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Ethnic differences in early blood tacrolimus concentrations after kidney transplantation: a retrospective observational study

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Abstract

Background Despite evidence of variation in CYP3A5 expressor status between different ethnic groups, many transplant centres operate a 'one size fits all' immunosuppression policy in which all kidney transplant recipients receive the same weight-adjusted daily dose of tacrolimus, adjusted subsequently to achieve target blood concentrations.

Methods We evaluated retrospective blood tacrolimus concentrations and tacrolimus doses in 382 patients based on self-described ethnicity.

Results Median tacrolimus concentrations were lower in Black patients than those from other ethnic groups for the first four weeks following transplantation. More than 70% of measurements in Black patients were below target in the first and second weeks, and Black ethnicity was strongly associated with early subtherapeutic tacrolimus concentrations (odds ratio 3.49, $p < 0.001$). There were no significant differences in transplant outcomes between ethnic groups, although the rate of acute rejection was higher in Black patients, despite greater use of anti-thymocyte globulin induction therapy in these patients.

Discussion There is emerging evidence to support either prescribing based on CYP3A5 genotyping, or the empirical use of higher starting doses in Black patients. However, notwithstanding the complexities inherent in our understanding of ethnic identity, we advocate an approach where clinicians act proactively to avoid under-dosing in Black patients.

Clinical trial number Not applicable. Bart's Health NHS Trust audit number: 13,204.

Keywords Transplant, Tacrolimus, Calcineurin inhibitor, Ethnicity, Race

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Background

Black patients worldwide face a higher incidence of end stage renal disease, longer waits for kidney transplantation and worse transplant outcomes compared to their counterparts in other ethnic groups [1, 2]. Adopting institutional practices to minimise these disparities is a key priority in achieving the equity of care that all patients deserve [3, 4].

Tacrolimus is a first-line immunosuppressive agent in kidney transplant recipients, which has been repeatedly shown to improve graft outcomes compared to other drugs [5–7]. The CYP3A5 expressor phenotype, characterised by the presence of at least one CYP3A5*1 allele, results in enhanced tacrolimus clearance from the blood and lower blood tacrolimus concentrations than in patients homozygous for the CYP3A5*3 allele. This 'expressor' phenotype is far more common in Black patients than those of other ethnic groups, who may require 1.5–2 times the dose of tacrolimus used in other patients to achieve therapeutic blood concentrations [8, 9]. However, a 'one size fits all' policy, where all patients being transplanted are started on the same daily tacrolimus dose per kilogram, subsequently adjusted to achieve target blood concentrations, ignores such potential interpatient variability and risks leaving some patients at risk of having sub-therapeutic tacrolimus concentrations in the early post-transplant period.

We sought to evaluate whether ethnic differences were present in the early tacrolimus concentrations within our cohort, and whether our policy may contribute to poorer transplant outcomes for Black patients in our unit.

Methods

Study design and approval

This study was conducted as an observational service analysis of the existing transplant immunosuppression policy at the Royal London Hospital.

The Institutional Review Board (IRB) granting approval was the ***Barts Health Clinical Effectiveness Unit*** (audit number 13204). It adheres to the Declaration of Helsinki.

Human Ethics and Consent to Participate declarations: Not Applicable.

Clinical trial number: Not Applicable.

Participant selection

All recipients of consecutive kidney transplants performed at the Royal London Hospital between April 2017 and April 2020 were screened for inclusion. Patients were excluded whose self-defined ethnicity was not Asian, Black or White, or who did not receive at least 12 weeks of tacrolimus immunosuppression after transplantation.

Immunosuppression policy

All kidney transplant recipients in our unit during the study period were classified either as standard or high immunological risk on the basis of recipient characteristics and characteristics of the donor kidney: recipients were deemed to be at high immunological risk if they had anti-human leucocyte antigen (HLA) antibodies present at >2000 mean fluorescent intensity in current or historical sera; if they had lost a previous kidney allograft due to rejection; if they were receiving a third or subsequent kidney allograft; if they were receiving a deceased donor transplant with a cold ischaemia time of >24 h; or if they were receiving a deceased donor transplant from an extended criteria donor. Such high-immunological risk recipients received anti-thymocyte globulin (ATG) as induction immunosuppression, whilst those deemed to be standard immunological risk received anti-IL-2 induction (basiliximab). All patients also received 500 mg pulsed methylprednisolone at induction.

