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Immune checkpoint inhibitor–associated nephritis—treatment standard

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ABSTRACT

Over the last 13 years, the use of immune checkpoint inhibitor (ICI) therapy has grown remarkably, owing to their unprecedented anti-tumor efficacy in certain tumor groups. With increased use of ICIs, we are seeing immune-related adverse events (irAEs) more frequently. Renal irAEs, such as ICI-associated acute kidney injury (ICI-AKI), are reported in 2%–5% of patients treated with ICIs, with acute tubulointerstitial nephritis (ATIN) as the most common histopathologic lesion, though various forms of glomerulonephritis have also been reported. Modifiable risk factors for ICI-AKI include concurrent use of ATIN-associated drugs, like proton pump inhibitors, non-steroidal anti-inflammatory drugs and antibiotics, and dual ICI therapy with both Cytotoxic T-lymphocyte Associated Protein 4 (CTLA-4) and Programmed Cell Death Protein 1 and its ligand (PD1/PDL-1) blockade. Kidney biopsies remain the diagnostic modality of choice, though several promising non-invasive biomarkers, which have not yet been broadly clinically validated have emerged. The treatment of ICI-AKI involves holding ICIs, discontinuation of ATIN-associated drugs and initiation of immunosuppression with corticosteroids as first-line therapy. With prompt treatment initiation, most patients achieve full or partial renal recovery, allowing for re-challenge with ICI. However, a subset of patients will require additional steroid-sparing therapies for corticosteroid-dependent or refractory ICI-AKI. Here we review developments in our understanding of the pathophysiology of ICI-AKI, the approach to diagnosis (with a focus on the emergence of novel diagnostic tools), prognostic factors and the current evidence for establishing treatment standards for ICI-AKI. As the evidence base remains largely retrospective, we identify questions that would benefit from future prospective studies in the diagnosis, management and prognostication of ICI-AKI.

Keywords: acute interstitial nephritis, acute kidney injury, immune checkpoint inhibitor, immune related adverse events, immunotherapy

In a nutshell

1. Immune checkpoint inhibitor–associated acute kidney injury (ICI-AKI), referring specifically to renal immune-related adverse events, is an uncommon complication of ICI therapy, reported in 2%–5% of patients receiving ICI therapy. Given the absence of distinctive clinical or biochemical features, kidney biopsy remains the most accurate diagnostic tool.
2. The most common histopathologic finding of ICI-AKI is acute tubulointerstitial nephritis (ATIN), with retrospective data suggesting that concurrent use of ATIN-associated drugs, such as proton pump inhibitors, increases the risk of ICI-AKI. Avoidance of all ATIN-associated drugs for the duration of ICI therapy is advisable, if feasible.
3. Most patients with ICI-associated ATIN achieve complete or partial renal recovery. Evidence suggests that early corticosteroid initiation, within the first 3 days of diagnosis, increases the likelihood of renal recovery. Increasing evidence is emerging in support of steroid-sparing therapies for those patients with corticosteroid-dependent or -refractory AKIs.
4. ICI re-challenge, potentially with secondary prophylaxis, is well tolerated, with one out of five patients developing recurrent ICI-AKI, the majority of whom will achieve some renal recovery.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have shifted the therapeutic focus in solid tumor oncology towards immunotherapy with their remarkable efficacy in certain tumor groups [1]. Since the Food and Drug Administration's (FDA) approval of ipilimumab in 2011 for the treatment of metastatic melanoma, there have been 10 FDA-approved ICIs (Table 1). With increased utilization of these agents, the number of patients presenting with autoimmune toxicities known as immune-related adverse events (irAEs) is increasing. The incidence of irAEs in patients on ICI therapy is estimated between 60% and 85% [2, 3]. Renal irAEs occur less frequently than dermatologic, gastrointestinal and other toxicities [4]. Based on data from retrospective studies, renal irAE are estimated to occur in 1.4%–3% of patients on ICI monotherapy, and up to 5% on ICI dual therapy [5–7]. However, all-cause acute kidney injury (AKI) in patients on ICI is reported in the range of 15%–25%, depending on the definition of AKI used; this includes acute tubular necrosis, obstruction, septic nephropathy and pre-renal etiologies [8–10].

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Table 1: FDA-approved ICI products, with both generic names and brand names, as well as their targets and indications (in part adapted from Sun *et al.* [80]).

Product	Target	Year	Indications
Ipilimumab (YERVOY)	CTLA-4	2011	Stage III and IV melanoma, renal cell carcinoma, colorectal cancer, hepatocellular carcinoma, non-small-cell lung cancer, malignant pleural mesothelioma, esophageal cancer
Pembrolizumab (KEYTRUDA)	PD1	2014	Melanoma, non-small-cell lung cancer, head and neck squamous cell carcinoma, classical Hodgkin's lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, microsatellite instability high or mismatch repair deficient cancer, colorectal carcinoma, gastric cancer, esophageal cancer, cervical cancer, Merkel cell carcinoma, renal cell carcinoma, endometrial carcinoma, tumor mutational burden-high cancer, cutaneous squamous cell carcinoma, triple negative breast cancer
Nivolumab (OPDIVO)	PD1	2014	Non-small-cell lung cancer, malignant pleural mesothelioma, renal cell carcinoma, classic Hodgkin's lymphoma, head and neck squamous cell carcinoma, urothelial cancer, colorectal cancer, hepatocellular cancer, esophageal cancer, gastric cancer, gastroesophageal junction cancer, esophageal adenocarcinoma
Atezolizumab (TECENTRIQ)	PDL-1	2016	Urothelial carcinoma, non-small-cell lung cancer, extensive stage small-cell lung cancer, hepatocellular carcinoma, melanoma
Avelumab (BAVENCIO)	PDL-1	2017	Metastatic Merkel cell carcinoma, urothelial carcinoma, renal cell carcinoma
Durvalumab (IMFINZI)	PDL-1	2017	Urothelial carcinoma, non-small-cell lung cancer, extensive stage small-cell lung cancer, biliary tract cancer
Cemiplimab-rwlc (LIBTAYO)	PD1	2018	Cutaneous squamous cell carcinoma, basal cell carcinoma, non-small-cell lung cancer
Dostarlimab-gxly (JEMPERLI)	PD1	2021	Endometrial cancer, mismatch repair deficient solid tumors
Nivolumab and Relatlimab-rmbw (Opdualag)	PD1 and LAG-3	2022	Unresectable or metastatic melanoma
Retifanlimab-dlwr (ZYNYZ)	PD1	2023	Metastatic or recurrent locally advanced Merkel cell carcinoma

