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Renal Complications of Immune Checkpoint Blockade

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Abstract

Immune checkpoint inhibitors have been approved for a variety of cancer species. Renal complications in use of these agents are not very common compared with other immune related adverse events (irAE). However, it is crucial for physicians to recognize and manage renal manifestations of irAE. In this review, we will summarize the up-to-date knowledge of the clinical presentation, pathological features and management of renal irAE. In addition, we will discuss the safety of immune checkpoint inhibitors in patients with chronic kidney disease as well as in kidney transplant recipients.

Introduction

Over the past decade, the emergence of immune checkpoint inhibitors has revolutionized the treatment of cancers. Since their initial clinical trials in melanoma¹, the checkpoint inhibitors have obtained FDA approval in a variety of cancer species, such as melanoma², non-small cell lung carcinoma^{3,4}, renal cell carcinoma⁵, classical Hodgkin's lymphoma⁶ and urothelial carcinoma⁷. Currently, there is one anti-cytotoxic T-lymphocyte antigen 4 (CTLA4) antibody (ipilimumab), two anti-program cell death protein-1 (PD-1) antibodies (nivolumab and pembrolizumab) and one anti-program cell death protein ligand 1 (PD-L1) antibody (atezolizumab) available in market as immune checkpoint inhibitors. Though immune checkpoint inhibitors have provided a dramatic improvement in patients' survival, immune-related adverse events (irAE) are common. In this review, we summarize the up-to-date knowledge on renal complications of immune checkpoint inhibitors and their clinical management. We also review the current available information on the safety and efficacy of

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None

immune checkpoint inhibitors in patients with chronic kidney disease population as well as kidney transplant recipients.

Immune checkpoint inhibitor—A double-edged sword

Immune checkpoint inhibitors have been developed with a goal of restoring anti-cancer immunity. The importance of the immune system in protecting the body against internal threats such as malignant cells has been described by Chen and Mellman⁸ as the “Cancer-Immunity Cycle” (Figure 1). The process starts with the release of cancer cell antigens (neoantigens), which are uptaken and processed by antigen-presenting cells, followed by presentation to T cells at secondary lymphoid organs. This leads to the activation of effector cytotoxic T cells that then migrate and infiltrate the tumor, recognizing and killing cancer cells. There are many factors that can regulate this process and current immune checkpoint inhibitors modulate mainly two phases of the immune response (Figure 1): (1) enhancing T cell activation in secondary lymphoid organs and (2) increasing tumor cell killing by cytotoxic T cells at target sites. Cytotoxic T cell immune responses require three signals to be fully activated: signal 1; engagement of T cell receptor (TCR) and major histocompatibility complex (MHC), signal 2; interaction with co-stimulatory or co-inhibitory signaling molecules, and signal 3; cytokines and other signaling molecules to fine tune immune response⁹. Checkpoint inhibitors modulate signal 2 by the following mechanisms. First, cytotoxic T-lymphocyte antigen 4 (CTLA4) negatively regulate T cell activation by competing for the binding of co-stimulatory receptor CD28 on T cells and B7 (CD80/86) on APCs. Anti-CTLA4 antibody blocks this negative regulation, allowing greater activation of the tumor-specific T cells (Figure 1). Another target of checkpoint inhibitors is PD-1-PD-L1 or PD-1-PD-L2 axes. PD-1 is a co-inhibitory molecule that is expressed on T cells. Tumor cells are reported to overexpress PD-1 ligands (PD-L1 or PD-L2) thereby evading host immune surveillance¹⁰. Anti-PD-1 or anti-PD-L1 antibodies unmask this shield, and unleash the cytotoxic T cell immune response at the target site (Figure 1).

By activating anti-tumor immunity by these mechanisms, immune checkpoint inhibitors have achieved a great improvement in patients’ survival¹¹. However, this treatment comes with a common set of complications called immune-related adverse effects (irAE), with spectrum of autoimmune diseases, such as rash, colitis, hepatitis, and hypophysitis¹². Acute kidney injury is a rare complication in this setting, but several severe cases have been reported. Herein, we will overview the clinical and pathological characteristics of renal irAE.

