DOI: 10.15825/1995-1191-2025-1-23-31

ADVERSE EFFECTS OF IMMUNOSUPPRESSIVE THERAPY AFTER KIDNEY TRANSPLANT

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This paper reviews the sources and generality of knowledge regarding the adverse effects of immunosuppressive therapy, which play an important role in the full functioning of a transplant. The article regarding the importance of the dynamic impact of immunosuppressant medications on transplant function and the need for reasonable regimen and dosage selection of individual drugs or their combination to minimize adverse effects.

Keywords: immunosuppression, immunosuppressive agents, kidney transplantation, nephrotoxic side effects.

Kidney disease has affected humans since time immemorial, but it is only in the last four decades that the actual incidence has been documented and identified as a global health problem [1]. Chronic kidney disease is an important public health problem that places a significant burden on patients, their families and health care systems [2]. Kidney transplantation (KT) is the preferred treatment for end-stage renal disease. Improvements in surgical techniques and immunotherapy have changed the field of KT. The 1-year and 5-year survival rates of KT patients are 95% and 90%, respectively [3]. KT provides better survival compared to dialysis but does not fully improve quality of life. The overall risk of death in transplant recipients is at least three times higher than in the general population, and transplant recipients have a significantly reduced quality of life even compared to patients with other chronic diseases. Strategies such as optimization of selection, cross-matching and surgical techniques, improved perioperative care, effective antiviral, antifungal and antibacterial therapy and chronic immunosuppression have led to improved patient outcomes and increased allograft survival over the past decades.

The first successful human kidney transplant was performed in 1954 by Dr. Joseph Murray between two genetically identical twins. Decades later, KT has become the standard care for patients with renal failure. Maintaining graft preservation requires immunosuppressive therapy (IST) or immune tolerance in genetically different individuals. To date, an understanding of immunological principles has been critical to successful management of KT patients [4].

After transplantation, a whole cascade of immune reactions of nonspecific (phagocytosis and cytokine release) and specific type (provided by T-cell and B-humoral immunity) occurs in the recipient's body. Antigen-specific response is activated by a huge number of potentially foreign antigens of the donor, including human leukocyte antigens (HLA) [5, 6] and the ABO system. Ischemia and reperfusion of the donor kidney are major factors in the development of graft injury, causing endothelial damage, free radical formation and induction of apoptosis, which is described as ischemia/reperfusion injury (IRI). Damage-associated molecular patterns (DAMPs), released from damaged or dying cells, are endogenous danger signals that activate the innate immune system, leading to inflammation and the release of anti-inflammatory cytokines like tumor necrosis factor, type I interferons, chemokines, and interleukins (IL-1 and IL-6) [7, 8].

Allograft rejection is tissue damage caused by effector mechanisms of the alloimmune response, resulting in impaired graft function. There are two main types of rejection: T cell (or cellular rejection) and antibody-mediated rejection. Both types of rejection may be early or late, fulminant or sluggish, isolated or concomitant, and may share pathomorphological features on biopsy [9]. Kidney allograft biopsies are graded according to the Banff classification, which helps clinicians to manage various allograft pathologies [10].

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The success of KT is largely due to advances in IST used in the induction and maintenance phases, as well as for the treatment of acute rejection [4]. There are so many foreign and domestic reports indicating the most common and serious complications of chronic IST in recipients, such as infectious diseases [11], malignant tumors, hypertension, leukopenia and thrombocytopenia, and others.

Cancer and infection appear to be the two most dangerous complications of immunosuppression and are often key research priorities for patients and clinicians [12]. To date, the risks of atypical infections and cancer remain high [13]. The cumulative incidence of *de novo* cancer (incidence of new cancer cases) 10 years after KT is about 40%, increasing to 60% after 20 years. The risk of cancer-related death in kidney transplant recipients is three times higher than in patients with cancer in the general population [14].

Infections are also a serious problem and the leading causes of early posttransplant death (within the first 12 months after transplantation), especially in low- and middle-income countries where prophylactic treatments for viral and bacterial infections are not available to all. The timing, severity and etiology of infections in recipients depend on the individual's state of immunosuppression [15]. To date, there are just few studies describing the adverse effects of immunosuppression directly on the kidneys.

