Netherlands
The Journal of Medicine

EDITORIAL

The ups and downs of sirolimus in kidney transplantation, and the importance of reporting negative findings

T. van Gelder

Departments of Internal Medicine and Hospital Pharmacy, Erasmus Medical Centre, Rotterdam, the Netherlands, tel.: +31 (0)10-463 32 02, e-mail: t.vangelder@erasmusmc.nl

We all know that trials with a positive outcome are more likely to be reported than trials with an inconclusive or negative outcome.[1] For studies that are prematurely discontinued, either for safety reasons, or for lack of efficacy of the medicinal product involved, publication of the outcome of the study is even less likely. However, for assessing the efficacy and safety of a drug it is imperative to consider the outcomes of all clinical trials. Inefficient or unsafe therapies may be retried by other investigators, unaware of the outcome of previous trials. Furthermore, individuals who participate in clinical trials typically provide consent in the belief that they are contributing to medical knowledge. But if the knowledge is never reported, the trust between patients and investigators is damaged. A comprehensive register of initiated trials has been proposed to reduce publication bias.[2] Registers will allow identification of unpublished studies and the possibility to find out more about these trials, which is especially crucial for systematic reviews of randomised trials. A trial register has also been initiated in the Netherlands.[3]
The importance of reporting negative findings is nicely exemplified by the paper from Van den Akker *et al.* in this issue of the Journal.[4] Their experience with a sirolimus-based immunosuppressive treatment regimen may serve as a red flag for other professionals in the field of solid organ transplantation. What did they do, what were their findings, and how did they decide to explore this treatment in their patients?
For the prevention of acute rejection after kidney transplantation the calcineurin inhibitors cyclosporin and tacrolimus have been, and still are, the cornerstone of immunosuppressive therapy. However, long-term use of calcineurin inhibitors is thought to be associated with an increased risk of cardiovascular disease and chronic renal allograft dysfunction.[5] Sirolimus blocks T-lymphocyte activation by a mechanism distinct from calcineurin inhibitors. Therefore, it may be expected that sirolimus would display a safety profile without the nephrotoxicity that is associated with the use of calcineurin inhibitors.
Two phase III randomised trials with sirolimus were conducted in human renal transplantation in 1996-1997. In these studies 2 or 5 mg of sirolimus a day was compared with either placebo (Global Study)[6] or azathioprine (United States Study)[7] in combination with full exposures to cyclosporine and corticosteroids. In both studies the sirolimus-treated patients had significantly lower incidences of biopsy-confirmed acute rejection than the control arm, but creatinine clearance values were reduced in the sirolimus groups. These trials raised the concern that sirolimus had a direct adverse effect on renal function, or exacerbated the nephrotoxicity of cyclosporine. It now appears that both pharmacokinetic and pharmacodynamic mechanisms are implicated, and subsequent experience has shown that cyclosporine dose reduction or discontinuation mitigates these effects.[8,9]
Other concerns with the use of sirolimus early after transplantation are prolongation of recovery from delayed graft function,[10] lymphocele formation and impaired wound healing,[6,7] and proteinuria following conversion from other immunosuppressive drugs to sirolimus.[11]
As an alternative to combining sirolimus with reduced-dose calcineurin inhibitor, or elimination of cyclosporine within the first six months after transplantation, a third option is complete avoidance of calcineurin inhibitors. Following two earlier studies applying a calcineurin inhibitor-free protocol,[12,13] Flechner *et al.* compared a sirolimus-based protocol with cyclosporin-based immunosuppression, in combination with basiliximab, mycophenolate mofetil and steroids.[14] This small study (n = 61) has received a lot of attention, as the investigators not only succeeded in achieving a very low incidence of rejection in the sirolimus-treated patients (6.4%), creatinine clearance at two years was also significantly better.[15] With the expectation that calcineurin avoidance would indeed lead

to better renal function and longer graft survival, many centres implemented calcineurin inhibitor-free protocols either as part of investigator-initiated studies, or for daily patient care.

