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CAMPUS GROSSHADERN
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HOSPITAL PHARMACY

PS-049

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, 53 (39%) with two and 35 (26%) with one of them. Drug combinations to be avoided (LexiInteract score X) occured in patients taking Ciclosporin (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).

Drugs	Patients
≥ 5	129 (95%)
≥10	59 (43%)
≥15	19 (14%)

Tab.1: Number of drugs (n,%) in patient medication

Drugs	C	D	X
Ciclosporin	61 (27%)	23 (10%)	3 (1%)
Mycophenolate	17 (8%)	14 (6%)	0 (0%)
Tacrolimus	24 (11%)	10 (4%)	4 (2%)

Tab.2: Number of drugs (n,%) with clinically relevant DDIs (score ≥ C)

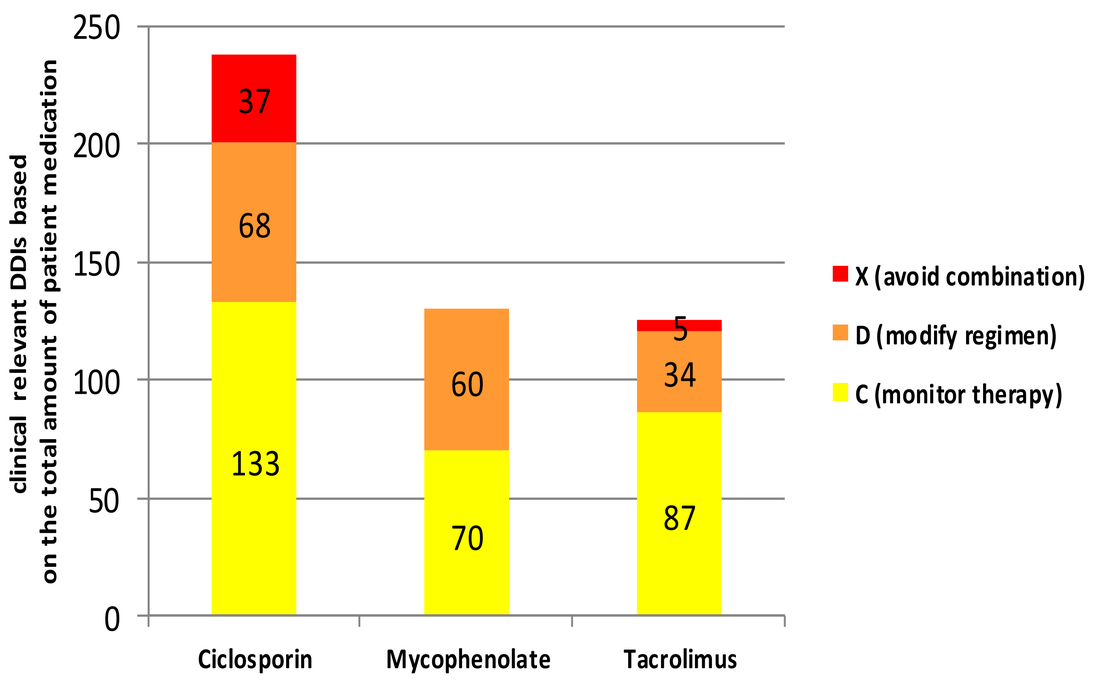

Fig.1: Clinically relevant DDIs (score ≥ C) based on the total amount of medication of all patients evaluated

DDI	Effect and Assessment
Ciclosporin (CIC) Simvastatin	**X** Possible increase of simvastatin-concentration. In a study with 19 renal transplant recipients the AUC of simvastatin was increased 8-fold [LexiInteract]. Case reports: development of rhabdomyolysis, partially with fatal outcome [Stockley's, Drugdex]. Potentially increased risk of myopathy/rhabdomyolysis. Monitor for symptoms of rhabdomyolysis [Stockley's, LexiInteract, Drugdex] Fluvastatin, pravastatin, lovastatin and rosuvastatin have a lower DDIs-risk [Stockley's, LexiInteract]
Mycophenolate (MYC) Magnesium carbonate	**D** Possible decrease of mycophenolate-concentration due to formation of an insoluble complex with magnesium and/or aluminum [SPC Cellcept®,07/13, Stockley's, LexiInteract, Drugdex]. In a study with 12 renal transplant recipients the AUC and the cmax of mycophenolate were decreased 37% and 25% respectively, when administered with magnesium-aluminum containing antacids [SPC Myfortic®, 09/12, Stockley's, Drugdex]. Avoid the combination. Separate doses of mycophenolate and antacids by at least 2 hours [LexiInteract, Drugdex]. Monitoring for mycophenolate-concentration is recommended [Stockley's, LexiInteract]. Possible and occasional occurence of dyspepsia with intermittent use of magnesium-aluminum containing antacids [SmPC Myfortic®, 09/12].
Tacrolimus (TAC) Carvedilol	**C** Possible increase of carvedilol-concentration due to P-Gp-inhibition of tacrolimus. Increased risk of adverse events for carvedilol, when tacrolimus is used or tacrolimus-dose is enhanced. Conversely, decreased effect of carvedilol, when tacrolimus is stopped or tacrolimus-dose is reduced [LexiInteract]. No known interaction [Stockley's, Drugdex].

Fig.2: Examples of DDI-assessment in individual DDI-risk-profiles

If there was a difference in DDI-severity between DDI-databases (39,6%), *i.e.* the DDIs were estimated clinically relevant by the databases Stockley's® or Drugdex®, but not relevant by Lexi-Interact *i.e.* score A: 'no known interaction' or B: 'no action needed', pharmaceutical assessment of the available data was performed and scored according to patient-safety aspects.

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 presciption.

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.

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