The handle http://hdl.handle.net/1887/29755 holds various files of this Leiden University dissertation.

**Author:** Moes, Dirk Jan Alie Roelof  
**Title:** Optimizing immunosuppression with mTOR inhibitors in renal transplant recipients  
**Issue Date:** 2014-11-18
General introduction
Introduction

Currently over one million humans are estimated to fulfill the criteria for chronic kidney damage in the Netherlands. More than 60,000 have serious kidney problems, ranging from renal failure to end stage renal disease (ESRD). Of these, 16,000 patients need lifelong renal replacement consisting of either dialysis or renal transplantation and this number is increasing every year. Dialysis treatment is associated with high mortality and reduces quality of life of the patients dramatically. One out of six patients dies every year because of this high mortality. Moreover, the health system costs associated with dialysis treatment per patient are very high. Currently over 6500 patients are treated with dialysis with an average annual cost of €75,000 per patient. The other option; renal transplantation became available in the Netherlands since 1966, but is limited by availability of donor organs. By the end of the year 2012, 855 patients were on the waiting list for a renal transplantation and every year 200 patients die because the shortage of donor organs. In 2012, 961 kidneys were transplanted and 50% of the donor organs were from a life donor [1–3]. Following transplantation immunosuppressive therapy is needed to prevent the recipient’s immune system of rejecting the graft. The last two decades the rejection rates have been significantly reduced to 10–20% with the introduction of the calcineurin inhibitors regimens. However, despite the low acute rejection rates and successful treatment in the first year after transplantation long term outcome after renal transplantation remains poor [4]. Optimal survival of the transplanted kidney depends on a number of factors; the donor and transplant procedure characteristics such as living versus deceased donor, cold ischemic time, donor age, HLA matching as well as co-morbidities of the recipient and optimal immunosuppressive therapy [5–8]. Immunosuppressive agents have a small therapeutic window and have often highly variable pharmacokinetics which makes therapeutic drug monitoring (TDM) of immunosuppressive drug concentrations essential for individualizing the dose and thereby preventing serious toxicity or rejection [9–12]. Suboptimal use of immunosuppressive medication such as under-immunosuppression and calcineurin-inhibitor toxicity plays a central role in the shortened long-term graft survival. Recent studies indicate that chronic antibody-mediated rejection is another important barrier to improve long term outcome [13]. Maintaining adequate overall immunosuppression is essential for prevention of chronic antibody-mediated rejection. Currently the most used immunosuppressive regimen consist of: induction therapy with an interleukin-2 blocking agent such as basiliximab, and maintenance therapy using a
calcineurin inhibitor (tacrolimus), mycophenolic acid and corticosteroids (prednisolone) [14]. Since the introduction of mTOR inhibitors the search to find the most optimal immunosuppressive regimen has further increased and different calcineurin inhibitor sparing regimens are emerging in an attempt to further improve long term outcome [15,16]. Although TDM has proven its effectiveness, still some patients experience toxicity and or rejection, therefore further optimization is warranted. In addition finding biomarkers, such as polymorphisms in genes coding for proteins involved in metabolism and dynamics of immunosuppressive drugs, which can predict altered pharmacokinetics or dynamics could further improve outcome for renal transplant recipients. Pharmacometrics; which uses mathematical models based on physiology, pharmacology and disease for quantitative analysis of interaction between drugs and patients [17] as used throughout this thesis can be a helpful tool to find such biomarkers.

Aim and Scope

The general aim of this thesis is to optimize immunosuppressive therapy, especially everolimus therapy in renal transplantation recipients by identifying pharmacological and pharmacogenetic risk factors influencing pharmacokinetics, and dynamics such as side effects and patient outcome. Chapter 2 describes the knowledge of clinical pharmacokinetics and dynamics of mTOR inhibitors in renal transplantation at the start of this PhD project and functions as an introduction for this thesis. TDM of oral immunosuppressive agents is essential to prevent toxicity and/or rejection. Therefore it is very important to use a reliable and accurate bioanalytical assay. In Chapter 3 the differences between the most used analytical assays of measuring everolimus in whole blood and its effect on dosing advice are investigated. TDM is performed based on either trough or AUC monitoring and pharmacogenetics might be a valuable addition to TDM to get the drug as soon as possible on target concentration. In Chapter 4 the population pharmacokinetics of everolimus in a calcineurin free regimen and the search for predictive factors such as pharmacogenetics as well the development of a limited sampling model is described which enables physicians to accurately predict everolimus exposure with limited patient discomfort. MTOR inhibitors are known for a variety of side effects and high discontinuation rates. Chapter 5 evaluates potential risk factors for the most severe side effect of mTOR inhibitors, interstitial pneumonitis, in a case control
study. Furthermore Chapter 6 describes a comprehensive analysis identifying risk factors for discontinuation and a number of side effects in a population of renal transplant patients on a regimen of everolimus and prednisolone dual therapy. In Chapter 7 the most promising polymorphisms in renal transplantation are investigated for influence on pharmacokinetics on the main stay immunosuppressive drugs cyclosporine, everolimus and tacrolimus. In addition Chapter 8 reports the findings of the effect of peroxide reductase (POR) and CYP3A5 polymorphisms and their combination on everolimus pharmacokinetics. Finally Chapter 9 aims at identifying risk factor associated with delayed graft function, acute rejection and subclinical rejection in patients on a cyclosporine based immunosuppressive regimen. This thesis ends with a general discussion in Chapter 10 and finally this thesis is summarized in an English and Dutch summary.
References


