Immune Checkpoint Inhibitor Nephrotoxicity: Update 2020

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Abstract

Immune checkpoint inhibitors (ICPIs) have transformed the landscape of oncology, but are associated with a variety of autoimmune adverse events, including AKI. ICPI-associated AKI (ICPI-AKI) is emerging as an increasingly frequent cause of AKI in patients with cancer, and poses unique diagnostic and management challenges to clinicians who care for these patients. In this review, we describe the incidence and risk factors for ICPI-AKI, including proton pump inhibitor use, CKD, and combination immunotherapy. We discuss the limitations of the various definitions used for ICPI-AKI in prior studies, and propose a novel classification system (definite, probable, and possible ICPI-AKI) that recognizes the diagnostic uncertainty inherent in many cases. We discuss the key clinicopathologic features and treatment strategies for ICPI-AKI, including the role of kidney biopsy versus empirical treatment with steroids. We also explore the under-studied area of ICPI use in the setting of solid organ transplantation, where nephrologists and oncologists must balance the risk of rejection versus treating the underlying malignancy. Finally, we summarize existing data on the role of ICPI rechallenge after an episode of ICPI-AKI.

Introduction

Targeted immune therapies have transformed the landscape of oncology, with immune checkpoint inhibitors (ICPIs) at the forefront. ICPIs are monoclonal antibodies that target inhibitory receptors expressed on T cells, other immune cells, and tumor cells. These receptors include cytotoxic T lymphocyte–associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and PD-ligand 1 (PD-L1). By inhibiting these receptors, ICPIs "remove the brakes" on the immune system, allowing T cells to become activated and exert antitumor activity (1,2).

ICPIs have been demonstrated to prolong overall- and progression-free survival in patients with melanoma (3,4), nonsmall-cell lung cancer (5,6), urothelial cancer (7,8), renal cell cancer (9,10), and many other malignancies (11,12), becoming first-line therapies for many types of cancer. As of 2019, one CTLA-4 inhibitor and five PD-1 and PD-L1 inhibitors have been approved by the Food and Drug Administration (Table 1), and others are undergoing testing in phase 3 clinical trials (13).

Despite their survival benefits, ICPIs can cause a unique spectrum of autoimmune phenomena known as immune-related adverse events (irAEs). The most common tissues involved are the skin, gastrointestinal tract, and endocrine system (14). The kidneys are less commonly involved; however, ICPI-associated AKI (ICPI-AKI) poses unique diagnostic and management challenges, including differentiation of ICPI-AKI from other causes of AKI, the requirement for often prolonged courses of steroids and/or interruptions of ICPI

therapy, and the potential for irreversible organ damage. Here we highlight ten burning questions on ICPI-AKI. We discuss our current understanding of the incidence, risk factors, clinicopathologic features, and treatment strategies for ICPI-AKI, along with gaps in knowledge that require future study.

How Is ICPI-AKI Defined?

Initial case reports and small case series of ICPI-AKI were based exclusively on biopsy-proven findings (15–17). However, because patients are increasingly diagnosed and treated for ICPI-AKI according to clinical features alone, there is a need for standardization of definitions across studies. The National Cancer Institute's Common Terminology Criteria for Adverse Events defines AKI, in part, by comparing changes in serum creatinine (SCr) to the "upper limit of normal" (18). However, patients with cancer often have decreased muscle mass and these definitions may therefore be insensitive to relatively large increases in SCr that fall within the "normal range." In contrast, the Kidney Disease: Improving Global Outcomes Work Group (KDIGO) consensus criteria define AKI according to relative changes in SCr (Table 2) (19). Even among studies that use the KDIGO criteria to define ICPI-AKI, some define ICPI-AKI as any stage (20), whereas others include only stage 2 or higher (21). Thus, there is a need for harmonization of definitions of ICPI-AKI across studies (discussed further below). Additionally, for all definitions of ICPI-AKI, it is

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Table 1. Food and Drug Administration–approved immune checkpoint inhibitors and timing of approval

Immune Checkpoint Inhibitor	Year of Approval	Indication
CTLA-4 inhibitor		
Ipilimumab	2011	Melanoma, renal cell carcinoma; in combination with nivolumab in CRC
PD-1 inhibitor		
Nivolumab	2015	Melanoma, nonsmall-cell lung cancer, small cell lung cancer, renal cell carcinoma, urothelial carcinoma, squamous cell carcinoma of the head and neck, Hodgkin lymphoma, hepatocellular carcinoma, colorectal carcinoma with microsatellite instability/mismatch repair
Pembrolizumab	2015	Melanoma, nonsmall-cell lung cancer, squamous cell carcinoma of the head and neck, Hodgkin lymphoma, renal cell carcinoma, urothelial carcinoma, gastric cancer, cancers with microsatellite instability, mismatch repair, cervical cancer, primary mediastinal B cell lymphoma
Cemiplimab	2018	Cutaneous squamous cell cancer
PD-L1 inhibitor		
Atezolizumab	2016	Nonsmall-cell lung cancer, urothelial carcinoma
Avelumab	2017	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	2018	Urothelial carcinoma, nonsmall-cell lung cancer

CRC, colorectal carcinoma; CTLA-4, cytotoxic T lymphocyte–associated protein 4; PD-1, programmed cell death protein 1; PD-L1, PD-ligand 1.

critical that the renal injury be directly attributable to the ICPI and not to an alternative etiology.

