidence of malignancy in renal transplants [Morath 2004]. Tacrolimus, the successor to cyclosporine, was found to slow chronic allograft nephropathy in patients treated with cyclosporine [Meier 2006]. It has gradually replaced cyclosporine and become indispensable in long-term immunosuppressive treatments.

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Several long-term follow-up studies of tacrolimus and cyclosporine have shown significantly lower incidences of organ rejection and no increase in adverse events in patients treated initially with tacrolimus [Vincenti 2002]. Although they are less frequent, adverse events are still common with tacrolimus treatment [Emre 2000].

Maintaining appropriate tacrolimus levels is necessary to prevent organ rejection while avoiding adverse effects. This goal is particularly difficult because of the high individual variation in drug metabolism [Kuypers 2010; Staatz 2010] and the small therapeutic index of this agent.

Immunosuppressive regimens often rely on multiple drugs and can be highly complex. This fact encourages patients to not comply with drug prescriptions, leading to disruption in the regular intake of these drugs [Dobbels 2010]. Patient vulnerability to organ rejection and other complications may be increased. To improve patient compliance requires simplifying drug administration.

Tacrolimus can be administered either twice a day (Prograf; Astellas Pharma, Northbrook, IL, USA) or once a day (Advagraf; Astellas Pharma). Prograf is the conventional form of application; however, Advagraf is a newer drug that promises to reduce patient effort and increase compliance. Advagraf has been in clinical use for treating renal and liver transplantation patients since 2008 [First 2008]. Additional studies have confirmed the clinical safety of conversion [Marin-Gomez 2009; Comuzzi 2010] to Advagraf therapy after initial Prograf treatment in liver transplantation patients and the clinical safety of de novo treatments with Advagraf [Krämer 2010; Trunečka 2010]. These studies have found no significant differences in clinical outcomes for patients treated with the extended-release formula, and they have generally supported the once-daily administration of tacrolimus.

Although the long-term effects on patient mortality are not yet known, a recent study suggested that the efficacy and safety of prolonged-release tacrolimus over a 4-year period were maintained in liver, kidney, and heart transplant recipients [van Hooff 2011]. The study found that survival rates were not different in a population treated with Advagraf. Additionally, Advagraf may produce significant reductions in such cardiovascular risk factors as glycemia and triglycerides, which could be associated with better long-term patient survival [Meçule 2010].

Advagraf has been shown to be a suitable replacement to Prograf for both liver and renal transplantation patients. This phenomenon has not yet been examined in a population consisting solely of heart transplantation patients. We compared trough levels and clinical follow-up results in patients who received Prograf or Advagraf (off label use) following heart transplantation.

METHODS

We enrolled 82 patients in this follow-up study who had received immunosuppressive regimens with either Prograf (n = 30) or Advagraf (n = 52) following heart transplantation surgery. Informed consent about cardiac transplantation and the immunosuppressive therapy was collected before the procedure from all patients. All patients received mycophenolate in addition to tacrolimus. The dose was adjusted individually to obtain the intended exposure to the therapeutic range (3-20 ng/L). Patients unable to swallow were treated with Prograf initially and later converted to Advagraf on a one-to-one basis with respect to total daily dose.

Sixty-seven patients were male, and 16 were female (mean age SD, 50.84 9.69 years). Tacrolimus was discontinued in 4 patients of the Advagraf group and replaced with cyclosporine. All 4 patients had had tacrolimus plasma levels within the therapeutic range before treatment was discontinued. The following comorbidities were diagnosed in the patients at the time of surgery: coronary heart disease, 29 patients (35%); amyloidosis, 12 patients (15%); hypertension, 43 patients (52%); diabetes, 21 patients (26%); and hyperlipoproteinemia, 39 patients (48%).

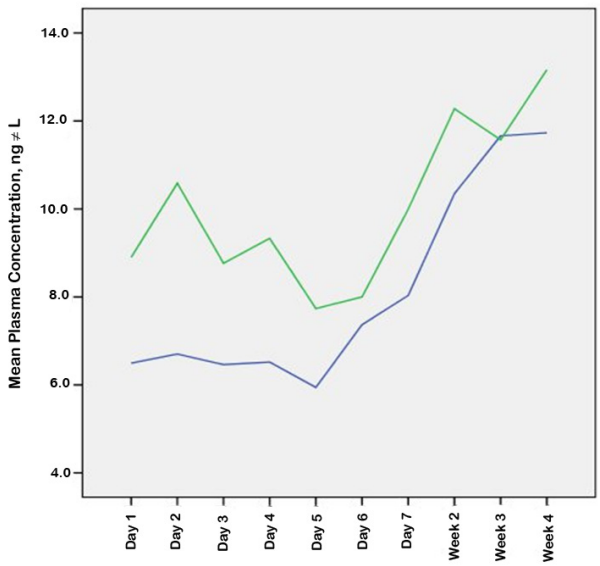
Trough levels were recorded over a 4-week period: daily during the first 7 days of monitoring and once each week thereafter. Monitoring started on the second postoperative day. Biopsy results were monitored for the first 3 months postoperatively. Biopsies were taken during the second and fourth weeks of the first month and once in each subsequent month. Results were graded according to the severity of rejection on a scale of 0 to 4.

