

LECTURE

Low toxicity immunosuppressive protocols in renal transplantation

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Abstract. With the development of increasingly potent new immunosuppressive agents, the outcomes after renal transplantation have continued to improve. However, patients continue to require long term chronic immunosuppression. The toxicities associated with cyclosporine, azathioprine, prednisone, and anti-lymphocyte antibodies are well known; those associated with the newer agents, tacrolimus, mycophenolate mofetil, and sirolimus, have also been described. In an attempt to minimize these side effects, a number of low toxicity protocols have been developed. They can be categorized into those that withdraw, minimize, or avoid calcineurin inhibitors, those that withdraw or avoid steroids, and those that withdraw adjunctive (third) agents. This presentation will review the various low toxicity protocols that have been utilized in clinical renal transplantation. While there are a number of combinations that have been tried, it is not yet clear which regimen(s) will prove to be the most efficacious and least toxic. In addition, the presentation will also describe preliminary outcomes with a new tolerogenic protocol developed at the University of Pittsburgh. This regimen combines steroid avoidance with low doses and gradual tapering of calcineurin inhibitors, and has shown considerable promise in kidney, pancreas, liver, and intestine recipients. (*Keio J Med* 53 (1): 18–22, March 2004)

Key words: low-toxicity, immunosuppression, renal transplant

Introduction

Transplantation is fundamentally an unnatural act; at some level, we were not meant to take an organ from one individual and place it into another, with a reasonable expectation that it would function indefinitely. The modern reality, of course, is that we have been rather successful in doing just that with a large number of different organs, and in spite of an imperfect understanding of the immune system. We have been successful because of the development of effective chemical and biological immunosuppressive agents. Although some of these agents have been relatively selective, all are non-specific, and virtually all have side effects. The toxicities associated with the conventional agents, namely cyclosporine, steroids, azathioprine, and anti-lymphocyte preparations, are well understood and have been extensively described.^{1–5} Similarly, the newer immunosuppressive agents, tacrolimus, mycophenolate

mofetil, and sirolimus, all have well described toxicities of their own.^{5–18} The only two recently introduced agents that seem to have few, if any toxicities, are the anti-IL2 receptor monoclonal antibodies, daclizumab and basiliximab; however, both of these are useful for induction only, and neither is being used as a maintenance immunosuppressive agent.^{19–24} Given these well understood toxicities, there have been a number of studies over the years that have utilized regimens that have attempted to minimize toxicity in transplant recipients. This review will focus on renal transplantation, and will look at the five main areas that can be put into the category of “low toxicity”: calcineurin inhibitor withdrawal, calcineurin inhibitor avoidance, steroid withdrawal, steroid avoidance, and third agent withdrawal. These studies will be described chronologically in each group, and an attempt will be made to identify the risks and benefits associated with each particular regimen.

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Calcineurin Inhibitor-Sparing

Calcineurin inhibitor withdrawal

The first major study on calcineurin inhibitor withdrawal came early in the development of cyclosporine. In Oxford, England, Peter Morris' group took patients who had initially been placed on cyclosporine and converted them three months after transplantation to azathioprine/prednisone. Sixty-four patients were studied. While there was improvement in renal function in this group of patients, there was also a 32% incidence of acute rejection, with 2 graft losses. Thus, this early experience was not favorable.^{25–27} A subsequent randomized trial, from Glasgow, in 102 patients, randomized patients to conversion to azathioprine-based therapy one year after transplantation. With 10 years of follow up, there was no difference in the 10-year patient or graft survival, although there was an early increased incidence of rejection in the patients converted to azathioprine. Advantages in the azathioprine group included lower serum creatinine levels and a lower requirement for antihypertensive medication.²⁸

Kasiske in Minnesota performed a meta-analysis of cyclosporine withdrawal studies, looking at 10 randomized and 7 non-randomized trials. He found an increased incidence of rejection after conversion to azathioprine, but no difference in short-term patient or graft survival.²⁹

With regard to the newer third agents, at least two trials of conversion from cyclosporine to MMF have been performed, in the Netherlands and in France; both have shown reasonably good outcomes in small numbers of patients.

A large, prospective, randomized trial looking at the combination of cyclosporine, sirolimus, and steroids, was performed. Patients were randomized to continue with this regimen or to undergo cyclosporine withdrawal beginning three months after transplantation. With one-year follow up, patient survival, graft survival, and the incidence of rejection were similar between the two groups. The patients randomized to cyclosporine withdrawal had better renal function.

