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TRANSPLANT TRIAL WATCH

Edited by Reshma Rana Magar and Liset Pengel

To keep the transplantation community informed about recently published level 1 evidence in organ transplantation ESOT and the Centre for Evidence in Transplantation have developed the Transplant Trial Watch. The Transplant Trial Watch is a monthly overview of 10 new randomised 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

Randomised controlled trial 1

A Randomized Clinical Trial of Anti-IL-6 Antibody Clazakizumab in Late Antibody-Mediated Kidney Transplant Rejection. Doberer, K., et al. Journal of the American Society of Nephrology 2020; 32(3):708-722.

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Aims

The aim of this study was to assess the efficacy and safety of clazakizumab, an anti-interleukin-6 (IL-6) antibody, in late antibody-mediated renal transplant rejection (ABMR).

Interventions

Participants were randomised to either the clazakizumab group or the placebo group.

Participants

20 adult kidney transplant recipients.

Outcomes

The primary outcome was the evaluation of safety and tolerability. The secondary outcome was the analysis of efficacy.

Follow-up

52 weeks

CET Conclusion

The pilot randomised, double-blind, controlled trial investigated the safety and tolerability of clazakizumab and its efficacy in late antibody-mediated rejection (ABMR) in kidney transplantation. Twenty kidney transplant recipients with DSA-positive ABMR after a median of 10.6 years post-transplantation were randomised to clazakizumab or placebo according to an allocation sequence. The 12-week study period was followed by a 40-week open-label extension in which all participants received clazakizumab. Four patients (three patients receiving clazakizumab) experienced serious adverse events during the 12-week study period and nine patients during the open-label extension. There were two cases of diverticulitis. The authors stress the need for patient selection and monitoring and suggest that the preliminary efficacy data would need validation in a larger trial with longer term follow up.

Jadad score

5

Data analysis

Per protocol analysis

Allocation concealment

Yes

Trial registration

European Union Drug Regulating Authorities Clinical Trials Database - 2017-001604-30;
ClinicalTrials.gov - NCT03444103

Funding source

Non-industry funded

Clinical Impact Summary

AUTHOR: John Matthew O'Callaghan, Consultant Transplant Surgeon, University Hospitals Coventry & Warwickshire, and Deputy Director, Centre for Evidence in Transplantation, University of Oxford, UK.

The primary aim of this pilot study was to assess the safety of clazakizumab, an anti-interleukin-6 (IL-6) antibody, in late antibody-mediated rejection (ABMR) in renal transplantation. IL-6 is a promising therapeutic target and there is a high unmet need in the treatment of late ABMR. The trial was well-conducted with adequate randomisation, allocation concealment and blinding.

Participants were randomised to either the clazakizumab group or the placebo group for the first 12 weeks of treatment, and this was the blinded phase of the study. The second phase from 12 weeks to 52 weeks included all participants and all received clazakizumab

in an open-label phase. The study was small, including only 20 adult kidney transplant recipients, with DSA-positive ABMR more than 365 days after transplantation (median 10 years post-transplant).

Four patients (three of them receiving clazakizumab) experienced serious adverse events during the early 12-week study period. In the open-label extension, nine patients experienced serious adverse events, including diverticulitis with perforation, pneumonia, pyelonephritis, ovarian abscess, viral meningitis and pleural effusion requiring surgical drainage.

There was evidence that clazakizumab significantly reduced MFI during the first 12 weeks of the study, to median 77% of baseline. There was a further decrease in the extended phase of the study. The 11-week biopsies taken from both groups did not show significant differences in rejection-related morphological scores, or ABMR phenotypes. However, the 51-week biopsies did show a significant reduction in rejection scores. There was a reduction in ABMR activity in 22% and disappearance of group receiving clazakizumab from the start of the trial.

This study has shown a very concerning level of severe infectious complications when using clazakizumab alongside baseline immune suppression. Patient selection and monitoring will be very important and the preliminary efficacy data reported in this paper needs validation in a larger trial. A follow-up, phase 3 trial will make use of a reduce dose of clazakizumab (50%) and will have strictly defined exclusion criteria (history of gastrointestinal perforation; diverticular disease or diverticulitis, except if disease has been fully excised; or inflammatory bowel disease).

Randomised controlled trial 2

Combined low-dose everolimus and low-dose tacrolimus after Alemtuzumab induction therapy: a randomized prospective trial in lung transplantation. Benazzo, A., et al. Trials

[Electronic Resource] 2021; 22(1): 6.

DOI: 10.1186/s13063-020-04843-9

Aims

The aim of this protocol is to determine the effect of combining low-dose tacrolimus and low-dose everolimus following alemtuzumab induction therapy in lung transplant patients.

Interventions

Participants will be randomised to two groups: the treatment group, where patients will receive the new maintenance immunosuppression protocol with low-dose everolimus and low-dose tacrolimus; and the control group, in which patients will receive the standard immunosuppression protocol.

Participants

Adult lung transplant patients.

Outcomes

The primary outcome is the measurement of estimated glomerular filtration rate (eGFR).

The secondary outcomes include the incidence of acute cellular rejection, chronic lung allograft dysfunction, antibody-mediated rejection, lymphocytic bronchiolitis, de novo donor-specific antibodies (dnDSA), and survival.

Follow-up

24 months

CET Conclusions

This is the study protocol for an RCT in lung transplantation. The hypothesis is that, following induction with Alemtuzumab, maintenance immune suppression with a two-drug regimen consisting of low-dose everolimus and tacrolimus can improve kidney function. There are a number of good quality indicators in this protocol. 110 patients will be randomised to one of two study arms. Randomisation will be by centralised computer system, and it will not be possible to determine in advance to which arm they will be assigned (allocation concealment). However, there will be a degree of stratification to make sure that similar numbers of patients with high risk conditions are spread between the arms (CMV status and eGFR ranges). This will not impact on the allocation concealment aspect. I agree that it would be difficult to blind the study due to the requirement for drug dose monitoring and dose adjustment. Double-checking of data entry and external monitoring is planned. The primary end-point is change in eGFR and the study is powered for this. The sample size at first glance seems small (only 55 per arm). The sample size calculation was based upon a previous study of 231 patients treated in this centre with the control regimen. Previous monitoring has suggested that eGFR falls at first and stabilises by 12 months, at median 60mL/min. The authors speculate that with the new regimen eGFR will stabilise at 72ml/min, but it is not clear what this is based upon. It may be that a smaller improvement would be clinically significant, but the study would have to increase in size significantly to see a smaller effect. The authors have made allowance for a 20% dropout rate, which is good planning. Overall the protocol is well written and describes the conduct, oversight and monitoring in detail.

Trial registration

EudraCT - 2018-001680-24

Funding source

Non-industry funded