Review paper

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Neurologic complications in kidney transplant recipients

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Abstract

Transplantology experiences continuous growth and kidney transplantation is the most frequently transplanted solid organ. Metabolic, cardiovascular, infectious or kidney function-related aspects are widely recognised and are of key interest for transplant doctors. Neurological complications seen in these patients, although known, are less covered in the literature. According to some reports, neurologic symptoms are experienced by almost 9 per 10 transplant recipients. The intensity, severity and type of abnormalities may vary, and most frequently the complications seem to be associated with a direct or indirect effect of immunosuppressive medications, including their direct effect on cells, on blood vessels, and susceptibility to infections. Increasing age of transplant recipients and relaxation of transplantation eligibility criteria enriches the population with patients already compromised, with a higher present risk of stroke, neuropathy, malignancy etc. Research on and introduction to clinical practice of new agents like belatacept, proteasome inhibitors, or modified release formulations of tacrolimus, changes the picture and type of abnormalities within the nervous or neuromuscular system but does not eliminate them. Thus, it seems justified to remind the society of the whole array of neurologic complications they can see in their practice despite advances in the field.

Key words: *kidney transplantation, immunosuppression, neurotoxicity, PTLD, PRES, opportunistic infections, CNS.*

Introduction

Kidney is the most widely transplanted solid organ associated with high survival rates, which makes renal transplant a growing area of interest in the modern era of nephrology. One of the crucial drawbacks in successful renal transplantation is allograft rejection. Survival rates among transplant recipients have greatly improved due to better understanding of transplant biology and more effective immunosuppressive agents. In the US, less than 30% of the approximately 615,000 patients that were diagnosed with end-stage renal disease (ESRD) have received a kidney transplant and more than 100,000 patients are on the waiting list for a donor kidney [189]. In some other countries, like Spain or the Netherlands, more than 50% of ESRD patients are treated with kidney transplantation [19]. Current immunosuppressive protocols tend to prevent acute rejection of renal allografts better than the old ones despite lower doses of immunosuppressive drugs used nowadays in general. Post-transplant immune monitoring and optimization of the immunosuppressive therapy using non-invasive biomarkers can effectively predict impending graft rejection and may spare the need for renal biopsy. However, drug

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toxicity and the unfavourable effects of long-term immunosuppression are associated with significant morbidity and mortality.

The goals of pharmacotherapy in kidney transplantation are to prevent graft rejection, reduce morbidity, and prevent complications. Immunosuppressant drug classes include calcineurin inhibitors (CNIs), corticosteroids, antimetabolites, mammalian target of rapamycin (mTOR) inhibitors, and other immunosuppressants like depleting antibodies (Table I). Transplant recipients are maintained on an immunosuppression regimen based on 1-3 drugs. There is a number of regimens which can be used, including pre-transplantation induction therapy and simple postoperative maintenance therapy; the choice of regimen depends on the patient's profile, training and experience of the transplantation centre, local standards, and reimbursement status of drugs. According to the report of the United States Renal Data System (USRDS) [207], the majority (90% in 2012) of kidney transplant recipients received antibody induction. While the use of anti-IL-2R (interleukin-2 receptor) antagonists has fallen in the US from a peak of 41% in 2002 to 25% in 2012, the use of T-cell depleting agents continues to increase, reaching 65% in 2012 [207] and this trend may continue due to weak data supporting the use of IL-2R antagonists [86,227,228]. However, in Europe, IL2RA induction was more widely used than rabbit antithymocyte globulin (rATG) or other depleting agents [145]. Nearly all transplant recipients in 2012 received a calcineurin inhibitor and an anti-metabolite as components of their initial immunosuppressive regimen. 92% of these patients were prescribed tacrolimus (Tac) as their first-line CNI, and mycophenolate mofetil (MMF) has almost completely replaced azathioprine (Aza) as the anti-metabolite of choice. Use of mTOR inhibitors, both initially and at one year following transplantation, has declined to 2% and 4%,

Table I. Immunosuppressive agents used in organ transplant recipients*

Induction	Maintenance treatment	Treatment of rejections
Polyclonal and monoclonal antibodies	*Corticosteroids*	*Corticosteroids*
Polyclonal (ATG)	Prednisone	Polyclonal and monoclonal antibodies
Monoclonal anti-CD3 (OKT3/Muromonab), withdrawn	*Calcineurin inhibitors*	Reversible 26S proteasome inhibitor (Bortezomib)
Monoclonal anti CD-52 (Alemtuzumab)	Cyclosporine, Tacrolimus	Anti-C5 antibody (Eculizumab)
Monoclonal anti-CD20 (Rituximab)	*Anti-metabolites/Anti-proliferative agents*	
Interleukin-2 receptor antagonists, monoclonal anti-CD25	Azathioprine	
Basiliximab	Mycophenolate mofetil, Mycophenolic acid	
Daclizumab, withdrawn	Mizoribine	
Corticosteroids	Leflunomide	
Methylprednisolone	*m-TOR inhibitors*	
	Sirolimus, Everolimus	
	Co-stimulation blocker	
	Belatacept (fusion protein)	
	Protein kinase C inhibitor	
	Sotrastaurin	
	JAK 3 inhibitors	
	Tofacitinib	
	Alkylating agents	
	Cyclophosphamide	

**Including selected off-label, discontinued and/or currently developed products. Modified classification published by Kumar and Shrestha, 2016 [84,98,106]*

respectively, in 2012, while steroid use seems to be stabilizing at about 67% [207].

Immunosuppressive agents are known to show numerous side effects, including the ones affecting the nervous system directly or indirectly. Majority of solid organ transplant recipients experience neurologic complications after transplantation, and only minority of cases (e.g. femoral neuropathy, stroke) can be attributed to the surgery or the pre-existing comorbidities (e.g. atherosclerosis, hypertension, diabetes) alone [67,160,212]. Immunosuppressive medications, can induce direct or indirect neurotoxicity or increase the risk of central nervous system (CNS) infections and tumours. Neurotoxic effects can manifest either in the central or in the peripheral nervous system (PNS). Immunosuppressive medications used in transplantation that have most frequently been associated with neurologic complications include cyclosporine (CsA), tacrolimus (Tac, FK506), corticosteroids, and muromonab (OKT3) [53,63, 197,220,222,223]. In addition, frequent disturbances of hepatic and kidney metabolism may appreciably prolong the half-life of drugs and increase their plasma levels. The use of various medications interfering with cytochrome CYP3A function may alter the levels of Tac and CsA [130] and affect their safety profile.

Apart from a potentially detrimental effect of immunosuppression, an impaired kidney function itself can be a cause of adverse neurologic outcomes. For example, changes in creatinine, eGFR, serum nitrogen, CRP, 1,25-$(OH)_2D_3$, intact parathyroid hormone (iPTH), phosphorus were found to correlate with psychological and cognitive disorders in patients with treated chronic kidney disease [108].

Neurologic complications following kidney transplantation are more common compared to the general population and the incidence of neurologic alterations is reported in up to 85% of recipients [21,71,177,230]. Somewhat contrary to this prevalent opinion, in a relatively small retrospective analysis of magnetic resonance imaging of transplant recipients in Charleston, SC Medical University, frequency of posterior reversible encephalopathy syndrome, and both acute and chronic lesions/changes in brain did not differ significantly between patients before and after kidney transplantation [26]. They can be classified as several core groups: infection, drug toxicity, structural pathology (stroke, cancer, vasculitis), and metabolic abnormalities including those caused by graft dysfunction [230].

In a retrospective study, it was reported that most frequent neurologic complications following renal transplantation were focal neurologic deficits (20%), acute confusion (16%), seizures (15%) and headache (13%) [21]. An increased frequency of stroke in kidney allograft recipients is attributable to the progression of pre-existing vasculopathy and hypertension [1,173]. Kidney transplantation surgery is also associated with an increased incidence of femoral and lumbosacral plexopathy [56].

