Crimson Publishers
Wings to the Research

Mini Review

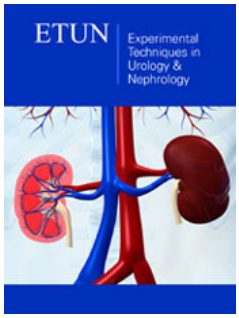
Is there Enough Evidence to Support Calcineurin Inhibitor Minimization or Avoidance in Renal Transplantation?

Althaf MM[1]*, Abdelsalam MS[2] and Wahid M[1]

[1]Jack Pryor renal unit, Norfolk and Norwich University Hospital-NHS Foundation Trust Colney Lane, Norwich, Norfolk, United Kingdom

[2]Nephrology Unit, Alexandria University, Alexandria, Egypt

ISSN: 2578-0395



***Corresponding author:** Mohammed Mahdi Althaf, Jack Pryor renal unit, Norwich University Hospital-NHS Foundation Trust Colney Lane, Norwich, Norfolk, United Kingdom

Submission: February 18, 2020

Published: March 06, 2020

Volume 3 - Issue 1

How to cite this article: Althaf MM, Abdelsalam MS, Wahid M. Is there Enough Evidence to Support Calcineurin Inhibitor Minimization or Avoidance in Renal Transplantation?. Exp Tech Urol Nephrol. 3(1). ETUN.000554.2020.
DOI: 10.31031/ETUN.2020.03.000554

Abstract

Renal transplantation is the modality of choice for renal replacement therapy in patients with end-stage renal disease. Following induction immunosuppression, most maintenance immunosuppressive regimens include a calcineurin inhibitor. While this class of immunosuppressive therapy is highly effective it has a toxic effect on the renal allograft termed calcineurin inhibitor toxicity which can contribute to graft loss over time. Thus, their minimization, withdrawal or avoidance is of interest to transplant clinicians as well to renal transplant recipients. This mini review takes an in-depth review and analysis of all published data in this field.

Keywords: Calcineurin inhibitor; Renal transplant; Kidney transplant

Abbreviations: CNI: Calcineurin Inhibitors; SRL: Sirolimus; ESRD: End Stage Renal Disease; CAN: Chronic allograft nephropathy; DFG: Death with functioning graft; mTORi: Mammalian Target of Rapamycin Inhibitors; CsA: Cyclosporine; TAC: Tacrolimus; MMF: Mycophenolate Mofetil; AZA: Azathioprine; BPAR: Biopsy Proven Acute Rejection

Introduction

For patients with end stage renal disease (ESRD) renal transplantation offers the best survival advantage compared to other modalities of renal replacement therapy [1]. After pairing of the donor and recipient and immunological risk is ascertained the next step in renal transplantation is immunosuppression. Immunosuppression is done in two stages; induction followed by maintenance immunosuppression. The induction phase is where intense immunosuppressive agents are administered at the very onset of transplantation to minimize the burden of acute allograft rejection. Protocols are not standard across all transplant units as optimal induction immunosuppression therapy remains controversial [2,3]. However, it can broadly be classified into two strategies. The first one is based on the use of significant doses of standard immunosuppressive therapy (a calcineurin inhibitor, an antimetabolite and glucocorticoids). The other strategy employs antibodies targeted at T-cells in addition to standard immunosuppressive therapy. The choice of agent is based on the recipient's risk of developing acute rejection. Gebel et al. [4] stratified the prospective renal transplant patients into various categories according to immunological risk in renal transplantations. Based on this with further additions the principles of risk assessment are as follows:

a. High Immunological risk: During transplant high titers of circulating antibodies targeting mismatched donor HLA also known as donor-specific antibodies are present. This can lead to hyperacute rejection. The presence of DSA precludes transplantation. However, there are reports of innovative pre-transplant desensitisation regimens to reduce this risk.

b. Intermediate immunological risk: The low titer of DSA at the time of transplantation and historic DSA is not detectable. It may be acceptable to consider intensified immunosuppression as well as immunological monitoring in the post-transplant period

c. Standard immunological risk: Where there is no evidence of donor-directed sensitization to HLA.

It is worth noting that recipients of a renal allograft who currently have a functioning solid-organ transplant (such as heart, lung or liver) and are on maintenance immunosuppression are often spared from induction immunosuppression. However, this is not the standard in all centers, and some still prefer some form of induction agent [5]. Recipients of two haplotype identical living related kidneys who are Caucasian have a significantly low risk of acute rejection and do not require induction therapy [6].

