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MINIREVIEWS

Introduction of everolimus in kidney transplant recipients at a late posttransplant stage

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Abstract

This minireview focuses on the current knowledge about the introduction of everolimus (EVL), a mammalian target of rapamycin inhibitor, with calcineurin inhibitor (CNI) elimination or minimization in kidney transplant recipients at a late posttransplant stage. Within, we have summarized two major clinical trials, ASCERTAIN and APOLLO, and seven other retrospective or nonrandomized studies. In the open-label multicenter ASCERTAIN study, the estimated glomerular filtration rate (eGFR) at 24 mo after conversion was not significantly different between three groups-EVL with CNI elimination, CNI minimization and continued CNI unchanged-at a mean of 5.4 years after transplantation. However, recipients with baseline creatinine clearance higher than 50 mL/min had a greater increase in measured GFR after CNI elimination. In the open-label multicenter APOLLO study, adjusted eGFR within the on-treatment population was significantly higher in the EVL continuation group than in the CNI continuation group at 12 mo after conversion at a mean of 7 years posttransplantation. Other studies on recipients without adverse events and already having satisfactory renal function showed favorable graft function by EVL late-induction with CNI elimination or reduction. These studies showed that chronic allograft nephropathy, CNI nephrotoxicity, CNI arteriolopathy, cancer and viral infection (especially cytomegalovirus infection) may be good indications for late conversion to EVL.

Key words: Kidney transplantation; Everolimus; mTOR inhibitor; Late conversion; Calcineurine inhibitor

Core tip: Current immunosuppressive protocols consisting of calcineurin inhibitors (CNIs) and mycophenolate mofetil have improved short-term graft survival. However, improvements in long-term graft survival are restricted by nephrotoxicity associated with CNI. Everolimus is an exceedingly useful immunosuppressant for kidney transplant recipients when administered in combination with low-dose CNIs or with elimination of CNIs. Here, we summarize the current knowledge about the introduction of everolimus with CNI elimination or minimization in

kidney transplant recipients at late posttransplant stage.

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INTRODUCTION

Excellent short-to medium-term graft survival has been achieved in kidney transplantation owing to the low acute rejection rate of calcineurin inhibitor (CNI), cyclosporine (CsA) and tacrolimus (Tac)-based immunosuppressive therapies[1]. Therefore, the next step is to determine how to improve long-term graft and patient survival rates. CNIs are known to induce nephrotoxicity, malignancies and cardiovascular diseases and to promote interstitial fibrosis/tubular atrophy[2-5], strongly influencing long-term graft and patient survival. Thus, efforts to reduce CNI exposure have become extremely valuable.

Everolimus (EVL) is an inhibitor of the mammalian target of rapamycin (mTOR), an evolutionarily conserved serine/threonine kinase playing an important role in the regulation of many cellular functions, which include metabolism, growth, proliferation, survival and memory[6]. EVL binds to the cytosolic FK-binding protein (FKBP)-12. The resulting complex then binds with high affinity to the FKBP12-rapamycin binding domain of mTOR, which inhibits mTOR activity, resulting in the inhibition of B cell and T cell proliferation, angiogenesis and cell metabolism[7,8]. EVL exhibits little nephrotoxicity and pleiotropic effects, such as antiproliferative[9], antineoplastic[10], antiviral[11] and antiatherosclerotic[12] properties. Therefore, it can be speculated that EVL is an exceedingly useful immunosuppressant for kidney transplant recipients in combination with low-dose or elimination of CNIs.

In the *de novo* use of EVL with low-dose CsA study (A2309) - a 24-mo randomized controlled study that compared EVL plus low-dose CsA against mycophenolate mofetil (MMF) plus standard-dose CsA in 833 kidney transplant recipients - the two treatment groups showed comparable graft function[13]. Meta-analysis of the CNI-sparing regimen in kidney transplantation showed an increase in graft failure rate associated with the combined use of mTOR inhibitors (mTORi) and mycophenolate, although improved graft function was noted among those surviving with functioning grafts[14].