For renal irAEs, or ICI-AKI, treatment approaches are tailored based on the suspected or biopsy-proven histopathologic lesion. Acute tubulointerstitial nephritis (ATIN) represents the most common manifestation of ICI-AKI, though acute tubular necrosis (ATN) in the absence of clear hemodynamic insults and glomerulopathies have been reported, some of which represent recurrence of previously treated disease [11–15]. In this review, we discuss risk factors for the development of ICI-AKI and the current standards of treatment of ICI-AKI, and highlight novel developments in the pathophysiology, diagnosis and outcome prediction of ICI-AKI.

NOVEL DEVELOPMENTS IN PATHOPHYSIOLOGY AND DIAGNOSIS

Pathophysiology

The anti-tumor effect of ICIs is mediated by augmenting host T-cell response to tumor antigens. This is achieved by impeding intrinsic attenuation mechanisms which, under normal physiologic conditions, exist to prevent potential harms related to excessive immune response to antigens, such as autoimmune injury [16]. These attenuation mechanisms are termed "immune checkpoints." Currently, FDA approval has only been granted for ICI therapy targeting three immune checkpoint pathways, Programmed Cell Death Protein 1 (PD1) and its ligand PDL-1, Cytotoxic T-lymphocyte Associated Protein 4 (CTLA-4) and Lymphocyte Activation Gene 3 (LAG3). There are multiple other immune checkpoint receptor signaling pathways currently under development as promising novel targets [17]. This review will focus on ICI-ATIN related to PD-(L)1 and CTLA-4 pathway inhibition (Figs 1 and 2).

Multiple hypotheses exist with regards to the mechanisms underlying renal irAEs (Fig. 3). These hypotheses are based on limited clinical data derived from cases of extrarenal irAEs, and preclinical studies using mouse models. In Nishimura *et al.*'s study, PD1 knockout mice developed lupus-like autoimmune manifestations, and in Waterhouse *et al.*'s study, CTLA-4-deficient mice developed T-cell lymphoproliferative disorders, in both instances demonstrating the importance of immune checkpoints to maintaining self-tolerance and providing negative regulation of T-cell activation [18, 19]. While the process of thymic negative selection exists to eliminate self-reactive T cells, it does so imperfectly. The resultant autoreactive T cells may depend on the action of immune checkpoint pathways to maintain anergy [20, 21]. The nature of the target antigen, or antigens, leading to renal irAEs remains unclear. However, given the prevalence of ATIN, it is likely that at least one of the antigens is expressed by tubular epithelial cells. In support of this theory, tubular epithelial cells have been demonstrated to express PDL-1 [22]. In addition, Valenzuela *et al.* demonstrated that in mice who developed ATIN after exposure to a combination of anti-PDL-1 antibodies and cisplatin, the renal interstitial infiltrate in all cases had positive PD1 staining. They also looked at the renal biopsies of 10 cancer patients who had developed ATIN post-ICI exposure and found that in all cases the interstitial infiltrate had positive PD1 staining [15].