Discussion

Maintenance immunosuppression

Standard immunosuppressive therapy for maintenance immunosuppression entails a calcineurin inhibitor, an antimetabolite and a glucocorticoid. Since the advent of calcineurin inhibitors (CNIs) in the 1980s; short and intermediate-term allograft survival had improved. However, post-transplant graft failure rate beyond ten years has remained unaffected [7]. The two leading causes of late renal allograft loss are chronic allograft nephropathy (CAN) and death with a functioning graft (DFG). Cardiovascular disease and malignancy are attributed as the primary causes of DFG. The underlying pathogenesis of CAN is not entirely understood. It which manifests histologically as interstitial fibrosis and tubular atrophy. Both immunological and non-immunological elements have been identified as causes of CAN [8,9]. Chronic CNI exposure has been recognized as a risk factor for CAN [10]. Treatment regimens have therefore focused to either minimize their use or to avoid them completely, however, this strategy has proven to be quite disappointing due to the resultant increase in rates of acute rejection [11-14]. Apart from the resultant allograft associated complications, CNI use has been associated with the development of new-onset diabetes after transplantation (NODAT), hyperlipidemia and hypertension [15,16]. In an attempt to move away from CNIs there has been significant focus on the employment of mammalian target of rapamycin inhibitors (mTORi) like everolimus and sirolimus in renal transplantation [17,18].

CNI minimization

Given the potential harm to both recipient and allograft from long term CNI exposure, several RCTs were conducted to test strategies to minimize exposure. Minimization is carried out by lowering the target blood levels which are routinely done to titrate dosing. Minimization of CNI target blood levels has been tested for both (Ciclosporin) CsA and (Tacrolimus) TAC. Minimization has also been tried with several combinations of induction agents and other immunosuppressive drugs. A total of 36 RCTs (Table 1) were conducted so far evaluating CNI minimization [19]. CsA minimization alone was studied in 22 RCTs and TAC alone in seven studies. Seven other studies pooled groups that received TAC or CsA. Mycophenolate is both its formulations were used as the main combination immunosuppressive agent in 19 studies. mTORi in combination with CNI were evaluated in 14 studies. Two studies had multiple therapies including CNI, mTORi, MMF and AZA. Vathsala et al. [20] evaluated a single agent CsA without an antimetabolite. Nearly all studies used a steroid (prednisone) in both intervention and control arm. Induction therapy was used in most of these trials except two of them, and eleven other studies did not report on induction. Basiliximab was the most employed induction agent used most of them. Three of them used daclizumab, two used rATG and one used alemtuzumab. In one study, the induction therapy was not uniform and followed local protocol. 29 studies had begun CNI minimization within the first six months post-transplantation, three of them delayed the process till six months had elapsed and four postponed until one year.

Table 1: CNI minimization studies.

Study	Study Year	Induction Agent	CNI Used	Other Agent
Xu [24]	2011	Not reported	CsA, TAC	MMF
Gaston [25]	2009	Basiliximab, Daclizumab	CsA, TAC	MMF
Spagnoletti [26]	2009	Basiliximab	CsA, TAC	MMF
Ekberg [27]	2007	Daclizumab	CsA, TAC	MMF
Hernandez [28]	2007	rATG, Basiliximab	CsA, TAC	MMF
Tang [29]	2006	Not reported	CsA, TAC	MMF, AZA
Cai [30]	2014	Not reported	CsA	MPS
Chadban [31]	2013	Basiliximab	CsA	MPS
Etienne [32]	2010	Not reported	CsA	MMF
Fangmann [33]	2010	Daclizumab	CsA	MMF
Budde [34]	2007	Basiliximab	CsA	MPS
Cibrik [35]	2007	Basiliximab	CsA	MPS
Ekberg [36]	2007	Daclizumab	CsA	MMF

Ghafari [37]	2007	No anti-T cell Induction agent used	CsA	MMF
Frimat [37,38]	2006	Not reported	CsA	MMF
Stoves [39]	2004	Not reported	CsA	MMF
Pascual [40]	2003	Not reported	CsA	MMF
de Sevaux [41]	2001	No induction anti-T cell agent used	CsA	MMF
Chan [42]	2012	Basiliximab	TAC	MPS
Kamar [43]	2012	Not reported	TAC	MPS
Bolin [44]	2008	Not reported	TAC	MMF, SRL, AZA
Holdaas [45]	2011	Not reported	CsA, TAC	EVR
Chadban [46]	2014	Basiliximab	CsA	EVR
Muhlbacher [47]	2014	No anti-T cell induction agent used	CsA	SRL
Cibrik [35]	2013	Basiliximab	CsA	EVR
Takahashi [48]	2013	Basiliximab	CsA	EVR
Oh [49]	2014	Basiliximab	CsA	EVR
Paoletti [50]	2012	Not reported	CsA	EVR
Bertoni [51]	2011	Basiliximab	CsA	EVR
Salvadori [52]	2009	Basiliximab	CsA	EVR
Nashan [53]	2004	Basiliximab	CsA	EVR
Bechstein [54]	2013	Basiliximab	TAC	SRL
Langer [55]	2012	Basiliximab	TAC	EVR
Chan [56]	2008	Basiliximab	TAC	EVR
Lo [57]	2004	rATG	TAC	SRL
Vathsala [58]	2005	Alemtuzumab, CsA	CsA	None

