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Editorial Comment

EDITORIAL COMMENT

Checkpoint inhibitor therapy-associated acute kidney injury: time to move on to evidence-based recommendations

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ABSTRACT

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment since their introduction ∼15 years ago. However, these monoclonal antibodies are associated with immune-related adverse events that can also affect the kidney, resulting in acute kidney injury (AKI), which is most commonly due to acute tubulointerstitial nephritis (ATIN). Limited data are available on the true occurrence of ICI-associated AKI. Furthermore, evidence to guide the optimal management of ICI-associated AKI in clinical practice is lacking. In this issue, Oleas *et al.* report a single-center study of patients with nonhematologic malignancies who received ICI treatment during a 14-month period, experienced AKI and underwent a kidney biopsy at the Vall d'Hebron University Hospital. Importantly, they demonstrate that only a minority of ICI-associated AKI patients was referred to the nephrology service and kidney biopsy was only performed in 6.4% of patients. Although the authors add to our knowledge about ICI-associated AKI, their article also highlights the need for the development of noninvasive diagnostic markers for ICI-associated ATIN, the establishment of treatment protocols for ICI-associated ATIN and recommendations for optimal ICI rechallenge in patients with previous ICI-associated AKI.

Keywords: acute kidney injury, acute tubulointerstitial nephritis, immune checkpoint inhibitors, immune-related adverse events

The immune system is designed to optimally control activation and suppression of T cell function. Effective CD4 T cell activation begins with antigen recognition by the CD4 T cell in combination with major histocompatibility complex class II molecules on the cell surface of antigen-presenting cells (APCs). Additional costimulatory signaling is delivered through CD28 present on T cells, which engages CD80 or CD86 receptors on APC. Overactivation of this process is prevented by the negative feedback loop involving cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which binds to CD80 and CD86 with a much higher affinity than CD28 where an inhibitory signal is delivered to the T cell. Administering antibodies such as the immune checkpoint inhibitors (ICIs) against anti-CTLA-4 inhibits this inhibitory signal, thus resulting in prolonged T cell activation. The programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) system, which is central in the maintenance of

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T cell responses, is activated by immune responses to inflammatory cytokines. Upon engagement with PD-L1, PD-1 transmits a negative costimulatory signal to attenuate T cell activation. Antibodies directed toward PD-L1 or PD-1 will eliminate this brake, resulting in T cell reactivation. Whereas ICIs were originally believed to act solely in an antagonistic manner, more recent data suggest that ICIs also give rise to cytotoxic reactions [1] and depletion of intratumoral regulatory T cells [2]. CTLA-4 inhibitors induce T cell overactivation and proliferation, impair regulatory T cell survival, cause overproduction of T helper 17 cells, cause cross-reactivity between anti-tumor T cells and antigens on healthy cells and increase autoantibody production. PD-1 and PD-L1 inhibitors result in T cell reactivation, reduced survival and inhibitory capacity of regulatory T cells and increased cytokine production. These effects on the immune system make the ICIs perfect candidates for cancer therapy but also raise the possibility for increased autoimmune reactions.

The ICIs have revolutionized cancer therapy and are currently approved in an expanding group of hematologic and solid malignancies. The first authorized antibody blocking an immune checkpoint was the CTLA-4 antagonist ipilimumab, followed by the PD-1 inhibitors nivolumab, pembrolizumab and cemiplimab and PD-L1 inhibitors atezolizumab, avelumab and durvalumab. Under physiologic conditions, an immune response is controlled by inhibitory signals (checkpoints) to prevent a prolonged and excessive immune response. In the cancer setting, removing these inhibitory signals allows for T cell activation and the generation of an effective antitumor immune response.

