Early Conversion from a Calcineurin Inhibitor-Based Regimen to Everolimus-Based Immunosuppression after Kidney Transplantation

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Abstract

Although advances in immunosuppression and clinical management have greatly reduced acute rejections and improved short-term graft survival, long-term survival has hardly improved over the last decades. The reasons for these failures are multifactorial, but chronic allograft damage with interstitial fibrosis and tubular atrophy seems to be an obligate finding in late graft biopsies. Calcineurin inhibitors are thought to be part of this problem. Several strategies have been tried to minimize the toxic effects of calcineurin inhibitor immunosuppressive regimens on graft function and histology. Mammalian target of rapamycin inhibitors exert no adverse hemodynamic effect and are not associated with fibrosis. Trials to convert from calcineurin inhibitors to mammalian target of rapamycin a long time after transplantation have shown mixed results. Early pre-emptive conversion to everolimus soon after transplantation seems an intriguing opportunity for improving renal graft function. (Trends in Transplant. 2012;6:28-33)

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Key words

Renal transplantation. Everolimus. Conversion. Calcineurin inhibitor.

Introduction

The preferred immunosuppressive regime over the last decades has been calcineurin inhibitor (CNI) regimens with a proliferative inhibitor with and without corticosteroids. These regimens have resulted in impressive reductions in rejection rates and excellent short-term results.

The caveat is that long-term graft survival for first diseased donor transplants has been stagnant for the last two to three decades. Part of this disappointing trend might be related to increased use of extended donor criteria, although this is not sufficient to explain the lack of improvement in long-term outcome.

The introduction of CNI, first cyclosporine in the late 1970s and later tacrolimus was marred initially by toxic dosing, resulting in a wide variety of side effects. The CNI use also lead to histological damage to the renal graft, characterized by interstitial fibrosis and tubular atrophy. With more moderate dosing of cyclosporine and tacrolimus, these adverse effects of CNI are less pronounced although still present.

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There is a renewed discussion of how toxic CNI are to the transplanted graft, and there are claims that there are no pathogenetic changes attributable specifically to CNI use[1,2]. However, the consequence of CNI dosing is repetitive hemodynamic damage by reduced renal blood flow and glomerular filtration rate (GFR) at peak concentration, and is associated with development of fibrosis and tubular atrophy in the long term[3,4]. The challenge over the last decade has been to restrict the damaging effects of CNI by minimizing or discontinuing their use and replacing CNI with alternative drugs[5].

Mammalian target of rapamycin (mTOR) inhibitors exert no adverse hemodynamic effects and are not associated with fibrosis. As a consequence, multiple trials have been designed with mTOR as a mean to avoid the nephrotoxicity of CNI. Mainly, the trial designs have had three principle different approaches: use of mTOR *de novo* without CNI, use of mTOR *de novo* with reduced dose of CNI, and probably the most successful so far, conversion trials at some time point after transplantation, preferably early after transplantation with discontinuation of CNI.

The mechanism of action and pharmacokinetics of mTOR everolimus and sirolimus is distinctive and different from other immunosuppressive drugs; a detailed description of these characteristics is beyond the scope of this review (as reviewed[6]).

The everolimus program has had a long list of trials for regulatory purposes, and an impressive ongoing program; this has recently been comprehensively reviewed[7].

Strategies for early elimination of calcineurin inhibitors in renal transplant recipients

The initial trials with CNI avoidance in *de novo* patients were hampered by an excessively high rejection rate, even in low-risk patients[8,9],

and more recently the CNI avoidance arm in the ORION trial (patients using sirolimus, CellCept [mycophenolate mofetil, MMF], and prednisolone) was premature terminated also due to a high rejection rate[10].

For the first months after transplantation, even under an umbrella of induction therapy, CNI seem to be a necessary part of immunosuppressive regimens. Given the potential toxic effects of CNI in maintenance therapy, trials of conversion to everolimus have been performed. There is, though, an uncertainty as to which time point after transplantation to convert from CNI-based to everolimus-based therapy.

In the CENTRAL pilot trial, the conversion was performed overnight at week 7 from a CNI- to an everolimus-based regime while maintaining mycophenolate acid (MPA) and corticosteroids[11]. There was a low rate of rejection episodes after the switch, which was easily resolved by corticosteroids. The rate of rejection observed in this cohort during the first three months after transplantation is similar to the anticipated rejection rate at our centre. The pilot trial showed a significant improvement in renal function at month 6. Estimated GFR increased from 51 to 57 ml/min (p = 0.001). There was an increase in proteinuria from the time point of conversion up to three months, but protein excretion subsequently remained stable. No nephrotic range proteinuria was observed. In general, the medication was well tolerated. Another finding was that the trial provided evidence that stepwise and protracted conversion to everolimus from a CNI regimen may be unnecessary as overnight conversion was easily managed. Based on this pilot trial, the large multicentre CENTRAL trial was performed.