Maintenance immunosuppression was the same irrespective of immunological risk, and consisted of triple therapy including tacrolimus (twice daily ProfGraf® from Astellas Pharma Lt., initial loading dose of 0.15 mg/kg ideal body weight followed by 0.075 mg/kg twice daily), mycophenolate mofetil 1 g twice daily, and prednisolone (initially 20 mg daily, weaning to 5 mg daily by week 12 after transplantation). Tacrolimus doses were adjusted to achieve trough levels of 8-12ng/μL for the first three months following transplantation, with dose changes to achieve this at the discretion of individual clinicians. Patients undergoing planned live donor transplantation were started on tacrolimus 5 days prior to transplantation and did not receive a loading dose prior to surgery. No patients were genotyped for the CYP3A5 allele.

Data collection

Trough blood tacrolimus concentrations were assessed three times weekly during patients' inpatient stay following transplantation, and subsequently at each clinic visit (typically twice weekly for the first 4–8 weeks following transplantation, and then weekly and two-weekly following this). Samples were analysed in the biochemistry laboratory at the Royal London Hospital using mass spectrometry on a Quattro Premier XE (Walters, Manchester, UK) and extracted, along with demographic and clinical details, from the electronic patient record.

The proportion of results that were below, within and above the target range (blood tacrolimus concentrations 8-12ng/μL) were recorded for all patients for each of the first twelve weeks following transplantation. Tacrolimus variability was assessed by calculating the coefficient of variation, by dividing the standard deviation by the mean of all available blood tacrolimus concentrations between day 14 and day 84 after transplantation.

Statistical analysis

Statistical analysis was carried out in SPSS v28.0 (IBM, New York). Non-parametric statistics using the Kruskal-Wallis and Chi-Squared tests were used to compare median tacrolimus levels between patients in different ethnic groups at different time points; as well as the proportion of patients in each group whose levels were below, within and above the target range. Binary logistic regression was used to perform multivariate analysis for the risk of having mean blood tacrolimus concentrations below the target range (< 8ng/μL) in the second week following transplantation, developing biopsy-proved rejection within the first 90 days of transplant, and suffering graft failure by three years following transplantation; factors assessed for contribution to each of these outcome variables included patient age quartile, sex, donor type (live vs. deceased) and induction immunosuppression as well as ethnic group.

Results

Study population

A total of 499 transplants occurred during the study period (April 2017-April 2020), of which 117 were excluded from the study, because these patients did not have a self-identified ethnic identity recorded ($n = 69$), reported mixed ethnicity ($n = 8$), reported an ethnic identity other than Asian, Black or White ($n = 21$), stopped tacrolimus treatment within three months of transplantation ($n = 18$) or did not receive any tacrolimus immunosuppression at all ($n = 1$). Table 1 describes the 382 patients included within the study, broken down between the three main ethnic groups, which were present in similar numbers (Asian 148, 38.7%; Black 106, 27.7%; White 128, 33.5%).

The median age of participants in the study was 50 (interquartile range 41–60 years). There was no difference between median ages in different groups (50 vs. 54 vs. 52 years in Asian, Black and White patients, $p = 0.16$). 236/382 patients were male (61.8%). Glomerular disease was the commonest primary renal disease overall (81/382, 21.2%), although diabetic nephropathy was commonest in Asian and Black patients.

White patients were more likely to have live donor transplants than patients in other ethnic groups (39.8% of transplants in white patients vs. 20.3% in Asian and 17% in Black patients, $p < 0.01$). Black patients had a significantly longer duration of renal replacement therapy prior to transplantation than patients in the other ethnic groups (median 1662 days in Black patients vs. 1038 in Asian and 1149 in White patients, $p < 0.001$). They received more ATG as opposed to IL-2 based induction therapy, although this was not significant (27.4% of Black patients received ATG induction vs. 16.2% and 19.5% of Asian and White patients respectively, $p = 0.09$).

Table 1 Characteristics of patients included in the study (number, percent) according to self-declared ethnicity. Significance is assessed using the Kruskal-Wallis test for continuous data and the Chi-squared for categorical data

