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Review

Commonly Used Immunosuppressant Agents in Post-Transplantation: Drug Class, Mechanisms of Action, Adverse Effects, and Toxicities

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ABSTRACT

Transplantation stands out as one of the most remarkable discoveries in medicine, offering patients with organ failure a second chance at life. This procedure involves replacing a failing organ or tissue with a healthy one, requiring immunosuppressant drugs to prevent graft rejection and ensure transplant viability. Immunosuppressants are a class of medications used to suppress the immune response. These medications work by targeting specific immune pathways to inhibit the proliferation of immune cells through targeted receptor interactions, thereby reducing the risk of graft rejection. However, these immunosuppressants may lead to undesirable side effects and toxicity, underscoring the need for further clinical trials to improve the long-term quality of life for transplant recipients. In this review, we will discuss the various classes of immunosuppressants, their mechanisms of action, therapeutic outcomes, and associated side effects.

Keywords: Autoimmunity, graft rejection, immunosuppressants, mechanism, side effects, transplantation.

Immunosuppression is a state of temporary immune system impairment resulting from attacks on the immune response of the body's immune system and its capacity to fight infections and other illnesses.[1] This approach is essential in transplantation, also known as grafting, which refers to a medical or surgical procedure in which cells, tissues, or organs are relocated from one location to another to replace or repair damaged, missing, or diseased structures. Transplantation is one of the most remarkable medical discoveries, offering patients with organ failure a second chance at life. However, this method brings with it challenges, among which transplantation rejection is one of the potentially unfavorable consequences that recipients can face after graft transplantation.[2]

Rejection is caused by inflammatory reactions that damage the transplanted tissues, resulting from the interaction between the adaptive and innate immune systems, which involve lymphocytes, macrophages, neutrophils, and natural killer cells. Within this dynamic process, transplantation requires immunosuppressant drugs to prevent graft rejection and ensure transplant viability. Immunosuppressants are a type of medication that inhibits or represses the immune response. These medications target specific immune pathways to inhibit immune cell proliferation through targeted receptor interactions, thereby reducing the risk of graft rejection.[3]

Immunosuppressant drugs can be categorized under numerous classes with different mechanisms and side effects. Immunosuppressants can be glucocorticoids, small molecules, or proteins.[4]

The standard therapy regimen in organ transplantation includes a continuous dosing regimen of glucocorticoids, an antiproliferative agent, and a calcineurin inhibitor (CNI).[5] The most common immunosuppressant drugs are cyclosporine A (CsA), tacrolimus (TAC), mycophenolate mofetil (MMF), sirolimus (SIR), everolimus (EvE), glucocorticoids (GCs), belatacept (BEL), and basiliximab (BAS). However, these medications may lead to undesirable side effects and toxicities. To reduce toxicity and side effects by decreasing doses of individual drugs, a

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combination therapy strategy, including agents with variant mechanisms of action and distinct toxicity profiles, is used. Immunosuppression typically involves three stages: induction, maintenance, and treatment of rejection. Stage one induction consists of the treatment of an increased-intensity agent directly post-transplantation. When the chances of rejection are greater, antibodies or greater doses of maintenance therapy drugs may be utilized in induction therapy, while to stop opportunistic infections, immunosuppressive treatments are frequently combined with antimicrobial, antiviral, and antifungal medications.[7] The side effects of these drugs include increased risks of cancer and infections. This results in a decreased long-term survival expectancy of transplant recipients. There is an increasing demand for innovative medicines that can establish immunological tolerance while limiting the adverse side effects of current immunosuppressive techniques.[6]

AUTOIMMUNITY

Allograft is when an organ is grafted between two genetically variant persons of the same species. An alloimmune response is formed because the immune system recognizes the grafted organ as foreign, triggering allorecognition, a sequence of reactions beginning with T-cell activation, followed by antibody formation, resulting in transplant rejection.[8]

Major Histocompatibility Complex and Human Leukocyte Antigens

Major histocompatibility complex (MHC) genes produce the most effective transplant antigens; in humans, these MHC particles can be defined as human leukocyte antigens (HLA).[9] It is subdivided into class I molecules and class II molecules. Class I molecules are present on all nucleated cells and generally exhibit endogenous minor antigens, such as viruses and self-protein fragments, in association with self-MHC to CD8+. Class II molecules are established only on professional antigen-presenting cells (APC), including dendritic cells, macrophages, and B cells. However, their expression can be upregulated in epithelial and vascular endothelial cells after exposure to pro-inflammatory cytokines. Class II molecules present more antigens acquired from extracellular proteins to CD4+ T-cells. The extent of HLA mismatch between the donor and recipient acts in identifying the risk of incurable or persistent rejection and graft loss.[10] The HLA-A,-B, and -DR (three sets, six antigens are commonly used for printing out and matching before transplantation. HLA-cw, -DP and DQ are now used in various transplant centers or clinics; long-term graft survival is outstanding for HLA-identical living-associated transplants. The most compelling effect comes from the coupling of the DR antigen, and the order of the effect in transplantation is DR>B>A.[11]

