Mycobacterial Infections in Solid Organ and Hematopoietic Stem Cell Transplantation

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KEYWORDS

• Mycobacterium tuberculosis • Nontuberculous mycobacteria • Transplantation

KEY POINTS

- Use of immunosuppression in transplantation significantly impairs host defenses and increases risk of mycobacterial infections.
- Mycobacterial infections after transplantation are uncommon but carry significant morbidity and mortality compared to regular population.
- Treatment of mycobacterial disease after transplant is challenging given interaction with immunosuppressive medications, protracted treatment course and paucity of clinical trials.

INTRODUCTION

Infectious complications are a major cause of morbidity and mortality in transplant patients.[1,2] These infections may appear de novo, may be acquired from the donor, or may develop secondary to reactivation from a latent state in the recipient. Immunosuppressive medications are administered to prevent/treat immune-mediated allograft injury after solid organ transplantation (SOT) and graft-versus-host disease (GVHD) after hematopoietic stem cell transplantation (HSCT); however, they also predispose transplant recipients to infectious complications. The focus of this review is on mycobacterial infections in recipients of SOT and HSCT.

EFFECTS OF IMMUNOSUPPRESSION

Immunosuppressive agents are crucial to prevent and treat graft rejection in SOT and GVHD in HSCT. In the case of SOT, patients receive early, aggressive, targeted anti–T-cell therapies to prevent acute graft injury and subsequently remain on lifelong immunosuppression. In HSCT, myelosuppression is in part related to biologic effects of the underlying malignancy and toxicity of chemoradiation administered pretransplant. Moreover, HSCT patients have lasting impairments in T- and B-cell function that portend increased infection risk.[3–6] For the subset of patients that develop GVHD, additional T-cell–targeted therapy is needed, which further exacerbates immune defects.

Most commonly used antirejection medications impair T-cell signaling and cytokine production. **Table 1** summarizes immunosuppressive drugs and their mechanisms of action.[7–12] The effects of these drugs are of particular importance in mycobacterial disease because cell-mediated immunity plays a central role in targeting intracellular pathogens.[13–17] Infected macrophages are eliminated by direct cell killing or by secretion of proinflammatory cytokines that augment macrophage killing mechanisms.[18,19]

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Table 1
Common immunosuppressive agents

Agent	Molecular Mechanism of Action	Immunologic Effect
Cyclosporine	Inhibit calcineurin activity by binding to cyclophilins. Calcineurin inhibition ultimately prevents Nuclear Factor of Activated T-cells (NFAT) activation along with other activation pathways in T cell	Inhibition of T-cell activation and cytokine production, which impairs innate and adaptive immune cell function
Tacrolimus	Inhibit calcineurin by binding to FK binding proteins. Calcineurin inhibition ultimately prevents NFAT activation along with other activation pathways in T cells	Inhibition of T-cell activation and cytokine production, which impairs innate and adaptive immune cell function
Sirolimus	Inhibits mTOR function. mTOR is a ubiquitous master regulator of cell growth and metabolism	Inhibition of immune cell proliferation and activation (especially T cells and dendritic cells)
Everolimus	Inhibits mTOR function. mTOR is a ubiquitous master regulator of cell growth and metabolism	Inhibits immune cell proliferation and activation (especially T cells and dendritic cells)
Alemtuzumab	Monoclonal antibody against CD52 (present on T, B, monocytes, NK cells, and macrophages)	Binds circulating cells and causes lysis
Polyclonal antithymocyte antibodies	Immunoglobulin G raised against reactive T lymphocytes in horse (Atgam) or rabbit (RATG)	Binds T cells directly, impairs function, and causes cell lysis
Monoclonal antibody against T-cell epitope	Anti-CD3 antibody (OKT3)	Binds CD3 and leads to reduced T-cell function and cell lysis
Daclizumab	Humanized monoclonal antibody against CD25 (interleukin-2 [IL-2] receptor α chain)	Binds CD25 on activated T cells, impairing IL-2-dependent T-cell activation
Basiliximab	Chimeric monoclonal antibody against CD25 (IL-2 receptor α chain)	Binds CD25 on activated T cells, impairing IL-2-dependent T-cell activation
Belatacept	Daughter molecule of CTLA4-Ig (abatacept) designed to bind avidly to CD80/86 and impair T-cell receptor signal 2	Impairs T-cell costimulation, which impairs innate and adaptive immune cell function
Azathioprine	Inhibits de novo purine synthesis	Inhibition of T- and B-cell activation and proliferation
Mycophenolate mofetil	Inosine-5′- monophosphate dehydrogenase inhibitor that inhibits de novo synthesis of guanosine nucleotides, somewhat selective for T and B cells	Inhibits proliferation and suppresses cell-mediated immune responses and antibody formation
Corticosteroids	Bind to intracellular glucocorticoid receptor. This leads to inhibition of proinflammatory cytokines gene expression and upregulation of anti-inflammatory gene expression	Nonspecific cytokine inhibition, nonspecific impairment in immune cell activation and function

Donor-Derived Mycobacterial Infections

In SOT, donor evaluation for *Mycobacterium tuberculosis* (MTB) is based on both disease prevalence and clinical characteristics. In contrast, there are no formal protocols for nontuberculous mycobacteria (NTM) screening. For MTB, risk stratification is based on donor history and imaging findings. To assess the risk of active and latent