NEFROLOGÍA. Volumen 26. Suplemento 2. 2006

PREFACE

Sirolimus and kidney transplantation

J. M. Campistol
Hospital Clínic de Barcelona. Spain.

Recent years have witnessed a profound change in the priorities and objectives of kidney transplantation. From the azathioprine era, with its > 85% acute rejection rates and repeated dosing with steroid pulses, we have moved to acute rejection rates which are currently below 10% and it is now possible to administer and/or eliminate corticosteroids. This spectacular change has come about thanks to the introduction of new immunosuppressive agents, with cyclosporine A now the pioneer in the control of acute rejection. More recently, the introduction of tacrolimus, mycophenolate mofetil and sirolimus has made it possible to reduce acute rejection to below 10%. This spectacular reduction has led to a significant improvement in the outcome of kidney transplant in the short term (1 year), with allograft and patient survival rates over 90% and difficult to improve upon. Despite this improvement in short-term results, mean allograft survival has not improved over the last 10 years, and results have stabilized in the long term. This is mainly due to chronic transplant nephropathy as the main cause of loss of allograft and death of the patient with a functioning graft, especially by cardiovascular causes and cancer. The pathogenesis of chronic transplant nephropathy has been severely affected by therapy with calcineurin inhibitors (cyclosporine and tacrolimus) and by their inherent nephrotoxicity.

A new family of immunosuppressive agents are currently available—the m-TOR inhibitors (sirolimus and everolimus). These drugs have a chemical structure similar to that of tacrolimus—they share the immunophilin FKBP-12 —although they have a completely different mechanism of action by blocking a central enzyme of cell proliferation such as m-TOR. Blocking this enzyme does not only achieve immunosuppression by blocking the effect of interleukin-2 on T lymphocytes, it also has important consequences for other cell strains with an important pathogenetic role in chronic rejection. Furthermore, their mechanism of action allows them to partly block the Akt enzyme pathway, which is one of the proliferation pathways used by many tumors with mutations in the PTEN tumor suppressor gene, by which they also develop a potent antitumor effect. In addition to its immunosuppressive, antiproliferative and antitumor capacity, it is not nephrotoxic, which clearly favors solid organ transplantation, especially kidney transplantation. The incorporation of sirolimus in kidney transplantation has been slower than expected given its potential characteristics and it appears not to be fulfilling the expectations for its use and development. Analyzing the reasons for this slow introduction would be an arduous task, although I think that an essential element is the confusion over its mode of application and safety profile. Compared with classic immunosuppression, sirolimus has provided an important qualitative change by eliminating calcineurin inhibitors, which always involve a certain resistance to change. Furthermore, reports of a series of uncommon and as yet unknown adverse events have left transplant physicians somewhat reserved about using sirolimus. We believe that its mechanism of action, and antiproliferative and antitumor effect, could make sirolimus the ideal drug for this type of maintenance therapy. A better knowledge of the drug and practical guidelines for both de novo kidney transplant and conversion should enable us to achieve our objectives—prolonging allograft and patient survival, and improving quality of life. This monographic issue aims to review the state of the art on sirolimus and

Correspondence: Dr. J. M. Campistol
Servicio de Nefrología
Hospital Clinic
Barcelona. Spain
E-mail: imcampis@clinic.ub.es

provide practical guidelines for management. I believe that a consensus meeting with experts on the use of the drug has made this an easy objective. I take this opportunity to thank all those involved in this monographic issue and Wyeth for their collaboration in the preparation of this document.