Due to their main mechanism of action, ICIs are associated with very specific side effects, termed immune-related adverse effects (irAEs), a unique spectrum of autoimmune phenomena. The frequency and type of associated irAEs differ between the various ICIs. Ipilimumab is associated with both an increased and broader range of irAEs compared with PD-1 antagonists [3, 4]. Colitis and hypophysitis occur more frequently with CTLA-4 antagonists, whereas pneumonitis and thyroiditis appear more often with PD-1 blockers. Although data are limited, it appears that the PD-L1 blockers are associated with relatively fewer irAEs, possibly due to sparing of the PD-1/PD-L2 axis [5]. The skin, gastrointestinal tract, lungs, liver and endocrine system are most commonly involved. Kidney involvement is less common but can be significant. The estimated incidence of all-grade kidney toxicity is ~2% for monotherapy and up to 4.9% for ICI combination therapy [6, 7]. Based on a review of Phase II and III clinical trials of ICIs enrolling 3695 patients, the incidence of high-grade kidney toxicity was 0.6% [7]. However, some authors have claimed that the incidence of kidney toxicity could be considerably higher [8, 9]. In fact, overall, AKI (not necessarily caused by the ICI) occurring in the setting of ICI therapy ranges from 7 to 24% [10–15]. When clinical adjudication or kidney biopsy (much less common) was undertaken, ICI-associated AKI decreased 0.7–3.8% [10–15]. Acute tubulointerstitial nephritis (ATIN) is the most common kidney lesion, while acute tubular injury and an assortment of glomerular lesions are observed less frequently with the ICIs.

In a study published in this issue, Oleas *et al.* [16] report a single-center study of patients with nonhematologic malignancies who received ICI treatment during a 14-month period, experienced AKI (based on the Acute Kidney Injury Network criteria) and underwent a kidney biopsy at the Vall d'Hebron University Hospital, Barcelona, Spain. During this period, 826 patients with nonhematologic organ malignancies received ICI treatment and AKI occurred in 125 patients (15.1%). Of the patients with AKI, only 23 (18.4%) were evaluated in the nephrology department and 8 (6.4% of all AKI patients) underwent a kidney biopsy. The Mayo Group recently reported on the occurrence of ICI-associated AKI (defined as a $\geq$1.5-fold increase in serum creatinine from baseline) in 2143 patients between January 2014 and June 2020 and reported similar numbers: 365 (17%) developed AKI, of which 52 patients with AKI were considered to be possibly directly due to the ICIs [17]. Of these patients, 37 (71%) had clinically suspected or biopsy-proven ICI-associated AKI [biopsy was performed in 14 patients (3.8% of all AKI patients)] [17]. Both studies demonstrate that the majority of AKI episodes in ICI-treated patients are not ICI related and only a minority of AKI patients is evaluated by a nephrologist and undergoes a kidney biopsy.

Cortazar *et al.* [18] published a large multicenter study that included 138 patients with ICI-associated AKI (defined as a $\geq$2-fold increase in serum creatinine or new dialysis requirement directly attributed to an ICI). In this study, the median time from ICI initiation to AKI was 14 weeks (range 6–37) [18]. In this study, the time between the start of ICI and the onset of AKI was a mean of 5.8 months (range 2–11) [16]. In the study by Isik *et al.* [17], AKI was found to develop earlier in the ICI-AKI patients compared with the non-ICI-AKI patients {median 4 months [95% condfidence interval (CI) 1.2–11.4] versus 8.5 months [95% CI 5.3–10.4], respectively; $P = 0.026$}. The most frequent urine findings were subnephrotic-range proteinuria, with a mean protein:creatinine ratio of 544 mg/g and eosinophiluria [5/8 patients (62%)]. In the study of Cortazar *et al.* [18], most patients also had subnephrotic proteinuria, approximately half had pyuria and extrarenal irAEs occurred in 43% of patients. Isik *et al.* [17] noted a higher serum creatinine, CRP, protein:creatinine ratio (although subnephrotic in both groups) and urinary leukocyte and erythrocyte counts in the ICI-AKI patients compared with the non-ICI-AKI patients. Also, eosinophilia was not a differentiating factor. Lower baseline eGFR, proton pump inhibitor use and combination ICI therapy have been identified as independent risk factors for ICI-associated AKI by Seethapathy *et al.* [12].

The limitations of this study are worth discussing. It is a single-center study with a limited number of patients, which contrasts with recently published studies that included more patients and provided important novel data regarding the clinical/biochemical presentation, predictors of occurrence and outcome and management of ICI-associated AKI. In addition, as is problematic in other studies, a lack of kidney biopsy in patients determined to clinically have ICI-associated AKI is a limitation. This limits examination of clinical and laboratory findings as potential predictors of ATIN or another kidney lesion. However, single-center studies can be helpful to provide detailed information about the occurrence of ICI-associated AKI and current practices in the management of these patients. In addition, single-center studies can provide more detailed mechanistic insights regarding the pathophysiology of ICI-associated ATIN and identify biomarkers for a safe rechallenge with ICIs. Besides these mechanistic studies, international, multicenter studies are needed to establish the optimal management of ICI-associated AKI patients to optimize their cancer and kidney outcomes.