Three measures of outcome were renal allograft function, the risk of BPAR and graft loss. Combinations with MMF and low-dose CsA have better results for all three measures as mentioned above compared with standard-dose CsA. With MMF and TAC, there is a sizeable benefit for renal function, but current evidence fails to make conclusions for the other outcomes. Combinations with mTORi and low-dose CsA revealed better renal function but no difference in BPAR compared to standard-dose regimens. Data for mTORi with TAC are scarce. Basiliximab induction with mTORi and low dose CNIs is associated with better renal allograft function but no difference in the risk of BPAR and graft loss. The evidence is too little to conclude the combination of basiliximab induction with MMF. CNI minimization started within the first six months post-transplantation in MMF combination is linked to improved allograft function, lowered BPAR, infection and graft loss compared to standard-dose combinations. However, minimization postponed to after six months or later of transplantation has been linked with greater rates of acute rejection. The Symphony trial compared four treatment protocols [16,21].

a) No induction followed by standard-dose CsA, MMF and corticosteroids.

b) Daclizumab induction followed by low-dose CsA, MMF and corticosteroids.

c) Daclizumab induction followed by low-dose TAC, MMF and corticosteroids.

d) Daclizumab induction followed by low dose sirolimus, MMF and corticosteroids.

Daclizumab induction followed by low-dose tacrolimus, 2g of MMF and corticosteroids had the most favorable results with better renal allograft function, lower incidence of BPAR and rate of graft loss. The Campath (alemtuzumab), CNI reduction and CAN (3C) study is an open label, multicenter randomized controlled

trial that aimed to answer two key questions. First to evaluate outcomes between campath (alemtuzumab) versus basiliximab induction for renal transplant recipients. Those receiving alemtuzumab will have low-dose TAC, MMF and no steroids, while those receiving basiliximab will have standard dose TAC, MMF and steroids. It includes most categories of patients eligible for renal transplantation. These include previously transplanted patients, those receiving a deceased or living donor kidney as well as those who are highly sensitized. Secondly, after six months of maintenance with immunosuppression with TAC based immunosuppression, they will be re-randomized to either stay on TAC for long term or switched to SRL based maintenance immunosuppression as a CNI minimization strategy [22]. 7% of 426 renal transplant recipients who received alemtuzumab had one occurrence of biopsy-proven acute rejection (BPAR) in the first six months post-transplantation. At the same time, 16% of those who received basiliximab had an episode of BPAR. This corresponds to a 58% reduction with alemtuzumab induction. The study is an ongoing and long-term follow-up with determining if these initial findings would translate to better transplant outcomes [23].

CNI withdrawal

As discussed previously CNI minimization has proven to be of benefit. Studies have been conducted to evaluate if recipients with a CNI based regimen could benefit by having the CNI withdrawn while continuing on alternative immunosuppressive drugs. To date, 15 randomised control trials (Table 2) have evaluated CNI withdrawal. MMF was included as a primary alternative to CNI in nine of them and mTORi in six of them. In ten studies CsA was withdrawn, four with EVR or SRL and six with MMF. In two studies TAC was withdrawn with SRL used. In three of the studies, MMF was used with combined data for those on CsA or TAC. Nine of them initiated CNI withdrawal within six months' post-transplant while five studies withdrew CNI after six months or longer after transplantation [67-72]. In conclusion, these studies revealed that CNI withdrawal is linked with a greater risk of BPAR for patients on mycophenolate acid formulations or mTORi compared to those on combination therapy with a CNI plus adjunctive therapy. Where CNI was withdrawn from patients continuing on MMF the risk of graft loss was higher as compared to those on combination CNI and MMF. Continuing on MMF after CNI withdrawal, however, was linked to improved renal function compared to combination therapy with a CNI.

Table 2: CNI withdrawal studies.

Study	Study Year	Withdrawn	Maintained
Mourer [59]	2012	CNI	MMF
Pascual [60]	2008	CNI	MMF
Suwelack [61]	2004	CNI	MMF
Asberg [62]	2012	CsA	MMF
Ekberg [27]	2007	CsA	MMF
Hazzan [63]	2006	CsA	MMF
Abramowicz [64]	2002	CsA	MMF
Schnuelle [65]	2002	CsA	MMF
Smak Gregoor [66]	2002	CsA	MMF

Early vs. late CNI withdrawal

When assessing the timing of CNI withdrawal, three studies began CNI withdrawal within the first six months after transplantation, and this is termed 'early withdrawal', and five studies began CNI withdrawal six months or later post-transplantation termed 'late withdrawal'. Early withdrawal revealed an increased risk of graft loss and death and the evidence was inconclusive for BPAR and allograft function. The ZEUS trial [73] investigated 300 de novo renal transplant recipients randomized to remain on CsA or switch to everolimus at four and a half months into the post-transplant period. This early withdrawal of CNI was associated with improved renal function with follow-up up to 5 years, and the resultant increase in mild BPAR did not impact long term allograft function. Similar results have been reported in the HERAKLES study [74]. The CONCEPT study [75] evaluated the conversion from CsA to SRL 3 months post-transplant. All patients also received MMF and oral steroids which were to discontinue at eight months. The conversion of CsA to SRL 90 days' post-transplant combined with MMF was associated with improved renal allograft function. In the CONVERT trial [76] renal transplant recipient on CsA or TAC were randomly assigned to either continue on the CNI or convert to SRL from CNI. This showed that at two years in patients who were converted to SRL had promising graft and patient survival with no significant difference in BPAR. Importantly it revealed a lower incidence of malignancy as compared to continuation of CNI therapy. In other studies, with late withdrawal, there was a greater risk of BPAR on maintenance MMF post-CNI withdrawal; there wasn't enough evidence to support any conclusion on infection outcomes in these subgroups. As with strategies employing conversion, induction therapy was not expected to have any clinically significant impact during the later period when most studies initiated CNI withdrawal [19].

