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Review Article

Viral infections in solid organ transplant recipients: immunological principles and intervention strategies

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Abstract: Objective: This review aims to examine the challenges of opportunistic viral infections in transplant recipients on long-term immunosuppression and to explore the potential of emerging immunotherapies to improve infection management. Methods: We summarize the mechanisms and effects of current clinical immunosuppressants, outline the incidence of viral infections following various organ transplants, and discuss the limitations of existing antiviral pharmacotherapies. Furthermore, we systematically review recent advances in novel immunotherapies that harness the patient's immune system. Results: While immunosuppressive regimens significantly improve graft survival, they increase susceptibility to viral infections. Emerging immunotherapies demonstrate promising potential in managing these infections, yet their application in transplant recipients remains underexplored. Conclusion: Innovative immunotherapies represent a promising avenue for overcoming the limitations of conventional treatments. Their integration into transplantation practice may enhance long-term outcomes, although further clinical validation is needed.

Keywords: Post-transplant viral infections, immunotherapy, organ transplantation, antiviral immune response

Introduction

Organ transplantation represents the definitive treatment for patients with end-stage organ failure. Its success depends on the refinement of surgical techniques and the meticulous regulation of immune rejection responses [1]. Calcineurin inhibitors (CNIs), such as cyclosporine, are widely used in clinical practice and have extended the median survival of transplanted organs to over eight years [2]. Despite these therapeutic advances, prolonged immunosuppressive therapy, essential for maintaining graft survival, significantly increases transplant recipients' risk of complications, with notably heightened susceptibility to viral infections. This increased vulnerability arises from the inherent impairment of antiviral immune defenses induced by standard immunosuppressive regimens. Common viral pathogens affecting transplant recipients include cytomegalovirus (CMV), Epstein-Barr virus (EBV), and BK polyomavirus. These viruses not only cause acute morbidity but also negatively impact long-term graft function and overall patient outcomes. As immunological research advances, novel immunotherapeutic strategies, ranging from cell therapies, vaccination, cytokine treatments, to immunomodulators, have demonstrated promising clinical benefits for the treatment of viral infections. However, in the context of organ transplantation, these therapies may either heighten the risk of graft rejection or exhibit diminished efficacy due to the immunosuppressive environment. Therefore, the application and overall effectiveness of immunotherapy in transplant recipients remain inadequately explored.

This review examines the scope of action and immunological mechanisms of immunosuppressants currently used in clinical practice, with emphasis on CNIs, mammalian target of rapamycin inhibitors, co-stimulation inhibitors, and interleukin-2 receptor antagonists (IL-2Ra). Additionally, the immunomodulatory roles of glucocorticoids and metabolic disruptors are considered. We also outline the rates of viral infections following organ transplantation in different regions and discuss the pharmacological

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treatment strategies for these infections and their limitations. Finally, we explore the potential application of novel immunotherapeutic strategies in organ transplant recipients, focusing on the research progress of emerging immunotherapeutic approaches, including how they mobilize the patient's own immune system and address the shortcomings of traditional treatments. This review aims to serve as a guide for clinical and basic researchers in transplantation medicine, promoting the advancement and application of novel immunotherapeutic approaches.

Epidemiology and clinical burden of CMV and BK polyomavirus infections in solid organ transplant recipients

Viral infections following organ transplantation represent a complex clinical challenge result ing from the interplay between the recipient's immunocompromised condition and the immunosuppressive regimens. Although these agents are crucial for preventing graft rejection, they simultaneously impair antiviral immune defenses, significantly increasing susceptibility to opportunistic viral pathogens. Among transplant recipients, infections caused by CMV, EBV, and BK polymavirus are the most common. Without preventive measures, 40-100% of renal transplant recipients in the United States may develop CMV infection [3]. A nationwide cohort study from Denmark reported that CMV infection occurred in 23% of patients following solid organ transplantation. In 49 studies across Asia, Latin America, and Oceania, the CMV infection rate post-solid organ transplantation ranged from 5.8% to 63.2% [4]. Notably, clinical studies conducted in China have reported significantly lower infection rates, ranging from 5.8% to 13.2% (**Table 1**).

Current evidence suggests that BK polyomavirus infection exhibits pronounced organ tropism, occurring predominantly in renal transplant recipients with a markedly lower incidence in other solid organ transplants. In the context of kidney transplantation, BK polyomavirus is the principal causative agent of polyomavirus-associated nephropathy (PyVAN), a serious complication that compromises allograft function and long-term graft survival. The incidence of BK polyomavirus reactivation following immunosuppressive therapy ranges from 30% to 60% [5] (**Table 1**).

Immunosuppressive agents in transplantation: mechanisms of action, cellular targets, and clinical implications

A major challenge in organ transplantation is the host immune system's recognition of the graft as "non-self", triggering immune responses that can lead to graft rejection. Central to this process is the major histocompatibility complex (MHC) expressed on donor cells, which serves as a key target for host immune surveillance. Donor antigens are recognized either through direct presentation by donor-derived MHC molecules or indirectly via processing and presentation by host antigen-presenting cells, ultimately activating recipient T lymphocytes. This adaptive immune response is orchestrated through the well-established "three-signal model": (1) antigen recognition via T-cell receptor (TCR) engagement with MHC-peptide complexes; (2) co-stimulatory interactions, such as CD28-B7 and CD40-CD40L binding; and (3) cytokine-mediated signaling that drives T cell proliferation and differentiation. In parallel, B cells can generate donor-specific antibodies that contribute to graft injury through complement activation and antibody-dependent cel lular cytotoxicity (ADCC). Immunosuppressive agents mitigate rejection by dampening both innate and adaptive immune responses, thereby markedly improving transplant outcomes. For example, CNIs, a cornerstone of current immunosuppressive regimens, have extended median graft survival to over eight years (**Table 2**).

Indeed, while these agents are effective in preventing rejection, they also compromise host immune surveillance, particularly against latent viral infections. As noted earlier, this immunosuppressive state facilitates the reactivation and replication of opportunistic pathogens such as CMV, EBV, and BK polyomavirus. Therefore, a comprehensive understanding of how immunosuppressive drugs influence immune cell subsets, intracellular signaling pathways, and virus-host dynamics is essential for optimizing post-transplant care and mitigating infection-related complications (**Figure 4**).

CNIs

CNIs are the cornerstone of immunosuppressive therapy following organ transplantation. The main representatives of CNIs include Cyclosporine A (CSA) and Tacrolimus (FK506). It

Table 1. Epidemiological data of viral infections in organ transplant recipients

	Kidney transplant	Liver transplant	Heart transplant
CMV	5.8-100% [3, 4, 109]	13.2-67% [4, 109]	42.5-72.1% [109, 115]
EBV	11.3-56% [110-113, 116]	60.4% [117]	-
HSV	6.5% [118]	8.4% [118]	9.4% [118]
BK Polyomavirus	30-60% [5]	15.9% [119]	-
JC Polyomavirus	22.3% [119]	22.7% [119]	-

Table 2. Commonly used immunosuppressive drugs and their main characteristics

Drug Type	Commonly Used Drugs	Features
CNIs	CSA FK506	Forms a complex that binds to calcineurin, thereby inhibiting its activity and preventing the transcription of pro-inflammatory cytokines such as interleukins.
mTORi	Sirolimus	Blocks cells from entering the S phase from the G1 phase, thereby preventing the proliferation and differentiation of immune cells; may increase the risk of infection.
Co-stimulation Inhibitors	Abatacept Belatacept	Binds to the B7 molecule, blocks its binding to CD28, and reduces T cell activation; may increase the risk of infection.
IL-2Ra	Basiliximab antibody Daclizumab antibody	Blocks the binding of IL-2 to its receptor, thereby inhibiting T cell proliferation and activation, and reducing the immune system's attack on transplanted organs.
GCs	GCs	Simulating the effects of naturally occurring cortisol in the human body, such as inhibiting the production of proinflammatory cytokines, reducing the release of inflammatory mediators, and reducing the migration and activity of inflammatory cells.
Anti-metabolities	MMF MPS	By inhibiting IMP dehydrogenase, it blocks the *de novo* synthesis of guanylate, inhibiting the proliferation and function of lymphocytes; finely regulating the immune response while managing the risk of viral infection.
Lymphocyte-depleting antibody drugs	ATG ATLG Alemtuzumab	Inhibits the immune response through direct cytotoxic effects, inducing apoptosis, blocking signaling molecules on the cell surface, and regulating the release of cytokines.