Clinical and laboratory features of renal complications in the setting of immune-checkpoint inhibitor use

Over the past decade, multiple clinical trials reported renal irAE in the use of immune checkpoint inhibitors^{1–7,13–22}. In addition, several case reports^{23–30} and case series^{31,32} were published to describe the clinical and pathological features of renal complication in the setting of immune checkpoint inhibitor use. Here we review the clinical and laboratory features of renal irAE.

Incidence of acute kidney injury

According to the clinical trials, the occurrence of acute kidney injury is relatively uncommon, compared with other manifestation of irAE. Table 1 summarizes the reported incidence of acute kidney injury cases in Phase II/III trials with immune checkpoint inhibitors. In ipilimumab monotherapy, elevated creatinine was reported in 1.4% (any grade) and 0.2% (grade 3 or 4) of the cases. Similarly, in nivolumab monotherapy, elevated creatinine was reported in 1.7% (any grade) and 0.8% (grade 3 or 4). Further, in pembrolizumab monotherapy, based on two clinical trials, 1.0% (any grade) patients experienced elevated creatinine, but no case of severe acute kidney injury was reported. However, in ipilimumab and nivolumab combination therapy, the incidence was higher, with 4.9% (any grade) and 1.7% (grade 3 or 4) creatinine elevation reported (Table 1). A similar trend was seen with sequential administration of ipilimumab and nivolumab, with 5.1% (any grade) and 2.2% (grade 3 or 4) of AKI events. Based on these results, the combination or sequential anti-CTLA4/anti-PD-1 therapy should be considered a higher risk for acute kidney injury, as well as for other irAEs reported in the literatures. More recently, an ongoing Atezolizumab trial⁷ reported no renal irAE but the final reporting of adverse events remain awaited.

Clinical presentation and laboratory findings

In the diagnosis of irAE, the knowledge of the timing of onset of acute kidney injury (AKI) may not be as helpful as hoped. In other irAE, the patterns of onset and resolution of irAE with use of ipilimumab have been described and found to be informative³³. For example, dermatological irAE occurs during the first few weeks of ipilimumab therapy initiation, while gastrointestinal irAEs develop after 5–10 weeks. Endocrinopathies tend to occur after 6 weeks as well as hepatic toxicity complications³³. However, in renal irAE, the natural history of complications is not that simple. Cortazar *et al.* and Shirali *et al.* recently reported case series of 13 and 6 biopsy-confirmed renal irAE cases, respectively, in the setting of anti-PD-1 and/or anti-CTLA4 use^{31,32}. Despite the bias of including only biopsy-proven severe cases (CTCAE v4 grade 3 or 4), these case series provide valuable information on the clinical presentation of irAE. Cortazar *et al.* showed that the onset of AKI was variable, between 21–245 days (median; 92 days, interquartile range (IQR) [60, 183 days]) after the initiation of checkpoint inhibitor (Table 2) and the median interval from the last immune checkpoint inhibitor use was 21 days (IQR: [18, 49 days]). In the series of Shirali *et al.*, the timing of AKI onset was also variable but slightly later than Cortazar's report, ranging 3–12 months after the first dose of the checkpoint inhibitor(s). The cumulative dosage of drugs before the onset of AKI also lacked predictive ability; for example, ranging from a single dose of ipilimumab 3 mg/kg to 10 consecutive doses of pembrolizumab 2 mg/kg every 3 weeks. Interestingly, extrarenal irAE preceded AKI in 10 out of 19 cases, such as hypophysitis (n=5) and colitis (n=3), the existence of which might have helped diagnose renal irAE. Most cases of renal irAE presented without any symptoms: with only a few (2/13 cases, 15%) that were associated with worsening or new-onset hypertension or oliguria (2/13 15%). Therefore, close monitoring of laboratory values is important in the diagnosis of irAE. In laboratory findings, urinalysis was associated with pyuria in most of the cases (WBC >5 high power field (hpf) in 10/19 cases), but microhematuria was not common (RBC >2 hpf in 3/19 cases). Lastly, the peak creatinine was severely elevated in Cortazar's case series

(median; 4.5 mg/dl, IQR [3.6–7.3 mg/dl]) and associated with mild proteinuria (0.12–0.98 g/g creatinine). In Shirali's case series, creatinine elevation was relatively moderate (median 1.9 mg/ml, IQR (1.9–2.5 mg/dl)). The characteristics of clinical and laboratory findings of renal irAE are summarized in Table 2.

