Biomarkers and TDM of Immunosuppressive Drugs in kidney transplantation
Focus on pharmacogenetics

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Scope of the lecture:

The purpose of this talk will be to establish a critical picture of current knowledge related to immunosuppressive therapy management through the use of Therapeutic Drug Monitoring (TDM) and biomarker characterization with a special focus on genetic traits. The objective is to dress up a summary of the synergistic benefits of both proactive and reactive strategies and their current applications in clinical settings.

Learning objectives:

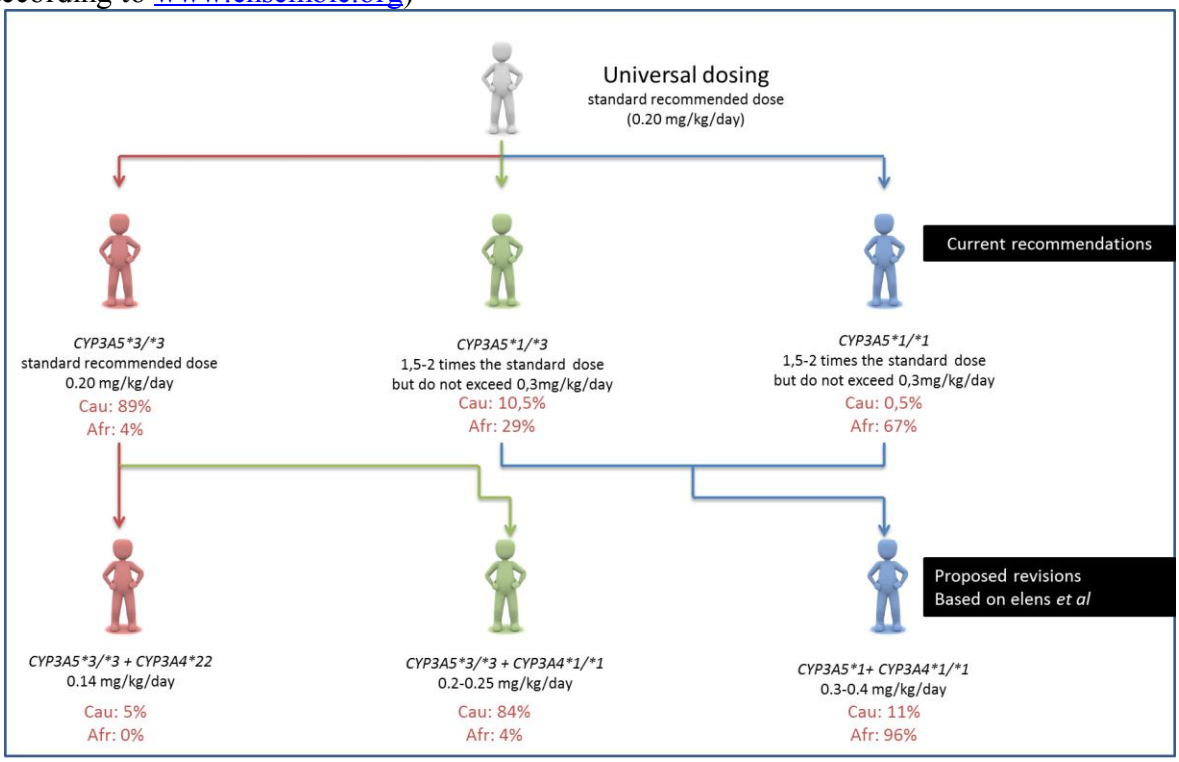
1. To review current knowledge related to TDM application for immunosuppressive therapy management in kidney transplantation
2. To draw a picture on the most relevant biomarkers used in kidney transplantation for predicting immunosuppressive drug pharmacological behavior and their potential applicability in clinics
3. To outline the principal perspectives we can expect from previous discoveries and the future directions that should take our researches in this area.

