Characterization of Prescribed Immunosuppression Reduction in Kidney Transplant Patients

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Background

- Antibody-mediated rejection (ABMR) is the predominant form of renal allograft loss following transplantation.
- ABMR occurs as a result of anti-HLA antibodies directed towards allograft endothelium.
- At present, there are few effective therapies at controlling the humoral response once ABMR has begun.
- Current practice aims at preventing ABMR through adequate immunosuppression beginning at the time of transplantation.
- In British Columbia (BC), standard immunosuppression regimen includes calcineurin inhibitor (CNI), usually tacrolimus, an antimetabolite, usually mycophenolic acid (MPA), and/or steroid.
- Therapeutic drug monitoring (TDM) is employed to ensure patients are receiving adequate CNI.
- However, TDM is not routinely used to monitor MPA, rather all patients empirically receive 1440mg of MPA-equivalents daily.
- Prescribed MPA dose reduction is common due to adverse effects, such as leukopenia, diarrhea, infection, and malignancy.
- While common, prescribed MPA dose reduction is largely uncharacterized, including the effect of dose reduction on graft survival.

Methods

- This study involved the PROOF cohort which enrolled over 600 kidney transplant patients in BC from 2005-2012 and were followed prospectively to better characterize their kidney transplant outcomes.
- PROOF data was extracted from the BC Provincial Renal Agency PROMIS database.
- Clinical data was available for 408 individuals; a further 74 were removed from analysis due to incomplete data, or because the date of transplant was before January 1st, 2005.
- MPA dosing was determined for the first 365 days following kidney transplant.
- Authors (RW, AK) assigned a rationale for each dose reduction based on bloodwork within 14 days preceding the dose reduction.
- Kaplan-Meier survival estimates were calculated for:
  1. Time to first dose reduction
  2. Time to graft failure (defined as time to dialysis) in relation to MPA exposure

Baseline Characteristics	Full dose (N=121)	Reduction (N=213)	P Value
Age ± SD (years)	50.2±13.2	49.0±13.1	0.4431
Female	37 (30.6%)	81 (38.0%)	0.1910
Race			0.5153
Caucasians	79 (65.3%)	154 (72.3%)	
Multiple Transplants	9 (7.4%)	21 (9.9%)	0.5524
PRA Peak Level*	N = 64	N = 106	0.2089
Mean	3.2	6.0	
Median	0.0	0.0	
Donor Type			0.1012
DCD	0	4 (1.9%)	
LD	82 (67.8%)	124 (58.2%)	
NDD	39 (32.2%)	85 (39.9%)	
Donor Age ± SD (years)	41.8 ± 13.2	45.2 ± 14.4	0.0318
Cold Ischemia Time*	N = 115	N = 205	0.0120
Mean ± SD (hours)	6.2 ± 4.3	7.8 ± 5.6	

PRA = Panel Reactive Antibody, DCD = Donation after Cardiac Death, LD = Living Donor, NDD = Neurologic Determination of Death

Table 1: Baseline characteristics of 334 patients from the PROOF cohort

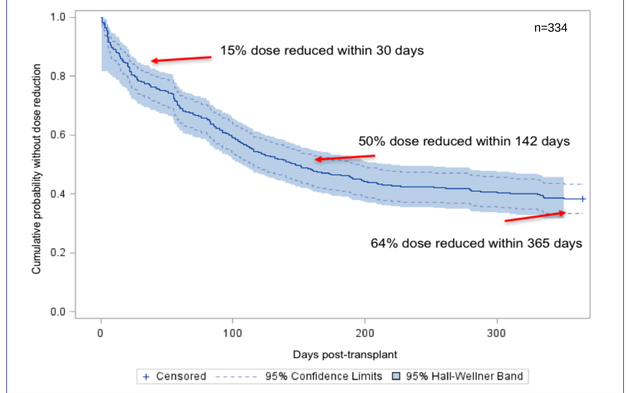


Figure 1: Kaplan-Meier survival curve for time to first MPA dose reduction

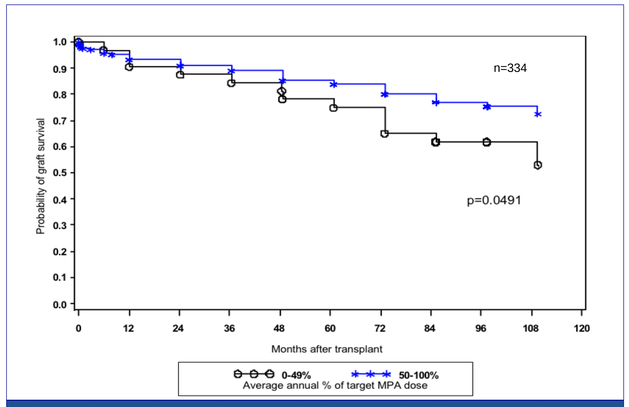
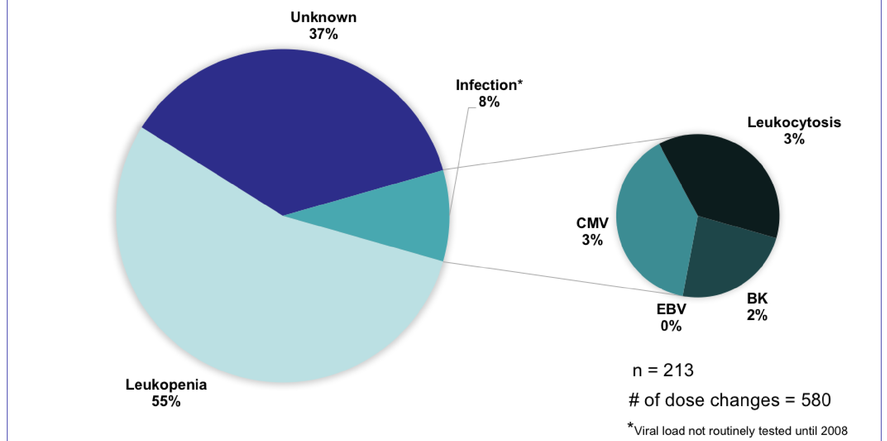


Figure 2: Kaplan-Meier survival curve for time to graft failure



CMV = Cytomegalovirus, EBV = Epstein-Barr Virus, BK = BK polyoma virus

Figure 3: Reasons for MPA dose reduction

Results

- Recipient characteristics did not differ among patients who maintained MPA dose and those who had prescribed reductions.
- Donor age was statistically older and cold ischemia time longer in the group of patients who had a prescribed dose reduction, but clinical importance is unclear.
- Median time to first dose reduction was 142 days; 64% of patients had at least one dose reduction by the first year post-transplant.
- Dose reductions occurred most frequently due to leukopenia, a marker of over immunosuppression.
- After a median 97 months of follow-up, there was a statistically significant increase in graft failure among patients who had a dose reduction in the first year post-transplant.

Conclusions

- Prescribed immunosuppression reduction occurred frequently in clinical practice, most commonly due to leukopenia.
- The safety of prescribed immunosuppression reduction is not known. Patients requiring dose reduction appeared to have inferior outcomes compared to those who did not.
- Further elucidating the cause for graft failure in these patient is warranted given the frequency at which dose reduction occurred.

Limitations

- Retrospective study that relied on accuracy of manually entered clinical data into electronic health record
- Potential confounders for graft failure might not have been characterized
- Assumption that patients were adherent to their immunosuppression regimen

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