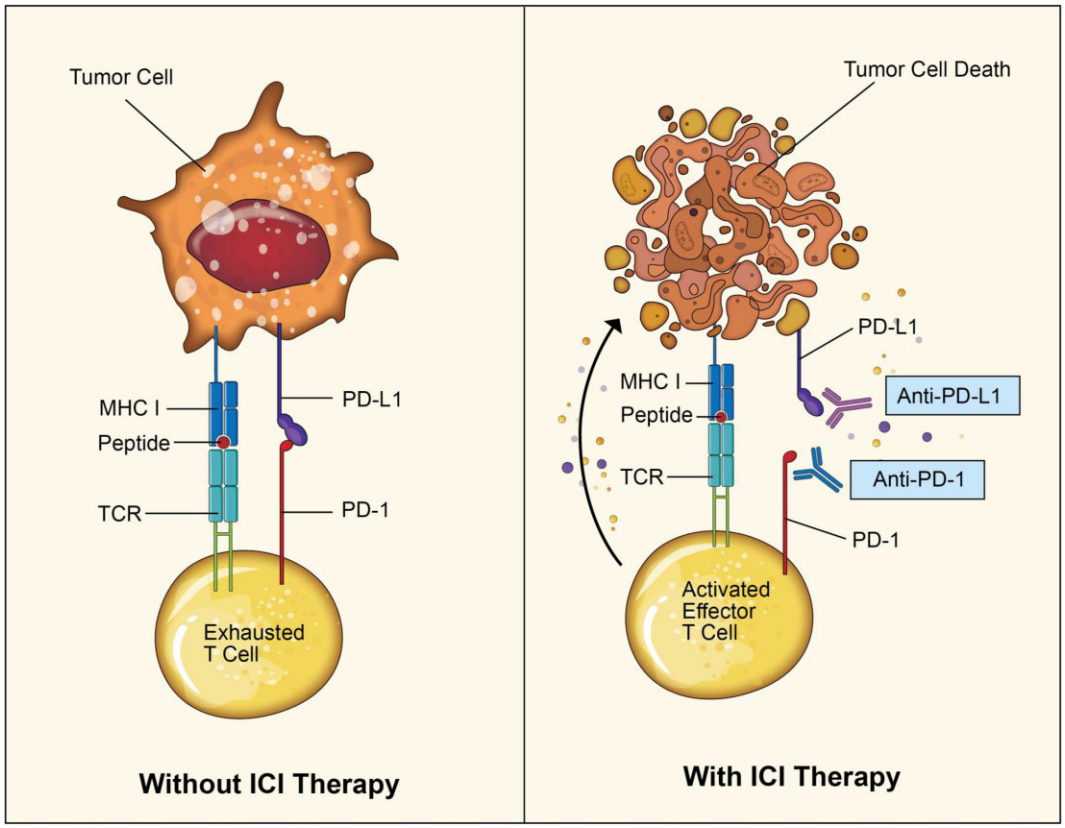

Figure 1: Mechanism of PD1/PDL-1 inhibitors. One mechanism of immune evasion by cancer cells is the expression of PDL-1. Some tumor cells constitutively express PDL-1, PD1's ligand. Peripherally circulating T-cells upregulate the expression of PD1 after they are activated. The binding of PD1 to its ligand, PDL-1, induces T-cell exhaustion, allowing tumor cells to evade cytotoxic T-cells. PD1/PDL-1 inhibitors competitively inhibit this mechanism, and allow T-cell mediated tumor lysis. MHC: major histocompatibility class; TCR: T-cell receptor.

Other potential mechanisms include disruption of immune tolerance by ICIs against renal antigens as it has been shown that an abundance of specific immune cells (e.g.CD4+ memory T cells, T helper and dendritic cells) were significantly increased in the kidney tissue of patients with ICI-ATIN [23]. Self-reactive T cells may also emerge due to shared structural homology between tumor antigens and autoantigens, as was shown in two melanoma patients who developed myocarditis post-ICI therapy [24]. Additionally, the inflammatory milieu generated by ICI therapy with the elevation of proinflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin-6 (IL6), may provide sufficient stimulus for the creation of autoantibodies to self-antigens expressed on tubular epithelial cells, podocytes or mesangial cells [16, 23]. The last hypothesis posits that ICI-AKI is a result of the activation of memory T cells formed during prior drug exposure or the activation of pre-existing drug specific effector T cells. With drug exposure referring specifically to ATIN-associated drugs like proton pump inhibitors (PPIs), antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs). These drugs can function as exogenous antigens independently and trigger an immune response, or as haptens by binding to renal tubular antigens [25]. This theory is supported by the results of three recent meta-analyses. The most recent meta-analysis included 779 patients with ICI-AKI from nine retrospective studies, and found an increased odds ratio (OR) of 1.84 [95% confidence interval (CI) 1.16–2.90] for the development of ICI-AKI while on PPI [26]. A second meta-analysis reported a higher OR of 2.07 (95% CI 1.58–2.71) [27, 28]. Furthermore, in Chen *et al.*'s meta-analysis, including 120 studies and 46 594 patients, the OR of ICI-AKI was similarly increased for concomitant PPI use and NSAID use, with an OR of 2.42 (95% CI 1.96–2.97) and 2.57 (95% CI, 1.68–3.93), respectively [29]. These results suggest a causative role of ATIN-associated drugs in the development of ICI-AKI, though we do not yet have definitive evidence of this.

NOVEL DEVELOPMENTS IN DIAGNOSIS

Clinical risk factors

Concurrent ATIN-associated drug use represents the only modifiable risk factor identified to date [26, 29]. Additional risk factors based on a large, international, multi-center retrospective cohort study include estimated glomerular filtration rate (eGFR) 45–59 mL/min/1.73 m^2 (OR 2.23, 95% CI 1.35–3.68) with a higher OR of 2.62 (95% CI 1.47–4.65) for eGFR <45 mL/min/1.73 m^2, and prior or concurrent extra-renal irAEs (OR 2.07, 95% CI 1.53–2.78) [11]. In reviewing the studies that included only biopsy-proven ICI-AKI, including a recent systematic review consisting of biopsy proven renal irAE, prior or concurrent extra-renal irAEs were reported in 50%–100% of cases [9, 30–32]. Dual ICI blockade with CTLA-4 and PD1/PDL-1 inhibitors represents a treatment-related risk factor, with an OR of 1.3 (95% CI 0.9–1.87) reported by Gupta *et al.* [11].

Diagnostic markers

At present, there are no clinical or biochemical features that can reliably distinguish between ICI-AKI and other etiologies of AKI, emphasizing the importance of pursuing a kidney biopsy