Non-HLA antigens/antibodies

Acute and chronic graft rejection can take place in HLA-identical sibling transplants, implying the reaction of an immune response to non-HLA antigens, diversity of non-HLA antigens, and their antibodies originating from alloimmunity or autoimmunity.[9]

Non-HLA antibodies can be directed to auto- or alloantigens, which may appear before or after transplantation.[12]

ABO blood group antigens

The ABO blood group antigens do not occur only in red cells but also in other cells. ABO-incompatible organ transplants initiate hyper-accuracy rejection as a result of the existence of preformed hemagglutinin A and B antibodies. ABO compatibility between donor and receptor is essential for organ transplantation. Various protocols have been used for ABO-incompatible transplants. Rhesus factor and other red cell antigens are irrelevant or insignificant for transplantation as they are not produced in the endothelium.[9,13]

Minor Histocompatibility Antigens

Minor histocompatibility antigens (MiHA) are known as the indirect allorecognition pathway, which activates immune responses against peptides originating from allo-MHC molecules or non-MHC polymorphic proteins. They are mostly recognized by CD8+ cytotoxic T-cells, leading to graft rejection.[14]

Unlike classical HLA molecules, MiHAs do not generate easily detectable serological epitopes, making their identification through antibody-based methods challenging. Instead, their discovery relied on advanced T-cell cloning techniques combined with immunopeptidomics, which was still in its early stages at the time.[15]

The three-signal model of T-cell activation

The three-signal T-cell activation model provides details on the molecular mechanism of immunosuppressive drugs; T-cell activation is a strictly regulated process entailing interactions of receptors like the T-cell receptor (TCR), also known as CD3 complex, costimulatory receptors, And other signaling molecules causing the production

of cytokines, clonal expansion and differentiation of effector T lymphocytes. This leads to the activation of autoreactive immune cells that cause graft rejection and damage.[16]

Discussing the immunosuppressive agent's immunological reaction to organ transplantation resilience is important.

Signal 1 of T-cell activation

The first signal of T-cell activation is initiated when APCs, like macrophages and dendritic cells, present alloantigens via MHC molecules to antigen-specific TCRs. This interaction is facilitated by the CD3 complex.[9,17,18]

Signal 2 of T-cell activation

Signal 2 of T-cell activation, also known as a costimulatory signal, depends on the receptor-ligand interaction between T-cells and APCs. There are many costimulatory pathways, like CD28-B7 and CD154-CD40. CD28 and CD154 are expressed on T-cells, and their ligands B7 and CD40 are expressed on APCs.[9]

Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), a molecule structurally similar to CD28 that is expressed on the T-cell, has a higher affinity for B7 ligands (CD80 and CD86). When the CTLA-4 binds to B7, it delivers an inhibitory signal, effectively suppressing the T-cell response. This inhibitory mechanism has led to the development of CTLA-4-Ig fusion proteins, such as BEL. The integration of signals 1 and 2 triggers the activation of three intracellular signal pathways: the calcium-calcineurin pathway, the RAS-mitogen-activated protein kinase pathway, and the inhibitor of kappa B (IκB) kinase-nuclear factor κB (NF-κB) pathway. Calcineurin inhibitors are capable of disrupting this signaling process.[8]

Signal 3 of T-cell activation

Signal 3 of T-cell activation is primarily driven by cytokines such as interleukin-2 (IL-2), IL-12, and interferons (IFN-α/β), which are essential for T-cell proliferation and differentiation. IL-2 plays a central role in activating the JAK-STAT5 and mammalian target of rapamycin (mTOR) pathways, regulating T-cell expansion and metabolic programming. Immunosuppressive agents can primarily affect cytokine release/production by activated T cells, inhibit T-cell proliferation and TCR signaling, or induce T-cell depletion.[19,20]

IMMUNOSUPPRESSANTS

Glucocorticoids

Glucocorticoids have long been used to initiate and maintain immunosuppressive therapy and to treat organ transplant rejection in patients. However, difficulties with GCs make them unsuitable for long-term usage.[21] Large dosages of GCs can have rapid effects through non-genomic pathways, but most glucocorticoid effects require time to manifest through genomic processes. It is impossible to distinguish between these consequences clinically.[22]

Glucocorticoids bind to their cytosolic receptors, enter the nucleus, and activate GC response elements that induce anti-inflammatory genes (transactivation) while stopping factors that cause expression of inflammatory elements, such as NF-κB and activator protein-1 (AP-1) (transrepression). These effects on the genome typically have a prolonged onset of action. The transactivation and transrepression effects of GCs are linked to their anti-inflammatory properties, but their transactivation impacts are primarily responsible for their negative consequences. The non-genomic mechanism of GCs is less recognized and is partially moderated by membrane receptors that regulate anti-inflammatory and anti-oxidant effects. The cumulative dosage during GC treatment often determines the genomic consequences.[21,23]

