Review

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Adverse Drug Events after Kidney Transplantation

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Abstract: *Introduction:* Kidney transplantation is the best option to treat end-stage kidney diseases. However, so far, tolerance has not been achievable. Therefore, patients need to take lifelong immunosuppressive therapies that rely on calcineurin inhibitors (mostly tacrolimus), in association with either mycophenolic acid or mTOR inhibitors, with or without steroids. *Area covered*: These drugs, particularly calcineurin inhibitors, have very narrow therapeutic windows, i.e., they have numerous drug-related side effects. Herein, we focus on the most frequent immunosuppressive drug-related side effects that we encounter in kidney-transplant recipients: namely nephrotoxicity, post-transplant diabetes mellitus, leukopenia, anemia, dyslipidemia, mouth ulcers, hypertension, and viral reactivations (cytomegalovirus and BK virus). However, other therapies that are used after kidney transplantation, e.g., valcancyclovir, may also contribute to adverse events such as leukopenia. For each side-effect, we suggest how it can be prevented and how to treat it when present.

Keywords: kidney transplantation; immunosuppression; adverse drug event; nephrotoxicity; NODAT; anemia; leukopenia; viral reactivation; hypertension; dyslipidemia

1. Introduction

Currently, worldwide, there is a huge burden of end-stage kidney disease (ESKD): the major causes are related to type 2 diabetes, obesity, and hypertension (1, 2). However, there are geographical variations globally. and its incidence and prevalence is increasing world-wide. ESKD is the ultimate stage of chronic kidney disease (CKD), In 2017, the global prevalence of CKD was 9.1%, which corresponds to roughly 700 million cases. Compared with other risk factors, reduced glomerular filtration rate (GFR) is an independent risk factor for cardiovascular disease and overall mortality. CKD was the 12th leading cause of death globally in 2017, representing an increase from 17th place in 1990 (3). ESKD needs to be treated with renal-replacement therapies (RRT), with dialysis being the most prevalent approach (2). Other RRT modalities include conservative care (3) and kidney transplantation (4). Indeed, kidney transplantation is the ideal treatment for patients with ESKD as there is a clear reduction in mortality to receiving a transplant regardless of co-morbidities and age. Thus, the gold standard of care should focus on attaining kidney transplantation and minimizing the need for dialysis. However, because as yet there is no means to achieve immunological tolerance after kidney transplantation, life-long immunosuppressive therapy is mandatory. The cornerstone of immunosuppression is based on calcineurin inhibitors, namely cyclosporine A (CsA) and tacrolimus. Currently, CsA is now rarely given to de novo kidney-transplant recipients because one of its major side effects is nephrotoxicity (5) even though tacrolimus is also, but to a lesser extent nephrotoxic (6). Maintenance immunosuppression in kidney transplantation relies, in most patients, on the calcineurin inhibitor tacrolimus as the primary agent in combination with mycophenolate, with or without corticosteroids (7). A tacrolimus trough target of 5-8 ng/mL seems to be optimal for anti-rejection prophylaxis, but long-term tacrolimus-related side effects and nephrotoxicity support the ongoing evaluation of non-calcineurin inhibitor-based

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regimens, such as belatacept (8). In some patients at risk or already experiencing post-transplant de novo cancers, mycophenolate can be replaced by mTOR inhibitors, such as sirolimus or everolimus (9).

Because immunosuppressive drugs have narrow therapeutic windows this can lead to many side-effects, some of which can be attributed to a single agent, whereas others are most likely attributed to a combination of drugs.

In this review, we will not address all the potential side-effects of immunosuppressive drugs but will focus on those that are of critical importance with regards to a patient's management and their quality of life. We will focus on nephrotoxicity, new-onset diabetes after transplantation (NODAT)/post-transplant diabetes mellitus (PTDM), leucopenia, anemia, dyslipidemia, mouth ulcers, hypertension, and viral reactivations.