Many oncologists manage AKI that develops in ICI-treated patients according to the American Society of Clinical Oncology (ASCO) clinical practice guidelines, which address management of irAEs in patients treated with ICI therapy [19], and the National Comprehensive Cancer Network (NCCN) practice guidelines, which address management of immunotherapy-

related toxicities [20]. The ASCO guidelines recommend a diagnostic work-up as follows: (i) exclusion of alternative etiologies of AKI (recent intravenous contrast, medications and fluid status) and (ii) monitoring of patients for elevated serum creatinine prior to every ICI dose [19]. Remarkably, routine urinalysis is not recommended other than to rule out urinary tract infections. For Grade ≥2 kidney toxicities, the guidelines recommend a nephrology consultation. In the ASCO guidelines it is explicitly stated that 'if no potential alternative cause of AKI is identified, then one should forego biopsy and proceed directly with immunosuppressive therapy' [19]. In the NCCN guidelines, in addition to an evaluation for alternative causes of AKI, discontinuation of nephrotoxic drugs and a spot urine protein:creatinine ratio is recommended [20]. Nephrology consultation is only recommended for Grade ≥2 kidney toxicities and kidney biopsy should be considered for Grade ≥3 kidney toxicities [20]. We believe that urinalysis (and urine sediment examination) should be performed in every ICI-treated patient with AKI. Although sterile pyuria and/or leukocyte casts lack both sensitivity and specificity for ICI-associated AKI, as noted by data showing that low-grade (tubular) proteinuria and urine abnormalities, such as pyuria and/or leukocyte casts and hematuria, occur in only approximately half and two-thirds of cases with ATIN, respectively, urinary findings can help identify non-ICI-related causes of AKI. Although both the ASCO and the NCCN guidelines recommend nephrology consultation in Grade ≥2 kidney toxicities, in actual practice this approach is rarely taken. We feel that nephrology consultation is probably not necessary in Grade 2 renal

Table 1. Current recommendations regarding management of AKI in ICI-treated patients

Factor	ASCO [19]	NCCN clinical practice guidelines [20]	Perazella and Sprangers [22]
Severity of AKI	Consideration of potential alternative etiologies (recent intravenous contrast, medications and fluid status) and baseline renal function	Limit/discontinue nephrotoxic medication and dose adjust to creatinine clearance Evaluate potential alternative etiologies (recent intravenous contrast, medication, fluid status and urinary tract infection) Spot urine protein:creatinine ratio (proteinuria >3 g/day: check antinuclear cytoplasmic antibodies, antinuclear antibodies, double-stranded DNA, rheumatoid factor and CH50/C3/C4)	Evaluate for other causes
Serum creatinine 1.5–2.0 × over baseline	Consider temporarily holding ICI	Consider holding ICI Check serum creatinine and urine protein every 3–7 days	Reevaluation after 1 week and continued monitoring
Serum creatinine 2–3 × over baseline	Hold ICI temporarily Consult nephrology If other etiologies ruled out, administer 0.5–1 mg/kg/day prednisone equivalent If worsening or no improvement: 1–2 mg/kg/day prednisone equivalent and permanently discontinue treatment	Hold ICI treatment Consult nephrology Check serum creatinine and urine protein every 3–7 days Start prednisone 0.5–1 mg/kg/day if other causes are ruled out (treat until symptoms improve to Grade ≤1 and taper over 4–6 weeks) For persistent Grade 2 over 1 week: increase prednisone/methylprednisolone 1–2 mg/kg/day	Hold ICI treatment Consult nephrology Kidney biopsy when no other cause of AKI identified and no other irAEs, bland urine, tubular cells in urine or granular casts in urine No kidney biopsy when no other cause of AKI identified and other irAEs present and sterile pyuria/leukocyte casts
Serum creatinine >3 × over baseline or >4.0 mg/dL; hospitalization indicated	Permanently discontinue ICI	Permanently discontinue ICI Consult nephrology and consider kidney biopsy Consider inpatient care Prednisone/methylprednisolone 1–2 mg/kg/day (treat until symptoms improve to Grade ≤1 and taper over 4–6 weeks) Consider other immunosuppressives if Grade >2 after 1 week of steroids (azathioprine, cyclophosphamide, cyclosporine A, infliximab and mycophenolate mofetil)	Halt ICI treatment Consult nephrology Kidney biopsy when no other cause of AKI identified and no other irAEs, bland urine, tubular cells in urine or granular casts in urine No kidney biopsy when no other cause of AKI identified and other irAEs present and sterile pyuria/leukocyte casts
Life-threatening consequences, dialysis indicated	Consult nephrology Administer corticosteroids (initial dose of 1–2 mg/kg/day prednisone or equivalent)	Permanently discontinue ICI Consult nephrology and consider kidney biopsy Consider inpatient care Prednisone/methylprednisolone 1–2 mg/kg/day (treat until symptoms improve to Grade ≤1 and taper over 4–6 weeks) Consider other immunosuppressive if Grade >2 after 1 week of steroids (azathioprine, cyclophosphamide, cyclosporine A, infliximab and mycophenolate mofetil)	

