Immunosuppression
Trends and Tolerance?

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KEYWORDS

• Immunosuppression • Minimization • Tolerance • Biomarkers

KEY POINTS

- Immunosuppression withdrawal or minimization should reduce the long-term morbidity associated with these drugs, but few studies provide evidence of a long-term benefit.
- Multiple approaches to immunosuppression minimization are practiced, but no optimal strategy has been devised.
- Immune tolerance in liver transplant recipients remains elusive and may be unnecessary.
- Biomarkers indicating a patient's immune responsiveness are desperately needed to guide immune management.

The excellent outcomes of contemporary liver transplantation can be directly attributed to improvements in pharmacologic immunosuppression over the last few decades. However, long-term toxicity of many of these agents remains significant; the transplant community continues to seek ways to minimize or discontinue the use of these drugs in liver transplant recipients, despite their critical and historic contribution to transplantation success. In this clinical update, the authors present an overview of current and evolving immunosuppression management in liver transplantation ("Part 1") with a focus on emerging efforts to minimize ("Part 2") or even eliminate ("Part 3") immunosuppression use.

PART I: CURRENT IMMUNOSUPPRESSION PRACTICES

To improve efficacy and diminish toxicity, most transplant centers in the United States use a combination of agents to prevent allograft rejection in liver recipients (**Fig. 1**).[1]

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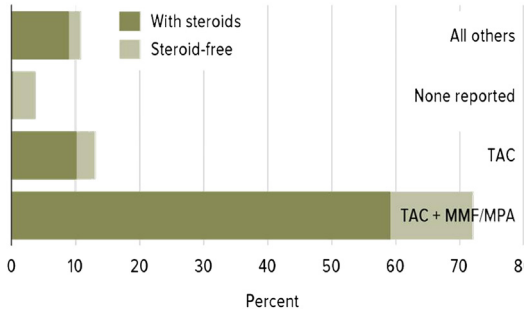

Fig. 1. Initial immunosuppression regimen in adult liver transplant recipients, 2011. Includes all patients transplanted in 2011 and discharged with a functioning graft. MMF/MPA, mycophenolate; TAC, tacrolimus. (*From* Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN/SRTR 2011 Annual Data Report. Rockville, MD: Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation; 2012.)

Although the specific mechanism of action of each drug varies widely, the primary goal of all agents currently used in contemporary immunosuppression regimens is to attenuate the allogeneic T-cell response to the donor antigen. This focus on T-cell control stems from decades of immunologic research that has clearly demonstrated the critical role of allogeneic T-cell activation in allograft destruction. Most agents, thus, aim to (1) diminish signaling through the T-cell receptor (TCR) (eg, calcineurin inhibitors), (2) truncate T-cell activation after the TCR has been engaged (eg, costimulatory blockade), or (3) prevent T-cell proliferation by blocking DNA synthesis (eg, antimetabolites) or altering energy metabolism within the cell (mammalian target of rapamycin [mTOR] inhibition). However, as our understanding of alloimmunity evolves and the contribution of additional immune populations to graft destruction is better appreciated (ie, B cells, natural killer [NK] cells), it is likely that additional cell populations will be targeted by immunosuppression agents of the future.

Since the introduction of cyclosporine in the early 1980s, *calcineurin inhibitors* (CNIs) have remained the foundation of immunosuppression in liver transplant recipients (see **Fig. 1**). *Tacrolimus* has replaced *cyclosporine* as the CNI of choice in liver transplant recipients since its introduction in the 1990s, given its improved graft and patient survival and decreased rejection rates.[2] Although tacrolimus is heavily relied on by most centers throughout the country,[1] this agent is rarely used alone early after transplantation. Although 60% of centers use tacrolimus as part of a triple-drug regimen within the first month after transplantation,[1] the number of pharmacologic agents in the regimen of any given recipient is gradually decreased by many centers with increasing time after transplantation. By 1 year after transplantation, more than 30% of centers use tacrolimus alone; this number approaches 50% of centers by 2 years after transplantation.[1]

For many liver recipients, tacrolimus alone may provide adequate immunosuppression given its overall potency and efficacy. However, calcineurin inhibitors are associated with a wide range of serious long-term complications, as discussed in additional detail in the following section of this review ("Part 2"). Arguably, the complications with the greatest impact on long-term patient survival include the development of diabetes mellitus (DM) and nephrotoxicity leading to end-stage renal disease (5% of liver transplant recipients 13 years after transplantation).[3] The avoidance of these complications

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