ELSEVIER

Once-a-day Administration of Everolimus, Cyclosporine, and Steroid After Renal Transplantation: A Review of the Rationale

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ABSTRACT

The Evidence study (EVerolImus once-a-Day rEgimen with Neoral® versus Corticosteroid Elimination) sought to compare once-a-day administration with steroid withdrawal versus twice-daily administration among de novo kidney transplant recipients treated with everolimus, cyclosporine, and steroids. This article describes the study design and rationale of once-daily administration and steroid withdrawal among recipients of de novo kidney transplants treated with everolimus and cyclosporine.

EVEROLIMUS (EVL) is an inhibitor of the mTOR1, the downstream effector of PIk-3, in response to various stimuli thereby providing a signal for proliferation of several cells, including T lymphocytes. Compared with its parent compound sirolimus, EVL shows increased solubility in aqueous solvents and distinct pharmacokinetic (PK) characteristics.[1,2] Two pivotal phase 3 studies in de novo renal transplant recipients showed that in combination with standard cyclosporine (CsA) exposure, EVL (0.75–1.5 mg b.i.d.) was as effective as mycophenolate mofetil (MMF) to prevent acute rejections episodes. However, the association of EVL with standard CsA exposure resulted in decreased renal allograft function as compared with MMF.[3,4] This unexpected nephrotoxicity was likely due to the combination of the 2 drugs prescribed at high dosages. In animal models of autoimmune diseases and in allotransplantation experiments, EVL has been shown to act synergistically with CsA, since the latter drug inhibits the synthesis of interleukin (IL)-2, whereas EVL inhibits the response to IL-2. This synergy results in a 10-fold reduction in EVL and a 3- to 4-fold reduction in CsA doses required to achieve equivalent effects of either drug alone in animal studies.[5] The pharmacological synergy[1,2] allows reduction of the doses of both agents when administered together in clinical trials. To confirm this assumption, the relationship between EVL/CsA pharmacokinetics (C0) and clinical events has been explored.[6,7] The results of a simulated scenario based on several prospective clinical trials[8] showed that the risk of biopsy-proven acute rejection (BPAR) was inversely related to trough blood levels of EVL. The highest risk was observed when the blood levels of EVL were <3 ng/mL. When EVL trough levels were >3 ng/mL, the blood levels of CsA had little, if any, influence on the risk of BPAR. In contrast, the risk of developing graft dysfunction was strictly related to blood CsA levels while there was little influence of EVL blood levels on the risk of nephrotoxicity. Additionally, in a randomized, exploratory, controlled trial in de novo kidney transplantation, it has been shown that reduced CsA exposure in combination with EVL improved renal function in comparison with standard CsA exposure.[9] Recently 2 randomized trials combining EVL at reduced CsA exposure (A2306/A2307) showed excellent efficacy and safety.[10,11] In a study with basiliximab (Simulect) induction and reduced CsA exposure, namely, mean C2 levels of 700 ng/mL at month 1, reduced to 350–450 ng/mL by month 12, in combination with 1.5 or 3 mg/d of EVL, the BPAR rates at 12 months were 13.7% and 15.8%, respectively, and the graft loss rates were 1.7% and 5.0%, respectively. Median creatinine clearance level at 12 months was 64 mL/min in both groups.

The possibility of obtaining excellent graft survival and a low rate of BPAR by combining EVL with even lower CsA exposure was recently confirmed by an Italian multicenter randomized trial (Everest study group).[12] This group explored the relationship between EVL/CsA blood levels and BPAR in the first 3 months after transplantation, showing that a simulated increase in EVL blood levels would have resulted in a further reduction of the BPAR rate, and a decrease of EVL blood levels would have led to an in-

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creased risk of BPAR. In contrast, changes in CsA blood levels within the first 3 months after transplantation would not have affected the risk of BPAR.[13]