The ***aim*** of our work is to study the sources and summarize the information on the adverse effects of immunosuppression, which play an important role in the full functioning of the transplant.

Currently, the main groups of immunosuppression drugs for KT patients are calcineurin inhibitors (cyclosporine A and tacrolimus), mycophenolates, mammalian target of rapamycin (mTOR) inhibitors, corticosteroids, azathioprine, and biologic polyclonal and monoclonal antibody preparations [4, 16–19].

IST protocols differ significantly in the immediate and late posttransplant periods. There are different protocols for initial and maintenance immunosuppression, variable in the number of drugs used (quadruple, triple and double) and their dosage [20–23].

A six-month randomized trial conducted across 47 European countries demonstrated that modern immunosuppressive regimens significantly reduce the incidence of acute rejection in KT recipients. This is achieved by combining calcineurin inhibitors (CNI) such as tacrolimus or cyclosporine with additional immunosuppressive agents like corticosteroids, mycophenolate mofetil (MMF), or azathioprine [24].

Glucocorticoids (GCS) have been a cornerstone in transplant immunosuppression for decades. Despite their numerous side effects, they remain widely used, particularly in pregnant transplant recipients, although there have been reports of fetal adrenal suppression. Among the abundance of widely known side effects of GCS, this report focuses on renal effects. Among them are known disorders of the hypothalamic-pituitary-adrenal (HPA) axis and the renin-angiotensin-aldosterone (RAAS) system – arterial hypertension, hypokalemia, increased glomerular filtration rate (GFR), sodium retention and diuretic resistance [25]. The advantage of using GCS is that their use is not associated with increased cancer risk. Most transplant centers advocate low maintenance doses, since it has been shown that early GCS withdrawal was associated with an increased risk of graft loss, especially in sensitized patients [26].

CNIs – cyclosporine A and tacrolimus – are fat-soluble small molecules derived from fungi (mycotoxins) and serve as the foundation of maintenance immunosuppression in organ transplantation [27]. The drugs selectively inhibit immune response by specifically targeting helper T cells, without affecting other immune cell functions, such as neutrophil phagocytosis or bone marrow activity. Target cells are inhibited but not killed (hence, the effects are reversible when treatment is discontinued). Administration of CNIs – cyclosporin A and later tacrolimus – in the mid-1980s significantly improved short-term kidney graft survival by reducing the incidence of acute rejection, but chronic nephrotoxicity was responsible for the decline in graft function [28]. Cyclosporin A and tacrolimus have similarities and differences in toxicity. But the most common and unpleasant problem with CNIs is nephrotoxicity [29]. Both drugs are nephrotoxic, cause hyperkalemia, hyperuricemia, hypomagnesemia and hypophosphatemia (secondary to urine loss), type 4 renal tubular acidosis, and diuretic resistance.

CNI nephrotoxicity is a result of both reversible hemodynamic effects and irreversible structural damage. Cyclosporin A causes thrombotic microangiopathic vasculitis and intrarenal vasoconstriction. Reversible vasoconstriction is caused by direct vascular effects and activation of the renin-angiotensin system, endothelin, thromboxane, and the sympathetic nervous system. Over time, chronic renal injury, characterized by afferent arterial hyalinosis and tubulointerstitial fibrosis, occurs, presumably as a result of prolonged renal vasoconstriction with ischemia and direct tubular toxicity. In fewer cases, CNIs can cause thrombotic microangiopathy (TMA) leading to direct endothelial cell damage and dysfunction [30].

CNI nephrotoxicity affects all histologic sections of the transplanted kidney. Although not specific for CNI toxicity, lesions include medial arteriolar hyalinosis, interstitial fibrosis, global glomerulosclerosis, and tubular microcalcification unrelated to other causes such as tubular necrosis and hyperparathyroidism. CNI-induced arteriolopathy is characterized by nodular hyaline deposits in afferent arterioles sufficient to cause luminal narrowing. Renal arteriolar hyalinosis is the most reliable diagnostic marker of CNI nephrotoxicity. The diagnosis is valida-

ted by excluding other causes such as donor hyalinosis (which can be detected on a biopsy specimen), diabetes mellitus, and hypertensive nephrosis [4, 30].

