Transplant International

Transplant Trial Watch

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To keep the transplantation community informed about recently published level 1 evidence in organ transplantation ESOT (https://esot.org/) the Centre for Evidence in Transplantation (www.transplantevidence.com) has developed the Transplant Trial Watch. 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

Pulmonary volume-feedback and ventilatory pattern after bilateral lung transplantation using neurally adjusted ventilatory assist ventilation. Grasselli, G., et al. *British Journal of Anaesthesia 2021;127(1):143-152*.

Aims

This study aimed to investigate whether neurally adjusted ventilatory assist (NAVA) ventilation, driven by diaphragm electrical activity (EAdi), would reveal if vagally mediated pulmonary volume feedback is preserved during the early phases following bilateral lung transplantation.

Interventions

Patients were randomized to two positive-end expiratory pressure (PEEP) levels: 6 and 12 cm H_2O. Patients were then randomized again to three NAVA levels: baseline NAVA, 50% of baseline NAVA level and 150% of baseline NAVA level.

Participants

Nineteen bilateral lung transplant recipients.

Outcomes

Effect of varying NAVA levels on ventilatory parameters, and effect of varying PEEP on ventilatory parameters.

Follow-up

N/A.

CET conclusion

This is an interesting and complex study of neurally adjusted ventilator assistance (NAVA) following bilateral lung transplant. Nineteen patients over the age of 18 years were randomized, although the method of randomization is not clear from the methods presented. There are two levels of randomization, initially to 2 PEEP levels, which have 4 levels of ventilatory assistance, then another randomization to 3 levels of NAVA. This design makes the results of the study incredibly difficult to interpret. A large proportion (11/30) did not have a stable signal from the diaphragmatic monitor (EADi) that was contained within a specialized nasogastric tube. This meant that they were excluded from the study. Due to the small number of patients and the nature of the data collected, the study was unlikely to show significant improvements in key parameters and there is no indication that it was powered for a specific outcome. Whilst the study is novel, having applied this new technique to lung transplant recipients soon after surgery, it does not show significant benefits, as there was no control arm. The claim that the technique is feasible is true; however, it was not possible in over a third of patients. More work is needed to assess this protocol.

Jadad score 1.

Data analysis Per-protocol analysis.

Allocation concealment No.

Trial registration ClinicalTrials.gov – NCT03367221.

Funding source Non-industry funded.

Randomized controlled trial 2

Mycophenolate mofetil versus azathioprine in kidney transplant recipients on steroid-free, low-dose cyclosporine immunosuppression (ATHENA): A pragmatic randomized trial. Ruggenenti, P., et al. *PLoS Medicine/Public Library of Science 2021; 18(6): e1003668.*

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Aims
This study aimed to compare the protective effect of mycophenolate mofetil (MMF) versus azathioprine (AZA) against acute cellular rejection (ACR) and chronic allograft nephropathy (CAN) in renal transplant patients on steroid-free, low-dose cyclosporine immunosuppression.
Interventions
Patients were randomized to either the AZA group or the MMF group.
Participants
A total of 233 kidney transplant patients.
Outcomes
The primary outcome was biopsy-proven chronic allograft nephropathy (CAN). The secondary outcomes included the cumulative incidence of acute clinical rejections (biopsy-proven), the combined outcome of biopsy-proven clinical and subclinical rejections, graft survival, patient survival and adverse events.
Follow-up
Median [interquartile range (IQR)] of 47.7 (44.2–48.9) months
CET conclusions
This multicentre Italian study randomized low-risk kidney transplant recipients to AZA or MMF-based immunosuppression in conjunction with cyclosporine microemulsion and basiliximab/ATG induction. Patients were followed up for 4 years, with the primary endpoint being biopsy-confirmed chronic allograft nephropathy. There was no difference in CAN, patient or graft survival. There was a numerical increase in biopsy-proven acute rejection in the AZA group (29.8% vs. 16.8%), in keeping with previous studies and meta-analyses, although not meeting statistical significance probably due to lack of power. There are some issues. The study recruited patients between 2007 and 2012, when cyclosporine was still in widespread use. Most centres have now switched to tacrolimus-based immunosuppression, and it is not clear why this study has taken 9 years to reach publication. Less than half of participants had the protocol surveillance biopsy, meaning that the primary endpoint was based on for-cause biopsies at varying timepoints in a large proportion of patients. Around one-third patients switched from AZA to MMF during the course of the study. Overall, the findings here are unlikely to challenge the idea that Tac/MMF-based immunosuppression is gold standard for most patients, but do provide a reminder that AZA offers a useful alternative in resource-constrained environments or in patients unable to tolerate MMF.

Jadad score 3.
Data analysis Modified intention-to-treat analysis.
Allocation concealment No.
Trial registration ClinicalTrials.gov – NCT00494741; EUDRACT 2006-005604-14.
Funding source Non-industry funded

Clinical impact summary

Initial clinical trials of mycophenolate mofetil (MMF) in kidney transplant recipients conducted in the 1990s demonstrated a reduction in the risk of acute rejection when compared to azathioprine (AZA), which was standard of care at the time [1,2]. This has led to a gradual replacement of AZA with MMF in standard immunosuppression protocols. Subsequent meta-analysis has shown that the benefits of MMF remain when used in conjunction with tacrolimus, and that this may translate to a reduction in the risk of graft loss [3]. However, MMF does come with an increased risk of gastrointestinal complications.

In a recent article in PLOS Medicine, Ruggenenti and colleagues report the results of the ATHENA trial, a randomized controlled trial comparing MMF and AZA in low-risk kidney recipients on steroid-free, low-dose immunosuppression [4]. Patients were followed up for 4 years, with the primary endpoint being biopsy-confirmed chronic allograft nephropathy (CAN). There was no difference in incidence of CAN or patient and graft survival. There was a numerical increase in biopsy-proven acute rejection in the AZA group (29.8% vs. 16.8%), in keeping with previous studies and meta-analyses, although not meeting statistical significance.

Based upon these results, the authors conclude equivalent efficacy of MMF and AZA in this patient cohort. Whist interesting that there was no difference in incidence of CAN over 4 years, the increased rate of acute rejection is of concern, and the trial is certainly not powered to demonstrate differences in graft survival. Less than half of participants had the protocol surveillance biopsy, meaning that the primary endpoint was based on for-cause biopsies at varying timepoints in a large proportion of patients. Furthermore, around one-third of patients switched from AZA to MMF during the course of the study. Intent-to-treat analysis was employed, meaning that AZA patients switching to MMF would have been analysed in the AZA group, potentially overestimating the clinical efficacy of AZA.

The timing of publication is slightly odd – the study recruited patients between 2007 and 2012, when

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cyclosporine was still in widespread use. Most centres have now switched to tacrolimus-based immunosuppression, and it is not clear why this study has taken 9 years to reach publication.

Overall, the findings here are unlikely to challenge the idea that Tac/MMF-based immunosuppression is gold standard for most kidney transplant recipients. They do, however, provide a reminder that AZA offers a useful alternative in resource-constrained environments or in patients unable to tolerate MMF.

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