## Editorial

# Transplantation Tolerance in Clinical Practice: Are We There Yet?

The first successful case of renal transplantation in humans was carried out more than 50 years ago [1]. Today, renal transplantation has become the treatment of choice for many patients suffering from end-stage renal failure. With the exception of transplantation between two identical twins, renal transplant recipients have to receive long-term immunosuppressive drugs in order to prevent the host's immune system from rejecting the allograft kidney. Unfortunately, the immunosuppressive drugs currently in use are still relatively non-specific, and lifelong administration of these drugs to transplant recipients is associated with significant immune and non-immune toxicities.

Transplantation tolerance, the specific immune unresponsiveness of the organ transplant recipient towards the foreign histocompatibility antigens of the transplanted organ without the need for ongoing immunosuppression, is regarded by many transplant clinicians as the ultimate goal of clinical transplantation [2]. Over the past few decades, the transplant community has devoted a great deal of effort to developing strategies for tolerance induction in organ transplantation. Excellent results of tolerance induction have been achieved, using a variety of methods, in experimental animals including rodents and non-human primates [3]. Mixed hematopoietic chimerism is among one of the most promising approaches for tolerance induction [4]. However, the application of a mixed chimerism strategy to achieve transplantation tolerance in humans has just begun over the past few years. The conventional approach entails combined hematopoietic stem cell and kidney transplantation with myeloablative pre-conditioning [5,6].

In this issue of the *Hong Kong Journal of Nephrology*, Vanikar et al report a novel and innovative protocol for tolerance induction in renal transplant recipients [7]. Their protocol consisted of pre-transplant intrathymic inoculation of donor renal tissue, and transplantation of donor hematopoietic stem cells with non-myeloablative minimum conditioning. The authors showed that patients who had undergone the tolerance induction protocol, as compared to patients who had undergone direct renal transplantation, had fewer and milder rejection. In another paper in this same issue of the *Hong Kong Journal of Nephrology*, the same group of investigators demonstrated mixed lympho-hematopoietic chimerism in seven patients who had undergone the tolerance induction protocol [8]. All these patients had stable graft function after complete withdrawal of immunosuppressive drugs. The results of both studies are impressive and the protocol developed by Vanikar et al has significant clinical implications as it offers the opportunity to minimize or withdraw immunosuppression after renal transplantation.

There are a number of remarkable features about the tolerance induction protocol developed by Vanikar et al. First, a large dose of donor hematopoietic stem cells was infused into the recipient in the absence of immunosuppression before transplantation. It appears that none of the study patients developed graft versus host disease. Second, in contrast to other reports on tolerance induction by mixed chimerism [5,6], no myeloablative regimen was used before the transplantation. It remains to be determined whether such a protocol without myeloablative conditioning can result in persistent and sustained mixed chimerism in the renal transplant recipients. Larger scale prospective studies should be carried out to confirm the long-term safety and efficacy of this protocol.

Although tolerance induction should remain the "holy grail" of clinical transplantation, the availability of newer immunosuppressive drugs and refinement of our current immunosuppressive protocols have prompted some investigators to question the value of tolerance induction in clinical practice. The work of Vanikar et al and others [5–8] has, no doubt, brought us one step closer towards true tolerance induction in renal transplant recipients. However, much work remains to be done if we are to make tolerance induction applicable to the majority of our transplant patients.

*Sing-Leung Lui*
*Assistant Editor*

## References

1. Merrill JP, Murray JE, Harrison JH, Guild MR. Successful homotransplantation of the human kidney between identical twins. *JAMA* 1956;160:277–82.
2. Fehr T, Sykes M. Tolerance induction in clinical transplantation. *Transpl Immunol* 2004;13:117–30.
3. Elster EA, Hale DA, Mannon RB, Cendales LC, Swanson SJ, Kirk AD. The road to tolerance: renal transplant tolerance induction in

nonhuman primate studies and clinical trials. *Transpl Immunol* 2004;13:87–99.
4. Cosimi AB, Sachs DH. Mixed chimerism and transplantation tolerance. *Transplantation* 2004;77:943–6.
5. Spitzer TR, Delmonico F, Tolkoff-Rubin N, McAfee S, Sackstein R, Saidman S, et al. Combined histocompatibility leukocyte antigen-matched donor bone marrow and renal transplantation for multiple myeloma with end-stage renal disease: the induction of allograft tolerance through mixed lymphohematopoietic chimerism. *Transplantation* 1999;68:480–4.
6. Millan MT, Shizuru JA, Hoffmann P, Dejbakhsh-Jones S, Scandling JD, Grumet FC, et al. Mixed chimerism and immunosuppressive drug withdrawal after HLA-mismatched kidney and hematopoietic progenitor transplantation. *Transplantation* 2002;73:1386–91.
7. Vanikar AV, Trivedi HL, Patel RD, Kanodia KV, Vakil JM. Effects of a tolerance induction protocol in renal allograft recipients – the Ahmedabad experience. *Hong Kong J Nephrol* 2005;7:22–6.
8. Trivedi HL, Vanikar AV, Modi PR, Shah VR, Khemchandani SI, Vakil JM, et al. Classical tolerance induction in renal transplantation – a study of 11 patients. *Hong Kong J Nephrol* 2005;7:27–33.