Acute Kidney Injury Induced by Immune Checkpoint Inhibitors

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\textbf{Keywords}
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\textbf{Abstract}

\textbf{Background:} Recent advances in immune therapy have focused on several agents that target tumor suppression; specifically, use of immune checkpoint inhibitors (ICIs), such as ipilimumab, pembrolizumab, and nivolumab, has become an important strategy in cancer therapy as they improve outcomes in malignant disease. However, the incidence of renal complications arising from the widespread use of ICIs may be underestimated. \textbf{Summary:} The most frequently reported renal condition caused by ICI use is acute interstitial nephritis, and for clinicians, the crucial question is how to effectively manage patients who develop renal side effects due to cancer treatment. Currently, treatment of kidney injury associated with ICIs adheres to clinical guidelines described in Kidney Disease Improving Global Outcomes, which entails drug withdrawal and glucocorticoids or combined immunosuppressant use based on disease stage; however, there is no consensus on renal biopsy. \textbf{Key Messages:} Despite significant progress in prevention and treatment, the incidence and mortality of ICI-induced acute kidney injury (AKI) remain very high. This article will discuss the general clinical manifestations, mechanisms of toxicity, renal complications of ICI therapy, and related biomarkers of renal damage. It is envisaged that this information would help clinicians effectively manage AKI due to ICI therapy.

\textbf{Introduction}

Immune checkpoint inhibitors (ICIs) are a new class of monoclonal antibodies that work by blocking intrinsic downregulating receptors of the immune system, i.e., “immune checkpoints.” They also selectively activate suppressed T cells to enhance antitumor-directed immune responses and have changed the landscape of advanced cancer treatment in the last few years [1]. There are three main types clinically used in ICIs, namely, anti-programmed cell death receptor-1 (PD-1) antibodies, anti-programmed cell death ligand-1 (PD-L1) antibodies, and anticytotoxic T lymphocyte-associated antigen-4 (CTLA-4) antibodies[2], which are mainly used for the treatment of advanced melanoma, Hodgkin’s lymphoma,
nonsmall cell lung cancer (NSCLC), renal cell carcinoma, and squamous cell carcinoma of head and neck [3]. However, the augmented immune response triggered by these agents results in immune-related adverse events (IRAEs) that occur as a consequence of impaired self-tolerance secondary to loss of T-cell inhibition and affect almost every organ and system [4]. While early adverse effects are usually seen in the endocrine system, e.g., hypophysitis and thyroiditis, late adverse effects may occur 6–10 months later and often involve dermatitis, rash, vitiligo, colitis, or kidney injury [5]. Kidney toxicity is relatively rare; however, increasing use of ICIs has led to more frequent reports of acute kidney injury (AKI), which is associated with greater mortality [6]. AKI represents a subgroup of acute kidney diseases and disorders (AKD), and clinical guidelines of the Kidney Disease Improving Global Outcomes (KDIGO) define AKI as increase in serum creatinine (sCr) clearance by ≥50% within 7 days or increase in sCr clearance by ≥0.3 mg/dL within 2 days or oliguria for ≥6 h, while AKD is defined as AKI or glomerular filtration rate <60 mL/min/1.73 m² or decrease in glomerular filtration rate by ≥35% of baseline or increase in sCr clearance by ≥50% of baseline [7, 8]. Major complications of AKI or AKD include volume overload, electrolyte disorders, cardiac arrhythmia, and urinemia. Despite great progress in prevention and treatment, mortality due to ICI-induced AKI remains very high and is associated with great family and social burdens. Thus, as a better understanding of the pathogenesis of ICI-induced AKI could improve disease management, this review will focus on current knowledge of clinical features, pathogenesis, diagnosis, treatment, and biomarkers of AKI associated with ICIs. Additionally, we discuss challenges associated with these drugs, long-term outcomes after development of AKI in the setting of ICI therapy and present a theoretical basis for nephrologists to improve ICI-related AKI outcomes.

Epidemiology and Clinical Features

In most patients, ICI-related AKI is typically suspected a few months after therapy initiation, especially when elevated sCr level is accompanied by hematuria, pyuria, and mild proteinuria, apart from elevated blood pressure, edema, elevated uric acid, and electrolyte abnormalities. If distal renal tubule injury is involved, manifestations include hypokalemia and metabolic acidosis [9]; only a few patients exhibit the classic symptoms of fever, eosinophilia, or rash.

