Analysis of potential drug-drug-interactions with immunosuppressive medication in patients on the waiting list for renal transplantation

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Objectives
In 2013 2,272 kidneys were transplanted in Germany. About 8,000 patients are currently on the waiting list for renal transplantation (Tx). Successful renal Tx requires stable and effective serum concentration of immunosuppressants i.e. Ciclosporin, Mycophenolate or Tacrolimus (CMT). Drug-Drug-Interactions (DDIs) could modify serum concentrations of CMT, potentially leading to ineffective transplant function or toxicity. Multimorbidity of renal transplant recipients and related polypharmacy lead to increased risk of DDIs. Half of the (50%) kidney-transplants at the Hospital of the University of Munich are 50 years and older. Our aim was to increase patient-safety with a clinical-pharmacist-based DDI-check of CMT with routine medication accessible to surgical staff at the time of Tx, when CMT is routinely started.

Study design
Current medication of 136 patients with planned renal transplantation in the Hospital of the University of Munich was recorded. Results were analysed descriptively by number of drugs per patient (Tab.1), clinically relevant DDIs per CMT drug (Tab. 2) and clinically relevant DDIs per drug (Fig. 1). Potential DDIs of each drug with CMT were analysed using three DDI-databases (LexiInteract, Drugdex, Stockley’s) and the up-to-date German SmPC. These data were assessed and detailed to physician’s information needs by clinical pharmacists including a second look. Additionally, the Swiss mediQ database was used for drugs not listed in the three DDI-databases routinely checked. DDI-severity was identified and evaluated according to the LexiInteract score (A-D,X). An individual DDI-risk-profile was prepared for each patient (Fig.2) and filed in their medical notes. Ethical approval was obtained.

Results
Patients (n=136, mean age 51 ± 13 years) were prescribed a mean of 9,8 drugs (range 2-22), 95% more than five drugs (Tab. 1). In total, DDIs of 225 drugs with CMT were checked. Of those, 19 patients (14%) had clinical relevant DDIs (LexiInteract score C, D, X) with all three immunosuppressives, (37.3%) or Tacrolimus (5.4%) (Fig. 1). Modification (D) and monitoring (C) of drug therapy were recommended for all investigated immunosuppressives (Fig. 1, Tab. 1). Clinically relevant DDIs were found in all of the CMT drugs (Tab.2).

Discussion
DDIs were commonly found amongst all renal Tx patients. A substantial amount required therapy modification or at least strict supervision/monitoring of the treatment. As dietary supplements such as magnesium also showed potential for CMT-DDIs, patients will have to be counselled latest on discharge about buying medication not requiring a medical prescription.

Conclusion
Starting CMT puts patients with planned renal Tx at risk for DDIs with concurrent drug therapies for comorbidities. Individual DDI risk evaluation for DDI-prevention prepared by clinical pharmacists may improve patient-safety after renal Tx. Further immunosuppressive medication should be checked for DDIs with patient’s routine medication. Recommended monitoring or modification of drug therapy should be investigated. Guidelines and evidence-based recommendations for routine use should be developed.