This review, although focusing on kidney transplantation is generally applicable to all solid organs as the medications used in e.g. heart or liver transplantology are merely the same although some differences exist when it comes to doses, regimes, and underlying diseases. In the review we analyse firstly the neurotoxicity from selected therapeutic agents perspective, and then we discuss selected most relevant neurotoxicities. Because of volume limitations of the paper we have not been able to cover all relevant topics, including e.g. neurologic complications related directly to an impaired kidney function, linked to use of other medications used in this population of patients, we have barely mentioned importance of genetics/epigenetics behind increased vulnerability to immunosuppression, psychological impact of the transplantation itself, available treatment of the complications etc. We also acknowledge availability of a number of review papers on this subject in contemporary literature. However, we hope that our approach will provide a unique perspective, and by encompassing recent advances in the field, will be a valuable summary for clinicians and scientists interested in this slightly overlooked aspect of transplantology.

Neurotoxicity of immunosuppressive drugs

Calcineurin inhibitors

Cyclosporine is an 11 amino acids polypeptide of fungal origin and a pro-drug, which has been a keystone of immunosuppression in transplantation for four decades. This agent is used for induction and maintenance of immunosuppression. Tacrolimus is a macrolide antibiotic and a calcineurin inhibitor with 2-3 times the potency of cyclosporine. Tac can be used at lower doses than cyclosporine, but its adverse effects include renal dysfunction, neurotoxicity (tremor, insomnia, and paraesthesia of the

extremities), and new-onset diabetes. Tacrolimus has essentially replaced cyclosporine as the CNI of choice, because of a claimed lower rejection rate including decreased steroid-resistant rejection, and according to some studies, superior graft survival [6,135,172]. Some other studies do not support the superiority of Tac vs CsA, though [12,129] and it may partly depend on CYP3A5 (6986 A>G, rs776746) polymorphism [117]. Currently, 80-90% of patients receive Tac after renal transplantation instead of cyclosporine, and this change has persisted for the past 10-15 years.

CsA and Tac induce immunosuppression by inhibiting the first phase of T-cell activation by binding to immunophilins. The immunosuppressive, and possibly neurotoxic, action of both CsA and Tac is exerted through inhibition of the calcium calmodulin-dependent protein phosphatase, calcineurin [82]. Calcineurin is essential for the dephosphorylation of the nuclear factor of activation of T cells (NFAT) which is responsible for activation of T-cells. The first phase of T-cell activation causes transcriptional activation of interleukin (IL)-2, IL-3, IL-4, tumour necrosis factor (TNF) alpha, and interferon gamma that allow T-cells to progress from the G0- to G1-phase [195]. Thus, CsA and Tac both work to inhibit IL-2, which is a critical link in the proliferation of helper T cells. These agents bind to a group of proteins called immunophilins, divided into CsA-binding cyclophilins and FK-binding proteins, to form complexes that then bind to and inhibit the activated calcineurin phosphatase. The tacrolimus: FKBP12 active complex inhibits calcineurin with greater potency than the corresponding cyclosporine complex [83].

Calcineurin and immunophilins have a widespread expression in the central and peripheral nervous systems, but the exact mechanism of CsA- or tacrolimus-induced neurotoxicity is not yet well understood. Protein dephosphorylation by calcineurin may play an important role in neuronal signal transduction due to its ability to regulate the activity of ion channels, glutamate release, and synaptic plasticity [235]. Calcineurin has been shown to regulate the activity of *N*-methyl-*D*-aspartate (NMDA) receptor channels by both altering their ion gating properties and promoting desensitization in cultured hippocampal neurons, which has been ascribed to the enhanced release of glutamate by the presynaptic cells [142,185,213]. Since NMDA receptors are highly permeable to Ca^{2+}, the influx of extracellular Ca^{2+} is considered to be the primary event responsible for glutamate toxicity and neuronal cell death [115].

Mechanisms underlying calcineurin inhibitors neurotoxicity may be related to: (1) upregulation of endothelin receptors A and B and stimulation of endothelin 1 synthesis; (2) damage of the blood–brain barrier (BBB); (3) alterations in the mitochondrial function; (4) interaction with neuromodulatory systems and (5) vascular toxicity. Circulating endothelin, produced in excess in the presence of CNIs can affect the cerebral vascular smooth muscle and could promote systemic hypertension [147,190,203]; the endothelin-mediated effect is also promoted by CsA-dependent upregulation of endothelin receptors A and B [141,238]. On the other hand, if endothelial integrity is disrupted, CsA and Tac could gain access to astrocytes. Under such conditions, local ischemia and consequent white matter oedema could show transient alterations observed in cases of acute hypertensive encephalopathy [143] or in PRES (Posterior Reversible Encephalopathy Syndrome). CsA and Tac are highly lipophilic and are bounded in plasma, especially to low-density lipoprotein (LDL). Since LDL receptors are also expressed on the cell membrane of astrocytes at the blood–brain barrier, increased uptake of these drugs can lead to damage of the BBB as well as the white matter. The vasoconstriction induced by CNI may cause microvascular damage and disrupt the blood-brain barrier [4,177]. In case reports of patients treated with relatively high doses of CsA, published by Shbarou *et al*. [182], lesions in the cerebral white matter associated with abnormally elevated cerebral blood flow velocities on transcranial Doppler ultrasound and abnormal vascular appearance on magnetic resonance angiography were seen. The authors reported the changes as resembling brain lesions seen in pre-eclampsia. CNI can lead to decrease the expression of p-glycoprotein in the brain endothelial cell and cause dysfunction of the blood-brain barrier leading to vasogenic oedema [221]. CsA and Tac increased proinflammatory cytokines and endothelial activation markers in cultured murine endothelial and vascular smooth muscle cells, and in *ex vivo* cultures of murine aortas through TLR4 and with no significant role of calcineurin. In TLR4 knockout mice CNIs were unable to induce inflammation and endothelial activation in aortas. The CNI-induced-TLR4 activity lead to increased $O_2(-)$/ROS production and NF-κB-regulated

synthesis of proinflammatory factors in cultured as well as aortic endothelial and VSMCs [170]. Part of CsA and Tac toxicity may arise from interference with mitochondrial functions [93], such as decrease of mitochondrial energy production and the subsequent activation of anaerobic glycolysis, impaired cellular calcium buffering, activation of proteases and phospholipases, activation of nitric oxide synthase (NOS) and generation of free radicals, leading to either apoptotic or necrotic cell death [180]. CsA and Tac appear to affect neuronal transmission in specific circuits via the following mechanisms: (1) inhibition of the gamma-amino butyric acid (GABA) system that amplifies excitatory response and limits inhibitory response, which may be the mechanism behind the increased seizure activity in transplant recipients; (2) neuronal serotonin depletion, which may explain depression and tremor; (3) glutaminergic NMDA receptor inhibition, suggesting a possible role for psychotic features. In a recent study it was shown in a model of chronic CsA or Tac microinjections into medial prefrontal cortex in rats that calcineurin-inhibition-induced depressive-like behaviour is mediated by blockade of the mTOR signalling pathway and can be reversed by NMDA [237]. Influence on NMDA-dependent signalling through potentiating presynaptic and postsynaptic NMDAR activity in the spinal cord may increase glutamate-mediated nociceptive input and be responsible for calcineurin inhibitor-induced pain syndrome (CIPS) linked to CsA or Tac use [42,45].

