Review Article

Limitations of current liver transplant immunosuppressive regimens: renal considerations

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BACKGROUND: The use of calcineurin inhibitor (CNI)-based immunosuppressive regimens following liver transplantation (LTx) has improved the outcomes of the recipients. However, CNI has nephrotoxicity and causes short- and long-term renal complications. The progressive structural changes can be irreversible in the long-term, leading to chronic kidney dysfunction. The present review was to evaluate the different strategies of CNI application to renal function in liver recipients.

DATA SOURCES: PubMed database was searched for relevant articles in English on the issue of immunosuppressive regimen and kidney injury that related to early minimization of CNI after LTx.

RESULTS: Total avoidance of CNI from post-LTx immunosuppressive regimens has been associated with unacceptable high rates of acute, steroid resistant rejections; late conversion from CNI to non-nephrotoxic immunosuppressant failed to recover renal function. Early CNI minimization and conversion to non-nephrotoxic immunosuppressant, although had no effect on patient survival rates, improved glomerular filtration rate. The combination of everolimus (a mammalian target of rapamycin inhibitor) and tacrolimus not only maintains immunosuppressive efficacy but also minimizes kidney injury.

CONCLUSIONS: Up to now, protocols entirely avoiding CNI have not passed the primary safety endpoint of patient and graft survival, as well as the FDA mandated endpoint of biopsy proven acute rejection. Thus, early CNI minimization after LTx is the most rational approach preserving post-transplant renal function.

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KEY WORDS: liver transplantation; immunosuppression; chronic kidney disease

Introduction

The immunosuppressive regimens initially used in liver transplantation (LTx) included anti-metabolite purine analog, azathioprine and steroids, with or without anti-lymphocyte globulin preparations. However, the 1-year patient survival rate was only 33%.[1] The introduction of the calcineurin inhibitors (CNIs), first exemplified by cyclosporine (CSA) in the early 1980s, significantly improved LTx patient survival, with 1-year survival rate of 70% under CSA and corticosteroids (CS).[2] Later improvements were associated with the introduction of another CNI, tacrolimus (TAC), with improved 1-year patient survival rate approaching 90%.[3]

Despite the improvement in short-term patient and graft survival through reduction of acute rejection (AR) rates, the association of these agents with complications, such as metabolic disturbances, increased rates of *de novo* malignancies, recurrent disease, cardiovascular complications and worsened renal function, compromises long-term LTx recipient survival. The significance of advanced chronic kidney disease (CKD) [defined as glomerular filtration rate (GFR) <30 mL/min/1.73 m^2] in LTx recipients was illustrated by an analysis of UNOS data.[4] In this registry analysis, the cumulative incidence of CKD Stages 4 and 5 approached 20% by 3 years post-LTx and was associated with more than a four-fold increased risk of recipient death. The rate of nephrotoxicity is particularly concerning in pediatric recipients, who have a longer lifetime exposure to immunosuppressive therapy. Indeed, renal dysfunction has been reported in as many as 32% of pediatric liver recipients at an average

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follow-up of 7.6 years after LTx.[5] In addition, the emphasis of prioritizing LTx candidates with pre-existing renal dysfunction in the MELD era has increased the incidence of renal dysfunction following LTx.[6]