In addition to the possibility of reducing the CsA dose to <50%, and thereby the CsA-related toxicity, EVL-based regimens may have further advantages: (1) in randomized double blind trials, transplant recipients given EVL showed a reduced risk of cytomegalovirus (CMV) infections compared with those receiving MMF[3]; (2) EVL has been shown to be an effective anticancer agent.[14] After solid organ transplantation, patients receiving an immunosuppressive regimen containing EVL or sirolimus showed a lower risk of developing cancer compared with patients prescribed other immunosuppressive regimens[15]; (3) in a phase 3 heart transplantation trial, EVL was more efficacious than azathioprine to reduce the severity and incidence of cardiac-allograft vasculopathy, a leading cause of late graft loss and death[16]; and (4) recent investigations have demonstrated that mTOR inhibitors reduce lipid retention by increasing adipose-tissue lipase activity and decreasing lipoprotein lipase activity.[17] Moreover, these agents would protect plaque from rupture by selectively clearing macrophages without affecting vascular smooth muscle cells.[18] Thus, there is a rationale for implementing the use of EVL-based treatments in organ transplantation. However, further studies are needed to maximize the therapeutic index of this agent.

ONCE-A-DAY IMMUNOSUPPRESSIVE REGIMENS

Low adherence to prescribed regimens[19,20] is a major cause of long-term graft failure. Although psychosocial status is a factor that heavily influences adherence to prescription,[21] an important barrier to adherence is represented by the complexity of the treatment, in particular, by the number of pills to be taken every day.[22] Among the possible interventions to improve adherence to prescriptions, simplification of the regimen with a reduced number of pills per day may play an important role. At present, most if not all available immunosuppressive regimens have to be given twice a day.

Once-a-Day CsA

CsA half-life is about 11 hours and the rate of drug absorption is formulation-dependent. The old formulation of CsA (Sandimmun) was usually given once daily, even if high dosages (up to 15 mg/kg/d at transplantation) were normally used. The absorption of CsA from this formulation was slow and highly variable, especially among liver transplant recipients. The new microemulsion formulation, Sandimmun Neoral (CsA-ME) improved absorption and reduced pharmacokinetic variability with clinically relevant improvements to prevent BPAR. However, as the new formulation produced higher and earlier C_{max}, CsA-ME was given twice daily to avoid side effects linked with high blood CsA peaks levels.

Many studies, however, have continued to explore once-daily regimens with CsA-ME. Tarantino et al showed that twice-daily and once-daily regimens of CsA-ME were equally effective and safe in de novo kidney transplant recipients.[23] In a clinical-pharmacokinetic, randomized study in stable maintenance liver transplant recipients, Kovarik et al showed that conversion from twice-daily to once-daily CsA-ME was feasible and well tolerated, maintaining a good graft function with no increased risk of rejection.[24] The 24-hour CsA-ME dose could be reduced by 25%–30% to maintain the same exposure to drug (AUC_{0-24h}). Nighttime CsA exposure was reduced, and the nighttime mean arterial blood pressure also decreased among a large proportion of patients receiving CsA once-a-day (67%–73%) versus b.i.d. (43%). This finding may be relevant, as it has previously been shown that the absence of a decrease in blood pressure during the nighttime is a strong predictor of cardiovascular morbidity and mortality after renal transplantation.[25] Thus, in addition to improved adherence to immunosuppressive therapy and reduced daily doses, once-daily administration of CsA-ME in maintenance renal transplant recipients may reduce long-term cardiovascular risk.

Once-a-Day EVL

Although the elimination half-life of EVL is 28 hours, which is appropriate for once-daily administration, the drug was developed in a twice-daily regimen in combination with CsA-ME, mainly because of the EVL-CsA pharmacokinetic interactions.[6] Pharmacokinetics of twice-a-day EVL in combination with CsA-ME were measured in kidney transplant recipients treated with 0.9–1.4 mg of EVL b.i.d.[26] Depending on the time since transplantation, the exposure to CsA varied largely from C2 values >1000 ng/mL to <500 ng/mL. The AUC of EVL was strictly proportionate to the dose, with a 12-hour AUC ranging from 83–100 ng*h/mL per milligram of EVL administered.