What Is the Incidence of ICPI-AKI?

Reliable data on the incidence of ICPI-AKI are scarce. We estimated the incidence of ICPI-AKI using pooled data from all phase 2 and 3 clinical trials published between 2014 and 2015 that included at least 100 patients treated with ICPIs (15). In this combined analysis of 3695 patients, the overall incidence of ICPI-AKI was 3%; the incidence among patients receiving combination ICPI therapy was 5%; and the incidence of severe AKI, defined as an increase in SCr more than threefold above baseline, an increase in SCr to >4.0 mg/dl, or the need for RRT, was 0.6% (15). A more recent meta-analysis of 48 clinical trials that included 11,482 patients reported similar findings, with an estimated incidence of ICPI-AKI of 2% (22). Although clinical trial data may not reflect the true incidence of ICPI-AKI, Seethapathy *et al.* (20) examined the incidence of ICPI-AKI in a real-world setting of 1843 patients treated at a single large academic center,

and determined the incidence to be 3%, consistent with earlier estimates.

What Are Possible Mechanisms of ICPI-AKI?

The precise mechanisms of ICPI-AKI are poorly understood, with hypotheses about its pathogenesis largely derived from data on extrarenal irAEs or from mouse models. Mutated mice that lack coinhibitory molecules such as PD-1 or CTLA-4 may develop autoimmunity against specific organs, which is driven by the emergence of antigen-specific T cells against self-antigens (23–25). Interestingly, the transfer of infiltrating T cells specific for a certain organ from one mouse to another leads to trafficking of those T cells to the same organ of origin, supporting the notion of antigen specificity of the response (25). Because self-reactive T cells are present in significant numbers in otherwise healthy humans (26,27), blockade of PD-1 or CTLA-4 with ICPIs may break self-tolerance and trigger an autoimmune response against a specific self-antigen on an organ like the kidney. The exact antigen is currently unknown, but is most likely expressed by tubular cells based on the dominant finding of acute tubulointerstitial nephritis (ATIN) on biopsy. An alternative hypothesis is that ICPI-associated ATIN occurs through loss of tolerance to effector T cells primed during prior drug exposure (*e.g.*, proton pump inhibitors [PPIs]). A drug exposure may, in some cases, act as an exogenous antigen and trigger an immune response either by itself or after binding to tubular antigens and acting as haptens (28). Further mechanistic studies in kidney biopsies from patients treated with ICPIs may allow the determination of the specificity of the T-cell response and elucidation of the potential antigen target of the immune response in the kidneys.

Table 2. Comparison of grading systems for AKI

System	Grade	Description
CTCAE	Grade 1	Higher than ULN to 1.5× ULN
	Grade 2	>1.5–3.0× baseline; >1.5–3.0× ULN
	Grade 3	>3.0× baseline; >3.0–6.0× ULN; hospitalization indicated
	Grade 4	>6.0× ULN; life-threatening consequences; RRT indicated
	Grade 5	Death
KDIGO	Stage 1	Increase in SCr of ≥0.3 mg/dl within 48 h or 1.5–1.9× baseline
	Stage 2	Increase in SCr to 2–2.9× baseline
	Stage 3	Increase in Cr to 3× baseline or to ≥4.0 mg/dl or initiation of RRT

CTCAE, Common Terminology Criteria for Adverse Events; ULN, upper limit of normal; SCr, serum creatinine.

What Are the Key Clinical Features of ICPI-AKI?

Unfortunately, no clinical features reliably distinguish ICPI-AKI from alternative etiologies of AKI, although certain features are suggestive. Patients with ICPI-AKI often

Table 3. Summary of clinical characteristics of patients with immune checkpoint inhibitor–associated AKI

