Re-establishment of target concentrations of immunosuppressive drugs using PKPD modeling

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Scope of the lecture:
Optimizing the treatment of immunosuppressive treatment following renal transplantation

Learning objectives:

1. Risk factors for acute renal transplant rejection
2. Evidence for target levels immunosuppressive drugs
3. Potential effect of intracellular tacrolimus concentrations

Extended abstract:
After solid organ transplantation, tacrolimus in combination with mycophenolic acid (MPA) is given to prevent rejection. Therapeutic drug monitoring (TDM) is used to reach target trough concentrations of tacrolimus and MPA in whole blood. Underexposure is associated with acute rejection, whereas overexposure is associated with an increased risk of toxicity.

However, and despite being in use for more than 20 years, the concentration range of tacrolimus needed to prevent acute rejection is not well-defined. Over the years, the target exposure of tacrolimus has been lowered empirically and currently low-exposure tacrolimus regimens have become the standard in many transplant centers. The site of action of tacrolimus is the lymphocyte, and tacrolimus the fact that binds for approximately 80% to the erythrocyte, the intracellular tacrolimus concentration in lymphocytes is possibly more relevant than whole blood concentrations in predicting treatment efficacy.

In contrast to tacrolimus, there is more evidence to support a target concentration range for MPA. Clinical studies trying to demonstrate the clinical benefit of performing TDM show variable results. MPA target trough levels, representing the AUC, are lower in patients cotreated with cyclosporine due to inhibition of the enterohepatic circulation.

The optimal target concentration range of tacrolimus and MPA to prevent graft rejection is not firmly established and may be different depending on the population studied (high *versus* low-immunological risk) and the type of induction and maintenance therapy used.

Two earlier studies tried to evaluate risk factors for acute rejection and to optimize therapy for renal transplant patients using time-to-event analysis. Frobel *et al*. did not find a correlation between acute rejection and any risk factor, including the cyclosporine concentrations in 87 children. Daher Abdi *et al*. described the association between the longitudinal MPA exposure and acute rejection in adult renal transplant recipients treated with cyclosporine and mycophenolate mofetil. The risk factors and association between tacrolimus concentration and acute rejection has never been analyzed using a time-to-event analysis in renal transplant recipients on a tacrolimus plus mycophenolate immunosuppressive regimen.

The aim of our study was to investigate the association between (longitudinal) risk factors and acute kidney allograft rejection in order to establish a target concentration range for tacrolimus therapy for individual renal transplant recipients.

For these analysis we used data collected in a randomized-controlled trial which compared the efficacy of a cytochrome P450 (CYP) 3A5 genotype-based tacrolimus dosing strategy with a standard, bodyweight-based tacrolimus dosing strategy. In this study, n = 237 adult renal transplant recipients received a kidney from a living donor were included. Extensive data on demographics, clinical variables, tacrolimus and MPA exposure, acute rejection, adverse events and genetics (both of the donor and the recipient) are available.

Time-to-event modelling using NONMEM was used to describe the time to the first biopsy-proven acute rejection (BPAR) using a survival function. Different functions were evaluated to describe the hazard for this survival function. In the second phase the covariate model was developed by evaluating the influence of all available covariates on the hazard. Pharmacokinetic models for tacrolimus and MPA in renal transplant recipients developed earlier by our group will be used to describe the influence of drug exposure. The covariates will be included into functions as factors modifying the base hazard. Inclusion of covariates will be evaluated using a forward inclusion and backward elimination procedure. The interim results of this analysis will be presented.