Statistical analysis was performed with PASW Statistics 17 (SPSS Inc./IBM, Chicago, IL, USA). Trough levels and biopsy results in the 2 groups were compared with linear regression analysis. In addition, the results at each time of measurement were compared via the Student t test. The end point for all patients in the study was the 1-year mortality rate. Differences between mortality rates were examined with the Fisher exact test; the numbers of days spent in the hospital and in intensive care were compared with the t test.

RESULTS

The linear regression analysis revealed significant differences between the 2 groups in both trough levels ($P < .01$) and biopsy results ($P < .01$). The means were compared for each monitored time point. Trough levels were significantly different during the first 6 days following surgery (Figure). The calculated P values for the individual monitoring points were as follows: day 1, $P = .245$; day 2, $P = .00$; day 3, $P = .04$; day 4, $P = .07$; day 5, $P = .14$; day 6, $P = .579$; day 7, $P = .211$; week 2, $P = .323$; week 3, $P = .725$; week 4, $P = .733$. Differences in biopsy results were statistically significant throughout the period of observation except at 1 month after transplantation. Biopsy results were as follows: week 2, $P = .021$; week 4, $P = .128$; month 2, $P = .014$; month 3, $P < .01$.

The 2 groups were not significantly different at a 95% confidence level with respect to the number of days spent under hospital care ($P = .856$) and in the time spent in intensive care ($P = .08$). The 1-year postoperative mortality rate was 20% in the Prograf group and 15% in the Advagraf group. The results of the Fisher exact test confirmed that the number of deaths in the 2 groups were not significantly different ($P = .762$). Kaplan-Meier survival analysis revealed an unremarkable distribution of deaths during the monitored postoperative period ($P = .284$, log rank test).



Tacrolimus trough levels during the first 4 weeks after surgery. Upper line, Prograf; lower line, Advagraf.

DISCUSSION

Trough levels were monitored daily during the first 7 days and then once a week during the 3 subsequent weeks of observation. We found that the development of the trough level differed in the 2 groups. Advagraf levels were generally lower during the first few days of the first week, whereas Prograf seems to have generated higher trough levels during the same period. This finding seems to confirm those made in previous studies, which reported that higher Advagraf doses were necessary in renal transplantation patients to produce the same trough levels generated with the equivalent Prograf dose [Crespo 2009]. The samples for the patients treated de novo with Prograf had significantly higher trough levels during the first 6 days. The 2 trough levels converged on the sixth day, with the differences no longer being significant. This observation was maintained throughout the 3 subsequent weeks. Trough levels were comparable following this period of adjustment.

The results of all biopsies taken, except for biopsies performed 4 weeks after surgery, were significantly different according to comparisons made with the Student t test. The results in the Prograf group indicated a stronger inclination for patients to develop stage 2 rejections (moderate), compared with patients treated with Advagraf. Only 1 patient treated with Advagraf and 1 patient treated with Prograf developed stage 3 rejections (after the first 2 weeks and 4 weeks, respectively). Biopsy results for both patients improved in the subsequent biopsies. Although statistically relevant, the clinical differences in biopsy results were of marginal importance. The 1-year mortality rate was a more suitable indicator of a prolonged clinical outcome.

One-year mortality rates for the Advagraf-treated patients and those treated with Prograf were similar (15% and 20%, respectively), in accordance with the results reported in other publications [Krämer 2010; Trunečka 2010; van Hooff 2011]. This finding is a strong indication that Advagraf is an acceptable alternative to Prograf. Despite this result, few studies have investigated the enduring effects of this alternative. Additional long-term follow-up studies are necessary to confirm prolonged patient safety.

The number of days the patients spent under hospital care was not high in the Advagraf group, suggesting that the adjustment of patients to the new regimen did not take longer compared with Prograf treatment. The 2 groups appeared to differ in the number of days spent in intensive care, although this difference was not statistically relevant. Two outliers were identified in the Prograf group. The correspondence was strongly increased once the 2 outliers were disregarded (P = .648). It is likely that the times spent in intensive care would be more similar if the investigation had a larger sample.

Advagraf has the important advantage of having to be administered only once a day, versus twice per day for Prograf administration. Patient noncompliance is a serious problem when trying to establish immunosuppression. Nonadherence to the immunosuppressive regimen may be expected in up to 6 of 100 cases [Dew 2009]. Patient compliance can be improved by simplifying the drug regimen. Reducing medication intake to once a day can increase compliance [Fischer 1980]. High interindividual variation in compliance makes close drug monitoring necessary.

This study found that the trough levels of patients treated with Prograf were significantly higher during the first 5 days than those for patients treated with Advagraf. Trough levels became comparable following a period of adjustment. There were no differences between the groups in their 1-year mortality rates. This result suggests that Advagraf is a suitable immunosuppressant for patients who have undergone heart transplantation.

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