Table II. Neurologic side-effects of calcineurin inhibitors

Tremors
Sleep disturbances, insomnia
Paraesthesia, pain syndrome, polyneuropathy
Mood disturbances
Mental status changes: confusion, disorientation, paranoia, hallucinations, lethargy, apathy, depression, irritability, aggression
Leukoencephalopathy, toxic encephalopathy
Seizures
Visual disturbances: hemianopsia, cortical blindness, blurred vision
Motor symptoms: paraplegia, quadriplegia, paresis, dystonia
Speech or language disturbances: akinetic mutism, aphasia, slurred speech
Other movement disorders: asterixis

It was shown that nerve excitability testing demonstrated abnormal nerve function in CNI-treated patients, reflecting nerve membrane depolarization [13]. This can translate into the reduced threshold for action potential generation and easier development of neuropathic symptoms, including paraesthesia and cramps [132]. More severe depolarization may lead to sodium channel inactivation and reduce the size of the action potential, leading to sensory loss and fatigue [105].

Of note, treatment with CsA significantly reduced plasma concentrations of adrenocorticotropic hormone (ACTH), cortisol, and noradrenaline whereas adrenaline levels and state of anxiety remained unaffected [8]. This effect was shown to attenuate stress-responsiveness in animal studies [99].

Neurologic complications have been reported to occur in 10% to 28% of the patients treated with CsA [77,200]. Common complications include tremor, headache, and less frequently, PRES [53,223] (Table II). Mild symptoms in patients treated with CsA are frequent, and encompass tremor, neuralgia, and peripheral neuropathy. Severe symptoms affect up to 5% of transplant recipients such as psychoses, hallucinations, blindness, seizures, cerebellar ataxia and motor weakness [24,40,53,97,111,156,204]. Hypocholesterolemia and hypomagnesemia were suggested as possible precipitating factors for CsA neurotoxicity, however CsA neurotoxicity may be seen in patients with normal cholesterol and magnesium as well [53]. Symptoms typically improve by discontinuation, dosage reduction, or substitution with Tac [223]. Further reports indicate less toxicity associated with the oral route of administration [222]. Epileptiform EEG changes and frank seizures have been described in patients treated with CsA [7,231]. In a small number of patients, myalgia and myopathy have been linked to treatment with CsA. Interference with the mitochondrial function was suggested as the causative mechanism [33]. Use of CNIs in clinical practice in transplantology has significantly changed over the last 20 years. Introduction of microemulsion formulation of cyclosporine, CNI minimization strategies, trough levels monitoring, and introduction of modified release preparations of tacrolimus can be expected to decrease the frequency and severity of neurotoxicity in the longer term [193]. Although in a 12-month large randomized prospective study, no difference in neurotoxicity was seen between standard-dose CsA and low-dose CsA or low-dose Tac groups, it has to be noted that the trough levels of CsA

were not that much different in that study (approx. 150 vs. 100 ng/ml) with levels not exceeding 250 ng/ml for most of the study duration in the standard dosing group [64]. Noteworthy, there was no significant difference in the prevalence of brain abnormalities in early compared with late post-transplant periods when exposure to CI is tapered, and the authors concluded that abnormalities seen in brain MR in kidney transplant recipients are likely not predominantly linked to CNI toxicity [26].

Neurologic complications may be more severe while on Tac than on CsA [120,136], particularly in children [73,126], and it was also reported in liver transplant patients (The US Multicenter FK506 Liver Study Group). Some studies show complications related to Tac are less frequent, 5.4% versus 25% than to CsA [63] while in other publications on solid organ transplantations frequency of neurologic complications is higher in Tac than in CsA-treated groups [126,205]. Complications typically occur in the early post-transplant period, when higher doses and intravenous formulations are used [63]. Common neurologic complications of Tac include tremor, encephalopathy, headache, and seizures [63,220] (Table II). Mild symptoms include tremor, insomnia, nightmares, headache, vertigo, dysesthesia, photophobia and mood disturbances. Severe manifestations include akinetic mutism, seizures, cortical blindness, focal deficits, psychosis and encephalopathy [52]. The most serious complication is PRES, presenting with nausea, hematemesis, headache, loss of vision, seizures and altered consciousness [149], associated with subcortical and deep white matter changes [74,94]. The spontaneous resolution of the syndrome is probably associated with the spontaneous reduction in hemodynamic disorders. A rare but severe side effect of Tac can be peripheral neuropathy. About 0.003% of patients developed severe multifocal demyelinating sensorimotor polyneuropathy 2-10 weeks after the start of treatment with Tac, though similar changes can also be observed with CsA [224]. In another report, a late onset severe chronic inflammatory demyelinating polyradiculoneuropathy was diagnosed 10 years after Tac initiation, and resolved after Tac withdrawal [165].

The treatment of immunosuppressive neurotoxicity consists of correction of electrolyte imbalance and hypertension, immunosuppressant dose reduction and switching from cyclosporine to tacrolimus or vice versa, if necessary [109,196,233]. Use of combinations, such as CNI plus mycophenolate or mTOR inhibitor, enables lower doses of cyclosporine or tacrolimus to be used without weakening the immunosuppressive effect [124]. These approaches lead in most cases to the disappearance of the symptoms and the reversal of neuroimaging anomalies [27].

Corticosteroids

Corticosteroids are used for induction and maintenance immunosuppression, as well as against acute rejection. These agents prevent production of cytokines and vasoactive substances, including IL-1, IL-2, IL-6, tumor necrosis factor-α, chemokines, prostaglandins, major histocompatibility class II and proteases. Corticosteroids act as agonists of glucocorticoid receptors, but at higher doses, have receptor-independent effects. Corticosteroids have three principal mechanisms of action: 1) inhibit the synthesis of inflammatory proteins blocking NF-κB, 2) induce the expression of anti-inflammatory proteins by IkB and MAPK phosphatase I, and 3) inhibit 5-lipoxygenase and cyclooxygenase-2 [44]. Some of the observed effects of corticosteroids depend on the increase in the adrenergic effects of catecholamines and of the synthesis of epinephrine from norepinephrine [65].

Glucocorticoids and, to a lesser extent, mineralocorticoids cross the blood–brain barrier to access corticosteroid receptors within the CNS [206]. There are two major classes of corticosteroid receptors: mineralocorticoid receptors and glucocorticoid receptors [167].

Glucocorticoid receptors in the cytoplasm are in an inactive complex with heat shock proteins. The binding of corticosteroids to the glucocorticoid receptors dissociates heat shock proteins from the glucocorticoid receptors. Active corticosteroid–glucocorticoid receptor complexes migrate to the nucleus and dimerize on palindromic DNA sequences in many genes. The binding of glucocorticoid receptors in the promoter region of the target genes can lead to either induction or suppression of gene transcripts.

The most common corticosteroids used in transplantation are oral prednisolone/prednisone and intravenous methylprednisolone. Their role in maintenance immunosuppression is still under investigation because of severe side effects during long-term use. These agents are metabolized by the liver and excreted by kidneys as inactive metabolites. Drug interactions with P450 inhibitors and inducers are common. The neurologic complications of corticosteroids are reversible with a reduction and/

or withdrawal of their intravenous administration [166]. Common neurological complications linked to steroids are myopathies of skeletal and respiratory muscles and psychiatric disorders [32,55,208]. Psychiatric disorders include confusion, mood disturbances, manic states, psychotic reactions, anxiety, sleeplessness, reduced concentration, cognitive impairment. Steroid-induced psychosis is rare, but complications such as schizophrenic syndromes, affective disorders or delirium can also occur due to steroids use [57,150,214,226]. It was suggested that 50% of patients treated with medium to high doses of steroids for more than 3 weeks develop a proximal myopathy starting in the hip muscles. Steroid myopathy usually resolves slowly and it takes 2 to 8 months following discontinuation [37,47].

High-dosage treatment with corticosteroids and neuromuscular blocking agents may lead to the development of critical illness myopathy [36,107]. Myopathy usually improves gradually with dosage reduction or discontinuation of therapy. Epidural lipomatosis is a rare complication of steroid therapy; spinal compression and radiculopathy have been reported [70].

It has been proposed that cognitive dysfunction caused by corticosteroids may be a result of a combination of impaired hippocampal neurogenesis and subcortical white matter dysfunction [57].