A multicenter study of 138 patients with ICI-related AKI, which defined AKI as a 2-fold increase in sCr, that most patients had proteinuria and pyuria was noted in the urine sediment in approximately half of all patients, and that about 21% patients had eosinophilia. An important finding was that, among the patients who developed ICI-related AKI, 43% had a concomitant history of extrarenal IRAEs, such as hypophysitis, thyroiditis, dermatitis, rash, or colitis [6]. Another report has stated that the overall incidence of AKI among patients undergoing PD-1 inhibitor treatment was approximately 4.19% [10]. However, the estimated incidence of AKI in a cohort study with projected AKI rates was ranging from 9.9% to 29% [11]. A retrospective pharmacovigilance study of 1,444 patients with renal adverse events after ICI use indicated that outcomes tended to be poor with 73.55% hospitalization and 23.13% death. Further, ICI-related AKI appeared to affect more men and individuals over 65 years of age, and interestingly, atezolizumab had the strongest association with renal adverse events among all ICI monotherapy regimens, whereas avelumab appeared to show a relatively weaker association with renal adverse effects [12]. Additional evidence is needed to support these conclusions.

A striking feature of ICI-related AKI is the large variation in time-to-disease from treatment initiation, probably because the drugs have a long half-life of 2–3 weeks. A study of clinical features and outcomes in ICI-associated AKI showed that the median time-to-disease was 14 weeks after treatment initiation [6]; similarly, in a case series of 13 patients, Cortazar et al. [13] reported that nephrotoxicity occurred between 21 and 245 days after ICI therapy with a median duration of 91 days. Data from The Anderson Cancer Center indicate that the median time-to-AKI was 14 weeks (range 6–56 weeks) in 16 cases of AKI, whereas avelumab appeared to show a relatively weaker association with renal adverse events [12]. Additional evidence is needed to support these conclusions.

The incidence of renal IRAEs may be higher in patients prescribed ICIs combined with proton-pump inhibitors (PPIs), nonsteroidal anti-inflammatory drugs (NSAIDs), or antibiotics [15], as similar phenomena have been described upon combination therapy with PPI, NSAIDs, or antibiotics, which led to shorter progression-free survival (PFS) and overall survival (OS) [16]. Among patients diagnosed with ICI-related kidney injury, 69% were provided combination therapy, including antibiotics (9%), NSAIDs (22%), or PPIs (54%) [6]. Essentially, exposure
to any drug that may be associated with acute tubulointerstitial nephritis (AIN) could potentially lead to the activation of drug-specific T cells, triggering the initiation of an immune reaction, and ICI combination therapy is a risk factor for kidney injury because the reported incidence of AKI in clinical trials is 2.1%. Notably, a combination of CTLA-1 and PD-1 inhibitor therapy increased this frequency to 5% compared to monotherapy [13]. A meta-analysis of 95 clinical trials involving 40,552 participants also reported that ICI combination therapy was associated with higher risk of AKI than monotherapy [17]. Interestingly, the overall incidence of PD-L1-inhibitor-induced AKI was <1% in that cohort, which may be lower than that seen in patients treated with PD-1 or CTLA-4 inhibitors, probably because PD-L1 inhibitors are a relatively new class of ICIs. Additionally, all patients suffering from anti-PD-L1-related AKI were also prescribed NSAIDs or PPIs at the time of diagnosis, which strengthens the evidence that concomitant medication use is associated with higher AKI incidence [18]. Given the universality of immune system disorders and individual differences in the immune system, larger study cohorts are merited to further discussion.