Nephrotoxicity

Tacrolimus nephrotoxicity was the focus of a longitudinal clinical study performed by Nankivell et al. (10), which included 119 kidney--pancreas-transplant recipients. Sequential kidney biopsies over the first 10 years post-transplantation were performed. Using previously defined tacrolimus-related lesions (11) (striped cortical fibrosis or new-onset arteriolar hyalinosis associated with tubular microcalcification), the authors showed that tacrolimus-related lesions developed in 76.4% of the patients after 1 year, 93.5% after 5 years, and 96.8% after 10 years. The authors suggest early immune-mediated lesions followed by chronic calcineurin-inhibitor nephrotoxicity translated into the deterioration of kidney function/survival beyond 1-year post-transplantation.

This was further investigated by the same authors in 2016 (12) in a larger cohort of 200 kidney—pancreas-transplant recipients. Pre-existing arteriolar hyalinosis was an exclusion criterion. Patients that received cyclosporine or tacrolimus were included in order to make comparisons between the two calcineurin inhibitors. The mean tacrolimus trough concentration was 9.4 µg/L. Overall, tacrolimus induced less frequent calcineurin-inhibitor nephrotoxicity, but arteriolar hyalinosis remained significantly associated with tacrolimus exposure.

Naesens et al. (13) provided an overview of CNI nephrotoxicity, with a more detailed explanation of the intrinsic mechanistic effects of tacrolimus in the kidney (all four sectors of the kidney, i.e., glomerulus, tubules, interstitium, vessels). They suggested that local exposure to cyclosporine or tacrolimus could be more important than systemic exposure. In addition, there are other local susceptibility factors for calcineurin-inhibitor nephrotoxicity, such as variability in P-glycoprotein and CYP3A4/5 expression, or activity, older kidney age, salt depletion, the use of nonsteroidal anti-inflammatory drugs, and genetic polymorphisms in genes, like TGF-beta and angiotensin-converting enzyme (ACE).

CNI-related nephrotoxicity can be either acute (and therefore reversible) or chronic, i.e., lasting for more than 3 months and can lead to irreversible kidney injury with eventual ESKD. Regarding tacrolimus therapy, due to its very narrow therapeutic window, early post-transplant tacrolimus-related nephrotoxicity can be partially avoided by using an induction therapy, i.e., either basiliximab or antithymocyte globulins to achieve lower tacrolimus trough levels, but that can still prevent acute rejection (14, 15), or by using algorithms to predict the desirable trough levels (16, 17). Another option is to minimize tacrolimus exposure (18) by replacing mycophenolate with everolimus, as was done in the TRANSFORM study (19). Finally, should chronic tacrolimus-related nephrotoxicity occur, as seen on a kidney-allograft biopsy using the Banf classification (20)), tacrolimus could be easily replaced with belatacept. This is a safe conversion as shown recently in a phase-3 trial (21).

Post-transplant diabetes mellitus (PTDM) or new-onset diabetes (NODAT) does not occur in all kidney-transplant recipients. Risk factors for PTDM have been classified as modifiable and non-modifiable (22, 23). Amongst non-modifiable factors are age, i.e., aged >40 years, and the likelihood of getting PTDM increases as beta-cell function becomes reduced, leading to insulin resistance. Patients with numerous predisposing single-nucleotide polymorphisms (SNP), like transcription factor 7-like 2 (TCF7L2), the protein-encoding gene potassium inwardly-rectifying channel subfamily J member 11 (KCNJ11), lipid-gated inward rectifier potassium ion channel (Kir6.2) (which is a major

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subunit of the adenosine triphosphate-sensitive potassium channel), interleukin (IL), and nuclear factor of the activated T-cell isoform c4 (NFATc4) are more likely to develop PTDM (24). Polymorphisms in the hepatocyte nuclear factor-4-alpha (HNF-4A) and insulin receptor substrate-1 genes have been linked to the development of PTDM in Hispanic renal-allograft recipients (25). The human leukocyte antigen (HLA) genotype either plays no role in PTDM or this is still unknown (26). In addition, a family history of diabetes mellitus is identified as a risk factor for PTDM. Recently, a meta-analysis of patients with autosomal dominant polycystic kidney disease indicated that those with the disease have a higher risk of developing PTDM than those who do not (27). According to a comparative case-control study, people of South Asian ancestry had a higher chance of PTDM than white people (28).

