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PROGRESS REPORT

Project / Program Title		Comparison of Immunosuppressant Drug Pharmacokinetics in Indigenous versus Non-Indigenous Australian Kidney Transplant Recipients.
Name		Dr Katherine A. Barraclough
Award Received		2017 Jacquot Research Establishment Fellowship
Report Date		12 June 2017
Chief Investigator / Supervisor		Alan Cass
Administering Institution		The Royal Melbourne Hospital
Funding Period	Start Date:	1 January 2017
	Finish Date:	31 December 2017

PROJECT SUMMARY

People who receive a kidney transplant need medicines to stop their body from rejecting the new kidney. These are called ‘immunosuppressive’ or ‘anti-rejection’ medicines. If too little of these medicines is given, the body will reject the new kidney. If too much is given, the body might struggle to fight infections. It can be difficult to find a balance between giving too much and giving too little.

Indigenous Australians who receive a kidney transplant experience more rejection and get more infections compared with non-Indigenous Australians. Because of this, they are more likely than non-Indigenous Australians to lose their kidney and die after kidney transplant surgery. There is an urgent need to further investigate why this is occurring.

Evidence suggests that some ethnic groups metabolise or process the anti-rejection medicine differently. This has not been studied in Indigenous individuals. The aim of this study is to investigate for differences in processing of anti-rejection medicines between Indigenous and non-Indigenous Australians. If differences between ethnic groups were identified, this would provide rationale for examination of differential dosing of these medicines between Indigenous and non-Indigenous kidney transplant recipients. This in turn might lead to reduced rejection, infection and other toxicities in Indigenous individuals, and thereby improved kidney transplant outcomes.

PROJECT AIMS / OBJECTIVES

Aims of this study:

Primary

- To compare immunosuppressant drug pharmacokinetic parameters and patient dosing requirements in Indigenous versus non-Indigenous adult kidney transplant recipients.

Secondary

- To establish the influence of Indigenous ethnicity as a covariate in a previously published population pharmacokinetic model for tacrolimus;
- To develop population pharmacokinetic models for mycophenolic acid (MPA) and prednisolone;
- To examine the relationship between tacrolimus pharmacokinetics and the CYP3A5 6986A>G single nucleotide polymorphism in Indigenous kidney transplant recipients;
- To examine the relationship between immunosuppressant drug pharmacokinetics and markers of immune function (torque teno virus (TTV) and CXCL-9) in Indigenous kidney transplant recipients;
- To investigate the correlation between serum and saliva levels of MPA and prednisolone in Indigenous kidney transplant recipients.

To achieve these aims, a prospective observational cohort study is underway. The study will enroll 40 Indigenous and 40 non-Indigenous (Caucasian) kidney transplant recipients matched 1:1 for age, gender, diabetic status, time post-transplantation and diltiazem use. All patients enrolled need to be receiving tacrolimus and mycophenolate mofetil (MMF) ± prednisolone and undergo blood sampling pre- and at 1, 2, and 4 hours post-dosing of medications. Tacrolimus, free and total mycophenolic acid (MPA; the activity drug moiety of MMF) and MPA-7-O-glucuronide (MPAG, the major MPA metabolite), free and total prednisolone and cortisol binding globulin concentrations will be measured from plasma separated from each sample using high performance liquid chromatography (HPLC) methodology. Patient CYP3A5 6986 genotype and TTV plasma load will be determined from a single whole blood sample using real-time PCR methodology. Urine CXCL-9 concentrations will be determined from a urine sample collected while the patient is in hospital for blood sampling. Saliva samples will be collected from patients simultaneously with blood samples pre- and at 1, 2, and 4 hours post-dosing of medications and tested for MPA concentrations.

Area under the concentration time-curve from 0-4 hours post-dose (AUC0-4) will be calculated for each patient using non-compartmental analysis (trapezoidal rule) and estimated using various previously published multiple regression derived limited sampling strategies (7). AUC values will be used to calculate a surrogate estimate of total immunosuppressant oral clearance (CL/F) (Dose/AUC). Tacrolimus, MPA and prednisolone CL/F will be compared in Indigenous and non-Indigenous groups based on a Student's t-test or other appropriate statistical analysis, depending on parameter distribution.

Population modelling will be performed using NONMEM, an industry and FDA endorsed program. Different distribution models (one-, two- and three- compartment) with first order elimination and which allow for enterohepatic recirculation (in the case of MPA) will be tested to determine which is most appropriate. The influence of patient covariate factors (e.g. indigenous ethnicity, weight, age, renal function and CYP3A5 6986 genotype) on the pharmacokinetics of the immunosuppressive agents will be investigated using a stepwise covariate analysis in NONMEM, in which covariates will be incorporated in linear, exponential and power relationships and retained if identified as both clinically and statistically significant.

The degree of association between TTV and CXCL-9 concentrations and each of the immunosuppressant drugs will be assessed using the Spearman's correlation coefficient test and the Wilcoxon rank-sum test. Multivariate logistic regression with stepwise elimination will be used to examine the influence of drug exposure and relevant clinical covariates on TTV and CXCL-9 concentrations.

Correlations between plasma and saliva drug concentrations will be evaluated using regression analysis.

SIGNIFICANCE AND OUTCOMES

If differences in drug exposure between ethnic groups are identified, this would provide rationale for examination of differential immunosuppressant drug dosing strategies depending on ethnicity. This in turn might lead to reduced immunosuppressant drug inefficacy and toxicities in Indigenous individuals, and thereby improved kidney transplant outcomes. Furthermore, because there has been no study of drug disposition in Indigenous individuals in any context, this study, if positive, could have much broader implications beyond immunosuppressant drug therapies. Specifically, it might provide rationale for pharmacokinetic investigations of other drugs in this patient group, with the potential for improved dosing strategies and thereby clinical outcomes.

The population modelling will add significantly to our knowledge of the disposition of these drugs in Australian kidney transplant recipients, and provide a sophisticated way of testing the influence of Indigenous ethnicity. This study allows development of population models that can be used specifically in Indigenous patients. Use of a population model in combination with a Bayesian dosage prediction method should provide a very powerful means of tailoring immunosuppressant therapy to maintain efficacy while minimising graft and life-threatening toxicities, thereby addressing one of the major ongoing challenges facing kidney transplantation today. Implementation of probability-based computerised dosing could lead to more efficient immunosuppressant treatment with improved patient outcomes and reduced health care costs.

In addition, this study will examine the CYP3A5 6986 genotype of study participants to allow determination of its contribution to any differences in tacrolimus pharmacokinetics between racial groups. Measurement of blood concentrations of torque teno virus (TTV) and urine concentrations of CXCL-9 will also allow examination of the impact of immunosuppressive drug exposure on immune function and hopefully add to the limited literature that currently exists on this.

Lastly, collection of saliva samples is more convenient and patient-friendly than collection of blood samples and thus may offer a promising alternative for drug monitoring. However, further clinical studies are required to establish the usefulness of saliva samples for immunosuppressant drug monitoring in Indigenous kidney transplant recipients.

The involvement of multiple major sites that care for Indigenous kidney transplant recipients provides a tremendous opportunity to ensure that findings from this project are applicable to the broader Indigenous kidney transplant population, and can be implemented in clinical practice and incorporated into guidelines.

PUBLICATIONS / PRESENTATIONS

None