Genomic actions can be triggered by both the direct activation and repression of particular genes, but they primarily arise from interactions with transcription factors. A key player in this process is the NF-κB and AP-1 complexes, which are cytoplasmic regulators of numerous genes that oversee the transcription and production of adhesion molecules and cytokines. The activation of NF-κB is hindered by the corticosterone-cytoplasmic receptor complex through the production of the inhibitory factor IκB. This interaction reduces pro-inflammatory cytokines (IL-1, IL-6, IFN, and nitric oxide) across various cell types. The effects observed are generally specific to each cell type, with different genes being influenced based on the GR binding site and the possible engagement of coactivators.[24]

The oral route is the most commonly utilized method for systemic glucocorticoid therapy due to its ease of use and high absorption rate, which remains effective regardless of food consumption, as GCs possess both lipid and water solubility, facilitating efficient gastrointestinal absorption, particularly when synthetic alterations like acetylation, observed in hydrocortisone, or the incorporation of phosphate

groups, as seen in prednisolone sodium phosphate, are utilized to enhance solubility and absorption. While intravenous administration circumvents the gastrointestinal system and results in a quicker onset of action, oral administration is essential for long-term treatment. Regarding distribution, GCs such as hydrocortisone and prednisolone exhibit strong binding to transcortin, also referred to as corticosteroid-binding globulin; however, when plasma levels surpass the capacity of transcortin, excess medication attaches to albumin or remains unbound, with albumin demonstrating a higher total binding capacity despite its reduced affinity. The protein binding of prednisolone is nonlinear and diminishes at elevated concentrations, whereas methylprednisolone, which does not bind to transcortin and only attaches to albumin, shows linear pharmacokinetics. Metabolism essentially takes place in the liver and kidneys, as well as in specific target tissues, through various enzymes, including cytochrome P450, reductases, and notably 11β-hydroxysteroid dehydrogenase type 1, which converts the inactive cortisone into active cortisol, thereby enhancing tissue sensitivity. Glucocorticoids are primarily eliminated by the kidneys as inactive glucuronide and sulfate conjugates, with only a small fraction being excreted in unchanged form, and their clearance is affected by circadian cycles, being lower in the morning, which explains the preference for morning dosing to align with the body's natural cortisol cycle and optimize therapeutic results.[25]

Acute psychosis can occur in patients receiving high-dose glucocorticoids, and the first step upon symptom onset is to stop the medication immediately. Various treatments have been attempted, but no consensus exists on the best approach, with medicines like chlorpromazine and lorazepam showing some success, though they may cause side effects like drowsiness and hypotension. Glucocorticoid toxicity includes a range of adverse effects, such as adrenal suppression, osteoporosis, hyperglycemia, and gastrointestinal complications, particularly in children or those with preexisting conditions. Before starting long-term therapy, healthcare providers should conduct a comprehensive evaluation, including assessments of weight, height, blood pressure, bone mineral density, eye exams, complete blood count, and lipids, as well as an assessment of nutritional and pubertal development in children. While hydrocortisone and potassium chloride have shown some benefit in reducing psychiatric symptoms, careful monitoring is essential to mitigate the risk of significant toxicity during therapy.[22]

Side effects typically start delayed and are linked to the cumulative dose of GC throughout the course of its administration since they are usually tied to the genomic mode of action of these medications, especially transactivation ones.[21] Side effects include hyperglycemia, peptic ulcer, osteoporosis, cataracts, increased appetite and weight gain, sleeplessness, skin changes, adrenal insufficiency, and cognitive impairment, including psychosis.[22,26]

Patients using corticosteroids can experience neurological adverse effects. Mood swings, behavioral issues, and cognitive impairments are among the neuropsychiatric symptoms brought on by corticosteroids, and they usually appear in the initial weeks of treatment. After prolonged usage, peripheral toxicity manifests as neuromyopathy, which causes muscle weakness in the lower and proximal limbs. It seems that steroid dementia syndrome is uncommon, and even once therapy stops, these symptoms cannot go away entirely.[27] Glucocorticoids enhance the possibility of viral, bacterial, and fungal infections. Additionally, they counteract the effects of vitamin D, reduce intestinal calcium absorption, suppress growth hormone secretion, prevent bone formation by inhibiting osteoblast differentiation and promoting osteoblast apoptosis, and promote bone resorption by stimulating the formation of osteoclasts.[21]

Calcineurin inhibitors: Cyclosporine and Tacrolimus

Calcineurin inhibitors play a major role in therapeutic regimens post-transplant; two common drugs are CsA and TAC, both having the same pharmacodynamic mechanism.[28]