Extended abstract:

Therapeutic drug monitoring is useful to prevent inadequate exposure to various immunosuppressants (IS) and to maintain blood concentrations within the target window. However, unfortunately, TDM cannot always precisely predict efficacy and the possibility of organ rejection.
Even if beneficial, TDM constitutes a phenotype characterization approach and, as such, represents a reactive strategy only applicable a few days after therapy initiation, *i.e.* when pharmacokinetic steady-state is reached. Prompt achievement of safe and effective IS drug levels is critical in organ transplantation, especially for calcineurin inhibitors, such as Tacrolimus.
Direct pharmacogenomic testing prior to transplantation, *i.e.* before the first drug intake, might be a superior or at least a complementary approach into managing immunosuppressive therapy compared to traditional TDM. In this context, numerous studies have shown that part of the inter-patient variability in IS pharmacokinetics can be explained by inherited genetic variations in biotransformation pathway genes, with a special focus on CYP450 system defects. A tremendous effort has been deployed on the study of Tacrolimus pharmacogenetics because of the large inter-patient variability observed in its PK behavior and our inability to predict the pharmacological response. Some studies have highlighted that *CYP3A4/5* genetic variations explains more than 50% of the variability observed in tacrolimus dose requirement. According the different results obtained in association studies, a classification system that takes into account both *CYP3A5* and *CYP3A4* allelic statuses has been recently validated. This system allows clustering the patient into CYP3A poor, intermediate or extensive metabolizers (PM, IM or EM) and new Tac dosage guidelines have been proposed for each of

the clusters (figure 1).

Figure 1: New tacrolimus genotype-based dose recommendations (Allelic frequencies according to www.ensemble.org)



Mycophenolate mofetil (MMF) is a prodrug that undergoes pre-systemic metabolism to be converted into its active moiety; mycophenolic acid (MPA). MMF is typically administrated in combination to other IS drugs at a fixed dose without routine monitoring of MPA concentrations. Some studies have considered the possibility of applying the concept of TDM to MMF by following MPA exposure during therapy. The approach is justified by the fact that dose-normalized MPA AUCs vary more than 10-fold between patients and because of its narrow therapeutic window. However, the universal adoption of TDM for MPA is limited by the poor correlation observed between pre-dose concentrations and AUC. To counteract this limitation, some Bayesian forecasting limited sample strategies have been considered but results are conflicting. Other questions such as the utility of free versus total MPA concentration measurements persist and there is a lack of evidence highlighting a correlation between MPA exposure and clinical outcomes. Other TDM strategies measuring inosine monophosphate dehydrogenase activity as well as pharmacogenetic association have also been considered and constitute interesting research leads.

Mammalian target of rapamycin inhibitors (mTORi) are narrow therapeutic indexed drugs for which optimal exposure levels are also essential. The measurement of pre-dose concentrations constitutes a reliable index for mTORi TDM. Indeed, for everolimus, it has been demonstrated that rates of acute rejection increased when pre-dose concentration declines below 3ng/ml. The evidence of an upper limit is less obvious but data suggest that a range of 3-8ng/ml is adequate and TDM should be started 4-5 days after the first dose and after any changes. As for other IS, many factors can influence mTORi exposure for a given dose. Some of these factors can help to fine-tune the first dose reducing the risk of inadequate exposure in during the first week and the consequent error-trial dosage adaptations. These factors include but are not limited to genetic variations but also hepaticfunction, concomitant

drug administration (predominantly CYP3A and ABCB1 inhibitors/inducers).
Apart from classical TDM based on total blood concentrations, new monitoring strategies have been proposed principally for calcineurin inhibitors (i.e. tacrolimus and cyclosporine). Some of these alternatives propose pharmacodynamics-monitoring approaches. A first strategy is the monitoring of drug-target enzyme activity. A second proposed method consists of measuring the cellular responsiveness after *in vitro* stimulated response. Another alternative to whole blood concentrations measurements is to directly quantitate the drug into target cells as it is considered that blood concentrations do not necessarily reflect the effective fraction of the drug. As they provide more reliable and interesting data on drug concentrations, all these substitute strategies might be eligible and useful but their applicability for clinical routine use remains to be demonstrated.