CNI avoidance

Given the degree of CNI-associated toxicity, studies were also done to assess if they could be completely avoided. To date nine RCT's have looked at immunosuppressive protocols which are CNI free and were based on SRL or belatacept (table 3). SRL was alone in one study, in combination with AZA in another and finally with MMF in 5 of them. BENEFIT [77] and BENEFIT-EXT study [78] were two large scale multinational trials that compared belatacept and MMF to CsA and MMF after BAS induction for both groups. Only expanded criteria donors were enrolled in the BENEFIT-EXT study as these were associated with suboptimal clinical outcomes. Strong and less intensive treatment regimens for belatacept was compared in both BENEFIT studies. The ORION trial [71] looked at the safety and efficacy of SRL. Recipients of renal transplantation were randomised to three groups:

A. Group 1 - SRL and TAC with the elimination of TAC at week 13

B. Group 2 - SRL and MMF

C. Group 3 - TAC and MMF

Group 2 resulted in greater than expected BPAR and so was terminated early on. The study concluded that SRL based failed to show improved outcomes for renal transplant recipients. Given the available data, it is difficult to conclude if CNI avoidance regimes are successful as these studies resulted in inconclusive results and included small patient numbers (Table 3). Furthermore, a uniform recommendation could not be drawn as the immunosuppressive therapeutic regimes, and induction agents in individual studies were heterogeneous. There was no difference in death or graft loss when belatacept was compared to CsA however belatacept was associated with better renal parameters [79-83]. CNI-free studies where mTORi and MMF were used revealed improved renal function, but the risk of graft loss was greater when compared to tacrolimus-based regimens. When compared to CsA regimens there was no difference in the risk of graft loss [19].

Table 3: CNI avoidance studies.

Study	Study Year	Induction	Intervention	Control
Vincenti [76]	2010	Basiliximab	Belatacept, MMF	CsA, MMF
Durrbach [77]	2010	Basiliximab	Belatacept, MMF	CsA, MMF
Flechner [78]	2002	Basiliximab	SRL, MM	CsA, MMF
Ekberg [27]	2007	Daclizumab [non-CNI arm]	SRL, MMF	CsA, MMF
Asher [79]	2013	Daclizumab	SRL, MMF	TAC, MMF
Glotz [80]	2010	rATG [non-CNI arm]	SRL, MMF	TAC, MMF
Schaefer [81]	2006	ATG	SRL, MMF	TAC, MMF
Groth [82]	1999	None used	SRL, AZA	CsA, AZA
Refaie [83]	2011	Alemtuzumab	SRL	TAC

Conclusion

With a lot of conflicting study results, the optimal immunosuppressive regimen remains controversial. Recipients of a renal allograft should have induction immunosuppressive therapy that consists of an antibody (rATG, basiliximab or alemtuzumab) plus maintenance immunosuppressive therapy (tacrolimus, mycophenolate mofetil or azathioprine and glucocorticoids) rather than maintenance immunosuppressive therapy alone [6]. Considering all the published data in the 36 trials focusing on CNI minimisation, it revealed that compared to standard dose immunosuppression, early minimization of CNI was clearly associated with positive outcomes - better renal function, lowered risk of BPAR and graft loss.

There was also a lower incidence of opportunistic infections in the immunocompromised host including a lower CMV incidence. BK virus infection was an exception as the evidence proved to be inconclusive. There was no difference observed amongst the different regimens for patient death [19]. CNI withdrawal was associated with a greater risk of BPAR for patients on mycophenolate acid formulations or mTORi compared to those on combination therapy with a CNI plus adjunctive therapy. Where CNI was replaced with mTORi studies have revealed that at two years in patients who were converted to SRL, there was promising graft and patient survival with no significant difference in BPAR. Importantly it revealed a lower incidence of malignancy as compared to continuation of CNI therapy. Given the literature, it is challenging to conclude if CNI avoidance regimes are successful as current studies had small patient numbers and moreover revealed inconclusive results, however, CNI minimization has a positive effect and should joudioulsy be reduced over time.

References

1. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, et al. (1999) Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. New England Journal of Medicine 341(23): 1725-1730.
2. Kahan BD (2003) Individuality: the barrier to optimal immunosuppression. Nature Reviews Immunology 3(10): 831-838.
3. (2009) KDIGO clinical practice guideline for the care of kidney transplant recipients. American journal of transplantation 9(3): 1-155.
4. Gebel HM, Bray RA, Nickerson P (2003) Pre-transplant assessment of donor-reactive, HLA-specific antibodies in renal transplantation: contraindication vs. risk. American Journal of Transplantation 3(12): 1488-1500.
5. Cassuto JR, Levine MH, Reese PP, Bloom RD, Goral S, et al. (2012) The influence of induction therapy for kidney transplantation after a non-renal transplant. Clinical journal of the American Society of Nephrology: CJASN 7(1): 158-166.
6. Vella M, Brennan DC (2017) Induction immunosuppressive therapy in renal transplantation in adults.
7. Mc Donald SP (2011) Australia and New Zealand dialysis and transplant registry. Kidney International Supplements 5(1): 39-44.
8. Pilmore H, Dent H, Chang S, McDonald SP, Chadban SJ (2010) Reduction in cardiovascular death after kidney transplantation. Transplantation 89(7): 851-857.