Pathological features of renal irAE

The majority of immune checkpoint inhibitor-related AKI presented as acute interstitial nephritis (AIN) pattern on kidney biopsies (20/23 cases, 88%), 25% of which were associated with granulomatous features. SLE-like changes²⁴ and acute thrombotic microangiopathy³¹ have also been reported in the literature. A single case of interstitial nephritis with concomitant minimal-change disease was reported³⁰. However, nephrotic syndrome on presentation is considered rare. In the cases of AIN pattern injury, their pathological findings were indistinguishable from other drug-induced AIN characteristics: T cell-dominant infiltration of the renal interstitium with occasional plasma cells and eosinophils present concomitantly. A reported case from our institute²⁹ also revealed AIN pattern with aggressive CD4⁺ and CD8⁺ T cell infiltration, co-stained with cytotoxic enzymes (granzyme B and perforin).

Management of renal complications of irAE

Current recommendations on the management of irAE are summarized in Table 3^{11,34}. As discussed above, the patients with renal irAE are largely asymptomatic on presentation and therefore, the routine monitoring of creatinine and urinalysis is necessary. Upon detection of elevated creatinine grade 2 and above (CTCAE v4), treatment with these agents should be withheld. The cause of AKI other than irAE should be explored first. Common causes of AKI in this setting may include but not limited to volume depletion due to concomitant colitis/diarrhea, poor fluid intake; renal obstruction; nephrotoxicity from antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs) or proton pump inhibitors as well as concomitantly administered cytotoxic chemotherapy. If the index of clinical suspicion for irAE is high, we would advocate treatment with systemic steroids. The dosage depends on the severity of acute kidney injury: methylprednisolone 0.5–1.0 or 1.0–2.0 mg/kg/day IV for grade 2/3 or 4, respectively³⁵ tapered over one month. In the abovementioned case series, two patients did not receive steroid treatment and did not recover their renal function, which may suggest benefit of systemic steroids in preserving long term kidney function, however more dedicated prospective studies are indicated. In addition, in a clinical trial of ipilimumab and nivolumab combination¹⁵, 6 patients developed grade 3 or 4 AKI with 3 fully recovering with steroid treatment and 3 recovering with additional immune suppressing agents. In contrast to the treatment of colitis and hepatic irAE, in which the recommendation includes infliximab or mycophenolate mofetil administration¹², currently no solid data on adjunctive immune modulatory medications are available in irAE and further studies is needed.

Reinitiating immune checkpoint inhibitor can be considered if the severity of AKI is less than grade 2 and response to the steroid treatment has been favorable. In the cases of grade 3 or 4 renal irAE, it may be advisable to have a risk/benefit discussion with the oncology team

with consideration of alternative therapies. It is noteworthy, three cases in Cortazar *et al.* were retreated with immune checkpoint inhibitors after grade 3 or 4 renal irAE without recurrent renal irAE. The first case developed AKI after a single dose of ipilimumab 3 mg/kg with peak creatinine of 6.2 from 0.9 mg/dl. The patient was treated with prednisone 60 mg daily, which was tapered over 3 months, leading to partial recovery of kidney function. The patient was then treated with a different immune checkpoint blockade agent (pembrolizumab) and did not develop recurrent irAE. The second patient developed AKI after 16 doses of nivolumab (cumulative dose 12.4 mg/kg) with peak creatinine of 3.8 from 1.0 mg/dl. After the steroid treatment with prednisone 70 mg twice daily with taper over 14 weeks, this patient was treated with ipilimumab but did not develop AKI. Lastly, the third case received 4 doses of ipilimumab (total 40 mg/kg) before development of AKI with peak creatinine 2.9 mg/dl from 1.0 mg/dl. This patient was conservatively managed without steroids and the kidney function remained unchanged. However, it is interesting to note that re-introduction of ipilimumab did not trigger further kidney injury. Hence, until further evidence emerges, case-by-case management with close collaboration of nephrology and oncology physicians may be prudent.