toxicities when an alternative cause of AKI is clearly identified (urinary obstruction, hypotension with ischemic acute tubular injury, etc.). In our opinion, kidney biopsy should be performed in ICI-treated patients with Grade ≥2 kidney toxicity when no potential alternative causes of AKI are identified and before treatment with corticosteroids is initiated. The histological information will help guide therapy, as finding non-ATIN lesions reduces unnecessary and potentially harmful corticosteroid exposure in cancer patients and may permit continued ICI use.

In ICI-treated patients with AKI where immunosuppressive treatment needs to be initiated to treat extrarenal irAEs, we recommend postponing kidney biopsy and observing the evolution of kidney function. Kidney biopsy would be recommended when there is no kidney function recovery with immunosuppressive treatment. Recently urinary interleukin-9 and tumor necrosis factor α have been suggested as markers to effectively differentiate between ATIN, acute tubular injury and other kidney lesions [21]. Further research is needed to validate these markers as diagnostic markers of ICI-associated ATIN and to provide clinicians with a useful noninvasive diagnostic tool.

In regards to therapy, the ASCO and NCCN guidelines recommend temporary cessation of ICI treatment and, when no other etiologies can be identified, the administration of 0.5–1 mg/kg/day prednisone equivalents for Grade 2 kidney toxicities (Table 1). With no improvement in kidney function, it is recommended that the dose of corticosteroid be increased to 1–2 mg/kg prednisone or equivalent in combination with ICI discontinuation. When there is a kidney recovery to Grade 1 or less, corticosteroids should be tapered over 4–6 weeks. For Grades 3–4 kidney toxicities, permanent discontinuation of ICI treatment is recommended in combination with a nephrology consultation, evaluation for other etiologies and initiation of 1–2 mg/kg/day prednisone or equivalent when no other identifiable etiologies exist. All of these interventions presume that all Grade ≥2 kidney toxicities without an alternative cause are ATIN. Given the nonspecific signs and symptoms of kidney injury, as well as multiple competing causes of AKI in cancer patients, we believe kidney biopsy is of far greater importance than suggested by these guidelines, not only to make a correct diagnosis, but—more importantly—to guide treatment regarding ICI discontinuation, treatment with corticosteroids and ICI rechallenge. Although corticosteroid treatment may not affect oncologic outcomes, they are still associated with an increased incidence of sepsis, venous thromboembolism and fractures in population-based cohort studies, even in patients with short and moderate corticosteroid exposure [23]. In the study by Oleas *et al.* [16], three patients (37%) received treatment with pulses of methylprednisolone 250–500 mg/day and five patients (62%) received prednisone 1 mg/kg/day. Seven of eight patients (87%) experienced recovery of kidney function and one patient (12%) progressed to chronic kidney disease. In the study by Cortazar *et al.* [18], most patients (86%) were treated with steroids and complete or partial recovery was obtained in 40 and 45%, respectively. Predictors of improved kidney prognosis included

Table 2. Current recommendations regarding rechallenge with ICI in patients with previous AKI