Modifiable factors include significant pre-transplantation risk factors such as body mass index (BMI) >30, metabolic syndrome, chronic hepatitis C virus infection, prediabetes, and occult diabetes. Post-transplantation risk factors include immunosuppressant drugs like corticosteroids and tacrolimus, and to a lesser extent cyclosporine. Conversely, belatacept-based therapy is associated with significantly less NODAT (29). In addition, cytomegalovirus infection (30) as well as hypomagnesemia (31) are also associated with the development of PTDM.

Amongst all the maintenance immunosuppressive drugs, steroids and tacrolimus are the major contributors to PTDM occurrence. A systematic review of the literature has shown that steroid-sparing and withdrawal strategies can reduce the need for antihypertensive drugs, serum cholesterol drugs, antihyperlipidemic drugs, NODAT that requires treatment, and cataracts (32). However, a randomized prospective controlled trial has shown that early steroid withdrawal (POD 7) has a limited impact in reducing NODAT when compared to low-dose prednisone (5 mg/day), i.e., NODAT developed in 36.3% of patients on chronic corticosteroid therapy and in 35.9% of those with early corticosteroid withdrawal (33).

We have shown in a prospective non-randomized clinical trial that even a late switch from tacrolimus-based to belatacept-based immunosuppression can be a valuable therapeutic option for diabetic kidney recipients and can substantially improve glycemic parameters. Indeed, in diabetic kidney-transplant recipients, HbA1c decreased from 7.2 ± 1 to 6.5 ± 1% (P = 0.001). Moreover, HbA1c significantly decreased whether diabetes was controlled at inclusion or not (i.e., HA1c ≤7% or >7%) (34). Therefore, in patients developing PTDM, conversion from tacrolimus to belatacept is a very good option.

Treatment of PTDM relies on diet, oral antidiabetic agents, and insulin therapy where required (e.g., very high fasting blood-sugar levels) (35). Novel agents, including sodium glucose co-transporter 2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP1RA), and dipeptidyl peptidase IV inhibitors (DPP4i), which demonstrate great promise for type 2 diabetes management in the non-transplant population. However, current experience with novel antihyperglycemic agents is primarily limited to single-center retrospective studies and case series (36).

Leukopenia

The word leucopenia is often used interchangeably with neutropenia. A variety of definitions for leucopenia and neutropenia are available; however, leucopenia is graded based on the Common Terminology Criteria for Adverse Events (CTCAE) (37). CTCAE has graded leucopenia into four levels: grade 1 (lower range of normal limits to 3000 cells /mm3), grade 2 (2000--3000 WBC/mm3), grade 3 (1000--2000 WBC/mm3), and grade 4 (less than 1000 WBC/mm3). Most laboratories consider 4000 cells/mm3 as the lower limit of normal and any level below this is considered as leucopenia. Others, such has transplant physicians, have used neutropenia to classify granulocytopenia according to its severity. They have used absolute neutrophil count (ANC) to assess the severity of neutropenia. ANC is calculated as follows: ANC = white blood cells (microliter) x percent (polymorphonuclear cells + bands)/100. An ANC <1500/microliter or <1.5 x 109/L is defined as neutropenia and is graded as mild, moderate, or severe. In mild neutropenia, ANC will be in the range of 1000 to 1500/microliter or 1 to 1.5 x 109/L. Moderate neutropenia is defined as 500 to