Risk factors predisposing for neuropsychiatric side effects of corticosteroids include a daily dose of prednisone greater than 40 mg, damaged blood-brain barrier, hypoalbuminemia, and prior history of steroid-related psychosis or mania [218].

Prolonged use of steroids may also indirectly lead to numerous non-specific neurologic complications, including those related to opportunistic infections, osteoporosis, diabetes mellitus, obesity, elevated blood pressure etc. [44,60].

Polyclonal and monoclonal antibodies

Biologic agents are polyclonal and monoclonal antibodies that are frequently used in transplantation for induction immunosuppression or treatment of rejection. The three antibodies used for induction therapy are the lymphocyte-depleting agents: (1) antithymocyte globulin (ATG), (2) basiliximab, and (3) alemtuzumab (Table I). However, alemtuzumab has not been granted market approval for use in transplantations and has not been endorsed by recent Cochrane review due to insufficient and inconclusive data [9,87]. Historically, immunosuppressant selection was based solely on efficacy for the prevention of rejection. In the current era of transplantation, it is a common practice in the transplant community to select induction therapy based on risk-benefit considerations for each patient.

Polyclonal antibodies induce lysis of lymphocytes. Antithymocyte globulin rabbit acts against human T-cell surface antigens and depletes CD4 lymphocytes. In addition to T-cell depletion, it induces B-cell apoptosis, interferes with dendritic cell function, modulates adhesion molecules and chemokine receptors and induces regulatory T-cells. Administration of ATG can induce a cytokine-release syndrome, which includes fever, chills and sometimes hypotension and pulmonary oedema, and may mimic neurotoxicity reported after OKT3 use. ATG has many adverse effects (fever, thrombocytopenia, leukopenia, haemolysis, respiratory distress, serum sickness, and anaphylaxis), but some of them may be ameliorated with steroids. It is indicated for prophylaxis and treatment of renal transplant acute rejection in conjunction with concomitant immunosuppression. In comparison with basiliximab it causes a higher rate of infections including opportunistic infections [9,20,87,106,199].

The monoclonal antibodies used (mostly in clinical research except for basiliximab) in transplant patients include anti-CD3 antibody (OKT3, muromonab), anti-CD25 antibody (basiliximab and daclizumab), anti-CD20 antibody (rituximab) and anti-CD52 antibody (alemtuzumab) (Table I). Except for OKT3, their administration to transplant patients is associated with a very low prevalence of neurologic adverse effects.

Basiliximab

Basiliximab is an IL-2R antagonist indicated for prophylaxis of kidney transplant rejection and is used as induction treatment. Its use has not been linked to specific neurotoxicities and has not been shown to increase occurrence of malignancies or opportunistic infections [20,106].

Alemtuzumab

Alemtuzumab is a humanized recombinant monoclonal antibody against CD52 which is present on T-cells, B-cells, NK cells and to a lesser extent on monocytes.

As with ATG, alemtuzumab infusion can be followed by a cytokine-release syndrome [225], however it is much milder than with ATG. It is used off-label as part of various induction regimens in patients undergoing kidney transplantation. The use of alemtuzumab as induction immunosuppression for renal transplantation introduces the possibility of long-term Tac monotherapy, avoiding maintenance with both corticosteroids and MMF. Renal transplantation with alemtuzumab induction followed by Tac monotherapy leads to good graft and patient outcomes, with no major differences detected compared with basiliximab induction and tacrolimus/mycophenolate mofetil maintenance at one year. Higher frequency of opportunistic infections comparing to basiliximab has been suggested [87,106,158], which may translate into the corresponding risk of neurologic complications.

OKT3

OKT3 is a murine monoclonal antibody targeted against the CD3 adhesion molecule on lymphocytes. It was most frequently used in the treatment of rejection, and it was associated with aseptic meningitis, encephalopathy and seizures [197]. OKT3 caused release of systemic proinflammatory cytokines in CSF, which are responsible for the flu-like syndrome and may be involved in the pathogenesis of the cerebral oedema [3]. Approximately 5% to 10% of patients treated with OKT3 developed an acute aseptic meningeal syndrome associated with aseptic meningitis presenting within 72 hours of its administration [90]. Diffuse encephalopathy was rarely seen with coma, seizures, psychosis and brain oedema. The encephalopathy may take up to 2 weeks to resolve. OKT3 is rarely associated with neurologic complications because of its reduced neurotoxicity and its current limited clinical indications. Its use was contraindicated in patients with underlying neurologic problems such as seizures. The product has been withdrawn from the market [22].

Rituximab

Rituximab is a chimeric anti-CD20 monoclonal antibody which acts through depletion of B cells [18]. It has not been approved for use in renal transplantation [169] but its use has been endorsed for specific subpopulations of organ transplant recipients by the international transplantology society expressed in national guidelines [39,159,229] e.g. for ABO blood group incompatible transplantation, for post-transplant lymphoproliferative disorder, HLA antibody incompatible renal transplantation and for treatment of acute rejections. It has been postulated that rituximab may prevent development of chronic antibody mediated rejection [18]. Regarding its toxicity, the drug can cause e.g. cytokine release syndrome, progressive multifocal leukoencephalopathy infusion-associated hypotension, cardiovascular disorders and infections [169]. Cases of PRES linked to rituximab administration were also reported [25].

Belatacept

Belatacept is a selective T-cell costimulation blocker. It comprises of a recombinant extracellular domain of human cytotoxic T lymphocyte antigen-4 (CTLA-4) and a fragment of a modified Fc portion of human IgG1. The drug binds to CD 80/86 ligands of antigen-stimulating cells and thereby inhibits the CD-28-mediated T-cell costimulation. T-cells activation requires two signals of which the first signal is mediated by the interaction of major histocompatibility complex (MHC): T cell receptor (TCR) and the second is mediated by the costimulatory molecules. The costimulatory molecules CD80/86 ligands in the antigen presenting cells bind to CD28 of the T-cells to induce the immunological response. The costimulatory molecules CD28:CD80/86 interaction is also essential for clonal proliferation of cytotoxic T cells which play a main role in the graft rejection [112].

Belatacept has been approved for use in combination therapy to prevent renal graft rejection in patients who are Epstein-Barr virus seropositive. Despite some advantages over calcineurin inhibitor-based regimens it bears a risk of post-transplant lymphoproliferative disorder (PTLD), a rapidly progressing and often lethal malignancy. The occurrence of PTLD, particularly PTLD involving the central nervous system was noted in 0-4% of belatacept-treated patients in clinical trials. Belatacept has also potential to induce progressive multifocal leukoencephalopathy [23,68,106,121].

mTor inhibitors

Mammalian target of rapamycin (mTOR) inhibitors inhibit T-cell activation and proliferation. Unlike calcineurin inhibitors, sirolimus and everolimus inhibit the second phase of T-cell activation [83].

The second phase involves signal transduction and clonal proliferation of T-cells. These agents inhibit interleukin-induced proliferation of T-cells resulting in the cell cycle arrest in the late G1-phase, which prevents progression to the S-phase [80]. Mammalian target of rapamycin (mTOR) is a serine/threonine kinase, integrating multiple signals such as nutrition, oxygen supply, and growth factors [38]. mTOR inhibitors (sirolimus and everolimus) need to bind to the 12-kD immunophilin FK-506-binding protein in order to block the serine/threonine kinase activity of the mTOR/raptor/GbetaL complex [85]. Two TOR proteins have been identified – TOR1 and TOR2 and both everolimus and sirolimus were long thought to act almost only through inhibition of TOR1 complex (TORC1) [239]. However, there has been increasing evidence that the additional hydroxyethyl group at the C(40) of the everolimus is linked to not only different tissue and subcellular distribution, but also to different affinities to active drug transporters and drug-metabolizing enzymes, and interaction with TORC2 than sirolimus [103]. It was suggested that everolimus, but not sirolimus, distributes to brain mitochondria and stimulates mitochondrial oxidation in the brain and contrary to sirolimus, everolimus counteracts CsA-related negative effects in the rat brain energy state [102,178,179]. In contrast to sirolimus, everolimus was shown not to affect cyclosporine concentrations in blood and brain tissue but it reduced cyclosporine concentrations in brain mitochondria by 65% [178].

