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Use of Everolimus in De Novo Renal Recipients: Initial Experience in the Greek Population

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ABSTRACT

Although everolimus has proven to be as clinically efficacious as mycophenolate mofetil (MMF), there are reports that proliferation signal inhibitors are associated with poor tolerability. This study reported the experience of a Greek transplant center using either everolimus or MMF in de novo renal transplant recipients. In this retrospective study, a cohort of 40 patients who received everolimus after renal transplant was matched for 10 descriptive parameters with a cohort of another 40 patients who received MMF. The primary endpoint was renal function measured by creatinine and its clearance as well as wound dehiscence and opportunistic infections. The mean creatinine clearance at month 3 was 61.03 ± 16.99 mL/min versus 60.99 ± 8.03 for living related recipients on everolimus versus MMF, respectively. The mean creatinine clearance at month 3 was 71.24 ± 12.61 and 62.61 ± 20.24 mL/min for cadaveric recipients on everolimus versus MMF, respectively. In addition, the incidence of wound dehiscence was 33.34% versus 3.92% and the incidence of cytomegalovirus infection, 8.33% versus 17.64% for the same two groups, respectively.

EVEROLIMUS HAS PROVEN TO BE as efficacious as mycophenolate mofetil (MMF) to preserve kidney graft function.[1] However, the synergistic effects of proliferation signal inhibitors and full dose of cyclosporine (CsA) have resulted in poor tolerability.[2] Randomized multicenter trials currently underway may answer questions concerning effective and safe combinations of immunosuppressive medications. This study sought to report the experience of a Greek transplant center using either everolimus or MMF in de novo kidney transplant recipients.

PATIENTS AND METHODS

This retrospective study compared the clinical efficacy and adverse reactions of everolimus versus MMF in combination with 50%

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0041-1345/08/$–see front matter
doi:10.1016/j.transproceed.2008.09.038

reduced doses of CsA, basiliximab, and corticosteroids. The study was performed in accordance with the declaration of Helsinki. Records of adult patients who underwent cadaveric or living donor kidney transplantation were studied up to their 12-month follow-up visit.

Patients

A cohort of 40 patients who received everolimus after renal transplantation was matched for 10 descriptive parameters with a cohort of another 40 patients who had received MMF. The 10 matching parameter included sex, age, body mass index, diabetes mellitus, hypertension, lipid profile (cholesterol, triglycerides), HLA matching, panel-reactive antibodies, postoperative antibiotics, and gastrointestinal prophylaxis. Everolimus (Certican, Novartis Pharma AG, Basel, Switzerland) was administered at 0.75 mg twice daily simultaneously with CsA. The minimum target everolimus trough level was set at 3 ng/mL.[3] MMF (Cell Cept, Roche, Basel, Switzerland) was administered at 1000 mg, twice daily for the first postoperative month; thereafter, the dose was reduced to 750 mg, twice daily. Adjustment of CsA dose to target levels was achieved through monitoring of CsA concentrations at 2 hours after dosing (C_2). Target C_2 was set at 800 ng/mL for weeks 0 to 8 and 400 ng/mL for week 9 to month 12 for the everolimus cohort[4] versus 1200 ng/mL for weeks 0 to 8 and 800 ng/mL for week 9 to month 12 for the MMF cohort. Corticosteroids were administered according to the department protocol. Basiliximab was given intravenously at 20 mg/dose on days 0 and 4.

Endpoints

The primary endpoint was renal function measured by serum creatinine at day 7 as well as months 1, 3, and 12, and calculated creatinine clearance at month 3.[5] Secondary endpoints included the incidence of an acute rejection episode (biopsy proven), cytomegalovirus (CMV) infection (polymerase chain reaction-proven), poor wound healing (skin dehiscence after removing the approximating clips on day 21), leukopenia (<4000/μL), thrombocytopenia (<100,000/μL), and hypertension (pretransplant mean blood pressure increased by 10%). We also recorded urinary tract wound and catheter infections as well as fever of unknown origin, atelectasis, and graft nephrectomy.

Statistics

Statistical analysis was performed using SPSS 11.0.3 (WASTE Text Engine). Continuous parameters between two data groups were compared using Student *t* test. The chi-square test was used to compare nominal parameters between the groups after checking the variances with Fisher exact test. One-way analysis of variance test was used for comparisons among more than two data groups. A *P* value <.05 was considered to be significant.

RESULTS

Baseline demographics and background characteristics (10 matching parameters) were not significantly different between the two cohort groups by the design of the study. Mean everolimus trough levels on day 7 were 3.38 ng/mL versus 4.23 ng/mL for cadaveric versus living related subgroups.