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999/microliter or 0.5 to 0.99 x 109/L. Severe neutropenia refers to ANC <500/microliter or <0.5 x 109/L (38). Neutrophils and lymphocytes play important roles against infections. Leukopenic kidney-transplant recipients are prone to develop opportunistic infections. An absolute neutrophil count of less than 1000 cells per/L increases susceptibility to infections. Frequency and severity of infections are increased with decreasing neutrophil counts and prolonged duration of neutropenia. Escherichia coli infections are more common in neutropenic kidney-transplant recipients (39). In addition, neutropenic kidney-transplant recipients have a higher incidence of intra-abdominal infection (22.5%) than a matched normopenic cohort (7--10%) (Khalil). Induction immunosuppression, when given, may rely on lymphocyte-depleting polyclonal antibodies, such antithymocyte globulins (ATG), which may cause transient leucopenia/neutropenia. ATG is not specific for T-cells. It contains antibodies directed against different blood--cell types (T-cells > B cells; NK cells > monocytes; neutrophils > platelets > erythrocytes). Because of the presence of cross-reacting antibodies against non-lymphoid cells, hemolytic anemia, thrombosis, thrombocytopenia, and neutropenia can occur. At high doses of ATG, nonspecific binding to neutrophils and platelets can lead to undesirable effects, such as transient neutropenia and thrombocytopenia (40). The incidence of leucopenia is variable in kidney-transplant recipients. This is largely due to inconsistency in the duration and dosing regimens among users. Various authors report incidences of leucopenia of between 10% and 50% (reviewed by Khalil et al. -41-). While treating ATG-induced cytopenia, the effect of other immunosuppressive medications should be taken into consideration, such as mycophenolate mofetil (MMF) or mycophenolic acid (MPA), substances given to almost all de novo kidney-transplant recipients. In addition, at the same time, many patients will receive anti-cytomegalovirus prophylaxis of valganciclovir, and anti-Pneumocystis jirovecii prophylaxis by sulfamethoxazole-trimethoprim (42).

A recent systematic literature review identified 73 studies reporting on the epidemiology of post-kidney-transplant leukopenia/neutropenia (43). The pooled incidence of neutropenia, defined as absolute neutrophil counts <1000/mm3, ranged from 13% to 48% within 1-year post-transplantation; absolute neutrophil count of <500/mm3 ranged from 15% to 20%. Leukopenia, defined as white blood cell counts <3500/mm3, were between 19% and 83%. Only 11 studies reported independent risk factors associated with post-kidney-transplant leukopenia. Donor (+)/recipient (-) cytomegalovirus serostatus, mycophenolic acid, and tacrolimus use were the most consistent risk factors across studies. Fourteen studies reported leukopenia/neutropenia-associated clinical outcomes. There was a trend towards a positive association between neutropenia and acute rejection/opportunistic infections. Mixed findings were noted on the association between leukopenia/neutropenia and graft failure or mortality. Dosage modifications of valganciclovir, mycophenolic acid, sulfamethoxazole-trimethoprim, and anti-thymoglobulin globulins, and the need for granulocyte colony-stimulating factor (G-CSF) were common with leukopenia/neutropenia.

Mycophenolate is a corner-stone of maintenance immunosuppression after kidney transplantation; in most cases it is given in addition to tacrolimus. Mycophenolate contributes to leukopenia, especially when it is associated with valganciclovir (44, 45). When a mycophenolate-treated patient develops neutropenia the abbreviated area under the curve (AUC) can be ascertained to rule out overexposure (46). Management of severe leukopenia relies on G-CSF to achieve quick recovery of WBC count when leukocytes are needed, in addition to changes in immunosuppression and prophylaxis medications (47).

Anemia

Post-transplantation anemia is a frequent problem after kidney transplantation (48). In 2003, a European survey (TRESAM study), which included 4263 kidney-transplant recipients; found that 38.6% of recipients presented with anemia. Of the 8.5% of patients that were considered severely anemic, only 17.8% were treated with epoetin. There was a strong association between hemoglobin and graft function; of the 904 patients with serum creatinine >2 mg/dL, 60.1% were anemic vs. 29.0% of those with serum creatinine that was ≤2 mg/dL ($p < 0.01$). Therapy with angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, mycophenolate mofetil, or azathioprine was also associated with a higher likelihood of anemia (49). More recently, a meta-analysis has shown