The CENTRAL trial was a one-year, prospective, randomized, controlled, parallel-group trial to evaluate the conversion from a CNI-based regimen to everolimus in *de novo* renal transplant recipients[12]. After kidney transplantation and basiliximab induction, all patients were treated with cyclosporin A (CsA), MPA, and steroids for

seven weeks. Eligible patients were then randomized to continue the same regimen (n = 100) or to be converted to everolimus (n = 102). The primary endpoint GFR at one year was significantly improved by 5.7 ml/min in the intent-to-treat analysis. In the per protocol analysis, the difference was 9.3 ml/min in favor of the patients randomized to the everolimus arm. There were no differences in graft or patient survival. Mean blood pressure at randomization was 138/83 and 138/81 mmHg in the everolimus and control arms, respectively. This decreased to 133/78 mmHg in the everolimus arm at month 12, but remained unchanged in the control arm at 138/81 mmHg. The reduction in blood pressure to month 12 was statistically significant (p = 0.030) for patients in the everolimus arm. An increase in proteinuria is frequently reported in conversion trials from CNI to mTOR. In the CENTRAL trial there was no increase in protein excretion following conversion to everolimus in the one-year follow-up[12].

The 12-month incidence of biopsy-proven acute rejection (BPAR) was 27.5% (n = 28) with everolimus and 11.0% (n = 11) in controls (p = 0.004). These rejection episodes occurred during the first three months following conversion; after that time no additional rejection episodes occurred. All but two episodes of BPAR in each group were mild. The increased incidence of BPAR in the everolimus group was accounted for by a higher rate of Banff grade I rejections. Indeed, there were a lower proportion of grade II rejections in the everolimus arm (14%) versus the controls (54%). Discontinuation due to adverse events was more frequent with everolimus (25.5%) than controls (3.0%) (p = 0.030). In a previous conversion study the same trend for reporting early adverse events with mTOR was noted, whereas late in the trial the adverse event reporting was more frequent in the CNI arm[13]. In a more detailed analysis it was apparent that indications for biopsies were more frequent in the everolimus arm versus the CNI arm. At one centre, 26 indication biopsies were performed in 12 patients in the Certican® (everolimus) arm compared to five biopsies (five patients) in the cyclosporine arm. Three patients in the everolimus arm were converted to CsA after being given treatment for rejection, although the biopsies failed to verify a histological confirmed rejection. All patients with a rejection episode in the everolimus arm were converted back to a CNI regime.

This might reflect uncertainty by the investigators in handling rejection episodes and also side effects in a non-CNI therapy based protocol. This is an enigma in open randomized trials and may represent a confounding factor for a sound efficacy and safety interpretation of novel immunosuppressive drug regimes.

The ZEUS trial design was also a one-year, open-label, prospective, multicentre trial assessing the conversion from a CsA-based regime to everolimus in *de novo* renal transplant patients[14]. In contrast to the CENTRAL trial, the randomized conversion to everolimus or continuation on CsA was later at 4.5 months after transplantation. The initial immunosuppression was induction therapy with basiliximab and maintenance therapy based on CsA, MPA, and steroids. For patients recruited to everolimus, the conversion was carried out gradually over a four-week period. Of the everolimus-treated patients, 118 (76%) of 155 completed treatment with the study drug up to 12 months after conversion; the corresponding number for the CsA arm was 117 (81%) of 145 patients. The everolimus regimen was associated with a significant improvement in GFR versus the CsA regimen, a difference of 9.8 ml/min per 1.73 m^2. This improvement mirrors the improvement of 9.3 ml/min observed in the CENTRAL study. As in the CENTRAL study, there were significantly more acute rejections after the conversion to everolimus. However, despite an increase in predominantly mild rejection episodes shortly after conversion, in CENTRAL and ZEUS the long-term benefits of increased GFR at one year were evident in both trials. The CENTRAL and ZEUS studies have demonstrated that pre-emptive conversion from CsA to everolimus at week 7 or at month 4.5 after kidney transplantation is associated with a significantly greater improvement in GFR 12 months later versus controls that remain on CsA therapy.