MMF is a prodrug of mycophenolic acid (MPA), an inosine monophosphate dehydrogenase inhibitor and provide lymphocyte-specific immunosuppression. MMF or enteric-coated mycophenolate sodium (EC-MPS) are potential components of immunosuppression regimens, and are associated with the most successful outcomes in kidney transplantation [31]. MMF is by far the most commonly used immunosuppressive agent in transplantology, primarily due to its high efficacy and relatively acceptable side effect profile. It is usually used in combination with CNIs. This group of drugs is not nephrotoxic (as does azathioprine), but has gastrointestinal toxicity, suppresses bone marrow function and increases the risk of infections, especially those of a viral nature [32].

mTOR inhibitors (sirolimus and everolimus) work by inhibiting lymphocyte proliferation and differentiation. Although they were originally used in drug regimens to minimize exposure to CNIs with their known side effects, mTOR inhibitors have been associated with their own set of toxic properties that have prevented their widespread use. A 2011 study comparing everolimus (EVR) and mycophenolic acid (MPA/MMF) in kidney transplant recipients did not show a clear superiority of EVR over MMF in terms of mean estimated GFR at 12 months when both were used in combination with similar doses of tacrolimus or cyclosporine A [33]. Many studies using mTOR inhibitors instead of CNIs have found a higher risk of renal allograft rejection with variable improvement in kidney function [34, 35]. Studies have shown that EVR with reduced-exposure CNIs has comparable efficacy to MPA/MMF with standard CNI exposure in KT recipients who have low to moderate immunologic risk [36]. EVR in combination with reduced-exposure CNI and low-dose steroids is an appropriate regimen for preventing kidney graft rejection in most adult patients with low to moderate immunologic risk when managed individually [37].

Although mTOR inhibitors are not inherently nephrotoxic, they cause renal graft injury by several mechanisms. When used in combination with a standard dose of cyclosporin A (and probably tacrolimus), sirolimus potentiates CNI-induced nephrotoxicity [36]. In patients with renal impairment, sirolimus is associated with marked but potentially reversible proteinuria and worsening of pre-existing proteinuria. Sirolimus may also cause delayed recovery from acute tubular necrosis and may be associated with podocyte injury, focal segmental glomerulosclerosis.

Finally, cases of thrombotic microangiopathy have been reported, and there is concern that higher doses of sirolimus may inhibit endothelial cell growth. Interestingly, sirolimus-based treatment regimens have been associated with a reduced incidence of post-transplant malignancies. Sirolimus is often considered the preferred immunosuppressant in post-transplant patients who develop malignancy because mTOR inhibitors have been shown to reduce the risk of malignancy [37, 38]. However, most data are limited to KT recipients with squamous cell carcinoma of the skin. When mTOR inhibitors (sirolimus, everolimus) are used together with CNIs (calcium inhibitors), there is a risk of synergistic nephrotoxicity and other complications, including delayed recovery from acute tubular necrosis, proteinuria, hypokalemia, and hypertension.

