Review

Recent topics on the mechanisms of immunosuppressive therapy-related neurotoxicities

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Abstract: Although transplantation procedures have been developed for patients with end-stagec hepatic insufficiency or other diseases, allograft rejection still threatens patient health and lifespan. Over the last few decades, the emergence of immunosuppressive agents, such as calcineurin inhibitors (CNIs) and mammalian target of rapamycin (mTOR) inhibitors, have strikingly increased graft survival. Unfortunately, immunosuppressive agent-related neurotoxicity is commonly occurred in clinical situations, with the majority of neurotoxicity cases caused by CNIs. The possible mechanisms whereby CNIs cause neurotoxicity include: increasing the permeability or injury of the blood-brain barrier, alterations of mitochondrial function, and alterations in electrophysiological state. Other immunosuppressants can also induce neuropsychiatric complications. For example, mTOR inhibitors induce seizures; mycophenolate mofetil induces depression and headache; methotrexate affects the central nervous system; mouse monoclonal immunoglobulin G2 antibody against cluster of differentiation 3 also induces headache; and patients using corticosteroids usually experience cognitive alteration. Therapeutic drug monitoring, individual therapy based on pharmacogenetics, and early recognition of symptoms have greatly reduced neurotoxic events. Once neurotoxicity occurs, a reduction in the drug dosage, switching to other immunosuppressants, using drugs to treat the neuropsychiatric manifestation, or blood purification therapy have proven to be effective against neurotoxicity. In this review, we summarize the recent topics on the mechanisms of neurotoxicity of immunosuppressive drugs. In addition, some information about neuroprotective effects of several immunosuppressants are also discussed.

Keywords: alloimmune response; immunosuppressants; calcineurin inhibitors; corticosteroids; mTOR inhibitors; neurotoxicity; neuroprotective effects

1. Introduction

The first kidney transplant, performed by Murray et al. in 1954 [1], heralded a new age for patients with terminal hepatic insufficiency, end-stage renal diseases, and other severe diseases. However, the one-year survival rate of transplant patients was only 35% in the 1960s and 1970s and did not significantly increase until the development of ciclosporin A (cyclosporine, CsA) and tacrolimus (FK506) [2]. Strikingly, the rapid development of drugs to induce and maintain immunosuppression, such as antibodies and anti-metabolic drugs, has helped to increase graft and one-year patient survival to more than 90% in recent years [3]. Based on pharmacological mechanisms, immunosuppressive agents can be divided into six categories, including calcineurin inhibitors (CNIs), mammalian target of rapamycin (mTOR) inhibitors, cell cycle inhibitors, corticosteroids, monoclonal and polyclonal antibodies, and other newly developed drugs [4].
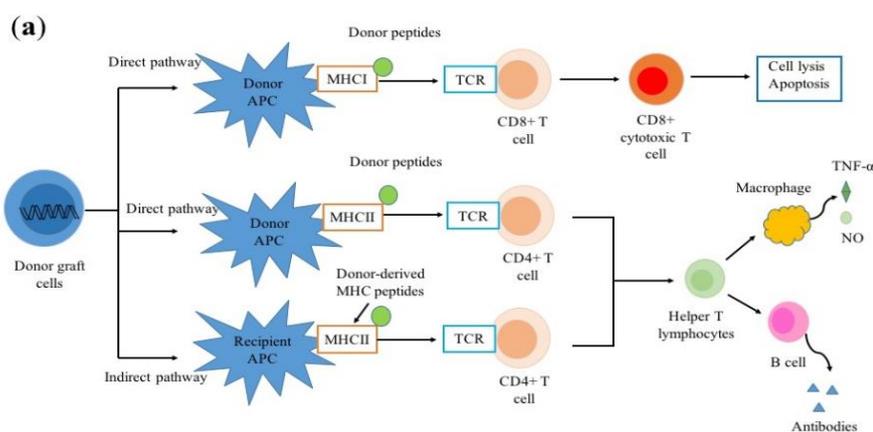
Although many benefits have been realized, postoperative complications remain unsolved and they influence the quality of life and long-term survival rates of transplant patients [5]. Among all of the postoperative complications, neurological problems are frequent, both in the immediate operation period and for many years after transplantation and they are associated with a poor
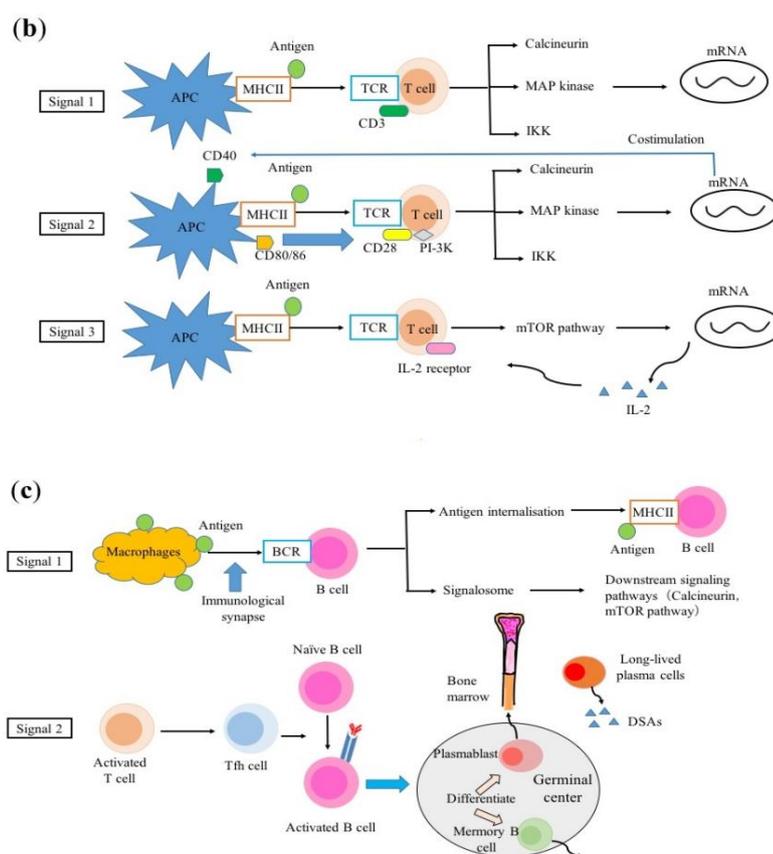
47 prognosis and significant morbidity [6,7]. For example, van de Beek and colleagues [8] reported that
48 the rate of perioperative neurological complications were associated with one-year mortality and
49 rose from 19% to 30% in the past 10 years in a retrospective cohort study. Furthermore, the risk of
50 neurological complications was shown to be 81% in patients over 18 years. Common complications
51 seen with all types of transplantation include alterations of consciousness, seizures, encephalopathy,
52 and cerebrovascular events [9-12]. The etiologies of neurological complications are diverse,
53 including immunosuppressant-related neurotoxicity [13,14], infections [15], metabolic disorders,
54 hemorrhage [9], and primitive disease prior to the transplant. Neurotoxicity induced by
55 immunosuppressive agents has remained as a severe problem in the clinical situations because of
56 worsening the patients' quality of life. For example, CNIs may induce mild symptoms, such as
57 tremor or severe symptoms, such as seizures, central pontine myelinolysis (CPM), and cortical
58 blindness. Treatment with mouse monoclonal immunoglobulin G2 antibody to cluster of
59 differentiation 3 (muromonab-CD3, trade name: Orthoclone OKT3®) is associated with headache
60 and aseptic meningitis. These clinical features and risk factors are well understood, however, the
61 specific mechanisms of immunosuppressant-related neurotoxicity and its predictive factors are still
62 obscure.