	Asian	Black	White	*p*	Whole cohort
Number	148	106	128		382
Male sex	95 (64.2)	65 (61.3)	76 (59.4)	0.709	236 (61.8)
Median age	50	54	52	0.16	52
Median days on replacement therapy	1038	1662	1149	< 0.001	1264
Primary renal disease					
Diabetic nephropathy	41 (27.7)	23 (21.7)	7 (5.5)		71 (18.6)
Hypertensive nephropathy	6 (4.1)	16 (15.1)	4 (3.1)		26 (6.8)
Glomerulonephritis	31 (20.9)	19 (17.9)	31 (24.2)		81 (21.2)
Hereditary nephropathy	12 (8.1)	5 (4.7)	16 (12.5)		33 (8.6)
Obstructive nephropathy	2 (1.4)	4 (3.8)	7 (5.5)		13 (3.4)
Tubulointerstitial disease	5 (3.4)	0	2 (1.6)		7 (1.8)
Other	4 (2.7)	9 (8.5)	5 (3.9)		18 (4.7)
Unclassified/unknown	47 (31.8)	30 (28.3)	56 (43.8)	< 0.001	133 (34.8)
Donor type					
Live	30 (20.3)	18 (17)	51 (39.8)		99(25.9)
Deceased	118 (79.7)	88 (83)	77 (60.2)	< 0.001	283 (74.1)
Induction immunosuppression					
ATG	24 (16.2)	29 (27.4)	25 (19.5)		78 (20.4)
IL-2	124 (83.8)	77 (72.6)	103 (80.5)	0.09	304 (79.6)
Graft number					
1	128 (86.5)	83 (78.3)	99 (77.3)		310 (81.2)
2	17 (11.5)	18 (17)	25 (19.5)		60 (15.7)
3	3 (2)	3 (2.8)	3 (2.3)		9 (2.4)
4	0	2 (1.9)	1 (0.8)	0.339	3 (0.8)

Differences in early blood tacrolimus concentrations between ethnic groups

Blood tacrolimus concentration measurements were significantly more likely to be below the target range of 8-12ng/ml in samples from Black patients than in those from Asian and White patients in the first two weeks following transplantation, when more than 70% of measurements from Black patients were subtherapeutic (Fig. 1). Whilst median blood tacrolimus concentrations were just within the target range in Asian and White patients in the first two weeks after transplant, they were well below the target range in Black patients at these time points (6.0 and 6.45ng/ml during the first and second weeks, respectively). In the third and fourth weeks, median blood tacrolimus concentrations in Black patients rose to within the target range, but remained lower than median concentrations in Asian and White patients during the same periods (8.23 vs. 9.05 and 9.3ng/ml in Black, Asian and White patients in the third week, $p = 0.042$; 8.78 vs. 9.43 vs. 10.05 in the fourth week, $p = 0.02$). Only by the fifth week after transplantation were differences in concentrations abolished between patients of different ethnicities (Fig. 2). Tacrolimus variability as assessed by the coefficient of variation for results between day 14 and 84 after transplantation was higher in Black patients than those of other ethnic groups (0.29 in Black patients vs. 0.25 in Asian and 0.23 in White patients, $p < 0.001$).

Multivariate analysis (Table 3) showed Black ethnicity to be a strong predictive factor (odds ratio 3.49, $p < 0.001$) for below-target tacrolimus concentrations in the second post-transplant week. Increasing age quartiles were associated with reduced risk of below-target concentrations (OR 0.78, $p = 0.023$) suggesting that younger patients may also require higher initial tacrolimus dosing (or perhaps closer monitoring for drug adherence). In univariate analysis within Black patients, there was no difference between mean tacrolimus concentrations between ATG-induced and IL2-induced transplant recipients in any of the time periods after transplantation, perhaps implying that lower tacrolimus concentrations in Black patients were not explained by a greater tolerance by clinicians of lower concentrations in the context of ATG induction immunosuppression.

Differences in tacrolimus dosing between ethnic groups

Differences between ethnic groups in tacrolimus dose were apparent from day 7 and increased through the study period (Table 2). By day 84 after transplant, the median tacrolimus dose in Black patients (0.22 mg/kg) was roughly twice that in Asian (0.11 mg/kg) and White patients (0.09 mg/kg, $p < 0.001$). Mean tacrolimus doses showed the same trend in patients from all three ethnic groups, rising to peak at around day 21–28