Although deterioration in renal function following LTx is clearly multifactorial,[7] CNI-induced nephrotoxicity plays a major role in short- and long-term deterioration, presumably mediated by afferent arteriolar vasoconstriction.[8] In addition, CNI-induced renal dysfunction initially is reversible. However, the progressive structural damage such as glomerular sclerosis, tubular atrophy and interstitial fibrosis may be irreversible and lead to chronic kidney dysfunction.[9] Thus successful efforts to improve renal function following LTx will depend heavily on the degree of structural changes associated with CNI.[10] Therefore, clinicians attempted to minimize or withdraw CNI to improve renal function after LTx. A large prospective, open-label, randomized trial evaluated conversion from CNI to the non-nephrotoxic immunosuppressive agent, sirolimus (SRL, rapamycin) for preservation of renal function in LTx patients. Eligible LTx patients had been maintained on CNI immunosuppression for 6-144 months prior to SRL conversion. A total of 607 patients were randomized (2:1) to abrupt conversion (<24 hours) from CNI to SRL (n=393) or CNI continuation (n=214) for up to 6 years of follow-up. This approach resulted in a higher rate of biopsy-confirmed AR (P=0.02) and discontinuations (P<0.001) in the SRL conversion group without any significant changes in baseline-adjusted mean Cockcroft-Gault (CG) creatinine clearance (CrCl) at month 12 (primary efficacy endpoint). While the authors stated that LTx patients showed no demonstrable benefit one year after conversion from CNI to SRL based immunosuppression, they cautioned that a substantial proportion of patients had extended CNI exposure (>85% for one year or more) and may have incurred irreversible renal damage prior to SRL conversion.[11]

Delaying the introduction of CNIs, reducing CNI exposure or avoiding CNI exposure entirely, have been strategies explored to lower the adverse events associated with CNIs. One approach in recipients has been to administer short-term induction therapy (polyclonal or monoclonal antibodies) with delayed introduction of CNIs. Other approaches have focused on reducing or eliminating CNIs within the first several months post-LTx. Lastly, avoidance of CNIs altogether with other immunosuppressive agents has also been examined. This review compared the patient outcomes of CNI avoidance, CNI delayed exposure, CNI early minimization or withdrawal after LTx (less than one year after LTx) and the associated impact on renal function.

Therapeutic strategies to avoid CNI-induced nephrotoxicity

CNI avoidance and CNI delay

Studies that have aimed at CNI avoidance or CNI delay have utilized antibody induction along with a non-nephrotoxic immunosuppressant. This approach avoids the synergistic vasoconstrictive effects of CNI with known early peri-operative risk factors associated with post-surgical acute kidney injury (AKI), such as volume depletion/shifts, hemodynamic instability and use of vasopressors, increased intra-abdominal pressures, poor liver allograft function and excessive blood transfusions.[12] Given the limitations of depending solely on the current armamentarium of non-nephrotoxic baseline immunosuppressive agents, this approach relies heavily on the use of induction antibody preparations and length of time that CNI introduction is delayed. Although mycophenolate mofetil (MMF) was evaluated as a strategy to avoid CNIs in a pilot study, the incidence of AR with the use of daclizumab (DAC) and MMF alone was 100% and all were steroid resistant rejections.[13] It has been concluded that MMF alone as a baseline immunosuppressant is insufficient.

An open, randomized, multicenter[14] trial evaluated the benefit of DAC induction with delayed but standard dose TAC on renal function post-LTx, and assessed the impact of simply delaying CNI under the cover of antibody induction. LTx patients with intact renal function received either delayed TAC with DAC induction (n=98) or standard TAC (n=101), both combined with MMF+CS. The primary endpoint was the incidence of serum creatinine >1.43 mg/dL at 6 months. The incidence of renal dysfunction using this arbitrary threshold was 22.4% with delayed TAC+DAC and 29.7% with standard TAC (not significant), which remained unchanged at 12 months (21.6% and 23.9%). This suggests that any benefit of delaying TAC was abrogated by chronic exposure to standard TAC levels.

Two studies also examined the effect of not only delaying introduction of TAC but also aiming for lower maintenance TAC levels on renal function with the premise that antibody induction with delayed low dose TAC would lead to improvement of renal function after LTx. Yoshida and other Canadian collaborators[15] conducted a multicenter, randomized trial in *de novo* LTx recipients where TAC was not only delayed, but was maintained at lower levels immediately following LTx, specifically DAC+MMF+CS+delayed low-dose TAC (target trough level 4-8 ng/mL, starting day 4-6) (n=72) compared to MMF+CS+standard TAC maintenance dosage (target trough level 10-15 ng/mL for first month,