Sirolimus and everolimus have shown their efficacy in kidney transplantation in a variety of immunosuppression regimes, but their wide use has been limited by relative high discontinuation rates and safety profile. Their most important adverse effects are thrombocytopenia, leukopenia, hypercholesterolemia, stomatitis, diarrhoea, and, interstitial pneumonitis [131]. In a long-term retrospective analysis of 10 prospective randomized trials in kidney transplantation it was shown that the efficacy of *de novo* use of mTOR inhibitor is similar to antimetabolites in kidney transplant recipients receiving calcineurin inhibitor. Patients on mTOR inhibitor benefited from the lower CMV infection rate, but the overall safety profile was unfavourable, showing higher treatment discontinuation rates and higher incidence of proteinuria [54]. In heart transplant recipients patients switched from CNI to mTORi had a higher creatinine clearance but also significantly higher occurrence of adverse effects, which included skin diseases, gastrointestinal side effects, bone marrow suppression, and infections [163]. Also, when compared with mycophenolate as part of the combination with CNI in kidney transplantation, mTOR-I showed no particular superiority to mycophenolate, and instead mTOR-I had an increased risk of graft loss when combined with CNI, even when combined with a reduced dose of CNI. In this retrospective analysis of 4930 patients treated with mTOR-it had a higher risk of new-onset diabetes mellitus, dyslipidemia, proteinuria, peripheral oedema, thrombocytopenia and lymphocele, but a lower risk of CMV infection, malignancy and leukopenia. Neurotoxicity was not reported [234].

Neurotoxicity with mTOR inhibitors is relatively low, however PRES associated with mTOR inhibitors was reported [134,162,202]. Sirolimus rarely causes neurotoxicity since it can alter cell metabolism of astrocytes, thus resulting in similar neurotoxicity as experienced by Tac and CsA (tremor, confusion, agitation and headache) [175]. For everolimus rare adverse effects are dizziness, hypoesthesia, paraesthesia, somnolence, and tremor [11]. Bilateral optic neuropathy was also reported [202]. As mentioned earlier, mTOR intermediates depression-like symptoms which may lead to corresponding psychiatric abnormalities during mTOR inhibitors use [2,237], although scarce evidence exists that mTOR inhibitors may have a more favourable profile than CNIs in this respect [111]. In a small study, no difference between CNIs and everolimus was shown in terms of negative impact on the cognitive function in heart transplant recipients. About 40% of subjects had cognitive impairment, defined as performance at least 1.5 standard deviations below normative mean in one or several cognitive domains in that population [35].

Other immunosuppressants

Apart from a variety of off-label agents used occasionally or in clinical trials in transplantology, there are two other important subgroups of medications which belong to standard of care in solid organ transplantations. The first group comprises agents inhibiting synthesis of nucleotides – purine synthesis inhibitors – mycophenolate and pyrimidine synthesis inhibitors – leflunomide. The second group comprises old drugs – so-called antimetabo-

lites: azathioprine and cyclophosphamide [171]. From this selection, mycophenolate derivatives (mofetil or sodium salt) are most frequently used. Mycophenolate inhibits enzyme – inosine monophosphate dehydrogenase (IMPDH) required for guanosine synthesis and suppresses *de novo* purine synthesis in lymphocytes, thus inhibiting their proliferation [127]. Mycophenolate impairs B and T-cell proliferation, sparing other rapidly dividing cells due to the presence of guanosine salvage pathways in other cells. This agent is frequently used in regimens containing a calcineurin inhibitor and corticosteroids for prevention of renal allograft rejection [171]. Mycophenolate has been shown to decrease prevalence of acute cellular rejection compared with azathioprine and prevalence of chronic rejection [6,154]. The prescribing information for MMF reports psychiatric disorders – common – agitation, confusional state, depression, anxiety, thinking abnormal, insomnia, and nervous system disorders – common – convulsion, hypertonia, tremor, somnolence, myasthenic syndrome, dizziness, headache, paraesthesia, dysgeusia as adverse reactions possible or probable related to MMF. Cases of JC virus related PML have also been reported. It is also possible that the rate of infections is increased in relation to mycophenolate use [137]. A case study reported a 64-year-old woman who developed a severe depressive disorder after the start of therapy [59]. However, it is generally believed that mycophenolate is not causing neurotoxicity [11].

According to Cochrane analysis, mycophenolic acid was superior azathioprine to AZA for improvement of graft survival and prevention of acute rejection after kidney transplantation. However it was noted that these benefits must be weighed against potential harms. The available evidence on safety outcomes is limited and inconsistent [215]. Azathioprine (Aza), a disease-modifying antirheumatic drug (DMARD), was also employed in renal transplantation to prevent graft rejection however due to reported higher efficacy of mycophenolate, its use in organ transplantations has been declining significantly. Its anti-proliferative properties are less selective than those of MMF [66,210]. Azathioprine antagonizes purine metabolism and inhibits synthesis of DNA, RNA, and proteins. It may decrease proliferation of immune cells, which results in lower autoimmune activity [6,156]. Azathioprine has been clearly identified as having potential to increase the neuromuscular blockade produced by depolarising agents such as succinylcholine and can reduce the blockade produced by non-depolarising agents such as tubocurarine [15]. An increased risk of infections and cases of PML were also reported for AZA [15]. Very rare cases of psychiatric complications of AZA were reported [31] and they comprised a complex picture of behavioural changes, forgetfulness, confusion, memory loss and communication difficulty, obsessive-compulsive disorder and panic attacks [31,209].

Neither leflunomide nor cyclophosphamide has been used as part of standard immunosuppression after organ and specifically kidney transplantation [101,159]. However, Johannes *et al*. [216] have published recently a systematic report on cyclophosphamide-based treatment of acute antibody-mediated rejection showing a positive effect of combined regimen (with plasmapheresis and i.v. immunoglobulins) proven with modern diagnostic measures. Cyclophosphamide has been linked with multiple toxicities. According to Summary of Product Characteristics [51], apart from an increased risk of infections, the following side effects are known or suspected to be related to cyclophosphamide a) psychiatric disorders (very rare confusional state), b) nervous system disorders (uncommon – peripheral neuropathy, polyneuropathy, neuralgia, convulsion, dizziness, dysgeusia, hypogeusia, paraesthesia, general neurotoxicity, unknown frequency – PRES, encephalopathy). Also, vision disorders, hearing disorders and muscle symptoms were noted.

Regarding other agents reported in the context of immunosuppression in organ transplantology, it is worth mentioning relatively new agents – bortezomib and eculizumab [106, 159]. Bortezomib (BTZ) is a proteasome inhibitor and an antineoplastic drug that reversibly inhibits mammalian 26S proteasome and interacts with the nuclear factor kappa B (NFκB) system, thus leading to cytoplasmic aggregate accumulation and cell cycle arrest in cancer cells [128]. It is also known to induce neurotoxicity in neuronal cells by several mechanisms that lead to apoptosis [176]. BTZ has been shown to induce peripheral neuropathy characterized by neuropathic pain in a stocking-and-glove distribution and by paraesthesias in distal extremities of limbs, mainly due to unmyelinated and thin myelinated sensory fibers impairment (C and Aδ fibers, respectively) [128]. Eculizumab is a fully humanized monoclonal antibody directed against the C5 component of the complement cas-

cade. There have been inconclusive data on its efficacy in kidney transplantation although some results have been encouraging PTT 2016 [96,114,236]. Eculizumab is known to increase the risk of infections, including increases in the patient's susceptibility to meningococcal infection (*Neisseria meningitidis*) [17]. According to the Summary of Product Characteristics [62], headache has been another typical adverse reaction of eculizumab. Other potential adverse reactions include: psychiatric disorders – insomnia, depression, mood disorder, anxiety, abnormal dreams, sleep disorders; neurologic disorders – dizziness, dysgeusia, tremor, paraesthesia, syncope; other – vision disturbances. tinnitus and vertigo, musculoskeletal symptoms [62].

