REVIEW

Critical appraisal on the use of everolimus in renal transplantation as an immunosuppressant to prevent organ transplant rejection

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Abstract: Everolimus is a proliferation inhibitor designed to target chronic allograft nephropathy including prevention of acute rejection. Acute renal allograft rejection incidence varies with the therapy used for immunosuppression. Registry data show that 15% to 35% of kidney recipients will undergo treatment for at least one episode of acute rejection within the first post-transplant year. Everolimus has been used as therapy with full- or reduced-dose cyclosporine A without evidence of increasing the acute rejection incidence. This review will summarize the available clinical trial data on the use of everolimus and its role in preventing acute rejection incidence in renal transplantation.

Keywords: calcineurin inhibitors, cyclosporine, everolimus, biopsy-proven acute rejection, renal transplantation, acute rejection

Introduction

With annual graft survival rates of more than 90% in the first year after a renal transplantation, the current clinical challenge is to develop immunosuppressive protocols to decrease the risk of losing the graft in the long term, while keeping the current low rates of biopsy-proven acute rejection (BPAR).[1,2]

Immunosuppressive therapy has improved considerably since the introduction of azathioprine in 1961. The incidence of acute rejection has decreased notably in the last decade thanks to the emergence of new immunosuppressive drugs like proliferation signal inhibitors (PSI).

The introduction of cyclosporine in the 1980s as part of immunosuppressive maintenance therapy in organ transplantation was a milestone in reducing the incidence of acute rejection during the first year after transplantation.[3]

Everolimus is a PSI that acts at a later stage of the cell cycle, blocking the proliferation signal provided by these growth factors and preventing cells from entering the S phase.[4] It has been evaluated in four different immunosuppressive algorithms, as replacement of a calcineurin inhibitor (CNI) or of an antimetabolite, in combination with a CNI either in low or high dose and with variable doses of CNI.

Most of surrogate endpoints of graft survival usually favor the use of mTOR (low rejection risk and good renal function).[5,6]

This review will summarize the clinical trial data for everolimus and its role in preventing acute rejection.

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Everolimus vs mycophenolate mofetil with full-dose cyclosporine A

Two randomized studies of similar design on *de novo* renal transplantation evaluated the efficacy and safety of everolimus vs mycophenolate mofetil (MMF) over a 3-year period, with a dose of everolimus of 1.5 mg/day, everolimus 3 mg/day, or MMF 2 g/day associated with a full dose of cyclosporine A (CsA) microemulsion (Neoral®) and steroids.[5,6] In both cases the primary objective was to compare the effect on incidence of failure in each treated group after 12 and 36 months. The results demonstrated that everolimus is equally effective as MMF in terms of acute rejection 3 years post transplantation.[5,6] The risk of BPAR was 3.4 times greater for patients with everolimus levels lower than 3 ng/mL compared with those with levels of 3 to 8 ng/mL ($P < 0.0001$). A meaningful difference between the treatment arms was noted in study B251, in which the incidence of antibody-treated acute rejection was significantly lower in patients taking everolimus 1.5 mg/day than patients taking MMF at 12 months (7.8% vs 16.3% $P = 0.01$) and at 36 months of follow-up (9.8% vs 18.4%, respectively; $P = 0.014$).[6]

Everolimus combined with full- or reduced-dose CsA

Data obtained from both the Vitko and Lorber studies showed that everolimus and full-dose CsA could improve renal function without increasing acute rejection incidence.[5,6] A randomized, phase II, open-label, 3-year study in 111 patients compared the efficacy and tolerability of everolimus (3 mg/day) in combination with basiliximab, steroids, and either full-dose Neoral (FDN) vs reduced-dose Neoral (RDN) (CsA trough levels [C0] 125 to 250 ng/mL and 50 to 100 ng/mL, respectively).[7] Efficacy failure (BPAR, death, graft loss, or loss to follow-up) were evaluated at 6, 12, and 36 months.