In the early conversion of CNI to EVL study (ZEUS[15]), kidney transplant recipients were randomized at 4.5 mo for either conversion to EVL or continuance of CsA, and a higher estimated glomerular filtration rate (eGFR) was observed in the EVL group at year 3. However, the biopsy-proven acute rejection (BPAR) rate was 13.0% in the recipients who converted to EVL and 4.8% in the recipients who continued CsA (P = 0.015), although a statistically significant difference was not associated with long-term graft loss. In addition, the discontinuation rate of the EVL group was high (28.4%).

In a recent open-label, 24-mo study (the ELEVATE trial[16]), 715 kidney transplant recipients were randomized for either conversion to EVL or continuance of CNI at 10-14 wk after kidney transplantation. As a result, eGFR was comparable between the two groups, but the BPAR and discontinuation rates were higher in the EVL group (9.7% *vs* 4.8%, P = 0.014). Subsequently, some studies have been undertaken to explore the benefits of delayed introduction of EVL following initial CNI therapy in kidney transplantation (Tables 1 and 2). Possible pros and cons of late conversion to EVL with CNI elimination or minimization are shown in Table 3.

The aim of this minireview was to summarize the current knowledge on the introduction of EVL in kidney transplant recipients at a late posttransplant stage.

GRAFT FUNCTION

Only two major clinical trials are available for the introduction of EVL in kidney transplant recipients at a late posttransplant stage, namely the ASCERTAIN[17] and APOLLO[18] trials (Table 1). In the open-label multicenter ASCERTAIN study, kidney transplant recipients receiving CNI were randomized to EVL with CNI elimination (n = 127), CNI minimization (n = 144) and continuation of CNI unchanged (controls, n = 123) at a mean of 5.4 years after transplantation. The eGFR at 24 mo was not significantly different among the three groups. However, recipients with baseline creatinine clearance higher than 50 mL/min had a greater increase in measured GFR after CNI elimination.

In the open-label multicenter APOLLO study, kidney transplant recipients were randomized to EVL with CNI elimination (n = 46) or for remaining on standard CNI-based immunosuppression (controls; n = 47) at a mean of 7 years after transplantation. Within the on-treatment population, adjusted eGFR was significantly higher in the EVL continuation group than in the CNI continuation group at 12 mo after conversion. In addition, the 5-year follow-up results showed that eGFR in the EVL continuation group was significantly higher, by 11 mL/min·1.73 m^2 (P = 0.031), in recipients who remained on their randomized study regimen until 60 mo[19].

Other studies[20-26] have shown that favorable graft function was sustained by EVL late-induction with CNI elimination or reduction (Table 2). Our previous study[24] demonstrated that eGFR was significantly improved in stable kidney transplant recipients already having favorable renal function, after remaining on EVL treatment for 12 mo after conversion. As a histological assessment, Chow *et al*[22] demonstrated that EVL rescue therapy and CNI inhibitor minimization strategy slowed down the disease progression by reducing the tubular atrophy and interstitial fibrosis score in renal transplant recipients with biopsy-confirmed chronic