is now understood that CNIs target calcineurin phosphatase, a protein composed of two subunits, CnA and CnB. During T-cell activation, the recognition of antigens by the T-cell receptor (TCR) leads to an increase in intracellular Ca^{2+} levels and the activation of CnB, thereby activating the phosphatase activity of CnA. Activated CnA dephosphorylates the cytoplasmic transcription factor NFATc, allowing it to translocate to the nucleus with activated calmodulin, where it upregulates the expression of various cytokines and costimulatory molecules required for complete T-cell activation [6]. CSA forms a complex with cyclophilin, whereas tacrolimus (FK506) binds to the FK-binding protein (FKBP). These drug-immunophilin complexes subsequently inhibit calcineurin phosphatase activity, thereby disrupting key T-cell activation pathways (**Figure 1**). This inhibition of T-cell activation secondarily impairs B-cell function by diminishing T-cell help (**Figure 2**) [7]. Besides, current evidence suggests that CNIs can affect humoral immunity by directly inhibiting the proliferation of naive B cells and the differentiation of plasmablasts [8].

Due to the limited biological role of NFAT in NK cells, which only regulates the expression of CD16, CNIs have almost no effect on the activity of NK cells [9, 10]. *In vitro* experimental results have shown that CNIs inhibit the ADCC of NK cells and significantly suppress the production of IFNγ in a dose-dependent manner (**Figure 3**) [11]. Through this mechanism, CNIs selectively suppress NK cell-mediated T cell activation while preserving NK cell proliferation, thereby reducing the risk of graft-versus-host disease (GVHD) without disrupting NK cell homeostasis.

Mammalian target of rapamycin inhibitors (mTORi)

mTORi are a class of important immunosuppressive drugs that inhibit the growth and proliferation of immune cells by suppressing the activity of mTOR. mTOR is a serine/threonine

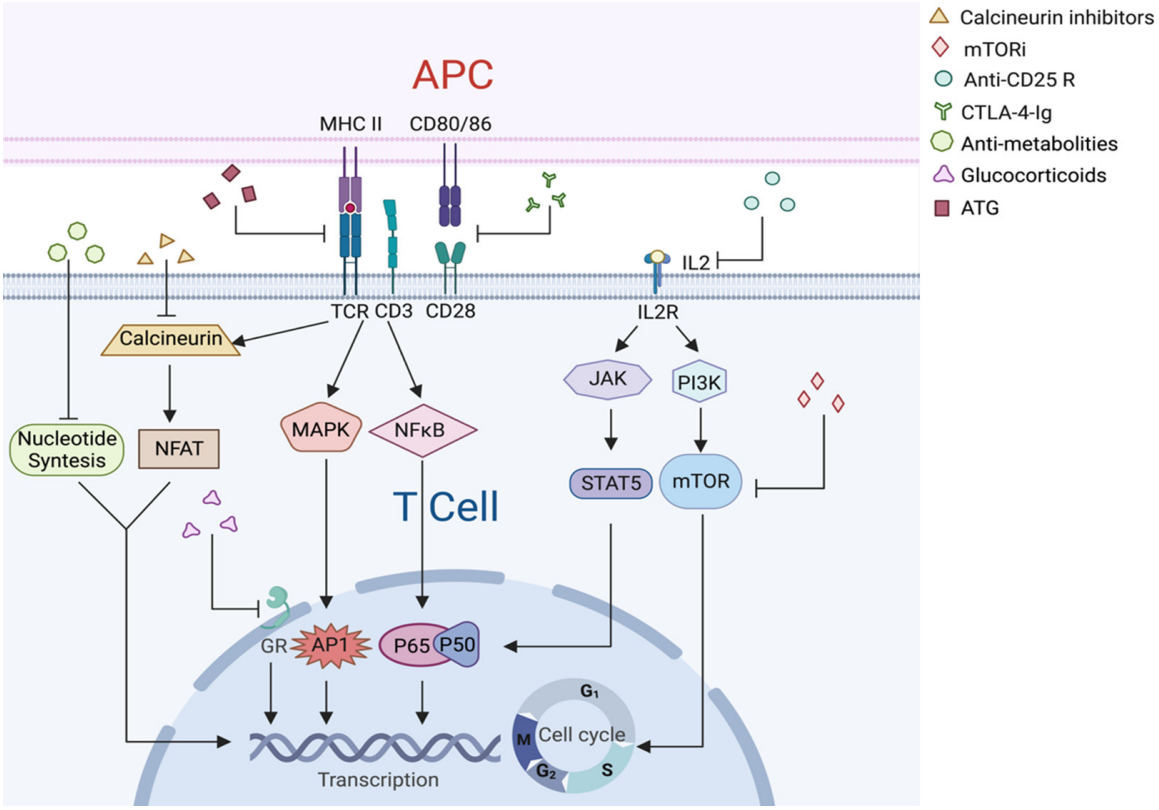

Figure 1. The functional effects and mechanisms of action of immunosuppressive agents on T lymphocytes. CNIs form complexes that bind to calcineurin, inhibiting its activity and preventing the transcription of pro-inflammatory cytokines such as interleukin through the NFAT signaling pathway. mTORi suppress the PI3K/AKT/mTOR signaling pathway, blocking cell transition from the G1 phase to the S phase, thereby inhibiting the proliferation and differentiation of immune cells. IL-2Ra directly blocks the binding of IL-2 to its receptor, causing internalization of the IL-2 receptor and blocking IL-2-dependent T cell clone expansion, which inhibits T cell proliferation and activation, reducing the immune system's attack on the transplanted organ. Co-stimulation inhibitors, exemplified by CTLA-4-Ig, bind to B7 molecules, preventing their interaction with CD28 and reducing T cell activation. Metabolism-disrupting drugs inhibit inosine monophosphate dehydrogenase, blocking *de novo* synthesis of guanosine nucleotides, which disrupts the transcription and translation of T cells, thereby interfering with their proliferation and function. GCs act directly on the glucocorticoid receptors in the T cell nucleus, exerting effects such as inhibiting the production of pro-inflammatory cytokines, reducing the release of inflammatory mediators, and decreasing the migration and activity of inflammatory cells. Lymphocyte-depleting monoclonal antibodies, exemplified by ATG, can suppress immune responses by blocking signaling molecules on the cell surface and modulating the release of cytokines.

protein kinase and a member of the phosphoinositide 3-kinase (PI3K)-related kinase family, interacting with different proteins to form mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) [12]. mTORC1 is involved in the regulation of multiple signaling pathways in immune cells and is directly sensitive to certain immunosuppressive drugs such as Sirolimus (also known as Rapamycin) [13]. After administration, the drug forms a complex with the protein FKBP12, which further interacts with mTORC1 to inhibit its activity. This inhibitory effect blocks cell cycle progression from the G1 to S phase, thereby suppressing the proliferation and differentiation of both T and B lymphocytes (**Figures 1** and **2**). In contrast, mTORC2 is generally insensitive to rapamycin; however, prolonged exposure can disrupt its structural integrity, impacting cell survival and cytoskeletal organization [14].