**Kidney Histopathology**

Many reports have suggested that AIN is the most common observation in ICI-related AKI, and it can occur either alone or in combination with other glomerular or tubule pathologies, such as granulomatous formations with multinucleated giant cells, thrombotic microangiopathy, lupus nephropathy, focal segmental glomerulosclerosis, membranous nephropathy (MN), IgA nephropathy, minimal change disease, renal tubular acidosis (RTA), or acute tubular necrosis (ATN) [14, 19]. In a survey of 13 patients with AKI due to ipilimumab, nivolumab, or combination therapy for malignant tumor, the primary pathologic classification in 12 patients was AIN, which was characterized by varying degrees of infiltration by CD4+ T lymphocytes, plasma cells, and eosinophils. Further characterization of the lymphocyte infiltrate in 3 patients revealed a predominance of CD3+ T lymphocytes, and granulomatous features were present in 3 out of 12 AIN cases. Immunofluorescence yielded background staining for C3 along vessel walls with no staining in the tubular basement membrane or the glomerulus [13]. Furthermore, renal biopsy of 3 patients treated with anti-PD-1 or anti-CTLA-4 antibody-developed AKI showed features of tubulointerstitial nephritis with predominantly infiltration of inflammatory CD3+ and CD4+ T lymphocytes, while immunostaining for IgA, IgG, IgM, C3, C1q, fibrinogen, and kappa and lambda chains was negative [20]. In a retrospective review of 23 patients diagnosed with ICI-related AKI, among the 12 renal biopsies, the histological pattern of injury was AIN with interstitial inflammation injury but without glomerular abnormality in 11 cases. Two patients showed granulomatous interstitial inflammation, with one demonstrating prominent perivascular inflammation [21]. A patient undergoing nivolumab treatment showed ICI-associated focal segmental glomerulosclerosis, specifically segmental collapse of capillaries spanning a few glomeruli with surrounding epithelial hyperplasia and epithelial protein droplets. Electron microscopy showed podocyte microvillus change with massive foot-process effacement, which is consistent with early focal segmental glomerulosclerosis [22]. Even though reports about IgA nephropathy are rare, in 2018, Kishi et al. [23] reported a case of IgA nephropathy after nivolumab therapy, and the patient had elevated sCr and new onset proteinuria at 10 months after nivolumab initiation. A kidney biopsy showed diffused mesangial matrix expansion and cell proliferation, and while immunofluorescence staining showed C3 and IgA deposition on mesangial areas, IgM, IgG, C4, and C1q were negative. Electron microscopy demonstrated a small amount of highly electron-dense deposits in the subepithelial and mesangial regions. Similarly, a case of IgA nephropathy due to nivolumab was described in 2020 [24]. A 72-year-old man was treated with pembrolizumab for mesothelioma, and he developed elevated sCr 5 months later. A renal biopsy revealed glomeruli with peripheral segmental mesangial proliferation under light microscopy, and electron microscopy showed mesangial electron-dense and immune complex deposits, indicating mild IgA nephropathy [25].

ICIs activate T cells and can enhance the cellular immune response; hence, physicians must beware of immune and autoimmune disorders caused by ICIs. Cappelli et al. [26] have reported that 4 patients developed nivolumab- and ipilimumab-induced sicca syndrome; one of the patients was diagnosed with interstitial nephritis, and a renal biopsy showed acute and evolving chronic interstitial inflammatory infiltrate with eosinophils and T lymphocytes, indicating hypersensitivity and autoimmune interstitial nephritis. Primary MN is an antibody-mediated autoimmune glomerular disease in which approximately 70% of the patients produce autoantibodies to the M-type phospholipase A2 receptor (PLA2R) present on glomerular podocytes. Importantly, those with au-
to immune disease are particularly vulnerable for exacerbation of preexisting autoimmune or underlying IRAEs; e.g., a case of nivolumab-induced immune reactivation of primary MN in a patient with pleural mesothelioma where biopsy results showed thick glomerular capillaries and immunofluorescence staining not only was strongly positive for PLA2R but also revealed capillary granular IgG and C3 deposits [27]. Youngho et al. [28] have also described a case of nephrotic syndrome relapse during PD-L1 inhibitor therapy for lung cancer in a patient with a history of MN. Immunofluorescence demonstrated the presence of IgG, IgA, C3, and κ and λ light chains in the glomerular basement; however, results of anti-PLA2R staining were not reported. Similarly, a case report describes a patient with no symptoms of proteinuria but presence of circulating antidouble-stranded DNA antibodies and glomerulonephritis after ipilimumab therapy. A kidney biopsy showed slight hypertrophy of podocytes and extramembranous deposits, and an immunofluorescence analysis revealed extramembranous and mesangial deposits of IgG, IgM, C3, and C1q; these findings are suggestive of lupus nephritis (LN) [29].