9. Pascual M, Theruvath T, Kawai T, Tolkoff RN, Cosimi AB (2002) Strategies to improve long-term outcomes after renal transplantation. The New England Journal of Medicine 346(8): 580-590.

10. Nankivell BJ, Borrows RJ, Fung CL, Connell PJ, Allen RD, et al. (2003) The natural history of chronic allograft nephropathy. The New England Journal of Medicine 349(24): 2326-2333.

11. Diekmann F, Campistol JM (2006) Conversion from calcineurin inhibitors to sirolimus in chronic allograft nephropathy: benefits and risks. Nephrology Dialysis Transplantation 21(3): 562-568.

12. Kasiske BL, Chakkera HA, Louis TA, Ma JZ (2000) A meta-analysis of immunosuppression withdrawal trials in renal transplantation. Journal of the American Society of Nephrology: JASN 11(10): 1910-1917.

13. Ekberg H, Grinyo J, Nashan B, Vanrenterghem Y, Vincenti F, et al. (2007) Cyclosporine sparing with mycophenolate mofetil, daclizumab and corticosteroids in renal allograft recipients: the CAESAR Study. American Journal of Transplantation 7(3): 560-570.

14. Abramowicz D, Carmen RM, Vitko S, Castillo D, Manas D, et al. (2005) Cyclosporine withdrawal from a mycophenolate mofetil-containing immunosuppressive regimen: results of a five-year, prospective, randomized study. Journal of the American Society of Nephrology 16(7): 2234-2240.

15. Chadban S, Morris R, Hirsch HH, Bunnapradist S, Arns W, et al. (2008) Immunosuppression in renal transplantation: some aspects for the modern era. Transplantation Reviews (Orlando, Fla) 22(4): 241-251.

16. Ekberg H, TedescoS H, Demirbas A, Vitko S, Nashan B, et al. (2007) Reduced exposure to calcineurin inhibitors in renal transplantation. The New England Journal of medicine 357(25): 2562-2575.

17. Webster AC, Lee VW, Chapman JR, Craig JC (2006) Target of rapamycin inhibitors (sirolimus and everolimus) for primary immunosuppression of kidney transplant recipients: a systematic review and meta-analysis of randomized trials. Transplantation 81(9): 1234-1248.

18. Russ G, Segoloni G, Oberbauer R, Legendre C, Mota A, et al. (2005) Superior outcomes in renal transplantation after early cyclosporine withdrawal and sirolimus maintenance therapy, regardless of baseline renal function. Transplantation 80(9): 1204-1211.

19. Leas BF, Uhl S, Sawinski DL, Clark J, Tuteja S, et al. (2016) AHRQ comparative effectiveness reviews. Calcineurin inhibitors for renal transplant, Agency for Healthcare Research and Quality, Rockville, Maryland, USA.

20. Cibrik D, Silva HT, Vathsala A, Lackova E, Artis C, et al. (2013) Randomized trial of everolimus-facilitated calcineurin inhibitor minimization over 24 months in renal transplantation. Transplantation 95(7): 933-942.

21. Ekberg H, Bernasconi C, TedescoS H, Vitko S, Hugo C (2009) Calcineurin inhibitor minimization in the symphony study: observational results 3 years after transplantation. American Journal of Transplantation: Official Journal of The American Society of Transplantation and The American Society of Transplant Surgeons 9(8): 1876-1885.

22. Haynes R, Baigent C, Harden P, Landray M, Akyol M, et al. (2013) Campath, calcineurin inhibitor reduction and chronic allograft nephropathy (3C) study: background, rationale, and study protocol. Transplantation Research 2(1): 7.

23. Haynes R, Harden P, Judge P, Blackwell L, Emberson J, et al. (2014) Alemtuzumab-based induction treatment versus basiliximab-based induction treatment in kidney transplantation (the 3C Study): a randomised trial. Lancet 384(9955): 1684-1690.

24. Dong LX, Jin-ming B, Xin Y, Qiang L, Chang-jun Y, et al. (2011) Application of low-dose calcineurin inhibitors in living-related donor renal transplantation. Journal of Clinical Rehabilitative Tissue Engineering Research. 15(18): 3417-3420.

25. Gaston R, Kaplan B, Shah T, Cibrik D, Shaw L, et al. (2009) Fixed-or controlled-dose mycophenolate mofetil with standard-or reduced-dose calcineurin inhibitors: the opticept trial. American Journal of Transplantation 9(7): 1607-1619.

26. Spagnoletti G, Citterio F, Favi E, Rossi E, Delreno F, et al. (2009) Cardiovascular risk profile in kidney transplant recipients treated with two immunosuppressive regimens: tacrolimus and mycophenolate mofetil versus everolimus and low-dose cyclosporine. Transplantation proceedings 41(4): 1175-1177.

