

# Immunosuppressive medication in treatment of organ rejection



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Since the pioneering experiments of allograft heart transplantation by Christiaan Barnard in 1967, there have been significant advances in the development of human organ transplantation. Indeed, over 35,000 patients in both the US and Europe benefit annually from organ transplantation (Hampton, 2005). Through the transplantation and engraftment of these organs, not only can biological function of organs be restored, but also the quality of life of recipients can be greatly increased. As a result the number of transplantation operations carried out each year has increased exponentially over the past decades. Despite improvements in surgical techniques, the hurdle of immunological rejection by the host of transplanted organs still remains a current obstacle. This represents a challenge both scientifically and clinically and, as a result, is a focus of both the medical and scientific communities.

Over the past 60 years, there has been an exponential increase in the development of immunosuppressive drugs in order to treat organ rejection, as well as autoimmune diseases (Gummert et al. 1999). These drugs seek to suppress various components of the immune system in order to prevent rejection in the context of organ transplantation. This essay seeks to examine the broad immunology of transplantation as well as the different classes of immunosuppressive drugs and their associated benefits and side effects.

Transplantation is broadly defined as the act of transferring cells, tissues, or organs from one site to another. In the context of organ transplantation, this is generally from one person to another, with transplantation classed as either from a living donor or cadaveric. Although less common, there has

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been some attempt to transplant organs from other animals, known as xenografts. This was initially attempted given the lack of availability of human donor organs. However, as transplantation occurs between two immunologically distinct persons, a degree of immunological mismatch occurs. Due to this mismatch, the host immune system recognises the donor organ as 'foreign' and, as a result, activates various arms of the immune system.

Several types of immune rejection can occur in individuals undergoing organ transplantation. Hyperacute rejection occurs when pre-existing antibodies within the host against donor antigens attack the graft and result in rapid rejection of the graft, typically within a few hours (Murphy et al. 2010). This results in rapid declining function of the graft and is often non-reversible, thereby causing the recipient to lose the graft. In contrast, acute rejection occurs within six months following transplantation and is the result of activated T cells against donor antigens (Murphy et al. 2010). The third type of rejection is known as chronic rejection and, as the name suggests, occurs years after transplantation and is mediated by both antibodies and T cells. In order to encourage graft survival, and prevent the aforementioned from occurring, effective regimes in order to suppress these immune responses have been developed, although as outlined, they often come with significant side effects.

Glucocorticoids, such as prednisone, are commonly used in immunosuppressive regimes. These drugs seek to prevent rejection by suppressing various arms of the immune system including T cells, B cells, macrophages, granulocytes and monocytes (Steiner and Awdishu, 2011). <https://assignbuster.com/immunosuppressive-medication-in-treatment-of-organ-rejection/>

These drugs are, therefore considered to be relatively non-specific and highly potent leading to a range of side effects. Glucocorticoids exert their effects by regulating the activity and expression of various cytokines through inhibition of intracellular signalling pathways such as NF- $\kappa$ B. Through modulation of this complex signalling pathway, the production of pro-inflammatory cytokines such as IL-1, IL-6 and TNF- $\alpha$  are greatly reduced (Schacke et al. 2002). Although these drugs feature heavily in clinical practice, they are associated with a significant number of side effects. Prolonged glucocorticoid use can lead to Cushing's syndrome: a constellation of symptoms characterised by increased central adiposity, 'buffalo hump', osteoporosis and a round face (Schacke et al. 2002). These symptoms are due to excess exogenous cortisol within the body and therefore have multiple endocrinological effects on various physiological processes. The concentration of such drugs are therefore closely monitored and patients are encouraged to monitor for symptoms suggestive of Cushing's syndrome.

As well as glucocorticoids, drugs known as antimetabolites are frequently used in immunosuppressive regimes. These drugs, such as azathioprine and mercaptopurine, amongst others, were originally developed in the 1950s, but remain used to this day. Azathioprine is commonly used for liver and kidney transplantation (Germani et al. 2009), as well as for the treatment of autoimmune conditions such as rheumatoid arthritis (Whisnant and Pelkey, 1982). Antimetabolites exert their immunosuppressive effects by blocking the synthesis of purine within cells (Murphy et al. 2010). Through the blockage of purine synthesis, DNA replication is unable to take place, thereby preventing expansion of rapidly dividing cells within the immune

system. Through the blockade of T and B cell expansion, the level of rejection against organ transplants can be controlled.

One considerable side effect associated with the use of azathioprine is the increased risk of skin cancer. A relatively recent review by Ulrich and Stockfleth (2006) has shown that sunlight exposure, pre and post transplantation in patients using azathioprine, correlates with an increased incidence of skin cancer. As exposure to UVA light damages skin cells: these cells are unable to undergo repair following damage, due to inhibition of DNA replication from azathioprine. In the long term, this accumulation of damage results in the increased propensity for patients to develop skin cancer. Current clinical guidelines suggest that clinicians discourage patients in spending prolonged periods of time in the sun following transplantation (Perrett et al. 2008).

Along with these classes, of drugs, another category of immunosuppressive medications, known as calcineurin inhibitors, also work efficaciously in organ transplantation. These drugs, which include tacrolimus and cyclosporine, act by inhibiting the protein calcineurin. Calcineurin is activated following the presentation of an antigen by an antigen presenting cell, such as a dendritic cell or macrophage, to a T cell, resulting from an increase in the concentration of intracellular calcium (Reynolds and Al-Daraji, 2002).