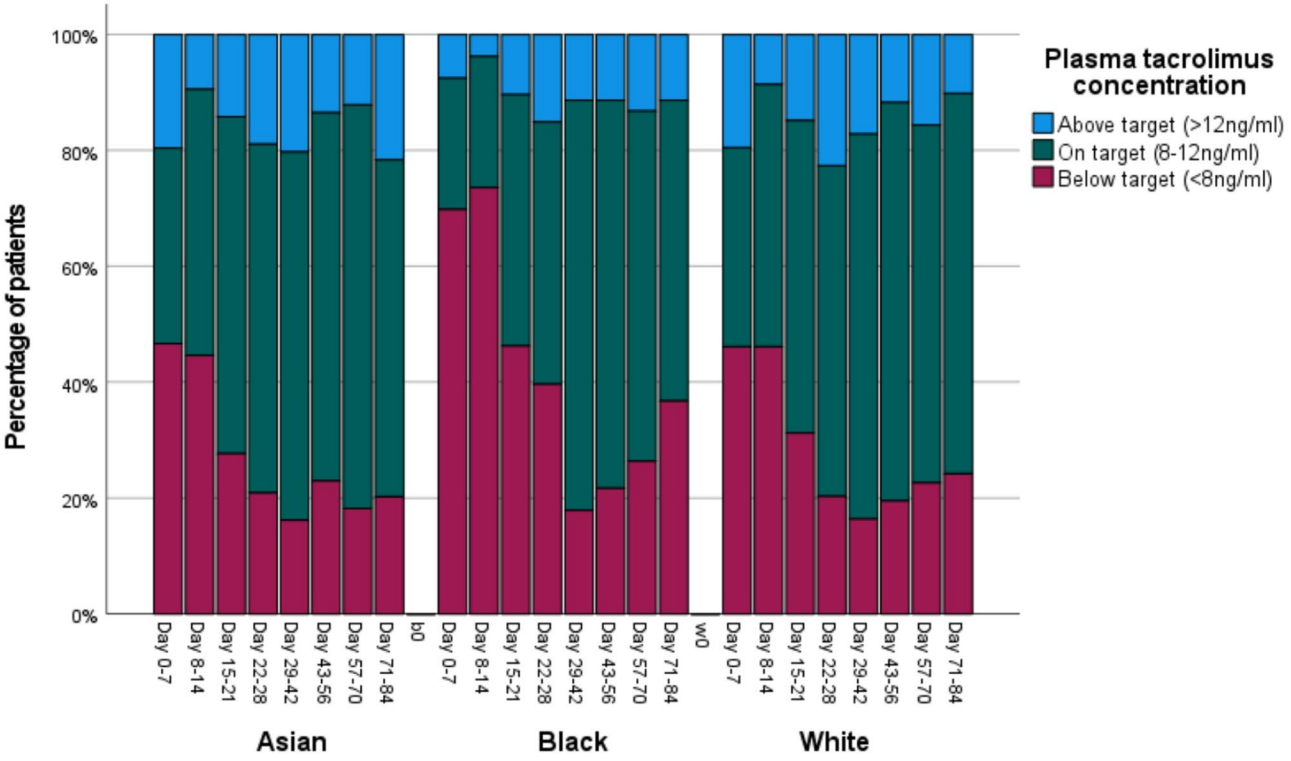

Fig. 1 Proportion of blood tacrolimus concentration measurements that were below, within or above the target range (8-12ng/ml) if different ethnic groups at different time periods after transplantation