Cyclosporine is categorized as an effective immunosuppressant drug that has been used in clinical practice since the early 1980s; it was first isolated from the fungus *Tolypocladium inflatum*.[29,30] It is considered chemically a cyclic peptide class drug and structurally an undecapeptide molecule. Cyclosporine is used primarily to prevent transplant rejection, and later, it was used in diseases such as uveitis, nephrotic syndrome, rheumatoid arthritis, and psoriasis.[31]

Cyclosporine acts as a CNI, influencing multiple cellular processes and suppressing immune responses.[29]

The immunosuppressive effect of CsA is primarily due to its strong binding affinity for immunophilins, especially cyclophilin A, a cytoplasmic receptor

protein found in target cells.[32] When CsA binds to cyclophilin A, the resulting complex interacts with calcineurin, inhibiting its phosphatase activity. Calcineurin normally plays a key role in activating the nuclear factor of activated T-cells (NFAT) by enabling its dephosphorylation and nuclear translocation. However, by blocking this process, the CsA-cyclophilin complex prevents NFAT from entering the nucleus in response to calcium signaling. As a result, the transcription of crucial cytokine genes such as IL-2, IL-4, TNF-α, and IFN-γ is suppressed. This leads to reduced activation and proliferation of T-lymphocytes, both helper and cytotoxic types, impairing their response to antigen stimulation and thereby weakening the immune response.[33,34]

Cyclosporine A's efficacy and pharmacokinetics vary depending on factors like age, gender, genetics, diet, health status, and medications used. Oral administration is preferred over intravenous routes. Bioavailability is low, around 30%, ranging from 5% to 70%, and highly unpredictable.[31]

Peak concentrations occur 1-8 hours post-dose. Cyclosporine A is metabolized mainly by liver CYP3A4 enzymes, producing over 30 metabolites, some enhancing immunosuppression and others causing toxicity. Cyclosporine A is primarily excreted in the bile, with minimal urinary elimination. Its clearance averages approximately 0.35 L/h/kg. The drug's half-life shows significant variability-ranging from 6.4 hours in heart transplant patients to 20.4 hours in individuals with liver impairment-highlighting the influence of metabolic capacity and organ function on its pharmacokinetics.[32]

Though CsA is highly effective in the prevention of organ transplant rejection, the use of CsA is restricted by severe side effects like toxicities, nephrotoxicity, hepatotoxicity, neurotoxicity, and myocardial toxicity. As well as complications like hypertension, arrhythmia, and drug contraindications with TAC, simvastatin, amphotericin B, bosentan, lomitapide, oral neomycin, sitaxentan, cidofovir, and pitavastatin.[35,36]

Nephrotoxicity is a key complication in CsA treatment that can be displayed as acute or chronic toxicity, marked by inflammatory cell infiltration, arteriolar damage, irreversible interstitial fibrosis, and tubular atrophy.[37] Especially in renal transplant patients CsA, induced nephrotoxicity remains a major clinical challenge.[36] Hepatotoxicity from prolonged CsA therapy is marked clinically by loss of appetite, weight loss, jaundice, fatigue, and, in severe cases, fatal outcomes. Early injury involves vacuolar degeneration, cellular swelling, necrosis, and nuclear breakdown in hepatocytes. This progresses to structural damage in liver lobules, disrupted cord-like arrangements, and inflammatory infiltration by lymphocytes and neutrophils. In later stages, cholestasis becomes prominent, accompanied by a proliferation of Kupffer cells and fibroblasts.[36]

Neurotoxicity linked to CsA has become increasingly recognized, with clinical reports of seizures, stroke-like episodes, hallucinations, delusions, reduced responsiveness, and cortical blindness. While most neurological complications are reversible upon dose reduction or discontinuation, central nervous system toxicity affects approximately 40% of patients.[36,38] Cyclosporine requires close monitoring to prevent organ rejection and minimize dose-dependent toxicities.[39]

Tacrolimus, mostly known as FK506, is a 23-membered macrolide lactone extracted from *Streptomyces tsukubaensis*, a soil fungus. In 1993, it was produced as an immediate-release immunosuppressant drug by the pharmaceutical company presently known as Astellas Pharma.[40]

Tacrolimus stands out as one of the most significant immunosuppressants used in the treatment of autoimmune diseases and in post-transplantation protocols.[41] It is usually paired with other immunosuppressants for treatment, commonly with corticosteroids and MMF as a dual- or triple-drug regimen.[42] Tacrolimus is available in two main oral formulations: immediate-release (IR) and modified-release (MR). The IR formulation is administered twice daily with relatively low and variable oral bioavailability, primarily due to its poor water solubility. In contrast, the MR formulation is designed for once-daily dosing and provides more consistent systemic exposure with improved bioavailability.[43]

Tacrolimus mechanism of action is similar to cyclosporine.[29] It binds to FKBP-12, which is an immunophilin that does the signal transduction. Binding to Ca2+, calmodulin, and calcineurin results in a complex that inhibits the action of the NFAT, which is required for IL-2 to signal the activation of T-lymphocytes.[44] Tacrolimus has higher inhibitory action against T-cells *in vitro* compared to CsA, and it is used for the prophylaxis of graft-vs-host disease.[45]

