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Advances in Immunosuppression

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Abstract: The past decade has witnessed the introduction of several new immunosuppressive agents. The availability of these new agents has led to attempts to determine which is the best combination of maintenance immunosuppression for the patients, based on efficacy and reduction of adverse effects. Steroid avoidance, withdrawal and minimization regimens are being assessed. Calcineurin withdrawal or minimization protocols are studied in an attempt to improve long term allograft function and survival. Immunosuppression regimens are no longer standard and are tailored to the patient's needs depending on risk profiles and benefits. The introduction of interleukin-2 receptor antibody inhibitors has further reduced the risk of acute rejections without any increase in the adverse profiles. Newer biologicals such as alemtuzumab and belatacept may allow the use of lower doses of immunosuppressive agent immediately posttransplant. The use of rituximab in combination with other measures has extended the frontiers of kidney transplantation to ABO and conventional crossmatch incompatible transplants.

INTRODUCTION

In the past 50 years of kidney transplantation, immunosuppression has changed significantly. The introduction of cyclosporine A in the 1970s made a dramatic breakthrough in the reduction of acute rejections and prolongation of allograft survival. The increasing use of tacrolimus in the 1990s and the subsequent combination with the inosine monophosphate dehydrogenase inhibitor, mycophenolate mofetil, an antiproliferative agent, has led to further reduction in acute rejection rates. The efficacy of these agents has produced remarkable short-term results with a 1-year cadaveric graft survival of 95% and the first year posttransplant rejection rate approximating 15%.¹ With the advances in immunosuppression and the increased availability of immunosuppressive agents, the focus of immunosuppression management in renal transplantation is on choosing the right combination for the patient so as to minimize adverse effects while preserving long term allograft function and minimizing rejection. Such strategies have involved steroid avoidance, withdrawal or minimization and calcineurin inhibitor minimization or withdrawal. The recent experiences with the use of near-lymphoablative induction regimens may allow minimization of both corticosteroids and calcineurin inhibitors.

CHOICE OF IMMUNOSUPPRESSION REGIMEN

In the past 10 years new renal transplant immunosuppressive regimens have improved short-term outcomes but with less marked effects on long-term graft survival. The numerous possible combinations of immunosuppressive agents are confusing and physicians have difficulty in deciding which is the preferred combination. Cianco et al compared tacrolimus/sirolimus versus tarcolimus/mycophenolate versus cyclosporine/sirolimus in a randomized trial. Their 3-year

interim analysis has indicated a trend towards better graft function, fewer endocrine disorders and fewer rejection episodes in the tacrolimus/mycophenolate arm.² In a prospective randomized trial of tacrolimus in combination with sirolimus or mycophenolate mofetil, Mendez et al showed that the tacrolimus/mycophenolate combination had superior graft function compared to the tacrolimus/sirolimus combination.³ The results of a meta-analysis by Webster et al showed that tacrolimus was superior to cyclosporine in improving graft survival and preventing acute rejection after kidney transplantation. Treating 100 recipients with tacrolimus instead of cyclosporine would avoid 12 suffering acute rejections, 2 losing their graft but cause an extra five to become insulin-requiring diabetes.⁴

CORTICOSTEROIDS AVOIDANCE, WITHDRAWAL, OR MINIMIZATION

Corticosteroids have been the cornerstone of immunosuppression for renal transplantation for decades despite its numerous side effects such as hypertension, diabetogenicity, osteoporosis, dyslipidemia, etc. Several earlier attempts to withdraw steroids have failed because of higher acute rejection rates.^{5,6} Recent literature has segregated steroid usage based on rapid and early steroid withdrawal or avoidance and late withdrawal. Early steroid withdrawal and avoidance regimens within 1-3 weeks posttransplant appear to be successful with the addition of prophylactic antibody induction therapies such as basiliximab, daclizumab, alemtuzumab and rATG.^{7,8} Matas, et al reported excellent 5-year graft survival results in a protocol incorporating steroid-free maintenance immunosuppression.⁹