BPAR incidence was less frequent in the RDN group than in the FDN group at every point of the follow-up (6 months: 3.4% vs 15.1%; 12 months, 6.9% vs 17%; and 36 months, 12.1% vs 18.9%, respectively). BPAR episodes were mild or moderate. This study therefore demonstrated the utility of the combination of everolimus and reduced-dose CsA, since it improved renal function without changing BPAR incidence.[7]

Based on these data, two multicenter, randomized controlled studies, 2306 and 2307, were designed to compare 12-month efficacy and safety of everolimus 1.5 and 3 mg/day with reduced-dose CsA guided by C2 monitoring and corticosteroids in *de novo* renal transplant recipients at 12 months.[8,9] The only difference was that the 2307 had

induction with basiliximab on days 0 and 4. When the study was limited to nonblack patients, study 2306 showed a lower incidence of acute rejection with 3 mg/day (16.4%) compared with 1.5 mg/day (25.9%) ($P = 0.08$). In study 2307, the inclusion of basiliximab lowered the overall incidence of acute rejection; 14.3% with 3 mg/day and 13.6% with 1.5 mg/day at 12 months ($P = 0.891$). The use of an inductor agent like basiliximab reduces the risk of acute rejection combined with a low dose of everolimus and a reduced dose of Neoral.[8,9]

In both studies, BPAR was more common in patients with average levels < 3 ng/mL compared to those with levels >3 ng/dL. A Cox regression model demonstrated that the risk of BPAR was affected by the exposure to everolimus, a relationship that was significant in study 2307 ($P = 0.001$).[8,9]

Everolimus with full- and reduced-dose tacrolimus

Although most of the studies with everolimus have been made in combination with cyclosporine, few data are available on the use of everolimus with tacrolimus.

Chang, in a prospective, multicenter, open-label, exploratory, randomized 6-month study in *de novo* renal transplant patients that evaluated the efficacy and safety of everolimus, steroids and basiliximab in combination with a reduced or full dose of tacrolimus, showed that BPAR incidence was 14% in each cohort (not significant).[9] All cases of BPAR were mild (Banff IA or IB). However, although this is considered to be a low incidence of acute rejection, additional studies are warranted because of the small differences in tacrolimus exposure in the two arms.[10]

Ongoing phase III–IV studies with everolimus

The use of everolimus in kidney transplantation is being studied in several phase III–IV clinical studies. The studies with BPAR as one of their outcomes are shown in Table 1. Some additional studies with partial results are described and discussed below.

EVEREST (The upper target EVErolimus RandomizEd Study)

This a phase III, 6-month randomized, multicenter, open-label study, designed to investigate whether increased everolimus exposure (uEVL) in combination with very low CsA is effective for preventing BPAR compared to standard

Table 1 Summary of clinical studies of everolimus and acute rejection

References	Design	Study length	Treatments	Patients (n)
18	Phase III, multicenter, randomized, parallel group, open-label	2 years	Everolimus 1.5 mg/day or everolimus 3 mg/day + dose reduced CsA vs EC-MPS + standard dose CsA	833 *de novo*
19	Phase IV, multicenter, randomized, open label, parallel group	1 year	Everolimus and basiliximab in combination with CsA, either discontinued after 3 month or minimized	119 *de novo*
20	Phase IV, multicenter, randomized, open-label, parallel group	1 year	Basiliximab + EC-MPS + CsA + steroids, randomized to 3 groups 1. Everolimus + steroids (CNI stopping) 2. Everolimus + CsA (steroids stopping) 3. EC-MPS + CsA + steroids (control group)	177 *de novo*
21	Phase IV, multicenter, randomized, open label-parallel group	1 year	Everolimus + basiliximab and steroids, in a maintained vs discontinued CsA regimen	51 *de novo*
22	Phase IV, multicenter, randomized, open label	1 year	basiliximab + everolimus + Tac + steroids for 3 months, further randomized to: 1. Everolimus + Tac very low dose 2. Everolimus + Tac low dose	230 *de novo*
23	Phase III, prospective, multicenter, randomized, open-label, parallel group	1 year	Everolimus in combination with low dose CNI free vs EC-MPS with standard dose CNI	450 *de novo*
24	Phase IIIb–IV, prospective, multicenter, randomized, open label, parallel group	2 years	Patients in maintenance with CNI ± EC-MPS/ AZA ± steroids , further randomized to: 1. Keep same treatment with CNI 2. Everolimus + stopping CNI 3. Everolimus + reduction CNI MPA/AZA and the steroids dose is kept in all the groups.	398 maintenance

