Transplant International

Transplant Trial Watch

THE PETER MORRIS CENTRE FOR EVIDENCE IN TRANSPLANTATION

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To keep the transplantation community informed about recently published level 1 evidence in organ transplantation, ESOT (https://esot.org/) and the Centre for Evidence in Transplantation have developed the Transplant Trial Watch (www.transplantevidence.com). The Transplant Trial Watch is a monthly overview of 10 new randomized controlled trials (RCTs) and systematic reviews. This page of Transplant International offers commentaries on methodological issues and clinical implications on two articles of particular interest from the CET Transplant Trial Watch monthly selection. For all high-quality evidence in solid organ transplantation, visit the Transplant Library: www.transplantlibrary.com

Randomized controlled trial 1

Oxygenated End-Hypothermic Machine Perfusion in Expanded Criteria Donor Kidney Transplant: A Randomized Clinical Trial. JAMA Surgery Husen, P., et al. 2021; 156 (6):517–525.

Aims

This study aimed to determine whether short-term oxygenated hypothermic machine perfusion preservation (end-HMPO2) following static cold storage (SCS) was more effective in improving kidney transplant outcomes in expanded criteria donor kidneys retrieved from brain-dead donors, compared with SCS alone.

Interventions

Patients were randomly assigned to either end-HMPO2 after SCS or SCS alone.

Participants

305 expanded criteria donor kidneys retrieved from brain-dead donors.

Outcomes

The primary outcome was graft survival at 1-year post-transplant. The secondary outcomes were patient survival, primary nonfunction, delayed graft function, acute rejection and estimated glomerular filtration rate.

Follow-up

Patients were followed up for 12 months.

CET conclusion

This good quality randomized, partially blinded, controlled trial was conducted as part of the Consortium for organ preservation in Europe (COPE). The study compared kidneys from expanded criteria donors that underwent static cold storage (SCS) alone or SCS plus oxygenated hypothermic machine perfusion (end-HMPO2) after arrival in the recipient transplant centre. Kidneys were randomized on arrival at the recipient centre according to a computer-generated randomization scheme using an online randomization tool. A sample size analysis was based on data from a previous trial and showed that 262 kidneys were needed to detect an improvement in 1-year graft survival from 80% to 92%. The intention-to-treat analysis excluded kidneys that were randomized but not transplanted and consisted of 262 kidneys. Fourteen kidneys of the end-HMPO2 group were cold-stored because machine perfusion was not possible and six kidneys received machine perfusion <2 hours for logistical reasons. One-year graft survival was similar between groups, and there were no statistically significant differences for any of the secondary outcomes, that is delayed graft function, primary nonfunction, estimated glomerular filtration rate and acute rejection. The authors comment that as the 1-year graft survival rate in the control group exceeded the baseline assumption, the study is statistically underpowered.

doi:10.1111/tri.13977

Jadad score 3.

Data analysis Per-protocol analysis.

Allocation concealment Yes.

Trial registration ISRCTN63852508.

Funding source Nonindustry funded.

Randomized controlled trial 2

Preformed T-cell alloimmunity and HLA eplet mismatch to guide immunosuppression minimization with tacrolimus monotherapy in kidney transplantation: Results of the CELLIMIN trial. Am J Transplant. Bestard O., Meneghini M., Crespo E., et al. 2021 [Online ahead of print].

Aims

This study reports the findings of the CELLIMIN trial, which aimed to examine whether minimization of post-transplant immunosuppression with tacrolimus (TAC) monotherapy would be effective enough while also reducing drug-related toxicity in low immunological-risk renal transplant recipients without pretransplant donor-specific alloantibodies (DSA) and donor-specific T cells.

Interventions

Participants were first allocated into two groups based on the results of their pretransplant donor-specific IFN-γ ELISPOT assessment. ELISPOT negative (E−) patients were then randomized to either the low-immunosuppression (LI) group or the standard of care immunosuppression (SOC) group.

Participants

167 kidney transplant patients were recruited, out of which 101 ELISPOT negative (E−) patients were randomized.

Outcomes

The primary outcome was the incidence of biopsy-proven acute rejection BPAR at 6-month post-transplant. The secondary outcomes were the incidence of clinical and subclinical BPAR, estimated glomerular filtration rate (eGFR), de novo DSA, graft survival, patient survival and impact of donor/recipient human leukocyte antigens (HLA) molecular mismatches on BPAR and dnDSA between the groups at 12-month post-transplant.

Follow-up

Patients were followed up for 1 year.

CET conclusions

This manuscript reports the findings of the CELLIMIN trial from the BIO-DrIM consortium. The study aimed to stratify renal transplant recipients by immunological risk assessed by pretransplant donor-specific ELISPOT assay, randomizing low-risk recipients to standard immunosuppression or tacrolimus monotherapy. The study was terminated early because of slow recruitment and is therefore underpowered to draw firm conclusions, but rejection rates were numerically higher in the minimization arm leading to concerns that ELISPOT alone may not select patients suitable for monotherapy. Despite the early termination, there are some interesting findings here. Firstly, T-cell ELISPOT was able to differentiate those patients at the highest risk of post-transplant rejection, suggesting that it may have a role to play in guiding pretransplant risk stratification. Secondly, a retrospective analysis showed that patients with a negative ELISPOT and good class-II eplet matching demonstrated the lowest post-transplant risk, suggesting that a combination of reactivity and eplet matching may improve patient selection for minimization in future studies.

Jadad score 2.

Data analysis Strict intention-to-treat analysis.

Allocation concealment No.

Trial registration ClinicalTrials.gov - NCT02540395.

Funding source Nonindustry funded.

Clinical impact summary

Historically, most transplant centres have used a 'one size fits all' regimen for immunosuppression, or applied

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various tiers of immunosuppression depending on easily measured pretransplant risk factors such as degree of sensitization, donor–recipient mismatch or donor type. The advent of newer biomarkers to assess immunological risk has led to interest in the ability to further personalize immunosuppression. Until now, few prospective studies have assessed the clinical impact of such personalization.

In this multicentre study from the BIO-DrIM consortium, the investigators attempted to stratify immunosuppression based upon pretransplant donor-reactive T-cell memory using a standardized IFN-gamma ELISPOT assay. Recipients without pretransplant DSA or donor-specific T cells were randomized to tacrolimus monotherapy or standard triple therapy following renal transplantation. Patients with detectable donor-reactive T-cell memory received triple therapy.

Unfortunately, perhaps because of the stringent inclusion criteria or a reluctance on the behalf of investigators to recruit to a study of monotherapy, the study failed to recruit at the required rate with only 167 of the 673 required patients included. While underpowered with respect to the noninferiority outcome planned, the study does still offer some interesting insights.

Rates of biopsy-proven acute rejection were numerically higher in the low-immunosuppression group compared with triple therapy (25% vs. 11.3% at 12 months), suggesting that T-cell ELISPOT alone may be insufficient to select patients suitable for tacrolimus monotherapy. However, in post hoc analysis, T-cell ELISPOT was able to predict those patients at highest risk of post-transplant rejection, suggesting that it may have some role to play. Further post hoc analysis also demonstrated that patients with a negative post-transplant ELISPOT and good class-II eplet matching (DQ eplet mismatches < 10) were at lower risk of both biopsy-proven rejection and de-novo donor-specific antibody (DSA) formation.

These findings suggest that refining risk stratification using a combination of ELISPOT, eplet matching and DSA may improve the safety of immunosuppression minimization. However, given the difficulties recruiting to the current study, demonstrating noninferiority in prospective studies with even more stringent inclusion criteria is going to be challenging without large-scale multicentre collaboration.

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