Reference	n	Centers, n	Drugs Received	AKI Criteria	Time to AKI, wk[a]	Concomitant ATIN Medications, n (%)	Combined Therapy[b], n (%)	Concomitant or Prior Extrarenal irAEs, n (%)	Pyuria or WBC Casts, n (%)	Biopsy, n (%)	ATIN, n (%)
Shirali et al. (16)	6	1	Nivo, $n=3$; Pembro, $n=2$; Ipi and Nivo, $n=1$	Biopsy-proven ATIN	40	PPIs, $n=33$ (83); NSAIDs, $n=2$ (33)	1 (17)	3 (50)[c]	5 (83)	6 (100)	6 (100)
Cortazar et al. (15)	13	7	Ipi, $n=6$; Nivo, $n=1$; Pembro, $n=2$; Ipi and Nivo, $n=4$	Biopsy-proven AKI	13	PPIs, $n=6$ (46); NSAIDs, $n=1$(8)	4 (31)	8 (62)[d]	8 (62)	13 (100)	12 (92)
Izzedine et al. (17)	12	1	Pembro, $n=12$	Biopsy-proven AKI	36	0	0[e]	NR	4 (33)	12 (100)	4 (33)
Mamlouk et al. (28)	16	1	Nivo, $n=6$; Pembro, $n=6$; Atezo, $n=1$; Treme, $n=1$; Ipi and Nivo, $n=2$	Biopsy-proven AKI; AKIN criteria	14	PPIs, $n=9$ (56) NSAIDs, $n=3$ (19)	13 (81)	9 (56)[f]	7 (44)	16 (100)	14 (88)
Seethapathy et al. (20)	30	1	Ipi, $n=12$; Nivo, $n=9$; Pembro, $n=7$; Durva, $n=1$; Ipi and Nivo, $n=1$;	SCr $\geq 1.5\times$ baseline for ≥ 3 d; expert adjudicated	15	PPIs, $n=23$ (77); NSAIDs, $n=13$ (43)	3 (10)	26 (87)[g]	13 (43)	1 (3)	1 (100)
Cortazar et al. (21)	138	18	Nivo, $n=40$; Pembro, $n=47$; Durva and pembro, $n=1$; Ipi, $n=4$; Atezo, $n=5$; Ipi and nivo, $n=32$; Ipi and pembro, $n=6$; Other combination tx, $n=3$	SCr $\geq 2\times$ baseline or need for RRT	14	PPIs, $n=75$ (54) NSAIDs, $n=30$ (22)	28 (20)	59 (43)[h]	76 (55)	60 (43)	56 (93)
Total[i]	215		Nivo, $n=59$; Pembro, $n=76$; Atezo, $n=6$; Durva, $n=1$; Treme, $n=1$; Any combination tx, $n=50$	—	16	PPIs, $n=146$ (68) NSAIDs, $n=49$ (23)	49 (23)	105 (49)	113 (53)	108 (61)	93 (91)

ATIN, acute tubulointerstitial nephritis; irAEs, immune-related adverse events; WBC, white blood cell; nivo, nivolumab; pembro, pembrolizumab; ipi, ipilimumab; PPI, proton pump inhibitor; NSAID, nonsteroidal anti-inflammatory drug; NR, not recorded; atezo, atezolizumab; treme, tremelimumab; AKIN, Acute Kidney Injury Network (70); durva, durvalumab; SCr, serum creatinine; tx, treatment.
[a]From immune checkpoint inhibitor initiation, mean or median.
[b]This refers to combination therapy with a cytotoxic T lymphocyte–associated protein 4 inhibitor and a programmed cell death protein 1 (PD-1)/PD-ligand 1 inhibitor.
[c]Two patients with hypophysitis; one patient with concomitant rash.
[d]Seven patients had an irAE preceding AKI onset, one had one concomitantly.
[e]All patients were treated with pembrolizumab, although one patient had received ipilimumab in the past.
[f]Five irAEs before diagnosis; three at the time of diagnosis; one after the diagnosis.
[g]Concurrent irAEs; thyroiditis most common, occurring in 13 patients.
[h]Concurrent or prior irAE; rash most common.
[i]Weighted average, based on number of patients in each study.
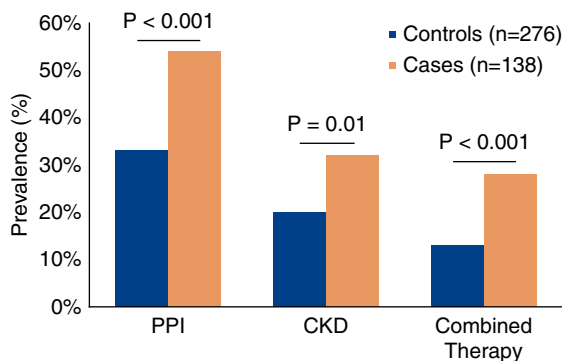
Figure 1. | **PPI use lower baseline eGFR and combination treatment with anti–CTLA-4 and anti–PD-1/PD-L1 agents are independently associated with ICPI-AKI.** Combined therapy refers to combination therapy with a cytotoxic T lymphocyte–associated protein 4 inhibitor and a programmed cell death protein 1 (PD-1)/PD-ligand 1 inhibitor. Ipilimumab/nivolumab was the combination therapy regimen in 75% of cases and 66% of controls. CKD was defined as a baseline (pretreatment) eGFR <60 ml/min per 1.73 m². P values were calculated with the chi-squared test. Data from Cortazar et al. (21). PPI, proton pump inhibitor.