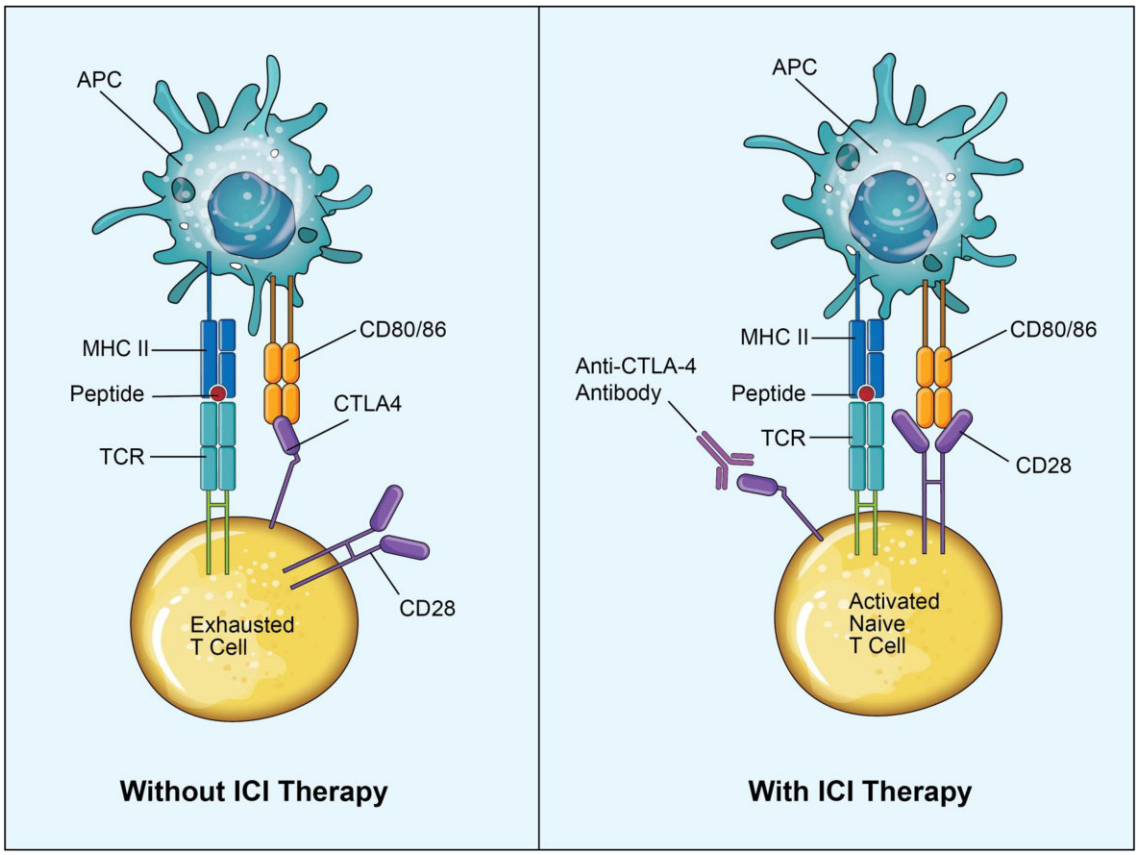

Figure 2: Mechanism of CTLA-4 inhibitors. Within lymphoid tissue, naïve T-cells are exposed to tumor associated antigens via antigen-presenting cells. Once the T-cell recognizes an antigen as non-self, a second signal, "co-stimulation," is required for activation. Co-stimulation describes the binding of CD28 on the T cell to CD80/86 on the antigen-presenting cell. Once a T cell is activated, it increases expression of CTLA-4 which binds to CD80/86 with a higher affinity than CD28, thus impeding co-stimulation. Anti-CTLA-4 antibodies bind to CTLA-4, allowing persistent co-stimulation. APC: antigen-presenting cell; MHC: major histocompatibility class; TCR: T-cell receptor.

when the risks are not prohibitive [33, 34]. Obtaining diagnostic certainty has multiple benefits: it avoids potentially unnecessary corticosteroid exposure, it allows for the early diagnosis of non-ATIN immune-related lesions which may warrant alternative therapies and it allows for the earlier introduction of steroid-sparing agents for patients whose ATIN rebounds as the steroid dose is tapered.

There are certain clinical features that increase the pre-test probability of ICI associated nephritis and can help guide decision making around pursuit of a confirmatory biopsy. While timing of ICI-AKI can be highly variable, most large retrospective studies report a median around 12–16 weeks post-ICI initiation [6, 8, 11, 12]. In relation to the last ICI dose, a median time of 3 weeks to ICI-AKI has been reported, though late-onset ICI-AKI has been recognized, and in about 20% of cases in Gupta *et al.*'s study AKI occurred >10 weeks later [11]. Of note, Gupta *et al.* found that 11% of patients in their cohort developed ICI-AKI more than a year after ICI initiation, and about 15% of cases were reported between 1 and 5 weeks post-initiation [8, 11, 12]. Most consistently, retrospective studies have identified sterile pyuria and sub-nephrotic-range proteinuria [8, 11, 12, 25, 35]. However, one large multi-center study reported the absence of proteinuria in 29% of patients with ICI-AKI and the absence of sterile pyuria in 45% of patients, emphasizing the absence of sensitivity [12]. Eosinophiluria has been less frequently identified, though when present may increase the pre-test probability of ICI-AKI [8, 30]. Lastly, patients may present with a distal renal tubular acidosis (RTA), which persists post ICI-AKI treatment [36].

Multiple protein biomarkers have been investigated in recent years as biochemical markers of ICI-AKI. In our single center, retrospective case–control study, which included 37 patients with ICI-AKI, and 13 controls with AKI not attributed to ICI, we found a statistically significant increase in C-reactive protein (CRP) and urine retinol binding protein to creatinine ratio (uRBP/Cr) in those patients with ICI-AKI, both of which resolved after corticosteroid treatment [8]. It has been clinically demonstrated that an increased ratio of uRBP/Cr is associated with proximal tubular cell injury or dysfunction, and is a useful prognostic marker [37, 38]. Notably, of the 37 patients with ICI-AKI included in the study, only 1 patient with biopsy-proven ICI nephritis had a normal CRP, and this patient was already on corticosteroids, which can normalize the CRP even in the presence of active nephritis [8]. As uRBP/Cr can be elevated in the setting of other renal lesions, including ATN, the presence of both elevated CRP and uRBP/Cr ratio may indicate the presence of ICI nephritis when other infectious and inflammatory causes are ruled out. To differentiate between ATN and ATIN, a biopsy would be recommended as the former would not require immunosuppression. Conversely, when both CRP and uRBP/Cr ratio are within normal limits, in the absence of immunosuppression, the presence of renal iRAE is unlikely.