In the living related kidney transplantation group, the mean serum creatinine value as day 7 was 1.28 ± 0.29 mg/dL versus 1.62 ± 0.61 mg/dL for patients receiving everolimus versus MMF, respectively (*P* = .075). The mean serum creatinine values at month 1 were 1.14 ± 0.3 mg/dL versus 1.28 ± 0.28 mg/dL for the patients receiving everolimus versus MMF, respectively (*P* = .434). The mean serum creatinine values at month 3 were 1.35 ± 0.43 mg/dL versus 1.36 ± 0.24 mg/dL for the patients receiving everolimus versus MMF, respectively (*P* = .995). Finally, the mean serum creatinine values at month 12 were 1.46 ± .28 mg/dL versus 1.42 ± .3 mg/dL for the patients receiving everolimus versus MMF, respectively (*P* = .863). The mean calculated creatinine clearances at month 3 were 61.03 ± 16.99 mL/min for the patients receiving everolimus versus 60.99 ± 8.03 for those receiving MMF (*P* = .9). In the cadaveric kidney transplantation group (Fig 1), the mean serum creatinine values at day 7 was 3.09 ± 4.47 mg/dL versus 3.27 ± 2.61 mg/dL for the patients receiving everolimus versus MMF (*P* = .872). The mean serum creatinine value at month 1 was 2.41 ± 2.76 mg/dL versus 1.08 ± 0.30 mg/dL for patients receiving everolimus versus MMF, respectively (*P* = .006). The mean serum creatinine values at month 3 were 1.16 ± .33 mg/dL versus 1.32 ± .46 mg/dL for patients receiving everolimus versus MMF, respectively (*P* = .404). Finally, the mean serum creatinine values at month 12 were 1.47 ± 0.01 mg/dL versus 1.32 ± 0.36 mg/dL for patients receiving everolimus versus MMF, respectively (*P* = .584). The mean calculated creatinine clearances at month 3 were 71.24 ± 12.61 mL/min for the patients receiving everolimus versus 62.61 ± 20.24 for those receiving MMF (*P* = .400). The incidence of rejection was 12.5% versus 23.53% in the everolimus versus MMF cohorts, respectively (*P* = .259). Most rejection episodes in the MMF group occurred at more than 6 months posttransplant.

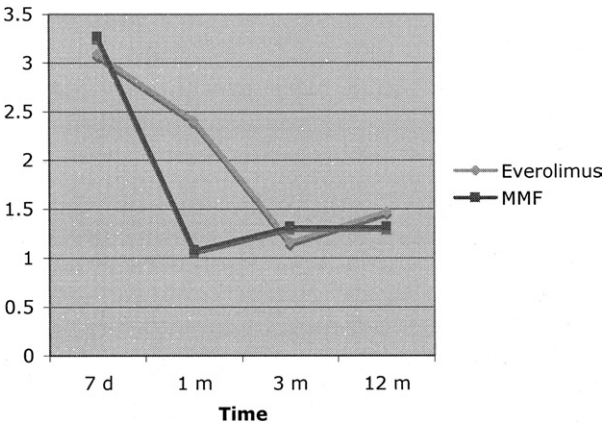

Fig 1. The creatinine value at month 1 was significantly higher (*P* = .006) in the everolimus cohort for cadaveric transplants. MMF, mycophenolate mofetil.

Morbidity within the first month was 41.67% among the everolimus versus 15.69% in the MMF cohort (Fig 2A).The incidence of poor wound healing was 33.34% versus 3.92%, significant difference. Other causes of early morbidity were atelectasis, wound infection, and catheter infection.

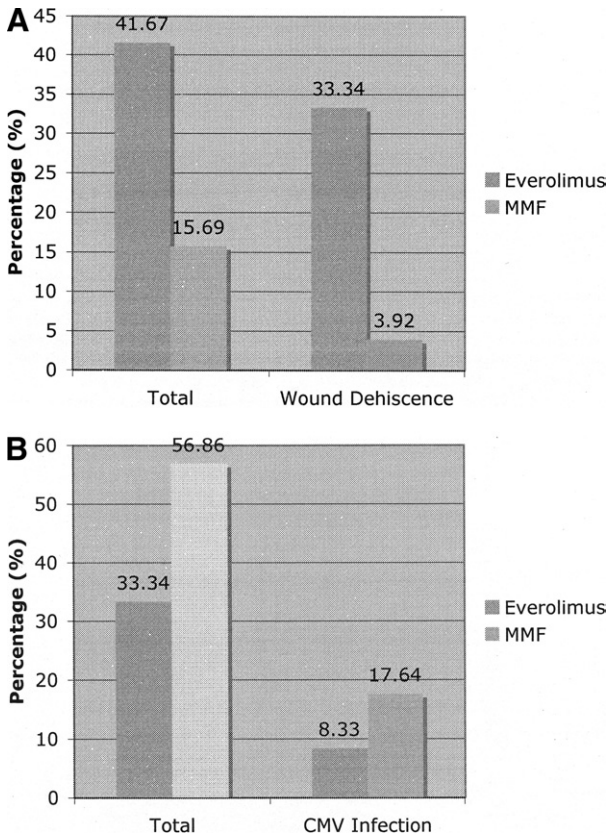

Fig 2. **(A)** The high early morbidity observed in the everolimus cohort is mainly due to the high incidence of wound dehiscence (8/24 patients). **(B)** The high late morbidity observed in the mycophenolate mofetil (MMF) cohort is due to the high incidence of infectious complications, mainly cytomegalovirus (CMV) infection and urinary tract infection (not shown).