In summary, renal irAE can present asymptotically and timely diagnosis by close monitoring is crucial. The management of renal irAE includes discontinuation of the agents with or without systemic steroid treatment depending on severity. Further studies are awaited to generate the solid evidence for effective treatment for renal irAE.

Pathophysiological mechanisms of irAE

Acute interstitial nephritis is a pathological kidney injury pattern frequently encountered in autoimmune diseases (e.g. Sjogren disease, IgG4 disease or sarcoidosis) or secondary to a type IV hypersensitivity reaction triggered by drug exposure (e.g. proton-pump inhibitors, NSAIDs or antibiotics). The exact mechanism how immune checkpoint blockade triggers AIN is unknown at this point. One possibility is that immune checkpoint inhibitors could lower the threshold of tolerance against potentially nephrotoxic agents as discussed in Shirali *et al.*³². Another possibility is the loss of “self-tolerance” mechanisms triggering an autoimmune response against kidney self-antigens. CTLA4 regulates peripheral tolerance by modulating the interaction between antigen-presenting cells and T cells in secondary lymphoid organs. Indeed, CTLA4-deficiency has been reported to result in early-onset severe lymphoproliferative autoimmune syndromes involving multi-organs, both in humans^{36,37} and in mouse models^{38,39}. This was due to aberrant T cell activation and loss of tolerance against tissue self-antigen⁴⁰. On the other hand, PD-1 contributes to tolerance primarily at the level of target organs. PD-L1 or PD-1 deficient animals also develop autoimmune disease, but the phenotype is milder and appears later in the life^{41,42}. From these phenotypes of mice, one can hypothesize that blocking CTLA4 and/or PD-1 pathway might potentiate antigen recognition—not only for tumor antigens but also for self-antigens in the lymph nodes and unleash self-reactive effector T cells—and thus provoke a untethered cytotoxic T cell activation against the tumor as well as normal tissues. This is particularly relevant since it is known that humans carry a few auto-reactive T cells that have escaped the negative selection process in the thymus^{43,44}. They are mostly dormant but could be activated under the use of immune checkpoint inhibitors. Our analysis in a renal irAE case

suggest this possibility²⁹. In the kidney biopsy, there was a significant infiltration of CD4⁺ and CD8⁺ T cells with positive cytotoxic enzymes (granzyme B). Interestingly, the patient's peripheral immune phenotyping revealed highly activated and proliferative T cell phenotype as well as aggressive pro-inflammatory cytokine profiles.

In addition to the enhanced cytotoxic T cell activity, the cancer microenvironment is thought to play a role in cancer immunity, and it might be reasonable to think this is the case in development of irAE. It is recently recognized that the tumors with high expression of PD-L1 have better response to anti-PD-1 immune checkpoint inhibitors¹⁰, providing a rational for PD-L1 as a biomarker to predict a response to cancer immune therapy. In addition, certain components contributing to the inflammatory milieu, such as IFN- γ , upregulate PD-L1 expression in the microenvironment⁴⁵, to halt the target organ damage from excessive immune response. If checkpoint inhibitors could indeed perturb such an environmental modulation, they could spur the uncontrolled activation of tissue-infiltrating T cells, and prompt the further target organ damage. Further mechanistic analyses of tumor and tissue microenvironment will lead to better understanding and management of irAE.