The immunosuppressive effects of mTORi extend across multiple immune cell populations, including T cells, B cells, and NK cells [15-17]. These agents function by disrupting critical cell cycle signaling pathways (**Figure 3**). Besides, mTORi impair dendritic cell (DC) maturation and their capacity to activate T cells [18]. While clinically valuable for immunosuppression, mTORi therapy carries significant consid-

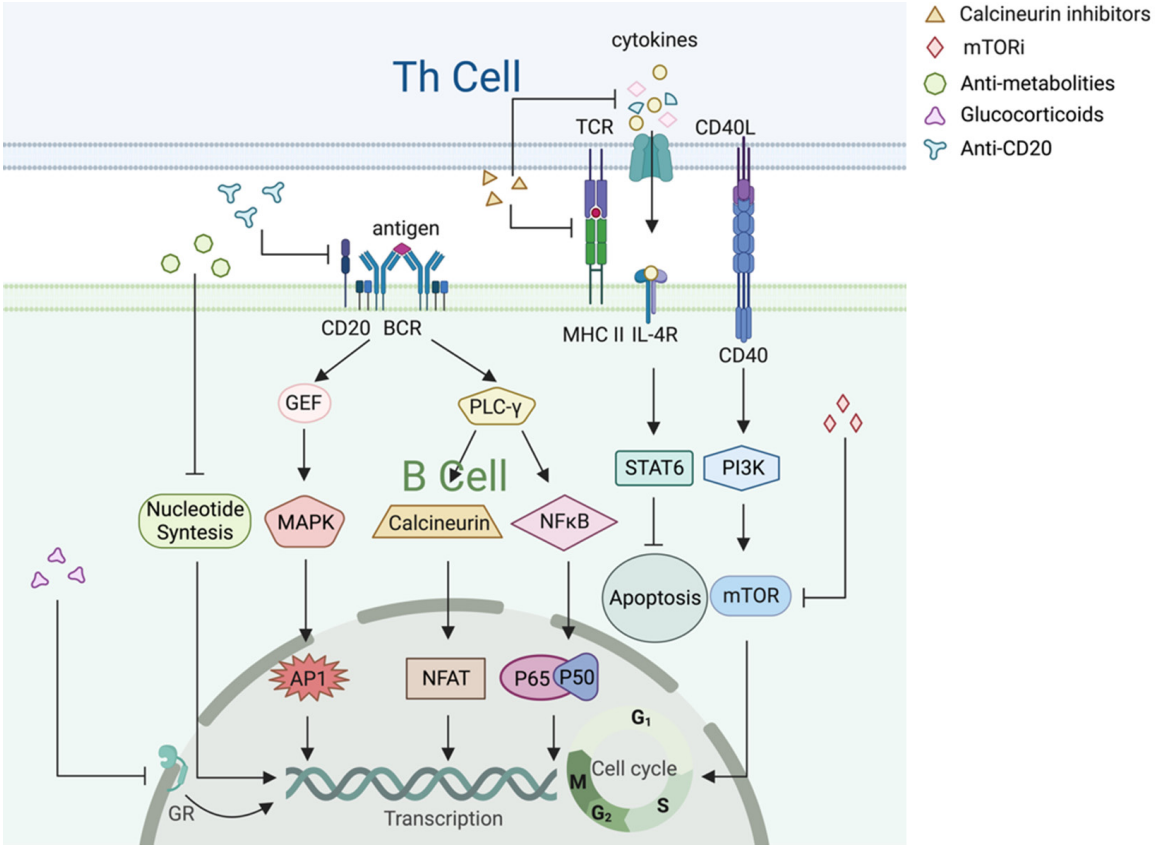

Figure 2. The functional effects and mechanisms of action of immunosuppressive agents on B lymphocytes. CNIs indirectly suppress B cell activation by preventing the transcription of pro-inflammatory cytokines such as interleukin in T cells. mTORi blocks cell cycle progression from the G1 phase to the S phase by inhibiting the PI3K/AKT/mTOR signaling pathway, thereby preventing the proliferation and differentiation of B cells. Metabolism-disrupting drugs impede the de novo synthesis of guanosine nucleotides by inhibiting inosine monophosphate dehydrogenase, disrupting the transcription and translation of B cells, and thus interfering with their proliferation and function. GCs exert pro-apoptotic effects by acting directly on the glucocorticoid receptors in the B cell nucleus and directly affect humoral immune responses by reducing the production of circulating immunoglobulins. Lymphocyte-depleting monoclonal antibody drugs, exemplified by CD20 monoclonal antibodies, exert cytotoxic effects by directly targeting the B cell surface molecule CD20 to deplete B cells.

erations, including increased infection risk and other medication-associated adverse effects that require careful monitoring.

Co-stimulation inhibitors

Co-stimulation inhibitors represent a class of immunomodulatory agents that selectively target secondary signaling pathways essential for T cell activation. By blocking the critical costimulatory signals required for full TCR engagement, these therapeutics effectively suppress T cell clonal expansion and effector function while preserving baseline immune surveillance. Current evidence suggests that T cell activation requires two distinct signals: (1) primary antigen recognition through TCR engagement with peptide-MHC complexes; and (2) costimulatory signaling, primarily mediated by CD28 receptor binding to B7 molecules (CD80/CD86) on antigen-presenting cells (APCs). This dual-signal mechanism ensures antigen-specific immune responses while maintaining peripheral tolerance [19]. Co-stimulation inhibitors effectively attenuate T cell-mediated immune responses by interrupting the second signal (**Figure 1**).

Co-stimulation blockade can be achieved via two principal strategies: (1) competitive inhibition using recombinant fusion proteins (e.g., CTLA4-Ig) that exploit the higher affinity of CTLA-4 for B7 molecules (CD80/86), thereby preventing CD28 engagement and subsequent T cell activation; and (2) direct targeting with