More recently, Sise *et al.* demonstrated that soluble IL2 receptor alpha (sIL2R), a cytokine correlating with T-cell activation, is

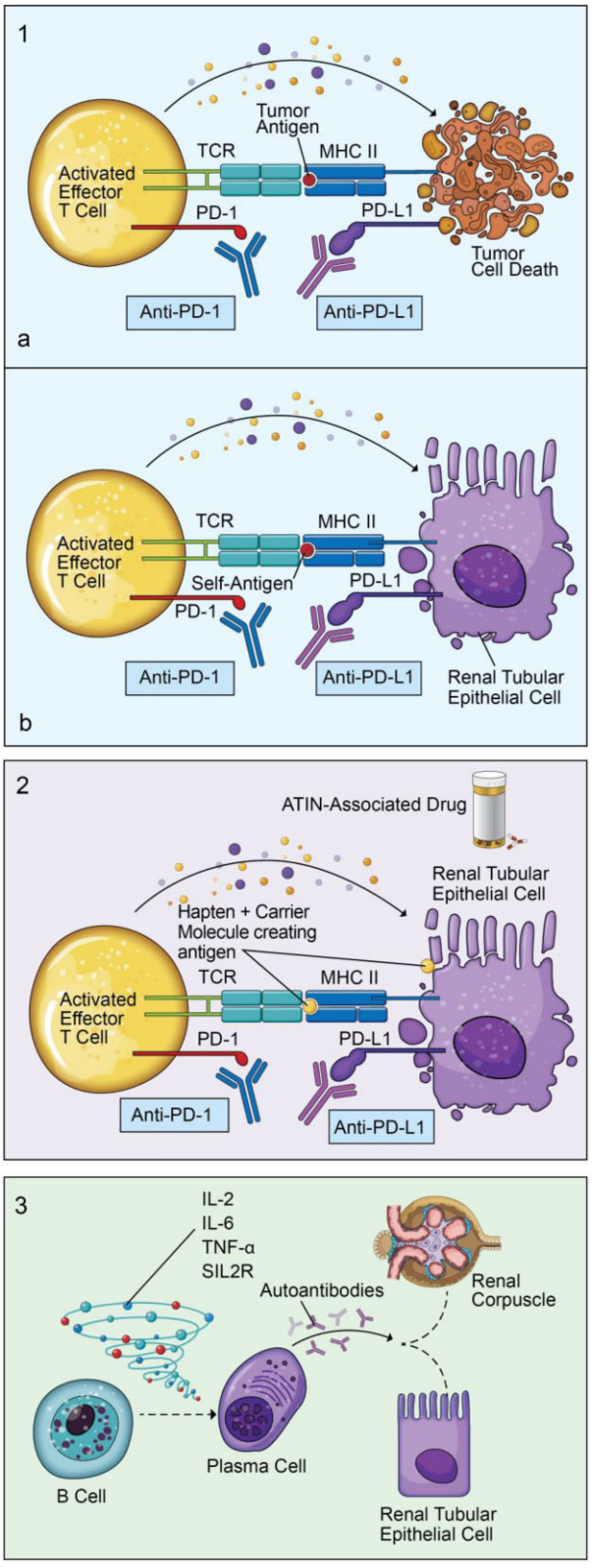

Figure 3: Potential mechanisms of ICI-associated AKI. (**1**) Self-tolerance in the presence of auto-reactive T cells is facilitated by the PD1/PDL-1 pathway, with its blockade, auto-reactive T cells can proliferate. Alternatively, tumor antigen and self-antigen homology may lead to the formation of auto reactive T cells in the presence of ICIs, leading to immune destruction of both tumor cells (a) and host tissue (b). (**2**) ATIN-associated drugs, such as PPIs, antibiotics and NSAIDs, can trigger an immune response either by acting as haptens by binding to tubular antigens as displayed here, or due to direct immunogenicity.

Figure 3: *(Continued)* Pre-existing, quiescent, drug specific effector T cells may become activated with ICI initiation leading to immune-mediated tubular injury. (**3**) The systemic immune response to ICI therapy creates an immunogenic milieu in which the formation of auto-antibodies directed toward self-antigens expressed on multiple types of renal cells may occur (i.e. podocytes, mesangial cells, glomerular basement membrane, tubular epithelium). MHC: major histocompatibility class; TCR: T-cell receptor; TEC: tubular epithelial cell.

elevated in patients with ICI nephritis. They derived a diagnostic threshold of sIL2R elevation at 1.75 times the upper limit of normal (ULN) to yield an 81% sensitivity, and 100% specificity for ICI nephritis [39]. However, just like with CRP, caution should be used when interpreting sIL2R elevation in patients with other extra-renal irAEs and hematologic malignancies as they can independently lead to a rise in sIL2R levels, not being specific only for renal irAEs [8, 39, 40].

In a recent exploratory, prospective study, our group demonstrated that in 14 ICI patients with renal irAE, of which 10 were biopsy proven, urinary TNF-α, IL2 and IL10 levels were higher than in patients on ICI with other causes of AKI [23]. Urinary TNF-α was found to have the strongest discriminatory ability, though plasma levels of TNF-α did not significantly differ between groups. While these results have not yet been clinically validated, urinary TNF-α represents a potential novel biomarker that will require further study in a larger cohort. Other potential biomarker for the diagnosis of ATIN supported by recent evidence includes urine CXCL9 and urine monocyte chemoattractant protein-1 (MCP-1) [15, 41]. However, prior to clinical integration, these biomarkers require validation for ICI-ATIN in a large-scale prospective study. Other sophisticated approaches include use of imaging mass cytometry to identify specific T-cell responses such as increased CD4+ memory and helper T cells, as well as dendritic cell dominance in a subset of kidney biopsy specimens from patients with ICI nephritis [23]. In addition, tertiary lymphoid structure signatures in ICI-ATIN may help differentiate it from other causes of ICI-AKI [41, 42].