Checkpoint inhibitors in chronic kidney disease and organ transplant recipients

According to the prescribing information of ipilimumab, nivolumab, pembrolizumab and atezolizumab, no dose adjustment is recommended based on a population pharmacokinetic analysis. Limited data are available on the efficacy and toxicity of immune checkpoint inhibitors in patients with chronic kidney disease (CKD) or kidney transplant recipients, since these patient populations are generally excluded from clinical trials. Recently, Herz *et al.*⁴⁶ reported three cases of metastatic melanoma complicated with CKD stage 3 (serum creatinine ranging from 1.48–2.10 mg/dl), who were treated with anti-PD-1 agents (nivolumab or pembrolizumab) and did not develop any significant deterioration of their kidney function.

For kidney transplant recipients, considering effective treatment options for melanoma is of particular importance, because of the higher incidence of melanoma among solid organ transplantation recipients than in the general population⁴⁷. Lipson *et al.* initially reported two successful cases of ipilimumab administration in kidney transplant patients⁴⁸. The allograft function of both patients had been stable for 8 and 11 years after transplant when ipilimumab was started. The immune suppression regimen for both patients was reduced at least 6 weeks prior to the ipilimumab (Table 4) and the treatment was well-tolerated with partial response of the melanoma. However, more recently, two cases of acute rejection of kidney allograft after nivolumab treatment have been reported^{49,50} as well as two additional cases of allograft rejections after a sequential administration of ipilimumab and nivolumab^{51,52}. In all the above cases, regardless of rejection episodes, the patients' immune suppression regimen was minimized prior to the initiation of immune checkpoint inhibitors. Why did the latter four cases experience a rejection event? The choice of checkpoint inhibitor (anti-CTLA4, anti-PD-1 or combination use) could be a possible contributor; PD-1 blockade with greater deleterious effect on transplant, compared to CTLA4 blockade.

Reinforcing this observation, cases of successful treatment with ipilimumab that targets CTLA4 in cardiac⁵³ and liver transplant patients have been reported^{54,55}. In addition, the timing of reduction in immune suppression might also be relevant. Lastly, previously administered chemotherapies could be possible contributors too, as they can affect the expression level of co-inhibitory molecules in target tissues. More studies are needed to explore the exact mechanism of rejection and how to safely use immune checkpoint inhibitors in solid organ transplant patients.

Concluding remarks

A larger number of immune checkpoint inhibitors are going to be clinically available, and be used in mono- or combination therapy. Renal complications are relatively rare irAE, however, nephrologists and oncologists should consider this diagnosis when faced with AKI in this population. Further studies to explore the biomarkers that predict the irAE will be needed to provide personalized treatment to patients.

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Figure 1.

Cancer-immunity cycle and immune checkpoint inhibitors. Cancer cells release tumor neoantigens (1), which are carried to lymph nodes by antigen-presenting cells (APCs) (2). APCs present tumor antigens to T cells, which are primed and activated (3). Once T cells are activated, they migrate from the lymphoid organ to the tumor (4), where they identify target tumor cells and deliver killing signals (5). Anti-CTLA4 antibody blocks CTLA4-B7 interaction (3) thereby helps B7-CD28 engagement and T cell activation in the secondary lymphoid organ, whereas anti-PD-1 antibody unleashes the inhibitory PD-1:PD-L1 signal (5), and enables cytotoxic killing of tumor cells by T cells in the target tissue.

Table 1

Incidence of Acute Kidney Injury in Clinical Trials (grades based on CTCAE v4 or v3)

