Combination therapy with everolimus and tacrolimus in kidney transplantation recipients: A systematic review

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ABSTRACT

Background and aims: Immunosuppressive regimens are a key component for successful kidney transplantation. This systematic review aimed to assess the efficacy and safety of combination therapy of everolimus with tacrolimus in kidney transplantation recipients.

Methods: Results were limited to English-language articles. Trials where recipients received another regimen were excluded. The Cochrane Central Register of Controlled Trials and MEDLINE were searched via the optimally sensitive strategies for the identification of randomized trials, combined with the following MeSH headings and text words: Everolimus, Certican, Zortress, tacrolimus, prograf, and kidney transplantation.

Results: Five relevant studies of everolimus in combination with tacrolimus were identified and results of them were interpreted. Two trials investigated Fix dose of everolimus in combination with low (1.5-3 mg) versus standard dose of tacrolimus (4-7 mg). One trial investigated variable doses of everolimus (1.5 mg/day or 3 mg/day) in combination with fix dose of tacrolimusand two trials compared fix dose of everolimus versus reduction or elimination of tacrolimus. Sample size of RCTs ranged from 20 to 398 and the follow up time ranged from six to 24 months. The quality score on the Jadad score was 3 in all five trials indicating moderate quality.

Conclusion: Immune suppressive regimens including everolimus in combination with tacrolimus therapy show better safety and efficacy compared with single-mode but these differences were not significant in overall studies. In general, compared with a regimen without combination of everolimus with tacrolimus, the newer immunosuppressive regimen consistently reduced the incidence of short-term biopsy-proven acute rejection. However, evidence about impact on side-effects, long term graft loss, compliance and overall health-related quality of life is limited.

Keywords: Everolimus, Tacrolimus, Kidney transplantation.

Review article

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INTRODUCTION

The occurrence of end-stage kidney disease is estimated to have reached 1,900,000 people worldwide, of whom 1,455,000 go through dialysis treatment, and the remaining 455,000 are living with a functioning renal allograft. The global rise in the number of patients with chronic kidney disease (CKD) and consequent end-stage renal disease (ESRD)necessitate renal replacement therapy is threatening to reach epidemic proportions over the next decade.[1-3] Kidney transplant recipients have better rates of mortality when compared with the general population. The new immunosuppressive drugs have enhanced short-term patient survival up to 95% at 1-2 years, but these data have to be confirmed in long-term follow-up. Additionally, no particular regime has proved to be superior over others with regard to patient survival.[4,5]

Kidney transplantation is the most excellent treatment for patients with ESRD. Data from registries have shown that a functioning kidney improves patient survival at what time compared with patients enrolled on waiting lists, even after adjusting for age, sex, primary renal disease and co-morbidities.[6] From early 70s to late 80s, totally patient survival improved by at least 8% at each of 1, 5 and 10 years post-transplant, and by the late 1990s overall survival with functioning graft at 10 years had reached 86%.[7,8] However, life expectancy in the general population is more than renal transplant recipients, and this has been attributed to increased mortality rates because of cardiovascular diseases, infections and likewise malignancies.[9]

Prevention of acute rejection was the main purpose of immunosuppressive maintenance therapy. However, efforts have been directed to prevent and control the onset of chronic transplant nephropathy and calcineurin toxicity, two of the main causes of long-term graft loss.The advent of a new type of agents-proliferation signal inhibitors (PSI): Such sirolimus and everolimus) offers an option to agents that block calcineurin. Additionally, PSI is the only immunosuppressive medications that seem to diminish the incidence of malignancy.[10,11] Mammalian target of rapamycin inhibitors characterize a new, promising therapeutic group of immunosuppressive drugs for kidney transplantation. sirolimus first, and recently everolimus, have been merged to clinical practice.[12]

Mammalian target of rapamycin Inhibitors have been increasingly proposed as alternative immunosuppressive agents in renal transplantation because of their inimitable mechanism of action and apparently favorable side effect profile.[13,14] Everolimus (EVL) was approved for clinical use in Europe in 2005 for the indication of use in de novo renal transplant patients combined with low dose cyclosporine.[15] One option that has been studied to conserve renal function and reduce the risk of cardio-vascular adverse events (AEs) is combining an m-TOR inhibitor (everolimus) with tacrolimus for organ transplant recipients.[10] The aims of this review, was to discuss about the safety and efficacy of combination therapy with everolimus and tacrolimus in kidney transplant.