Recently, a three-year follow-up of the ZEUS trial demonstrated that the superior effect on GFR was maintained[15]. There are indications that a beneficial effect on renal function observed 2-3 years after early conversion to mTOR regimens might be preserved or even enhanced in more long-term follow-up. The post-Concept study demonstrated that the improvement in renal function in the mTOR arm observed at 12 months was even more pronounced at five years[16].

MECANO is 24-month, open, randomized, three-arm study which randomizes patients to CsA and prednisolone (eliminates MPA), or MPA and prednisolone (eliminates CsA) or everolimus and prednisolone (elimination of both CsA and MPA)[17]. The conversion procedure to one of these three arms was initiated six months after transplantation. A scheduled biopsy was performed at month 6 prior to randomization. Only patients whose biopsy showed no sign of rejection whatsoever continued to one of the three study arms. The conversion to everolimus was performed overnight, while MPA was eliminated over a two-week period. All patients received an increased dose of prednisolone and continued on 10 mg of prednisolone daily to minimize the risk of rejection. A possible "side effect" of the increased dose of prednisolone was a reduction in everolimus-related side effects in that arm. The six-month interim analysis showed that conversion to prednisolone/CsA or prednisolone/everolimus was effective in preventing rejections. In contrast, double therapy with prednisolone and mycophenolate sodium resulted in an increase in severe acute rejections and this arm was prematurely stopped. The high rate of rejection episodes with only MPA and prednisolone as immunosuppressive drugs was seen in *de novo* low-risk patients[9]. Serum creatinine values at the latest follow-up 8 ± 5 months after conversion were lower in the prednisolone/everolimus arm. The primary endpoint of this ongoing study will be scheduled biopsy findings at month 24 after randomization.

There are several ongoing trials to explore the role of everolimus conversion early after transplantation. One ongoing Spanish trial is randomizing 195 patients from a tacrolimus-based regime to convert to everolimus at month 3 after transplantation or continue a CNI regimen. In the everolimus conversion arm, GFR at month 12 increased from 52.7 to 57.2 ml/min (p < 0.05)[18].

The ongoing ELEVATE study will evaluate whether conversion from CNI to everolimus will improve renal allograft function at one year[7]. As renal transplant patients suffer from premature vascular morbidity and mortality, this trial will include important cardiovascular secondary endpoints such as incidence of coronary disease, new-onset of diabetes mellitus, changes in pulse wave velocity, and left ventricular hypertrophy.

Determining the optimal timing of conversion from CNI-based to mTOR inhibitor-based immunosuppression represents a balance between avoiding the time period with the highest rejection risk shortly after transplantation and minimizing the progressive development of CNI-related nephrotoxicity[1]. While delaying conversion to mTOR later than six months shows mixed results on renal function, very early switch during the first couple of months posttransplantation necessitates a careful target setting and drug therapeutic monitoring to ensure adequate mTOR inhibitor exposure. Moreover, the high rate of study discontinuations to month 12 illustrates the challenge of achieving therapeutic exposure without side effects.

Late conversion from CNI to mTOR regimes has been modestly successful in improving renal function compared to trials a short time after transplantation. The ASCERTAIN trial converted patients to everolimus around five years after transplantation. In the intent-to-treat population there was clinically no substantial effect on renal function; however, there was an increase in GFR by 10 ml/min in patients with GFR above 50 ml/min at inclusion[19]. Although a switch to everolimus might improve renal function in patients with good renal function, the major message from the ASCERTAIN trial is that if late switch is considered for a cause (e.g. cancer), this can be performed safely and efficaciously.

Common side effects of mammalian target of rapamycin inhibitors as a barrier to maintaining patients on everolimus

Everolimus has been shown to provide low rates of acute rejection, avoid chronic allograph nephropathy interstitial fibrosis/tubular atrophy, and has demonstrated a superior GFR in a multiple of studies[7]. However, the challenge in conversion from a CNI-based to an mTOR-based regime is retaining the patients on a "new" immunosuppressive regimen.

The transplant population usually has a high rate of adverse events following surgery and treatment regimens. From the mid-1970s CsA, and since late-1980s tacrolimus, has been the mainstay of immunosuppression. The side effects associated with use of CNI regimens, such as tremors, muscle/bone pain, hair loss, or hirsutism, have generally been tolerated by patients and accepted by physicians. Introduction of mTOR as an alternative immunosuppressive regimen also introduced a new spectrum of side effects, challenging physicians used to handle the common CNI side effects.