63   Over the last few decades, several attempts have been made to shed light on the pathogenesis of
64 immunosuppressant-related neurotoxicity and to recognize the heralding symptoms. In this article,
65 we focus on the clinical features, risk factors, pathological mechanisms, and management of
66 neurotoxicity induced by immunosuppressive agents.

67 **2. The alloimmune response**

68   Once cells or tissues or an organ are transplanted between a donor and a genetically
69 non-identical recipient (allograft transplantation), many cells, including T cells, B cells, and
70 macrophages are activated and participate in immune events that can initiate an alloimmune
71 response, and finally, induce allograft rejection. As shown in Figure 1a, allorecognition is initiated by
72 two pathways: 1) activated T cells with direct alloreactivity interact with major histocompatibility
73 complex (MHC) molecule-peptide complexes on donor antigen presenting cells (APCs) and induce
74 donor cell apoptosis through cellular rejection [16] and 2) donor peptides bound to self-derived
75 MHC molecule peptide complexes processing by recipient APCs are recognized by recipient T cells
76 and then cause allograft destruction [17].

Figure 1. T cells, B cells, and macrophages initiate alloimmune responses and induce allograft rejection after transplantation. (**a**) Allorecognition can be initiated by direct or indirect pathways; (**b**) Three signals participate in the activation of T cells; (**c**) Two signal processes are involved in the activation of B cells. APC, antigen-presenting cell; BCR, B-cell receptor; DSA, donor specific antibody; IKK, inhibitor of NF-κB kinase; IL-2, interleukin-2; NO, nitric oxide; MAP, mitogen-activated protein; MHC, major histocompatibility complex; PI-3K, phosphatidylinositol 3-kinase; TCR, T-cell receptor; Tfh, T follicular helper; TNF-α, tumour necrosis factor alpha.

2.1. T-cell activation

T cells can be activated by three types of signals (Figure 1b). Firstly, the T-cell receptor-CD3 (TCR-CD3) complex on CD4+ T cells, which delivers cognate antigens and forms T-cell receptor-major histocompatibility-allopeptide complexes that activate a series of biochemical reactions. Secondly, T cells that have received an initial signal activation are activated by the interaction between CD80 or CD86 on APCs and CD28 molecule on T cells, finally generating a co-stimulatory signal, thereby initiating immunological activation. Several signalling pathways, including the calcineurin pathway, the Ras/mitogen activated protein (MAP) kinase pathway, and the nuclear factor kappa B (NFκB), inhibitor of NFκB kinase (IKK) pathway have been reported to participate in these two activation processes. The third type of activation signal involves the binding of interleukin-2 (IL-2) with the gamma chain of its receptor to initiate T cell proliferation, DNA synthesis, and cell division through the activation of mTOR pathways [18].

2.2. B-cell activation

Two signal processes account for the activation of B cells [19], as described in detail in Figure 1c. The first activation signal occurs when macrophages in the subcapsular sinus capture the cognate antigens and then these antigens on macrophages bind with the surface B cell receptors (BCRs) of naïve B cells, forming an immunological synapse [20]. Signaling BCR microclusters are involved in

the process of moving antigens into endosomal compartments of B cells and the expression of a series of factors that play an important role in regulating downstream signaling pathways, including calcineurin and mTOR pathways [19,21]. The antigens are then processed enzymatically, internalized, and ultimately selected to present on the surface of the B cell associated with MHC II molecules [22].

Naive B cells are activated with the help of follicular helper T (Tfh) cells, which initiate cell co-stimulation interactions that produce cytokines [23-25]. The activated B cells migrate into the germinal center where some of them differentiate into memory B cells or plasmablasts. Plasmablasts further differentiate into long-lived plasma cells on bone marrow, which can secrete high-affinity donor-specific antibodies that participate in antibody-mediated rejection [26,27].

3. Classification of immunosuppressants

The functions of T and B lymphocytes in the process of rejection have become gradually understood and the immunosuppressive regime has been optimized as a result of many experimental and clinical studies. Immunosuppressants are classified according to their mechanisms of action, as shown in Table 1 [3,4,18,28-34]. CNIs inhibit the activity of a calcium-dependent phosphatase named calcineurin, thereby impeding the transduction of nuclear factor of activated T cells (NFAT) and the production of cytokines, such as IL-2, tumour necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ). mTOR inhibitors suppress the translation of mRNA-encoding proteins, T cell proliferation, and cytokine production. Antimetabolites inhibit the synthesis of purine by diverse mechanisms, such as inhibiting inosine-5′-monophosphate dehydrogenase (IMPDH) or incorporating into newly synthesized DNA to block purine synthesis enzymes. Corticosteroids, in combination with CNIs and antimetabolites, are used as the cornerstones of immunosuppressive regimens. Their immunosuppressive mechanism is diverse and may relate to interference with intracellular transcription factors and the signalling pathways of several surface receptors. Monoclonal and polyclonal antibodies may interact with cell surface antigens, such as CD3, CD20, and CD25. Immunosuppressants currently being developed include antibodies, FK778, janus kinase (JAK) inhibitors, fingolimod, and blinatumomab. Among these immunosuppressive agents, those that can cause neuropsychiatric complications are CNIs; mTOR inhibitors; mycophenolate mofetil; corticosteroids; and some monoclonal antibodies, such as OKT3, belatacept, and blinatumomab.

131 <p align="center">**Table 1.** The details of various immunosuppressive agents shown according to their classification</p>

Class	Generic name	Trade name	Mechanism of action	Role in therapy protocol	Adverse effects	Monitoring parameters	Other information
Corticosteroids	Prednisone	Prelone®, Orapred®, Millipred®, Orapred ODT®	The mechanisms of action are diverse and include interference with intracellular transcription factors and signalling pathways of several surface receptors, including the T cell antigen receptor and downstream kinases, thereby blocking the transcription of cytokine genes and inhibiting cytokine production by T	Maintenance; high doses of corticosteroids (> 1 mg/kg), used for induction therapy in transplantation; treatment of acute cellular rejection and AMR	Hypertension, hyperlipidaemia, glucose intolerance, malignancy, Cushingoid features, sleep disturbances, mood changes, impaired wound healing, osteoporosis, psychosis, photosensitivity, acne hirsutism, avascular necrosis, weight gain, fluid retention, increased appetite, menstrual irregularities, growth inhibition, GI disturbance,	Glucose, blood pressure, fasting lipid panel, weight, DEXA scan, eye exam, intensive organ function monitoring	Their role in the maintenance of immunosuppression is under investigation because of severe side effects during long-term use, but a immunosuppressive strategy without steroids could be only tried in low immunological risk transplant recipients; it also seems that treatment of steroids 1 h prior to ATG preoperatively may minimize CRS.
	Prednisolone	Prednisol®, Pred Forte®, Pred Mild®, Omnipred®					
	Methylprednisolone	Medrol®, Medrol Dosepak®, MethylPREDNISolone Dose Pack®, Solu-Medrol®					
	Dexamethasone	Decadron®, Dexamethasone Intensol®, Dexasone®, Hexadrol®					

