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RACP Foundation Research Awards

FINAL REPORT

Project / Program Title		Personalised medicine: kinetic strategies to optimize renal transplant outcome
Name		Dr David Metz
Award Received		2016 Jacquot Research Entry Scholarship
Report Date		2 June 2017
Chief Investigator / Supervisor		Prof Francesco Ierino
Administering Institution		Murdoch Children's Research Institute
Funding Period	Start Date:	1 January 2016
	Finish Date:	31 December 2016

PROJECT SUMMARY

Kidney transplantation is the optimal treatment for most individuals with end-stage (irreversible) kidney failure. Successful transplantation requires chronic administration of medication to suppress the immune system and prevent rejection of the transplant. Unfortunately, this suppression of the immune system can lead to serious toxicities from the drugs themselves. Thus, dosing of anti-rejection drugs aims to tread the line between rejection from inadequate therapy, and drug-induced harms from excessive therapy.

Individuals differ in the way their body absorbs and eliminates therapeutic drugs from the body. For certain drugs, these differences can lead to clinically important differences in response, including a lack of benefit from the treatment or excessive toxicities. For such drugs, increasing precision by adjusting the dose in each individual to measured concentrations in the blood can help to optimise response. Mycophenolate mofetil (MMF) is an anti-rejection drug used in the majority of individuals undergoing kidney transplantation. Though current outcomes in the year post transplant are very good, we know that a proportion of patients will have suboptimal exposure in the initial weeks. There is currently no way to identify these individuals prior to transplantation.

We hypothesise that a detailed assessment of drug exposure in individuals taking MMF prior to kidney transplant will allow prediction of their optimal dose of this critical anti-rejection drug from time of transplant. We are testing this hypothesis by taking a series of blood samples before transplant after several days taking MMF, then again at in the early days and weeks after transplant. This trial is recruiting adults and children undergoing kidney transplantation in multiple transplant centres across Australia. If correct, this technique would be expected to reduce both transplant rejection and serious toxicities, improving both short and long term outcomes in kidney transplantation.

PROJECT AIMS / OBJECTIVES

- Examine the effect of kidney transplantation on free mycophenolic acid drug clearance. If pre-transplant pharmacokinetic parameters are predictive of posttransplant exposure, with acceptable random variability, this will provide proof-of-concept of a technique to optimise MMF dose from time of transplant.
- Examine in detail the relationship peri-transplant and in the initial post-transplant months between total MPA, free MPA and covariates that affect plasma protein binding.
- We are doing this through pharmacometric analysis of pharmacokinetic data collected from "The ADOPT Trial: Dose Optimisation Prior to Transplantation". This is a prospective, multisite pharmacokinetic trial involving adults and children undergoing kidney transplantation.

SIGNIFICANCE AND OUTCOMES

A technique to optimise MMF dose prior to kidney transplantation will for the first time offer the opportunity to identify a priori individuals requiring larger MMF doses to achieve optimal exposure from time of kidney transplantation. Underexposure in the initial week after kidney transplantation is causally associated with increased risk of rejection, is casually associated with increased risk of rejection particularly in recipients at high risk.

If successful, we plan to follow this proof-of-concept trial with a larger randomised concentration-controlled trial testing the benefit of concentration-controlled dosing to a target free mycophenolic acid exposure, commencing prior to transplantation.

PUBLICATIONS / PRESENTATIONS

Through knowledge and expertise gained through this work, the recipient (David Metz) has presented on mycophenolic acid therapeutic drug monitoring as invited speaker at the Transplantation Society of Australia and New Zealand "Transplantation Masterclass" 2017, and the ASCEPT Australia and New Zealand Therapeutic Drug Monitoring Meeting 2017.