Table 1 Summary of late everolimus conversion clinical trials

Ref.	No. of subjects/ follow-up	EVL treatment	Groups	Outcomes
ASCERTAIN[17] (2011)	394/2 yr	Conversion to EVL with CNI elimination or minimization at mean of 5.6 yr	Gp 1: CNI elimination (EVL C0, 8-12 ng/mL), *n* = 127 Gp 2: CNI minimization (EVL C0, 3-8 ng/mL and CNI reduced to 80%-90% below baseline), *n* = 144 Gp 3: control (CsA C2, > 400 ng/mL; Tac C0, > 4 ng/mL), *n* = 123	Graft survival: 96.9%, 94.6%, 95.1% (*P* = NS) Patient survival: 97.6%, 97.1%, 100% (*P* = NS) Comparable eGFR in 3 groups; recipients with baseline CrCl > 50 mL/min had greater increase in measured GFR after CNI elimination Adverse events resulted in discontinuation: 28.3%, 16.7%, 4.1% (Gp 1 *vs* GP 3, *P* < 0.001; Gp 2 *vs* Gp 3, *P* = 0.020)
APOLLO[18] (2015)	93/1 yr	Conversion from CNI to EVL at mean of 7 yr	Gp 1: CNI elimination (EVL C0, 6-10 ng/mL), *n* = 46 Gp 2: control (CsA C0, 80-150 ng/mL; Tac C0, 5-10 ng/mL), *n* = 47	Graft survival: 100%, 100% Patient survival: 97.8%, 97.9% (*P* = NS) Adjusted eGFR was significantly higher in Gp 1 within on-treatment population Adverse events resulted in discontinuation: 32.6%, 10.6% (*P* < 0.01)

C0: Zero hour blood level; CNI: Calcineurin inhibitor; CrCl: Creatinine clearance; CsA: Cyclosporine; eGFR: Estimated glomerular filtration rate; EVL: Everolimus; Gp: Group; No.: Number; NS: Not significant; Tac: Tacrolimus.

Table 2 Summary of retrospective or nonrandomized studies for late everolimus conversion

Ref.	No. of subjects/ follow-up	EVL treatment	Outcomes
Morales *et al*[20] (2007)/ retrospective	8/1-16 mo	Conversion to EVL with CNI elimination or reduction at mean of 5 yr	CrCl increased by 42% in recipients with CAN (grade 1 or 2) and CNI nephrotoxicity (*P* = 0.017)
Sanchez-Fructuoso *et al*[21] (2012)/ retrospective	220/1 yr	Conversion from CNI to EVL at mean of 69.4 mo	CrCl increased in recipients with baseline CrCl ⩾ 40 mL/min and baseline proteinuria < 550 mg/d (*P* = 0.005) Median proteinuria increased from 304 mg/d to 458 mg/d (*P* < 0.001) EVL discontinuation rate was 24%
Chow *et al*[22] (2015)/ open-label, single arm	17/1 yr	Conversion to EVL with CNI minimization in recipients with CAN at mean of 4.2 yr	Mean slope of eGFR was - 4.31 mL/min/1.73 m^2 per yr before conversion, as compared with 1.29 mL/min/1.73 m^2 per yr at 12 mo after conversion (*P* = 0.036) Renal biopsy showed significant decrease of tubular atrophy (15.7% *vs* 7.1%, *P* = 0.005) and interstitial fibrosis (14.8% *vs* 7.2%, *P* = 0.013)
Miura *et al*[23] (2015)/ retrospective	13/1 yr	Conversion to EVL with Tac reduction in recipients with CNIA at mean of 43 mo	aah scores improved in 5 recipients (38%); No improvement was observed in recipients with aah3; No deterioration was observed. eGFR improved from 44.3 mL/min/1.73 m^2 to 49.8 mL/min/1.73 m^2 (P < 0.01).
Uchida *et al*[24] (2016)/ retrospective (our report)	26/1 yr	Conversion from antimetabolites (MMF or MZ) to EVL with CNI minimization at mean of 39.5 mo	eGFR significantly increased from 50.7 mL/min/1.73 m^2 to 53.6 mL/min/1.73 m^2 in the EVL continuation group EVL discontinuation rate was 42.3%
Nojima *et al*[25] (2017)/ retrospective	56/1 yr	Conversion to EVL with CNI reduction in recipients with CNI nephrotoxicity or IF/TA at mean of 7.4 yr	eGFR increased by 7% (*P* < 0.005) EVL discontinuation rate was 11%
Nanmoku *et al*[26] (2017)/ nonrandomized	86/ 1 yr	Conversion to EVL with Tac minimization, MMF reduction and steroid withdrawal in cases of complications such as diabetes, viral infection *etc*	Conventional group (*n* = 50); EVL group (*n* = 36) Biopsy-proven acute rejection rate exhibited no significant difference between these groups (12% *vs* 17%, *P* = 0.55) Serum creatinine significantly improved in the EVL group (*P* = 0.031) EVL discontinuation rate was 13.8%