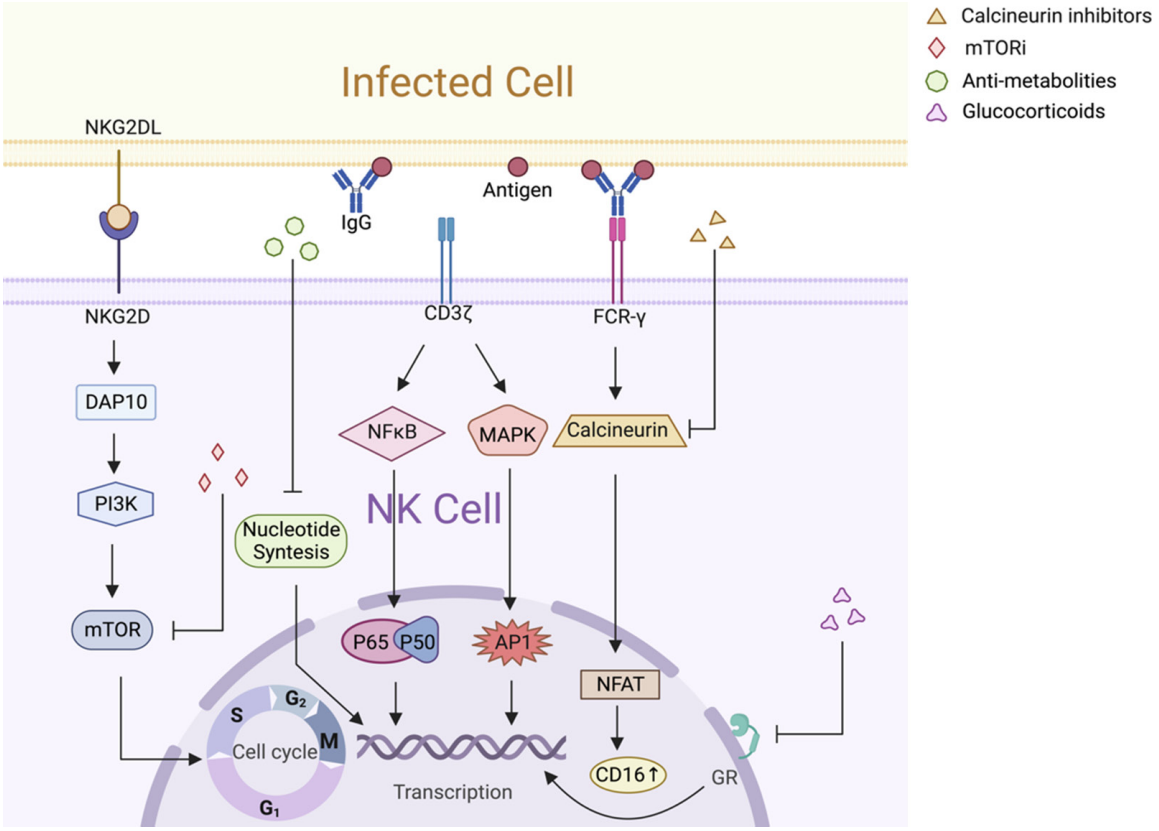

Figure 3. The functional effects and mechanisms of action of immunosuppressive agents on NK cells. CNIs modulate the expression of CD16 in NK cells by inhibiting the NFAT signaling pathway, suppressing the ADCC effect of NK cells. mTORi prevent the transition of cells from the G1 phase to the S phase by inhibiting the PI3K/AKT/mTOR signaling pathway, thereby inhibiting the proliferation and differentiation of NK cells. Metabolism-disrupting drugs block the de novo synthesis of guanosine nucleotides by inhibiting inosine monophosphate dehydrogenase, reducing the expression of all activated NK cell receptors. GCs act directly on the glucocorticoid receptors in the NK cell nucleus, inhibiting the expression of effector molecules such as perforin, granzyme B, and granzyme A, as well as the production of interferon-γ, thereby suppressing the cytotoxic activity of NK cells and their activating effect on T cells.

monoclonal antibodies against either B7 ligands or CD28 itself [20]. Currently, clinical co-stimulation inhibitors are all derivatives of CTLA4, including Abatacept [21] and Belatacept [22]. Abatacept is a fusion protein comprising the extracellular domain of human CTLA4 linked to the Fc segment of the IgG1 antibody [21], while Belatacept is an optimized version of Abatacept with an enhanced amino acid sequence that increases the drug's affinity for CD80 and CD86 [22]. While co-stimulation inhibitors reduce the need for long-term immunosuppressants (such as CNIs), their use can increase the risk of certain infections.

IL-2Ra

IL-2Ra represents a class of biological agents specifically targeting the IL-2 receptor α chain CD25. Current evidence suggests that IL-2 is a key cytokine essential for the activation and maintenance of T cell function. In the context of post-transplantation, IL-2Ra functions by blocking the binding of IL-2 to its receptor, thereby suppressing T cell proliferation and activation, thereby mitigating immune-mediated rejection of the transplanted organ. The IL-2 receptor is composed of three non-covalently bound subunits: IL-2Rα (CD25), IL2Rβ (CD122), and IL-2Rγ (CD132). Naïve T cells constitutively express the intermediate-affinity IL-2 receptor composed of βγ subunits (IL-2Rβγ). Following antigen recognition and initial activation, these cells upregulate expression of the α chain (CD25), forming the high-affinity trimeric IL-2 receptor (IL-2Rαβγ) that confers maximal responsiveness to IL-2 signaling [23]. After IL-2 binds to the high-affinity receptor, it activates

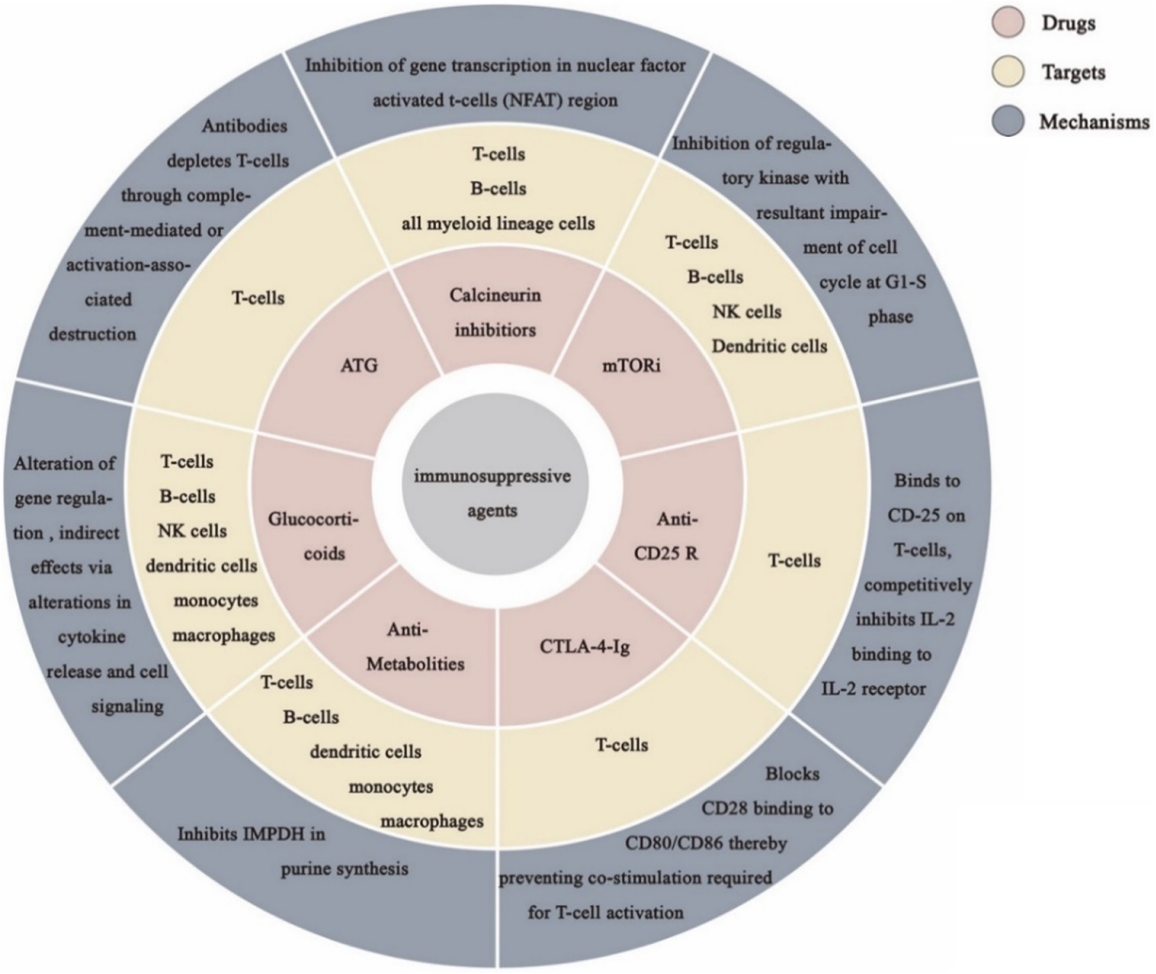

Figure 4. The functional effects and mechanisms of action of immunosuppressive agents on major immune cells. The seven main classes of immunosuppressive agents exert their immunosuppressive effects through distinct mechanisms targeting a variety of immune cells, including lymphocytes, neutrophils, and mononuclear phagocytes.

JAK1 and JAK3, leading to the recruitment and phosphorylation of STAT5, which drives T cell proliferation. IL-2 receptor antagonists exert their immunosuppressive effects by competitively binding to the α subunit of the high-affinity IL-2Rαβγ complex. This binding triggers receptor internalization and subsequent lysosomal degradation, thereby preventing IL-2-mediated signaling and inhibiting clonal expansion of activated T cells (**Figure 1**).

Clinically approved IL-2 receptor antagonists include the monoclonal antibodies basiliximab and daclizumab, which are primarily employed as induction immunosuppressants in the peri-transplant period. These biologic agents are typically administered as part of a multidrug regimen, combining with CNIs (cyclosporine or tacrolimus), mTORi, and other immunosuppressive agents to achieve synergistic therapeutic effects while minimizing individual drug toxicities [24].

Glucocorticoids (GCs)

GCs are a class of potent anti-inflammatory and immunosuppressive drugs widely used in organ transplantation. They play a pivotal role in post-transplant management by mimicking the effects of naturally occurring cortisol in the human body. GCs achieve their potent anti-inflammatory effects through multiple complementary mechanisms: (1) transcriptional suppression of pro-inflammatory cytokines; (2) inhibition of inflammatory mediator synthesis; and (3) impairment of inflammatory cell trafficking and effector functions [25]. In the context of organ transplantation, GCs are commonly used

during the early stages to prevent and treat acute rejection. Furthermore, their inclusion in long-term regimens contributes significantly to graft preservation.

