Preventing kidney transplant failure by screening for antibodies against human leucocyte antigens followed by optimised immunosuppression: OuTSMART RCT

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Plain language summary

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Scientific summary

Background

Kidney transplants do not last for the natural lifespan of most recipients, and many patients eventually suffer progressive decline in transplant function leading to graft failure and need to return to dialysis. Around the world, this problem is significant, as 3% of kidney transplant patients return to dialysis each year. The single biggest cause of allograft dysfunction leading to transplant failure is immune-mediated damage and a prevalent hypothesis in the field is that inappropriately low levels of immunosuppression, either physician-led or due to patient non-adherence, is an important contributor to the initiation and progression of this immune-mediated damage. There are still no effective treatments for allograft dysfunction that is proven to be due to immune-mediated damage. Enhancing baseline immunosuppression appears to stabilise graft function in some patients. Two recent randomised trials of the anti-CD20 monoclonal antibody rituximab showed no impact, although both were stopped prematurely as they were underpowered. More recent reports indicate that anti-IL-6 monoclonals show promise at stabilising estimated Glomerular Filtration Rate (eGFR), but these have yet to be tested in large randomised trials.

Since the development of circulating antibodies (Ab) against human leucocyte antigens (HLA) has been validated as a strong prognostic biomarker of kidney transplant failure, and there is genuine equipoise about whether increasing or optimising immunosuppression can benefit patients at risk of transplant failure, in the OuTSMART trial we tested the hypothesis that screening for these Ab followed by optimising oral immunosuppression treatment, could prevent allograft failure.

Objectives

Primary

Determine the time to graft failure in patients testing positive for HLA Ab at baseline or within 32 months of randomisation who receive an optimised anti-rejection medication intervention with prednisolone, tacrolimus (Tac) and mycophenolate mofetil (MMF) ('treatment'), compared to a control group who test positive for HLA Ab at baseline or within 32 months post-randomisation who remain on their established immunotherapy and whose clinicians are not aware of their Ab status. The primary endpoint was to be assessed remotely when 43 months post-randomisation was achieved by all.

Secondary

1. Determine the time to graft failure in patients randomised to 'unblinded' HLA Ab screening, compared to a control group randomised to 'blinded' HLA Ab screening.
2. Determine whether treatment influences patient survival.
3. Determine whether 'treatment' influences the development of graft dysfunction as assessed by presence of proteinuria (protein:creatinine ratio > 50 or albumin:creatinine ratio > 35) and change in eGFR.
4. Determine whether 'treatment' influences the rates of acute rejection in these groups.
5. Determine the adverse effect profiles of 'treatment' in this group, in particular whether they are associated with increased risk of infection, malignancy or diabetes mellitus.
6. Determine the cost-effectiveness of routine screening for HLA Ab and prolonging transplant survival using this screening/treatment protocol.
7. Determine the impact of biomarker screening and 'treatment' on the patients' adherence to drug therapy and their perceptions of risk to the health of the transplant.

Methods

OuTSMART was an investigator-led, prospective, open-labelled marker-based strategy (hybrid) randomised trial. Eligible patients were recipients of cross-match negative transplants aged 18–75, more than 1 year post-transplant with an eGFR ≥30 ml/min willing to consent to the screening/treatment process. Patients were excluded if they were recipients of cross-match positive transplant requiring HLA desensitisation to remove Ab, recipients of additional solid organ transplants (e.g. pancreas, heart, etc.), had a history of malignancy (except non-melanomatous lesions restricted to the skin), had recent acute rejection, had a history of hepatitis B, C or human immunodeficiency virus (HIV), were known to have HLA Ab and received specific treatment for that Ab, had known hypersensitivity to any of the investigational medicinal products (IMPs), had known hereditary disorders of carbohydrate metabolism, were pregnant at the time of consent, or were females who refused to consent to using suitable contraception through the trial. Additionally, patients enrolled in any other studies involving administration of another IMP at time of recruitment were excluded.

Stratified randomisation was 1 : 1 to two arms, blinded standard care (SC) or unblinded biomarker-led care (BLC). Randomisation was stratified first by the result from blood test screening for HLA Ab. The HLA Ab+ patients were further screened with single antigen beads to determine whether donor-specific Ab (DSA) were present or whether the only Ab detected was non-DSA. Thus, biomarker stratification led to three groups within each arm (DSA+, non-DSA+ and HLA Ab-neg). The second stratification was based on current immunosuppression, to ensure balanced numbers already on Tac or MMF in each group. The final stratification was by site.