Tacrolimus is a substrate for both P-glycoprotein (P-gp) and the CYP3A4 enzyme.[46] Primarily metabolized by CYP3A enzymes, including CYP3A4, CYP3A5, CYP3A7, CYP3A43. Around 95% of TAC

metabolites are excreted via bile, and 2% is excreted in the urine. Tacrolimus has a low clearance rate, approximately 0.06 L/(h·kg)$^{-1}$, and a relatively long and variable half-life ranging from four to 41 hours, with an average of 12 hours. Its metabolism can vary depending on factors such as age, gender, genetic factors, and the usage of other medications.[47]

Therapeutic drug monitoring (TDM) helps ensure medications work effectively while minimizing side effects. When it comes to TAC, doctors typically adjust the dose by checking how much of the drug is present in the patient's whole blood, using that level as a guide to manage treatment safely and effectively.[41] Though TAC has shown remarkably improved results in solid organ transplant patients, there are significant side effects correlated with TAC, like nephrotoxicity, neurotoxicity, diabetes mellitus, hypertension, and gastrointestinal upset.[29]

Nephrotoxicity is the main adverse effect that results from the use of TAC. TAC-related nephrotoxicity typically presents as a decline in glomerular filtration rate, elevated serum creatinine levels, and in severe cases oliguria or the need for renal replacement therapy.[41]

TAC-induced neurotoxicity presents a variety of symptoms like tremors, neuralgia, and peripheral neuropathy. They can even appear at TAC-therapeutic levels and can continue after the stoppage of the drug. 5% of patients are affected with acute symptoms, including psychoses, hallucinations, dysarthria, vision loss, seizures, cerebellar ataxia, paresis, and leukoencephalopathy.[28,48]

Minor changes in systemic exposure to TAC can be useful due to the narrow therapeutic index of TAC. Therefore, drug monitoring is required and routinely implemented in clinical practice.[42] Yet, if the dose goes above the therapeutic level, adverse effects may occur, while low levels of TAC can lead to graft rejection.[29]

Mycophenolate mofetil

Mycophenolate mofetil is a strong immunosuppressive agent that is highly selective for lymphocytes and inhibits antibody production by B cells better than other immunosuppressant agents.[49] It is an esterified prodrug of mycophenolic acid (MPA), which gives it higher bioavailability than the parent compound. Mycophenolate mofetil was used to prevent solid organ and hematopoietic stem cell transplant rejection, and after that, it was adopted for use in the treatment of autoimmune diseases.[50]

Mycophenolate mofetil is widely used with various combinations of regimens of immunosuppressive agents like CsA and TAC.[51] It was first used to replace azathioprine (AZA), a drug that was used in the 1970s as an initial treatment for graft rejection; however, AZA is now primarily used in the treatment of other autoimmune diseases.[52]

Mycophenolate mofetil suppresses immune responses by directly inhibiting lymphocyte proliferation, preventing the maturation of T- and B-cells into functional effector lymphocytes. Its active metabolite MPA, blocks *de novo* purine synthesis by targeting inosine monophosphate dehydrogenase. By depriving lymphocytes of essential DNA precursors, MMF disrupts clonal expansion and impairs antigen presentation, weakening adaptive immunity. This inhibition reduces the pro-inflammatory cytokine environment necessary for lymphocyte differentiation and activation of innate immune effector mechanisms.[50,53,54]

Mycophenolate mofetil is converted to the active MPA by plasma esterase after gastrointestinal tract absorption, which reaches peak plasma concentration within one hour. MPA is extensively bound to albumin (97-99%), with free fractions varying based on serum albumin levels and renal function. Metabolism primarily occurs in the liver. Mycophenolic acid undergoes enterohepatic circulation, showing a secondary peak plasma concentration at 6-12h after oral or intravenous dose; this contributes 10-61% of MPA exposure. Mycophenolic acid's systemic clearance is affected by hepatic extraction, protein binding, and enzymatic activity, while renal excretion eliminates >95% of the dose as glucuronide metabolites. The half-life of the MPA average is approximately 17 hours.[54]

Gastrointestinal toxicity is the most common side effect, affecting up to 30% of patients, with symptoms ranging from mild nausea and diarrhea to severe erosive enterocolitis.[55] Hematologic effects such as anemia, leukopenia, and thrombocytopenia can also occur, necessitating regular blood count monitoring. Mycophenolate mofetil heightens susceptibility to infections, cytomegalovirus, and Epstein-Barr virus and increases the risk of malignancies such as post-transplant lymphoproliferative disorder. Long-term use carries a slight rise in cancer risk, including lymphoma and skin cancer. Drug-drug interactions should be considered. Therapeutic monitoring of MPA levels with pharmacodynamic assessments can help guide dosing**.** Yet, balancing efficacy with toxicity remains a clinical challenge.[51]

mTOR inhibitors: Sirolimus - Everolimus

Sirolimus and EvE are mTOR inhibitors nowadays used to prevent rejection in transplantation patients.[56] They can substitute CNI such as CsA and TAC.[57]