present with sterile pyuria or subnephrotic-range proteinuria (Table 3) (15,16,28), similar to patients with ATIN from other causes (29), but neither finding is sufficiently sensitive or specific to confirm or rule out ICPI-AKI. Eosinophilia is found only in a minority of patients (15,16,21), but may be helpful when present. Finally, the latency period between ICPI initiation and AKI is often longer than observed with other more commonly reported irAEs, with dermatitis usually occurring within 4 weeks of treatment (4,30,31) and colitis within 6 weeks (32). In our multicenter study, the median time from ICPI initiation to AKI onset was 14 weeks (interquartile range, 6–47 weeks), and many patients presented much later (21).

Interestingly, ICPI-AKI often occurs concomitantly or after other irAEs. In our multicenter study, an extrarenal irAE occurred before or concomitantly with AKI in 43% of cases, with rash being the most common manifestation (21). Seethapathy et al. (20) also found a high rate of concomitant extrarenal irAEs in patients with ICPI-AKI, with at least one extrarenal irAE occurring in 26 of 30 (87%) patients. In their study, thyroiditis and colitis were the most common coexisting irAEs. Case series have found variable rates of irAEs occurring before or at the time of AKI, ranging from 33% (16) to 62% (15). Thus, the presence of concomitant or prior extrarenal irAEs is an important clinical clue that should heighten suspicion for ICPI-AKI.

What Are the Risk Factors for Development of ICPI-AKI?

In our multicenter study of 138 patients with ICPI-AKI, which included 276 unmatched control patients who received ICPIs contemporaneously but did not develop AKI, we identified three independent risk factors for development of ICPI-AKI: concomitant use of PPIs, combination treatment with anti–CTLA-4 and anti–PD-1/PD-L1 agents, and lower baseline eGFR (Figure 1) (21). Smaller studies

have also implicated PPI use as a risk factor for ICPI-AKI (15,16,20), and PPI use is associated with an increased risk of ATIN in the general population (33). One possible explanation for the finding that PPI use increases the risk of ICPI-AKI is that T cells may be primed by prior exposure to drugs such as PPIs, and ICPIs reactivate these drug-specific latent T cells, leading to loss of tolerance. PPIs, along with other drugs known to cause ATIN such as nonsteroidal anti-inflammatory drugs, should thus be used with caution in patients receiving ICPIs, and should be discontinued in those who develop ICPI-AKI. Our finding that combination therapy is a risk factor for ICPI-AKI is not surprising because combination therapy is known to result in greater immune activation and a higher risk of irAEs in general (3,34–37). Given the heightened risk of ICPI-AKI associated with each of the above risk factors, patients receiving PPIs, those receiving combination ICPI therapy, and those with a lower baseline eGFR may warrant closer renal surveillance to detect ICPI-AKI earlier.

Which Patients Should be Biopsied versus Treated Empirically?

Our suggested approach to the evaluation and management of patients with suspected ICPI-AKI is shown in Figure 2. This approach is similar to other published algorithms (38), but with several notable exceptions. Patients who develop stage 1 AKI should be evaluated for reversible causes of renal injury—such as prerenal azotemia, urinary obstruction, or drug-induced injury from agents other than ICPIs—and ICPI therapy should be held until the AKI has resolved. Patients with persistent stage 1 AKI, and those who develop stage 2 or 3 AKI, should be referred to nephrology for consultation and consideration of kidney biopsy.

Selection of which patients to biopsy is one of the most complex and subjective decisions in all of nephrology. Particularly in the setting of suspected ICPI-AKI, in which an effective therapy exists for most patients (i.e., glucocorticoids), there is a temptation to treat empirically without a biopsy. Guidelines published by the National Comprehensive Cancer Network similarly lack emphasis on the importance of kidney biopsy in the evaluation of patients with suspected ICPI-AKI, only recommending "consideration" of kidney biopsy in patients with more than a threefold increase in SCr (39). In our view, empirical treatment with steroids should only be considered for patients with an absence of an alternative plausible etiology for AKI and in those with an absolute contraindication to kidney biopsy due to safety concerns (e.g., solitary kidney, uncontrolled hypertension, or anticoagulation that cannot be safely held) (Figure 2). Patients treated empirically with steroids whose kidney function does not improve should undergo kidney biopsy, if feasible, to assess for alternative etiologies of AKI (e.g., glomerulonephritis, which may require additional immunosuppressive therapies). Patients with stage 2 or 3 AKI who have plausible alternative etiologies for AKI other than ICPIs, or in whom there is a concern for GN that may or may not be ICPI related, should proceed directly to kidney biopsy (Figure 2).