Purine synthesis inhibitors	Azathioprine (a prodrug of 6-mercaptopurine)	Imuran®	cells and macrophages. Two distinct mechanisms participate in the inhibition of *de novo* DNA synthesis block cell division and then block cell division. AZA blocks purine synthesis enzymes by incorporating into newly synthetized DNA and finally, impedes DNA and RNA synthesis. MPA selectively and noncompetitively inhibits a key enzyme in the de novo synthesis of purine named	Maintenance	cataracts, infection		
					Hepatotoxicity, bone marrow suppression, malignancies (high dosages), macrocytic anaemia, GI disturbance, alopecia, pancreatitis, infections	CBC, LFT, amylase, lipase, TPMT enzyme level	Newer trials have shown that AZA and MMF have similar efficacy. Low or absent TPMT activity is associated with increased azathioprine-associated myelosuppression.
	Mycophenolate mofetil (a prodrug of MPA)	Cellcept®			Dyslipidaemia, DM, infections, bone marrow suppression, GI symptoms and anaemia are common, while nephrotoxicity, neurotoxicity, and hepatotoxicity are uncommon.	CBC, REMS	MPA is associated with pregnancy loss and congenital malformations when used during pregnancy. MPA may be of special interest in preventing the rise of DSA titers in pre-sensitized recipients. Patients with renal dysfunction need
	Mycophenolate sodium (an enteric-coated formulation of MPA)	Myfortic®					

	Cyclophosphamide	Cytoxan®, Neosar®, Endoxan®	IMPDH and thus, inhibits proliferation of T and B lymphocyte.		Low blood count, alopecia, GI symptoms, poor appetite, discoloration of the skin or nails	CBC, LFT, KFT	dosage adjustment. CP is associated with pregnancy loss and congenital malformations when used during pregnancy.
Calcineurin inhibitors	Tacrolimus	Prograf®, Graceptor®, Advagraf®, Envarsus XR®, Astagraf XL®	CNIs block signal transduction by activated NF-AT through two distinct mechanisms. tacrolimus binds to FKBP12 while CsA in combination of cyclophilin inhibits calcineurin-mediated dephosphorylation of NFAT, ultimately preventing cytokine transduction	Maintenance	Often dose- and concentration-dependent, nephrotoxicity, infections, hyperkalaemia, hypomagnesemia, hyperuricemia, cholelithiasis, GI symptoms, malignancy; tacrolimus > CsA: insulin-dependent diabetes mellitus, neurotoxicity; CsA > tacrolimus: hypertension, hypercholesterolemia, hyperlipidaemia;	Trough levels, serum creatinine, potassium, magnesium, uric acid	tacrolimus seems more effective than CsA-based immunosuppressive regimens, so tacrolimus-based immunosuppression usually used as a first-line therapy after transplantation. tacrolimus is metabolized by CYP3A and has potential drug interactions. Neurotoxicity more likely occurs in liver transplant patients with low serum
	Cyclosporine	Neoral®, Gengraf®, Sandimmune®					

			including IL-2 and IFNγ and T cell activation. In humoral immune response, CNIs interfere with T helper signals rather than targeting B cell directly.		CsA only: gingival hyperplasia, hirsutism; tacrolimus only: alopecia		cholesterol levels. Patients with hepatic dysfunction or advanced age have high risk of drug interactions after CSA.
mTOR inhibitors	Sirolimus (Rapamycin) Everolimus	Rapamune® Certican®, Zortress®	These drugs in combination of FKBP12 inhibit mTOR and impede the translation of mRNA-encoding proteins which are necessary to the cell cycle, thus reducing IL-2-mediated T cell proliferation and cytokine production. In contrast to CNIs,	Maintenance	Dyslipidaemia, mucositis, oedema, proteinuria, wound-related reactions, mouth ulcers, bone pain, diarrhoea, pneumonitis, venous thromboembolism, infections, low blood count	Trough levels, fasting lipid panel, CBC, LFT	Only sirolimus is reported to have direct inhibitory effects on the proliferation of B cells and their differentiation into plasma cells. An mTOR inhibitor–based regimen is under investigation for low risk of nephrotoxicity or neurotoxicity when used alone.

			they seem to do not influence the early phase of T-cell activation.				
Monoclonal antibodies	Muromonab-CD3 (first monoclonal antibody approved for use in solid-organ transplantation)	Orthoclone OKT3®	A drug directed against the CD3 marker on all mature human T cells.	Withdrawn	Serious CRS		
	Rituximab (a murine/human chimeric monoclonal antibody)	Rituxan®	A drug directly targets the CD20 surface marker on B cells.	Desensitization, treatment of AMR, and for cases of PTLD	Bone marrow suppression, infusion-related events		Has been trialled as an induction agent in cell therapy
	Basiliximab (a murine/human chimeric monoclonal antibody)	Simulect®	A drug competitively inhibits CD25 complex, the alpha subunit of the IL-2 receptor which present only on activated and non-resting T cell, thereby inhibiting T cell proliferation.	Induction	Rare; infections, bone marrow suppression, hypersensitivity reactions	None	Induction therapy using basiliximab has higher rejection rates
	Daclizumab (a humanized	Zinbryta®	Similar to Basiliximab, this	Induction	GI disturbance, rare		

monoclonal antibody)		drug has high specificity and affinity against CD25 complex.		lymphoproliferative disorders and malignancies		
Alemtuzumab (a recombinant DNA-derived, humanized anti-CD52 monoclonal antibody)	Campath®, Lemtrada®	A drug targets T and B lymphocytes, NK cells, monocytes, and macrophages, finally leading to rapid and powerful depletion of T and B lymphocytes, and monocytes.	Induction, treatment of AMR and steroid-resistant rejection	Bone marrow suppression, infusion reaction, infections, mild CRS, headache, induction of autoimmune disease, a possible increased risk of PTLD	Vital signs, CBC, absolute lymphocyte count	Usage in induction and acute rejection treatment is still under study; has similar immunosuppressive effect compared to ATG, but less side effects. Pre-treatment of diphenhydramine and acetaminophen can decrease side effects.
Eculizumab (a humanized monoclonal antibody against C5)	Soliris®	This drug binds to complement C5 with high affinity and blocks complement cascade by preventing the formation of the	Desensitization, treatment of AMR	Increased risk for gram-negative bacterial infection, bone marrow suppression		The usage for immunosuppressants has been only reported in case reports and observational studies, has limited efficacy and high cost