Although severe AKI is a rare complication of ICIs, fulminant cases do occur and can be resistant to therapeutic intervention. A melanoma patient underwent ICI therapy and developed severe AKI. The biopsy showed granulomatous interstitial nephritis, vasculitis, and thrombotic microangiopathy-like lesions, and despite being provided systemic steroid therapy for extrarenal IRAEs, the patient developed acute progressive kidney injury that required renal replacement therapy (RRT) [30]. In contrast, a patient on nivolumab with minimal change in disease confirmed by renal biopsy was managed with corticosteroids and cessation of nivolumab; however, these measures failed to improve kidney function or nephrosis [31]. Thus, nephrologists should be aware of the spectrum of kidney pathologies associated with ICI use, and beware of the various outcomes, even if incidence of a specific pathology is very low.

It is also important to remember that distal RTA seems to be an emerging adverse effect that is not yet well recognized with very few cases reported till date. In 2018, Bitar et al. [32] described the case of a female with NSCLC who was treated with anti-PD-1 therapy. After the 4th dose of nivolumab, her serum sodium level was 137 mmol/L, potassium was 2.4 mmol/L, chloride was 116 mmol/L, and bicarbonate was 11 mmol/L, implying distal RTA, however, as pathological changes in renal tissue were not reported. Other reports of 3 cases of RTA caused by ICIs described prominent electrolyte abnormalities at 1–3 months after the last dose of ICIs in all patients, and biochemical evaluations were remarkable for persistent sCr elevation and hypokalemia. Representative kidney biopsy in cases 1 and 2 showed moderate tubulitis with partially atrophic tubules, indicating severe RTA [33]. Charmetant et al. [9] have reported that a man was hospitalized for metabolic acidosis induced by ICIs, and the kidney biopsy revealed that the tubulitis had exclusively affected the distal convoluted tubules and collecting ducts, signifying distal RTA. Distal RTA has also been reported in various autoimmune disorders, including Sjogren syndrome [34], systemic lupus erythematosus [35], and autoimmune hepatitis [36]. Thus, those patients have distal RTA after ICI therapy is not surprising. We would like to empathize that clinicians must be aware of electrolytic disorders and hyperkalemia as tubular dysfunction can precede sCr increase.

The clinical manifestation of ICI-induced AIN is similar to that of ATN, even though AIN has a more insidious onset and is frequently associated with interstitial edema and inflammatory cell infiltration and ATN arises from direct tubular epithelial injury and rapid deterioration of renal function [37]. Nevertheless, the frequently delayed onset of ICI-induced AKI argues against a direct toxic effect of these agents. Arguably, there were 6 patients who had no AIN but showed ATN and biopsy specimens showed mild focal interstitial inflammation and relative severe tubular epithelial cell injury; the average onset time of AKI was significantly earlier at 4.6 months compared to AIN. Importantly, clinical and laboratory parameters were unhelpful in differentiating AIN from ATN in these cases [38]. It is worth noting that a mean initiation time of 4.6 months does not seem to be consistent with the clinical characteristics of ATN, which may be related to insidious onset and the time of biopsy. As ICI-induced ATN is currently rare, whether ICIs are directly responsible for nephrotoxicity leading to ATN remains to be further explored. It is necessary for the clinician to be alert about AKI onset time and establish a timely diagnosis based on renal biopsy findings. Pathological features are shown in Table 1.

