Titre de thèse : ***Quantitative systems pharmacology approach to optimize personalized medicine: case of immunosuppressive therapy in solid organ transplantation***

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Mots clés : Quantitative Systems Pharmacology/ Mechanistic PK/PD modelling/ Modelling and Simulations/ Immunosuppressants

Profil et compétences recherchées : Life Sciences (Medicine, Pharmacy, etc.), Statistics, computational sciences

Description de la problématique de recherche :

The fact that drugs are used more widely and for longer periods after marketing authorization than during development has created a gap between what pharmaceutical research and development provides as evidence of safety/efficacy and what is observed in real life. There is therefore a need to anticipate the implications of differences in patients' characteristics and clinical practice between real life and drug development on treatment response. Good understanding and quantitative characterization of the processes leading to treatment outcomes and their determinants is crucial to achieve this goal. Our working hypothesis is that pathway (systems) models are powerful tools to describe the systems and drug behaviors as well as their determinants is a manner that ultimately will allow predicting patient outcome in yet unobserved scenarios and optimizing dosing regimens in real life. The aim of this research project is to propose/evaluate practical tools aiming to decrease treatment failure and adverse drug reactions, beyond what is achieved with the currently applied methods. Immunosuppressive drugs (in solid organ transplantation) are selected as paradigm compounds.

Thématiques Domaine Contexte :

The temporal behavior of the immune response (so-called disease model) in the presence of different combinations of immunosuppressive drugs will be described using a systems-based approach. The impacts of incorporating mechanistic pathways at different levels on model outcome will then be assessed using sensitivity analyses. The developed model shall then undergo qualification processes including: consistence with the known pathophysiology and mechanisms of action of drugs, assessment of the quality of model's estimated parameters, cross-correlations of performances on independent data from different sources. We shall also

determine the clinical impacts of the different intrinsic and extrinsic factors on the clinical response using covariate analysis as appropriate.

Objectifs :

The potential additive or synergistic effects of different drug combinations as frequently used in solid organ transplantation will be characterized for the first time in a quantitative manner.

Méthode : Quantitative Systems Pharmacology/ Mechanistic PK/PD modelling

Résultat attendu : Quantitative Systems Pharmacology-based models and Mechanistic PK/PD models for different immunosuppressants and simulations of optimal dosing in different situations/contexts.

Références bibliographiques :

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4. Wieland E, Olbricht CJ, Susal C *et al*. Biomarkers as a tool for management of immunosuppression in transplant patients. *Ther.Drug Monit.* 2010; 32: 560-572.
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6. Mussen F, Salek S, Walker S. A quantitative approach to benefit-risk assessment of medicines – part 1: the development of a new model using multi-criteria decision analysis. Pharmacoepidemiol Drug Saf. 2007 Jul;16 Suppl 1:S2-S15