Reduced Dose Calcineurin Inhibitor

An additional category of studies has looked at reducing cyclosporine dosages as opposed to complete withdrawal. The group in Barcelona studied patients with cyclosporine nephrotoxicity and looked at the impact of reducing the dosage by nearly half, with the concomitant introduction of mycophenolate mofetil. Renal function improved, as did blood pressure and TGF beta levels, and no rejection was noted.

Another study looked at the impact of reduced dose cyclosporine with sirolimus and steroids, and compared the outcomes to those in patients receiving full dose cyclosporine with sirolimus and steroids. Although the overall incidence of rejection was somewhat higher, increasing from 8.5% to 19.5%, much of the impact of this increased incidence of rejection was in African Americans. The incidence of rejection in non-African Americans receiving reduced dose cyclosporine with sirolimus was 11%, whereas in African-Americans it was 39%. This study had 149 patients.

A smaller, non-randomized study looking at the combination of basiliximab, sirolimus, and steroids with the delayed introduction of low dose cyclosporine, found, in 40 patients, excellent patient and graft survival rates, an incidence of rejection of 16%, and an incidence of steroid-resistant rejection of 2%.

A few studies have been performed looking at the combination of low dose tacrolimus with sirolimus and steroids, from Halifax, Cleveland, and Pittsburgh. In general these trials have shown excellent patient and graft survival rates, with relatively low incidences of rejection, and reasonable renal function; cholesterol levels in the Pittsburgh study were under 200 mg/dl.

Calcineurin Inhibitor Avoidance

A number of studies have been performed in this category, looking at combinations of antibody and mycophenolate mofetil, sirolimus and azathioprine, sirolimus and mycophenolate mofetil, antibody with sirolimus and mycophenolate mofetil, and antibody with sirolimus monotherapy.

The first study performed looked at the combination of daclizumab, mycophenolate mofetil, and prednisone, in 98 patients. Although excellent patient and graft survival was seen, the incidence of rejection was 48%, and 62% of the patients in the trial were started on calcineurin inhibitors.

A smaller trial, utilizing antithymocyte globulin, mycophenolate mofetil, and steroids in 17 patients, from Barcelona, had excellent patient and graft survival, with a need for calcineurin inhibitors in 30% of the patients.

Two European randomized trials utilizing sirolimus as the main maintenance immunosuppressive agent have been performed. One compared sirolimus, azathioprine, and steroids with cyclosporine, azathioprine, and steroids. The other compared sirolimus, mycophenolate mofetil, and steroids with cyclosporine, mycophenolate mofetil, and steroids. In both trials, comparable patient and graft survival was noted between the sirolimus and the cyclosporine groups, and a comparable incidence of rejection was noted. Renal function was better in the patients treated with sirolimus, and

less hypertension was noted, but cholesterol levels and triglyceride levels were elevated, and platelet counts were also lower.

A recent study from Cleveland looked at basiliximab, sirolimus, mycophenolate mofetil, and steroids in 31 patients, with excellent patient and graft survival and an incidence of rejection of less than 10%. Cholesterol levels were elevated, as were triglyceride levels.

Two small trials have been performed utilizing the combination of Campath 1-H with sirolimus monotherapy; 15 patients have been studied at the NIH and 24 at the University of Wisconsin. This combination certainly appears to be promising, although one allograft has been lost to rejection in the Wisconsin series. Rejection of an atypical type has been seen routinely in the NIH series, and histologically typical rejection has been seen in 25% of the Wisconsin series. This research, avoiding both calcineurin inhibitors and steroids, is quite promising.

Steroid Sparing Regimens

Steroid withdrawal

A number of trials have looked at steroid withdrawal in renal transplant recipients. One of the early important, and somewhat discouraging studies, was a Canadian randomized multicenter trial, which randomized patients to withdrawal three months after transplantation ($n = 260$) or to alternate day steroids ($n = 263$). Patient survival at five years was comparable, but allograft survival in the group randomized to steroid withdrawal was significantly inferior, 73%, compared to the group that remained on every other day steroids, 85% ($p = .03$). A more recent randomized multicenter trial of steroid withdrawal under cyclosporine and mycophenolate mofetil based therapy ($n = 266$) was stopped by its Data Safety and Monitoring Board, because of the increased incidence of rejection in the patients randomized (beginning three months after transplantation) to steroid withdrawal. Again, a more detailed analysis suggests that while the patients randomized to continue on steroids had an incidence of rejection of 10%, and the group randomized to steroid withdrawal had an incidence rejection of 31%, within the group of patients randomized to steroid withdrawal, non African-Americans had an incidence of rejection of 16%, and African-Americans had an incidence of rejection of 40%. There was no difference in one year patient or graft survival between the steroid withdrawal and steroid continuation group.