The pharmacokinetics of once-a-day EVL were documented by Kahan et al.[27] Stable renal transplant recipients treated with CsA-ME b.i.d. were also given EVL (0.75, 2.5, and 7.5 mg/d) once a day for 28 days. At steady state, the 24-hour AUC, C0, and C_{max} increased proportionate to the administered dose. The AUC_{0-24h} adjusted for the EVL dose was 84 at 2.5 mg/d, and varied between 62 and 90 ng*h/mL at the extremes of the dose range. After administration of 2.5 mg EVL, the C0 was 4.4 ng/mL. The relationship between C0 and AUC after once-daily administration was excellent, confirming that C0 blood levels are useful predictors of EVL exposure even with once-daily administration.

A comparison of pharmacokinetic data after once versus twice-daily EVL administration in kidney transplant recipients treated with CsA-ME indicated that the exposure to EVL over the 24 hours appeared to be proportionate to the EVL daily dose, independent from the administration schedule (Table 1). Furthermore, the EVL trough blood levels (C0) were dose-proportional for both once- and twice-daily administration. Last but not least, the dose-adjusted AUC was proportionate to the dose, independent

Table 1. EVL PK in Renal Transplant Recipients Receiving CsA-ME

EVL mg Twice a Day	Time After Transplantation	CsA C2 ng/mL (Estimated)	EVL AUC (0–12) ng*h/mL	EVL Ratio AUC/mg	EVL C0 ng/mL
0.9	Wk 2	1100	84.00	93.33	3.9
1	Mo 2	900	87.00	87.00	4.3
1	Mo 3	680	82.00	82.00	4
0.9	Mo 6	590	84.00	93.33	4.3
1.4	Wk 2	1150	124.00	88.57	5.9
1.3	Mo 2	850	130.00	100.00	6.6
1.4	Mo 3	750	135.00	96.43	6.6
1.4	Mo 6	580	130.00	92.86	6.4

Modified from Kovarik JM et al.[26]
Note: EVL was administered twice a day.

of CsA blood concentrations as shown by the similar values obtained in patients tested at various times after transplantation.

Once-a-Day Steroid

The endogenous cortisol blood concentration peaks around 8 AM with a nadir around 12 PM. Therefore, a glucocorticoid given in a single morning dose produces only slight adrenal suppression; in contrast, the same glucocorticoid dose given at midnight will nearly completely suppress the adrenal glands for about 24 hours.[28] For this reason a single morning dose between 7 and 9 AM is strongly recommended for chronic steroid administration.

STEROID WITHDRAWAL

Steroids are routinely used to reduce the risk of early and late renal transplant rejections. However, steroids have frequent side effects that can impair the quality of life of transplant recipients and also exert life-threatening complications. In addition to the long list of side effects that are usually dose- and time-dependent, glucocorticoids can induce or impair known risk factors for cardiovascular diseases, the main cause of death in renal transplant recipients: hypertension, glucose intolerance, hyperlipemia, obesity, hyperuricemia, and so on.[29–31] In a large retrospective study, only 47% of surviving patients at 15 years after transplantation had not experienced cardiovascular events, the risk of such complications being 5-fold less frequent among patients who had withdrawn steroids.[31] Other studies reporting, long-term follow-ups have shown significantly lower risks of death or cardiovascular complications among patients who had withdrawn glucocorticoids.[32,33] There is, therefore, a rationale for eliminating the use of steroids in renal transplantation. Recently, there has been a significant increase in the use of steroid avoidance regimens as the initial treatment for kidney transplant recipients. These studies are often small with usually short follow-up. Apparently, the results seem to be influenced by the clinical and immunological characteristics of the recipients as well as by the medications. To the best of our knowledge, only 1 randomized controlled trial evaluated the possibility of avoiding steroids in renal transplant recipients treated with EVL and CsA.[34] The results were encouraging, with 95% of patients assigned to stop steroids at 1 week after transplantation still being alive with kidneys functioning after 3 years; however, the risk of BPAR during the study increased from 18%–32%. Older and more recent meta-analyses of randomized trials[35–37] clearly indicated that the risk of BPAR was significantly higher among patients assigned to eliminate than those who continued steroids. However, this increased risk did not affect patient or graft survivals, which were similar among patients with or without steroid withdrawal.