Many physicians not experienced with mTOR will have to handle different aspects of common side effects such as edema, rash, acne, and mouth ulcers. These side effects are to a large extent dose-dependent[20]. Our experience from the CENTRAL and the ASCERTAIN trials was that discontinuation was more frequent in small centers with little or no experience with mTOR. It is absolutely mandatory that therapeutic drug monitoring is performed to detect subtherapeutic concentrations and, more important, to detect levels in excess of recommended drug exposure. Depending on the time after transplantation and the combination of concomitant medication, we recommend trough levels in the range 3-8 up to 5-10 ng/ml[7]. Everolimus has a half-life of 26 hours and steady state is obtained after four days. The experience from the CENTRAL pilot/CENTRAL and the ASCERTAIN studies is that 1.5 mg twice daily will bring the majority of patients into a" target" area of 3-8/10 ng/ml[11,12,19]. Many common side effects are associated with supratherapeutic levels of mTOR. Once the drug concentrations have stabilized within the recommended range, subsequent measurements can be spaced according to clinical routines.

However, any change in everolimus dose or in concomitant immunosuppressive drugs must be accompanied by new therapeutic drug measurements.

A mTOR therapy might be associated with bone marrow suppression, an effect which is dose-dependent. A usual pitfall is that conversion from a regimen of CsA/MMF(MPA)/prednisolone to everolimus/MMF(MPA)/prednisolone will give a substantially increased exposure of MMF, which may contribute to bone marrow suppression. Dosing of MPA/MMF should be reduced by about 25% and everolimus dosing should be adjusted to the lower end of therapeutic range when experiencing bone marrow depletion.

Common patients' side effects initially are mouth ulcers, acne/rash, and edema. Mouth ulcers are one of the major causes for discontinuation of mTOR therapy[21]. These are generally dose-dependent and can usually be effectively treated with local steroids (clobetasol)[22]. Acne and edema are also usually transient and can be treated with lymecycline/tetracycline and loop diuretics, respectively[7].

Proteinuria may be associated with mTOR use. It is noteworthy that only some patients treated with everolimus develop proteinuria and nephrotic syndrome. Everolimus and sirolimus may have a complex effect on podocyte structure and function[23], and/or some of the effects might be tubular[24]. The mTOR may aggravate elevated existing proteinuria, and it has been shown that proteinuria above 0.8 g/day has a negative predictive effect on subsequent proteinuria[25]. Proteinuria is more common in a switch to everolimus long term after transplantation[13,19],

but is more rarely seen in early conversions after transplantation[12]. Moderate proteinuria is usually well controlled with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers[26].

Hyperlipidemia is frequently seen with mTOR therapy and includes increased levels of cholesterol and triglycerides[27]. Long-term studies have shown that dyslipidemia improves over time and administration of statins and fibrates are effective in lowering hypercholesterolemia and hypertriglyceridemia, respectively[27,28].

Summary

Evidence from clinical trials indicates that everolimus is a feasible drug to be used in CNI elimination strategies in renal transplant patients. The preferred timing for introducing the drug to improve renal function seems to be in the first months after transplantation in a pre-emptive way to avoid CNI side effects[12,14,17]. However, conversion in the long term may also be safely performed years after transplantation[19].