If a kidney biopsy is not possible due to prohibitive risk or patient preferences, it is reasonable to initiate corticosteroids empirically for patients who present with clinical features in keeping with ICI-AKI, and have an elevated CRP, uRBP/Cr ratio and sIL2r (especially in the absence of other non-renal irAEs), as depicted in our proposed treatment algorithm (Fig. 4). Prior case reports suggest that the use of positron emission tomography computed tomography (PET CT) may provide additional diagnostic clarity, as they noted increased renal F-18 fluorodeoxyglucose avidity at the time of suspected ICI-AKI as compared with pre-existing PET CTs [43, 44].

Outcomes

Overall, the majority of patients will experience renal recovery post ICI-AKI when timely, appropriate treatment is initiated. Different definitions of renal recovery and follow-up periods have been used, rendering it challenging to directly compare studies. In their retrospective study, Gupta *et al.* demonstrated that the chance of renal recovery decreases based on the initial AKI stage graded by the Kidney Disease: Improving Global Outcomes (KDIGO) consensus criteria, with a 90% recovery for stage 1 AKI, 70% for stage 2 AKI and 50% for stage 3 AKI [11]. Similarly, in a single-center retrospective study by Koks *et al.*, a renal recovery rate of 59% was reported, where renal recovery was defined as a serum creatinine less than 1.3 times the baseline [45]. Other studies that only included patients with KDIGO stage 2 AKI or

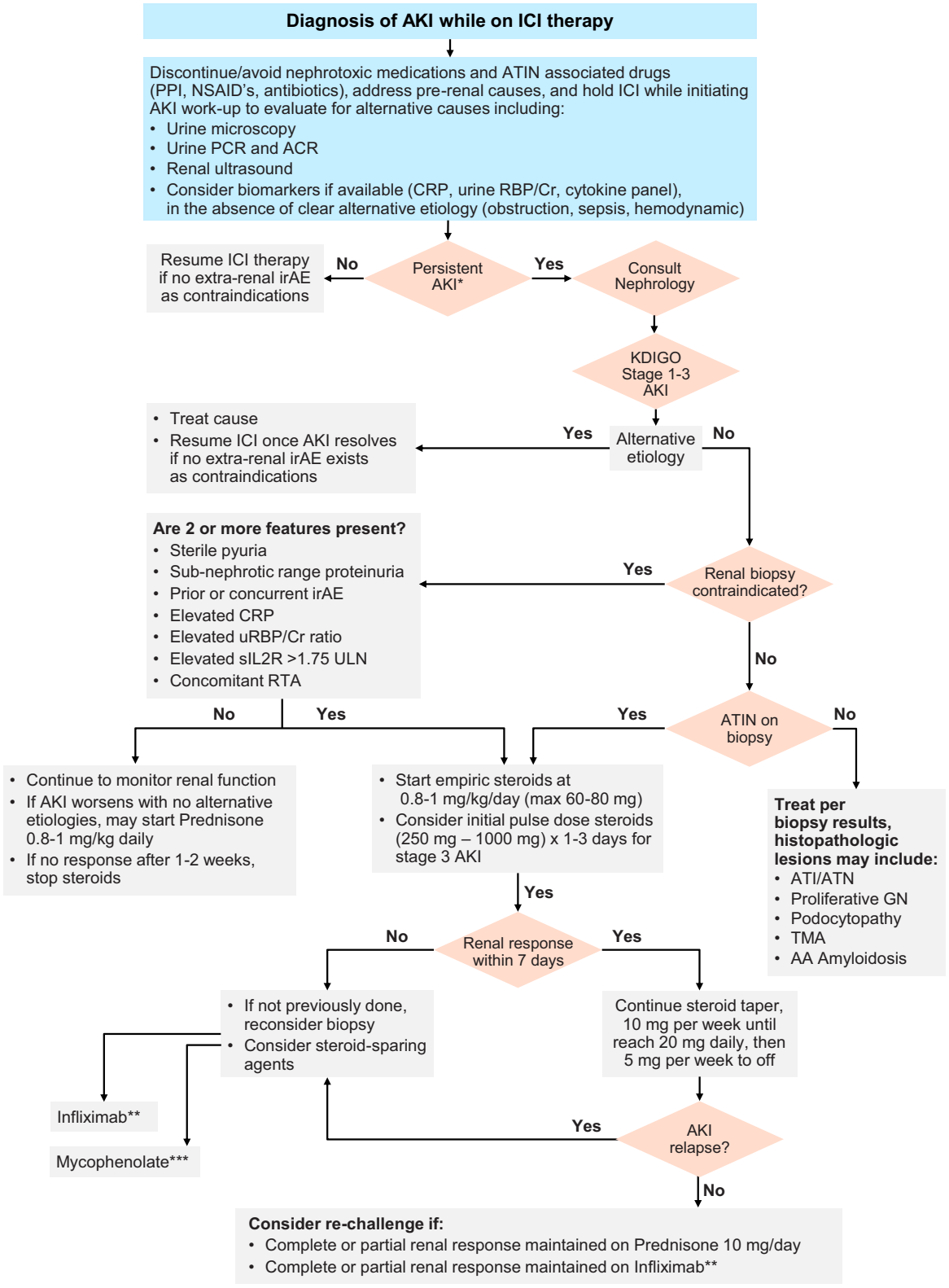

Figure 4: Treatment algorithm for ICI-AKI. *AKI persisting more than 72 h per KDIGO criteria. **Infliximab is the preferred steroid-sparing agent to trial initially, in the authors' opinions. For those patients who are corticosteroid-dependent or -refractory, but who responded to infliximab, ICI re-challenge while on maintenance infliximab can be considered. Please see text for more details. ***As mycophenolate is an anti-proliferative agent, it is the authors' least preferred option for the management of corticosteroid-dependent/refractory ICI-ATIN, as it may affect ICI anti-tumor efficacy, though in resource-limited settings this may be the only accessible option.