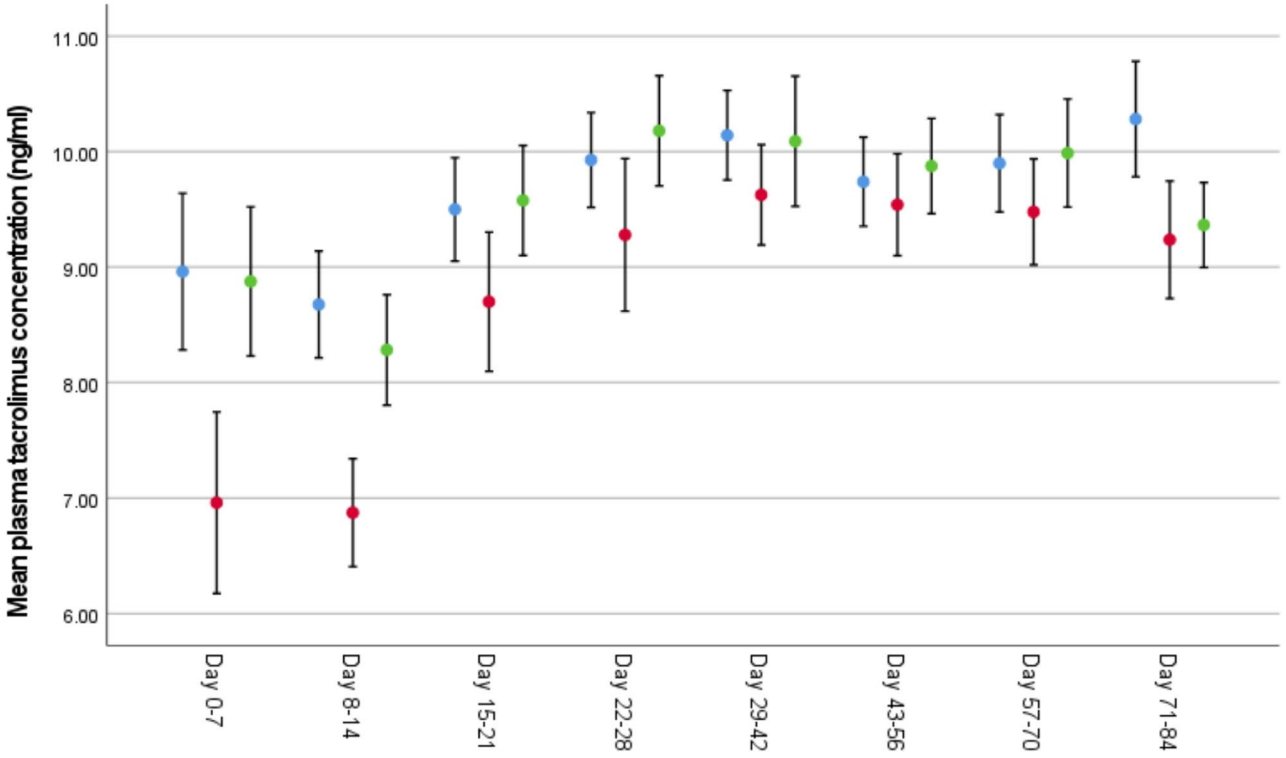

Fig. 2 Mean plasma tacrolimus concentrations in Asian (blue circles), Black (red circles) and White patients (green circles) at different periods after transplantation, with standard error

post-transplant and then reducing towards the end of the study period (Fig. 3).

Transplant outcomes

There were no significant differences between ethnic groups in transplant outcomes including graft and patient survival at 1 year, graft function, biopsy proven rejection at 90 days or various infective complications (Table 2). Multivariate analysis revealed that rejection was more common in live donor transplants (OR 2.29, $p = 0.037$), and (non-significantly) in those receiving IL2 induction (OR 4.115, $p = 0.06$, Table 3). Rejection was commoner in Black patients (affecting 11.3% of transplants into Black recipients vs. 8.8% in Asian recipients and 6.3% in White recipients), but this was not significant in univariate analysis ($p = 0.388$), and although Black ethnicity was associated with an increased rate of rejection in multivariate analysis this narrowly escaped significance (OR 2.675, $p = 0.05$).

Discussion

We have shown that a 'one size fits all' approach to tacrolimus dosing in kidney transplantation is associated with lower blood tacrolimus concentrations in the early post-transplant period in Black patients. This was associated with an increased rate of acute rejection which did not prove statistically significant (perhaps mitigated by higher ATG use in Black patients), although there were no differences in longer-term transplant outcomes between ethnic groups. Black patients were receiving around twice as much tacrolimus than patients in other ethnic groups at day 84 after transplantation. Although the association between race/ethnicity and tacrolimus metabolism is not new, our study highlights the scale of the problem and the potential need for pre-emptive strategies to address it.

One possible alternative explanation is that the differences in tacrolimus concentrations we have demonstrated reflect differences in drug adherence between patients in different ethnic groups. Although we feel (based on the wider published literature) that the differences in CYP3A5 expressor phenotype are more likely to be responsible, it is nevertheless critical that all patients are adequately educated about their medication prior to hospital discharge after transplantation, with particular reference to their level of health literacy.

Although we were unable to prove that below-target tacrolimus concentrations in Black patients were associated with rejection rates or poorer transplant outcomes, evidence from elsewhere suggests that this may be the case, and that kidney allografts are at their most immunogenic in the early post-transplant period [10–13]. Reassuringly, despite receiving higher doses of tacrolimus than other groups, Black patients in this study did

Table 2 Tacrolimus concentrations, variability, dosing and transplant outcomes. Significance is assessed using the Kruskal-Wallis test for continuous data and the Chi-squared for categorical data

