EDITORIAL

The need for collaborative research in transplantation medicine: illustrated by the immunosuppression conversion trials

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In this issue of the Netherlands Journal of Medicine, Bouamar et al.[1] report the results of their prematurely terminated randomised controlled trial in renal transplantation recipients on the early conversion of tacrolimus, a calcineurin inhibitor (CNI), to everolimus, a mammalian target of rapamycin inhibitor (mTORi), with concomitant withdrawal of steroids. An excess in acute rejections (30% versus 6.7%) resulted in the decision to terminate the study after the inclusion and randomisation of 60 of the intended 194 subjects.

Current standard immunosuppressive regimens in renal transplantation include CNIs and result in low rates of allograft rejection, and good long-term allograft survival. However, CNIs have chronic nephrotoxic effects and there is a search for further improvement of immunosuppressive regimens to reduce these adverse long-term effects. Late (i.e. more than one year after transplantation) conversion from CNI to mTORi showed no improvement in long-term renal function. Early conversion studied in the ZEUS trial showed better renal function with a benefit of 6.4 ml/min/1.73 m^2 for everolimus compared with cyclosporine five years after transplantation.[2] However, cyclosporine is no longer the most prescribed CNI in current transplantation care, as immunosuppression with low-dose tacrolimus, mycophenolic acid and prednisolone after daclizumab induction was found to result in superior renal allograft survival after 12 months compared with low-dose cyclosporine and low-dose sirolimus after induction or standard dose cyclosporine without induction.[3,4] The recently published ELEVATE trial is the largest study to date on early conversion from CNI to mTORi and included 715 subjects. No difference in renal function after one year was observed.[5] However, CNI and in particular tacrolimus treatment resulted in superior prevention of biopsy-proven acute rejection (BPAR) with a 2.4-fold increased risk in the everolimus arm. Long-term effects are awaited and are the main outcome of interest, especially with the tacrolimus subgroup as comparator, since tacrolimus is the standard CNI of choice. Tacrolimus was used as sole CNI in the study by Bouamar et al. and this could partially explain the high relative risk of rejection for everolimus.

Another important issue that needs to be mentioned is the concomitant withdrawal of steroids. The ELEVATE trial did not eliminate steroids which could be relevant for explaining the lower overall rate of biopsy-proven acute rejection. A recent Cochrane review discussed the effects of steroid withdrawal and concluded that there is no scientific basis to advise in favour of steroid withdrawal since it resulted in higher biopsy proven rejection rates and did not reduce the number of adverse effects. However, the overall quality of included studies was poor.[6] The study by Bouamar et al. resulted in an unacceptable acute rejection rate in the intervention arm within the first year after renal transplantation. This was obviously not the trial's intention, but a design based on the prevailing institutional protocol including steroid withdrawal unintentionally illustrated the lower limit of acceptable immunosuppression in an everolimus-based regimen. This negative trial is therefore relevant and should be published, even if one can question the initial design in hindsight.

THE NEXT STEP

Alternative strategies are being explored in order to reduce CNI exposure. The combination of lower tacrolimus dosing plus mTORi in combination with steroids seems promising. In the Cochrane review on CNI avoidance this strategy seems non-inferior in acute rejection risk and is associated with a lower incidence of viral infections.[7] The recently presented TRANSFORM study (2037 subjects) supports these data with similar allograft function and BPAR rates at one year after transplantation.[8] A more

definitive answer regarding the long-term effects on renal function is awaited. It should be noted that both tacrolimus and cyclosporine are used as CNI in the TRANSFORM study.[9]

In this editorial, we would like to highlight two observations that can be made with respect to the discussion above. First, few large collaborative efforts with harmonised protocols studying alternative strategies in immunosuppression after renal transplantation to optimise efficiency, validity and quality were initiated to address this topic. Looking back at the history of the CNI-mTORi conversion trials and steroid withdrawal studies, it is striking that there are multiple small studies with different designs, missing information and absent long-term follow-up data. A publication bias is likely to exist with negative results that never reached publication. Also, the inclusion of cyclosporine as CNI of choice does not aid in deciding whether the studied strategy is superior to tacrolimus-based regimens. Sub-analysis could address this issue, but only if studies are sufficiently powered.

Second, in the study of Bouamar et al. there were individuals that fared well by the studied regimen. What characterised them? Can they be identified shortly after transplantation to benefit from this regimen? The term *transplantomics* was coined several years ago; this suggests an aim of collective characterisation and quantification of the biology that translates into the function and dynamics of the graft and its recipient. In the mentioned trials deep phenotyping and genotyping of recipients and donors is lacking. Larger trials should include thorough (immuno)phenotyping and genotyping in order to come to individualised immunosuppression.

To maximise yield and optimise outcome for future renal transplant recipients, collaborations with molecular biology as well as between clinical institutions should be intensified.

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