Immunosuppression Minimization and Avoidance Protocols: When Less Is Not More

Rohini Prashar and K. K. Venkat

Kidney transplantation is well established as the best treatment option for end-stage kidney disease. It confers not only a better quality of life but also a significant survival advantage compared to dialysis. However, despite significant improvement in short-term kidney transplant graft survival over the past three decades, long-term graft survival remains suboptimal. Concerns about the possible contribution of chronic calcineurin inhibitor (CNI) nephrotoxicity to late allograft failure and other serious adverse effects of currently used immunosuppressive agents (especially corticosteroids) have led to increasing interest in developing regimens which may better preserve kidney allograft function and minimize other immunosuppression-related problems without increasing the risk of rejection. The availability of newer immunosuppressive agents has provided the opportunity to formulate such regimens. Approaches to this end include minimization, withdrawal, or avoidance of corticosteroids and CNIs. Currently, replacement of a CNI with a mammalian target of rapamycin inhibitor while continuing mycophenolate and discontinuation of corticosteroids within the first post-transplant week is being increasingly utilized. Belatacept-based, CNI-free immunosuppression is an emerging alternative approach to avoiding CNI-mediated nephrotoxicity. We also discuss the evolution, results, and pros and cons of corticosteroid- and CNI minimization protocols. Recent studies suggest that chronic alloimmune damage rather than chronic CNI nephrotoxicity is the major contributor to late kidney allograft failure. The implications of this finding for the use of CNI minimization protocols are also discussed.

Key Words: Immunosuppression, Minimization, Avoidance, Corticosteroids, Calcineurin inhibitors (CNIs)

INTRODUCTION

The advent of cyclosporine, the first-in-class calcineurin inhibitor (CNI) in the early 1980s, decreased the incidence of rejection and increased 1-year graft survival significantly in kidney transplant recipients (RTRs).[1] Since the mid-1980s, the choice of immunosuppressive drugs has expanded greatly to include antilymphocyte antibodies (polyclonal equine and rabbit antithymocyte globulin), monoclonal muromonab-CD3/OKT3, monoclonal interleukin-2 receptor antibodies (basiliximab/Simulect and daclizumab/Zenapax), a second CNI (tacrolimus/Prograf), antiproliferative agents (mycophenolate mofetil/CellCept and mycophenolate-sodium/Myfortic), mammalian target of rapamycin-inhibitor (mTORi) drugs (sirolimus/Rapamune and everolimus/Zortress), and most recently, a lymphocyte costimulation blocker (belatacept/Nulojix).[2] Alemtuzumab/Campath, rituximab/Rituxan, and boretezomib/Velcade are also being used off label in some RTRs.[2] Currently, in the USA, the most commonly used immunosuppressive regimen in RTRs is immediate post-transplant induction therapy with r-ATG/Thymoglobulin or basiliximab (in 60-65% of RTRs and in 15-20% of patients, respectively) and maintenance immunosuppression with a combination of a CNI (tacrolimus or cyclosporine in 90-95% and 5-10% of patients, respectively) + mycophenolate (in 90-95% of RTRs) ± corticosteroids.[3]

Given the availability of a variety of potent drugs which in combination have markedly decreased first year rejection rates to <10-15% and increased 1-year graft survival >90%,[3] it is not surprising that immunosuppressive regimens in RTRs have increasingly focused on avoiding the adverse effects of individual agents that contribute to patient morbidity/mortality and/or to progressive impairment of kidney function/allograft failure due to their nephrotoxicity. Physicians and RTRs generally agree that corticosteroids cause more unacceptable problems compared to other immunosuppressants. Chronic CNI nephrotoxicity may be a major contributor to interstitial fibrosis and tubular atrophy beyond the first post-transplant year.[4] In this review, we discuss the evolution, results, and the pros/cons of corticosteroid and CNI minimization/withdrawal/avoidance protocols increasingly utilized over the past 3 decades to improve long-term outcomes in RTRs.

CORTICOSTEROID MINIMIZATION/WITHDRAWAL/AVOIDANCE IN KIDNEY TRANSPLANTATION

Corticosteroids have been an integral part of post-transplant immunosuppression since the beginning of clinical kidney transplantation 60 years ago, both for maintenance therapy and (in higher doses usually given as daily intravenous boluses for 3-5 days) as first-line treatment for rejection. The well-known adverse effects of long-term corticosteroid therapy include weight gain, cushingoid facies and habitus, growth retardation in children, new onset diabetes mellitus or aggravation of pre-existing diabetes, de novo hypertension or worsening of pre-existing hypertension, hyperlipidemia, psychological changes, osteoporosis with increased fracture risk, avascular bone necrosis, ocular cataracts, increased susceptibility to infection, and wound-healing problems. Cardiovascular disease is the major cause of morbidity and mortality in RTRs after the first year and corticosteroid-induced weight gain, diabetes, hypertension, and hyperlipidemia may worsen the

From the Division of Nephrology and Transplant Institute, Henry Ford Hospital, Detroit, MI.