Following the activation of calcineurin, there is an increase in the production of interleukin 2 (IL-2), which causes the activation of T cells. As a result, this further propagates an immune response. Calcineurin inhibitors are,

therefore, useful in dampening an immune response, preventing the

activation of T cells against a transplanted organ. Calcineurin inhibitors are <https://assignbuster.com/immunosuppressive-medication-in-treatment-of-organ-rejection/>

popular drugs used in renal transplantation. However, evidence over the past decade has suggested that drugs such as tacrolimus may induce renal failure in some patients (Ponticelli, 2000). Obviously this a key consideration when considering patients who already have poor renal function to being with. As a result, these drugs are often combined with other immunosuppressive agents and tailored to the lowest dosage possible.

The understanding into the way in which the immune system functions has been exploited over the past thirty years with the development of monoclonal antibodies. Monoclonal antibodies were first developed in the 1970s through the fusion of rapidly proliferative myeloma cells with B cells to produce hybridomas (Liu, 2014). Antibodies are protein molecules that have a specific antigen-binding region enabling them to have a high degree of specificity. Antibodies have, therefore, been exploited therapeutically in order to target pathogenic molecules within the body.

Recently, monoclonal antibodies have been developed to target various components of the immune responses in order to modulate organ rejection seen in patients. In particular, monoclonal antibodies have been developed to target T and B cells. Some examples of these therapeutics are discussed below.

Muromonab is a monoclonal antibody, which is specific for cluster of differentiation 3 (CD3), a molecule found primarily on T cells (Murphy et al. 2010). By targeting T cells and preventing their activation against the transplanted organ, there is considerable evidence to show that this can significantly prolong the survival of the organ following transplantation,

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compared to glucocorticoid steroids (Authors not listed, 1985). However, despite the success of anti-CD3 therapy, there are substantial side effects associated with clinical use. Use of anti-CD3 has been associated with severe fever in patients, as well as the unwanted release of pro-inflammatory cytokines (Norman et al. 2000). As a result the use of anti-CD3 has declined in clinical practice and is reserved for treatment resistant cases of organ rejection.

As well as muromonab, another mainstay treatment for organ rejection are antibodies directed against cluster of differentiation number 25 (CD25). Organ rejection is heavily mediated by T cells, in combination with other arms of the immune system (Ingulli, 2010). When activated, T cells produce large amounts of IL-2, a cytokine that acts in an autocrine fashion to further expand T cells via the IL-2 receptor CD25. Therefore, blockade of CD25 with a monoclonal antibody was hypothesised to offer a novel target in treating immunological rejection by T cells. As a result, daclizumab was developed and was shown by Vincenti et al. in 1998 to be a successful tool in treating renal transplantation compared to using a combination therapy of cyclosporine, azathioprine and corticosteroids. Furthermore, more long term studies have examined the function of renal transplants and concluded that patients on daclizumab showed improved renal function, as established by estimated glomerular filtration rate (GFR) (Ferran et al. 1990). However, like other pharmacological treatments, daclizumab has also been shown to cause a significant number of side effects such as hypertension and insomnia (EPAR for Zenapax).

More recently, the scientific community has sought to develop more refined immunological tools in order to modulate rejection. Through the development of monoclonal antibodies targeting cluster of differentiation 52 (CD52), clinicians are able to target lymphocytes for destruction, sparing the destruction of resident haematopoietic stem cell populations (Flynn and Byrd, 2000). Anti-CD52 drugs were originally developed for multiple sclerosis (Coles et al. 2008) and trials are currently being undertaken to establish their efficacy in organ transplantation.

The overarching side effect with immunosuppressive regimes is the relatively blanket level of immunosuppression which they cause. Although immunosuppression is required to maintain organ survival, immunosuppression also results in a reduced ability to fight infections. In particular, pulmonary infections are common in organ transplant patients, with Hoyo et al. (2012) detailing that around 1 in 5 patients in their study developed pulmonary infections. It is clear that clinicians dealing with organ transplantation patients must remain vigilant for infections. It is similarly clear, therefore, that a fine balance of the level of immunosuppression should be reached: a heavily weighted level will pre-dispose to opportunistic infections, and, conversely, a lightly weighted level will result in organ rejection.

With respect to future outlooks in transplantation immunology, the development of pluripotent stem cells has been hypothesised to overcome immunological issues associated with organ transplantation. Through the use of induced pluripotent stem cells (iPS cells) developed by Takahashi et al. (2006) it has been shown that it is possible to differentiate nearly all existing <https://assignbuster.com/immunosuppressive-medication-in-treatment-of-organ-rejection/>



cell types. As these cells are derived from the patient, they are immunologically matched to the individual and, as a result, patients would not require harsh immunosuppressive regimes. Although this technology has not been tested clinically in patients extensively yet, it is hoped that within the next twenty years this method will provide an unlimited source of organ replacement for patients. Use of such cells is currently being explored for regeneration of certain organs such as the heart (Masumoto, 2014). Use of these cells will require a significant amount of clinical testing to determine their immunological properties, as well as their propensity to develop into tumours. It is likely, therefore, that the clinical applications of stem cells are still many years away.

In conclusion, despite significant improvements in targeted immunosuppressive regimes, significant side effects are associated with current pharmacological treatments. Clearly, as patients treated with these agents are often susceptible to opportunistic infections, their progress must be monitored closely by a clinician who is familiar with such patients, and the complications they can present with. Through our increased understanding of the immune system, alongside new technologies such as stem cell replacement therapy, it is hoped that the immunological issues associated with organ transplantation will in the near future be overcome.

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