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The Evolution of Immunosuppressant Therapy in Renal Transplantation

For patients with end-stage renal disease (ESRD), kidney transplantation offers the greatest chance for survival and improved quality of life. However, with the limited supply of kidneys available for transplantation, and a growing number of patients with ESRD, the importance of optimizing each transplant has never been greater. Recent studies have shown significant reductions in the incidence of acute rejection following transplantation, probably related to the availability of newer immunosuppressive therapies. However, these short-term gains have not been translated into a significant increase in long-term graft survival. Indeed, the rate of graft loss after the first year has not really changed. Since the greatest reasons for graft loss after 1 year are patient death and progressive allograft fibrosis (chronic allograft nephropathy/interstitial fibrosis/tubular atrophy not otherwise specified), many approaches have focused on potential strategies for reducing these complications.

Many of the immunosuppressive agents that form the mainstay of treatment following renal transplantation have been associated with toxicities and chronic allograft nephropathy. The calcineurin inhibitors (CNIs), which have been responsible for major improvements in early rejection, also have the potential to cause renal toxicity. Thus CNI-sparing immunosuppressive protocols, often utilizing sirolimus, have become the focus of growing interest. This supplement to *Drugs* provides Canadian experience on the potential ways that sirolimus might be used to improve transplant outcomes.

Over the past decade, the renal transplantation community has witnessed a multitude of changes. The growing shortage in donor organs has resulted in increased wait times for transplantation. Donor characteristics and the quality of available organs have also changed. Dr Gregory Knoll provides an overview of the evolving renal transplant landscape in Canada and the US and discusses how these changes have impacted clinical practice.

With changing donor characteristics and the growing shortage in organ supply, renal transplant practitioners have increasingly utilized expanded criteria donor kidneys. Despite the poorer outcomes associated with expanded criteria donor kidneys, the trade-off may be acceptable if overall patient survival is improved by reduced wait times. However, these kidneys may be more likely to suffer from calcineurin nephrotoxicity. Accordingly, Dr Andrew House and his colleagues discuss the encouraging initial results of their pilot study suggesting that a CNI-free drug regimen in renal

transplant patients with expanded criteria donor kidneys might yield improved results.

Unfortunately, biochemical parameters of renal function are relatively insensitive markers of progressive renal scarring and do not help elucidate the aetiology in individual patients. Drs Serdar Yilmaz and Aylin Sar have written an interesting article discussing the important role of renal pathology and protocol biopsies in assessment and management of this complication.

Patient death from malignancy after transplantation is an increasing problem. This issue is highlighted in the article by Dr Anil Kapoor, who also discusses the potential beneficial role of sirolimus and other target of rapamycin (TOR) inhibitors in reducing post-transplantation malignancy. As sirolimus use is increasing, the problem of proteinuria in association with the use of this agent has become apparent. While the pathogenesis is unclear, Dr Azemi Barama provides an update on the aetiology and potential treatment approaches based on animal experiments.

What is considered the 'optimal' immunosuppression regimen for renal transplant recipients is continuously evolving. Efforts to maximize patient and graft survival with minimal adverse effects have given rise to a multitude of approaches, with promising results. Although prevention of acute rejection remains a primary goal of treatment, agents that do not compromise long-term renal function are needed. Whether this will ultimately be accomplished through the use of sirolimus in CNI-sparing regimens is not yet known. This supplement consolidates the experiences of some of Canada's transplant specialists, providing the reader with an enhanced understanding of some newer aspects of this novel approach to the optimal management of renal transplant recipients.

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