Biological agents in the form of polyclonal antibodies and monoclonal antibodies (mAb) are often used in KT, either as induction therapy or to treat rejection. Polyclonal anti-lymphocytic agents are produced by immunizing animals with human thymic lymphoid cells; they bind to numerous elements on the surface of T cells and induce rapid lymphocytopenia by several mechanisms including complement-dependent cytolysis, cell-dependent phagocytosis, and apoptosis. Alemtuzumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody directed against human CD52, a glycoprotein found in circulating T and B cells, monocytes, macrophages, natural killer cells and granulocytes. Anti-CD25 monoclonal antibodies: the alpha subunit of the IL-2 receptor (CD25) is activated by T cells and leads to the expression of highly sensitive interleukin-2 (IL-2) receptors. Basiliximab is a CD25-specific chimeric monoclonal antibody (mAb) drug; it causes relatively mild immunosuppression and is used as an inducer to prevent rejection but not to treat established rejection. Rituximab (a monoclonal antibody that attaches to CD20, a protein on the surface of B cells, to destroy them) is an engineered chimeric mAb that contains murine variegated heavy and light chain regions and is directed against human IgG1 CD20. Rituximab is used as induction therapy after desensitization therapy for ABO blood group incompatibility and cross-over kidney transplantation. A study of the pharmacokinetics and pharmacodynamics of obinutuzumab, a novel type II, humanized, CD20 mA, in highly sensitized patients with kidney failure, demonstrated good tolerability and effective B cell depletion [16, 19]. However, its effect on reducing HLA alloantibody levels was inconsistent and not clinically significant [39]. No reports of adverse effects of biotechnological drugs on the kidneys were found in available literature. We do not dwell on the side effects of azathioprine because it is now rarely used and there is no reported nephrotoxicity.

Costimulation blockade therapy is an alternative to immunosuppression for KT recipients. Belatacept, a first-in-class co-stimulation blocker, is a fusion protein that binds to CD80 and CD86 to prevent T cell activation and proliferation. The drug primarily affects the CD28 costimulation pathway, preventing T cell activation. On renal biopsy, belatacept has been shown to improve renal function in patients with chronic vascular lesions [40]. As

early as 2003, a retrospective study of a scientific registry of transplant recipients was conducted comparing the outcomes of treatment with belatacept and tacrolimus. This study found no No significant difference in long-term graft survival between belatacept and tacrolimus, but belatacept was associated with better renal function, despite belatacept-treated patients having a higher incidence of acute rejection [41]. Recent studies have shown that belatacept attenuated acute rejection and increased graft survival. The drug may be a good alternative to CNI-based regimens after KT [42–45]. Nevertheless, there is evidence that low-dose tacrolimus maintenance therapy is often necessary when switching to belatacept early after transplantation, especially in steroid-free regimens, to reduce the risk of acute rejection [46].

Costimulators are still being investigated (CD28 receptor T cells in particular are of interest) [47]. Abatacept is another co-stimulator with proven efficacy [48]. Studies initiated several years ago indicated a potentially high efficacy of the drug [49]. Specifically, there has been a case series of 9 kidney transplant recipients who were switched to abatacept as an emergency immunosuppressive therapy due to CNI intolerance when belatacept was unavailable. A retrospective review reported successful allograft recovery and 100% patient and graft survival (median follow-up: 115 months) in kidney transplant recipients who were switched to abatacept. Patients who switched to abatacept had stable long-term renal function (median 82 months on abatacept). Further studies, conducted for the first time in a large patient cohort, showed that once-weekly abatacept administration is feasible and safe for post-KT patients previously receiving belatacept (and the efficacy is comparable) [50].

BK virus-associated nephropathy (BKVN) should be considered as a renal side effect of immunosuppressants. It was first reported in 1995 and is now considered an important cause of kidney graft loss. BK virus (also known as human polyomavirus 1) is a virus with double-stranded DNA that affects 75% of the general population. Primary infection with the virus occurs during childhood, resulting in an indeterminate flu-like illness. The route of transmission varies. The BK virus (BKV) then persists in the urinary tract. The disease is more severe in immunocompromised individuals, especially in KT recipients, due to the effects of immunosuppressants. In KT recipients, BKV disease has a wide range of manifestations, including ureteral stenosis, temporary graft dysfunction, or irreversible allograft failure secondary to BKVN. BKVN was first recognized as a significant cause of kidney allograft dysfunction in KT recipients approximately two decades ago. It presents as progressive deterioration of graft function, associated with histologically distinct allograft infection with BKV [51]. This lesion has been detected in about 8% of KT patients [52], and the incidence is increasing with better diagnostic capabilities, such as detection of decoy cells in urine sediment and polymerase chain reaction (PCR) tests. This may also be partly a result of the use of more potent immunosuppressants and increased awareness and improved diagnostic tools [53]. Definitive diagnosis of BKVN requires allograft biopsy. BKVN in biopsy specimens manifests as intranuclear inclusions in tubular epithelial cells with enlarged nuclei.