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that post-transplantation anemia was associated with greater overall mortality (pooled risk ratio = 1.72 [1.39, 2.13], I2 = 56%), graft loss (pooled risk ratio = 2.28 [1.77, 2.93], I2 = 94%), cardiovascular death (pooled risk ratio = 2.06 [1.35, 3.16], I2 = 0%), and cardiovascular events (pooled risk ratio = 1.33 [1.10, 1.61], I2 = 0%). Early anemia (≤6 months), compared with late anemia (>6 months), is associated with a higher risk of overall mortality and graft loss, with a pooled risk ratio of 2.63 (95% CI 1.79-3.86; I2 = 0%) and 2.96 (95% CI 2.29-3.82; I2 = 0%), respectively (50). An open-label, French multicenter, randomized, controlled trial investigated the effect of epoetin-β to normalize hemoglobin values (13.0-15.0 g/dl, n=63) compared with partial correction of anemia (10.5-11.5 g/dl, n=62) on progression of nephropathy in transplant recipients with hemoglobin <11.5 g/dL and an estimated creatinine clearance (eCrCl) <50 ml/min per 1.73 m2. After 2 years, mean hemoglobin was 12.9 and 11.3 g/dL in the normalization and partial-correction groups, respectively (P<0.001). From baseline to year 2, eCrCl decreased by a mean of 2.4 mL/min per 1.73 m2 in the normalization group compared to 5.9 ml/min per 1.73 m2 in the partial-correction group (P=0.03). Furthermore, fewer patients in the normalization group progressed to end-stage kidney disease (3 vs. 13, P<0.01). Cumulative death-censored graft survival was 95% and 80% in the normalization and partial-correction groups, respectively (P<0.01). Finally, complete correction was associated with a significant improvement in quality of life at 6 and 12 months (51). Indeed, iron deficiency is highly prevalent in kidney-transplant recipients and has been independently associated with higher mortality risk in this population.

Several causes lead to iron deficiency in kidney-transplant recipients, including inflammation, medication, and an increased need for iron after transplantation (52). Recently, it was shown that after kidney transplantation routine parenteral iron treatment was associated with a lower prevalence of early- and late-onset anemia, and a lower requirement for either erythropoietin-stimulating rescue agents or blood transfusions (53).

Based on these data it is mandatory to recognize and to treat post-transplant anemia.

Dyslipidemia

Immunosuppressive medications are associated with dyslipidemia. Each drug class is associated with individual variations in affected lipid particles and, more importantly, in the conferred risk of atherosclerosis. Indeed, kidney-transplant recipients have many factors that contribute to cardiovascular risks. The pathogenesis of cardiovascular disease after kidney transplantation is multifactorial. Apart from non-modifiable risk factors, such as age, gender, genetic predisposition, and ethnicity, several traditional and non-traditional modifiable risk factors contribute to its development. Traditional factors, such as diabetes, hypertension, and dyslipidemia may be present before and may worsen after transplantation. Immunosuppressants and impaired graft function may strongly influence the exacerbation of these co-morbidities (54). Calcineurin inhibitors are the cornerstone of post-transplant immunosuppression. It was early recognized that cyclosporine A (CsA) use is associated with a dose-dependent increase in total cholesterol and low-density lipoprotein (LDL) cholesterol, a decrease in high-density lipoprotein (HDL) cholesterol, and an increase in serum triglycerides (55). Tacrolimus is associated with a similar but milder dyslipidemia profile compared to CsA (56). CsA appears to be associated with an increase in oxidized LDL, which confers a higher risk of atherosclerosis, while the data for tacrolimus effect on LDL oxidation are mixed (57, 58).

In most kidney-transplant recipients, calcineurin inhibitors are associated with mycophenolate mofetil. However, in some patients mycophenolate mofetil can be replaced by inhibitors of the mechanistic target of rapamycin (mTOR), e.g., sirolimus, everolimus. They have unique anti-atherosclerotic effects, such as depletion of plaque macrophages, induction of autophagy, and activation of cholesterol efflux. However, a common side effect of their use is dyslipidemia, a well-known risk factor for atherosclerosis. Indeed, mTOR inhibitors prevent lipid storage, increase low-density lipoprotein cholesterol levels, and activate lipolysis. Although the net effect of mTOR inhibition seems favorable, the use of cholesterol-lowering drugs to manage dyslipidemia remains the most recommended strategy (59). Interestingly, despite the increase in serum lipids, mTOR inhibitors are associated with an overall lower risk of atherosclerosis (60). Both mycophenolate

