INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

Current Status of Immunosuppressive Therapy in Renal Transplantation

Mubasira V, Manju C S*

College of Pharmaceutical Sciences, Government Medical College, Calicut, Kerala, India.

ARTICLE INFO

Published: 22 Sept 2025
Keywords:
Kidney transplantation, immunosuppression, calcineurin inhibitors, mTOR inhibitors, induction therapy, maintenance treatment, transplant immunology
DOI:
10.5281/zenodo.17175169

ABSTRACT

For individuals with end-stage renal disease, kidney transplantation remains the leading treatment choice, offering significant benefits in terms of survival and life satisfaction. However, long-term graft survival is challenged by acute and chronic rejection, drug toxicity, infections, and malignancies. Traditional immunosuppressive regimens, including calcineurin inhibitors, antimetabolites, corticosteroids, and mTOR inhibitors, have significantly improved short-term outcomes but are associated with serious side effects. Recent advancements in immunosuppressive therapy focus on novel strategies such as co-stimulation blockers, protein kinase C inhibitors, JAK-STAT inhibitors, complement inhibitors, and regulatory T-cell therapies. Additionally, precision medicine approaches, including biomarker-guided immunosuppression and pharmacogenomics, are being explored to optimize therapy while minimizing adverse effects. This review outlines current immunosuppressive approaches and emerging therapies, highlighting how these drugs modulate immune system activity in renal transplant recipients. It also discusses the complications linked to immunosuppressive treatment, with an emphasis on enhancing long-term graft survival and patient outcomes.

INTRODUCTION

The final stage of long-term chronic kidney illness is end-stage kidney disease (ESKD). Kidney transplantation has become an established treatment modality for individuals with end-stage kidney disease. Advances in surgical procedures and the development of immunosuppressive therapies have significantly improved both graft longevity and patient survival following transplantation. However, with the extension of life expectancy, greater emphasis must now be placed on managing complications such as immunosuppressive drug side effects, recurrence of the underlying kidney disease, malignancies, and chronic conditions like diabetes, hypertension,

***Corresponding Author:** Manju C S
Address: *College of Pharmaceutical Sciences, Government Medical College, Calicut, Kerala, India.*
Email : manjusreeniajith@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

dyslipidemia, obesity, and cardiovascular disease. As a result, optimizing post-transplant care and immunosuppressive strategies is essential for improving long-term graft function and overall patient outcomes. [1] Each immunosuppressive medication exhibits inherent toxicity and adverse effects, which may result from either the intended therapeutic pathways or unintended secondary effects of the drug.[2]. It is crucial to note that post-organ transplant treatment should be tailored to each patient's specific needs[3].

The three types of immunosuppressive drugs currently in use are rejection treatment, maintenance therapy, and induction agents. Interleukin-2 receptor antagonists and polyclonal antibodies are common examples of induction agents. Emerging induction agents include alemtuzumab, efalizumab, and alefacept. Four medication groups make up maintenance regimens: corticosteroids, mTOR inhibitors (sirolimus and everolimus), calcineurin inhibitors (cyclosporine and tacrolimus), and antiproliferative medicines (azathioprine and mycophenolic acid). Belatacept, a newly licensed costimulation blocker; tofacitinib, a JAK 3 inhibitor; and sotrastaurin, a protein kinase C inhibitor, are three new maintenance medicines with distinct modes of action.[4] The purpose of this review is to assess the safety and effectiveness of the immunosuppressive medications currently used in kidney transplantation.It also explores emerging therapies that may enhance long-term graft survival while minimizing adverse effects. This analysis offers important insights into enhancing post-transplant care and enhancing patient outcomes by examining recent developments and difficulties in immunosuppressive regimes.