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Address correspondence to Rohini Prashar, MD, Division of Nephrology and Transplantation Institute, Henry Ford Hospital, 2799 West Grand Blvd., CFP-5, Detroit, MI 48025. E-mail: Rprasha1@hfhs.org

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cardiovascular risk in this population. Given their myriad adverse effects, corticosteroid-free maintenance immunosuppression is an attractive goal in kidney transplantation. The percentage of US RTRs discharged without corticosteroids immediately after transplantation has increased progressively: 5% in 2000, 23% in 2004, and 35% in 2008.[5] However, more recent data suggest that the trend has slightly reversed, with fewer patients being discharged with corticosteroids.

Evolution of Corticosteroid Minimization/Withdrawal/Avoidance Protocols

Bolstered by the greater immunosuppressive efficacy of cyclosporine, the use of lower initial doses of prednisone (eg, 30 mg/d instead of 1 mg/kg/d in the precyclosporine era) with more rapid prednisone taper to maintenance doses of 5-10 mg/d within the first 3-6 months became common practice in cyclosporine-treated patients. This was followed by attempts to completely withdraw maintenance corticosteroids (over weeks to few months) either after the first post-transplant year or between 3 and 6 months post-transplant ("very late" and "late" corticosteroid withdrawal, respectively). More recently, "very early" corticosteroid discontinuation between 3 and 14 days post-transplant has become popular.[6-8] Less commonly, total corticosteroid avoidance (both in maintenance therapy and treatment of acute rejection) from the day of transplantation has also been attempted.[7] In these protocols, steroid-free maintenance immunosuppression usually consists of a CNI (tacrolimus increasingly preferred to cyclosporine) in combination with an antiproliferative agent (mycophenolate supplanting azathioprine since 1995) or, less commonly, an mTORi (sirolimus or everolimus). CNI monotherapy after corticosteroid discontinuation has been tried in the past, but is no longer in common use.[9]

CLINICAL SUMMARY

- There is an increasing interest in developing immunosupressive regimens aimed at minimizing immunosuppression related complications without increasing the risk of rejection.
- Corticosteroid minimization protocols may be justified in children and patients with marked cushingoid features as well as patients at low risk of rejection.
- The rationale underlying the use of CNI minimization protocols may have to be reexamined in light of recent data suggesting that chronic alloimmune damage rather than chronic CNI nephrotoxicity is the major pathogenic factor in late allograft failure.

Effects of Corticosteroid Minimization/Withdrawal/Avoidance Protocols in RTRs

These protocols are based on the expectation that they would mitigate corticosteroid-related adverse effects and improve quality of life and longevity in RTRs, without increasing the risk of rejection which will impair allograft and patient survival. In clinical practice, both beneficial and adverse effects have resulted from the use of these protocols. A major limitation in assessing the outcomes of these protocols is that while there are numerous reports of small, single-center, uncontrolled or retrospectively controlled, short-term studies limited to RTRs at low risk for rejection, there are very few high-quality, large, randomized, controlled trials with long-term follow-up to draw upon.[10-14]

Beneficial Effects of Corticosteroid-Free Protocols

Amelioration of many corticosteroid-related adverse effects has been reported with the use of these protocols in RTRs with statistically significant (compared to indefinite maintenance prednisone doses of 5- to 10-mg daily) decreases in weight gain, incidence of new onset diabetes after transplant (NODAT), insulin requirement, blood pressure, antihypertensive medication requirement, hyperlipidemia, osteoporosis, fracture risk, and development of ocular cataracts post-transplant.[15] Linear growth is markedly impaired by CKD/ESRD in children, and long-term corticosteroids decrease catch up growth in pediatric RTRs. Thus, corticosteroid-free immunosuppression is particularly beneficial in the pediatric population.[16] To many patients, especially the young, the reversal of cushingoid facies/habitus after complete discontinuation of corticosteroids by itself is a highly attractive cosmetic benefit.

However, certain caveats have to be mentioned vis-à-vis the reported benefits of these protocols. In some studies, the incidence of corticosteroid-related adverse effects is not different when an indefinite maintenance prednisone dose of 5 mg/d is compared to corticosteroid-free immunosuppression.[12] Also, obesity, diabetes, hypertension, and dyslipidemia are important risk factors for cardiovascular disease, which is a major contributor to RTR mortality, and amelioration of these risk factors by corticosteroid-free regimens should ideally translate into improved post-transplant patient survival. One study involving more than 1000 RTRs reported improved 7-year recipient and graft survival with corticosteroid-free immunosuppression compared to retrospectively matched controls on indefinite corticosteroid maintenance.[14] Another study found a direct correlation between maintenance corticosteroid dose at 1 year post-transplant and subsequent RTR mortality.[17] Disappointingly though, in most studies, there is no difference in recipient survival when corticosteroid-free immunosuppression is compared to indefinite low-dose corticosteroid maintenance. This is not surprising since CNI therapy, which is the cornerstone of immunosuppression without corticosteroids, is diabetogenic (tacrolimus) and aggravates hypertension, hyperlipidemia, and bone loss (cyclosporine), thereby countering many of the benefits of corticosteroid-free regimens. Belatacept and mycophenolate are devoid of nephrotoxicity and diabetogenicity and do not cause hypertension or dyslipidemia. Therefore, corticosteroid-free regimens based on these two drugs may decrease long-term cardiovascular risk. Short-term outcomes of belatacept + mycophenolate-based corticosteroid-free