THE EVIDENCE STUDY: RATIONALE FOR THE STUDY DESIGN AND CONCLUSIONS

In the Evidence study, the following immunosuppressive regimens are compared among recipients of kidney transplantation: (1) EVL, CsA, and steroids once-daily; (2) EVL, and CsA twice-daily with steroid withdrawal; and (3) EVL and CsA twice-daily and continuous steroids. The once-daily immunosuppressive regimen is started when the patient is stabilized, that is, at 3 months after transplantation. In fact, the drug dosages in the immediate posttransplantation setting are higher, therefore, administration as a single morning dose may lead to increased adverse events. As a more reasonable approach, we decided to switch to a once-daily regimen when the drug dosages were lower and stable.

The advantages versus disadvantages of early steroid avoidance versus steroid withdrawal have been debated; although early steroid avoidance may enhance benefits, it also carries an increased risk of BPAR. Furthermore, allowing more flexibility in the management of immunosuppressive drugs, the initial use of steroids may be of benefit in elderly patients and in recipients of a kidney from an extended criteria deceased donor. In the Evidence study, steroids will be gradually withdrawn starting at 3 months after transplantation, when kidney function is established and the patient is stable.

The available data on EVL support a 1:1 switch from twice-daily to once-daily; in other words, the total daily dose given in the 2 daily administrations should be given in the morning. According to Kahan et al,[27] the C0 after once-daily EVL administration should be 30% lower to maintain the same AUC_{0-24h}. For example, for a range 8–12 ng/mL when given twice-daily, the range after once-daily administration should be 5–8 ng/mL.

According to the available PK data, the conversion of CsA-ME from twice-daily to once-daily should be performed 1:1, followed by a 25%–30% reduction of the total daily dose of CsA-ME. The once-daily administration will result in C2 levels about 30%–50% higher than those observed after twice-daily administration. If monitored using blood C2 levels, the targeted range selected for b.i.d. administration (eg, 250–400 ng/mL) should be increased by 50%–69% (400–600 ng/mL).

It appears, therefore, worthwhile to evaluate feasibility, efficacy, and tolerability of the following: (1) a once-daily triple regimen, and (2) a steroid-withdrawal regimen, both based on the EVL/CsA-ME combination in a clinical confirmatory study in kidney transplant recipients. In fact the possibility to explore once-daily and steroid-withdrawal regimens in the same study, by making use of the same control arm, is attractive as it may answer 2 relevant clinical questions in a relatively short time-span. The primary endpoint of the study should be to demonstrate noninferiority of the 2 experimental arms (steroid withdrawal arm and once-daily arm) compared with the standard b.i.d. regimen using the main endpoint of treatment failure rate—the composite of death, graft loss, and BPAR.

There has been much debate about the use of noninferiority studies. According to Garattini et al[38] "non-inferiority trials are unethical because they disregard patients' interests" and should therefore be avoided. These authors argue that these studies might allow approval for drugs that are not as efficacious as the standard of care, in the end even leading to approval of drugs that are not different from the placebo. The same opinion was mentioned in an official document of the "Consulta" of the Italian Ministry of Health.[39] They argue that "non-inferiority studies are not justified because they do not offer any advantage to the present or future patients." The European Medicine Agency (EMEA) also express the same concerns for confirmatory registration trials, but, in the document "Determination of the non-inferiority limit,"[40] they define the areas "where a non-inferiority trial might be performed as opposed to, or in addition to, a superiority trial." These cases include studies where "the use of a placebo arm is not possible and an active control trial is used to demonstrate the efficacy," or where "products with a potential safety advantage over the standard might require an efficacy comparison to the standard to allow a risk-benefit assessment to be made," or, most importantly, "cases where no important loss of efficacy compared to the active comparator would be acceptable." In this document, the EMEA proposes guidelines on how to compute the noninferiority margin in a clinical trial to minimize the risk of approval of new drugs with lower efficacy than the standard.

The Evidence study fulfills the situations mentioned above. For this reason we believe that a noninferiority trial is not only feasible, but mostly recommended. In fact, only an adequately sized noninferiority trial will allow strict control of the efficacy of the "experimental" in comparison with the control regimens.

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