			terminal membrane attack complex.				
Polyclonal antibodies	Antithymocyte globulin	Thymoglobulin®	This drug depletes the number of circulating T lymphocytes by antibody–dependent cell–mediated or complement-depend cytotoxicity and their interaction with T cell surface antigens, may result in apoptosis, which alters T cell activation and homing.	Induction; treatment of steroid-resistant rejection	Malignancies, infections, bone marrow suppression, CRS, pulmonary oedema, phlebitis, pruritis, erythema, serum sickness	White blood cells, platelet count, vital signs, CD3 count	To prevent an intense CRS, pre-treatment with systemic glucocorticoids, antihistamines and antipyretics should precede drug administration; preferred in sensitized patients without DSAs
Co-stimulation blockade agent	Belatacept	Nulojix®	An agent mimics soluble CTLA-4 and binds to CD86/80 on APCs, thus	Induction; maintenance	Malignancies, bone marrow suppression, diarrhoea, infection, oedema,	EBV serostatus (prior to treatment)	Only used for adult patients; no drug-drug interactions; patients with renal

		blocking T-cell activation. Moreover, it maybe indirectly prevent production of antigen-specific antibody (IgG, IgM, and IgA) by B lymphocytes or directly affect B lymphocytes.		hypertension, dyslipidaemia, DM, proteinuria, electrolyte disorders, dyspnoea, purpura, transaminitis, temporal lobe epilepsy. More than 20% of patients experience side effects.	or hepatic impairment need no dosage adjustment; contraindicated in recipients who are EBV seronegative or with unknown EBV serostatus.
Immunosuppressants in development	FK778 (a synthetic malononitrilamide derivative of teriflunomide)	An agent blocks pyrimidine synthesis by blockade of DHODH and inhibition of tyrosine kinase activity, thus inhibiting both T-cell and B-cell function; moreover, it can directly inhibit	Further development for the treatment of transplantation has been discontinued		There have been no results proving the efficacy of FK778 in phase III studies; therefore, its development was been discontinued for organ transplantation in 2006.

			lymphocyte activation, attenuate lymphocyte-endothelium interactions.			
	Tofacitinib (CP-690550)	Xeljanz®	A JAK3 inhibitor, that exerts its effects by uncoupling cytokine receptor signaling from downstream STAT transcriptional activation and subsequently, suppressing various cytokine-regulated signaling, thus influencing lymphocyte activation, proliferation, differentiation, and function.	Withdrawn in transplantation	Infection, CMV disease, PTLD, anaemia, neutropenia	Drug serum levels	When combined with MMF, the rates of viral infection and viral-associated malignancies may increase.

Bortezomib (PS341)	Velcade®	A reversible 26S proteasome inhibitor that can delete non-transformed plasma cells, which is critical to alloantibodies.	Desensitization, treatment of AMR	GI syndromes, asthenia, neurotoxicity, bone marrow suppression, shingles	Small, non-randomised trials suggest efficacy in AMR; may decrease AMR in highly sensitised individuals
Tocilizumab	Actemra®	A first-in-class, humanized, monoclonal antibody directed against IL-6R	Desensitization	Infections	
IdeS (imlifidase)		An enzyme from Streptococcus pyogenes that specifically cleaves human IgG antibodies	Desensitization		IdeS has been proven to effectively reduce anti-HLA antibody levels in highly sensitized patients by a phase II study; clinical trials in sensitized kidney patients are ongoing.
Fingolimod (FTY720)	Gilenya®	A structural analogue of sphingosine,	No further development for the treatment of	Bradycardia, macular oedema, increased airway	It is now approved for use in MS, but its mechanism is still

		metabolized by sphingosine kinases to fingolimod-phosphate in the cell; this active metabolite can entrap lymphocytes in secondary lymphoid organs and reduce their number in peripheral blood, thus reducing cell-mediated immune responses.	transplantation	resistance, a "first-dose" negative chronotropic effect	unknown.
	Alefacept (a humanized LFA-3Ig fusion protein)	Amevive®	Alefacept directed against the extracellular CD2 receptor expressed on T lymphocytes thus inhibiting lymphocyte activation and	Withdrawn in transplantation	Malignancies	Its use for the prevention of graft-versus host disease is under investigation.

		production; blocks the CD2/LFA-3 interaction and impedes helper T-cell adhesion to APCs.			
ASKP1240		A novel, fully human anti-CD40 monoclonal antibody, is currently under study in phase II clinical trials in kidney transplantation	Immunosuppressive effects in nonhuman primates have been proven.		Further clinical III studies are needed
Voclosporin (ISA247)	Luveniq®	A novel oral semisynthetic analogue of CsA, inhibits calcineurin.	Its efficacy in preventing acute rejection is as potent as tacrolimus by a phase 2b PROMISE study.		Low-dose voclosporin may reduce incidence of new-onset diabetes after transplantation.
Sotrastaurin (AEB071)		An oral protein kinase C inhibitor that can	May be an alternative therapy for CIs	GI events are common	High-dose sotrastaurin may be associated with

		block T-cell activation			faster heart rates.
Siplizumab		A novel humanized monoclonal antibody, binds to CD2 antigen on T lymphocyte or NK cell.	This agent has been tested as an induction drug in a human study.		
TOL101		A highly selective murine monoclonal antibody targeting the $\alpha\beta$-TCR.	This agent has been tested as an induction agent to prevent rejection is currently under study in phase II clinical trials.		
Efalizumab (a recombinant humanized monoclonal antibody)	Raptiva®, Genentech®, Merck Serono®	An anti-lymphocyte function-associated antigen molecule that inhibits lymphocyte activation and migration	Withdrawn	Infections, PML, PTLD	
Belimumab	Benlysta®	A human monoclonal	The usage as supplement to	Infection, hypersensitivity,	

		antibody that inhibits BAFF.	standard-of-care immunosuppressive therapy in renal transplantation has been proven by a phase II study.	malignancy	
Sutimlimab (BIVV009, a novel humanized monoclonal antibody)		Selectively blocks the classical pathway of complement-specific serine protease C1s to prevent the formation of the classic C3 convertase pathway.	A single-arm pilot trial showed that BIVV009 effectively blocks the alloantibody-triggered classical pathway activation in kidney transplant recipients.		Undergoing phase clinical III trail.
C1-INH (C1 esterase inhibitor)	Berinert®, Cinryze®, Haegarda®	A serine-protease inhibitor inhibits complement system by binding to and inactivating C1r and C1s and dissociating the C1 complex.	The results of a recent placebo-controlled trial suggested that C1-INH replacement may be useful in the treatment of AMR.		Further studies are needed to confirm the safety and efficacy of C1-INH in the treatment of AMR.

132   Abbreviations: AMR, antibody-mediated rejection; APC, antigen-presenting cell; ATG, anti-thymocyte globulin; AZA, azathioprine; BAFF, B-cell activating factor; CBC,
133   complete blood count; CNIs, calcineurin Inhibitors; CP, cyclophosphamide; CRS, cytokine release syndrome; CsA, cyclosporine; CTLA4, cytotoxic T lymphocyte–associated
134   antigen 4; CYP3A4, cytochrome P3A4; C1-INH, C1 esterase inhibitor; DEXA, dual-energy X-ray absorptiometry; DHODH, dihydroorotic acid dehydrogenase; DM, diabetes
135   mellitus; DSA, donor-specific antibodies; EBV, Epstein-Barr virus; FKBP, FK506-binding protein; GI, gastrointestinal; HUS/TMA, hemolytic uremic syndrome/thrombotic
136   microangiopathy; Ides, immunoglobulin G-degrading enzyme derived from *Streptococcus pyogenes*; IL-2, interleukin-2; IL-6R, IL-6 receptor; IMPDH, inosine-5'-monophosphate
137   dehydrogenase; JAK, janus kinase; KFT, kidney function test; LFT, liver function test; MHC, major histocompatibility complex; MMF, mycophenolate mofetil; MPA,
138   mycophenolic acid; MS, multiple sclerosis; mTOR, mammalian target of rapamycin; NF-AT, nuclear factor of activated T-cells; PML, progressive multifocal
139   leukoencephalopathy; PTLD, post-transplant lymphoproliferative disorder; REMS, pregnancy test in women of childbearing age; STAT, signal transducers and activators of
140   transcription; TPMT, thiopurine methyltransferase, TCR, T cell receptor.