What Are the Histopathologic Features of ICPI-AKI?

ATIN is far by the most common histopathologic finding of ICPI-AKI on kidney biopsy (15,16,20,28). In our multicenter
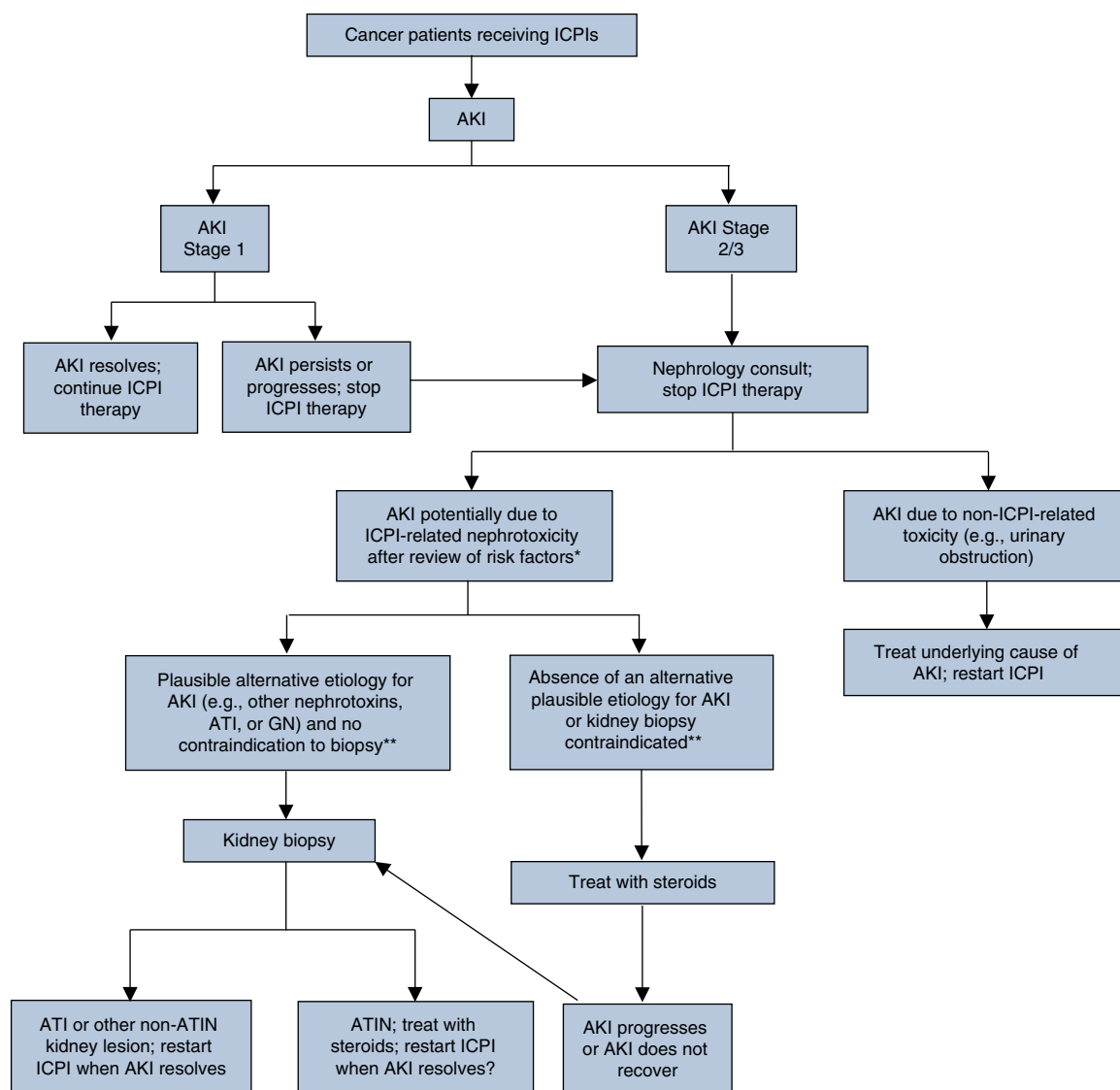
Figure 2. | **Evaluation and treatment algorithm for suspected immune checkpoint inhibitor–associated AKI.** Stages 1, 2, and 3 AKI are based on the Kidney Disease: Improving Global Outcomes AKI staging definition (19). *Clinical review of risk factors (*e.g.*, prior or concomitant PPI use, prior or concomitant extrarenal irAEs). **Contraindications to kidney biopsy include solitary kidney, anticoagulation use that cannot be safely discontinued, or uncontrolled hypertension. ATI, acute tubular injury; ATIN, acute tubulointerstitial nephritis; ICPI, immune checkpoint inhibitor; irAE, immune-related adverse event.

