Summary

Transplantation, which is the transfer of organs, cells, and tissues from one location to another, began many centuries ago as a primitive practice and has since evolved into a modern reality. Modern medicine has triumphed over many challenges and overcome many hurdles to achieve successful organ transplantation. The contemporary practice of medicine includes transplantation of tissues, partial organs, and whole organs. In addition, successful bone, heart valve, cartilage, vein, and cornea transplantations are being performed on a daily basis***(Sharma et al., 2006)***.

The importance of the immune system in protecting the body against harmful foreign molecules is well recognized. However, in some instances, this protection can result in serious problems. For example, the introduction of an allograft can elicit a damaging immune response, causing rejection of the transplanted tissue ***(Harvey and Champe, 2009)***.

Rejection of transplanted organs is the main barrier of transplantation today. It occurs as a result of humoral and cell-mediated responses by the recipient to specific antigens present in the donor tissue. These antigens are known as major histocompatibility complex (MHC) molecules. In humans, this group of molecules is referred to a human leukocyte antigen (HLA) complex molecule in humans. The recognition of these foreign MHC antigens initiates rejection, which occurs in two stages. During the first stage, known as sensitization, lymphocytes are alerted and respond to the foreign MHC molecules. Rapid proliferation occurs in this stage. In

the second 'effector' stage, the graft is destroyed by several cellular and molecular mechanisms ***(Kuby, 2007)***.

Once graft rejection has begun, it can be classified in one of three ways in humans, either hyperacute rejection, acute rejection, or chronic rejection. These categorizations are based on how quickly rejection occurs***(Divate, 2002)***.

Immunosuppressive drug regimens usually consist of anywhere from two to four agents with different mechanisms of action that disrupt various levels of T-cell activation. The immune activation cascade activate several intracellular signal transduction pathways, one of which is the calcium-calcineurin pathway, which is targeted by cyclosporine and tacrolimus***(Finkel et al., 2009)***.

Despite these glamorous advances, it is important to bear in mind the mechanism behind immunosuppression: immunosuppressants dampen the body's immune system. With current therapy, there are adverse side-effects that include, among others, a high incidence of opportunistic infection and transplant-related malignancies in patients. These are the unfortunate consequences of overimmunosuppression. Accordingly, a major goal of immunosuppression is to identify the optimal balance of therapy such that there is effective prevention of allograft rejection, while drug-related adverse effects, infection, and malignancies are minimized. Because this compromise is largely unsatisfactory, there is a constant search for more effective and specific immunosuppressive agents and strategies ***(Keith et al., 2002).***

Immunosuppression must be balanced carefully against the patient's own immune system. Adjusting the dose specifically for each patient helps avoid the risk of postoperative infections, tumor development, and rejection. The dose of Immunosuppression agents varies between patients and may vary with time in a particular patient ***(Tian et al., 2004).***

Immunosuppressive drugs can be categorized according to their mechanisms of action: 1) Some agents interfere with cytokine production or action; 2) others disrupt cell metabolism, preventing lymphocyte proliferation; and 3) mono- and polyclonal antibodies block T-cell surface molecules ***(Finkel et al., 2009)***.

Selective Inhibitors of Cytokine Production and Function

Cytokines are soluble, antigen-nonspecific, signaling proteins that bind to cell surface receptors on a variety of cells. The term cytokine includes the molecules known as ILs, interferons (IFNs), tumor necrosis factors (TNFs), transforming growth factors, and colony-stimulating factors. Of particular interest when discussing immunosuppressive drugs is IL-2 a growth factor that stimulates the proliferation of antigen-primed (helper) T cells, which subsequently produce more IL-2, IFN-γ, and TNF-α. These cytokines collectively activate natural killer cells, macrophages, and cytotoxic T lymphocytes. Clearly, drugs that interfere with the production or activity of IL-2, such as cyclosporine, will significantly dampen the immune response and, thereby, decrease graft rejection ***(Finkel et al., 2009)***.

Immunosuppressive Antimetabolites

Immunosuppressive antimetabolite agents are generally used in combination with corticosteroids, and the calcineurin inhibitors, CsA and TAC.

Antibodies

The use of antibodies plays a central role in prolonging allograft survival. They are prepared either by immunization of rabbits or horses with human lymphoid cells, or by hybridoma technology (producing antigen-specific, monoclonal antibodies). Recombinant DNA technology can also be used to replace

part of the mouse gene sequence with human genetic material, thus the antibodies produced, making them less antigenic ***(Harvey and Champe, 2009)***.

Corticosteroids

The corticosteroids were the first pharmacologic agents to be used as immunosuppressives both in transplantation and in various autoimmune disorders. They are still one of the mainstays for attenuating rejection episodes. For transplantation, the most common agents are prednisone or methylprednisolone, whereas prednisone or prednisolone are employed for autoimmune conditions. The steroids are used to suppress acute rejection of solid organ allografts and in chronic graft-versus-host disease. In addition, they are effective against a wide variety of autoimmune conditions, including refractory rheumatoid arthritis, systemic lupus erythematosus, temporal arthritis, and asthma ***(Finkel et al., 2009)***.

Low toxicity immunosuppressive protocols

Transplantation is fundamentally an unnatural act; at some level, we were not meant to take an organ from one individual and place it into another, with a reasonable expectation that it would function indefinitely. The modern reality, of course, is that we have been rather successful in doing just that with a large number of different organs, and in spite of an imperfect understanding of the immune system. We have been successful because of the development of effective chemical and biological immunosuppressive agents ***(Fung, 2007)***.

Although some of these agents have been relatively selective, all are non-specific, and virtually all have side effects. The toxicities associated with the conventional agents, namely cyclosporine, steroids, azathioprine, and

antilymphocyte preparations, are well understood and have been extensively described ***(McCauley, 2007)***.

Similarly, the newer immunosuppressive agents, tacrolimus, mycophenolate mofetil, and sirolimus, all have well described toxicities of their own ***(Myers et al., 2008)***.

The only two recently introduced agents that seem to have few, if any toxicities, are the anti-IL2 receptor monoclonal antibodies, daclizumab and basiliximab; however, both of these are useful for induction only, and neither is being used as a maintenance immunosuppressive agent ***(Nashan, 2009)***. Given these well understood toxicities, there have been a number of studies over the years that have utilized regimens that have attempted to minimize toxicity in transplant recipients ***(Vincenti et al., 2008)***.