Neurologic complications of kidney transplantation

Ischemic stroke

Ischemic strokes are relatively common in heart and kidney transplant recipients. Stroke may occur in 8% of renal transplant recipients and may be facilitated by hypertension, diabetes and accelerated atherosclerosis, which may be acquired during dialysis or after transplantation [160]. Apart from immunosuppressive treatment, ischemic strokes may be related to the surgical procedure of transplantation, complications typical for surgery (e.g. bacterial infections, anaesthesia-related negative outcomes, bleeding etc.), presence of bacterial endocarditis and vasoinvasive fungal CNS infections, hypercoagulable states, accelerated atherosclerosis, vasculitis and cardiac arrhythmias after transplantation [160]. While aetiology of strokes in the transplant recipient population is shifted toward perioperative and infectious causes, in medium- and long-term survivors accelerated atherosclerosis after transplantation [48,146] will affect cerebrovascular circulation increasing the risk of stroke [140]. In heart and liver allograft recipients, strokes occur early after transplantation and they tend to occur late after kidney transplantation. In kidney transplant recipients, age over 40 and diabetes were found to be major risk factors for cerebrovascular disease [4].

Ischemic strokes after kidney transplantation are frequently related to atherosclerosis [144]. A significant reduction in stroke incidence has been reported in diabetic patients receiving simultaneous kidney and pancreas transplantation [140]. Concomitant control of the main risk factors (cholesterol, glycaemia and hypertension) is critical as is preventive treatment with antiplatelet agents like aspirin. Cyclosporine, mTOR inhibitors, and to a lesser extent, Tac, may cause hypercholesterolemia, accelerating cerebrovascular disease, especially in patients with prolonged survival [174]. Also, patients who converted from CNI to mTOR inhibitor have a substantially greater risk of e.g. anaemia, hyperlipidaemia and hypercholesterolemia [116]. According to a recent paper published by Simha *et al*. [186], sirolimus is associated with elevation in PCSK9 levels, which is not associated with sirolimus-induced hypercholesterolemia. This suggests an independent pathway for mTOR-inhibitors-induced hypercholesterolemia, as PSCK9 plays a major regulatory role in cholesterol homeostasis, mainly by reducing LDL receptor (LDLR) levels on the plasma membrane. Reduced LDLR levels result in decreased metabolism of LDL-particles, which could lead to hypercholesterolemia [76]. Substituting CsA with Tac may reduce cholesterol levels [198]. On the other hand, it has been postulated that mTOR inhibitors may offer a cardioprotective effect as in experimental settings delayed progression of atherosclerosis is observed consistent with evidence from heart transplant patients where coronary artery intimal thickening and the incidence of cardiac allograft vasculopathy are reduced with everolimus versus cyclosporine therapy. Earlier data exist as well showing that mTOR inhibitors may improve arterial stiffness, which precedes cardiovascular (CV) events, and may reduce ventricular remodelling and decrease left ventricular mass through an anti-fibrotic effect [89]. Thus, cardiovascular /hypercholesterolemia-related effects of mTOR inhibitors may not necessarily contribute to CV-dependent neurologic complications seen during their use. Clinical data support this hypothesis. In a retrospective analysis, patients receiving SRL after liver transplantation had no increased risk of coronary artery disease or cardiovascular accidents (CAD/CVA) as compared with patients maintained on a calcineurin inhibitor [217].

Stroke is more common after kidney transplantation, while encephalopathy, seizures and CPM (central pontine myelinolysis) are characteristic of liver transplantation. In kidney transplant patients, stroke is the most common neurologic complication, whereas cerebral infarction and bleeding are more typical after heart transplantation. Kidney allograft recipients frequently develop post-transplant poly-

cythaemia (17% of patients) and hypercoagulability, which may increase the risk of stroke [5,100]. The risk for aneurismal subarachnoid haemorrhage is increased 10-fold in kidney allograft recipients transplanted for polycystic kidney disease [219]. Diabetic nephropathy as a cause of pre-transplant kidney failure also increases the risk of post-transplant intracranial haemorrhage [219] and it can be anticipated that the same consequence follows from diabetes related to use of immunosuppressants. Calcineurin inhibitors and steroids are best known to induce post-transplant diabetes, with a higher risk of this complication seen with tacrolimus. In a retrospective analysis of kidney transplant recipients, post-transplantation diabetes mellitus occurred more frequently in patients receiving a cadaver organ compared with a living donor organ and in those receiving tacrolimus therapy vs cyclosporine therapy [29,61]. However, also mTOR inhibitors were associated with an increased risk of new-onset diabetes after transplantation (NODAT) [29].

Encephalopathy

Metabolic encephalopathy is common among transplant recipients; the aetiology is as variable as in non-transplant patients, commonly including electrolyte and changes in glucose levels. Patients with pre-existing diabetes are sensitive to treatment with steroids, in addition Tac may precipitate diabetic ketoacidosis. Abrupt, inadvertent steroid discontinuation may also cause a disturbance of consciousness. Patients with a severe systemic infection without CNS involvement typically develop sepsis-related encephalopathy [30,91]. Delayed graft function in orthotopic liver and kidney transplantation is associated with hepatic and uremic encephalopathy, respectively [91].

Common causes of encephalopathy include neurotoxicity from non-immunosuppressive drugs, various metabolic derangements, CNS or systemic infections, and stroke. Immunosuppressant-related encephalopathy has been also described with e.g. CsA, Tac, OKT3 [16,43,88,110,164,194], and as mentioned earlier – rituximab, belatacept and cyclophosphamide. Although neurotoxicity of mTOR inhibitors is relatively low, they can induce PRES in kidney transplantation patients [134,162,202]. Neurotoxicity is usually associated with higher serum concentrations of immunosuppressants, but may also become apparent at serum levels within the therapeutic range. Common adverse signs are tremor, headache and cerebellar or extrapyramidal signs [157].

Neurotoxicity of CNIs is clinically indistinguishable and classical neuroimaging findings are indistinguishable from PRES in eclampsia or hypertensive encephalopathy [88,110,191]. It is not fully understood why posterior circulation is usually more severely affected, but this has been attributed to the less extensive sympathetic vascular innervation posteriorly. Clinically, PRES commonly presents with akinetic mutism, visual symptoms, occipital seizures, and overall impairment of consciousness [16]. Most commonly, Tac or CsA-related PRES presents within the first month after transplantation, but rarely occurs more than a year later [43,164].

Neuromuscular complications

Femoral neuropathy and meralgia paresthetica have been reported in renal and liver transplantation, while phrenic nerve injury is seen in the setting of heart and lung transplantation [14,161,183]. Lumbosacral plexopathy may be associated with retroperitoneal bleeding or iliac artery pseudoaneurysms [119]. Peripheral mononeuritis and polyneuritis may also occur. An acute femoral neuropathy can develop in 2% of the patients as a result of perioperative nerve compression by retractors or nerve ischemia. Patients complain of weakness in the thigh and pain or sensory deficits on the thigh and inner calf. Most patients have an excellent chance of recovery [181,212].

Peripheral toxicity occurs weeks to months after starting immunosuppressive treatment. Both the nerve and the muscle may be involved. Axonal and demyelinating neuropathy have been reported. The more severe forms have been observed during Tac therapy, such as multifocal demyelinating neuropathy resembling chronic inflammatory demyelinating neuropathy (CIDP). Moreover, akinetic mutism and various aphasic and apractic syndromes may be seen in the setting of both Tac and CsA toxicity [28,168]. These usually improve with dosage reduction and careful monitoring of serum drug levels. Paradoxically, Tac showed neuroprotective properties in some experimental models of peripheral nerve injury [113]. The evidence for the existence of Tac-related peripheral neuropathy is still equivocal, and further studies are needed to firmly establish its pathophysiology and relevance.