higher, or had a more stringent definition for renal recovery, noted a proportion of about 40% [8, 12]. The recent systematic review and meta-analysis by Mohan *et al*. reports complete or partial renal recovery in 67% of patients [26]. Notably, patients on ATIN-associated medications have been noted to have higher rates of renal recovery following discontinuation of the drug [11, 12]. Timing of therapy is an important determinant of renal outcome; Gupta *et al*. showed that initiation of steroids within 3 days of ICI-AKI diagnosis was independently associated with a higher odds of renal recovery compared with later initiation (OR 2.09, 95% CI 1.16–3.79) [11].

ICI-ATIN has not been consistently shown to be associated with an increased mortality risk [10, 45]. This observation holds for patients who are re-challenged with ICI therapy after the initial development of ICI-ATIN [8, 11]. However, other types of AKI sustained while on ICI therapy have shown associated increased risk in mortality (i.e. hemodynamic, obstructive) [10, 29, 45, 46]. This finding potentially correlates to the overall survival benefit that has been documented in certain tumor groups for patients who develop irAEs, perhaps as a marker of improved response to ICI therapy [47, 48].

Current standards of treatment

Currently, clinical practice guidelines for the treatment of irAE have been published by five different associations as depicted in Table 2 [3, 49–52]. The guidelines offer recommendations for AKI grade based on criteria established by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) and by KDIGO criteria (Table 3) and the proposed treatment algorithms suggested by these societies are included in Table 2 [3, 49–52].

We are limited in our ability to provide high-grade evidence-based recommendations on the optimal management of ICI-AKI as the data available to date are largely retrospective in nature, with limited numbers of biopsy-confirmed cases of ICI-AKI [16]. Frequently, the diagnosis of ICI-AKI for study inclusion is based on expert review of the clinical presentation, with the response to corticosteroid therapy as a subsequent confirmatory diagnostic tool, and this is not without its limitations. Prospective studies are needed to determine optimal dosing, duration and type of immunosuppressive therapy for confirmed cases of ICI-AKI.

We include our proposed diagnostic and treatment algorithm in Fig. 4, and we include immunosuppressive dosing recommendations, and major adverse events and precautions in Table 4. We favor referral to nephrology and pursuit of a kidney biopsy for KDIGO stage 2 or 3 AKI or sustained stage 1 AKI, especially in the presence of RTA if there are no other clear AKI etiologies. Alternative etiologies to consider include obstructive nephropathy, hemodynamic causes, and other nephrotoxic drugs or chemotherapeutic agents. In situations where a biopsy would delay therapy initiation by more than 3 days, and the clinical suspicion for ICI-AKI is high, holding ICI therapy and starting treatment empirically while awaiting biopsy results is recommended.

ICI-associated ATIN

Once the diagnosis of ICI-associated ATIN is confirmed, ICI therapy should be held until the AKI has resolved or kidney function has stabilized. ATIN-associated medications (PPI, allopurinol, NSAIDs, antibiotics) should be permanently discontinued if possible. For KDIGO stage 1 and 2 AKI we recommend starting systemic corticosteroid therapy with prednisone 0.8–1.0 mg/kg (or equivalent), with a maximal dose of 60–80 mg per day. For stage 3 AKI, it is reasonable to start with a short course of pulsed-dose intravenous corticosteroids for 1–3 days in hospitalized patients (i.e. methylprednisone 0.25–1 g/day), prior to initiating an oral corticosteroid taper [11, 53, 54]. We recommend higher initial steroid doses than the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines based on the observation by Manohar *et al*. in their single-center retrospective cohort study that higher initial doses of steroids were associated with a higher rate of complete renal response [55].

We suggest tapering the dose of prednisone by 10 mg per week until a dose of 20 mg is reached, followed by a 5 mg per week taper to off. This amounts to a 6- to 10-week taper, depending on the acuity of the initial insult and steroid dose. We recommend a longer taper due to the long half-life of ICIs, ranging from 6.1 days (avelumab) to 27.3 days (pembrolizumab), causing irAEs lasting at least 3 months [56, 57]. As the steroids are tapered, renal function should be followed closely the first week and then every 2 weeks until the end of therapy, to monitor for (i) effectiveness of corticosteroid therapy, which should be evident within the first week, and (ii) to monitor for relapse which can occur at lower doses of steroids, and would provide an indication for steroid-sparing therapies [58]. Notably, accelerated tapers over a period of <4 weeks have not been shown to be associated with increased rates of renal relapse or decreased rates of renal response in a sub-group analysis of Gupta *et al*.'s multi-center retrospective cohort [59]. The patients were initiated on prednisone ≥40 mg and tapered to ≤10 mg in less than 4 weeks. These results need to be interpreted cautiously as only 23% of patients had undergone a diagnostic biopsy. However, in clinical situations where steroid therapy is associated with significant clinical complications (i.e. a patient with diabetes and challenging glycemic control, refractory hypertension), these data suggests that it may be reasonable to consider an accelerated taper, with close follow-up. Prospective studies are needed to guide decisions regarding optimal corticosteroid dose, and tapering schedules as a function of AKI severity and ICI agents, given the significant difference in half-life between agents. As corticosteroid therapy will be required for at least 4 weeks, we recommend *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis, preferably with non-ATIN inducible drugs such as pentamidine or atovaquone. NCCN immunotherapy guidelines recommend pentamidine as second line when trimethoprim/sulfamethoxazole is not an option and suggest considering initiation when patients require >2 weeks of prednisone, with firm recommendations for those patients on Prednisone for >4 weeks [47].