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mofetil and azathioprine appear to have a neutral effect on lipids with no significant changes observed in lipid profile in clinical studies (61). Currently, statins are the pharmacologic intervention of first choice if lifestyle changes fail adequately to lower LDL-C levels in the setting of normal or moderately elevated triglycerides. Statins have been extensively studied in a large variety of patient populations and have proven efficacy in the treatment of dyslipidemia and in reducing cardiovascular mortality (62). However, side-effects (e.g.. myopathy) may occur. In these cases, ezetimibe (which does not affect kidney function) alone or with statins can be given for severe cases and is suggested by the most recent Guidelines (63). Hepatic transaminase elevations may occur in 1 to 2% of statin-treated patients and is dose related. Myalgia, myopathy, and rhabdomyolysis occur infrequently and are more common in kidney-transplant recipients and patients with chronic kidney disease. This effect appears to be dose related and may be precipitated by administration with agents that inhibit cytochrome P-450 isoenzymes (64).

Mouth Ulcers

Mouth ulcers are not frequently observed after kidney transplantation but, when they occur, they may worsen the patient's quality of life. Sarmento et al. recently published a prospective observational cohort study that included 80 adult kidney-transplant recipients (65). The patients were assessed for mouth lesions at three different times: 24 hours before transplantation (1st time point), 15--20 days after (2nd time point), and 45--60 days (3rd time point) after transplantation. Sarmento et al. found that in the first, second, and third time points, 3.7% (3/80), 23.7% (18/76), and 25.7% (19/74) of the participants had oral soft-tissue lesions. Ulcers and candidiasis were the most frequent oral lesions, and were associated with the use of everolimus (P = 0.005) and azathioprine (P = 0.034), respectively. Indeed, it is well known that both sirolimus (66, 67) and everolimus, i.e., mTOR-inhibitors, can cause mouth ulcers. The first evidence came from a randomized, multicenter trial in which 33 steroid-free kidney-transplant recipients were receiving a steroid-free maintenance treatment of tacrolimus and mycophenolate mofetil and at 1 year after transplantation were randomized either to continue tacrolimus and mycophenolate mofetil (control group, n=18), or were converted from tacrolimus to sirolimus (study group, n=15). The study was prematurely stopped as a result of a cluster of nine patients (50%) suffering from painful oral ulcerations in the study group. Oral ulcerations did not occur in the control group (66). In another case study, sirolimus-related mouth ulcers were observed in 21.6% of patients. Histological examination revealed non-specific ulcerations associated with a polymorphous inflammatory infiltrate. Topical treatment with clobetasol reduced pain and shortened healing times between two- and three-fold (67).

In the setting of liver transplantation, a single-center, randomized, controlled trial, was conducted that included 30 maintenance patients that were randomized to remain on calcineurin (CNI)-based immunosuppression or be switched to sirolimus-based immunosuppression. They observed that one-third of patients converted to sirolimus experienced aphthous-type mouth ulcers that resolved over the course of the first 2 weeks with dose adjustment to the lower end of the target range, although three patients developed coincidental herpes simplex (68). Everolimus is also associated with mouth ulcers (69, 70) and with perianal ulcers (70, 71). It is often dose-related, and occurred especially in those who were on steroid-free immunosuppression, and after conversion from CNIs.

Management of m-TOR-inhibitor-related mouth ulcers relies on minimizing (where possible) trough levels, increasing (or adding) systemic steroids, and applying topical clobetasol (67). Indeed, in the setting of oral chronic graft-versus-host disease (GVHD), a randomized, double-blind clinical trial compared topical clobetasol and dexamethasone: it was found that clobetasol was significantly more effective than dexamethasone at ameliorating symptoms and clinical aspects of oral lesions in chronic GVHD (72).

Hypertension

The 2021 Kidney Disease Improving Global Outcomes BP guidelines defined hypertension as office blood pressure (BP) of ≥ 130/80 mmHg and ambulatory BP monitoring (ABPM) as ≥ 125/75

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mmHg, in agreement with the 2017 ACC/AHA guidelines (73). In a recent cohort study of 260 kidney-transplant recipients followed-up for 3.9 years, the agreement between 785 paired office and 24-h ABPM measurements was assessed, revealing significant discordance in 37% of all visits (κ-statistics = 0.25, indicating poor agreement) 74). The prevalence of post-kidney transplant hypertension ranges between 55% and more than 95% (75, 76).