Sirolimus was discovered in the early 1970s and was made from an extraction of *Streptomyces hygroscopicus*.[58] Sirolimus was initially approved in 1999 by the Food and Drug Administration (FDA) and registered in 2003. The drug was first investigated as an adjunct to CsA for the prevention of acute rejection in kidney transplant recipients. Later studies demonstrated its effectiveness in combination with various other immunosuppressive agents.[59]

Everolimus originates from natural macrocyclic lactone SIR by an additional hydroxyethyl group.[60,61] The FDA approved EvE in 2009.[62]

Sirolimus and EvE can be used in cases of transplant impairment due to their potential to limit and slow the progression of graft vascular disease. They are also used to support the treatment of post-transplant complications associated with chronic immunosuppression in cardiac transplant recipients.[57]

Sirolimus and EvE share a comparable mechanism of action, functioning as inhibitors of mTOR, a serine/threonine kinase. These drugs work by binding to FK506-binding protein (FKBP12), which then interacts with mTOR. Both SIR and EvE disrupt the normal function of mTOR by forming a complex with FKBP12, which ultimately leads to the inhibition of mTORC1. This interaction inhibits the cellular response to signals such as interleukins IL-2, IL-3, IL-5, and IL-6, which are essential for the G1 phase of cell proliferation. Through this inhibition, both drugs significantly reduce the secretion of pro-inflammatory cytokines, including vascular endothelial growth factor and IL-8, by neutrophils, thereby impeding the immune response and inflammatory processes. Additionally, EvE promotes the secretion of IL-1RA, an anti-inflammatory cytokine, which provides an additional layer of immune suppression.[63,64]

mTOR is a central cellular metabolism and proliferation regulator, existing in two distinct complexes: mTORC1 and mTORC2. Both SIR and EvE primarily target mTORC1, which is activated by signals like amino acids, oxidative stress, growth factors, and cellular energy status. Once activated, mTORC1 promotes anabolic processes like protein synthesis and cell growth while downregulating catabolic processes like autophagy to ensure continued cell cycle progression. The inhibition of mTORC1 by SIR and EvE interferes with these anabolic mechanisms, halting cellular proliferation. mTORC2, on the other hand, plays a crucial role in maintaining cellular metabolism, cytoskeletal dynamics, and survival pathways. While it is not acutely affected by mTOR inhibitors, prolonged treatment with these drugs can impair its function, potentially affecting cell survival and response to stress.[59,60]

The complex formed between SIR or EvE and FKBP12 inhibits the activation of mTORC1, leading to the deactivation of p70S6 kinase, a critical mediator of protein synthesis and ribosome formation. This interruption in protein synthesis directly impacts cell cycle progression, particularly by preventing the formation of essential proteins required for cell division. The inhibition of mTOR also disrupts the activity of cyclins and cyclin-dependent kinases, which are necessary for the continuity of the cell cycle. As a result, both SIR and EvE induce cell cycle arrest and halt the proliferation of immune cells, such as lymphocytes. This mechanism plays a central role in the immunosuppressive effects of these drugs, making them useful in transplantation to prevent rejection, as well as in cancer therapies to limit tumor cell growth.[65]

The immunosuppressive action of SIR and EvE extends beyond lymphocytes. These drugs also restrict the growth of non-immune cell types, including hepatocytes, endothelial cells, fibroblasts, and smooth muscle cells. By inhibiting mTOR signaling, both drugs reduce cell proliferation and differentiation, diminishing antibody production and preventing non-immune cell expansion. This property of SIR and EvE makes them effective in minimizing tissue damage and inflammation in transplant recipients, where excessive immune responses can lead to graft rejection. Additionally, the suppression of mTOR signaling by these drugs has anti-neoplastic effects, making them beneficial in the treatment of certain cancers, such as renal cell carcinoma, where EvE specifically interferes with tumor angiogenesis and growth.[60,65]

Sirolimus and EvE share similar pharmacokinetic properties, including rapid gastrointestinal absorption following oral administration. However, both drugs exhibit low and variable bioavailability due to significant first-pass metabolism and efflux mechanisms. Everolimus reaches peak plasma concentrations approximately 1.3-1.8 hours after oral administration, while SIR achieves peak levels

around 2–3 hours post-dose. The oral bioavailability of SIR is estimated at 15%, whereas EvE has a slightly higher bioavailability.[64,66] Both drugs are substrates of cytochrome P450 (CYP) 3A4, CYP3A5, and CYP2C8 enzymes, as well as P-gp, leading to variability in drug exposure. The co-administration of CsA significantly affects systemic exposure, particularly for EvE. Food intake can also alter the absorption kinetics of both drugs; therefore, dosing should be consistent with meals to maintain stable drug levels.[66,67]