Clinical Trial	Study name	Cancer species	N patients	Cases of elevated creatinine (%) Any Grade	Grades 3 or 4	Ref.
<u>Ipilimumab Alone</u>						
Hodi et al., N Engl J Med, 2010	MDX010-20	Melanoma	121	2 (1.7)	0 (0)	(1)
Robert et al., N Engl J Med, 2011		Melanoma	247	2 (0.8)	0 (0)	(13)
Hodi et al., JAMA, 2014		Melanoma	238	ND	1 (0.4)	(14)
Larkin et al., N Engl J Med, 2015	CheckMate 067	Melanoma	311	8 (2.6)	1 (0.3)	(15)
Postow et al., N Engl J Med, 2015	CheckMate 069	Melanoma	46	1 (2.2)	0 (0)	(16)
Robert et al., N Engl J Med, 2015	KEYNOTE-006	Melanoma	256	1 (0.4)	0 (0)	(17)
Total			1,219	14 (1.4)	2 (0.2)	
<u>Nivolumab Alone</u>						
Larkin et al., N Engl J Med, 2015	CheckMate 067	Melanoma	313	3 (1.0)	1 (0.3)	(15)
Robert et al., N Engl J Med, 2015	CheckMate 066	Melanoma	206	4 (1.9)	1 (0.5)	(18)
Weber et al., Lancet Oncol, 2015	CheckMate 037	Melanoma	268	4 (1.5)	1 (0.4)	(2)
Borghaei et al., N Engl J Med, 2015	CheckMate 057	NSCLC	287	5 (1.7)	0 (0)	(4)
Brahmer et al., N Engl J Med, 2015	CheckMate 017	NSCLC	131	4 (3.1)	1 (0.8)	(3)
Rizvi et al., Lancet Oncol, 2015	CheckMate 063	NSCLC	117	3 (2.6)	0 (0)	(19)
Motzer et al., N Engl J Med, 2015	CheckMate 025	RCC	398	ND	8 (2.0)	(5)
Motzer et al., J Clin Oncol, 2015		RCC	167	2 (1.2)	0 (0)	(20)
Younes et al., Lancet Oncol, 2016		Classical HL	80	ND	4 (5)	(6)
Total			1,967	25 (1.7)	16 (0.8)	
<u>Pembrolizumab Alone</u>						
Robert et al., N Engl J Med, 2015	KEYNOTE-006	Melanoma	555	7 (1.3)	0 (0)	(17)
Ribas, et al., Lancet Oncol, 2015	KEYNOTE-002	Ipilimumab-refractory Melanoma	357	2 (0.6)	0 (0)	(21)
Total			912	9 (1.0)	0 (0)	
<u>Ipilimumab + Nivolumab</u>						
Larkin et al., N Engl J Med, 2015	CheckMate 067	Melanoma	313	17 (5.4)	6 (1.9)	(15)
Postow et al., N Engl J Med, 2015	CheckMate 069	Melanoma	94	3 (3.2)	1 (1.1)	(16)
Total			407	20 (4.9)	7 (1.7)	

Clinical Trial	Study name	Cancer species	N patients	Cases of elevated creatinine (%) Any Grade	Grades 3 or 4	Ref.
<u>Sequential Ipilimumab and Nivolumab</u>						
	Weber et al., Lancet Oncol, 2016	Melanoma	138	7 (5.1)	3 (2.2)	(22)
Total			138	7 (5.1)	3 (2.2)	
<u>Atezolizumab</u>						
	Rosenberg et al., Lancet, 2016	Urothelial carcinoma	310	0 (0)	0 (0)	(7)
Total			310	0 (0)	0 (0)	

NSCLC; non-small cell lung carcinoma, RCC; renal cell carcinoma, HL; Hodgkin's Lymphoma

Readers should refer to the prescribing information for each agent for updated information.

Table 2

Clinical Characteristics of Reported Renal irAE (References 23–32)

Clinical presentation (n=13, in Cortazar et. al.)	
Time of onset from the first dose	Median; 92 days, IQR [60, 183 days]
Time of onset from the last dose	Median; 21 days, IQR [18, 49 days]
Cumulative dosage	Variable
Extrarenal irAE	7 (54%)
Oliguria (<500 ml/day)	2 (15%)
Laboratory findings (n=19)	
Urinalysis	
WBC>5 hpf	10 (52%)
RBC>2 hpf	3 (16%)
Proteinuria	Minimal to mild (0.12–0.98 g/gCre)
Pathological findings (n=23)	
Acute interstitial nephritis	20 (88%)
(with granulomatous features)	5/20 cases of AIN)
Thrombotic microangiopathy	1 (4%)
SLE-like changes	1 (4%)
Minimal change disease	1 (4%)
Response to steroid (n=22)	
No recovery	2 (9%)
Partial recovery	8 (36%)
Complete recovery	12 (54%)

irAE; immune-related adverse event, IQR; interquartile range, WBC; white blood cell, RBC; red blood cell, Cre; creatinine, AIN; acute interstitial nephritis, SLE; systemic lupus erythematosus