CAN: Chronic allograft nephropathy; CNI: Calcineurin inhibitor; CNIA: Calcineurin inhibitor arteriolopathy; CrCl: Creatinine clearance; eGFR: Estimated glomerular filtration rate; EVL: Everolimus; IF/TA: Interstitial fibrosis/tubular atrophy; MMF: Mycophenolate mofetil; MZ: Mizoribine; No.: Number; Tac: Tacrolimus.

allograft nephropathy. Miura *et al*[23] reported that Tac reduction with EVL addition histologically improved CNI arteriolopathy in 5 out of 9 selected recipients, whose alternate quantitative scoring for hyaline arteriolar

Table 3 Pros and cons of late conversion to everolimus with calcineurin inhibitor elimination or minimization in kidney transplant recipients

Advantage	Disadvantage
Due to EVL introduction	Due to EVL introduction
Antitumoral effect (especially on nonmelanoma skin carcinoma)	Adverse events (gastrointestinal disorders, hyperlipidemia, interstitial pneumonitis, edema, mouth ulcers, proteinuria, impaired wound healing, hematotoxicity and so on)
Antiviral effect (especially on CMV and BKV infection)	
Antiproliferative effect	
Antiatherosclerotic effect	
Due to CNI elimination or minimization	Due to CNI elimination or minimization
Favorable graft function	Risk of *de novo* DSA

BKV: BK virus; CMV: Cytomegalovirus; CNI: Calcineurin inhibitor; DSA: Donor-specific HLA antibodies; EVL: Everolimus.

thickening (aah scores) was under 3.

REJECTION

There was no significant difference in the number of BPAR episodes between the intervention group and the control group in both the ASCERTAIN and APOLLO studies. It was reported that EVL-based immunosuppression in early conversion from CNI was associated with an increased risk of developing donor-specific HLA antibodies (DSA) and antibody-mediated rejection[27]. In contrast, late conversion to CNI-free therapy with mTORi did not appear to affect the risk of *de novo* DSA[28], but there is concern about the development of DSA and antibody-mediated rejection because CNI level variability is a strong risk factor for *de novo* DSA development and death-censored graft loss[29].

ADVERSE EVENTS

Generally, mTORi administration has been associated with several adverse events, such as gastrointestinal disorders, hyperlipidemia, interstitial pneumonitis, edema, mouth ulcers, proteinuria, impaired wound healing, hematotoxicity and so on[7]. It was reported that adverse events of mTORi accounted for 20%-40% of the drop-out rate in a clinical phase Ⅲ trial[30]. In the late conversion to EVL studies, the discontinuation of EVL treatment due to adverse events occurred at about the same rate (approximately 30%). In our report[24], the discontinuation rate of EVL treatment was relatively high, at 42.3%.

The common adverse events leading to discontinuation have been aphthous stomatitis, pneumonitis, progressive renal deterioration and proteinuria. Proteinuria is a well-known prognostic factor for graft and patient survival rates in kidney transplantation[31]. Sanchez-Fructuoso *et al*[21] reported that risk factors for the development of proteinuria ⩾ 900 mg/d at 1 year after late conversion were creatinine clearance of < 60 mL/min, serum triglycerides of ⩾ 150 mg/d, no treatment with steroid, baseline proteinuria of ⩾ 550 mg/d and conversion at ⩾ 3 years after transplantation. An interaction was observed between baseline proteinuria and time to conversion, and the authors concluded that the success of EVL conversion with CNI elimination depended on not making so late conversions and not converting recipients with high baseline proteinuria. On the other hand, Nojima *et al*[25] demonstrated that late immunosuppression conversion, at > 3 years after kidney transplantation, using EVL in addition to a reduction in CNI dose safely and significantly improved graft function.