**Mechanism of Kidney Injury**

ICIs provide inhibitory signals to costimulatory receptors and target lymphocyte receptors or their ligands to unleash an antitumor immune response. PD-1 is expressed on the surface of T cells, B cells, natural killer T cells, activated monocytes, and dendritic cells (DCs),
| Type of kidney disease | Drug | Typical clinical symptoms | Histological changes | Reference |
|-----------------------|------|--------------------------|----------------------|-----------|
| AIN                   | Ipilimumab, nivolumab, or combination | Elevated sCr; mild proteinuria | Infiltrates of CD3+, CD4+ lymphocytes, plasma cells, and eosinophils; immunofluorescence revealed C3 along vessel walls | [13] |
|                       | Nivolumab or pembrolizumab or ipilimumab | | | [20] |
|                       | Ipilimumab, nivolumab, pembrolizumab | | | [21] |
| Focal segmental glomerulosclerosis | Ipilimumab and nivolumab | Elevated sCr, urea, and potassium and a decreased albumin; macroproteinuria | Glomeruli segmental collapse of capillaries; podocyte microvillous change with massive foot-process effacement | [14] |
|                       | Nivolumab | | | [22] |
|                       | Pembrolizumab | | | [23] |
| IgA nephropathy       | Nivolumab | Elevated sCr and minimal proteinuria | Diffused mesangial matrix expansion and cell proliferation; C3 and IgA deposition on mesangial areas; electron microscopy showing mesangial electron-dense and immune complex deposits | [23] |
|                       | Nivolumab | | | [24] |
|                       | Pembrolizumab | | | [25] |
| MN                   | Nivolumab | Elevated sCr, urea; hypoproteinemia | Thick glomerular capillaries; immunofluorescence revealed capillary granular IgG and C3 deposits and strongly PLA2R positive | [27] |
|                       | Duvelumab | | | [28] |
| Lupus nephropathy     | Ipilimumab | Elevated sCr; macroproteinuria; hematuria; antinuclear and anti-dsDNA antibodies positive | Slight hypertrophy of podocytes and extramembranous deposits; extramembranous and mesangial deposits of IgG, IgM, C3, and C1q | [29] |
| Thrombotic microangiopathy | Nivolumab and ipilimumab | Elevated sCr; acute progressive kidney failure | Arterioles exhibited pronounced fibrinoid necrosis of the walls; massive fibrin thrombi in the lumens | [30] |
| Minimal change disease | Nivolumab | Elevated sCr and reduced serum albumin; proteinuria; edema; hypoalbuminemia | Mildly ischemic glomeruli with periglomerular fibrosis; electron microscopy revealed podocyte effacement | [31] |
| RTT                  | Nivolumab | Elevated sCr; hypokalemia and metabolic acidosis | Moderate tubulitis in distal convoluted tubules and collecting ducts with partially atrophic tubules | [32] |
|                       | Pembrolizumab | | | [33] |
|                       | Nivolumab and pembrolizumab | | | [9] |
| ATN                  | Pembrolizumab | Elevated sCr; proteinuria | Mild focal interstitial inflammation; severe tubular epithelial cell injury | [38] |
|                       | Nivolumab | | | |
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while PD-L1 is expressed on cancer cells [39]. The interplay between PD-1 and PD-1 ligands inhibits T-cell activity, which then maintains immune homeostasis and prevents autoimmune reactions. Specifically, CTLA-4 is constitutively expressed on T cells and attenuates the immune response by competing with CD28 for binding to costimulatory molecules, namely, CD80 or CD86, expressed on DCs: this reduces the stimulation of antitumor-specific T cells [40]. Moreover, CTLA-4 can regulate peripheral tolerance by modulating the interaction between antigen-presenting cells and T cells in secondary lymphadens. Regulatory T cells (Tregs) lose their suppressive capacity, and autoreactive T cells are abnormally activated when the CTLA-4 pathway is blocked [41]. Therefore, blocking the PD-1/PD-L1/CTLA-4 axis activates T cells in the tumor microenvironment or peripheral blood, thereby releasing inflammatory cytokines and cytotoxic granules that will eliminate tumor cells. However, once this blockade is initiated, it may disturb immune tolerance by unleashing quiescent tissue-specific self-reactive T cells.