4. Clinical features induced by different immunosuppressants

4.1. CNIs

Neurotoxicity induced by CNIs occurs at three distinct time points after transplantation: early, intermediate, and late. Most patients who use tacrolimus intravenously develop neurotoxicity on the first day after transplantation [35]. Patients who develop neurotoxicity in the intermediate or late stage demonstrate only short or intermediate survival times [36].

The neurological complications of CNIs are various and can involve both the central nervous system (CNS) and the peripheral nervous system [37]. Mild neurological manifestations related to CNI toxicity are common and include tremor, insomnia, nightmares, sleep disturbances, headache, vertigo, mood disturbance, and paraesthesia (e.g. electric shock–like pain and severe itching) [38,39]. Serious adverse neurological effects have been relatively rarely observed and include seizures, speech disorders, cortical blindness, coma, encephalopathy, central pontine/extrapontine myelinolysis, and neuromuscular complications [14]. Tacrolimus treatment has a significantly higher incidence of neurological syndromes than CsA treatment in solid organ transplantation recipients [40,41].

Tremor is the most pronounced neurological complication associated with CNI toxicity and a fine tremor of the upper limbs can help diagnose neurological complications at early stages [13]. Tremor is significantly more common in patients treated with tacrolimus than those treated with CsA. In a more recent trial, less than 20% of patients treated with CsA experienced tremors, while tacrolimus-related neurotoxic events occurred in up to 40% of patients [42]. In general, tremors involved both upper and lower limbs, with some patients even experiencing tremors in the head/facial muscles. Tremors exclusively involving the trunk, lower limbs, or the craniofacial area are rare in the clinic [42]. Considering that the main goal of immunosuppressive therapy is to increase the survival rates of transplant recipients and tremors appear to be isolated, with cerebellar or neuropathic involvement, this symptom tends to be ignored when its severity is not significant and does not influence the patient's quality of life.

Seizures are common in transplant recipients undergoing CNI therapy, occurring in up to 27% of organ transplant patients [43]. Although seizures frequently occur with posterior reversible encephalopathy syndrome (PRES), new onset of seizures are not indicative of a poor prognosis, because most patients do well and do not require long-term antiepileptic therapy [44]. In patients with seizures, generalized tonic-clonic type and occipital lobe seizures are usually observed [45]. Simple or complex partial seizures represent a localized process that may be reflected by focal electro-encephalogram (EEG) abnormalities, whereas seizures that occur secondary to PRES frequently show short single grand mal episodes with variable theta/delta slowing [44]. Seizures associated with CNI neurotoxicity frequently originate from occipital regions [46]. PRES is a serious complication associated with immunosuppressive therapy after transplantation [47]. It is a neurotoxicity characterized by headache; confusion; nausea and vomiting; altered mental status; visual disturbances; intracranial haemorrhage; altered sensorium; and occasionally, focal neurological deficit [45,48-51]. In most cases, immunosuppression-associated leukoencephalopathy occurs within the first three months after transplantation and it is usually associated with intravenous treatment methods [52]. PRES appears to be significantly more common in hematopoietic or liver transplantation than other transplantations [53].

Cranial computed tomography (CT) finding is insensitive to detect PRES and often shows no abnormalities, while magnetic resonance imaging (MRI) has been proven to be most sensitive imaging test. Vasogenic oedema, which is a symptom of PRES, can be easily identified. Radiologists can reliably differentiate these changes from cytotoxic oedema using diffusion weighted image (DWI) and apparent diffusion coefficient (ADC) maps. Moreover, the extent of abnormal T2-weighted signal intensities and DWI signal intensities correlate well with prognosis [47]. PRES predominantly affects the posterior cerebrum and the cerebral white matter, causing focal reversible vasogenic oedematous changes in specific posterior regions of the parietal and occipital lobes, which

191 can lead to irreversible cytotoxic oedema in some cases [44,54]. Grey and white matter lesions can be
192 observed by MRI on fluid attenuated IR (FLAIR) and T2-weighted sequences, and deeper structures
193 such as the basal ganglia, brain stem, and deep white matter tracts may be also affected [44,55].
194 Cytotoxic oedema and haemorrhage are uncommon findings in these patients [44]. Typically, the
195 characteristic of PRES is bilateral symmetric patterns of oedema, usually including diffuse white
196 matter hyperintensity with a parieto-occipital predilection [56,57]. If PRES is not diagnosed at an
197 early stage, cerebral ischemia and massive infarction may result in an increase in morbidity and
198 mortality [47]. Hypertension is another important symptom of PRES and therefore, when
199 immunosuppressants need to be continued in the clinic, blood pressure should be effectively
200 monitored and controlled.

201 CPM is one of the most detrimental neurological complications after organ transplantation and
202 the mortality due to this neurotoxicity is more than 50% [58]. The incidence of CPM is more common
203 in liver transplantation and in patients treated with CsA than in those treated with
204 tacrolimus[59-61]. MRI features include hyperintense lesions in the centre of the pons on T2 images.
205 Rapamycin is recommended as a replace for CNIs, because it is rarely associated with CPM.
206 However, rapamycin is unstable and requires frequent monitoring of blood concentrations when
207 used in clinical practice.

208 The number of case reports related to catatonic symptoms and akinetic mutism induced by CNI
209 administration after organ transplantation has increased in recent years [62,63]. Even when used to
210 treat psoriasis, CNIs have been shown to exacerbate the symptoms of paranoid schizophrenia, then
211 disappear a few days after the discontinuation of CNI treatment [64].

212 In addition to CNIs, other immunosuppressants may also manifest neuropsychiatric
213 complications, although neurotoxicity reports are rarer for these drugs than for CNIs [37].
214 Mycophenolate mofetil rarely induces depression and headache, but seizures were frequently
215 observed in several reports concerning neurological complications during rapamycin therapy. The
216 main neurological complication of muromonab-CD3 treatment is headache, whereas patients treated
217 with corticosteroids may experience anxiety, insomnia, mood disorders, psychotic episodes, and
218 cognitive symptoms [65,66].

219 *4.2. Antimetabolites*

220 Methotrexate (MTX) can induce CNS toxicity that presents in the form of encephalopathy,
221 myelopathy, or meningitis [67]. Neurological symptoms are caused by MTX are usually classified
222 into acute, subacute, or chronic neurotoxicity. Patients who experience subacute neurotoxicity
223 usually recover completely and spontaneously within a week and therefore, subsequent MTX
224 treatment is safe for most patients [68]. Neurological symptoms induced by mycophenolate mofetil
225 are rare and mild, manifesting as depression and headache.