SIROLIMUS AND CALCINEURIN INHIBITORS AVOIDANCE, WITHDRAWAL, OR MINIMIZATION

Both calcineurin inhibitors, cyclosporine and tacrolimus have made a significant impact on acute rejection rates and short-term graft outcomes in renal transplantation. However, long-term graft outcomes have not improved and chronic allograft nephropathy remains as one of the most challenging problems. Chronic exposure to the nephrotoxic effects of calcineurin inhibitors has been implicated as a main cause of allograft function deterioration. The introduction of m-TOR inhibitors, sirolimus and everolimus, has provided an opportunity for manipulation of the dosage of calcineurin inhibitors. As such, immunosuppression regimens that incorporate calcineurin avoidance, withdrawal or minimization have been attempted to reduce the toil of calcineurin inhibitor nephrotoxicity. Sirolimus-based immunosuppression regimens generally replace the calcineurin inhibitor with sirolimus as the combination of sirolimus and a calcineurin inhibitor results in a higher serum creatinine level.¹⁰ Larson, et al showed that a calcineurin-inhibitor-free regimen using sirolimus/mycophenolate/prednisone produced similar acute rejection rates and graft survival 1-2 years after transplantation compared to tacrolimus/mycophenolate/prednisone.¹¹ Everolimus in combination with cyclosporine had a nonsignificant increase in death and graft loss compared to the mycophenolate mofetil/cyclosporine arm. In addition, renal function was poorer and serum creatinine was higher in patients receiving everolimus.¹² In another 3-year study, everolimus 1.5 mg/day showed comparable results with mycophenolate mofetil in *de novo* renal transplant patients. The use of everolimus 3.0 mg/day resulted in inferior graft survival.¹³ A recent systematic review of randomized trials was performed comparing immunosuppressive regimens containing mTOR inhibitors with other regimens. Regimes using low dose mTOR inhibitors had higher acute rejection rates whereas regimens using high dose mTOR inhibitors had more adverse effects. The authors cautioned that long-term hard-endpoint data from robust randomized trials are still required.¹⁴ Conversion from a calcineurin inhibitor to sirolimus has been used as a strategy to improve deteriorating renal allograft function. Mulay et al. found that conversion to sirolimus is associated with an improvement in short-term renal function. However, the discontinuation rates

and potential side effects were of genuine concerns. As such, adequately powered randomized trials with longer follow-up of hard outcomes are needed to determine whether this strategy leads to a lasting benefit.¹⁵

NEW BIOLOGICALS

The non depletional anti-interleukin 2 receptor antagonists have been shown to reduce the incidence of acute rejections with exceptional patient tolerability.¹⁶ Recent studies comparing basiliximab to conventional dosed ATGAM or rATG in regimes using cyclosporine, mycophenolate and steroids have shown comparable results.¹⁷ This induction approach has allowed the use of steroid avoidance immunosuppression regimens. However, they have not allowed the use of calcineurin inhibitors avoidance regimens.

Alemtuzumab, a potent depletional CD52-specific humanized monoclonal antibody rapidly depletes CD52 expressing lymphocytes both centrally and peripherally. Preliminary studies showed that alemtuzumab facilitated reduced maintenance immunosuppression. Alemtuzumab was comparable to basiliximab in its efficacy in a prednisone-free maintenance immunosuppressive protocol.¹⁸

However, alemtuzumab does not permit the use of a calcineurin-inhibitor free maintenance immunosuppressive regimen.¹⁹ Further studies are needed to determine the role of alemtuzumab in induction therapy.

CO-STIMULATORY BLOCKADE AGENTS

T cells require at least 2 signals for complete recognition of alloantigens and activation of the immune response. The CD28/B7 pathway is one of the most potent and well characterized co-stimulatory interactions. CD28-B7 co-stimulation regulates both the Th1/Th2 balance and the production of chemokines. The disruption of the CD28/B7 interaction reduces the frequency of proliferating cells. Belatacept is a humanized anti-B7, CD152Ig. In a phase III trial of belatacept in renal transplantation, belatacept was shown to be equivalent to cyclosporine in preventing acute rejections. The incidence of acute rejections was 7% in the belatacept arm and 8% in the cyclosporine arm. The authors concluded that belatacept facilitated calcineurin inhibitor avoidance when used as an induction agent.²⁰ More studies are needed to determine its role in lowering the dose of maintenance immunosuppression post-transplant.

CONCLUSIONS

The next decade of renal transplantation immunosuppression will see new ways of using induction therapies to reduce the load of maintenance immunosuppression. Different immunosuppressive regimens will be studied to achieve better long-term allograft outcomes. Steroid and calcineurin inhibitor avoidance or minimization protocols may be implemented to reduce the adverse effects.

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