Continued viral replication leads to an associated inflammatory response with fibrosis and eventually tubular atrophy. Infected cells are excreted in the urine. Quantitative PCR for BKVN DNA in serum is the most commonly used non-invasive test that has a sensitivity of 100% and a specificity of 88% [52]. Antiviral treatment with cidofovir may be effective, but it is potentially nephrotoxic and the benefit/harm ratio has not yet been evaluated in randomized trials. It is believed that everolimus-treated patients had a lower rate of BKV infection [54].

Immunosuppression in pediatric KT patients is more complex, and treatment regimens based on MMF in combination with low-dose CNIs and corticosteroids are preferred. In KT recipients with chronic allograft dysfunction and excessive immunosuppression leading to recurrent infections, MMF and corticosteroids represent the most appropriate therapy option. Studies have shown that CNI-based immunosuppressive regimens, when combined with MMF and corticosteroids, more than 90% of all renal grafts are functional at 1 year, with 77% and 56% at 5 and 10 years, respectively [29].

Attention should be paid to the choice of therapy in the older age group of patients: the relationship between pharmacokinetics and immunological reactivity in elderly and senile patients should be taken into account when administering IST [55, 56].

Urine biomarkers have emerged as a non-invasive and promising strategy for monitoring kidney allograft status post-transplant. Since urine can be obtained non-invasively and, in the case of KT, its production is closely related to the function of the target organ. However, biomarkers related to immune function/hypoxia/ferroptosis/epithelial-mesenchymal transformation are of much greater interest in predicting allograft rejection. Five diagnostic genes were identified, including CCR5, CD86, CD8A, ITGAM and PTPRC, which positively correlated with allograft rejection after KT [57].

DISCUSSION

Over the past 40 years, immunosuppressive agents have facilitated the development of allogeneic transplantation, which has significantly improved graft survival. However, several problems remain, such as nephrotoxicity (especially CNIs, which are the mainstay of immunosuppressive regimens), and/or increased risk of opportunistic infections and cancer. Most immunosuppressants target T cell activation and may not be effective enough to prevent alloimmunization in the long

term. Many drugs have been tested in the last decade, but very few have found clinical use. The most recent of these is CTLA4-Ig (belatacept), a costimulation blocking molecule that targets a second T cell activation signal and is associated with improved kidney function in the long term compared to CNIs, and abatacept, which has shown comparable efficacy to belatacept. Importantly, these drugs have no nephrotoxic properties and can even improve graft function in the long term. Studies of new long-acting immunosuppressive agents are aimed at costimulation blocking. Agents that inhibit CD40-CD40-ligand interactions may provide good control of both T cell and B cell responses. Anti-CD28 antibodies can stimulate regulatory T cells. Drugs targeting these costimulation pathways are being evaluated in clinical trials. New drugs targeting antibody (imlifidase), B cell and plasmablast depletion (anti-IL-6/IL-6R, anti-CD38) and complement inhibition are being developed, but their evaluation is still an unresolved challenge.

Monitoring of ongoing IST to prevent undesirable effects due to cumulation, polyprogmasy, pharmacokinetic interactions, will help patients from different age groups to better tolerate treatment regimens. A dynamic urine clinical and biochemical study (sediment, leukocyte count, trapped cells, microalbuminuria, protein-creatinine ratio, and AKI/CKD biomarkers) will make this therapy more traceable and safer.

Thus, summarizing the above, IST today is necessary, and it is worth emphasizing the importance of the dynamic effect of IST on transplant function, the need for a reasonable selection of the scheme and dosage of a particular drug or combination of drugs to minimize nephrotoxic effects, the need to monitor the functions of the transplanted kidney in during postoperative patient care.

The authors declare no conflict of interest.

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The article was submitted to the journal on 13.03.2024