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Objectives: There is a clear lack of clinical evidence guiding immunosuppressive management in long-term stable liver transplant recipients. As a result, anecdotal experience suggests wide variability across transplant centers. We aimed to identify patterns of immunosuppression practices in liver transplant centers across Canada and the United States.

Materials and Methods: From February 9 to May 31, 2015, we invited clinicians from all liver transplant centers in Canada and the United States to answer a 6-question survey generated using SurveyMonkey.

Results: Seventeen respondents from 15 liver transplant centers completed the survey. Although immunosuppressive practices are relatively uniform for induction and early maintenance therapy, significant variations exist in the management of long-term immunosuppression in stable transplant recipients with a relative lack of minimization protocols.

Conclusions: Our survey confirms a wide variability in immunosuppression practices across Canadian and US liver transplant centers. Research and practice priorities include design of pragmatic randomized controlled trials and development of clinical practice guidelines to standardize immunosuppressive management of long-term stable liver transplant recipients with a focus on immunosuppression minimization.

Key words: Alloreactivity, Rejection, Transplant tolerance

Introduction

Undoubtedly, the introduction of effective immunosuppression was the seminal event that made possible the transition of liver transplantation from the experimental realm into the treatment of choice for end-stage liver disease and hepatic malignancies. During the early days of transplantation, when rates of acute cellular rejection and related graft loss were high, immunosuppression intensification became the focus of pharmacologic optimization in transplantation, leading to dramatic improvements in patient and graft survival.1,2 However, the improvements in short-term graft survival have not been mirrored by improvements in long-term graft survival.3 Today, the long-term complications of immunosuppression have replaced rejection as the major therapeutic challenge in transplantation. In fact, a significant proportion of late graft loss or patient death with functioning graft is attributed to long-term exposure to immunosuppression, such as renal dysfunction, metabolic syndrome, and malignancies.4 At the same time, insight into liver immunology has revealed the liver allograft to be immunologically privileged, with lower rates of acute and chronic rejection, a relative resistance to antibody-mediated rejection, and a propensity to develop spontaneous tolerance.5,8 It is also known that alloreactivity decreases with time after transplantation and perhaps immunosuppression can be minimized in long-term transplant recipients.9,10 Given the significant morbidity and mortality directly attributed to immunosuppression burden, the propensity of the liver allograft to develop tolerance, and its relative resistance to acute rejection, immunosuppression minimization, especially in long-term transplant recipients, has been proposed as an ideal approach to improve long-term graft outcomes.11,12 However, there is a clear lack of evidence and
evidence-based guidelines to guide immunosuppression minimization and management in liver transplant recipients. To date, no organization in North America has published or disseminated a clinical practice guideline for the management of immunosuppression after liver transplantation. As a result, there seems to be substantial variability in immunosuppressive practices across transplant centers. We aimed to survey clinicians at liver transplant centers across Canada and the United States to describe standard immunosuppression practices early and late after liver transplantation, as well as to identify any institutional immunosuppression minimization protocols.

Materials and Methods

We surveyed pharmacists, hepatologists, and surgeons across all Canadian and US liver transplant centers from February 9 to May 31, 2015. We sent a total of 3 E-mail invitations at 2-week intervals with a link to the survey. Using SurveyMonkey (SurveyMonkey, San Mateo, CA, USA), we created 6 questions spanning 4 key domains: induction immunosuppression, standard early immunosuppression, and immunosuppressive minimization or cessation protocols. Respondents answered questions using a combination of drop-down menus and free-text boxes to elaborate when necessary.

Results

Seventeen clinicians representing 15 centers responded to our survey. Respondents were evenly balanced among countries (8 from Canada and 9 from the United States) and professions (9 pharmacists and 8 physicians).

Figure 1 illustrates survey responses to questions 1 and 2, which concerned induction and early maintenance immunosuppression practices. Most centers (80%) used induction with methylprednisolone, which was combined with antibody induction, either the interleukin 2 antagonist basiliximab or antithymocyte globulin, in about half the centers. The choices of early immunosuppressive agents and regimen compositions are also somewhat uniform, with the entire cohort utilizing tacrolimus as the preferred calcineurin inhibitor and over 80% using mycophenolate and steroids in the initial immunosuppression regimens. Not surprisingly, only a minority of centers (14%) included mammalian target of rapamycin inhibitors as part of the early maintenance immunosuppression regimen.

Discussion

In recent years, there has been increased research interest in allograft tolerance and total immunosuppression withdrawal with the goal of achieving tolerogenic stimulation and immunosuppression withdrawal.
and maintaining stable allograft function without immunosuppression, thus avoiding morbidity and mortality associated with long-term use of these agents.14 The most notable of such efforts is a multicenter prospective cohort study by Benitez and colleagues, where total immunosuppression withdrawal was attained in up to 80% of carefully selected stable adult liver transplant recipients.15 The “A-WISH” trial (Gradual Withdrawal of Immune System Suppressing Drugs in Patients Receiving a Liver Transplant) is another ongoing randomized multicenter trial focused on achieving allograft tolerance in liver transplant recipients (ClinicalTrials.gov identifier NCT00135694). However, until predictive and clinically robust immune markers for tolerance and alloreactivity are identified, total immunosuppression withdrawal remains firmly in the experimental realm. Immunosuppression minimization, on the other hand, is a practical and immunologically sound strategy in liver recipients given the immune privileged state of liver allografts and their propensity for tolerance. This strategy follows a good rationale for maintaining patients on minimal immunosuppression to allow the allograft to function normally without putting patients at risk for rejection. Unfortunately, immunosuppression minimization and long-term immunosuppression strategies have not been the focus of clinical research; therefore, there is little evidence guiding long-term immunosuppression strategies in liver transplantation.

Our survey, which included responses from across North America, illustrates the substantial variability in most domains of immunosuppression management of liver transplant recipients. Interestingly, there was less variability in early immunosuppression protocols, with most centers using a triple immunosuppression regimen consisting of steroids, antimetabolite, and tacrolimus. This consistency is perhaps due to existence of prospective clinical data guiding early immunosuppressive strategies. However, the gap between immunosuppression practices grew as we looked at long-term management and minimization strategies employed in stable transplant recipients. Nearly half the centers reported having no formal protocol for conversion to a single-agent immunosuppression in the late maintenance phase. The other half, which reported minimization strategies, varied greatly in terms of the optimal time for immunosuppression reduction, ranging from less than 3 months to up to 10 years after liver transplantation. Again, this variability highlights a lack of standard evidence-based guidelines for long-term immunosuppression management.

We acknowledge the limitation of our survey, namely, our inability to address all aspects of immunosuppression management in liver transplantation. Although brief in nature, our survey questions focused on 4 key aspects of immunosuppression management, and we were able to confirm our preexisting hypothesis of varied immunosuppression practices across different transplant centers. This variability could only stem from a lack of evidence-based clinical practice guidelines in such domains.

**Conclusions**

Based on our survey results, we identified urgent practice and research priorities. First, a pressing need exists for pragmatic randomized controlled trials focused on evaluating optimal immunosuppression protocols in stable liver transplant recipients, tracking clinically relevant long-term outcomes, and identifying clinical features, biomarkers, and molecular diagnostic assays for alloreactivity and tolerance. We also propose the formation of a multicenter clinical working group charged with the creation of evidence-based clinical practice guidelines for the management of immunosuppression in liver transplant recipients. These guidelines should be based on an updated systematic review of the best available evidence, incorporating newer clinically robust data as they become available. Our proposed guideline and research agenda should identify and resolve uncertainties and variations in practice, leading to better patient outcomes.

**References**