2. Immunology of transplants: the alloimmune reaction

The recipient's immune response to a transplanted organ is known as the alloimmune response. Comprehending this procedure is essential to understanding the role immunosuppressive medications play in kidney transplantation. In the absence of these drugs, the recipient's immune system perceives the transplanted tissue as alien and tries to get rid of it. Major histocompatibility complex (MHC) proteins, sometimes referred to as human leukocyte antigens (HLA), which are encoded on the short arm of chromosome 6, interact with donor tissue to cause an immunological response. The probability of chronic rejection and graft failure is influenced by the degree of donor-recipient HLA mismatch. Antigenic peptides are presented to T cells more easily via MHC molecules. To start the alloimmune response, antigen-presenting cells (APCs) that express HLA molecules engage with the recipient's T cells.[5]

The direct and indirect pathways are the two main ways that HLA alloantigen recognition takes place. The direct approach identifies donor cell surfaces that contain intact donor HLA alloantigens. On the other hand, alloantigens are taken up, processed, and presented as peptides attached to recipient HLA molecules in the indirect pathway. Because donor antigen-presenting cells (APCs) are only available during the first several weeks or months after transplantation, the direct channel has historically been linked to acute rejection in the early post-transplant phase. On the other hand, late graft failure has been connected to the indirect approach.[6]

3. Current Immunosuppressive Strategies

The most often prescribed immunosuppressive medications for recipients of kidney transplants fall into five types. [3]

3.1. Immunosuppressive Induction Therapy

During kidney transplantation, it is common practice to use induction immunosuppressive agents. These agents fall into two categories: those that deplete lymphocytes, such as anti-thymocyte globulin and alemtuzumab, and those that inhibit lymphocyte activation and proliferation, like IL-2 receptor antagonist.[7] Antithymocyte globulin, alemtuzumab, and basiliximab are the primary induction medications used in kidney transplantation. [8] A chimeric monoclonal antibody called basiliximab targets the interleukin-2 receptor's (IL-2R) alpha chain. It completely occupies the IL-2R alpha chain for four weeks when administered intravenously at a dose of 20 mg both during transplantation and four days later. There are not many side effects or drug interactions with basiliximab. [9] In peripheral blood, alemtuzumab causes T and B lymphocytes, monocytes, and NK cells to be destroyed. As a result, T lymphocytes are reduced over time, while B lymphocytes and monocytes are reduced over a shorter period of time. [3]. Serious infections, antibody-mediated graft rejection, and significant and prolonged lymphocyte depletion were all consequences of the first administration of alemtuzumab to kidney transplant recipients. Only a few modest randomised trials had been published on this subject before recently.[4]

In addition to these monoclonal antibodies, organ transplant recipients frequently use polyclonal antibodies. Anti-thymocyte globulin is one such polyclonal antibody commonly employed[3]. Thymoglobulin® (rATG) is a polyclonal antibody that depletes lymphocytes and is approved for treating acute renal allograft rejection, though its use in transplant induction is not officially sanctioned. Research conducted both in vitro and in vivo has indicated several potential mechanisms of action, including the modification of lymphocyte surface antigens and the activation of transcription factors. rATG may interfere with various immune cell functions, such as the production of cytokines, chemotaxis, endocytosis, stimulation, proliferation, and the adhesion of leukocytes to endothelial cells. Additionally, rATG might encourage cell death through various means, including the induction of apoptosis, antibody-dependent lysis, and complement-mediated lysis of diverse immune cells .[10]

In some clinical situations, other biologic medications like rituximab, belatacept, and eculizumab are frequently utilised**.**

3.2. Immunosuppressive Maintenance Therapy Calcineurin inhibitors

Calcineurin inhibitors (CNIs), chiefly cyclosporine and tacrolimus, constitute the foundation of immunosuppressive therapy in renal transplantation, significantly contributing to the prevention of acute rejection and enhancement of graft survival. These medications function by blocking calcineurin, a crucial enzyme in T-cell activation, hence diminishing interleukin-2 (IL-2) synthesis and lowering the immunological response towards the transplanted kidney. Tacrolimus is favoured over cyclosporine in numerous procedures because of its reduced rejection rates and enhanced graft life; however, it poses a greater risk of diabetes and neurotoxicity. A significant problem associated with CNIs in renal transplantation is nephrotoxicity, which may result in chronic kidney injury and graft failure over time. To alleviate this danger, therapeutic drug monitoring (TDM) is crucial for sustaining medication concentrations within the therapeutic range while reducing toxicity. CNIs are frequently utilised alongside other immunosuppressants such as mycophenolate mofetil, azathioprine, or corticosteroids to attain optimum immunosuppression. Nonetheless, prolonged

usage necessitates meticulous oversight owing to potential drug interactions, metabolic issues, and heightened susceptibility to infections. Notwithstanding their detrimental effects, CNIs are an essential element of post-transplant immunosuppression owing to their effectiveness in thwarting rejection and extending graft longevity.[3][11]

