Transplant Immunology I

Tolerance trials: Lessons learned and next steps forward

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Operational tolerance – biochemical and histological allograft stability in the complete absence of immunosuppression – has long been the “Holy Grail” of solid organ transplantation. Among the organs transplanted, it is widely recognized that the liver is the most “tolerogenic” of the organs that we transplant. As a result, during the past 10-15 years, several pivotal clinical trials have been conducted in both adults and children which have yielded many lessons that lead to recommendations.

Even among recipients with normal liver tests, liver biopsy shows a high prevalence (>30%) of subclinical histopathology. Thus, decisions to withdraw or substantially minimize immunosuppression should likely be based on both biochemical and histological assessment. A possible exception are for recipients with very low ALT (<15 U/L) who are at very low risk of having histologically abnormal allografts.

The success rate of complete withdrawal, even after excluding those with subclinical histopathology, has been modest: approximately 15% for adults and 40% for children. However, rejection has typically not occurred until immunosuppression was substantially reduced. Many who experienced rejection ended on less immunosuppression at study end. Thus, immunosuppression minimization rather than complete withdrawal may be a more generalizable strategy.

The modest success rates of complete withdrawal have driven intense interest in two separate directions:

Identify biomarkers of operational tolerance

In spite of much effort, there have not yet been any non-invasive markers of operational tolerance that have been derived and validated. More recently, a tissue-based biomarker related to the liver microenvironment has emerged from the immunosuppression withdrawal trial in children and validated in adults. This biomarker, or one with adjusted thresholds, may be useful to guide immunosuppression minimization.

Use of regulatory cell therapies to increase the success rate of immunosuppression withdrawal. There are multiple trials testing, T cell, dendritic cell, and CART cell regulatory products as tolerance induction strategies.
Efforts to mitigate the wide-ranging and cumulative toxicities of conventional immunosuppression are widely recognized as critical to improve long-term outcomes – both quantity and quality of life – for both adult and pediatric liver transplant recipients.