Management of Immunosuppression in Liver Transplantation

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KEYWORDS

• Transplantation • Rejection • Calcineurin • Immunosuppression • Hepatitis C

KEY POINTS

- The liver has a unique tolerogenic immune environment; thus, liver transplantation is usually well tolerated and rejection is easily managed.
- Newer steroid-free regimens with T-cell–depleting antibodies and IL-2R antibodies are effective and safe for induction of posttransplant immunosuppression.
- Antibody-mediated rejection is increasingly recognized as a contributor to graft dysfunction.

INTRODUCTION

Liver transplantation (LT) is a life-saving surgery for patients with liver failure, cirrhosis, and early-stage hepatocellular carcinoma (HCC). The first LT was performed as early as 1963 by Dr Thomas Starzl,[1] but throughout the 1960s and 1970s, the procedure was not very popular because it was fraught with complications, and 1-year survival was less than 25%.[2] However, the introduction of cyclosporine in the 1980s, as the immunosuppressant of choice, rapidly changed the scenario because it led to significantly decreased rates of rejection and improved survival.[3] Subsequently, multiple other challenges have been overcome, and the 1-year survival rate after LT is now 85% to 95%. For the past 20 years, around 4000 to 6000 LTs are performed annually in the United States alone,[4] and worldwide, more than 20,000 LTs have been performed since 2008.[5] Several advances related to LT in the control of infection, treatment of rejection, and improvisation of surgical techniques have also contributed to improved graft and patient survival. However, it is true that the tremendous progress made in the field of LT is mainly due to the advent of safe and effective immunosuppression agents. Various features of these agents are discussed in this review.

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The liver, as an organ, is unique in several aspects relevant to this discussion on immunosuppression. The liver is supplied by dual blood supply—the portal venous system and the hepatic arterial system. The portal venous system, which is the predominant source of blood supply, drains the intestinal system. The liver is thus exposed to multiple gut microbial products, metabolic products, and toxins constantly, and hence, has developed mechanisms to circumvent overreaction to this antigen load. Some of the major mechanisms include effective scavenging of antigens by Kupffer cells and dendritic cells; abundance of tolerogenic antigen-presenting cells (APCs) in the liver; expression of interleukin-10 (IL-10) and transforming growth factor-β, which induce regulatory T cells, and a low level of expression of major histocompatibility (MHC) class of proteins.[6–8] It overall has a distinctive immune environment, which has been coined as being "tolerogenic." Compared with other organ transplants like the kidney or the heart, patients who undergo LT usually need lower doses of immunosuppression, and LT is associated with less frequent episodes of rejection. Also, interestingly, when dual organ transplants are performed along with the liver, like liver and kidney or liver and heart, the LT reduces the chance of rejection of the second organ.[9,10]

Despite the relatively tolerogenic environment in the liver, rejection remains a dreaded complication and approximately 25% of the patients suffer at least one episode of rejection after transplantation.[11,12] Hence, adequate immunosuppression that can prevent rejection and prevent graft loss while being accompanied by minimal adverse effects is essential. Broadly speaking, there are 3 periods in the utilization of posttransplant immunosuppression: (1) induction phase (early posttransplant); (2) maintenance phase (long term); and (3) treatment of rejection. In this review, the author broadly discusses the immune environment of the liver, management of posttransplant immunosuppression, treatment of rejection, immunosuppression in special populations, and future directions.

PATHOPHYSIOLOGY OF IMMUNE RESPONSE AFTER LIVER TRANSPLANTATION

In general, the immune response elicited after LT is predominantly driven by T cells. Antibody-mediated rejection (AMR) is relatively uncommon in ABO-compatible LTs compared with other organs (like kidney), although it is being increasingly recognized as an important phenomenon influencing graft survival.[13,14] The immunologic response elicited by the donor liver is immediate, swift, and complicated.[15–18] **Fig. 1** provides an outline of the immune response after LT and also demonstrates the mechanism of action of the different classes of immunosuppressants. The basic steps can be broken down into the following:

1. *Antigen presentation:* The alloantigens in the donor liver are complexed with MHC proteins existing on donor and recipient APCs (like Kupffer cells and dendritic cells) and are presented to recipient's T-cell receptors. Simultaneously, ligands on APCs engage costimulatory receptors on T cells like CD28 and CD154.
   Drugs affecting this step: Antithymocyte globulin (ATG)[19] and antilymphocyte globulin (ALG) can prevent antigen presentation because they can deplete the recipient's T cells.
2. *T-cell activation and expansion:* Once the alloantigen is presented to the TCR in the presence of the appropriate costimulation, the receptor complex is internalized. Internalization of T cell receptor complex activates a downstream activation mechanism that involves immunophilin and calcineurin, ultimately resulting in activation of nuclear factor of T-cell activation (NFAT). NFAT translocates to the nucleus and enhances transcription of IL-2. IL-2 plays the crucial role of driving clonal expansion of T cells.