Muscle-related or neuromuscular adverse reactions have been reported with most of the immunosuppressive medications. As mentioned earlier, those include e.g. steroid-induced myopathy, myalgia and myopathy during CNIs use, myalgia observed in thymoglobulin-treated patients, tremor after mTOR inhibitors use, myasthenic syndrome reported for mycophenolate and neuromuscular block seen with azathioprine, musculoskeletal symptoms described as potentially related to cyclophosphamide and eculizumab.

Behavioural disorders

Corticosteroid therapy is one of cornerstones of immunosuppression protocols, used for maintenance therapy as well as for treatment of acute rejection. Direct neurologic complications include steroid-related psychosis, myopathy, and epidural lipomatosis. The incidence of acute side-effects is 3–4% and the most common neurologic complications are behavioural disorders including confusion, mood disturbances, manic states and psychotic reactions [150]. Behavioural changes associated with steroid use range from minor mood disturbances to florid psychosis. Symptoms usually improve with dosage reduction or discontinuation of therapy, but occasionally, adjunct antidepressant and neuroleptic therapy needs to be considered. Repeated exposure to steroids does not routinely increase the risk of developing psychosis. Behavioural disorders, as already cited, were also linked to CNI, mTOR inhibitors and mycophenolate. Uncommon, rare or very rare cases of psychiatric/behavioural changes were reported with AZA, cyclophosphamide, mycophenolate and eculizumab [9,106].

De novo CNS malignancies

Organ transplant recipients have a three- to fourfold higher incidence of malignant disease compared with the general population [153], due to their reduced immunosurveillance and high incidence of infections involving oncogenic viruses. The incidence of post-transplant lymphoproliferative disorders has been estimated at less than 2% (with higher rates in the paediatric population) and 27% of cases involve the CNS and meninges [46,95,155]. In a recent report from database of 1421 adult patients who underwent renal transplantation from deceased or living donors in the period from 2007 to 2015 in the Slovak transplant centres, frequency of PTLD was found as 2.4% [240]. Patients undergoing heart–lung or liver–bowel transplantation are at the highest risk (5%) for CNS malignancies, while the risk is lower with liver, cardiac and bone marrow allografts (1-2%), and lowest with kidney transplantation (< 1%) [95]. The most frequent malignancies of the brain in renal transplant recipients are lymphomas and metastatic tumours which are, for the most part, *de novo* malignancies from immunosuppression. The most common malignant PTLD subtype is post-transplant diffuse large B-cell lymphoma (PT-DLBCL), followed by Burkitt lymphoma (PT-BL) and plasmablastic lymphoma (PT-PBL). PT-BL and PT-PBL are aggressive, but poorly studied malignant PTLD subtypes [133]. Many of the reported cases of CNS lymphomas are associated with prior EBV infections [151]: this condition is estimated to occur in 3% of liver recipients [194] and in 1-2% of kidney recipients [75]. The clinical manifestations vary and the final diagnosis is often based on cerebral biopsy [152]. Treatment options include reduction of immunosuppression, anti-CD20 monoclonal antibodies, and/or chemotherapy [118]. Localized disease may be successfully treated with radiotherapy or surgery [81].

Immunosuppressed allograft recipients have an increased incidence of cancer. An increased incidence of post-transplant lymphoproliferative disorder (PTLD) was also observed with use of antithymocyte immunoglobulin, OKT3, belatacept, CNIs [9,10,50,106,121,138]. Mycophenolate has not been linked to PTLD while for mTOR inhibitors the data have been inconclusive. As mTOR signalling pathways were shown to be activated in PTLD cases, protective effects were proposed for mTOR-inhibition in PTLD. However, recent studies reported slightly increased PTLD incidences during maintenance therapy with mTOR-I-based immunosuppression [138].

CNS infection

All immunosuppressive medications are associated with an increased rate of opportunistic infections. The presentation of CNS infection in transplant recipients can vary from that seen in normal population, as the anti-inflammatory effects of immunosuppressive therapy may obscure signs of meningeal inflammation associated with meningitis and changes in the level of consciousness may be subtle [72]. CNS infections in renal transplant recipients are associated with significant mortality and morbidity, which makes understanding of the need of special

methods for detection and isolation of pathogens extremely important.

Opportunistic bacterial infections include pathogens such as: *Legionella*, *Nocardia*, *Mycobacterium tuberculosis* and *Listeria monocytogenes*. The involved fungal organisms are often: *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Candida*, *Pneumocystis carinii*. Common viruses include *Cytomegalovirus* (CMV), Varicella-Zoster virus and Epstein-Barr virus (EBV), Herpes viruses 1 and 2 (HSV 1 and 2) and BK/JC polyoma virus are less common. Acute meningitis, usually caused by *L. monocytogenes*, subacute and chronic meningitis caused by *C. neoformans*, focal brain infections caused by *A. fumigatus, Toxoplasma gondii* or *Nocardia asteroids*, and progressive dementia caused by Polyoma J virus were reported to be the most common CNS infections in kidney transplant recipients [160].

Acute and chronic allograft rejections require higher doses of immunosuppressive drugs and thus increase the risk of CNS infection. In reports published before 2000, CNS infections complicated the post-transplant course of 5% to 10% of allograft recipients with a high mortality rate of up to 75% [47] and in autopsy series, the incidence of CNS infections was even higher, reaching 10% to 16% [122,123]. Recent reports indicate a declining incidence of CNS infections, which may be explained by declining immunosuppressive burden especially with polyclonal antibodies, doses of CNIs and steroids, and better diagnostics enabling earlier detection of the infection, and thus preventing its development into CNS infection. According to a review published in 2014, the incidence of the most common CNS infections stands approximately for: 0.1-0.2% for aspergillosis, cryptococci, fungal infection, and less than 0.05% for other infections including nocardiosis, JC virus – PML, and moulds [230]. In a prospective, nation-wide population-based study in the Netherlands [211], carried out between 2006 and 2014, in data from 68,526 patient-years of follow-up of patients after solid organ transplantation, the annual incidence of bacterial meningitis was 7-fold higher (95% confidence interval [CI]: 2.94-17.02, $p < 0.001$) for renal transplant recipients as compared with the general population (9.56 [95% CI: 3.98-22.96] vs. 1.35 [95% CI: 1.28-1.43] per 100,000 patients per year). However, overall, only 6 cases were identified, with one case with the classic presentation of bacterial meningitis (fever, neck stiffness, and change in the mental status). Seizures were more common and were seen in 33% of patients. Pathogens responsible were *Streptococcus pneumoniae* and *Listeria monocytogenes* identified in 2 patients each, and *Escherichia coli* and *Pseudomonas aeruginosa* in the remaining patients [211].

Fungal CNS infections in solid organ transplantation seem more frequent. The overall cumulative incidence during the first year after transplantation is considered to be at the level of 3% depending on the type of the organ transplanted [184]. In the decreasing order, the risk seen in transplantations stands for (incidence rate in brackets) – small bowel (11.6%), lung (8.6%), liver (4.7%), heart (4.0%), pancreas (3.4%) and kidney (1.3%). Candidiasis is the most common invasive fungal infection in SOT recipients and accounts for 50-60% infections, followed by aspergillosis accounting for 20-25% of fungal infections, then *Cryptococcus* species (6-7%), the endemic fungi (5%) and other species [148].

The CNS infection commonly results from dissemination of the systemic infection, where the lungs and gastrointestinal tract constitute common points of entry to the bloodstream. The paranasal sinuses are also critical routes of entry to the CNS, explaining, for instance, how fungal sinusitis may easily become fungal meningitis [139].

