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Original Article

Replacement of calcineurin inhibitors with everolimus: Long-term impact in renal transplant recipients – A single center study

Kesiraju Sailaja [a,*], *Uma Maheswar Rao Chikkam* [b], *Purna Paritala* [b], *Shreedhar Reddy* [b], *V.S. Reddy* [b], *S. Sahariah* [b]

[a] *Transimmun – Transplantation Immunology & Research Centre, Somajiguda, Hyderabad 500082, AP, India*
[b] *Department of Nephrology and Transplantation, Krishna Institute of Medical Sciences, Hyderabad 500003, AP, India*

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ABSTRACT

Background: Calcineurin inhibitor withdrawal with introduction of mammalian target of rapamycin inhibitors is associated with improvement in the renal function. The aim of the study was to evaluate the long-term allograft function after a complete switch over to everolimus from CNI at different time points.

Methods: Single center prospective, observational, follow-up study, in which 136 renal transplant patients received everolimus or continued CNI based therapy in de novo (day zero of transplantation), switch early (<6 months) and late (>6 months) groups. Patients were followed for 108 months.

Results: 88 patients completed the 108-month study. At month 108, the mean mGFR was 33.94 (95% CI 42.67–57.25) ml/mt/1.73 m^2 in de novo group, 49.19 (95% CI 55.29–64.99) ml/mt/1.73 m^2 in early switch over, 25.95 (95% CI 34.34–7.38) ml/mt/1.73 m^2 in late switch over and 34.54 (95% CI 41.57–54.06) ml/mt/1.73 m^2 in CNI group. Patient and graft survival were comparable among groups ($p = 0.698$). There were 5 (13.1%) deaths in the de novo, 3 (10.3%) in early switch, 5 (21.7%) in late switch, and 6 (13%) in CNI group. Biopsy proven acute rejection rates were comparable among the groups: 28.9%, 20.7%, 26.7%, and 19.5% in de novo, early, late and CNI groups respectively ($p = 0.057$).

Conclusion: Improvement in the renal function was observed in early switchover. Furthermore, patients with good renal function may benefit from conversion even at a late stage, and in patients with suboptimal renal function everolimus may not add any further benefit.

* *Corresponding author.*
E-mail address: kesirajusailaja@gmail.com (K. Sailaja).

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1. Introduction

Since three decades calcineurin inhibitors (CNI) have been playing a significant role in organ transplant immunosuppression. CNIs are associated with nephrotoxicity as well as one of the factors in developing chronic allograft nephropathy (CAN), which can cause a negative impact, on long-term outcome.[1,2] It has been reported that nearly 90% of patients suffered from CAN and nephrotoxicity after 10 years post transplantation possibly due to calcineurin inhibitors.[3] To avoid the CNI related complications, new immunosuppressive agents as well as innovative strategies are being introduced, which resulted in focusing on the use of proliferation signal inhibitors (PSI)/mammalian target of rapamycin inhibitors (mTORi) like everolimus (EVL) and sirolimus (SRL). Several trials using mTORi with different doses of cyclosporine (CsA) demonstrated good efficacy without compromising renal function.[4] mTORis, when used in combination with full-dose CNI, have been shown to exacerbate CNI nephrotoxicity.[5] Trials have demonstrated the beneficial effects of CNI withdrawal for selected patients receiving mTORi in terms of improved renal function.[6,7]

Many trials reported the use of everolimus in de novo renal transplant patients with minimized CNI exposure maintains immunosuppressive efficacy.[8–10] Preemptive conversion of kidney transplant patients from CNI based to mTORi based therapy within the first 6 months post transplant has proven effective in improving renal function.[11,12] No significant renal benefit was observed in patients converted to sirolimus from CNI at 3 years in CONVERT study.[13] In ASERTAIN study, patients converted to everolimus at a mean of 5.6 years showed improved GFR, if their baseline GFR was >50.[14] Hence we hypothesized major problem after kidney transplantation is the occurrence of chronic interstitial fibrosis and tubular atrophy (IF/TA), leading graft loss. Calcinuerine inhibitor (CNI) induced nephrotoxicity is one of contributors in the development of IF/TA. By converting from CNI based regimen to everolimus the nephrotoxic side effects of CNI's will be eliminated and renal function may be preserved.

Therefore, we aimed to investigate if the conversion of CNI-based immunosuppression to everolimus-based immunosuppression results in the improvement/preservation of renal function as compared to continued CNI-based immunosuppression. Changes in the renal function, graft and patient survival following conversion to everolimus-based immunosuppression at different time points were compared. In addition to that also evaluated whether long-term improvements in patient and graft survival can be achieved by withdrawing CNI's.

2. Study design

Single center prospective, observational, follow-up study, in which 136 renal transplant patients were included to start (de novo), to switch (early, late) from CsA based regimen to Everolimus or to continue CNI based therapy. Patients were enrolled between May 2005 and April 2006. Patients were followed up at regular interval of 108 months. The study protocol was approved by the institute's ethical committee, and written informed consent was obtained from all patients and study was conducted in compliance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

3. Patients and methods

Adult renal transplant recipients aged between 18 and 65 years, receiving first transplant from a deceased or living donor were eligible for enrollment. Patients positive for human immunodeficiency virus, patients who deviated from the study drug were excluded from the study. Presence of hypersensitivity to the study drug, patients with current systemic infection and patients who are breastfeeding were also excluded from the study.

De novo: Patients who received everolimus on day 0 of kidney transplantation. Thirty-eight patients (males 27 and females 11), in the age group of 21–49 years with mean age of 36.8 years were included in the study who were administered low-dose cyclosporine with everolimus. CsA was withdrawn in a step-wise manner over ≤4 weeks, with an everolimus target trough concentration of 6–10 ng/ml following CsA discontinuation. 10 out of 38 patients, who had received deceased donor transplantation, were administered two doses of 50 mg daclizumab (Zenapex, Roche Pharma) on day 0 and on day 14 post operatively as induction therapy.

Early switchover: Patients who were converted to everolimus regimen from CNI within first six months post transplant. Twenty-nine renal transplant recipients with a mean age of 37.5 yrs 20 male and 9 females were included in the study. All the patients were switched over to EVL within first six months after transplantation. Of the twenty-nine patients, 16 were treated with tacrolimus (TAC) and 13 with cyclosporine. Three received two doses basiliximab (Simulect, Novatis) induction 20 mg, intravenously, on day 0 (2 h before transplantation), and on day 4. Immunosuppression before switch over comprises of either tacrolimus or cyclosporine, with MMF and steroids administered according to local practice. On the day of conversion 1.5 mg/day of everolimus was administered and CsA/TAC was reduced by 50%. CNI was totally withdrawn within a period of ≤4 weeks.

Late switchover: Patients who were converted to everolimus from CNI regimen after six months post kidney transplant. Twenty-three renal transplant recipients with a mean age of 39.4 (17 men and 6 women) were included in the study and the mean time of conversion after transplantation was 49.8 ± 29.4 months. Conversion to everolimus based regimen in this group was due to creeping serum creatinine levels. All the patients, except one, were on CsA, MMF and prednisolone, and one patient was on azathioprine and prednisolone immunosuppression prior to the switch over. On the day of conversion 1.5 mg/day of everolimus was administered, and CsA was reduced by 50%. Cyclosporine was further reduced to 50%. CsA was totally withdrawn within a period of ≤4 weeks.

CNI based group: Patients who did not receive EVL and continued CNI based therapy. Forty six renal transplant recipients 33 male, 13 females with mean age of 38.2 were included. Nineteen patients were on CsA and twenty-seven were on TAC.