

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/>) 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

Circulating cell-free nucleosomes as biomarker for kidney transplant rejection: a pilot study. Verhoeven, J., *et al.* *Clin Epigenetics* 2021; 13(1): 32.

Aims

This study aimed to determine whether circulating cell-free nucleosomes (CCFN) could serve as a biomarker for detecting acute rejection in kidney transplant patients who participated in a randomized controlled trial comparing belatacept with tacrolimus following kidney transplantation.

Interventions

Participants in the original trial were randomized to either the belatacept group or the tacrolimus group.

Participants

40 de novo kidney transplant recipients

Outcomes

The main outcome of interest was the measurement of CCFN values during acute rejection compared with no acute rejection.

Follow-up

180 days post-transplant.

CET conclusion

This paper reports an analysis based on the results from a previously published trial. The previous paper, published by De Graav *et al.* in 2017, compared rejection rates between tacrolimus and belatacept in de novo renal transplant recipients. (A Randomized Controlled

Clinical Trial Comparing Belatacept With Tacrolimus After De Novo Kidney Transplantation. de Graav *et al.*; Transplantation. 2017;11:11.) This study demonstrated a very high rejection rate in the belatacept arm (55%) and less in the tacrolimus arm (10%). The current paper assesses whether or not circulating cell-free nucleosomes (CCFN) are useful biomarkers for acute rejection, particularly with specified modifications, such as citrulline. The authors monitored serum CCFN at several time points up to 180 days after transplantation (Days: 1, 3, 4, 5, 6, 30, and 180). For all of the variations of CCFN, they generally followed the same pattern, with a rise in circulating levels after transplantation and then a fall to baseline at day 30. During episodes of acute rejection, the overall levels of CCFN + H3 Citrulline rose significantly, by about 50%, compared with samples without rejection. When assessing the performance of CCFN (H3) with ROC curves, it showed moderate sensitivity and specificity for acute rejection (69% and 71%, respectively). The positive predictive value was poor (15%) but the negative predictive value was relatively good (93%). The low positive predictive value of high CCFN (H3) is related to the fact that circulating levels are higher in many diseases. It may therefore be a better tool for excluding rejection rather than diagnosing rejection. However, on the basis of this study, I do not think that it yet can be used to spare renal transplant recipients the risk of transplant biopsy either.

Trial registration Dutch national trial registry - NTR4242.

Funding source Nonindustry funded.

Randomized controlled trial 2

Personalized physical rehabilitation programme and employment in kidney transplant recipients: A randomized trial. Kastelz, A., et al. *Transplant International* 2021 [Online ahead of print].

Aims

This study aimed to examine whether a personalized physical rehabilitation programme has an effect on the employment status of renal transplant patients.

Interventions

Participants were randomized into two groups: the intervention group, in which the patients participated in a personalized exercise rehabilitation programme in addition to standard care, or the control group where the patients received standard care alone.

Participants

135 kidney transplant patients.

Outcomes

The outcomes of interest were employment status, kidney rejection, perceived physical and mental health and functional capacity.

Follow-up

1 year.

CET conclusions

This is a well-written report of a good quality study. Following at least 2 months after renal transplantation, patients were randomized to standard care or to receive one-to-one resistance training for 60 min twice per week. The intervention lasted 12 months and the primary outcome was employment rate, with a sample size based on a pilot study. The statistical analysis was actually per protocol, as a significant number did not complete 12 months in the intervention arm (28/80 assessed at baseline dropped out). The study had been powered for this and also was randomized in a 2:1 ratio assuming that more patients would drop out from the intervention arm than the standard care arm. Computerized randomization was used. For those unemployed at baseline, a significantly higher proportion found work in the intervention group than in the standard care group (52% vs. 13%). For those in employment at the start of the study, rates stayed at 100% in both arms. Both groups showed an improvement in Global Physical Health as well as Global Mental Health, but there were larger benefits in the treatment arm. An

intention to treat analysis would have given a better understanding of the interventions effect. The per protocol analysis allows for patients who were struggling with employment, physical or mental health to possibly withdraw from the treatment arm. However, the documented reasons for drop outs in the intervention arm indicate that the main reason for doing so was finding a job and this was the whole point of the study. The control arm was also small, so may give an inaccurate idea of employment numbers compared with the wider transplant population.

Jadad score 3

Data analysis Per protocol analysis.

Allocation concealment Yes.

Trial registration ClinicalTrials.gov - NCT02409901.

Funding source No funding was received.

Clinical Impact Summary

This is a good quality study looking at physical rehabilitation following renal transplantation. At least 2 months after transplantation, the patients were randomized to standard care or to receive one-to-one resistance training for 60 min twice per week. The intervention lasted 12 months and the primary outcome was employment rate, with a sample size based on a pilot study. The decision to go for a 'real-world' outcome that is dependent on many factors, such as employment rate, is a bold decision, but obviously of critical importance to patients. It has been previously reported that there is a very low post-transplant employment rate for recipients unemployed at the time of transplant (5%, [1] Efforts to facilitate the potential future employment are therefore of great importance.

In this study, a significant number did not complete 12 months in the intervention arm (28/80 assessed at baseline dropped out). However, the study had been powered to account for this and also was randomized in a 2:1 ratio, assuming that more patients would drop out from the intervention arm than the standard care arm. For those unemployed at baseline, a significantly higher proportion found work in the intervention group than in the standard care group (52% vs. 13%). For those in employment at the start of the study, rates stayed at 100% in both arms. Both groups showed an improvement in Global Physical Health as well as Global Mental Health, but there were larger benefits in the treatment arm. A key concern in interpreting the results is that the per-protocol analysis allows for patients who were struggling with employment, physical or mental health to

possibly withdraw from the treatment arm. However, the documented reasons for drop-outs in the intervention arm indicate that the main reason for dropping out was finding a job, and this was the whole point of the study! The control arm was also small, so may give an inaccurate idea of employment numbers compared with the wider transplant population, but seems to be consistent with previous reports.

Taken altogether, this study gives further support to the value of physical rehabilitation after renal

transplantation, demonstrating beneficial effects on physical and mental health, as well as employment prospects.

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