2 Research Objectives

Given the fact that proton pump inhibitors are known to be interfering with the amount of drugs available for absorption (139) and low MPA exposure is associated with acute rejection risk (88), it is necessary to evaluate the impact of pantoprazole as a proton pump inhibitor on the pharmacokinetics of MPA after intake with mycophenolate mofetil and EC-MPS in renal transplant patients.

A randomized, open, single center, 4-treatment, 4-sequence crossover study in stable renal transplant patients was conducted at the Charité transplant center to evaluate the impact of pantoprazole, not only on MPA pharmacokinetics, but also on MPAG pharmacokinetics and IMPDH activity after pantoprazole intake with MMF and EC-MPS. The crossover study design had the advantage of minimizing inter-patient variability of MPA and focusing on the effect of PPI on both formulations in each patient.

1. MPA pharmacokinetics were analyzed to evaluate a possible significant change in PK parameters and whether bioequivalence is established with PPI co-treatment (with focus on MPA AUC\(_{0-12h}\), C\(_{\text{max}}\), t\(_{\text{max}}\)).
2. Changes in MPAG pharmacokinetics and bioequivalence were analyzed because EHC of MPAG/MPA contributes to overall MPA exposure (49).
3. IMPDH activity was determined and evaluated in order to detect changes in PD response (PD parameters like minimal activity, area under enzyme activity curve, t\(_{\text{min}}\), IC\(_{50}\)).

To determine MPA and MPAG concentrations, an in-house method for measuring trough concentrations of both analytes was adjusted to the need of PK clinical studies. It was important to ensure that at high concentration range the assay measures accurately. The method was validated according to recent bio-analytical guidelines (145, 146) and compared to a reference method (114).

Only one tube with lithium heparin blood was used to evaluate PK/PD profiles. Stability studies were performed to exclude wrong storage conditions causing falsely measured MPA concentrations due to degradation or other enzyme reactions of MPA or other metabolites in a complex matrix like human blood/plasma. These included short-term stability evaluation of unprocessed blood.
and plasma, processed plasma, freeze-and-thaw stability and long-term evaluation at -80 °C as samples from clinical trials require long-term storage.
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