MALIGNANCIES

Kidney transplant recipients late-converted to sirolimus-based, CNI-free immunotherapy had a lower risk of malignancies at 2 years postconversion, with a high degree of heterogeneity attributed in the CONVERT trial[32]. The reduction was driven by a significant reduction in nonmelanoma skin carcinoma rate ($P < 0.001$), while the rate of all other malignancies was numerically lower, although without statistical significance ($P = 0.058$). It has been reported that switching from CNIs to sirolimus had an antitumoral effect among kidney transplant recipients with previous nonmelanoma skin carcinoma[33]. In the cases of late EVL conversion, however, the ASCERTAIN study[17] showed that the incidence rates of malignancies were 7.1%, 7.6% and 5.7%, respectively in the CNI elimination, CNI minimization and control groups at 2 years after EVL conversion.

CAUSE OF LATE CONVERSION TO EVL

Chronic allograft nephropathy, CNI nephrotoxicity and CNI arteriolopathy may be good indications for late conversion to EVL[20-23,25]. Furthermore, cancer is one of the main indications for late conversion to EVL[20,21]. As mentioned in the above section on "malignancies", there is no evidence to date for the superiority of EVL in suppressing malignancies at late conversion. However, Lim *et al*[34] published that *de novo* use of EVL with reduced exposure to CNIs may enable a reduction in malignancy burden after transplantation.

Viral infection is also an indication for late conversion to EVL. It is well known that kidney transplant recipients receiving mTORi have a lower risk of developing cytomegalovirus (CMV) infection[35]. Furthermore, cases with ganciclovir-resistant cytomegalovirus infection have been reported to be cured after switching to mTORi[36].

Kidney transplant recipients who have BK virus infection may benefit from conversion to mTORi[35]. Polanco *et al*[37] reported a recent prospective study of 15 recipients with BK virus-associated nephropathy. As a result, MMF elimination and conversion from Tac to EVL occurred in 9 recipients (60%), and 6 (67%) of the 9 recipients had improvement and 3 maintained stable renal function. In addition, BK viremia cleared in 5 (56%) of the recipients and decreased more than 95% in the remaining 4. With respect to Epstein-Barr virus infection, there is lack of evidence on whether the use of mTORi reduces the risk of infection in solid organ transplant recipients[35].

ABO-INCOMPATIBLE KIDNEY TRANSPLANTATION

Only two short-term pilot studies have been published about the introduction of EVL in ABO-incompatible kidney transplant recipients at a late posttransplant stage[38,39]. In our study, 16 stable ABO-incompatible kidney transplant recipients were switched from MMF to EVL with CNI minimization. Our results showed that conversion to EVL with CNI minimization for 3 mo did not induce acute rejection and C4d deposition in all recipients, and the mean eGFR value significantly increased at 3 mo after conversion compared to baseline[38]. In another study, 7 stable ABO-incompatible kidney transplant recipients were converted from mycophenolate acid to EVL at a late posttransplant phase because of active BK virus replication, and then compared with a reference group of 14 ABO-incompatible patients receiving standard Tac and mycophenolate acid[39]. Conversion from mycophenolate acid to EVL decreased the BK viral load in 5 patients. Thus, this study demonstrated that ABO-incompatible kidney transplant recipients with an active BK virus infection may benefit from conversion to EVL[39].

CONCLUSION

In this minireview, we summarized reports published on the introduction of EVL in kidney transplant recipients at a late posttransplant stage. Selected recipients, who can continue EVL treatment without adverse events and who already have satisfactory renal function, may profit by late conversion to EVL with CNI elimination or minimization. In addition, chronic allograft nephropathy, CNI nephrotoxicity, CNI arteriolopathy, cancer and viral infection (especially cytomegalovirus infection) may be good indications for late conversion to EVL.

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