References

1. El-Zoghby ZM, Stegall MD, Lager DJ, et al. Identifying specific causes of kidney allograft loss. Am J Transplant. 2009;9:527-35.
2. Matas AJ. Chronic progressive calcineurin nephrotoxicity: an overstated concept. Am J Transplant. 2011;11:687-92.
3. Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. Clin J Am Soc Nephrol. 2009;4:481-508.
4. Chapman JR. Chronic calcineurin inhibitor nephrotoxicity-lest we forget. Am J Transplant. 2011;11:693-7.
5. Grinyo JM, Bestard O, Torras J, Cruzado JM. Optimal immunosuppression to prevent chronic allograft dysfunction. Kidney Int Suppl. 2010;S66-70.
6. Taylor AL, Watson CJ, Bradley JA. Immunosuppressive agents in solid organ transplantation: Mechanisms of action and therapeutic efficacy. Crit Rev Oncol Hematol. 2005;56:23-46.
7. Campistol JM, de Fijter JW, Nashan B, Holdaas H, Vitko S, Legendre C. Everolimus and long-term outcomes in renal transplantation. Transplantation. 2011;92:S3-26. **A detailed review of use of everolimus in renal transplantation.*
8. Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med. 2007;357:2562-75.
9. Asberg A, Midtvedt K, Line PD, et al. Calcineurin inhibitor avoidance with daclizumab, mycophenolate mofetil, and prednisolone in DR-matched de novo kidney transplant recipients. Transplantation. 2006;82:62-8.
10. Flechner SM, Glyda M, Cockfield S, et al. The ORION study: comparison of two sirolimus-based regimens versus tacrolimus and mycophenolate mofetil in renal allograft recipients. Am J Transplant. 2011;11:1633-44.
11. Holdaas H, Bentdal O, Pfeffer P, Mjornstedt L, Solbu D, Midtvedt K. Early, abrupt conversion of de novo renal transplant patients from cyclosporine to everolimus: results of a pilot study. Clin Transplant. 2008;22:366-71.
12. Mjørnstedt L, Sørensen SS, von Zur Muhlen B, et al. Improved renal function by overnight switch from cyclosporine to everolimus at week 7 after renal transplantation. One year results from a randomized controlled trial. Transplant Int. 2011;24(Suppl 2):94. *A randomized controlled trial demonstrating the feasibility of conversion to everolimus short-time (7 weeks) after transplantation.*
13. Schena FP, Pascoe MD, Alberu J, et al. Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. Transplantation. 2009; 87:233-42.
14. Budde K, Becker T, Arns W, et al. Everolimus-based, calcineurin-inhibitor-free regimen in recipients of de-novo kidney transplants: an open-label, randomised, controlled trial. Lancet. 2011;377:837-47. *A randomized controlled showing the safety and efficacy of conversion to everolimus 4.5 months after transplantation.*
15. Budde K, Arns W, Sommerer C, et al. Improved renal function of an everolimus/enteric coated mycophenolate sodium regimen after calcineurin inhibitor withdrawal in de novo renal transplant patients: 3 years follow-up of the ZEUS trial. Am J Transplant. 2011;11(Suppl 2):66.
16. Lebranchu Y, Touchard G, Bühler M, et al. Efficacy and safety of early cyclosporine (CsA) conversion to sirolimus (SRL) with mycophenolate mofetil (MMF): 5-year results of the post-concept study. Transplant Int. 2011;24(Suppl 2):57.
17. Bemelman FJ, de Maar EF, Press RR, et al. Minimization of maintenance immunosuppression early after renal transplantation: an interim analysis. Transplantation. 2009;88:421-8.
18. Ruiz JC, Sanchez Fructuosa A, Hernandez A, et al. Better renal function with early everolimus introduction and calcineurin inhibitor withdrawal at third month in kidney recipients at month 12: Results of the ERIC study. Am J Transplant. 2011;11(Suppl 2):407.
19. Holdaas H, Rostaing L, Seron D, et al. Conversion of long-term kidney transplant recipients from calcineurin inhibitor therapy to everolimus: a randomized, multicenter, 24-month study. Transplantation. 2011;92:410-18. *Shows that conversions for cause to everolimus long-term after transplantation can be performed safely and efficaciously.*
20. Pascual J, Marcen R, Ortuno J. Clinical experience with everolimus (Certican): optimizing dose and tolerability. Transplantation. 2005;79:S80-4.
21. Montalbano M, Neff GW, Yamashiki N, et al. A retrospective review of liver transplant patients treated with sirolimus from a single center: an analysis of sirolimus-related complications. Transplantation. 2004;78:264-8.
22. Chuang P, Langone AJ. Clobetasol ameliorates aphthous ulceration in renal transplant patients on sirolimus. Am J Transplant. 2007;7:714-17.
23. Schonenberger E, Ehrich JH, Haller H, Schiffer M. The podocyte as a direct target of immunosuppressive agents. Nephrol Dial Transplant. 2011;26:18-24.
24. Franz S, Regeniter A, Hopfer H, Mihatsch M, Dickenmann M. Tubular toxicity in sirolimus- and cyclosporine-based transplant immunosuppression strategies: an ancillary study from a randomized controlled trial. Am J Kidney Dis. 2010;55:335-43.
25. Diekmann F, Budde K, Oppenheimer F, Fritsche L, Neumayer HH, Campistol JM. Predictors of success in conversion from calcineurin inhibitor to sirolimus in chronic allograft dysfunction. Am J Transplant. 2004;4:1869-75.
26. Stallone G, Infante B, Grandaliano G, Gesualdo L. Management of side effects of sirolimus therapy. Transplantation. 2009;87:S23-6. *A "must" for handling common side effects in conversion regimens to mTOR therapy.*
27. Kasiske BL, de MA, Flechner SM, et al. Mammalian target of rapamycin inhibitor dyslipidemia in kidney transplant recipients. Am J Transplant. 2008;8:1384-92.
28. Blum CB. Effects of sirolimus on lipids in renal allograft recipients: an analysis using the Framingham risk model. Am J Transplant. 2002;2:551-9.