TRANSPLANT TRIAL WATCH

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THE PETER MORRIS CENTRE FOR EVIDENCE IN TRANSPLANTATION

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## Randomized 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. https://doi.org/10.1681/ASN.2020071106

**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 randomized 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 randomized, 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 randomized 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

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 randomization, allocation concealment and blinding.

Participants were randomized to either the clazakizumab group or the placebo group for the first 12




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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 by 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 need validation in a larger trial. A follow-up, phase 3 trial will make use of a reduced 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).

## Randomized 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. https://doi.org/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 randomized 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 randomized to one of two study arms. Randomization will be by centralized 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 the allocation concealment aspect. I agree that it would be difficult to blind the study as a result of the requirement for drug dose monitoring and dose adjustment. Double checking of data entry and external monitoring is planned. The primary end-point is changed 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 stabilizes by 12 months, at median 60mL/min. The authors speculate that with the new regimen eGFR will stabilize 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.

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