Morbidity beyond month 1 occurred among 33.34% in the everolimus versus 56.86% in the MMF cohort (Fig 2B). The incidence of CMV infection was 8.33% versus 17.64% for the two groups, respectively ($P = .029$). The incidence of urinary tract infection was 12.5% versus 17.64% for the two cohorts ($P = .050$). Other causes of late morbidity were fever of unknown origin and graft nephrectomies (one for each group).

In the living related kidney transplantation group, the mean serum cholesterol levels at month 3 were 254 ± 79 mg/dL versus 146 ± 81 mg/dL for patients receiving everolimus versus MMF, respectively ($P = .050$). In the cadaveric kidney transplantation group, the mean serum cholesterol levels at month 3 were 309 ± 42 mg/dL versus 217 ± 91 mg/dL for patients receiving everolimus versus MMF, respectively ($P = .015$). In the living related kidney transplantation group, the mean serum triglyceride levels at month 3 were 276 ± 54 mg/dL versus 230 ± 50 mg/dL for the patients receiving everolimus versus MMF, respectively ($P = .051$). Moreover, in the cadaveric kidney transplantation group, the mean serum triglyceride levels at month 3 were 286 ± 77 mg/dL versus 261 ± 100 mg/dL for patients receiving everolimus versus MMF, respectively ($P = .545$).

DISCUSSION

The current regimen of everolimus with 50% reduced exposure to CsA may be associated with better preservation of renal function compared with high-exposure treatment. Everolimus seems to be as efficacious as MMF in preserving kidney graft function.[1,6] It is evident from the serum creatinine values and the creatinine clearance calculations that the present study yielded similar results. One exception was observed in the cadaveric kidney transplantation group, where creatinine levels at month 1 remained elevated (more than doubled) among patients receiving everolimus compared to those receiving MMF. This finding was not observed at months 3 or 12. Perhaps, the acute tubular necrosis (ATN) that usually ensues after cadaveric grafts did not resolve in the usual manner, due to the antiproliferative effects of everolimus.[6] However, healing was "catching up," ATN resolving and creatinine values normalizing after month 1.

Despite the absence of statistical significance (most likely due to a type II error), there was a clear trend in the incidence of acute rejection episodes in favor of the everolimus group. Although this is in concert with other reports,[7] it may also be explained by physicians' fear for the evolution of the polymerase chain reaction–proven CMV infections with subsequent lowering of the immunosuppression. Actually, for the MMF cohort, rejection episodes followed CMV infections with a concomitant decrease in immunosuppression within 1 month in more than 70% of cases. Most rejection episodes were corticosteroid-sensitive, easily treated with no significant residual graft dysfunction, at least over the 1-year follow-up.

In the present study, CMV infection incidence was higher among patients receiving MMF, namely twofold greater than that among patients receiving everolimus, mainly because of a nonuniform policy of prophylactic gancyclovir use. While only 50% of the patients on MMF received prophylactic gancyclovir, 75% of the patients on everolimus received the prophylactic regimen.

Previous trials that studied the synergistic effect of proliferation signal inhibitors and full exposure to CsA have resulted in adverse reactions. For example, relatively high doses of sirolimus used after slightly lowering CsA doses led to an increase in wound complications among other adverse events.[2] This is in concert with the present study where a striking 33.34% incidence of wound dehiscence was observed among the everolimus cohort. Furthermore as in our study, dose-related elevations in serum lipid levels were observed more frequently in renal transplant recipients receiving everolimus versus MMF.[6]

In conclusion, this Greek population study verified that renal transplant recipients receiving everolimus showed comparable graft function to those receiving MMF, despite the former cohort displaying prolonged ATN. We need to

stress the trend for a higher incidence of acute rejection episodes in the MMF group did not apparently come from poor drug efficacy but rather inappropriate use. These observations suggest appropriate immunosuppressive strategy to be starting with MMF, CsA, and corticosteroids so as to avoid wound dehiscence and prolonged ATN. Switching to everolimus with low-dose CsA, if desired, might be performed at 1 or more months later. This therapeutic maneuver may prove beneficial because it will allow reduced CsA exposure, possibly improving long-term renal function[8] and ameliorating other well-known CsA-related, side effects.

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