In typical ICI-induced kidney IRAE, kidney injury is initiated by the aberrant activation of a clone of self-reactive immune cells [42]. The DCs then present the antigen to activated self-reactive T cells in the peripheral immune organs, and these activated T cells home to the kidney through circulation, where they infiltrate the parenchyma and participate in the inflammatory reaction by releasing cytokines [2]. Furthermore, uninhibited T lymphocytes may mobilize the typical antibody-induced hypersensitivity reaction pathway more vigorously compared to when an immunogenic compound is involved [43]. ICI-induced AKI may also be due to reprogramming of the immune system, which leads to the loss of tolerance against endogenous or exogenous kidney antigens. On the one hand, ICIs could bind to and be identified as an antigen by tubular epithelial cells, mesangial cells, or podocytes [44]. On the other hand, these agents act as haptens and acquire immunogenicity when metabolized by tubular cells, or upon binding with carrier proteins to form antigen-antibody complexes. Subsequently, they are trapped in the parenchyma whence they are recognized by local DCs [45], and last but not least, when ICIs change the immune microenvironment, renal tissue may be recognized as a native antigen, and the activated drug-specific T cells produce antibodies that target native antigens or circulating autoantibodies against native antigens, leading to the development of immune complex-related AIN [46]. Reactivation of drug-specific T cells due to ICIs may reduce normal tolerance to prescribed medications associated with AIN, which can account for the greater incidence of kidney IRAEs in patients provided combined treatment with ICIs and PPI or NSAIDs.

Studies have revealed that, in normal human kidneys, PD-L1 is constitutively expressed in various proximal tubular segments, but not in glomeruli or tubulointerstitial space [47]. Clinically, PD-L1 is upregulated upon rejection after a renal transplant [48]. In mice with kidney transplants, administration of PD-1 and PD-L1 antibodies increases T-cell infiltrates and urinary lipocalin 2 (a marker of tubular injury), leading to terminal acute rejection [49]. Interestingly, inhibition of PD-L1 may have divergent effects on immune regulation. Blocking PD-L1 signaling leads to greater pathogenic renal Th1 immune response and more severe nephrotoxic nephritis. However, lack of PD-L1 results in higher Treg numbers in the inflamed kidney, which may play a protective role [50]. In a model of ischemia-reperfusion injury in the kidney, administration of PD-L1 or PD-L2 antibodies abrogates Treg-mediated protection and significantly exacerbates renal inflammation and tubular injury [51]. Therefore, PD-L1 inhibitors have divergent effects during immune regulation of renal injury by controlling multiple cell types. Based on the above, we hypothesize that ICIs could directly attack ligands in the renal tubular epithelial cells leading to ATN and that all of the above events combine to cause ICI-induced kidney damage. A possible mechanism of kidney injury that accommodates our hypothesis is shown in Figure 1.

Treatment Strategy

Effective management of IRAEs depends on early recognition and severity of nephrotoxicity. According to KDIGO guidelines, stage 1 AKI is defined as sCr: 1.5–1.9 times baseline, or ≥0.3 mg/dL increase, or urine output: <0.5 mL/kg/h for 6–12 h; stage 2 as sCr: 2.0–2.9 times baseline, or urine output: <0.5 mL/kg/h for ≥12 h; and stage 3 as initiation of RRT, or sCr: 3.0 times baseline, or ≥4.0 mg/dL, or urine output: <0.3 mL/kg/h for ≥24 h, or anuria for ≥12 h.

General Management

Corticosteroids have been used in most patients with at least partial improvement in kidney function, and biopsy is of greater importance in diagnosis [52]. For stage 1 AKI, continued ICI therapy should be considered until its etiology is determined. For patients developing stage 2, kidney biopsy and withholding use of ICIs may be considered until partial symptom improvement. Oral prednisone 0.5–1 mg/(kg × day) with maximal dosage of 60–80
Fig. 1. Mechanism of ICI-related AKI. Autoreactive immune cells get activated through the PD-1 inhibitor nivolumab, PDL-1 inhibitor atezolizumab, or CTLA-4 inhibitor ipilimumab, and subsequently proliferate and differentiate. The mechanism of ICI-induced AKI can be roughly divided into three categories. ICIs are trapped in renal parenchyma and directly identified as antigen; ICIs act as haptons, may acquire immunogenicity, and form antigen-antibody complexes that are deposited in kidney tissue; these immune cells secrete antibodies that bind to native antigens on kidney tissue because of the changes in the immune microenvironment. All of these cause kidney damage.
mg daily is given for patients whose symptoms persist for more than 1 week. For those developing stage 3, kidney biopsy should be implemented immediately to identify the etiology of AKI and simultaneous discontinuation of ICI therapy, and intensive i.v. methylprednisolone (0.5–1.0 g/day) for 3 days must be implemented. Oral administration of prednisone for 8–12 weeks may be required, which is the recommended course of treatment for drug-induced AKI [29, 53]. Of note, corticosteroid therapy should be longer in these patients as they may experience frequent relapse. In practice, pausing the ICI treatment and administering corticosteroids are often pursued empirically. If improvement to stage 1 or remission is more conspicuous, corticosteroids can be reduced gradually and the necessity of resuming ICIs can be discussed if sCr does not increase after withdrawal. However, methylprednisolone or prednisone treatment may not be effective in ICI-induced AIN [13], and in such patients whose symptoms are refractory to corticosteroid therapy or have significant steroid side effects, other immunosuppressant drugs such as mycophenolate, azathioprine, cyclophosphamide, cyclosporine, or infliximab should be considered [53–55]. If these measures do not afford effective relief from kidney damage, timely RRT is necessary.