study, we defined ICPI-AKI as doubling of SCr or need for RRT (21). Additionally, the AKI had to have been attributed to the ICPI by the treating provider. Kidney biopsy was performed in 60 (43%) patients, 56 (93%) of whom had ATIN as the dominant lesion. Other pathologic entities have also been observed, including various glomerulonephritides (28,40). In one study of 16 patients with biopsy-proven ICPI-AKI, ATIN was present in 14 of the 16 cases, but co-occurred with glomerular disease in nine cases, including IgA nephropathy, pauci-immune GN, and other pathologies (28). Other small series have reported nephrotic syndrome with minimal change disease (41). These observations underscore the heterogeneity of histopathologic patterns of injury from ICPIs, as well as the immune activation seen in patients with ICPI-AKI, including both B cell–driven, autoantibody-mediated disease and

T cell–driven lesions. These studies also highlight the importance of performing a kidney biopsy even in patients with a clinical history highly suggestive of ICPI-AKI.

How Should Patients with Suspected or Confirmed ICPI-AKI be Treated?

Glucocorticoids are the mainstay of treatment for ICPI-AKI (Table 4). Although no randomized placebo-controlled trial has ever established the efficacy of steroids for treatment of ICPI-AKI, observational data supporting the efficacy of steroids in this setting are quite strong: in our multicenter study, 103 of 119 patients (87%) treated with steroids had complete or partial renal recovery (21). Interestingly, although the route of administration, dose, and

Table 4. Renal outcomes among patients with immune checkpoint inhibitor–associated AKI

Reference	Patients, n	Treatment with Steroids, n (%)	Renal Outcome Data	Rechallenge
Shirali et al. (16)[a]	6	5 (83)	4/5 patients treated with steroids had return of SCr back to baseline; one had an improvement from a peak SCr of 2.5 mg/dl to 1.3 mg/dl, but not back to baseline. One patient who did not receive steroids had furosemide/PPI discontinued, with improvement of SCr back to baseline.	One patient rechallenged and had recurrence of AKI; one patient with ATIN continued on pembrolizumab
Cortazar et al. (15)[b]	13	11 (92)	9/10 patients with ATIN treated with steroids had complete or partial renal recovery. Two patients did not receive IS and had no renal recovery.	Two patients rechallenged without AKI
Izzedine et al. (17)[c]	12	7 (58)	10/12 patients had ICPIs stopped, of whom seven received steroids; one died because of disease progression, the other six had some renal recovery. 2/12 were continued on ICPIs, with some improvement in renal function.	One patient rechallenged with recurrence of ATIN
Mamlouk et al. (28)[d]	16	14 (88)	3/5 ATIN cases all had partial renal recovery after prednisone, one of whom was also treated with infliximab. Two cases had no renal response; 3/16 died because of disease progression.	NR; 13 survivors continued treatment
Seethapathy et al. (20)[e]	30	21 (70)	Of the 82 patients with sustained AKI, 54 (67%) died in the follow-up period, death occurred a median of 22 d (IQR 6–84) after the sustained AKI episode.	17 patients (57%) rechallenged, with nine developing recurrent AKI
Cortazar et al. (21)[f]	138	119 (86)	Complete, partial, and no renal recovery after ICPI-AKI occurred in 40%, 45%, and 15% of patients, respectively. Treatment with steroids associated with a 1.7 greater odds of renal recovery in multivariable models among biopsied patients. Patients with no renal recovery had higher mortality than those with complete or partial recovery.	22% of patients were rechallenged, with recurrent AKI in 23%

SCr, serum creatinine; PPI, proton pump inhibitor; ATIN, acute tubulointerstitial nephritis; IS, immunosuppression; ICPI, immune checkpoint inhibitor; NR, not recorded; IQR, interquartile range.
[a]Renal recovery not explicitly defined.
[b]Complete recovery defined as return of SCr to <0.35 mg/dl above the baseline value. Partial renal recovery defined as a return of SCr to >0.35 mg/dl but less than twice the baseline value, or liberation from RRT.
[c]Renal recovery not explicitly defined; six patients had a "favorable" renal recovery defined as 50% improvement in eGFR.
[d]Complete recovery defined as return of SCr to <0.35 mg/dl above the baseline value. Partial renal recovery defined as a return of SCr to >0.35 mg/dl but less than twice the baseline value.
[e]Renal recovery not explicitly defined.
[f]Complete recovery was defined as a return of SCr to <0.35 mg/dl of the baseline value, and partial recovery was defined as a return of SCr to >0.35 mg/dl but less than twice the baseline value, or liberation from RRT.

duration of steroid treatment is highly variable across studies (15,16,28), we did not identify any differences in the steroid regimen between patients who achieved complete renal recovery versus those who did not (21). However, defining the optimal glucocorticoid regimen from retrospective data is challenging, because dosing is often confounded by severity of injury and response to treatment.