Abbreviations: CsA, cyclosporine; CNI, calcineurin inhibitor; EC-MPS, enteric-coated mycophenolate sodium; MPA, mycophenolic acid; AZA, azathioprine; Tac, tacrolimus.

exposure (sEVL).[11] All patients received basiliximab induction and steroids and were further randomized to:

- Everolimus high dose (8 to 12 ng/mL) and very-low-dose CsA (C2 600 ng/mL reduced to 300 ng/mL at 3 months).
- Everolimus standard dose (3 to 8 ng/mL) and low-dose CsA (C2 600 ng/mL reduced to 500 ng/mL at the third month).

After 12 months, the incidence of BPAR with high levels of everolimus was 14.9% vs 15% with standard levels (not significant). In conclusion, everolimus in combination with low-dose CsA or very-low-dose CsA is effective in preventing BPAR and is well tolerated.[12]

CALLISTO

This is a 12-month, phase III, multicenter, randomized, open-label study in 139 *de novo* renal transplant patients at risk of developing delayed graft function (DGF), designed to compare immediate vs delayed everolimus treatment. All patients received basiliximab and steroids and were randomized to everolimus (1.5 mg/day) immediately post transplant from day 1 (IE) or after 4 weeks of mycophenolic acid treatment (DE) in combination with CsA.[13]

BPAR composite was one of the primary endpoints. Results at 12 months showed that BPAR was 20% in the group with immediate everolimus vs 20.3% in the group with delayed everolimus (P = 1.00). In conclusion, the time to start everolimus in patients with risk of developing DGF does not affect the incidence of BPAR.[14]

ZEUS

This study has been conducted in *de novo* renal transplant patients to investigate efficacy and safety of everolimus/ enteric-coated mycophenolate sodium (EC-MPS) regimen after CNI withdrawal.[15] After induction therapy with basiliximab, all patients were treated with CsA, EC-MPS, and corticosteroids for the first 4.5 months post transplant. Subsequently, patients were randomized 1:1 to either continue the current regimen of CsA and EC-MPS or to change from CsA to everolimus. The primary objective of this trial was to show superiority of a CNI-free regimen with respect to the renal function at 12 months post transplant as assessed by glomerular filtration rate (Nankivell method) compared with the standard CNI-based regimen. It has 300 patients.

The BPAR in the follow-up of the first 147 patients was 16.3% in the everolimus/EC-MPS group vs 12.9% in the CsA/EC-MPS group. These results show that in this group of patients the conversion from CsA to everolimus is safe.[16]

Currently, the follow-up of all patients in this study was completed at 12 months (n = 300) at which time the BPAR was 14.8% for the everolimus/EC-MPS group vs 15.2% for the CsA/EC-MPS group. This finding confirms that the introduction of everolimus/EC-MPS in *de novo* renal transplant patients alters CNI withdrawal and offers a novel therapeutic approach which significantly affects renal function without compromising efficacy and safety.[17]

Conclusions

Several clinical trials have shown the efficacy and tolerability of everolimus. The results have shown that everolimus is as effective as MMF in preventing acute rejection. Preliminary clinical trial results (EVEREST, CALLISTO, and ZEUS) indicate that the use of everolimus in combination with CNI minimization/withdrawal is safe as part of maintenance immunosuppressant therapy in renal transplant patients, and the incidence of BPAR is similar to that with other immunosuppression protocols; however, it should be noted that these results have been obtained in association with the use of an induction agent (basiliximab). Ongoing clinical studies will provide further information about the effectiveness of everolimus to prevent renal transplant rejection.

Acknowledgments

Disclosures

The authors declare no conflicts of interest.

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