The experience from Van den Akker *et al.*, described in this issue of the Journal, challenges this hope.[4] In their prematurely stopped study they found a very high rejection incidence (70%) in the first ten patients treated with a calcineurin inhibitor-free protocol. Subsequently Van den Akker *et al.* decided to change the protocol to better reflect the Flechner regimen, and increased the overall amount of immunosuppression. With this approach rejections no longer occurred, but toxicity was unacceptable. Obviously, the reader of this paper is discouraged from trying to initiate calcineurin inhibitor-free kidney transplantation protocols. The so far unpublished results of the Symphony study, which included 1645 (!) patients, also shed some new light on the optimistic Flechner data. In the Symphony study conventional immunosuppression (cyclosporine, mycophenolate mofetil and steroids), was compared with three low-toxicity regimens, one of which consisted of treatment with basiliximab, sirolimus, mycophenolate mofetil and steroids.[16] In this calcineurin inhibitor-free arm (n = 399) the incidence of biopsy-proven acute rejection was 37.2%, three times higher than that in the low-dose tacrolimus arm (12.3%). These results will convince most physicians not to embark on calcineurin inhibitor-free protocols.

This does not mean there is no future for sirolimus. There is still a need to reduce the burden of calcineurin inhibitor-related nephrotoxicity. And sirolimus still carries the promise of a reduced risk for developing cancer.[17] Other strategies need to be explored. Possibly, a delayed introduction of sirolimus in the second or third quarter after transplantation is the way to go. This would maintain the early benefits of calcineurin inhibitor therapy in preventing acute rejection episodes, and at the same time allow for improving, or stabilising, renal function thereafter.

REFERENCES

1. Bardy AH. Bias in reporting clinical trials. Br J Clin Pharmacol 1998;46:147-50.
2. Dichersin K, Rennie D. Registering clinical trials. JAMA 2003;290:516-23.
3. Hooft L, Assendelft WJJ, Hoeksema HL, Scholten RJM. Een nationaal prospectief trialregister voor gerandomiseerde en gecontroleerde trials; ethisch en praktisch noodzakelijk. Ned Tijdschr Geneeskd 2004;148:1866-9.
4. Van den Akker JM, Hené RJ, Hoitsma AJ. Inferior results with basic immunosuppression with sirolimus in kidney transplantation. Neth J Med 2007; [YK Invullen]
5. Solez K, Vincenti F, Filo RS. Histopathological findings from 2-year protocol biopsies from a U.S. multicenter kidney transplant trial comparing tacrolimus versus cyclosporine. Transplantation 1998;66:1736-40.
6. MacDonald A, for the Rapamune global study group. A worldwide, phase III, randomized, controlled, safety and efficacy study of a sirolimus/cyclosporine regimen for the prevention of acute rejection in recipients of primary mismatched renal allografts. Transplantation 2001;71:271-80.
7. Kahan BD, for the US Study Group. Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomized multicentre study. Lancet 2000;356:194-202.
8. Knight RJ, Kahan BD. The place of sirolimus in kidney transplantation: can we reduce calcineurin inhibitor renal toxicity? Kidney Int 2006;70:994-9.
9. Kreis H, Oberbauer R, Campistol JM, et al. Long term benefits with sirolimus-based therapy after kidney transplantation. J Am Soc Nephrol 2004;15:809-17.
10. McTaggart RA, Gottlieb D, Brooks J, et al. Sirolimus prolongs recovery from delayed graft function after cadaveric renal transplantation. Am J Transpl 2003;3:416-23.
11. Van den Akker, Wetzels JFM, Hoitsma AJ. Proteinuria following conversion from azathioprine to sirolimus in renal transplant recipients. Kidney Int 2006;70:1355-57.
12. Groth CG, Bäckman L, Morales JM, et al. Sirolimus (rapamycin)-based therapy in human renal transplantation. Transplantation 1999;67:1036-43.
13. Kreis H, Cisterne JM, Land W, et al. Sirolimus in association with mycophenolate mofetil induction for the prevention of acute rejection in renal allograft recipients. Transplantation 2000;69:1252-60.
14. Flechner SM, Goldfarb D, Modlin C, et al. Kidney transplantation without calcineurin inhibitor drugs: a prospective, randomized trial of sirolimus versus cyclosporine. Transplantation 2002;74:1070-6.
15. Flechner SM, Kurian S, Solez K, et al. De novo kidney transplantation without use of calcineurin inhibitors preserves renal structure and function at two years. Am J Transplant 2004;4:1776-85.
16. Ekberg H, Tedesco-Silva H, Demirbas A, et al. Symphony comparing standard immunosuppression to low-dose cyclosporine, tacrolimus or sirolimus in combination with MMF, daclizumab and corticosteroids in renal transplantation. Presented at World Transplant Congress, 2006, Boston, abstract 49.
17. Campistol JM, Eris J, Oberbauer R, et al. Sirolimus therapy early after cycloporine withdrawal reduces the risk for cancer in adult renal transplantation. J Am Soc Nephrol 2006;17:581-9.