Other immunosuppressive agents have also been investigated in the setting of ICPI-AKI. Mycophenolate mofetil was used in seven patients with ICPI-AKI in our multicenter study: complete renal recovery was achieved in one patient, with partial recovery in the remaining six (21). Other agents that have been studied include rituximab and cyclophosphamide. Mamlouk and colleagues (28) observed a case of ATIN that was refractory to high-dose steroids but responded partially to infliximab. Another patient in the same series with IgA nephropathy also failed to respond to both high-dose steroids and mycophenolate, but responded to infliximab. TNF-α is upregulated in the circulation of patients receiving ICPIs, which may explain why infliximab is successful in treating some patients with ICPI-AKI (42). The use of infliximab to treat extrarenal irAEs has been proposed by others (43), but more data are needed before routine use of infliximab can be recommended for ICPI-AKI.

Our practice is to use prednisone 1 mg/kg daily as a starting dose, with a slow taper over 2–3 months. Rapid tapers may lead to AKI recurrence; however, in some patients with side effects from steroids, shorter tapers can be considered. In patients with severe ICPI-AKI requiring inpatient hospitalization, intravenous steroids (*e.g.*, methylprednisolone 250–500 mg daily for 3 days) may be used as initial therapy.

Regardless of the treatment strategy, we recommend prompt initiation of immunosuppressive therapy in patients with ICPI-AKI. Although we did not detect an association between treatment delay and complete renal recovery in our multicenter study (21), an association between longer treatment delay and worse renal outcomes has been reported in patients with ATIN from other causes (44). Finally, although treatment with immunosuppressive medications could theoretically interfere with the antitumor immune response elicited by ICPIs, most studies have found that such treatment does not appear to negatively affect tumor response or survival (31,45,46).

## Which Patients Can be Safely Rechallenged?

When treating patients with severe ICPI-AKI, it is reasonable to temporarily hold the ICPI. However, permanently discontinuing an ICPI in patients who have exhausted other options for chemotherapy can have dramatic implications on overall survival. Deciding which patients should be rechallenged with ICPIs after experiencing a serious irAE such as AKI is extremely challenging and carries enormous weight. According to the American Society of Clinical Oncology guidelines, ICPI therapy should be permanently discontinued in all patients who develop grade 3 or higher AKI (*i.e.*, an increase in SCr more than three times baseline or need for RRT) (39); however, in our view this approach may deprive patients of a potentially life-saving therapy. In our multicenter study, 31 patients were rechallenged with an ICPI after the initial episode of ICPI-AKI, and only seven (23%) experienced recurrent AKI, six of whom had complete or partial renal recovery. Thus, only one of 31 patients (3%) who were rechallenged developed AKI that did not recover. Clearly additional data on the safety of rechallenge after ICPI-AKI are needed, but based on currently available data and the life-saving nature of these medications, rechallenge should not be routinely withheld due to concern for recurrence of AKI. Rather, we recommend reinitiating ICPIs once renal injury has resolved or stabilized.

What Are Special Considerations in Transplant Patients?

Cancer is the third leading cause of death in solid organ transplant recipients, and the risk of cancer is fourfold higher in transplant recipients compared with matched patients in the general population (47). Immunosuppression may predispose to cancer by inhibiting immune surveillance, suppressing DNA repair, and predisposing to oncogenic viral infections (48–50). Although transplant recipients have been excluded from all clinical trials of ICPIs to date, based on the concern of triggering rejection upon blockade of immune inhibitory signals, case reports and small case series of transplanted recipients receiving ICPIs have begun to emerge with conflicting results (51–62). We reviewed all published case reports and case series and found that the rejection rate with ipilimumab monotherapy was 33% compared to 52% in patients receiving anti–PD-1 monotherapy (Figure 3) (63). Sequential use of ipilimumab followed by anti–PD-1 was associated with rejection in 55% of cases (Figure 3) (63). Only two cases of combined anti–CTLA-4 and anti–PD-1 therapy have been reported, one of whom developed rejection (64). Based on the importance of PD-1 to PD-L1 signaling in peripheral organ transplant homeostasis (65), the higher rate of rejection with PD-1 as compared to CTLA-4 blockade is not surprising. However, it is difficult to draw any definitive conclusion because patients had undergone different reductions or changes of immunosuppression upon metastatic cancer diagnosis, which could strongly influence the rejection rates.