Table 3

Management of Renal Toxicity (Based on CTCAE v4.0 grade)

Grade		Recommendation		
		Work-up	Immunotherapy	Initial Treatment
Grade 1	Serum creatinine 1–1.5 $\times$ baseline; > 1–1.5 $\times$ ULN, 1+ proteinuria or urinary protein < 1.0 g/24h	Monitor creatinine at least weekly	Continue	If creatinine worsens, treat as grade 2/3 or 4
Grade 2	Serum creatinine 1.5–3.0 $\times$ baseline; > 1.5–3.0 $\times$ ULN, 2+ proteinuria or 1.0–3.4 g/24h	Monitor creatinine at least every 2–3 days	Withhold therapy and resume if symptoms are mild severity, resolve or return to baseline	(I) Administer methylprednisolone 0.5–1.0 mg/kg/day IV or equivalent and continue until improvement to mild severity. Taper over 1 month. (II) If creatinine increased >7 days or symptom worsen, treat as grade 4
Grade 3	Serum creatinine > 3.0 $\times$ baseline; > 3.0–6.0 $\times$ ULN, proteinuria >3.5 g/24h			
Grade 4	Serum creatinine 6.0 $\times$ ULN	(I) Monitor creatinine daily; (II) Consider nephrologist consultation with consideration of renal biopsy	Permanently discontinue	Administer methylprednisolone 1–2 mg/kg/day IV or equivalent and continue until improvement to mild severity. Taper over at least 1 month

ULN: upper limit of normal

Table 4
Immune Checkpoint Inhibitor Use in Solid Organ Transplant Recipients and Allograft Outcomes

	Allograft Outcome	Checkpoint Inhibitor	Years from tx to ICI	IS regimen	Cancer Response	Interval between IS reduction and ICI initiation
Kidney						
Lipson et al., J Clin Oncol, 2014	Non-rejected	Ipilimumab	11	Tac+Pred--> Pred 5 mg daily	PR	6 weeks
	Non-rejected	Ipilimumab	8	MMF+Tac+Pred--> Pred 5 mg daily	PR then PD	> 4 months
Lipson et al., N Engl J Med, 2016	Rejected	Nivolumab	25	CyA+Pred--> Pred 5 mg daily	PR	> few months
Boils et al., Am J Transpl, 2016	Rejected, HD	Nivolumab	5	CyA+pred--> low dose CyA+Pred	N.D.	2 years
Alahmed et al., Am J Transpl, 2016	Rejected, HD	Ipi × 4 then Nivolumab	15	CyA+Pred--> Pred 5 mg daily	N.D.	N.D.
Spain et al., Ann Oncol, 2016	Rejected, HD	Ipi × 2 then Nivolumab	15	Tac+Pred--> Pred 5 mg daily	PR	Days
Liver						
Morales et al., J Immunother Cancer, 2015	Non-rejected	Ipilimumab	8	Rapa+MMF-->Rapa	PR	3 months
Ranganath et al., J Immunother, 2015	Non-rejected	Ipilimumab	N.D.	N.D.	N.D.	N.D.
Heart						
Gastman and Ernstoff, Ann Oncol, 2016	Non-rejected	Ipilimumab	15	MMF+Tac--> Tac only	SD	N.D.

CyA; cyclosporine, HD; hemodialysis; ICI; immune checkpoint inhibitor, Ipi; ipilimumab, IS; immunosuppression, MMF; mycophenolate mofetil, N.D.; not described, PR; partial response; SD; stable disease, Tac; tacrolimus, tx: transplant