27. Ekberg H, TedescoS H, Demirbas A, Vítko Š, Nashan B, et al. (2007) Reduced exposure to calcineurin inhibitors in renal transplantation. New England Journal of Medicine 357(25): 2562-2575.

28. Hernández D, Miquel R, Porrini E, Fernández A, Posada JM, et al. (2007) Randomized controlled study comparing reduced calcineurin inhibitors exposure versus standard cyclosporine-based immunosuppression. Transplantation 84(6): 706-714.

29. Tang SCW, Chan KW, Tang CSO, Lam MF, Leung CY, et al. (2006) Conversion of ciclosporin A to tacrolimus in kidney transplant recipients with chronic allograft nephropathy. Nephrology Dialysis Transplantation 21(11): 3243-3251.

30. Cai L, Zeng F, Liu B, Wei L, Chen Z, et al. (2014) A single-centre, open-label, prospective study of an initially short-term intensified dosing regimen of enteric-coated mycophenolate sodium with reduced cyclosporine a exposure in Chinese live-donor kidney transplant recipients. International Journal of Clinical Practice 68(181): 23-30.

31. Chadban S, Eris J, Russ G, Campbell S, Chapman J, et al. (2013) Enteric-coated mycophenolate sodium in combination with full dose or reduced dose cyclosporine, basiliximab and corticosteroids in Australian de novo kidney transplant patients. Nephrology 18(1): 63-70.

32. Etienne I, Toupance O, Bénichou J, Thierry A, Najjar A, et al. (2010) A 50% reduction in cyclosporine exposure in stable renal transplant recipients: renal function benefits. Nephrology Dialysis Transplantation 25(9): 3096-3106.

33. Fangmann J, Arns W, Marti HP, Hauss J, Ketteler M, et al. (2009) Impact of daclizumab, low-dose cyclosporine, mycophenolate mofetil and steroids on renal function after kidney transplantation. Nephrology Dialysis Transplantation 25(1): 283-292.

34. Budde K, Bosmans J, Sennesael J, Zeier M, Pisarski P, et al. (2007) Reduced-exposure cyclosporine is safe and efficacious in de novo renal transplant recipients treated with enteric-coated mycophenolic acid and basiliximab. Clinical Nephrology 67(3): 164-175.

35. Cibrik D, Meier KHU, Bresnahan B, Wu YM, Klintmalm G, et al. (2007) Renal function with cyclosporine C2 monitoring, enteric-coated mycophenolate sodium and basiliximab: a 12-month randomized trial in renal transplant recipients. Clinical transplantation 21(2): 192-201.

36. Ghafari A, Makhdoomi K, Ahmadpour P, Afshari A, Fallah M, et al. (2007) Low-dose versus high-dose cyclosporine induction protocols in renal transplantation. Transplantation Proceedings 39(4): 1219-1222.

37. Frimat L, Cassuto VE, Charpentier B, Noël C, Provôt F, et al. (2006) Impact of cyclosporine reduction with MMF: a randomized trial in chronic allograft dysfunction. The 'reference'study. American Journal of Transplantation 6(11): 2725-2734.

38. Frimat L, Cassuto VE, Provôt F, Rostaing L, Charpentier B, et al. (2010) Long-term impact of cyclosporin reduction with MMF treatment in chronic allograft dysfunction: REFERENECE Study 3-year follow up. Journal of Transplantation pp. 1-11.

39. Stoves J, Newstead CG, Baczkowski AJ, Owens G, Paraoan M, et al. (2004) A randomized controlled trial of immunosuppression conversion for the treatment of chronic allograft nephropathy. Nephrology Dialysis Transplantation 19(8): 2113-2120.

40. Pascual M, Curtis J, Delmonico FL, Farrell ML, Williams WW, et al. (2003) A prospective, randomized clinical trial of cyclosporine reduction in stable patients greater than 12 months after renal transplantation. Transplantation 75(9): 1501-1505.

41. Sevaux RG, Gregoor PJS, Hene RJ, Hoitsma AJ, Vos P, et al. (2001) A controlled trial comparing two doses of cyclosporine in conjunction with mycophenolate mofetil and corticosteroids. Journal of the American Society of Nephrology 12(8): 1750-1757.

42. Chan L, Andres A, Bunnapradist S, Gugliuzza K, Parasuraman R, et al. (2012) Renal function and NODM in de novo renal transplant recipients treated with standard and reduced levels of tacrolimus in combination with EC-MPS. Journal of Transplantation pp. 1-9.

43. Kamar N, Rostaing L, Cassuto E, Villemain F, Moal MC, et al. (2012) A multicenter, randomized trial of increased mycophenolic acid dose using enteric-coated mycophenolate sodium with reduced tacrolimus exposure in maintenance kidney transplant recipients. Clinical Nephrology 77(2): 126-136.

44. Bolin P, Shihab FS, Mulloy L, Henning AK, Gao J, et al. (2008) Optimizing tacrolimus therapy in the maintenance of renal allografts: 12-month results. Transplantation 86(1): 88-95.