It is now understood that GCs exert comprehensive immunomodulatory effects across both innate and adaptive immunity (**Figures 1-3**). GCs suppress innate immune responses by: (1) Inhibiting pro-inflammatory cytokine production (e.g., TNF-α, IL-1β) in monocytes, macrophages, and dendritic cells (DCs), while impairing their antigen-presenting capacity [26]; and (2) Reducing NK cell cytotoxicity by downregulating perforin and granzymes (A/B) [27, 28] and suppressing Interferon-γ (IFN-γ) production [29].

GCs modulate adaptive immunity through: (1) Upregulating immunomodulatory proteins (e.g., CTLA-4, PD-1) and pro-apoptotic genes while inhibiting pro-inflammatory cytokines (e.g., IL-2, IFN-γ) and cell cycle progression [30]. (2) Strongly inhibiting Th1 responses while moderately suppressing Th2, skewing immunity toward type 2 responses [30]. (3) Promoting regulatory T cell (Treg) differentiation and expansion, enhancing immune tolerance [31, 32], and (4) Inducing apoptosis in developing B cells and reducing circulating immunoglobulins, dampening humoral immunity [33]. Collectively, these mechanisms highlight the broad immunosuppressive effects of GCs, underscoring their central role in suppressing excessive immune activation. As such, GCs remain a cornerstone of maintenance in immunosuppressive therapy in transplantation medicine. However, their long-term use necessitates careful monitoring and management of associated metabolic and infectious complications.

Metabolism-disrupting drugs

In transplant recipients, immune metabolic modulators are employed to achieve precise immune regulation, balancing graft protection against infection risks. These agents exert their effects by selectively targeting metabolic pathways crucial for lymphocyte activation and proliferation, thereby modulating immune responses while maintaining viral surveillance. The IMPDH inhibitors mycophenolate mofetil (MMF) and mycophenolic acid (MPA) mediate immunosuppression via targeted disruption of purine metabolism. By competitively inhibiting IMP dehydrogenase, these drugs deplete guanosine nucleotide pools in lymphocytes, which lack the hypoxanthine-guanine phosphoribosyl transferase (HGPRT)-dependent salvage pathway available to other cell types [34]. Moreover, MMF exerts additional immunomodulatory effects by suppressing STAT3 phosphorylation and downstream signaling, leading to a marked reduction in key growth factor production (e.g., VEGF-A and PDGF-BB) and chemokines (e.g., MIG/CXCL9 and SDF-1α/CXCL12), thereby disrupting the differentiation of CD4+ T lymphocytes and the development of B lymphocytes [35]. Besides, MMF therapy compromises NK cell functionality through multiple mechanisms. Clinical studies have demonstrated that MMF treatment: (1) selectively depletes the immunoregulatory $CD16^-$ CD56 bright NK subset; and (2) downregulates expression of activating receptors, including NKG2D, NKp30, NKp44, and NKp46 [36, 37], collectively impairing NK cell immune surveillance capacity.

Lymphocyte-depleting monoclonal antibodies

For acute rejection prophylaxis and treatment in transplantation, T-cell depleting agents like anti-thymocyte globulin (ATG) and anti-human T-cell immunoglobulin (ATLG) remain essential. These polyclonal IgG fractions, produced by immunizing horses or rabbits with human lymphocytes, are now understood to induce rapid peripheral T-cell clearance through multiple effector mechanisms, including direct cytotoxic effects, induction of apoptosis, blocking of cell surface signaling molecules, and modulating the release of cytokines [38]. Besides, ATG depletes pre-activated T cells through ADCC or Fas-dependent apoptosis [39]. Beyond T cell depletion, ATG exhibits additional immunomodulatory effects *in vitro*, including upregulation of PD-L1 expression on monocytes. This PD-1/PD-L1 axis activation significantly suppresses $CD8^+$ T cell proliferation and cytotoxic function, as evidenced by reduced granzyme B production [40]. Intriguingly, a study revealed that B cells (CD20+) and NK cells (CD16+/CD56+) may only be affected at higher doses of thymoglobulin [41]. ATLG shares fundamental mechanisms of action with ATG, although subtle differences in epitope recognition profiles may lead to variations in their clinical efficacy and side effect profiles (**Figure 1**).

Alemtuzumab is a recombinant DNA-derived humanized monoclonal antibody targeting CD-52, designed to deplete lymphocytes. Initially developed for chronic B-cell leukemia and multiple sclerosis, clinical trials have established its efficacy in preventing acute rejection following transplantation with a favorable safety profile and high graft survival rates [42, 43]. CD52 is a cell surface antigen highly expressed on T and B lymphocytes and at lower levels on NK cells, monocytes, dendritic cells, macrophages, and eosinophils [44]. Alemtuzumab exerts its immunosuppressive effect through complement-dependent cytotoxicity (CDC), ADCC, and the induction of lymphocyte apoptosis [42], leading to the depletion of T and B lymphocytes, NK cells, dendritic cells, and monocytes [45]. Furthermore, the expression of the surface molecule CD20 on B cells at various stages of differentiation makes it a highly specific target for monoclonal antibodies like rituximab [46]. The application of anti-CD20 monoclonal antibodies (e.g., rituximab) in immunosuppressive regimens has significantly improved the success rate of ABO-incompatible kidney transplants [47] (**Figure 2**).

Pharmacological management of opportunistic viral infections in organ transplant recipients: challenges and therapeutic strategies

The functional impacts and mechanisms of immunosuppressive agents on key immune cell populations have been extensively characterized. The seven principal classes of immunosuppressants exert their immunomodulatory effects via distinct pathways, targeting a broad spectrum of immune cells, including lymphocytes, neutrophils, and monocyte-macrophages. In the context of post-transplant immunosuppressive therapy, this systemic immune suppression compromises the host's antiviral defenses, leading to increased susceptibility to viral infections. Therefore, managing viral infections in transplant recipients requires a carefully balanced therapeutic strategy that controls viral replication while causing further immune impairment.

Pharmacological strategies for CMV infection treatment

CMV infection is one of the most prevalent and detrimental viral infections following organ transplantation. The pharmacotherapy for CMV primarily encompasses a range of antiviral agents, which are detailed as follows.

1) Ganciclovir (GCV) [48]: GCV is a nucleoside analogue that mimics guanosine and incorporates into the viral DNA chain, thereby terminating viral replication [49]. GCV is indicated for the treatment and prophylaxis of CMV disease, particularly in patients undergoing high-risk renal and cardiac transplantations. However, its clinical use poses certain challenges. First, its intravenous administration can be inconvenient for hospitalized patients and complicates outpatient treatment protocols. Besides, GCV may trigger side effects, most notably bone marrow suppression, which can manifest as a significant decrease in neutrophil counts and subsequently elevate the risk of infection. For patients with impaired renal function, careful dose adjustment of GCV is essential to mitigate the risk of toxicity.

2) Valganciclovir (VGCV) [50]: VGCV serves as the oral prodrug of GCV, which is converted into GCV after absorption in the body. It offers a more convenient oral administration route, particularly suitable for long-term prophylactic treatment or the management of mild to moderate active CMV disease. A study conducted among adult recipients of renal, hepatic, cardiac, and pulmonary transplants demonstrated that the long-term efficacy of oral VGCV is comparable to that of intravenous GCV in treating solid organ transplant recipients with CMV syndrome and tissue-invasive CMV disease [51]. However, high-dose oral GCV can be employed for prophylaxis and maintenance treatment of immunosuppressed transplant patients, yet the oral dosage is insufficient for treating active CMV disease [48]. Similar to GCV, VGCV also presents side effects such as bone marrow suppression.

3) Letermovir: This novel antiviral agent for CMV infection operates through a mechanism distinct from that of GCV, primarily by preventing the terminal stage of viral DNA cleavage and packaging. Letermovir provides a new therapeutic option for patients with drug-resistant or treatment-intolerant CMV infections.