Factor	ASCO [19]	NCCN clinical practice guidelines [20]	Perazella and Sprangers [22]
Serum creatinine 1.5–2.0× over baseline	If improved to baseline, resume routine creatinine monitoring	Upon resolution to Grade ≤1, consider resuming concomitant with steroid if creatinine is stable	Resolves: continue ICI treatment Progresses: stop ICI treatment
Serum creatinine 2–3× over baseline	If improved to Grade 1, taper corticosteroids over at least 3 weeks before resuming treatment with routine creatinine monitoring If elevations persist >7 days or worsen and no other cause found, treat as Grade 3	Upon resolution to Grade ≤1, consider resuming concomitant with steroid if creatinine is stable	Non-ICI-related: restart ICI when AKI resolves ICI-related and no need for biopsy: treat with steroids (perform biopsy when AKI progresses) ICI-related and biopsy: no ATIN: restart ICI when AKI resolves; ATIN: treat with steroids and restart ICI when AKI resolves
Serum creatinine >3 × over baseline or >4.0 mg/dL; hospitalization indicated	If improved to Grade 1, taper corticosteroids over at least 4 weeks If elevations persist >3–5 days or worsen, consider additional immunosuppression (e.g. mycophenolate)	Permanent discontinuation of ICI is warranted in the setting of severe (Grades 3–4) proteinuria	Non-ICI-related: restart ICI when AKI resolves ICI-related and no need for biopsy: treat with steroids (perform biopsy when AKI progresses) ICI-related and biopsy: no ATIN: restart ICI when AKI resolves; ATIN: treat with steroids and restart ICI when AKI resolves
Life-threatening consequences, dialysis indicated	If improved to Grade 1, taper corticosteroids over at least 4 weeks If elevations persist >2–3 days or worsen, consider additional immunosuppression (e.g. mycophenolate)	Permanent discontinuation of ICI is warranted in the setting of severe (Grades 3–4) proteinuria	

concomitant TIN-causing medications prior to AKI and treatment with corticosteroids. Failure to achieve kidney recovery after ICI-associated AKI was independently associated with higher mortality [18].

Another important issue is whether ICI treatment can be safely reinitiated after ICI-associated AKI. The ASCO and NCCN guidelines recommend permanent discontinuation of ICI treatment in patients with Grades 3–4 kidney toxicities (Table 2). For patients with Grade 2 kidney toxicities, ICI rechallenge can be considered after discussion with the patient when there is neither recurrence nor CKD [19]. Recently Allouchery *et al.* [24] reported an analysis based on the French pharmacovigilance database evaluating ICI-treated patients with at least one Grade ≥2 irAE resulting in ICI discontinuation, with subsequent ICI rechallenge. The authors demonstrated that 61.1% of the patients who discontinued ICI treatment for Grade ≥2 irAEs experienced no recurrent Grade ≥2 irAEs after ICI rechallenge [24]. In the study of Cortazar *et al.* [18], ICI rechallenge was performed in 22% of patients, of whom only 23% developed recurrent AKI. In the study by Isik *et al.* [17], rechallenge with an ICI was attempted in 16 (43%) of the ICI-AKI patients and recurrence was reported in 3 (19%) of the rechallenged patients. Interestingly, in this study, survival tended to be higher in the group not rechallenged compared with the group that was rechallenged; however, results were not statistically significant [17]. So the risk of recurrence appeared to be acceptable and, as such, we do not agree with the ASCO and NCCN guidelines. In contrast, we recommend ICI reinitiation in all patients where an alternative cause of AKI has been identified [22]. Also, in patients with histology-proven ICI-associated ATIN, we recommend rechallenge with ICI with close monitoring after kidney function recovery. Although not supported by data, clinicians may consider using low-dose corticosteroids in patients with ATIN who had Grade ≥3 kidney toxicities.

In conclusion, the study of Oleas *et al.* [16] further adds to the existing evidence regarding the frequency, diagnosis and management of ICI-associated AKI in clinical practice. In this area, single-center studies can be helpful to provide more detailed mechanistic insights regarding the pathophysiology of ICI-associated ATIN and identify biomarkers for safe rechallenge with ICI. Additionally, international, multicenter studies are needed to establish the optimal management of ICI-associated AKI patients to optimize their cancer and renal outcomes. Importantly, an evidence-based approach is required to facilitate the creation of rigorous guidelines on the appropriate clinical approach for ICI-associated kidney toxicity.

CONFLICT OF INTEREST STATEMENT

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