	Asian	Black	White	*p*	Whole cohort
Tacrolimus concentration (median, interquartile range), ng/ml					
Days 0–7	8.2 (5.25)	6.0 (4.04)	8.2 (5.15)	< 0.001	7.65 (4.7)
Days 8–14	8.35 (3.7)	6.45 (2.6)	8.35 (3.7)	< 0.001	7.6 (3.7)
Days 15–21	9.05 (3.11)	8.23 (3.41)	9.3 (3.25)	0.042	8.8 (3.35)
Days 22–28	9.43 (3.41)	8.78 (3.63)	10.05 (3.55)	0.02	9.45 (3.45)
Days 29–42	10.05 (2.95)	9.28 (2.66)	9.5 (2.9)	0.526	9.55 (2.75)
Days 43–56	9.63 (2.9)	9.1 (2.03)	9.9 (2.8)	0.208	9.55 (2.7)
Days 57–70	9.7 (2.24)	9.38 (3.06)	9.7 (3.05)	0.146	9.6 (2.8)
Days 71–84	9.8 (3.46)	9.15 (2.74)	9.3 (2.6)	0.068	9.5 (2.93)
Tacrolimus concentration variability (coefficient of variation)	0.25 (0.14)	0.29 (0.2)	0.23 (0.13)	< 0.001	0.26 (0.16)
Tacrolimus dose (median, interquartile range), mg/kg/day					
Day 7	0.15 (0.06)	0.17 (0.08)	0.14 (0.04)	< 0.001	0.15 (0.06)
Day 14	0.16 (0.08)	0.22 (0.14)	0.14 (0.07)	< 0.001	0.16 (0.1)
Day 21	0.16 (0.1)	0.25 (0.13)	0.14 (0.08)	< 0.001	0.16 (0.13)
Day 28	0.15 (0.1)	0.25 (0.16)	0.13 (0.09)	< 0.001	0.16 (0.13)
Day 42	0.13 (0.1)	0.24 (0.16)	0.12 (0.1)	< 0.001	0.15 (0.14)
Day 56	0.12 (0.1)	0.23 (0.17)	0.11 (0.09)	< 0.001	0.14 (0.14)
Day 70	0.12 (0.1)	0.23 (0.16)	0.1 (0.08)	< 0.001	0.13 (0.12)
Day 84	0.11 (0.09)	0.22 (0.15)	0.09 (0.08)	< 0.001	0.12 (0.13)
Transplant outcomes					
1-year graft survival (number, %)	135 (91.2)	97 (91.5)	118 (92.2)	0.958	350 (91.6)
1-year patient survival (number, %)	142 (96.6)	102 (96.2)	128 (100)	0.095	372 (97.6)
90-day eGFR (median ml/min, interquartile range)	45 (27)	34 (19.75)	43.5 (23)	0.329	42 (24)
1-year eGFR (median ml/min, interquartile range)	46 (21)	36 (23.25)	41 (28)	0.092	42 (25)
Biopsy-proven acute rejection within 90 days (number, %)	13 (8.8)	12 (11.3)	8 (6.3)	0.388	33 (8.6)
CMV viraemia in first year (number, %)	63 (42.6)	43 (40.6)	53 (41.4)	0.949	159 (41.6)
BK viraemia in first year (number, %)	32 (21.6)	23 (21.6)	26 (20.3)	0.955	81 (21.2)
Bacteraemia in first year (number, %)	23 (15.6)	13 (12.3)	14 (10.9)	0.505	50 (13.1)

not have a higher rate of infective complications. Furthermore, recently published data suggests that a high dose: concentration ratio is not a predictor for poor early transplant outcomes as had previously been thought [14], supporting the assertion that Black patients should and can safely receive higher doses earlier in the post-transplant period. We excluded patients from the study who reported mixed ethnicity, ethnicity other than the three main groups described, or who did not disclose their ethnicity, meaning we can draw no conclusions about patients in these categories from the data presented here.

Our findings suggest that Black patients at our unit are often being under-dosed with tacrolimus in the early post-transplant period with our existing immunosuppressive policy, and that a more tailored approach may be more suitable. Interestingly, it has recently been shown that in predominantly Caucasian populations with a dominant CYP3A5 non-expressor phenotype, even lower starting doses of tacrolimus (0.05 mg/kg/day) may be used safely, resulting a greater proportion of patients achieving each target tacrolimus concentrations than when using the higher 0.075 mg/kg/day maintenance dose [15]. This suggests that the benefits of targeting dosing strategies may also extend to non-Black populations.

The criteria on which the tailoring of the immunosuppressive regime should be based is less clear. Pre-transplant genetic screening for CYP3A5 polymorphisms would offer an objective and rational basis for differential tacrolimus dosing, however the evidence supporting this approach is conflicting. Some studies evaluating such a strategy have demonstrated improvements in the proportion of patients achieving therapeutic early tacrolimus concentrations in both kidney [16, 17] and liver transplantation [18]. However, a dedicated randomised controlled trial of genotype-directed dosing did not demonstrate any improvement in either achievement of target tacrolimus concentrations or subsequent transplant outcomes using this strategy [19]. Such an approach may also not be possible for individual transplant units based on the availability of genetic testing and cost constraints.