4) Maribavir: Maribavir, an oral drug that inhibits the CMV UL97 protein kinase, is indicated for the treatment of drug-resistant or refractory CMV infections. It exhibits activity against CMV

both *in vitro* and *in vivo*, including strains resistant to ganciclovir, foscarnet, or cidofovir [52]. In transplant recipients with resistant/refractory CMV, Maribavir has been shown to be superior to GCV and VGCV in achieving CMV viremia clearance rate and symptom control rate post-treatment, resulting in a higher overall response rate [53].

Pharmacological treatment of EBV infection

EBV infection has been associated with the development of post-transplant lymphoproliferative disorders (PTLD), a potentially fatal complication. Although direct antiviral treatments against EBV have limited efficacy, the following strategies have shown benefits: 1) Acyclovir and Ganciclovir [54]: These drugs exhibit activity against EBV *in vitro* but have not demonstrated significant efficacy in the treatment of EBV-PTLD. They are primarily used as prophylactic measures for EBV infection, particularly to prevent primary infection in EBV seronegative organ transplant recipients. 2) Rituximab [55]: Rituximab is a monoclonal antibody that specifically targets CD20+ B cells and is utilized in the treatment of EBV-associated B cell PTLD. By selectively targeting B cells, Rituximab not only reduces the risk of PTLD development but also effectively treats early-stage cases of this disorder.

Pharmacological treatment of BK virus infection

BK virus is a common infection in transplant recipients, especially among renal transplant recipients. Currently, no FDA-approved antiviral therapies exist specifically for BK virus infection. Clinical management primarily focuses on the following approaches: 1) Adjustment of Immunosuppressive Dosage [56]: Reducing the dosage of immunosuppressive agents helps to restore the patient's immune system, thereby enhancing the defense against the BK virus. 2) Intravenous Immunoglobulin (IVIG) [56]: Although the precise mechanism of action remains to be fully elucidated, IVIG has been employed in some instances to treat BK virus-associated nephropathy, functioning as a means to augment the host's immune response. However, its high cost and inconsistent efficacy among individuals have constrained its broader application.

Emerging immunotherapeutic strategies for managing post-transplant viral infections: advances, mechanisms, and clinical challenges

Current clinical treatments for viral infections in solid organ transplant recipients are mainly non-immunotherapies, including antiviral drug therapy and chemotherapy. While these methods have demonstrated success, they also have limitations. In this respect, drugs like leflunomide (LFM) and preemptive therapy (PET) are effective at suppressing CMV reactivation with favorable safety profiles [57]. However, clinically significant late-onset CMV viremia develops in at least 30% of high-risk transplant recipients following treatment cessation [58]. This recurrence may be attributed to the emergence of CMV genetic mutations conferring resistance to LFM, underscoring the limitations of current antiviral strategies [59]. To address this, the management of other opportunistic viral infections in transplant recipients, including BK viremia and PTLD, has increasingly incorporated novel immunotherapeutic approaches. These clinical challenges collectively highlight the urgent need for immunotherapies capable of simultaneously preventing viral escape and maintaining graft tolerance.

Recent advances in immunotherapeutic strategies for viral infections have demonstrated promising clinical potential (**Table 3**). Current evidence suggests that active immunization, which includes treatments like cytokines [60] and vaccines [61], stimulates endogenous immune activation, resulting in both immediate antiviral effects and long-term immunological memory. In contrast, passive immunization provides immediate but transient protection. This approach bypasses the need for endogenous immune activation by administering pre-formed antiviral effectors such as neutralizing antibodies or immune globulins. Examples of passive immunization include adoptive T cell therapy [62], NK cell therapy, and IVIG therapy [63]. While these interventions are well established for treating common viral infections, their efficacy and safety in the context of post-transplant viral infections remain to be fully elucidated.

Immunity-related therapeutic approaches have the potential to overcome certain limitations associated with antiviral drugs, including toxic-

Table 3. Efficacy, safety, and limitations of current immunotherapies

Immunotherapy strategy	Representative product	Therapeutic effect	Safety	Limitations
Cytokine Therapy	IFN-α [120]	Control and eliminate of difficult-to-treat HEV infection	Risk of acute transplant rejection	High risk of rejection; Efficacy confirmed only in ribavirin-non-responsive patients
	IFN-λ [121]	Significantly reduces all markers of intrahepatic HDV infection	Based on animal models; no human safety data	Lack of clinical trial data in transplant recipients
Therapeutic vaccine	High-dose influenza vaccine and MF59 adjuvant influenza vaccine [122]	Triggers a stronger antibody response	Higher incidence of reactions compared to standard vaccine	No significant change in the incidence of influenza
	Recombinant Zoster Vaccine [123]	81% effectiveness in preventing herpes zoster	Frequent mild to moderate adverse reactions (e.g., pain, myalgia, fatigue)	A relatively high incidence of adverse reactions
	CpG adjuvant hepatitis B vaccine [124]	Good protective effect before transplantation	No obvious adverse reactions	Affected by the immunosuppressive state
Adoptive T Cell Therapy	CMV-specific T cells [125]	Significantly reduces the viral load and eliminate the virus	No adverse events occurred	Highly individualized; Persistent uncertainty
	EBV-specific cytotoxic T cells [126]	High objective response rate; Long-lasting virological and immunological control	Rare, mild, localized acute graft-versus-host disease (GVHD)	High cost; slow to take effect
	BK virus-specific T cells [96]	Clear viremia and stabilize the transplanted renal function	No adverse events occurred	Non-response in 20% of patients; Lack of large-scale data
Immunoglobulin Infusion	Cytomegalovirus Immune Globulin [127]	Low therapeutic effect; primarily for prevention	No obvious adverse reactions	High cost; limited efficacy against established/active viral infection

ity, drug-drug interactions, and the risk of treatment-emergent resistance. Among these immunotherapies, CAR-T cell therapy, vaccine infusion, and NK cell therapy hold huge promise as they can further reduce the risk of viral drug resistance by specifically targeting multiple antigenic epitopes.

The differences of CMV, EBV and BK viruses in immune responses

To better identify the most suitable immunotherapeutic approaches for different viral infections, it is essential first to understand the characteristics of the immune responses they elicit. CMV, a member of the betaherpesvirinae subfamily, is the most frequently encountered opportunistic pathogen, present in 20% to 60% of transplant recipients. Moreover, CMV is cell-associated, primarily establishing latency in T lymphocytes, though it can also be found in polymorphonuclear cells, vascular endothelial tissue, and epithelial cells [64]. This cell-associated nature enables viral transmission via the transplanted organ. CMV can significantly influence host immune responses. After infecting a cell, CMV produces immediate-early antigens that regulate DNA synthesis. Within the following 6 to 24 hours, the virus generates late antigens that direct nucleocapsid protein production. It also upregulates interleukin-2 (IL-2) and can counteract the inhibitory effect of cyclosporine on IL-2 gene expression. Additionally, CMV downregulates MHC class I molecules on infected cells to evade immune recognition by the host [65].

EBV, a gammaherpesvirus with a double-stranded DNA core, remains latent in lymphocytes after primary infection, similar to other herpes viruses. EBV can drive the replication and clonal expansion of B cells, which serve as its primary reservoir, as well as other cell types. However, an effective immune system, particularly T-cell responses, normally restricts the proliferation of these cells. In cases of impaired T-cell function, such as in renal transplant recipients, this surveillance mechanism may fail, leading to PTLD [66].

BK virus, a polyomavirus with a circular double-stranded DNA genome, was first described in a renal transplant patient with ureteral stenosis and is now recognized as a significant cause of

renal allograft dysfunction. The clinical course and treatment response in BK viral infection are largely influenced by the functional competence of virus-specific cellular immunity [67]. During early infection, when intragraft inflammation remains low, BK virus-specific T cells play a protective role. At this stage, modifying or reducing immunosuppression can facilitate recovery of cell-mediated antiviral immunity. However, in patients with persistent viral replication due to inadequate T-cell responses, sustained intragraft inflammation may develop. This inflammatory milieu can accelerate viral replication and promote infiltration of alloreactive cytotoxic T cells, further amplifying tissue inflammation. In such cases, reducing immunosuppression may be not only ineffective but also potentially harmful to the allograft [68].