Among the traditional and non-traditional risk factors, post-transplant hypertension remains one of the major contributors to post-transplantation cardiovascular morbidity and mortality, and the most common causes of chronic graft dysfunction and kidney-transplant failure (75). Cardiovascular pathology is responsible for approximately 40% of deaths among kidney-transplant recipients (77). Therefore, it is important to recognize and treat post-kidney-transplant hypertension. There are many non-modifiable and modifiable factors. These include factors associated with immunosuppression (cyclosporine, tacrolimus, glucocorticoids), with the allograft (delayed graft function, chronic allograft nephropathy, de novo and recurrent glomerular disease, acute rejection), with the recipient (underlying kidney disease, essential hypertension, native kidney presence, excessive weight gain, secondary hyperparathyroidism), donor factors, and surgery, e.g., renal-allograft artery stenosis. Once post-kidney transplant hypertension has been identified and a treatable cause ruled out (and managed where present) the KDIGO guidelines recommend the use of a calcium-channel blocker or an angiotensin-receptor blocker as the first-line antihypertensive agent (1C) (73). The nocturnal use of calcium-channel blockers has shown good performance in reversing the altered sleep patterns; in addition they are indicated especially in the first few months of renal transplantation when the risk if ureteric stricture is maximal and because the risk of acute kidney injury is greater when angiotensin II AT1 receptor blockers are used; therefore the latters are only to be used when renal function is stable (78).

Viral Reactivation

Induction and maintenance immunosuppressions can result in impaired immune responses, including antiviral responses. This may favor opportunistic infections, particularly cytomegalovirus (CMV) and BK virus (BKV) infections (79, 80). These infections can result in graft-function impairment and may contribute to transplant rejection.

Cytomegalovirus is frequently reactivated after kidney transplantation. In order to prevent this, we have the choice between universal prophylaxis with valganciclovir or preemptive therapy, i.e., CMV DNAemia is regularly monitored and should it be positive then valganciclovir therapy is implemented. A recent literature review has shown that despite preventative approaches, approximately one-fourth of kidney-transplant recipients developed CMV infection. Age and D+/R- CMV serostatus were consistent risk factors for CMV infection/disease; in addition, CMV infection/disease was associated with increased mortality and graft loss (81).

Recently Reischig et al. reported on an open-label, single-center, randomized clinical trial of valganciclovir prophylaxis versus preemptive therapy in 140 de novo kidney-transplant recipients after excluding CMV-seronegative recipients with transplants from seronegative donors. The patients were randomized 1:1 to receive valganciclovir prophylaxis (900 mg, daily for 3 or 6 months for CMV-seronegative recipients who received a kidney from a CMV-seropositive donor) or preemptive therapy (valganciclovir, 900 mg, twice daily) that was initiated after detection of CMV DNA in whole blood (≥1000 IU/ml) and stopped after two consecutive negative tests (preemptive therapy patients received weekly CMV PCR tests for 4 months). The primary outcome was the incidence of biopsy-confirmed acute rejection at 12 months. They observed that the incidence of acute rejection was lower with valganciclovir prophylaxis than with preemptive therapy (13%, 9/70 versus 23%, 16/70); in addition, subclinical rejection at 3 months was lower in the prophylaxis group (13% versus 29%, P = 0.027). Both regimens prevented CMV disease (in 4% of patients in both groups). Compared with universal prophylaxis, preemptive therapy resulted in significantly higher rates of CMV DNAemia (44% versus 75%, P <0.001) and a higher proportion of patients experiencing episodes with a higher viral load (≥2000 IU/ml) (82).

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When a kidney-transplant recipient has experienced a first CMV infection episode, the question is whether maintenance immunosuppression should be modified. Indeed, it has already been shown that mTOR inhibitors (sirolimus, everolimus) have anti-CMV properties (84). Recently, Viana et al. performed a single-center prospective randomized trial in 72 kidney-transplant recipients immediately after treatment of the first episode of CMV/infection disease with a 12-month follow-up. The patients were either maintained on the same treatment (antiproliferative agent plus CNIs) or the antiproliferative was replaced with sirolimus. They found that the sirolimus group had no recurrence as compared to 43% recurrence in the control group (P = <0.0001) (85). In de novo kidney-transplant recipients, CMV infection/disease can be avoided to some extent by replacing the antiproliferative agent (mycophenolic acid) with everolimus (86, 87).