METHODS

All randomized controlled trials where drug regimens contained everolimus in combination with tacrolimus were compared with an alternative drug regimen when treating recipients of a first or subsequent kidney transplant in the post-transplant period were included. There was no restriction by age of recipients, or dosage of immunosuppressive drugs. Results were limited to English language articles. Trials

where recipients received another regimen were excluded. The Cochrane Central Register of Controlled Trials and MEDLINE was searched via the optimally sensitive strategies for the identification of randomized trials, combined with the following MeSH headings and text words: everolimus, certican, zortress, tacrolimus, prograf, and kidney transplantation. Outcomes assessed were mortality, graft loss, acute rejection, graft function (any measure of creatinine or measured or calculated glomerular filtration rate), infection (including symptomatic cytomegalovirus infection), malignancies, and a variety of treatment-related adverse reactions. The study quality was assessed by two reviewers independently, and any disagreements were resolved by consensus. RCTs were appraised using the JADAD scale(is a procedure to independently assess the methodological quality of a clinical trial using three items include; randomization, blinding, withdrawals and dropouts).To assess heterogeneity I2 and P were used (Values between 0% and 25% indicated that heterogeneity might not be important. Values between 25% and 50% indicated moderate inconsistency. Values of 50% to 75% were indicated substantial heterogeneity. Values between 75% and 100% indicated considerable inconsistency and p<0.05 indicated high heterogeneity).

RESULTS

In general, five studies were included in these review and all of them were randomized clinical trial.[16-20] The main features of the final studies are summarized in Table 1.

Table 1: Main characteristics of included studies

Study	Publication year	Study design	Number of samples	Duration of follow up	Arm of study	
					Intervention Group	**Comparison Group**
Chan, et al.	2008	RCT	92	6 month	1.5 mg EVL+ Low TAC (1.5-3 mg)	1.5 mg EVL + Standard TAC (4-7 mg)
Cataneo-davila, et al.	2009	RCT	20	12 month	EVL+CNI withdrawal	EVL+CNI reduction
Pascual, at al.	2010	RCT	35	6 month	1.5 mg/day EVL+TAC	3 mg/day EVL+TAC
Holdaas, et al.	2011	RCT	398	24 month	EVL+CNI minimization EVL+CNI elimination	EVL+CNI unchanged
Langer, et al.	2012	RCT	228	12 month	EVL+TAC (1.5-3 ng/ml)	EVL+TAC (4-7 ng/ml)

EVL: everolimus; TAC: tacrolimus; RCT: randomized clinical trial; CNI: calcineurin inhibitor

All Five trials have compared different doses of everolimus in combination with tacrolimus. Two trials investigated fixed dose of everolimus in combination with low (1.5-3 mg/kg) versus standard dose of tacrolimus (4-7 mg/kg).[16,19] One trial investigated variable doses of everolimus (1.5 mg/day or 3 mg/day) in combination with fixed dose of tacrolimus and two trials compared fixed dose of everolimus versus reduction or elimination of tacrolimus.[17,18,20]

Most of these trials had two arms, but one trial had three arms and also compared fixed dose of everolimus in combination with tacrolimus minimization or elimination versus fixed dose of everolimus with unchanged dose of tacrolimus.[18] High number outcomes were not reported by all trials or if reported, no comprehensible definitions were provided. For example, four trials reported serum creatinine, four trials reported GFR (eGFR or mGFR), and

two trials reported creatinine clearance.[16-20] Age of participant was different in trials (from 18-65 years, mean age was 46.7). In all, we identified five randomized controlled trials involving 773 patients. Sample size of RCTs ranged from 20 to 398 and the follow up time ranged from six to 24 months. The quality score on the Jadad score was 3 in all five trials indicating moderate quality. All five studies were published as full Journal articles.

All five trials reported mortality. In three of the five studies, no deaths occurred in the study groups.[16,17,20] In one study, three deaths occurred in the tacrolimus elimination group, all with no suspected relation to study drug, and there were three deaths in the tacrolimus minimization group, one suspected to be related to study drug and no deaths occurred in the control group.[18] In one study, three deaths occurred in each of the study groups.[19] In all five studies there was no significant difference in mortality between the groups. The main causes of death in different studies were cytomegalovirus infection, viral encephalitis, hemolytic uremic syndrome and invasive as pergillosis.

In four studies of all included studies there was no significant difference in acute rejection between the groups.[16-18,20] One study showed significant difference between two groups of the study (20 cases in low tacrolimus group and 9 cases in standard tacrolimus group, P=0.0138).[19] Chan et al reported that 13 Biopsy-proven acute rejection (BPAR) occurred in 13 patients: seven in the low tacrolimus group (14%) and six in the standard tacrolimus group (14%) (P=0.872).[16] Cataneo-davila et al reported that one patient in the tacrolimus reduction group experienced an acute rejection episode (Banff grade Ib), and two patients in tacrolimus reduction group and one patient in tacrolimus withdrawal group demonstrated borderline changes, all related to everolimus blood concentration less than

3 ng/mL.[17] In one study, three acute rejections occurred in each of the study groups; Acute rejection incidence rate was similar in both groups: 3(20%) for low everolimus group (A) and 3(15%) for high everolimus group (B). Acute rejections in group A were IA (n_1), IB (n_1), and IIB (n_1), whereas in group B, they were IA (n_1), IB (n_1), and antibody-mediated rejection (n_1).[20] Holdaas et al reported 7 BPAR in tacrolimus elimination group, 8 BPAR in tacrolimus minimization group and 3 BPAR in everolimus unchanged group, all differences were not significant.[18]