Interferons

Cytokines currently used in clinical treatment for viral infections are primarily IFNs. Based on sequence homology, IFNs are divided into three families (Type I, II, and III), which can activate interferon-stimulated genes (ISGs) through multiple pathways to exert their antiviral activity, antitumor activity, and various immunomodulatory effects [60]. IFN-I plays a pivotal role in establishing cellular antiviral defenses by inducing uninfected cells to express antiviral proteins that effectively block viral entry, nucleic acid replication, and protein synthesis. Furthermore, IFN-I potentiates the activity of antigen-presenting cells, thereby enhancing T cell-mediated viral recognition and elimination. In parallel, IFN-γ primarily secreted by activated T cells and NK cells - exerts its immunomodulatory effects through two key mechanisms: (1) augmenting the phagocytic and bactericidal capacity of macrophages and (2) orchestrating the functional regulation of diverse immune cell populations.

Moreover, IFN treatment may exacerbate post-transplant immune responses, increasing the risk of rejection. For example, IFN-α may activate T cells and NK cells, leading to immune-mediated damage to the transplanted organ [69]. In addition, interferon therapy has been associated with significant adverse effects, including flu-like symptoms, bone marrow suppression, and the risk of triggering or aggravating autoimmune disorders, which substantially restrict its clinical use for treating viral infections in transplant recipients.

Viral vaccines

Vaccines represent a major tool for combating viral infections, including adenovirus vaccines, inactivated vaccines, and mRNA vaccines, etc. Indeed, selecting the optimal vaccine according to the characteristics of different viruses can often achieve good prevention or treatment effects [70]. From an epidemiological standpoint, vaccine technology for viral infections is well-established. By stimulating both antibody-mediated and cell-mediated immune responses, vaccines can induce long-lasting protection against viral attacks. In this respect, vaccines for Hepatitis B, yellow fever vaccines, and HPV have shown good preventive and therapeutic outcomes [71].

Although no vaccine is currently licensed for CMV prevention, several are being evaluated in clinical trials for their potential to prevent and treat CMV in solid organ transplant recipients. Several clinical studies have evaluated the recombinant glycoprotein B (gB) vaccine formulated with Novartis MF59 adjuvant [72-74]. The results demonstrated that the gB/MF59 vaccine could significantly increase the gB antibody titers in both seronegative and seropositive patients, shorten the duration of viremia, and thus reduce the use of antiviral drugs. The antibodies induced by the gB/MF59 vaccine could bind to the virus in the donor organ, thereby preventing the transmission of CMV to the recipient [74]. The MVA vector CMV vaccine (Triplex) is a modified Ankara cowpox (MVA) vaccine that encodes three full-length CMV antigens: pp65, IE1-exon4, and IE2-exon5 [75]. Research suggests that the antigen stimulation driven by the triple vaccine may enhance the recovery of the T cell compartment by increasing the production of naive T cells in the thymus [76]. In addition, clinical trials are currently underway for other vaccines such as ASP0113 [77] and PepVax [78]. As more vaccine strategies are clinically tested, the goal is to develop vaccines that offer both preventive and therapeutic effects against CMV.

The envelope proteins of EBV, including gH/gL, gB, and gp350, play a key role in the entry and infection of target cells by EBV [79, 80]. The

body's B cells produce neutralizing antibodies against these proteins, which can prevent EBV from infecting target cells and significantly reduce the virus's titer in the peripheral blood of humanized mice [81]. Recent studies have shown that a combination of serum containing EBV gH/gL and EBV gB antibodies can significantly enhance the synergistic neutralizing activity of EBV compared to either antibody alone [97]. Furthermore, clinical trials for therapeutic EBV vaccines are underway, primarily aiming to enhance preexisting antiviral adaptive immune responses or induce novel adaptive immunity in patients with EBV-associated malignancies [82]. These vaccines predominantly target EBNA1, LMP2, and/or LMP1, as these proteins regulate key factors driving normal cell transformation into tumor cells [83-85]. Incorporation of EBV envelope proteins (gH/gL, gB, and gp350) may further enhance the efficacy of these therapeutic vaccines [86].

Furthermore, vaccine safety must be rigorously assessed based on key immune parameters, including: (1) Antibody-mediated responses: serum neutralizing antibody titers and antigen-specific IgG levels; (2) Cellular immunity: magnitude and breadth of T-cell responses; (3) Durability of response: persistence of immune memory over time [75]. Live-attenuated and recombinant viral vector vaccines are generally contraindicated in transplant recipients due to the risk of disseminated infection or uncontrolled replication. Instead, safer vaccine platforms like subunit, mRNA, or inactivated platforms are preferred. An ideal vaccine for transplant recipients should combine a high safety profile with protection against primary infection and a therapeutic effect against preexisting or reactivated latent infection.

In summary, vaccines typically exert their ef fects by inducing immune responses against multiple pathogen targets, particularly through B cell-mediated humoral immunity [87]. However, many immunosuppressants interfere-with B cell proliferation, such as glucocorticoids, mTOR inhibitors, and metabolic disruptors, which may limit the efficacy of vaccines. Besides, immunocompromised populations require heightened vaccine safety profiles. For instance, recombinant adenoviral vaccines and live-attenuated vaccines are contraindicated in organ transplant recipients. Vaccines that combine sufficient safety with dual therapeutic and prophylactic capabilities remain to be developed.

Adoptive T cell therapy

Adoptive T cell therapy involves obtaining T cells from patients or healthy donors, culturing and modifying them *in vitro* to enhance their targeting and killing abilities, and reinfusing them back into the patient to control infection and rebuild immune responses. Modalities that directly target immune deficits, the underlying cause of CMV infections in transplantation, are promising tools for CMV prevention and treatment. Currently, CMV-specific T cell transfer has been widely studied and applied in hematopoietic stem cell transplantation (HSCT) patients [88], which can rebuild protective antiviral immunity and treat refractory CMV infection. In contrast, there is less research on solid organ transplant recipients, and patients are more likely to be treated with drug therapy first. However, accumulating evidence demonstrates that CMV-specific T cells confer protective immunity against infection, thereby enhancing post-transplant clinical outcomes [89]. Clinical results have demonstrated the efficacy of adoptive T cell therapy in controlling CMV infection while maintaining an excellent safety profile, with no significant treatment-related complications reported [90], indicating that patients have achieved stable immune reconstruction. Adoptive transfer of autologous, donor, or third-party virus-specific T cells (VSTs) represents an attractive concept for preventing and treating CMV infections in transplant recipients [91]. Several VST products have been used in non-randomized clinical trials for prevention and treatment of CMV infections in solid organ transplant recipients (SOTr) and hematopoietic cell transplant recipients (HCTr), and numerous VST products are under active investigation [92].

However, T cell therapy still faces difficulties and challenges. First, the immunosuppressive drugs that transplant recipients must take to prevent rejection may affect the overall efficacy of T cells [93]. The second major concern is the uncertainty of T cell durability in the recipient's body. The duration of T cells varies significantly among different patients, leading to uncertainty in their efficacy. The precise mechanisms governing this variability remain to be elucidated [94].

Similar to CMV, virus-specific T cell therapies have shown success in treating infections from other viruses, including EB virus [95], and BK virus [96]. Importantly, adoptive T cell therapy demonstrates significant potential for treating post-transplant viral infections. However, critical challenges remain regarding how to maintain T cell functionality and prolong survival in immunosuppressed environments. Further research is imperative to optimize these cellular therapies for clinical application.

