Over-exposure of obese patients with standard body-weight based tacrolimus dosing

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Introduction

Tacrolimus has significant pharmacokinetic variability between patients, which is further complicated by its significant side effect profile and very narrow therapeutic window, with frequent under and over exposure during initiation of treatment (**Figure 1**). Initial dose is usually based on body-weight, in spite of the fact that body weight is not a significant predictor of tacrolimus exposure in a number of multivariate analyses¹. The difficulty in dosing Tacrolimus is, in part, related to pharmacogenetic heterogeneity in patient expression of functional Cytochrome P450 (CYP) 3A enzymes CYP3A4 & CYP3A5 involved in first-pass metabolism. Additionally, ethnicity is predictive of tacrolimus exposure with Black patients requiring two-fold higher initial dose to achieve target blood concentrations (irrespective of CYP3A5 genotype).

Hypothesis

We have tested the hypothesis that obese patients are over-exposed to tacrolimus as a consequence of body-weight based dosing. CYP3A5 Genetics and ethnicity were tested as potential confounding factors.

Figure 1: Observed patient induction patterns of under and overexposure and associated side effects. TDM allows correction and optimisation of exposure eventually.

1 - Overexposed Scenario
(Tacrolimus concentration >12 ng/mL)

Nephrotoxicity
Neurotoxicity
Hypertension
Diabetes Mellitus (insulin resistance)

2 - Therapeutic Window (Ideal Scenario)
(Tacrolimus concentration between 8-12 ng/mL)

3 - Underexposed Scenario
(Tacrolimus concentration <8 ng/mL)
Acute Renal Failure/Delayed Graft Function
Acute Rejection

Methods

The study had ethical approval and all patients gave written informed consent. Initial tacrolimus total daily dose was 0.15-0.2 mg/kg, or 0.3 mg/kg for Black patients (n=36). The first blood concentration measured by immunoassay between days 1 and 3 after transplantation was analysed. Height and weight at the time of transplantation were used to calculate BMI. CYP3A5 genotype was determined using a Roche Lightcycler.

Results

A total of 323 patients had complete data to be included in the study. Data was analysed using GraphPad Prism Version 7 (CA, USA). Patient demographics are listed in **Table 1** below

	Underweight (n=14)	Normal weight (n=151)	Overweight (n=113)	Obese (n=42)
Age	17 to 55 (42)	21 to 61 (48)	22 to 58 (44)	19 to 62 (51)
Gender	F=10, M=4	F=81, M=70	F=63, M=50	F=17, M=25
Donor Status	14% L 86% D	24% L 76% D	19% L 81% D	17% L 83% D

BMI Comparison

Kruskal-Wallis analysis comparing different BMI categories with tacrolimus concentration found normal weight individuals had a lower tacrolimus concentration compared with overweight patients (P=0.0038) and obese patients (P=0.0009). (**Graph 1**)

Graph 1: Comparison of BMI against first tacrolimus concentration

Genetic and Ethnicity Comparison

Kruskal-Wallis analysis comparing D1 tacrolimus concentrations between the CYP3A5 expressers and non-expressers found no significant differences (P=0.56) (**Graph 2**). Kruskal-Wallis analysis comparing black patients of various BMIs to the general population found no significant differences between each category (P=0.51). (**Graph 3**)

Graph 2

Graph 3

Discussion

The results clearly show that obese patients tend to be over-exposed to tacrolimus with standard body-weight based dosing (**Graph 1**) as already demonstrated by Andrews et al (2017)¹. Genetic and ethnic secondary analysis to test for possible confounding influences found no significant differences which adds further weight to evidence that linear based dosing is the over-exposing larger individuals and exposing them to potentially severe consequences as per **Figure 1**.

Conclusion

Overall this study suggests that it may be more appropriate to use ideal body weight than actual weight when dosing patients with tacrolimus, particularly if they're overweight or obese.

References

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