Sirolimus is highly lipophilic, with a large volume of distribution (7-19 L/kg), and is extensively sequestered in red blood cells and peripheral tissues. It binds primarily to blood cells, with minimal presence in plasma and lymphocytes, supporting the use of whole blood for TDM. Everolimus, though less lipophilic, also partitions significantly into erythrocytes and exhibits moderate plasma protein binding. Its volume of distribution is influenced by body weight and co-medications, expanding considerably in the absence of cyclosporine.[67] The clearance of both agents is primarily hepatic, with metabolism facilitated by CYP3A enzymes and P-gp. Sirolimus has a long elimination half-life, typically exceeding 60 hours, enabling once-daily dosing. Everolimus has a shorter half-life of approximately 24-35 hours, necessitating twice-daily administration to maintain effective plasma concentrations. Both drugs are predominantly eliminated via biliary excretion following hepatic metabolism, with negligible renal clearance. Sirolimus is excreted largely through faeces (over 90%), with only a small fraction appearing in the urine. Everolimus follows a similar excretory route, with nearly all metabolites cleared through the bile.[56]

The most common observed side effects associated with mTOR inhibitors include hematologic abnormalities such as anemia and thrombocytopenia, along with elevated serum triglyceride and cholesterol levels. In SIR-treated patients, increased trough concentrations have been significantly linked to thrombocytopenia (platelet count $<100 \times 10^9$/L), leukopenia (white blood cell count $<4 \times 10^9$/L), and severe hypertriglyceridemia (>750 mg/dL), though no clear association was found with hypercholesterolemia (>400 mg/dL).[64] For EvE, thrombocytopenia has demonstrated dose dependence, whereas leukopenia has not. Similarly, lipid disturbances such as hypertriglyceridemia and hypercholesterolemia occur independently of dosage.[68]

Gastrointestinal complaints like aphthous stomatitis and diarrhea appear more commonly with more use than with CNI or mycophenolic acid regimens. Fortunately, early-detected oral ulcers typically respond well to therapeutic intervention. Dyslipidemia is a frequent but manageable side effect, often controlled with lipid-lowering agents.[69,70]

A rare yet serious complication of mTOR inhibition is non-infectious pneumonitis, characterized by diffuse inflammatory infiltrates in the lungs without incidence of infection or malignancy. This condition typically develops within two to six months after initiating therapy, presenting symptoms such as cough, dyspnea, and hypoxemia; systemic symptoms, including fatigue and fever, may also be observed. Although the exact pathophysiological mechanism remains unclear, a T cell-mediated autoimmune reaction or delayed-type hypersensitivity to cryptic antigens has been proposed. The reported incidence of pneumonitis associated with SIR and EvE ranges between 1% and 12%. To date, no definitive patient-related risk factors have been identified. Once diagnosed, prompt discontinuation of the mTOR inhibitor is advised, and an alternative immunosuppressive strategy should be employed.[71,72]

Monitoring SIR levels in the blood has shown a strong association with both therapeutic effectiveness and the risk of toxicity. Toxicity has been associated with SIR concentrations exceeding 15 µg/L. Suggested therapeutic windows include 5-15 µg/L or 6-12 µg/L when used in combination with CNIs and 10-20 µg/L when used independently of CNIs.[73,74]

As with SIR, blood concentrations of EvE are closely linked to both immunosuppressive efficacy and the likelihood of adverse reactions, making TDM essential. For patients receiving EvE alongside CNIs, the recommended trough range is typically between 3 and 8 µg/L. In CNI-free regimens, trough levels of 6-8 µg/L have been associated with an AUC of approximately 120 µg·h/L. For these CNI-sparing strategies, target trough levels may extend to 6-10 µg/L. A simplified monitoring approach involving two-time points has been proposed and could also be suitable for regimens combining EvE with TAC.[64]

Basiliximab

Basiliximab is a chimeric monoclonal antibody that targets and inhibits IL-2 receptors. It has been revealed to efficiently limit post-transplantation rejection.[75,76]

Basiliximab can be used as a supplement or substitute for immunosuppression, and a monthly infusion of BAS was utilized for immunotherapy.[77]

This process starts when the cytokine IL-2 attaches to the multi-subunit, high-affinity receptor on activated T cells. The monoclonal antibody BAS binds to the α-subunit of the IL-2 receptor (also known as the CD25 or TAC antigen) with high specificity and affinity. Basiliximab blocks the interaction between IL-2 and its receptor by occupying the binding site, thereby preventing T lymphocytes involved in rejection from proliferating. According to *in vitro* research, BAS concentrations of ≥1 mg/L are adequate to prevent over 90% of IL-2 from binding to T cell lines that express the IL-2 receptor. Patients who receive renal transplants frequently reach such serum concentrations.[78]