An alternative might be empirically to prescribe higher starting doses of tacrolimus to patients who report Black ethnicity. Making healthcare decisions on the basis of ethnicity is controversial because neither race nor ethnicity are straightforwardly biological categories, and have

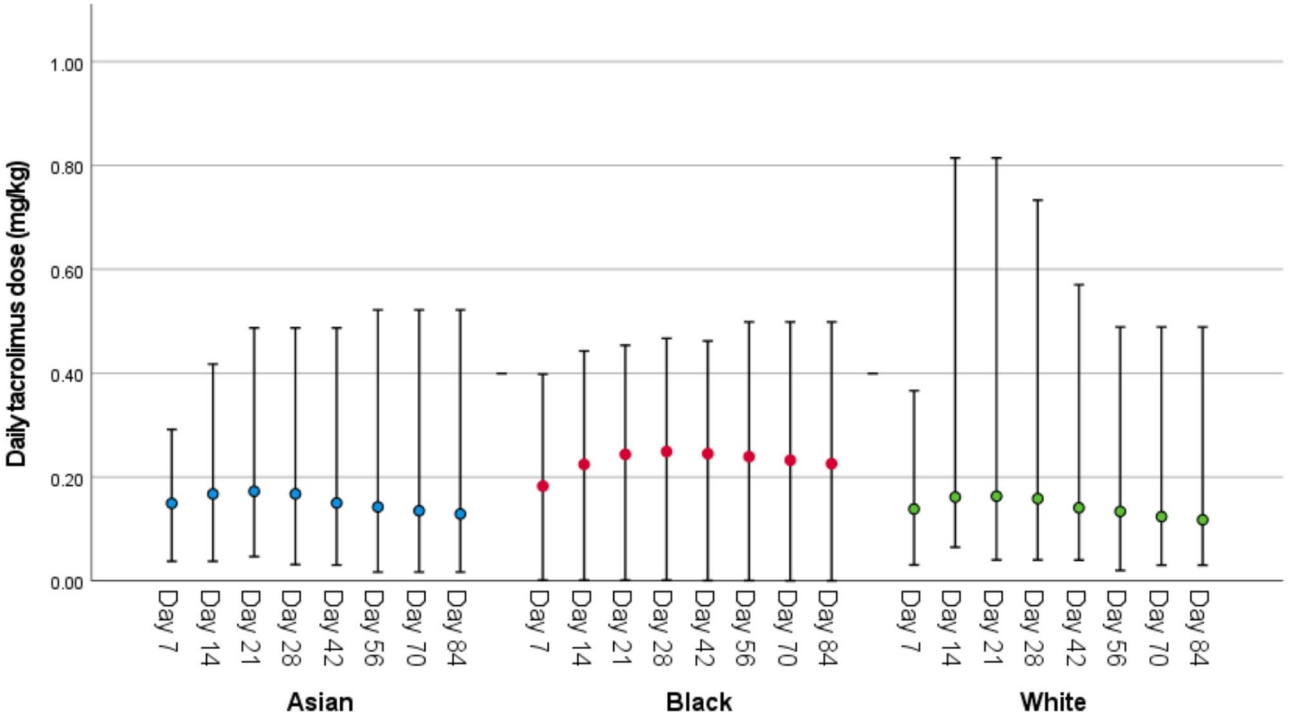

Fig. 3 Median tacrolimus dose (mg/kg) at different time points after transplantation, by ethnic group. Bars represent the range; one white patient with low body mass required a high tacrolimus dose for the first 6 weeks after transplantation explaining the high maximum dose in this group

Table 3 Binary logistic regression to predict three outcomes: tacrolimus concentrations below the target range in week 2 after transplantation, biopsy-proven acute rejection by day 90 and graft loss by three years after transplantation. OR, odds ratio. CI, confidence interval. IL2, anti-interleukin 2 induction therapy

Predictor variables	Outcome variable					
	Tacrolimus concentration < 8ng/ml at day 7–14		Biopsy-proven acute rejection by day 90		Graft loss by three years after transplantation	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Live donor transplant	0.889 (0.536–1.473)	0.647	2.229 (1.05–5.034)	0.037	0.535 (0.271–1.055)	0.071
IL-2 induction	1.409 (0.818–2.426)	0.216	4.115 (0.94-18.021)	0.06	0.96 (0.506–1.823)	0.902
Age quartile	0.799 (0.659–0.97)	0.023	0.888 (0.641–1.231)	0.477	1.167 (0.921–1.48)	0.201
Male sex	0.685 (0.441–1.063)	0.092	0.926 (0.437–1.962)	0.841	1.475 (0.855–2.544)	0.162
Asian ethnicity	0.903 (0.551–1.48)	0.685	1.731 (0.667–4.493)	0.26	0.748 (0.397–1.409)	0.369
Black ethnicity	3.49 (1.96–6.214)	< 0.001	2.675 (1.002–7.141)	0.05	1.257 (0.665–2.376)	0.482

been criticised as misrepresenting genuine genetic diversity [20]. Within the field of nephrology, most guidelines now advise against correction of estimated glomerular filtration rate (eGFR) for ethnicity because of the historic role of race underpinning structural racism and racial inequality, its tendency to ignore heterogeneity within ethnic groups, and its propensity to under-estimate the degree of renal impairment in Black patients [21].