Poliomavirus BK virus (BKV) is highly infective, causing asymptomatic infections during childhood. After the initial infection, a stable state of latent infection is recognized in kidney tubular cells and the uroepithelium with negligible clinical consequences. BKV is an important risk factor for BKV-associated diseases, and for BKV-associated nephropathy (BKVN) in renal-transplant recipients. BKVN affects up to 10% of renal-transplant recipients, and results in graft loss in up to 50% of those affected. Unfortunately, treatments for BK virus infection are restricted, and there is no efficient prophylaxis (88, 89, 90). Because there is no efficient BKV prophylaxis we have to regularly monitor for BKV replication in the blood and urine at least during the first-year post-kidney transplantation and every time serum creatinine changes subtly with no identifiable cause.

Recently, Blasquez-Navarro et al. reported on a prospective cohort of 540 de novo kidney-transplant recipients that were analyzed for BKV, CMV, and EBV viral loads using qPCR. Measurements were performed throughout eight visits during the first post-transplantation year (91). BKV had the highest prevalence and viral loads. BKV viral loads over 10,000 copies·mL-1 led to significant impairment of estimated glomerular filtration rate (eGFR). Both BKV and CMV reactivations were significantly associated (P = 0.005). In addition, combined reactivation was associated with a significant reduction in eGFR at 1-year post-transplantation of 11.7 mL·min-1·1.73 m-2 (P = 0.02) at relatively low thresholds (BKV >1000 and CMV >4000 copies·mL-1) (91).

It has been shown that the use of the mTOR inhibitor everolimus, in place of mycophenolate acid, and in association with low doses of calcineurin inhibitors in de novo kidney-transplant recipients, resulted in significantly less BKV replication (86). Thus in the TRANSFORM study, BK-virus infection (viruria or viremia) occurred in 4.3% and 8.0% of everolimus- and mycophenolic acid-treated patients, respectively (RR, 0.54; 95% CI, 0.38 to 0.77), with histologic evidence of organ involvement in 1.2% (12/1014) and 2.1% (21/1012).

Conversely, when BKV replication is already present, we have several options. The first is to minimize stepwise immunosuppression, i.e., by reducing or eliminating mycophenolic acid (92, 93), or to convert mycophenolic acid to everolimus with calcineurin-inhibitor minimization (93, 94). We know that i) patients with high titers of BKV-neutralizing antibodies (NAbs) are protected against BKV replication, ii) and that intravenous immunoglobulin (IVIg) infusion can increase NAb titers. Thus, based on NAb titers on the day of kidney transplantation, those patients with low NAb titers have a greater risk of BKV reactivation. Benotmane et al. have shown that, at 12 months after transplantation, the incidence of BKV viremia in the high-risk group treated with prophylactic IVIg (6.8%) was similar to that observed in the low-risk group (10.1%) that received no IVIG, and was markedly lower than that of the untreated high-risk group (36.6%; P <0.001). In addition, Benotmane et al. found similar results with regards to BKVAN (95). Anyaegbu et al. have shown that IVIg was an effective treatment for persistent BKV infection after reduction in immunosuppression and for BKVN (96). Another option for overt BKV-associated nephropathy is either calcineurin-inhibitor free immunosuppression based on either everolimus (97) or leflunomide (98, 99).

2. Conclusions

Following kidney transplantation, lifelong immunosuppression is mandatory to achieve good long-term results, i.e., there is no immune tolerance. Maintenance immunosuppression is based on a combination of drugs that have narrow therapeutic windows, thereby resulting frequently is adverse

drug events. These events may contribute to allograft failure (e.g., nephrotoxicity, hypertension) or increase cardiovascular disorders (e.g., dyslipidemia, hypertension, post-transplant diabetes mellitus), or to drug dropouts, such as mTOR inhibitor-induced mouth ulcers.

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