45. Holdaas H, Rostaing L, Serón D, Cole E, Chapman J, et al. (2011) Conversion of long-term kidney transplant recipients from calcineurin inhibitor therapy to everolimus: a randomized, multicenter, 24-month study. Transplantation 92(4): 410-408.

46. Chadban SJ, Eris JM, Kanellis J, Pilmore H, Lee PC, et al. (2014) A randomized, controlled trial of everolimus-based dual immunosuppression versus standard of care in de novo kidney transplant recipients. Transplant International 27(3): 302-311.

47. Mühlbacher F, Neumayer HH, Castillo D, Stefoni S, Zygmunt AJ, et al. (2014) The efficacy and safety of cyclosporine reduction in de novo renal allograft patients receiving sirolimus and corticosteroids: results from an open-label comparative study. Transplant International 27(2): 176-186.

48. Takahashi K, Uchida K, Yoshimura N, Takahara S, Teraoka S, et al. (2013) Efficacy and safety of concentration-controlled everolimus with reduced-dose cyclosporine in Japanese de novo renal transplant patients: 12-month results. Transplantation Research 2(1): 14.

49. Oh CK, Huh KH, Ha J, Kim YH, Kim YL, et al. (2015) Safety and efficacy of the early introduction of everolimus with reduced-exposure cyclosporine a in de novo kidney recipients. Transplantation 99(1): 180-186.

50. Paoletti E, Marsano L, Bellino D, Cassottana P, Cannella G (2012) Effect of everolimus on left ventricular hypertrophy of de novo kidney transplant recipients: a 1 year, randomized, controlled trial. Transplantation 93(5): 503-508.

51. Bertoni E, Larti A, Rosso G, Zanazzi M, Di Maria L, et al. (2011) Good outcomes with cyclosporine very low exposure with everolimus high exposure in renal transplant patients. J Nephrol 24(5): 613-618.

52. Salvadori M, Scolari MP, Bertoni E, Citterio F, Rigotti P et al. (2009) Everolimus with very low-exposure cyclosporine a in de novo kidney transplantation: a multicenter, randomized, controlled trial. Transplantation 88(10): 1194-1202.

53. Nashan B, Curtis J, Ponticelli C, Mourad G, Jaffe J, et al. (2004) Everolimus and reduced-exposure cyclosporine in de novo renal-transplant recipients: a three-year phase II, randomized, multicenter, open-label study. Transplantation 78(9): 1332-1340.

54. Bechstein W, Paczek L, Wramner L, Squifflet JP, Zygmunt A, et al. (2013) A comparative, randomized trial of concentration-controlled sirolimus combined with reduced-dose tacrolimus or standard-dose tacrolimus in renal allograft recipients. Transplantation Proceedings 45(6): 2133-2140.

55. Langer RM, Hené R, Vitko S, Christiaans M, Tedesco SH, et al. (2012) Everolimus plus early tacrolimus minimization: a phase III, randomized, open label, multicentre trial in renal transplantation. Transplant International 25(5): 592-602.

56. Chan L, Greenstein S, Hardy MA, Hartmann E, Bunnapradist S, et al. (2008) Multicenter, randomized study of the use of everolimus with tacrolimus after renal transplantation demonstrates its effectiveness. Transplantation 85(6): 821-826.

57. Lo A, Egidi MF, Gaber LW, Hosein SM, Nazakatgoo N, et al. (2004) Observations regarding the use of sirolimus and tacrolimus in high-risk cadaveric renal transplantation. Clinical Transplantation 18(1): 53-61.

58. Vathsala A, Ona ET, Tan SY, Suresh S, Lou HX, et al. (2005) Randomized trial of alemtuzumab for prevention of graft rejection and preservation of renal function after kidney transplantation1. Transplantation 80(6): 765-774.

59. Mourer JS, Hartigh J, Zwet EW, Mallat MJ, Dubbeld J, et al. (2012) Randomized trial comparing late concentration-controlled calcineurin inhibitor or mycophenolate mofetil withdrawal. Transplantation 93(9): 887-894.

60. Pascual J, Bloom D, Torrealba J, Brahmbhatt R, Chang Z, et al. (2008) Calcineurin inhibitor withdrawal after renal transplantation with Alemtuzumab: Clinical outcomes and effect on t-regulatory cells. American Journal of Transplantation (7): 1529-1536.

61. Suwelack B, Gerhardt U, Hohage H (2004) Withdrawal of cyclosporine or tacrolimus after addition of mycophenolate mofetil in patients with chronic allograft nephropathy. American Journal of Transplantation 4(4): 655-662.

62. Åsberg A, Apeland T, Reisæter AV, Foss A, Leivestad T, et al. (2013) Long-term outcomes after cyclosporine or mycophenolate withdrawal in kidney transplantation-results from an aborted trial. Clinical Transplantation 27(2): 151-156.

63. Hazzan M, Buob D, Labalette M, Provot F, Glowacki F, et al. (2006) Assessment of the risk of chronic allograft dysfunction after renal transplantation in a randomized cyclosporine withdrawal trial. Transplantation 82(5): 657-662.