Others, whilst acknowledging the problems of historical approaches to race within medicine, have argued that modern understandings of ethnic diversity necessitate a tailored approach in which race and ethnicity are justifiably used in medical algorithms [22]. A recent study employing large UK and US biobank populations found a strong correlation between patients' defined ethnic identity and genome-wide patterns of pharmacogenomic variability. The authors conclude that self-defined race and ethnicity should not be discounted as markers for pharmacogenomic risk [23].

Limitations of this study include use of self-defined ethnicity, and in particular the term 'Black ethnicity' as self-reported by participants, which we recognise encompasses diverse populations with varying genetic, cultural, and geographical backgrounds. Furthermore, because we do not genotype patients as part of our routine transplant care, we were unable to clarify how well self-defined ethnicity correlates with the CYP3A5 genotype. A further limitation was the relatively small population included; a larger patient population would have allowed clear conclusions to be drawn about the impact of subtherapeutic

early tacrolimus concentrations on subsequent transplant outcomes. We also did not assess the tolerability or side-effect profile of tacrolimus between different ethnic groups.

The implications of our findings are not straightforward. We have identified that patients who define their ethnicity as 'Black' receive clinical care (dosing of tacrolimus) that fails to achieve its intended effect (concentrations of tacrolimus within the target range). Health equity as defined by the US Health Resources and Services Administration is "the absence of avoidable differences among socioeconomic and demographic groups or geographical areas in health status and health outcomes such as disease or mortality" [24], and this would appear to place a duty on clinicians to try to act in such a way that Black patients are not disadvantaged in this way. Options for addressing this may involve genotype-based prescribing if resources allow (accepting the mixed evidence for this), empirically starting patients who identify as Black on higher initial doses of tacrolimus (perhaps 1 or even 1.5 mg/kg/d), or commencing all ethnic groups on the same dose but adopting a more aggressive approach to uptitrating the tacrolimus dose if early blood concentrations are subtherapeutic in Black patients. Typically, dose uptitration may involve increasing the tacrolimus dose by 20 or 25%; it may be that in Black patients, increases of 50% may be more appropriate. In one study, a computer dosing algorithm (based on patient and transplant factors as well as prior pathology data) was shown to outperform human decision making for achieving target tacrolimus concentrations in patients without CPP3A5 genotype data; [25] it may be that adding ethnicity to this or other algorithms improves performance further.

Conclusions

Regardless of the approach taken, differential outcomes between ethnic groups should be a cause for concern to those of us providing clinical services to patients, and prompt reflection on how we can proactively review our protocols to promote health equity.

Abbreviations

ATG	Anti-thymocyte globulin
CYP3A5	Cytochrome P450 3A5
IL-2	Interleukin 2
UK	United Kingdon of Great Britain and Northern Ireland
US	United States of America

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Author contributions

ET and DR were the principle researchers, responsible for data acquisition and analysis. MMY and MK helped conceive the project and were involved in interpretation of the data. ET produced the first draft of the manuscript. All authors contributed to the final version of the work.

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The work presented in this paper was carried out as a medical school project by the lead author (ET). Supervision by the other authors was carried out within existing working arrangements requiring no additional project funding.

Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted as an observational service analysis of the existing transplant immunosuppression policy at the Royal London Hospital. Research ethics committee approval was deemed unnecessary under the terms of the *UK Policy Framework for Health and Social Care Research*, using their online decision support tool (https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/). The project adheres to the Declaration of Helsinki.

Human ethics and consent to participate

Not applicable.

Informed consent

Informed consent to for their data to be used in this project was not sought from patients. It is not required under UK law for use of patient data in clinical audit (see General Medical Council document *Using and Disclosing Patient Information for Secondary Purposes* paragraphs 95 and 96 (https://www.gmc-uk.org/professional-standards/professional-standards-for-doctors/confidentiality/using-and-disclosing-patient-information-for-secondary-purposes). Institutional approval came from the *Barts Health Clinical Effectiveness Unit*.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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