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Tacrolimus: In Heart Transplant Recipients

A Viewpoint by Nicholas R. Banner

Consultant in Cardiology and Transplant Medicine, The Royal Brompton and Harefield NHS Trust, Harefield Hospital, Harefield, Middlesex, England

Ciclosporin dramatically improved the results of heart transplantation and made it the standard therapy for severe heart failure. A decade later, tacrolimus (FK506) was introduced into clinical practice. Intriguingly, tacrolimus has a completely different molecular structure and different intracellular binding proteins from ciclosporin, but has the same principal mechanism of action, inhibition of the calcium-dependant phosphatase calcineurin.[1]

Clinical trials in liver and kidney transplantation demonstrated that tacrolimus provided better prophylaxis against acute rejection than the original oil-based formulation of ciclosporin (Sandimmune®).[1] Uncontrolled studies found that tacrolimus had a role in 'rescue therapy' for refractory rejection after heart transplantation. The first clinical trials in *de novo* heart transplantation lacked statistical power and yielded inconclusive results. The situation was confused further by the introduction of a microemulsion formulation of ciclosporin (Neoral®). However, the initial studies with tacrolimus demonstrated important differences in the adverse effect profile of the two drugs, with tacrolimus causing less hypertension and dyslipidaemia, but being associated with a higher incidence of diabetes mellitus. Tacrolimus also lacked the cosmetic adverse effects of gingival hyperplasia, hirsutism and abnormal facial bone growth in children. This led to tacrolimus becoming the preferred agent in many paediatric transplant programmes and an important alternative for female patients. Although some studies have shown an advantage for tacrolimus over ciclosporin, most have found the two drugs to be associated with similar nephrotoxicity. Data from one small trial have also indicated that tacrolimus may provide better prophylaxis against acute rejection in patients of African descent.

Two recent randomised trials have found that tacrolimus reduced the rate of acute rejection after *de novo* heart transplantation compared with ciclosporin microemulsion when both agents were used in combination with corticosteroids and either azathioprine or mycophenolate mofetil (MMF), but there was no difference in patient or graft survival. However, the incidence of graft loss from acute rejection is very low in the current era and so it is no longer possible to power clinical trials for an endpoint of survival. Nevertheless, there are real psychological and cost benefits to be gained from reducing the incidence of acute rejection episodes.

Since tacrolimus and ciclosporin share the same primary mechanism of action, it is not clear why tacrolimus provides better prophylaxis against acute rejection. Possible explanations include differences in potency, pharmacokinetics, protein binding/tissue distribution or cytokine modulation.

A formal meta-analysis may further clarify the role of tacrolimus after heart transplantation. The additional cost of tacrolimus therapy may be offset to some extent by the reduced dose of MMF that is needed when it is administered with tacrolimus instead of ciclosporin. Further savings may arise from a reduced need for treatment of acute rejection. However, a formal cost-effectiveness analysis is needed. In the meantime, tacrolimus has become an important alternative to ciclosporin after heart transplantation and data from the International Society for Heart and Lung Transplantation Registry indicate that it is being used in an increasing proportion of heart transplants.[2] ▲

References

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1 The use of trade names is for product identification purposes only and does not imply endorsement.