Antiproliferative Agents

Antiproliferative drugs are essential in immunosuppressive therapy for kidney transplantation, as they reduce the growth of T and B lymphocytes, thus diminishing the chance of graft rejection. Mycophenolate mofetil and mycophenolate sodium are commonly used agents that inhibit inosine monophosphate dehydrogenase (IMPDH), selectively suppressing lymphocyte proliferation. Azathioprine (AZA), a purine analogue, also prevents DNA synthesis in rapidly dividing immune cells but is used less frequently due to its higher toxicity and lower efficacy compared to MMF. These medicines, frequently utilised alongside calcineurin inhibitors and corticosteroids, assist in preserving long-term graft viability while mitigating the risk of problems associated with immunosuppression.[12]

Mammalian Target of Rapamycin Inhibitors

mTOR inhibitors, including sirolimus and everolimus, are essential for immunosuppression in kidney transplants as they obstruct the mTOR signalling pathway, therefore inhibiting T-cell proliferation and activation. In contrast to calcineurin inhibitors (CNIs), these medicines do not immediately impair renal function, rendering them a beneficial alternative, particularly for patients vulnerable to nephrotoxicity from CNIs. They provide advantages like decreased chronic allograft nephropathy, a reduced rate of post-transplant cancers, and the potential to minimize the use of CNIs and corticosteroids. However, their application is restricted by side effects, including delayed wound healing, dyslipidemia, proteinuria, and a heightened risk of infections such as CMV and BK virus. In clinical settings, mTOR inhibitors are frequently employed in regimens that either exclude CNIs or minimize their use, with some strategies advocating for a late switch from CNIs to enhance graft survival while reducing nephrotoxicity. Everolimus, in particular, is being increasingly combined with lower doses of CNIs and mycophenolate mofetil (MMF) to optimize immunosuppression, though their use is tailored to individual patient risk factors and tolerance.[13][14]

Corticosteroids

Since corticosteroids have strong anti-inflammatory and immunosuppressive properties, they have been a mainstay of immunosuppressive treatment in kidney transplantation for many years. They act by inhibiting cytokine production, reducing T-cell activation, and suppressing antigen presentation, thereby preventing acute rejection. Typically, corticosteroids such as prednisone or methylprednisolone are used in induction therapy as high-dose pulses during the perioperative period, followed by gradual tapering to lower doses in maintenance regimens. In some cases, they are also administered to manage acute rejection episodes. Their primary advantage lies in their broad-spectrum immunosuppressive properties, which contribute to reduced graft loss, particularly in high-risk patients. However, there are serious side effects linked to long-term corticosteroid usage, such as weight gain, diabetes mellitus, hypertension, osteoporosis, dyslipidaemia, poor wound healing, and an elevated risk of opportunistic infections..[3] These complications have led to the development of steroid-minimization, steroid-withdrawal, and

steroid-free protocols, particularly in low-risk transplant recipients, in an attempt to improve metabolic outcomes while maintaining adequate immunosuppression. According to certain research, early steroid withdrawal can lessen metabolic and cardiovascular issues without appreciably raising the risk of rejection, particularly when paired with strong induction drugs like anti-thymocyte globulin (ATG) or basiliximab. Complete steroid removal is still debatable, though, because it may raise the risk of chronic allograft malfunction and late acute rejection, especially in patients with high immunological risk. Individualised treatment plans are therefore crucial, taking into account immunological profiles, risk factors unique to each patient, and the possibility of long-term graft survival.[15]