ICI Rechallenge

ICIs may be the only therapeutic option available to effectively treat the underlying cancer and maintain tumor remission, and approximately 22% of patients diagnosed with ICI-related AKI still need to attempt ICI reuse [56] even though the median time-to-resumption after withdrawal is unknown. If AKI remission is more pronounced, or corticosteroid taper is complete or even only nearly complete, some oncologists may either restart the same ICI therapy or switch to a different one, sometimes concurrently with low-dose prednisone; however, the efficacy and safety of reuse should be taken into full consideration. In a multicenter study, 23% of the patients who rechallenged ICIs and the latency period for ICI-related AKI after retreatment were shorter than during first use, all but 1 patient achieved complete or partial recovery of kidney function after rechallenge [6]. In contrast, Meraz-Munoz et al. [57] have reported a 12.5% recurrence rate, which may be related to differences in evaluation criteria for resuming therapy. It is important to note that, in patients with limited choice for ICI reuse, a combination of ICIs and PPI or NSAIDs should be avoided as much as possible [16]. Patients with severe renal insufficiency before ICI administration and who require longer for renal function recovery (>6 weeks) are at a higher risk of permanent renal failure when they resume ICI therapy [58]. Once therapy is resumed, sCr, urine and electrolytes should be monitored regularly, and proteinuria or microalbuminuria quantified as needed. The recommended management algorithm for ICI-induced AKI is shown in Figure 2.

Sequelae of AKI

Long-term sequelae of ICI-induced AKI have been reported. Many clinical studies have uniformly shown that most patients recover renal function after ICI withdrawal or glucocorticoid use; nevertheless, others will require immunosuppression or long-term RRT [57, 59]. In a pooled analysis of all IRAEs, almost all patients with stage 3 kidney dysfunction due to ICIs reverted to at least stage 1, although the overall number of patients with kidney IRAEs was itself very small [60]. Complete or partial kidney recovery after ICIs-AKI occurred in 85% of patients, and the distribution did not significantly differ based on AKI severity [6]. A survey that included a total of 63 cases indicated that 88.9% of patients were treated with corticosteroids during the course of AKI that about 27.0% patients recovered fully but that 54.0% only recovered partially, 12.7% did not recover, and one patient died of disease progression [61]. ICI-induced kidney damage did not appear to affect 10-year OS, regardless of how AKI was defined [62]. However, even though it is known that overall prognosis in ICIs-AKI is better, clinicians must be aware of concomitant extrarenal IRAEs which are associated with worse renal prognosis and that those receiving steroid therapy were more likely to have renal recovery [6, 63]. A lower degree of interstitial fibrosis in the kidney parenchyma appears to correlate with better AKI outcomes [13]. We emphasize the necessity for earlier disease diagnosis by renal biopsy and initiation of glucocorticoid treatment.