The high rates of rejection with ICPI use in transplant recipients has led to the development of potential preventative strategies, including the use of pre-emptive steroids and sirolimus at the time of ICPI initiation in one case report (61). The aggressiveness of immunosuppression reduction in the setting of cancer is also under debate. Although immunosuppression reduction is a crucial management strategy in some cancers, such as post-transplant lymphoproliferative disorders and skin cancer, its importance in other solid cancers such as prostate or breast cancer is less clear (66). Based on the high rate of rejection with anti–PD-1 therapy, continuation of calcineurin inhibitors (CNIs) during treatment with anti–PD-1 medications may be warranted. An alternative approach is to convert patients from CNIs to mammalian target of rapamycin (mTOR) inhibitors due to their potential antiangiogenic properties in skin cancer and their reduced immunosuppressive effects as compared to CNIs (49,67). However, mTOR inhibitors are associated with a higher risk of rejection than CNIs, even in
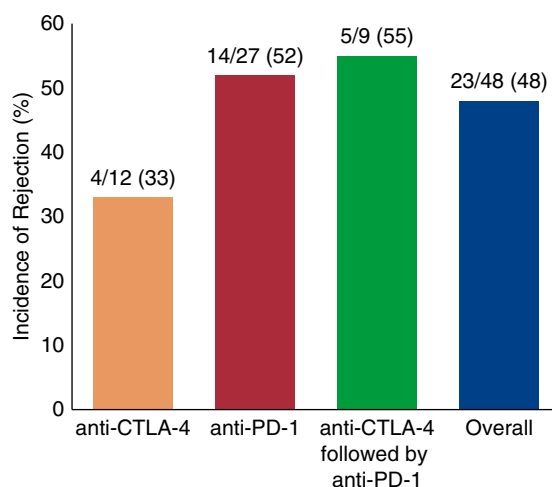
Figure 3. | **Incidence of solid organ transplant rejection may be higher after anti–PD-1 therapy.** Data are derived from published case series and case reports of rejection after immune checkpoint inhibitors. CTLA-4, cytotoxic T lymphocyte–associated protein 4; PD-1, programmed cell death protein 1; PD-L1, PD-ligand 1.

Table 5. Proposed definition and classification of immune checkpoint inhibitor–associated AKI

Classification	Definition
Definite ICPI-AKI	Kidney biopsy confirmed diagnosis compatible with ICPI-AKI, and after clinical review of risk factors[a]
Probable ICPI-AKI	**BOTH of the following** Sustained increase in SCr ≥50% on at least two consecutive values or need for RRT, after clinical review of risk factors[a]Absence of an alternative plausible etiology **AND at least one of the following** Sterile pyuria (≥5 WBCs/hpf) Concomitant or recent extrarenal irAEEosinophilia (≥500 cells per μl)
Possible ICPI-AKI	**BOTH of the following** Increase in SCr ≥50% or need for RRTAKI is not readily attributable to alternative causes

ICPI-AKI, immune checkpoint inhibitor–associated AKI; SCr, serum creatinine; WBC, white blood cell; hpf, high-power field; irAE, immune-related adverse event.
[a]Risk factors include prior or concomitant proton pump inhibitor use, prior or concomitant extrarenal irAEs.

the absence of cancer (68). Depending on the individual immunologic risk between donor organ and recipient pair, a decision about reduction or interruption of immunosuppression must be balanced with the higher risk of rejection with ICPIs. Further studies are needed to assess the potential effect of prophylactic steroid mini-pulses with ICPI cycles, and the conversion from CNIs to mTOR inhibitors, on both rejection rate and cancer response.

Proposed Definition and Classification of ICPI-AKI

We propose a definition and classification system for ICPI-AKI that we hope will aid in the harmonization of definitions used in future studies (Table 5). By including definite, probable, and possible ICPI-AKI, this classification system emulates those proposed for extrarenal irAEs (*e.g.*, myocarditis) (69) in recognizing varying degrees of diagnostic uncertainty in the absence of a biopsy (Table 5). We chose a threshold rise in SCr of 50% or need for RRT to be consistent with the KDIGO criteria (19), and we included the requirement that the increase in SCr be sustained on at least two consecutive values to reduce the likelihood of prerenal azotemia being misadjudicated as ICPI-AKI. Similar criteria were used in a recent ICPI-AKI study (20).

Future Directions

As the indications for ICPI use continue to expand, nephrologists and oncologists will undoubtedly be tasked with caring for a larger number of patients with ICPI-AKI. Differentiation of AKI caused by ICPIs versus other factors remains a key challenge, particularly given the high incidence of AKI in cancer patients, and the lack of sensitive or specific clinical features to reliably diagnose ICPI-AKI in the

absence of a kidney biopsy. Development of noninvasive biomarkers—including urinary, blood, and imaging-based biomarkers—is thus urgently needed. Because ICPIs are often life-saving therapies, future studies are also needed to better understand which patients can be safely rechallenged after an episode of ICPI-AKI. Additionally, these studies should include analyses of overall survival after irAEs, rather than solely focusing on renal survival. Finally, studies are needed to better characterize the underlying mechanisms of ICPI-AKI.

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