Patients in the SC arm were blinded to their biomarker status, as were their physicians, and remained on baseline immunotherapy, whereas patients in the BLC arm were told their HLA Ab status and were offered intervention. HLA Ab-negative patients in either arm remained on their existing immunotherapy and were rescreened for new HLA Abs every 8 months. Those patients who become positive during subsequent screening rounds were moved to the appropriate HLA Ab positive groups (DSA+ or non-DSA+) for final data analysis. All patients in the unblinded arm found to be positive on second or subsequent rounds were offered the same intervention as those patients who were positive in the first screening round, and these were intensively followed up for an additional 32 months from the time they become positive. Thus the maximum amount of time any single patient remained in intensive follow-up was 64 months. New patients were recruited to the study at each successive screening round.

Intervention in the unblinded HLA Ab + patients consisted of informing patients of their HLA Ab status, followed by, in those with DSA or non-DSA, an interview to encourage medication adherence followed by medication changes to optimised doses of Tac, MMF and Prednisolone. Medication changes were tailored to each individual and failure to change, or to tolerate changes was not regarded as treatment failure, so some patients stayed on the same drug regimen. Patients with DSA and non-DSA were offered the same intervention.

The primary outcome was originally transplant failure rates over 3 years, but this was changed to time to graft failure after an audit revealed that the prevalence and incidence rates of HLA Ab + patients were less than expected when planning the trial. With a planned minimum follow-up period of 43 months, the trial had 80% power to detect a hazard ratio (HR) of 0.49 in donor-specific antibody+ patients. Secondary endpoints were collected at 32 months and included patient death/survival, rates of biopsy-proven acute rejection, diabetes, infection and cancer, a health economic analysis and formal assessment of adherence.

Results

Recruitment started in September 2013. Over 37 months, 5519 patients were screened for eligibility and 2037 were randomised (1028 to unblinded BLC and 1009 to double-blinded SC). We identified 198

with DSA and 818 with non-DSA, and at the end of screening, there were 1021 in the Ab-neg groups. Baseline variables were well-matched between groups at the end of Ab-screening. Forty-five per cent of the DSA detected were directed against HLA-DQB antigens. Although the majority of patients were taking Tac (73%), MMF (67%) or prednisolone (55%), only 22% with DSA and 27% with non-DSA were taking all three drugs. Baseline immunosuppression use was balanced across arms and did not change during the trial in the SC arm. Ninety-seven per cent of HLA Ab+ recruits in the BLC arm had the formal interview, and the proportion taking all three drugs in the BLC arm increased to 54% (DSA) and 44% (non-DSA).

There were 34 graft failures in HLA Ab+ recruits in the SC arm over the course of the study compared to 42 in the BLC arm. The HRs for graft failure in BLC DSA+ and non-DSA+ groups were 1.54 [95% confidence interval (CI) 0.72 to 3.30] and 0.97 (0.54 to 1.74), respectively, providing no evidence of a difference. The data for DSA+ groups confirmed that the presence of DSA was associated with an increased risk of graft failure, but non-DSA were not associated with graft failure compared to patients without Ab.

Non-inferiority for the overall unblinded versus blinded comparison was not demonstrated as the upper confidence limit of the HR for graft failure exceeded 1.4 : (1.02, 95% CI 0.72 to 1.44). The HR for the secondary endpoint biopsy-proven rejection in the overall unblinded BLC group was 0.5 (95% CI 0.27 to 0.94; $p = 0.03$), but there were no significant differences in patient survival, biopsy-proven rejection, proven infections, malignancies, diabetes, development of proteinuria or mean eGFRs at the end of the trial. After adjusting for baseline quality of life, there was no significant gain of quality-adjusted life-year (QALY) in the BLC arm, but an incremental cost-effectiveness ratio per QALY that was significantly higher than the threshold set by the National Institute for Health and Care Excellence. Our analysis of adherence revealed significantly improved adherences for all three drugs in the BLC DSA+ group.

Conclusions

Thus, we conclude that the development of DSA (but not non-DSA) is associated with an increased risk of graft failure, but there is no evidence to support the primary hypothesis, that optimisation of immunosuppression in DSA+ patients can prevent this from happening.

Trial registration

This trial is registered as EudraCT (2012-004308-36) and ISRCTN (46157828).

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