Under tacrolimus-based therapy, retrospective non-randomized studies from the University of Pittsburgh in 795 adults and 82 pediatric patients have demonstrated an ability to withdraw steroids routinely in 71% of

adults and over 90% of children. Predictably, over 20% of the patients withdrawn from steroids had to have steroids resumed because of late rejection. Five year patient survival has not been different in the adults withdrawn from and restarted on steroids, although graft survival has been worse, compared to the group discontinuing steroids and not needing to resume them. In pediatric patients there has been no difference in five year patient or graft survival between the children withdrawn from steroids or those who had resume steroids, although renal function was worse in the patients who resumed steroids. In both adults and children, the worst outcomes were in the patients who were never withdrawn from steroids; they obviously represented a higher risk group, and had more early rejection and delayed graft function than the groups withdrawn from steroids.

Steroid Avoidance/Near-Avoidance

In this category, one of the early studies was performed over 20 years ago in Europe, comparing patients randomized to cyclosporine monotherapy or to azathioprine and prednisone. Five-year graft survival was 55% in cyclosporine patients and 40% in the azathioprine patients; however, 47% of the cyclosporine-treated patients had steroids added to the maintenance immunosuppression. A randomized trial in England comparing cyclosporine monotherapy, cyclosporine/steroids, and azathioprine/prednisone in 465 patients, with a follow up of seven years, showed no differences in patient or graft survival between the two cyclosporine groups; 15% of the cyclosporine monotherapy group had steroids added to the immunosuppressive regimen.

More recent studies, out of Minnesota, have looked at a 5 day course of Thymoglobulin, cyclosporine, mycophenolate mofetil, and six days of steroids post-operatively, in 51 patients, with excellent patient and graft survival, and an incidence of rejection of less than 10%.

In a trial from Cambridge, England, 31 patients were given two doses of campath 1-H and low dose cyclosporine monotherapy, with excellent patient and graft survival and a relatively low incidence of rejection of 19%. A three-year analysis of this series has continued to show excellent medium term outcomes, with 97% patient survival and 85% graft survival.

Studies with tacrolimus-based therapy have looked at the combination of tacrolimus, mycophenolate mofetil, and one week of steroids, with excellent three-year outcomes; the incidence of rejection was 25%, and 85% of the patients remained off prednisone. This study was performed on 52 patients and was from the University of Chicago.

Another study, looking at 192 patients at randomized to daclizumab, tacrolimus, MMF, and just three doses of steroids, was associated with nearly perfect patient and graft survival and an incidence of rejection of 14%. Subsequent studies from this group have looked at six days of steroids with Thymoglobulin induction, tacrolimus, and MMF or sirolimus, with excellent outcomes and essentially no rejection, in kidney-pancreas recipients.

Two studies in pediatric patients have been performed, one from Denmark, and one from Stanford. The Danish study included 14 patients who received antithymocyte globulin, cyclosporine, and in half of the patients, mycophenolate mofetil. There were three patients who experienced rejection, for an incidence of 21%. The initial Stanford study looked at 10 patients receiving daclizumab, tacrolimus, and either MMF or sirolimus; the daclizumab was continued for an extended period of time. No clinical rejection was seen in these patients, and a 20% incidence of sub-clinical rejection was noted.

A final study has been initiated in Pittsburgh, looking at Thymoglobulin preconditioning with tacrolimus monotherapy and steroid avoidance post transplantation, in a number of different organ recipients. The follow up on these patients is quite short, but the majority of the patients appear to be able to tolerate this regimen well, and tapering of tacrolimus dosing to as low as twice a week has been attempted in some patients. This latter experience, obviously, will require more follow up.

Third Agent Sparing

Azathioprine withdrawal

In this section there are two studies, one from Knoxville, Tennessee (n = 103), and one from Iowa City, Iowa (n = 129). In both studies azathioprine was successfully withdrawn from stable renal transplant patients, without an increased incidence of acute or chronic rejection or deterioration in graft survival.

Conclusions

There have been a large number of studies that have attempted to look at reduced toxicity immunosuppressive regimens. A number of combinations have been tried, and many of them have been extremely successful, particularly in low risk recipients. Ultimately, it is not yet clear which regimen(s) will be the most effective from the point of view of maximizing patient and graft survival, minimizing rejection, and minimizing adverse events. It is likely that there will be several reasonable candidate regimens that will emerge over the next several years. Important questions will be long-term out-

comes, looking especially at half-lives and chronic rejection on the one hand and the development of adverse side effects on the other. What is encouraging from the point of view of both transplant patients and those caring for them is that a number of low toxicity options exist, as increasing numbers of agents become available.

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