226 *4.3. Corticosteroids*

227 Neurological side effects occur in approximately 3–4% of patients who use corticosteroids [69].
228 Corticosteroid-induced neuropsychiatric symptoms include mood changes, behavioural disorders,
229 and cognitive symptoms that typically manifest during the first few weeks of therapy [66].
230 Peripheral toxicity occurs after long-term use, usually in the form of neuromyopathy, with muscular
231 weakness, affecting the proximal and lower extremities [70]. Steroid dementia syndrome appears to
232 be rare [71] and these symptoms may not recover completely even after the cessation of treatment
233 [72]. Epidural lipomatosis can also induce radiculopathy due to spinal compression [73].

234 To improve neurological symptoms, adjustment or discontinuation of corticosteroids may
235 improve some of these adverse effects. If the psychiatric symptoms are serious, short regimens of
236 low-dose psychotropic agents are often required (e.g. haloperidol, olanzapine, quetiapine, or
237 risperidone).

238 *4.4. Monoclonal antibodies*

239   Polyclonal and monoclonal antibodies are usually used to induce immunosuppression and the
240   treat of graft rejection [72]. With the exception of OKT3 and belatacept, biologic agents show low
241   incidences of adverse neurological effects. The neurotoxicities induced by OKT3 range from
242   headache and fever to confusion, aseptic meningitis, cerebral oedema, encephalopathy, seizures,
243   hemiparesis, nuchal rigidity, and myoclonic activity [37,74]. Furthermore, treatment with CsA after
244   OKT3 results in an additive or synergistic adverse effect on neurological complications [75]. In
245   general, pathological changes can be detected by a head MRI and neurological abnormalities resolve
246   after the cessation of OKT3 treatment [75,76]. However, cytokine release syndrome in patients
247   treated with OKT3 is so serious that it limits the usage of this agent. Blinatumomab, a novel
248   recombinant murine protein, is used for the treatment of Philadelphia chromosome–negative,
249   relapsed or refractory precursor acute lymphoblastic leukaemia. There are a variety of neurological
250   symptoms induced by blinatumomab treatment, such as somnolence, confusion, dizziness, tremor,
251   seizure, encephalopathy, speech disorders, and loss of consciousness, which appear to be more
252   common in patients over 65 years of age [77].

253   Conditions that increase the neurotoxicity of immunosuppressant agents include pre-existing
254   mental disorders [78]; hypertension [79]; electrolyte disorders, including hyper- and hyponatremia
255   and hypomagnesemia [37]; dysmetabolic alterations, such as hyperglycaemia [37]; infections that
256   impair the function of the blood-brain barrier (BBB); hypocholesterolaemia, which increases the
257   uptake of immunosuppressant drugs in the brain [80]; polymorphisms of the ATP-binding cassette
258   transporter B1 (ABCB1) gene and cytochrome pigment (CYP) gene, which decrease
259   immunosuppressant efflux or elimination [81,82]; drug interactions [82,83]; a prolonged surgical
260   period [84]; and low liver function or acute liver failure [85].

261   **5. Mechanisms of neurotoxicity induced by different immunosuppressants**

262   *5.1 CNIs*

263   The biochemical basis of CNI-induced neurotoxicity remains unclear. It appears that high blood
264   concentrations of the drugs are correlated with neurological symptoms, but they can also occur in
265   patients with concentrations within the therapeutic range [13,14,86]. Although both CNIs are used as
266   immunosuppressants are lipophilic, with CsA being more lipophilic than tacrolimus, they do not
267   easily pass through the BBB [87,88]. One possible hypothesis is that tacrolimus and CsA increase the
268   permeability of the BBB by inducing apoptosis and nitric oxide (NO) production and inhibiting
269   P-glycoprotein (P-gp) function, which leads to further accumulation of drugs in the brain,
270   extravasation of proteins and fluid into the interstitium, and impaired BBB function. An
271   investigation of the effects of tacrolimus and CsA on mouse brain capillary endothelial cells
272   (MBEC4) found that drug-treated cells experienced 1) loss of junctions with neighbouring cells and
273   detachment from the substratum, 2) chromatin condensation and fragmentation, and 3) DNA
274   fragmentation [89]. The two drugs induced dose-independent apoptosis of the brain capillary
275   endothelial cells, with similar effects between CsA and tacrolimus [89]. Dohgu et al. [90] reported
276   that CsA increases NO production in brain endothelial and astroglial cells, which then participates
277   in the impairment of BBB function. The expression of P-glycoprotein decreases with high
278   concentrations of CNIs, leading to inhibition of the efflux process and enhancement of permeability.
279   This may partly explain the mechanism of CNI-induced encephalopathy [91]. It should be
280   mentioned that the drug concentrations in above studies were quite high compared to clinical doses
281   and further investigation is required to determine whether normal brain capillary endothelial cells
282   are impaired. In fact, a recent study using an *in vitro* BBB model, consisting of a co-culture of bovine
283   brain capillary endothelial cells (ECs) and neonatal rat glial cells, showed that repeated exposure to 1
284   μM CsA, found in human plasma, had no toxic effect on BBB integrity [92]. This result was
285   confirmed by a kinetics study, in which intracellular CsA uptake and permeability across the BBB
286   were minimal [93]. It is also important to stress that, despite no cell damage, some key
287   neurotransmitters, factors metabolically linked to neurotransmitters, or energy metabolism related

288 to electrical activity that are altered at this concentration range may be responsible for the
289 neurological disorders induced by CsA or other CNIs [94].

290 An alternative hypothesis is that alterations in mitochondrial function induced by CNIs
291 contribute to neurotoxicity. A study in human umbilical endothelial cells showed that tacrolimus
292 significantly compromised respiratory chain (RC)-complexes II and III and the mitochondrial
293 marker enzyme, citrate synthase (CS), thus indicating partially impaired mitochondrial function [95]
294 Furthermore, a similar analysis found that tacrolimus decreases oxygen consumption in human cell
295 lines and causes a slight reduction in the synthesis of mitochondrial DNA-encoded proteins [96].
296 These studies suggest that the direct inhibition of the electron transport chain by CNIs, rather than
297 effects on mitochondrial density or electron transport chain (ETC) quantity, are responsible for
298 impaired mitochondrial function. This conclusion is contrary to an early study reporting that
299 tacrolimus inhibits both complex III, where reactive oxygen species (ROS) are generated and
300 complex V, where adenosine triphosphate (ATP) is depleted by ATPase activation [97]. Two studies
301 in glioma cells and glial cells demonstrated that tacrolimus can increase the production of ROS and
302 decrease antioxidant status [98,99], indicating that mitochondrial function may be impaired by
303 tacrolimus treatment.