There is a correlation between time after transplantation and the organism that is most likely responsible for CNS infection [47]. In the acute perioperative period (first 30 days), the CNS infection is most likely related to nosocomial, pre-existing, or donor-related organisms. The risk of viral and fungal opportunistic infection is greatest one month post-transplantation, as immunosuppression becomes effective. Six months post-transplantation, infections reportedly result from reactivation of infections acquired earlier, opportunistic infections related to chronic immunosuppression, or common organisms found in immunocompetent patients. During the initial month, CNS infection is most often caused by common bacterial pathogens or opportunistic pathogens present in either the transplant environment (e.g. *Aspergillus* species), or host (e.g. *Mycobacterium tuberculosis*). At 1 to 6 months, there is increased susceptibility to CNS infection by the herpesviruses, especially CMV and Epstein-Barr virus (EBV), fungi, and atypical bacteria. Finally, after 6 months, reduction of immunosuppression is accompanied by decreased susceptibility to CNS infection [241].

One of the most frequent opportunistic bacteria infecting immunocompromised patients is *Legionella pneumophila*. It causes serious infection particularly in patients with impaired cellular immunity. However *Legionella* is not known as a frequent cause of CNS infections in solid organ transplant recipients [230].

Acute meningitis is usually caused by *L. monocytogenes*, subacute and chronic meningitis by *C. neoformans*, and focal brain infections by *A. fumigatus*. *L. monocytogenes*, contracted through ingestion of contaminated food, needs to be considered in transplant patients with symptoms and signs of meningoencephalitis. The classic pathogens like *Haemophilus* and *Streptococcus pneumoniae* are infrequently seen in the transplant population. Meningitis, with or without focal neurological signs, is the commonest form of CNS listeriosis; in addition, listeriosis may cause rhombencephalitis, abscesses, and even myelitis [58].

Mycobacterium is rarely implicated as a CNS pathogen in transplant patients [34]. Immunosuppression may facilitate the progression of a latent, quiescent mycobacterial infection. Pulmonary tuberculosis and atypical mycobacterial CNS infections share similar treatment algorithms. CNS infections may be exceedingly difficult to diagnose, requiring multiple lumbar punctures and polymerase chain reaction studies. Three main presentations of *M. tuberculosis* in the CNS have been described: cerebral tuberculoma, meningitis and myelopathy [192].

Nocardia asteroides is another organism that is rarely recognised in immunocompetent persons, but in transplant patients it may cause subacute or chronic meningitis as well as cerebritis. *Nocardia* infections were reported in 1% to 6% of solid organ transplant recipients and in fewer than 5% of renal transplant recipients [41,49]. In nocardiosis, pulmonary infection usually precedes CNS involvement [47]. Guillain-Barré syndrome may also develop, associated in some cases with CMV or *Campylobacter jejuni* infection [79].

Cryptococcal meningitis is the most common subacute meningitis seen in renal transplant recipients, especially in patients who are exposed to birds, and is universally fatal without treatment. Like all other fungi, cryptococci enter the body through the respiratory tract but CNS is the primary target [92,232]. Symptoms may show and disappear over time and include e.g. headaches, fever, lethargy, abnormal mental status, and coma. Elevated CSF pressure without evidence of obstructive hydrocephalus, believed to result from basilar meningitis and impaired reabsorption of CSF across arachnoid villi, was reported as an important complication of cryptococcal meningitis [92]. In a retrospective analysis of solid organ transplant recipients with cryptococcosis, it was found that 30% of them had changes in computed tomography (CT) or MR. Abnormal neuroimaging findings corresponding with the cryptococcal lesions included leptomeningeal lesions in 50% (8/16), parenchymal lesions in 37.5% (6/16), and hydrocephalus in 12.5% (2/16) [188].

It needs to be mentioned that some immunosuppressive agents (cyclosporine, tacrolimus, mTOR inhibitors) have *in vitro* activity against fungi, including *C. neoformans* [92], and its clinical relevance was confirmed by a multivariable analysis of data from a large study showing that the receipt of a CNI was independently associated with a lower mortality (adjusted HR, 0.21; $p = 0.008$) [187].

In invasive aspergillosis, CNS involvement frequently presents with altered mental status, seizures, focal neurologic deficit, with brain abscess most common location being the fronto-parietal region of the cerebral hemispheres, though the cerebellum and brainstem may also be involved. As *Aspergillus* is an angioinvasive pathogen, cerebral infarcts or haemorrhagic lesions can be found [201]. In a recent summary of a series of cases it was reported that mortality among CNS aspergillosis patients remains high, and suggested that the infection may be more common among patients with previous brain pathology [104].

Herpes virus infections are extremely common in renal transplant recipients but meningoencephalitis is a rare and potentially life-threatening complication mostly caused by HSV-1. Varicella-zoster virus, apart from varicella (chickenpox) and herpes zoster (shingles), may lead to CNS complications such as post-varicella cerebellitis, meningoencephalitis (including the Ramsay Hunt syndrome), vasculopathy, and acute aseptic meningitis. Comparing to normal population, post-transplant patients with zoster are more likely to develop post-herpetic neuralgia [241].

Cytomegalovirus (CMV) is an uncommon cause of encephalitis or Guillain-Barré syndrome in solid organ transplant [237]. Reactivated latent JC virus is found in more than 90% of patients with PML [125]. PML symptoms may include mental status changes, visual field deficits, focal neurologic deficit, while in neuroimaging single or multiple non-enhancing

white matter lesions in CT or MRI lesions most often in the parieto-occipital region are seen [241].

In post-transplant patients, EBV infection can be a primary infection or reactivation of latent infection. It can be associated with meningoencephalitis and an abnormal proliferation of lymphoid cells, causing aseptic meningitis, seizures, encephalitis, or PTLD [230,241]. Twenty-eight percent of patients with PTLD have CNS involvement, and EBV-associated PTLD may be characterized by a mental status change, hemiparesis, or other focal neurologic deficit. In neuroimaging, the focal lesion with variable enhancement can be seen and may have associated haemorrhage or leptomeningeal spread [241].

Immunocompromised kidney transplant recipients may also develop other opportunistic infections, like parasite infections, although rarely affecting the nervous system [241]. Toxoplasmosis is an example with CNS involvement occurring very rarely. In a long, multicentre, matched case-control study in Spain, toxoplasmosis developed in 0.14% of solid organ transplant recipients and toxoplasma-related brain abscesses or meningitis developed in approx. 25% of those very few cases [69].

Future considerations

Organ transplantation is one of the most dynamic fields in medicine and continuously improving outcomes have been achieved in the field of renal transplantation. A significant reduction in acute rejection has been attained at many renal transplant centres using contemporary immunosuppressive therapy. Long-term use of these drugs has been associated with the development of chronic allograft nephropathy and other adverse events. The common neurologic complications such as stroke, encephalopathy, behavioural disorders, neuromuscular complications, CNS *de novo* malignancies, and opportunistic infections still persist. Functional data in healthy human subjects are required to clarify the genuine CNS effects of immunosuppressants in order to be able to differentiate between these drug effects and the CNS effects of transplantation. As more patients are experiencing prolonged survival, the number of patients at risk for chronic complications is increasing, therefore personalizing the immunosuppression therapy to the individual needs of the patient may be favourable. The perfect immunosuppressive regimen would limit or eliminate calcineurin inhibitors neurotoxicity while providing enhanced allograft outcomes. Potential improvements to the calcineurin inhibitor class include a prolonged release tacrolimus formulation. On the other hand, PTLD risk has challenged introduction of belatacept, otherwise a promising novel solution. Moreover, new immunosuppressive agents which eliminate these issues are desirable. As the field of organ transplantation continues to evolve, research should be conducted to create suitable drugs that sustain immunotolerance in transplantation medicine, eliminating the previously mentioned adverse effects.

Disclosure

Authors report no conflict of interest.

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