In vivo, BAS rapidly saturates IL-2 receptors. Within 24 hours of a single intravenous dose ranging from 2.5 to 25 mg, approximately 90% of IL-2 receptors on peripheral T lymphocytes were rendered unavailable for IL-2 binding in renal transplant recipients. In adult patients, administration of BAS at 20 mg given two hours before transplantation and again on postoperative day 4 maintained IL-2 receptor saturation for approximately four to six weeks. In representative cases, about 90% of IL-2 receptors remained unavailable for IL-2 binding for a period of 30 to 45 days following treatment. Similarly, in pediatric renal transplant recipients aged two to 12 years, BAS at a dose of 12 mg/m^2 administered on the same schedule resulted in IL-2 receptor saturation lasting for an average of 29 days.[79]

According to Kovarik et al.[80] BAS (40 mg total, administered as two 20 mg doses on days 0 and 4) exhibits a clearance of 36.7 ± 15.2 mL/h, a volume of distribution of 8.0 ± 2.4 L, and an elimination half-life of 7.4 ± 3.0 days. CD25 receptor saturation (serum levels >0.2 μg/ml) was maintained for approximately 33-37 days, with no significant difference in duration between patients who experienced rejection and those who remained rejection-free (P=0.162). The study found no association between BAS concentrations (0.2–5.0 μg/ml) and acute rejection episodes, nor any evidence of accelerated drug clearance in rejection cases (P=0.322).

Side effects linked with BAS are varied and comprise chills, fever, rash, tiredness, diarrhea, nausea, headache, anorexia, leukopenia, and infections. These side effects are relatively common and are acknowledged as manageable within the context of treatment. The usage of BAS may result in serious adverse effects. These include acute allergic reactions, which can manifest rapidly and intensely; anaphylaxis, a life-threatening systemic allergic reaction that requires immediate medical intervention; capillary leak syndrome, which involves a sudden leakage of fluid from the capillaries that can lead to shock; cytokine release syndrome, a serious inflammatory reaction that can be life-threatening; and progressive multifocal leukoencephalopathy, a rare brain infection that leads to sign. Awareness in a timely manner of these side effects can have a major impact on patient comfort and treatment adherence.[76]

Belatacept

Belatacept is a drug that blocks CD28-mediated T-cell costimulation. It is a recombinant immunoglobulin fusion protein with the modified extracellular domain of CTLA4.[7,81] A modified form of abatacept with improved affinity, making it suitable for transplantation, while abatacept remains in the treatment of other autoimmune diseases.[82] It is designed as an alternative to CNI. It made their avoidance easier, as mentioned earlier in the review; CNI-based therapy holds significant side effects and toxicities that are a challenge, yet they remain at the cornerstone of standard treatments to prevent allograft rejection.[83]

Belatacept is widely used with various combinations of immunosuppressive agents to prevent graft rejection in treatment, including BAS, MMF, and glucocorticoids.[81] Research has proved an improved cardiovascular and metabolic profile with decreased chronic allograft nephropathy and incidence of dnDSAs and improved renal function in patients receiving BEL treatment in comparison to those who received cyclosporine, yet an increased rate of biopsy-proven acute rejection in patients receiving BEL.[84]

Belatacept's mechanism works by blocking the CD28-CD80/86 costimulatory pathways, resulting in the inhibition of T-cell activation.[85]

Belatacept is more powerful in inhibiting primary and secondary T-cell responses than abatacept.[82] Belatacept is given as a 30-minute IV infusion with a half-life of 8-10 days. Unlike some drugs, it does not require dose adjustments in liver or kidney failure. It is compatible with other immunosuppressants and has no known drug interactions. Further research is needed to define optimal target concentrations and their impact on efficacy and safety.[86]

Belatacept-induced treatment increases the risk of developing post-transplant lymphoproliferative disease. Epstein-Barr virus-negative patients are at

higher risk of developing this disease, so BEL is only given to Epstein-Barr virus-positive patients for treatment post-transplantation.[87] Other reported adverse effects are bone marrow suppression, hypertension, and dyslipidemia.[7] Although BEL doesn't carry the risk of nephrotoxicity, some ambiguity remains in clinical practice, such as the risks of acute rejection and infections.[88]

In conclusion, immunosuppressive therapy plays an essential role in preventing graft rejection after transplantation. Drugs such as cyclosporine, TAC, SIR, and MMF effectively suppress immune responses, protecting the transplanted organ and giving the graft a second chance at life. Although this is a very effective treatment regimen that has successfully shown improvements in graft survival, its use comes with significant challenges, including toxicity, side effects, and the need for careful TDM to maximize efficacy and safety while minimizing side effects. Improvements in immunosuppression therapy have focused on personalized dosing, new drug combinations, and the development of targeted agents to reduce adverse effects and maintain graft survival. There are still a lot of unanswered questions, especially about reducing long-term issues that threaten recipient survival, like infections, metabolic diseases, and cancers. Future research should focus on developing safer, more selective immunosuppressants.

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