304 There is also evidence that the complex of CNIs and immunophilins may be associated with
305 neurotoxicity. Calcineurin is expressed in several areas of the brain, including the cerebral cortex,
306 striatum, substantia nigra, cerebellum, and hippocampus, where it regulates the dephosphorylation
307 of Ca2+ channels, the activity of the N-methyl-D-aspartate (NMDA) receptor, the ryanodine
308 receptor, and the inositol trisphosphate (IP3) receptor and even memory and synaptic plasticity
309 [100-102]. These neurotoxic effects may depend on immune dysregulation in the nervous system,
310 due to the pharmacologic effects of the CNI-immunophilin complex [91,103,104]. The maximal
311 inhibitory effect of tacrolimus on calcineurin is approximately 60% (while CsA is more effective at
312 inhibiting calcineurin) [105], but tacrolimus has no pharmacological effect in FK506-binding protein
313 (FKBP) 1A (FKBP12)-null mice [106]. These findings suggest that the FK506-FKBP complex has some
314 unknown molecular mechanisms besides its calcineurin inhibitory effect. It is noteworthy that the
315 level of FKBP12 expression is 10–50-fold higher in the brain than in the immune system [107,108].
316 Tacrolimus-induced toxicity is consistent in organs with high FKBP levels, such as the brain and
317 kidneys. Moreover, once tacrolimus enters the brain, it is eliminated slowly by binding to FKBP
318 [109]. In an *in vitro* model, CsA inhibits calcineurin in the brain, even at concentrations as low as 200
319 nM, in a relatively short time frame and this inhibitory effect is sustained during drug
320 administration [93]. With the exception of calcineurin inhibition by the tacrolimus-FKBP complex,
321 the exact mechanism of neurotoxicity is not completely elucidated. Research on calcineurin
322 inhibition-induced depressive-like behaviour in a prefrontal cortex model raises the possibility that
323 blockade of the mTOR signaling pathway accounts for the neurologic disorders [110]. In support of
324 this, another study showed that receptor-associated FKBP12 participated in the intracellular mTOR
325 activation pathway, which is well known for its critical roles in the integration of neuronal activity
326 and synaptic inputs in multiple physiological and pathological processes [111,112]. These
327 experimental findings are in agreement with a clinical study showing that tacrolimus induces a
328 higher incidence of neurotoxicity than CsA [113,114].

329 Vasoconstriction or vascular injury [115] may also be involved in the mechanism of
330 CNI-induced neurotoxicity. Tacrolimus may be associated with the blood vessel contraction.
331 Moreover, some investigators have suggested that, in addition to vasoconstriction caused by
332 tacrolimus, the high infiltration pressure of the tacrolimus dissolution liquid may also affect
333 neurotoxicity. However, although this hypothesis is interesting, it does not explain the phenomenon
334 where patients experience CNI-induced neurologic disorders, even though their blood pressure is
335 maintained within the normal range throughout hospitalization [63,116].

336 Other proposed mechanisms of CNI-induced neurotoxicity include a possible modulation of
337 excitability properties, causing nerve membrane depolarization [117] and alterations in electrical
338 activity [94,118]; suppression of brain-derived neurotrophic factor (BDNF) and its receptor, tyrosine

339 kinase receptor B (TrkB), mRNA and protein expression in the hippocampus and midbrain [119];
340 and significant intracellular CNI uptake, thus increasing the toxicity of other drugs administered at
341 the same time [93]. Metabolites of CNIs may also be neurotoxic, even though they are usually not
342 assessed in clinical practice.

343 *5.2 Antimetabolites*

344 Several biochemical pathways including a decreased S-adenosylmethionine/
345 S-Adenosylhomocysteine (SAM/SAH) ratio, elevated levels of homocysteine, and elevated levels of
346 adenosine and direct toxic effects on neurons and astrocytes may be the causes of MTX-related
347 neurotoxicity [68].

348 *5.3 Corticosteroids*

349 Corticosteroids are often used in combination with other immunosuppressive agents. They
350 cause neurological complications through two mechanisms that involve direct and indirect toxic
351 effects on CNS biochemistry and electrophysiology. These include glutamate excess and
352 neurotrophin mobilization [120] or elevated blood pressure and vulnerability of the vasculature
353 through regulation of the renin-angiotensin system. There are also some reports suggesting that
354 corticosteroids can make certain hippocampal and prefrontal cortical cells more vulnerable to other
355 exogenous agents [71].

356 *5.4 Monoclonal antibodies*

357 The mechanisms of muromonab-CD3- and belatacept-related neurotoxicity have rarely been
358 reported. It has been postulated that cerebral complications are related to the OKT3-mediated
359 release of cytokines [75]. This hypothesis may explain the cases of aseptic meningitis, but it cannot
360 explain why neurological symptoms persist after cytokine levels return to baseline. Other studies
361 have suggested that circulating lymphocytes and cells of the nervous system share some of the same
362 surface antigens, such that OKT3 combines with cell surface antigens to facilitate OKT3 antibodies
363 crossing the BBB [76]. Cytokine release syndrome induced by blinatumomab may be responsible for
364 some of the adverse neurological effects, but further studies are warranted to clarify the precise
365 mechanism of blinatumomab-induced neurotoxicity [77].

366 **6. Management**

367 Immunosuppressants, particularly CNIs, can induce neurotoxicity in solid organ
368 transplantation cases. The management of blood concentrations of the drugs by therapeutic drug
369 monitoring, individual therapy based on pharmacogenetics, and the early recognition of symptoms
370 using electrophysiological and imaging strategies, may help avoid neurotoxicity [82,121,122].
371 However, even with these measures in place, the incidence of neurotoxic symptoms remains high
372 (3–32 %) [79,123,124]. Once neurotoxicity occurs, reducing in the drug's dosage, switching from
373 tacrolimus to CsA or vice versa, or using an alternative immunosuppressant agent, such as
374 mycophenolate mofetil, have proven to be effective approaches to reverse this neurotoxicity
375 [63,125,126]. A study comparing the effects of tacrolimus and rapamycin on bioelectrical activity and
376 evoked field excitatory postsynaptic potential (fEPSP) in the CA1 area of hippocampal tissues has
377 also suggested that rapamycin could replace to CNIs in the event of seizures [127]. However, in
378 some cases, switching between tacrolimus and CsA has not been effective at improving
379 neurotoxicity. Moreover, considering that switching immunosuppressants may elevate the risk of
380 graft rejection in some patients and reducing the CNI dosage does not always improve the
381 symptoms, continued administration of CNIs in combination with drugs that treat the
382 neuropsychiatric manifestations may be the best approach. For example, olanzapine coupled with
383 the continued use of tacrolimus has been shown to resolve manic episodes [128]. Olanzapine has
384 also been considered for the treatment of catatonic mutism after liver transplantation [129].
385 Benzodiazepines can improve catatonia, especially akinetic–hypokinetic catatonic syndromes
386 [40,130]. The neurotoxicity associated with CNIs is strongly correlated with the intracerebral

387   concentration of the drugs [131]. Sakamoto et al. showed that continuous administration of
388   tacrolimus is more advantageous than intermittent administration to reduce neurotoxicity in rats
389   [132]. In addition, tacrolimus-induced neurotoxicity and nephrotoxicity can be ameliorated, while
390   maintaining its immunosuppressive effects, by treating rats in the dark phase [133]. According to a
391   case report, red-blood cell exchange improved the clinical status of a 60-year-old woman with severe
392   neurological impairment due to tacrolimus overexposure. Hence, red-blood cell exchange may be an
393   effective therapy to reduce tacrolimus neurotoxicity [134]. This blood purification therapy has also
394   been shown to be effective in ifosfamide-induced severe concurrent neurotoxicity and
395   nephrotoxicity [135].