64. Abramowicz D, Manas D, Lao M, Vanrenterghem Y, Del Castillo D, et al. (2002) Cyclosporine withdrawal from a mycophenolate mofetil-containing immunosuppressive regimen in stable kidney transplant recipients: a randomized, controlled study1, 2. Transplantation 74(12): 1725-1734.

65. Schnuelle P, Heide JH, Tegzess A, Verburgh CA, Paul LC, et al. (2002) Open randomized trial comparing early withdrawal of either cyclosporine or mycophenolate mofetil in stable renal transplant recipients initially treated with a triple drug regimen. Journal of the American Society of Nephrology 13(2): 536-543.

66. Gregoor PJS, Sévaux RG, Ligtenberg G, Hoitsma AJ, Hené RJ, et al. (2002) Withdrawal of cyclosporine or prednisone six months after kidney transplantation in patients on triple drug therapy: a randomized, prospective, multicenter study. Journal of the American Society of Nephrology 13(5): 1365-1373.

67. Stallone G, Di Paolo S, Schena A, Infante B, Grandaliano G, et al. (2003) Early withdrawal of cyclosporine A improves 1-year kidney graft structure and function in sirolimus-treated patients. Transplantation 75(7): 998-1003.

68. Gonwa TA, Hricik DE, Brinker K, Grinyo JM, Schena FP (2002) Improved renal function in sirolimus-treated renal transplant patients after early cyclosporine elimination1, 2. Transplantation 74(11): 1560-1567.

69. Johnson RW, Kreis H, Oberbauer R, Brattstrom C, Claesson K, et al. (2001) Sirolimus allows early cyclosporine withdrawal in renal transplantation resulting in improved renal function and lower blood pressure. Transplantation 72(5): 777-786.

70. Flechner SM, Glyda M, Cockfield S, Grinyó J, Legendre C, et al. (2011) The ORION study: comparison of two sirolimus-based regimens versus tacrolimus and mycophenolate mofetil in renal allograft recipients. American Journal of Transplantation 11(8): 1633-1644.

71. Freitas TV, Harada KM, Felipe CR, Galante NZ, Sampaio ELM, et al. (2011) Steroid or tacrolimus withdrawal in renal transplant recipients using sirolimus. International Urology and Nephrology 43(4): 1221-1228.

72. Budde K, Lehner F, Sommerer C, Reinke P, Arns W, et al. (2015) Five-year outcomes in kidney transplant patients converted from cyclosporine to Everolimus: the randomized Zeus study. American Journal of Transplantation 15(1): 119-128.

73. Budde K (2015) Month 48 follow-up results of the HERAKLES study: superior renal function after early conversion to an everolimus-based calcineurin free regiman. Journal of the American Society of Nephrology, pp. 26:76.

74. Lebranchu Y, Thierry A, Toupance O, Westeel P, Etienne I, et al. (2009) Efficacy on renal function of early conversion from cyclosporine to sirolimus 3 months after renal transplantation: concept study. American Journal of Transplantation 9(5): 1115-1123.

75. Schena FP, Pascoe MD, Alberu J, Oberbauer R, Brennan DC, et al. (2009) Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. Transplantation 87(2): 233-242.

76. Vincenti F, Charpentier B, Vanrenterghem Y, Rostaing L, Bresnahan B, et al. (2010) A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). American Journal of Transplantation 10(3): 535-546.

77. Durrbach A, Pestana J, Pearson T, Vincenti F, Garcia V, et al. (2010) A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). American Journal of Transplantation 10(3): 547-557.

78. Flechner SM, Goldfarb D, Modlin C, Feng J, Krishnamurthi V, et al. (2002) Kidney transplantation without calcineurin inhibitor drugs: a prospective, randomized trial of sirolimus versus cyclosporine1. Transplantation 74(8): 1070-1076.

79. Asher J, Vasdev N, Wyrley BH, Wilson C, Soomro N, et al. (2013) A prospective randomised paired trial of sirolimus versus tacrolimus as primary immunosuppression following non-heart beating donor kidney transplantation. Current Urology 7(4): 174-180.

80. Glotz D, Charpentier B, Abramovicz D, Lang P, Rostaing L, et al. (2010) Thymoglobulin induction and sirolimus versus tacrolimus in kidney transplant recipients receiving mycophenolate mofetil and steroids. Transplantation 89(12): 1511-1517.

81. Schaefer H, Kizilisik AT, Feurer I, Nylander W, Langone A, et al. (2006) Short-term results under three different immunosuppressive regimens at one center. Transplantation Proceedings 38(10): 3466-3467.

82. Groth CG, Bäckman L, Morales JM, Calne R, Kreis H et al. (1999) Sirolimus (rapamycin)-based therapy in human renal transplantation: similar efficacy and different toxicity compared with cyclosporine. Sirolimus European renal transplant study group. Transplantation 67(7): 1036-1042.

83. Refaie AF, Mahmoud KM, Ismail AM, Sheashaa HA, Kamal AI, et al. (2011) Alemtuzumab preconditioning allows steroid-calcineurin inhibitor-free regimen in live-donor kidney transplant. Experimental and Clinical Transplantation 9(5): 295-301.