Biomarkers

Screening for biomarkers associated with ICI-induced IRAEs could improve clinical diagnosis, therapy, and prognosis, and systemic inflammatory status has been demonstrated to be closely correlated with a high incidence of AKI; thus, inflammatory biomarkers found to be associated with ICI-induced AKI include serum IL-17, IL-6, IL-10, TGF-β1, lactate dehydrogenase (LDH), C-reactive protein (CRP), lymphocyte count, and neutrophil/lymphocyte ratios which may be the potential markers. IL-6 is a cytokine involved in immune regulation that induces acute phase protein synthesis in the liver. CRP is a type of acute phase protein, and its levels are usually ele-
vated prior to manifest clinical symptoms of IRAEs. It is a prognostic factor with higher levels of serum CRP, IL-6, or neutrophil/lymphocyte ratios associated with a shorter OS in patients with metastatic melanoma receiving nivolumab or ipilimumab therapy [64]. Similarly, Ozawa et al. [65] reported 31 patients with NSCLC and state that early elevation of serum CRP and IL-6, i.e., within 7 days after the administration of nivolumab or pembrolizumab, is associated with survival and that it is a predictor of therapeutic efficacy. Serum IL-17 was found to correlate significantly with the incidence of grade 3 diarrhea or colitis, and a trend toward significance was seen at 6 weeks. A combination of baseline TGF-β1 and IL-10 levels was associated with therapeutic PFS after ipilimumab therapy [66]. One study quantified serum proteins in 34 patients with advanced NSCLC who had suffered chemotherapy failure followed by nivolumab monotherapy. Multivariate analysis revealed that serum levels of RANTES (CCL5) were correlated to IRAEs, and that CCL5 levels decreased after initiation of corticosteroid use [67]. LDH level is a classic inflammatory marker in patients with cancer, and studies have suggested the importance of the baseline-derived neutrophil to lymphocyte ratio (baseline-derived neutrophil to lymphocyte ratio = absolute neutrophil count/[white blood cell count − absolute neutrophil count]), and LDH level as prognostic markers could predict PFS and OS of ICI-treated patients [68, 69]. In a review of 1,746 metastatic breast cancer patients who were treated with ICIs, tumor-infiltrating lymphocytes ≥5% and tumor-infiltrated CD8+ T cell were determined to be ideal predictors of treatment efficiency; i.e., patients with high tumor-infiltrating lymphocytes and tumor-infiltrat-
ed CD8+ T cells have longer PFS and OS [70]. High levels of CD16+ monocytes at baseline were found to be associated with a higher response rate and lower Treg counts in the tumor tissue of ipilimumab-treated patients [71]. CD163 is a receptor expressed in M2 macrophages and activated macrophages, and plays a role in tissue injury and inflammation in animal models of kidney disease [72]. High levels of urinary soluble CD163 were found in 87% of all patients with active antineutrophil cytoplasmic antibodies-associated AKI, which showed better diagnostic performance than traditional urine biomarkers [73]. Furthermore, urinary soluble CD163 had the best receiver operating characteristics (AUC = 0.76) at baseline for differentiating between active LN and active nonrenal disease, which also strongly correlated with glomerular inflammation and severity of LN [74, 75]. Intestinal flora regulates multiple physiological processes, including metabolism, inflammation, and immunity. Dubin et al. [76] sequenced fecal bacterial flora from melanoma patients and found that those with a melanoma rich in Bacteroidetes had a lower incidence of colitis after use of the CTLA-4 antibody ipilimumab. Despite the above, there are no specific indicators for the diagnosis of ICI-related AKI.

Prospective studies and standardized sample collection may contribute to the discovery of biomarkers that can help identify AKI in the absence of tissue diagnosis. Therefore, more clinical studies are needed to clarify the mechanism of IRAEs to identify biomarkers with stronger specificity for ICI-induced AKI.

**Conclusion**

In conclusion, the incidence of ICI-induced renal damage is becoming prevalent due to increasing use of ICIs in cancer patients. ICI-related AKI can occur at weeks or months after initiation of ICI treatment and the most commonly reported pathology is AIN; nevertheless, thrombotic microangiopathy, lupus nephropathy, focal segmental glomerular sclerosis, MN, and IgA nephropathy have also been observed. Discontinuation of ICIs and treatment with corticosteroids are effective in patients with severe renal injury but not in all cases. Treatment of certain pathological types of AKI is likely to be delayed during empirical glucocorticoid therapy, and the risk of infection, bleeding, and other glucocorticoid adverse reactions is higher. Importantly, some patients develop distal tubular dysfunction with multiple electrolyte disorders such as hypokalemia, hypocalcemia, and hyponatremia that require regular laboratory monitoring. Given the complicated factors of renal damage in tumor patients, and the nonspecific manifestations that can be easily attributed to other reasons, AKI incidence may be underestimated; hence, more rigorous criteria are needed for disease assessment and diagnosis.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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