Natural killer (NK) cell-based therapies

NK cells constitute 5-10% of circulating lymphocytes and mediate immune responses against cancerous and virally infected cells. Beyond conventional T-cell-mediated immunity, NK cells play a pivotal role in controlling viral infections in solid organ transplant (SOT) recipients via their innate cytotoxicity and cytokine production [97]. Previous studies on severe combined immune-deficient (SCID) or $Rag^{-/-}$ mice suggest that NK cells likely do not significantly contribute to the rejection of solid organ transplants. Despite the presence of functionally competent NK cells, these T cell- and B cell-deficient mice failed to mount a rejection response against skin allografts, suggesting that immunotherapeutic strategies leveraging NK cell activity could potentially offer an enhanced safety profile for controlling viral reactivation in the post-transplant setting [98]. Furthermore, current immunosuppressive regimens exhibit limited targeting of NK cell function. Among available agents, only glucocorticoids, mTORi, select metabolic inhibitors, and CNIs modulate NK cell activity, primarily through downregulation of CD16 expression and consequent impairment of ADCC. Current research indicates a potential involvement of activated NK cells in acute and chronic rejection of solid organ transplants [99]. The functional activity of NK cells is governed by a delicate balance of signals derived from numerous activating and inhibitory receptors. For instance, the efficacy of NK cells is significantly influenced by the interaction between killer immunoglobulin-like receptors (KIRs) and human leukocyte antigen (HLA) class I molecules [100]. KIR-HLA mismatching, particularly the absence of HLA ligands for inhibitory KIRs, enhances NK cell activation and antiviral activity. Studies in both animals and humans suggest that NK cells are critical in the host defense against EBV. *In vitro* studies have shown that autologous NK cells can kill EBV-infected B cells [101]. The adoptive transfer of allogeneic NK cells from KIR-mismatched donors may offer a potential therapeutic benefit for controlling EBV reactivation in transplant recipients, though its efficacy and safety require further validation in clinical studies.

Furthermore, cytokine-induced memory-like (CIML) NK cells, preactivated with IL-12, IL-15, and IL-18, exhibit enhanced antiviral responses and persistence upon reinfection [102]. CMV infection reshapes the NK cell receptor landscape, driving the expansion and long-term maintenance of memory-like $NKG2C^{+}KIR^{+}$ NK cells [103]. A recent cohort study indicated that KIR genes can affect CMV infection and provide potential clinical value following liver transplantation [104]. These advances highlight NK cell therapy as a strategy to bridge the gap between immunosuppression and antiviral defense, offering a graft-friendly alternative by leveraging innate immunity without exacerbating alloreactivity.

Immunoglobulin infusion

In the management of post-transplant viral infections, combination therapy with immunoglobulins and antiviral drugs often demonstrates superior prophylactic and therapeutic efficacy. For instance, CMV immunoglobulin (CMVIG) neutralizes viral particles before they reach host cells, while antiviral drugs inhibit viral DNA polymerase to block intracellular replication. High-dose immunoglobulins derived from healthy donors exhibit an excellent safety profile. Studies have shown that CMVIG monotherapy or combination regimens significantly reduce mortality and graft loss in heart/lung transplant recipients [105]. However, due to limited data, this therapy is primarily used for prevention or as an adjunctive treatment. The American Transplant Society guidelines do not recommend CMVIG for prophylaxis in kidney/liver transplants. Further clinical trials are needed to establish its therapeutic value [106].

Conclusion and future perspectives

The feasibility of organ transplantation was first established through surgical advances [1]. The subsequent development of immunomodulatory drugs targeting both innate and adaptive immune responses has significantly improved

the success of non-HLA-identical solid organ transplantation and the management of autoimmune diseases, effectively addressing the historical limitations imposed by the absence of effective anti-rejection therapies [2].

Various types of immunosuppressants regulate autoimmunity by acting at different levels of the immune response, including the innate immune level, where DCs, macrophages, and NK cells play a role, and the adaptive immune level, where T cells and B cells are involved. CNIs primarily inhibit their activity by binding to calmodulin, preventing the transcription of proinflammatory cytokines such as interleukins, thereby inhibiting T cell activation [107]. An increasing body of evidence suggests that mTORi prevent the proliferation and differentiation of immune cells such as T cells, B cells, and NK cells by blocking the cell cycle from the G1 phase to the S phase [15-17]. Costimulation inhibitors have a high affinity for B7-1 on antigen-presenting cells, leading to a reduced T cell response to specific antigens [20]. IL-2 receptor antagonists mainly act by blocking T cell clone expansion dependent on IL-2 [108]. GCs act on the glucocorticoid receptor, affecting various levels of immune response through genomic and non-genomic mechanisms [25]. Metabolite-disrupting drugs exert immunosuppressive effects by hindering DNA synthesis, interfering with the differentiation of CD4+ T lymphocytes and the development of B lymphocytes [35]. Moreover, lymphocyte-depleting antibody drugs primarily exert immunosuppressive effects by causing severe depletion of T and B lymphocytes, NK cells, dendritic cells, and monocytes [45].

While immunosuppressive therapy has made organ transplantation the standard treatment for end-stage organ failure, it comes with substantial adverse effects. The primary concern is a significantly increased risk of opportunistic viral infections. In solid organ transplant recipients, the most clinically significant viruses include CMV, EBV, and BK virus, which collectively contribute to a considerable burden of post-transplant morbidity. Although the rate of viral infections after solid organ transplantation varies across different countries and regions, CMV [3, 4, 109] and EBV generally have a higher infection rate [110-113].

In this context, the prevention and treatment of viral infections after organ transplantation are crucial. The current clinical treatments for viral infections after solid organ transplantation mainly include antiviral drug therapy and chemotherapy, which are non-immunological approaches. For CMV, which has a high infection rate in clinical practice, GCV [48] and its oral prodrug VGCV [50] are currently used as first-line therapies for prevention and treatment. Maribavir has also shown promising results in the treatment of resistant/refractory CMV infection [52]. LMV and PET have demonstrated effective suppression of CMV reactivation with a favorable safety profile [57]. However, these pharmacological treatments still present notable limitations. Following drug discontinuation, there remains a significant risk of late-onset CMV viremia. These clinical challenges underscore the urgent need for immunotherapeutic strategies that can concurrently prevent viral escape and sustain graft tolerance.

The past few years have witnessed burgeoning interest in developing immunological therapies for viral infections, such as interferons [60] and vaccines [61] that exert antiviral effects through active immunization pathways, and adoptive T cell therapy [62] and IVIG therapy [63] that directly kill viruses. Among them, clinical trials of vaccines and research on adoptive T cell therapy are areas of considerable interest. Vaccines often induce immune responses against multiple targets of pathogens, especially humoral immunity, where B cells play a major role [87]. However, the use of many immunosuppressants affects B cell proliferation, such as glucocorticoids, mTORi, and metabolite-disrupting drugs, which may limit the effectiveness of vaccines. In addition, individuals with compromised immunity have high demands for vaccine safety. Despite its therapeutic potential, adoptive T cell therapy confronts several critical challenges. First of all, the overall efficacy of T cells is also affected by immunosuppressants [93]. Moreover, the durability of T cells in the recipient's body varies from person to person [94]. Indeed, further research is warranted to overcome immunosuppressive barriers to ensure durable T cell persistence and functional competence.

In summary, while viral infections following organ transplantation have garnered significant attention, current clinical treatment methods still exhibit certain limitations. Emerging immunotherapeutic strategies show significant promise for improving long-term outcomes in

transplant recipients. Notably, the development of dual-purpose vaccine platforms that confer concurrent therapeutic and prophylactic efficacy while maintaining rigorous safety profiles represents a critical research priority. Equally critical are advancements in adoptive T cell therapies capable of retaining functional efficacy within immunosuppressive microenvironments and achieving prolonged persistence through optimized cellular kinetics in clinical settings, thereby maximizing their therapeutic potential while optimizing treatment durability. Furthermore, current immunosuppressive regimens exhibit limited targeting of NK cell function, primarily through downregulation of CD16 expression and consequent impairment of ADCC. Notably, NK cells play a critical role in innate immunity by recognizing and eliminating infected cells exhibiting MHC class I downregulation, a process enhanced by cytokines such as IFN-γ [114]. These unique immunological properties suggest that adoptive NK cell therapy may represent a promising novel approach for managing post-transplant viral infections.

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None.

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