7. Neuroprotective effects

396

397   *7.1 CNIs*

398   The immunosuppressants, tacrolimus and CsA, have neuroprotective effects in animal models
399   of focal and global cerebral ischemia [136-138], portacaval anastomosis and hyperammonaemia
400   [139], intracerebroventricular streptozotocin-induced neurotoxicity [140], and temporal lobe
401   epilepsy (the turnover of tacrolimus is much faster in rats than in humans) [141].

402   When wild-type mice are treated with tacrolimus for one week, their neocortices show longer
403   total dendritic arbors and more complex branching further away from the cell body, compared to
404   untreated animals [142]. There is some experimental data to indicate that the neuroprotective effects
405   induced by tacrolimus and CsA may be related to calcineurin inhibition; NFκB activation [143];
406   downregulation of proinflammatory/cytotoxic cytokines [144]; decreased NO synthetase-mediated
407   NO production [136,139,145]; inhibition of $Ca2+$ release by the endoplasmic reticulum (ER)
408   (tacrolimus) [146]; inhibition of $Ca2+$ release by both the ER and mitochondria, as well as
409   mitochondrial permeability transition (mPT) (CsA) [147]; deceased apoptosis and c-jun protein
410   expression in neurons[148]; calcineurin-independent mechanisms [149]; activation of pro-survival
411   pathways by BDNF and its receptor, tropomyosin receptor kinase A (TrkA) [150]; and excitotoxic
412   neuronal death [151].

413   However, although the neuroprotective functions of tacrolimus have been demonstrated in
414   various nerve injury models, this has been challenged by models of inherited peripheral
415   myelinopathies treated with tacrolimus. For example, tacrolimus exacerbates neurological
416   abnormalities, including demyelination and dysmyelination-associated axon loss in inherited
417   de/dysmyelination mice, while the peripheral nerves of wild-type mice do not show any neurotoxic
418   symptoms after treatment with tacrolimus [152].

419   Interestingly, a recent study found that tacrolimus and CsA treatment had no better long-term
420   effects than treatment with vehicle alone (cremophor and ethanol mixture). Moreover, the
421   drug-treated group showed even more significant decreases in brain weight. Therefore, Setkowicz
422   and Guzik [153] concluded that the neuroprotective effects observed in rat brains injured
423   mechanically at early developmental stages may result from the influence of the vehicle alone.
424   Further studies and more investigations are needed to clarify the potential neuroprotective effects
425   and mechanism of CNIs.

426   *7.2 mTOR inhibitors*

427   mTOR is associated with the pathogenesis of neurological, cognitive, and psychiatric disorders,
428   such as epilepsy, stroke, traumatic brain injury, parkinsonism, spinal cord injury, and Alzheimer's
429   disease [154]. In a mouse model of epilepsy induced by knocking-out the protein phosphatase and
430   tensin homolog (PTEN), mTOR activity increases in neurons. Therefore, reducing mTOR activity
431   may effectively suppress epileptogenesis and alleviate this disease [155]. The role of mTOR in
432   cerebral ischemia has also been reported in some rodent experiments. Some studies have shown that
433   mTOR pathway has neurotoxic effects, while others have reported the opposite finding that the

434   mTOR pathway has neuroprotective effects. Some reports have suggested that suppressing the
435   pharmacological effects of the mTOR pathway can regulate autophagy and result in
436   neuroprotection, whereas other reports have suggested that the neurotoxicity of mTOR inhibitors is
437   related to the promotion of autophagic processes, long-term activation of Akt, and activation of S6
438   kinase 1 (S6K1) occurring in brain cells after a stroke [154,156-158]. The study by Chen and
439   co-workers [159] may explain the paradoxical effects of the mTOR inhibitor, rapamycin. In that
440   study, rapamycin was shown to cause a paradoxical, but transient, increase in mTOR pathway
441   activation in a kainite injection model and in normal rats, by increasing the phosphorylation of S6.
442   These results suggest that the effects of rapamycin on mTOR are related to the type or period of
443   stimuli and the dose administered [160].

8. Conclusions

445   Neurological disorders are common after solid organ transplantation. The reasons for these
446   neurotoxicities are multifactorial, ranging from the effects of immunosuppressive agents to
447   pre-transplantation disease. In this article, we mainly discuss the neurological complications
448   resulting from immunosuppressive therapy in five topics, including the process of alloimmune
449   responses, the classification of immunosuppressive agents, their clinical features, their mechanisms,
450   and their clinical management. Interestingly, some studies have also shown that these
451   immunosuppressive agents may have neuroprotective effects. However, two recent studies have
452   reported contradictory findings, suggesting that further studies are required to clarify these
453   potential neuroprotective effects of immunosuppressive agents.

458   **Conflicts of Interest:** The authors declare that they have no conflict of interest to this work.

459   **Abbreviations**

ABCB1	ATP-binding cassette transporter B1
ADC	Apparent diffusion coefficient
APC	Antigen presenting cell
ATP	Adenosine triphosphate
BBB	Blood-brain barrier
BCR	B-cell receptor
BDNF	Brain-derived neurotrophic factor
CD	Cluster of differentiation
CNI	Calcineurin inhibitor
CNS	Central nervous system
CPM	Central pontine myelinolysis
CS	Citrate synthase
CsA	Cyclosporin A
CT	Computed tomography
CYP	Cytochrome pigment
DWI	Diffusion weighted image
EC	Endothelial cell
EEG	Electro-encephalogram
ER	Endoplasmic reticulum
ETC	Electron transport chain
fEPSP	Field excitatory postsynaptic potentials
FKBP	FK506-binding protein
FLAIR	Fluid-attenuated IR
IFN-γ	Interferon-gamma

IL-2	Interleukin-2
IMPDH	Inosine-5′-monophosphate dehydrogenase
IP3	Inositol trisphosphate
JAK	Janus kinase
MAP	Mitogen activated protein
MBEC4	Mouse brain capillary endothelial cells
MHC	Major histocompatibility complex
mPT	Mitochondrial permeability transition
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
MTX	Methotrexate
muromonab-CD3	Mouse monoclonal immunoglobulin G2 antibody to cluster of differentiation 3
NFAT	Nuclear factor of activated T cells
NFκB	Nuclear factor kappa B
NMDA	N-methyl-D-aspartate
NO	Nitric oxide
P-gp	P-glycoprotein
PRES	Posterior reversible encephalopathy syndrome
PTEN	Phosphatase and tensin homolog
RAS	Renin–angiotensin system
RC	Respiratory chain
ROS	Reactive oxygen species
SAH	S-adenosylhomocysteine
SAM	S-adenosylmethionine
S6K1	S6 kinase 1
TCR	T-cell receptor
Tfh	T follicular helper
TNF-α	Tumor necrosis factor-alpha
TrkA	Tropomyosin receptor kinase A
TrkB	Tyrosine kinase receptor B

460

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