Overview of Immunosuppressive Therapy in Solid Organ Transplantation

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KEYWORDS

• Solid organ transplantation • Immunosuppression • Immunosuppressive strategies

KEY POINTS

- Solid organ transplantation is a life-saving treatment option for patients with end-stage organ failure.
- Lifelong immunosuppressive agents are administered to modulate a transplant recipient's immune system response to the donor organ by using induction, maintenance, and rescue therapy.
- Clinicians must comprehend the implications of using immunosuppressive agents; these include their mechanisms of action, pharmacokinetics, dosing and monitoring strategies, clinical efficacy, adverse effects and drug interactions, and clinical indications.

INTRODUCTION

Improvements in surgical techniques and availability of immunosuppressive options have led to current successes in the arena of solid organ transplantation. Historically, transplantation was limited by acute rejection, leading to graft loss and poor patient survival. These results have dramatically improved over recent years, with 1-year patient and allograft survival approaching or exceeding 90% for many solid organ transplant recipients. This has allowed transplantation to become the treatment of choice for many patients who would otherwise expire or require lifelong dialysis. Long-term allograft survival has not, however, kept pace with short-term success. Chronic rejection remains an unsolved and poorly understood complication in transplantation medicine. Although its occurrence is rare in liver transplants, it is a leading cause of late allograft loss in kidney transplants. Although transplant clinicians are successfully maintaining most patients with functional grafts for 5 or more years, they have created

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a large population at risk for chronic rejection and other complications, such as infection, lymphoproliferative diseases, and organ dysfunction related to chronic exposure to immunosuppressants. In this review, the immunology of transplant rejection and the immunosuppressive agents currently in use in adult solid organ transplantation are described.

TRANSPLANT IMMUNOLOGY

The immune system is the major barrier to long-term graft survival in solid organ transplant recipients. Donor organs are detected as foreign material by the recipient immune system and may be attacked and rejected. The ultimate goal of transplant recipients is graft acceptance, also known as tolerance, ideally without the use of long-term immunosuppressant medication. The major known pathways involved in acute rejection are outlined.

RECOGNITION

Identification of self or nonself occurs on chromosome 6 of the human genome. Within this chromosome is the major histocompatibility complex, also referred to as HLA complex. It contains the coding sequences of several different genes that code for HLA molecules. The purpose of HLA molecules is to display peptides on the surface of immune system cells so they can be identified as self or foreign. In transplant rejection, these peptides are usually components of a donor's HLA molecules that have been captured and broken down for display on a recipient's own HLA molecule. Antigen-presenting cells (APCs) are cells that display HLA molecules with their respective peptides. In transplant rejection, APCs can be of donor or recipient origin and may include passenger cells transplanted with the organ and/or the organ's own cell lines.[1] Recipient interaction occurs when passenger cells migrate to secondary lymphoid tissues or when recipient cells encounter graft vasculature.

PROCESSING

Immune system activation occurs when APCs display their foreign peptides to an immunologic target cell. In the cell-mediated response of transplantation, this target is the T lymphocyte. Each T cell displays thousands of individual T-cell receptors and each can bind thousands of HLA-peptide complexes.[1–5] The T-cell receptor is coupled with a cluster of differentiation (CD) molecule, specifically the CD3 molecule, and forms a complex responsible for T-cell activation.[6] A wide array of CD molecules exists among various immune cells. In addition, secondary signals via other pathways are required for full cellular activation.[5,7] On the surface of T cells, various molecules interact with APCs, providing secondary signals and increasing cytokine production, resulting in full stimulation of the immune response.[8–10]

MECHANISMS OF TARGET CELL DESTRUCTION

T cells possess 2 mechanisms for target cell destruction. One mechanism is used by cytotoxic $CD8^+$ cells; a second mechanism is used by cytotoxic $CD4^+$ cells. Both mechanisms result in activation of pathways that lead to destruction and cellular death of foreign cells.[11] In addition to T cells, other immunologic components contribute to graft rejection. Encounters between B cells and donor HLA molecules lead to the display of donor HLA–derived peptides on B-cell receptors. Subsequent interactions with T cells lead to immune globulin production against the donor HLA.[4] These antibodies bind to target donor HLA molecules and trigger foreign cell destruction via