In four studies of all included studies there was no significant difference in acute rejection rate between the groups.[16-18,20] One study showed significant difference between two groups of the study.[19] In one study no graft loss was registered in each of the study groups.[17] In one study, one graft loss occurred in the standard tacrolimus group and no graft loss occurred in low tacrolimus group.[16] One study reported one graft loss, but it is not mentioned in which group it occurred.[20] Holdaas et al reported 8 graft losses in tacrolimus minimization group, 4 in tacrolimus elimination group and 6 in control group, differences between groups were of no significant.[18] Langer et al reported 8 graft losses in low tacrolimus group and 2 graft losses in standard tacrolimus group, this difference was significant between two groups of study.[19] Overall mean graft loss was 0-7% in these studies. The main reasons for graft loss were: Thrombotic microangiopathy, necrosis, kidney bleeding with possible infected arterial anastomoses, immunosuppression withdrawal, and technical issues and acute rejection.

Renal function has been reported in several studies by various indices, including serum creatinine (sCr), creatinine clearance (CrCl) and glomerular filtration rate (GFR). There was no significant difference in renal function between all included studies. In Chan

et al Mean serum creatinine at six months was 118±41 mol/L (1.33±0.46 mg/dL) for the whole study population, and 112±31 mol/L (1.26±0.35 mg/dL) and 127±50 mol/L (1.44±0.57 mg/dL) in the low and standard tacrolimus groups, respectively. Estimated GFR(Nankivel) and creatinine clearance for the total study population at six months were both very well preserved (mean GFR 69.0±22.3 mL/min; mean creatinine clearance 75.2±27.9 mL/min) and there were no significant differences amongtwo treatment groups.[16] Cataneo-davila et al reported that at 12 months after conversion to everolimus therapy, no significant difference among baseline concentrations and those at month 12 for both Scr and eGFR was observed in each study group. At baseline and at 12 months, Scr and eGFR concentrations in group one were 1.27±0.35 mg/dL vs 1.24±0.4 mg/dL (not significant) and 72.4±19.8 mL/min vs 76.2±22.6 mL/min (not significant), respectively, and in group 2 were 1.27±0.36 mg/dL vs 1.25±0.3 mg/dL (not significant) and 66.2±12.9 mL/min vs 66.2±13.7 mL/min (not significant), respectively.[17] In Langer et al study, At Month 12, mean eGFR was higher in the tacrolimus 1.5–3 ng/ml group versus the 4–7 ng/ml group (57.1±19.5 vs. 51.7±20 ml/min/1.73 m2, respectively; treatment difference: 5.3 ml/min/1.73 m2; 95% CI: -0.2, 10.9) although statistical significance was not observed (P=0.0299) at the level of 0.025. A post-hocANOVA of the eGFR (MDRD) difference at Month 12 adjusting for the eGFR (MDRD) value at Month 3 (start of different treatment regimens) as a sensitivity analysis yielded similar results (P=0.0445).[19] In Holdaas et al study, renal function measured with GFR was stable in all groups to month 24.[18]

Differences in adverse events between treatment groups were not statistically significant in all studies.The main adverse events of interest to clinicians included hypertension, diabetes mellitus, and malignancies. The most frequent serious adverse events were urinary tract infection.[16,18-20] Then, edema, peripheral edema, and anemia were the most frequently reported in the literature.Adverse events with a suspected relation to everolimus were reported in 30 patients and 24 patients in the low and standard tacrolimus groups, respectively.[16] One study reported there was no opportunistic viral or bacterial infection which could be assessed as a serious adverse event.[17] Other adverse events reported in all studies included; hypercholesterolemia, dyslipidemia, hyperlipidemia, hypokalemia, diabetes mellitus, hypertriglyceridemia, diarrhea, constipation, pyrexia, procedural pain, hypertension, Lymphocele, proteinuria, acne, headache and insomnia.

CONCLUSION

Clinical trials have confirmed that the everolimus, in combination with low dose tacrolimus, is effective in preventing rejection episodes and graft loss. We identified a total of 5 relevant studies in literature that specifically evaluated combination therapy of everolimus with tacrolimus in kidney transplant recipients. 773 patients participated in these studies. Results of the present study do not enable us to make any favorable statement about the use of CNI elimination rather than CNI reduction to preserve graft function.Our review suggests that immunosuppressive regimens including everolimus in combination with tacrolimus therapy show better safety and efficacy compared with single-mode, but these differences are not significant in overall studies. In general, compared with a regimen without combination of everolimus with tacrolimus, the newer immunosuppressive regimen consistently reduced the incidence of short-term biopsy-proven acute rejection. However, evidence of the impact on

side-effects, long term graft loss, compliance and overall health-related quality of life is limited. Differences between the various modes of combination therapy (include reduction, elimination or fix dose of each drug) are generally not significant in the included studies. Everolimus was also associated with the lowest incidence of dyslipidemia, new-onset diabetes mellitus (NODM), and wound healing postponement in kidney transplant recipients receiving reduced tacrolimus. Data about combination therapy of everolimus with tacrolimus are much less in kidney transplantation, but evidence to date suggests combination therapy in kidney transplant recipients. Long-term hard endpoint data from methodologically robust randomized trials are still required.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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