4. Novel Immunosuppressive Therapies in Renal Transplantation

Co-Stimulation Blockade Therapy

Co-stimulation blockade therapy, which targets the CD28-CD80/CD86 pathway necessary for T-cell activation, is one of the most recent developments in immunosuppression. Belatacept is a selective co-stimulation blocker which emerged as an alternative to CNIs, reducing nephrotoxicity while maintaining effective immunosuppression. Clinical trials have demonstrated superior graft function and lower cardiovascular risk compared to cyclosporine-based regimens. Belatacept, however, is linked to an increased risk of acute rejection, particularly in patients who do not have Epstein-Barr virus..Ongoing research is evaluating next-generation co-stimulation blockers with improved efficacy and reduced rejection risk, including novel CD28 antagonists and fusion proteins targeting alternative co-stimulatory pathways.[16][17]

Novel Biologic Agents

Monoclonal antibodies (mAbs) targeting immune pathways beyond traditional T-cell suppression are under investigation.Anti-IL-6 and Anti-IL-17 Therapies play key roles in inflammation and graft rejection. Monoclonal antibodies such as tocilizumab (anti-IL-6R) and secukinumab (anti-IL-17A) are being explored for their potential in reducing rejection episodes while preserving immune function.JAK-STAT Inhibitors: Janus kinase (JAK) inhibitors, such as tofacitinib and baricitinib, modulate multiple immune pathways and have shown promise in reducing T-cell-mediated rejection while offering steroid-sparing benefits. Complement Inhibitors: The complement system is a key mediator of antibody-mediated rejection (AMR). C5 inhibitors like eculizumab and novel C3 inhibitors are being investigated to prevent chronic rejection and improve long-term allograft function.[17]

Protein kinase C inhibitors

are emerging as potential immunosuppressive agents in renal transplantation due to their role in T-cell activation, inflammation, and immune signaling. By blocking PKC-mediated pathways, these inhibitors help prevent graft rejection while potentially reducing dependence on nephrotoxic calcineurin inhibitors. In CNI-free regimens, sotrastaurin (AEB071), a specific PKC inhibitor, has shown promise in suppressing T-cell activation and reducing the risk of rejection. However, early trials reported higher rejection rates, limiting its widespread adoption. Despite their potential benefits, including reduced nephrotoxicity and cardiovascular risks, PKC inhibitors require further research to optimize their use in combination with other immunosuppressive agents.[18]

5. Personalized and Precision Medicine in Transplant Immunosuppression

Advancements in genomics, biomarkers, and artificial intelligence (AI)-driven models are transforming immunosuppressive therapy toward personalized approaches

- **Biomarker-Guided Immunosuppression:** The use of molecular markers such as donor-derived cell-free DNA (dd-cfDNA), gene expression profiling (AlloMap), and urinary chemokine levels (CXCL9) enables real-time monitoring of rejection risk and allows for individualized immunosuppression.[19]
- **Pharmacogenomics:** Genetic variations in drug metabolism (e.g., CYP3A5 polymorphisms affecting tacrolimus metabolism) are being used to tailor drug dosing, reducing toxicity and improving therapeutic outcomes.[19]
- **AI and Machine Learning:** Predictive models using AI are being developed to assess rejection risk, optimize drug regimens, and improve long-term graft outcomes based on patient-specific immunological and clinical data.[20]

CONCLUSION

Immunosuppressive treatment has revolutionised renal transplantation by increasing graft survival and decreasing rejection rates. However, long-term use of traditional agents presents challenges such as nephrotoxicity, infections, malignancies, and metabolic complications. To address these issues, novel therapies including biologics, targeted inhibitors, and personalized immunosuppressive approaches offer promising alternatives with fewer adverse effects. Emerging strategies, such as co-stimulation blockers, complement inhibitors, and cellular therapies, aim to enhance immune tolerance while minimizing drug toxicity. Furthermore, advancements in precision medicine, including biomarker-based monitoring and AI-driven predictive models, are laying the foundation for individualized treatment plans. Also, further clinical trials and real-world studies are essential to establish their long-term efficacy and safety. optimizing immunosuppressive protocols and balancing efficacy with safety will be critical to improving post-transplant care and enhancing patient outcomes.

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HOW TO CITE: Mubasira V, Manju C S, Current Status of Immunosuppressive Therapy in Renal Transplantation, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 9, 2440-2446. https://doi.org/10.5281/zenodo.17175169