A minority of biopsy-proven ICI associated ATIN cases have previously been demonstrated to be steroid refractory, and some patients remain dependent on higher doses of steroids to avoid relapse, which is associated with significant drug-related toxicity, as well as a concern for decreased progression-free survival and overall survival [5, 60–62]. In these cases, we recommend initiation of steroid-sparing therapies. Here we review the limited data available on the use of alternative immunosuppression.

Infliximab

Infliximab is a monoclonal antibody that inhibits TNF-α. TNF-α is a cytokine with both immunosuppressive and anti-tumoral activity. Pre-clinical studies using mouse models have demonstrated that TNF-α blockade can synergize with ICI therapy to induce tumor response in PD1 refractory disease, and can reduce the incidence of ICI-associated colitis in dual ICI therapy without compromising cancer response [63, 64]. Similarly, multiple clinical studies, including one small prospective study, suggest

Table 2: The current guideline recommendations for the management of ICI-AKI from the different oncology associations.

KDIGO AKI stage	ASCO	NCCN	ESMO	SITC	Onco-nephrology Working Group of the Spanish Society of Nephrology
Stage 1	- Consider holding ICI temporarily - Monitor closely	- Consider holding ICI - Consider Nephrology consult if sustained Cr elevation	- Continue ICI - Repeat Cr weekly - If renal function worsens, proceed as below	- Hold ICI until AKI resolves - Consult Nephrology for persistent or progressive AKI	- Hold ICI - If ICI-AKI suspected or biopsy proven, start prednisone 1 mg/kg/day and repeat Cr weekly - Taper steroids over 4–6 weeks
Stage 2	- Hold ICI temporarily - Consult nephrology - Start prednisone 0.5–1 mg/kg day - If Cr fails to fall by 1 week, increase prednisone to 1–2 mg/kg/day and permanently discontinue ICI - If AKI improved to less than Grade 1, taper steroids over at least 4 weeks - Consider re-challenge once steroids tapered to <10 mg/day	- Hold ICI - Consult Nephrology - Consider renal biopsy if no improvement in Cr within 5–7 days - Start prednisone 0.5-1 mg/kg/day; do not delay start while waiting for biopsy - For persistent stage 2 AKI for more than 1 week, start Prednisone/IV Methylpred 1-2 mg/kg/day	- Hold ICI therapy - If Cr fails to fall post-IVF in 2–3 days, consult nephrology - Consider renal biopsy - Start prednisone 0.5–1 mg/kg/day - Repeat Cr, K+ every 2 days - If AKI improved to less than grade 1, re-start ICI when on prednisone 10 mg/day or less	- Hold ICI - Consult Nephrology - Strongly consider renal biopsy, especially in the presence of active urine sediment, or if other plausible causes of AKI present - Start corticosteroid therapy - If steroid refractory, consider infliximab or mycophenolate	- Hold ICI - Oral prednisone 1 mg/kg/day vs methylprednisone bolus 125–250 mg (×3) followed by oral taper (0.5–1 mg/kg/day) over 4–6 weeks - Repeat Cr every 48 h to weekly depending on clinical scenario - If steroid refractory, consider infliximab or mycophenolate
Stage 3	- Permanently discontinue ICI - Consult Nephrology - Start Prednisone 1–2 mg/kg/day - If AKI improved to less than grade 1, taper steroids over at least 4 weeks - If Cr elevation persists more than 3–5 days, consider adding: infliximab, azathioprine, cyclophosphamide, cyclosporine or mycophenolate - For CTCAE Grade 4 AKI, if Cr elevation persists >2–3 days, then consider additional agents as above	- Hold ICI - Consult Nephrology - Consider inpatient care - Renal biopsy if Cr fails to improve in 5–7 days - Start Prednisone/IV Methylprednisone 1-2 mg/kg/day. Do not delay while waiting for biopsy - If AKI remains greater than stage 2 after 4–6 weeks of steroids or if Cr increases during steroid taper, consider adding azathioprine, infliximab or mycophenolate	- Hold ICI - Admit patient - Repeat Cr daily - Consult Nephrology and consider renal biopsy - If Cr fails to improve, start IV methylprednisone 1 mg/kg or pulse dose 250–500 mg IV for 3 days - Same recommendation holds for CTCAE grade 4	- As above: stage 2 AKI recommendations hold for stage 3 AKI	- Hold ICI - Bolus methylprednisone 250 mg IV (×3) followed by oral taper (0.5–1 mg/kg/day) over 4–6 weeks - Repeat Cr every 48 h initially - If steroid refractory, consider infliximab or mycophenolate
General recommendations	- Rule out alternative etiologies of AKI - Renal biopsy is typically not necessary or recommended unless the AKI is refractory to steroids and other immunosuppressant agents - Monitor Cr weekly - Corticosteroid dosing recommendations are for prednisone dose equivalents	- Rule out alternative etiologies of AKI; consider IVF and re-assess - Limit/discontinue nephrotoxic medications, and dose adjust to CrCl - Check sCr every 3–7days - Avoid PPI's, use H2RB for GI prophylaxis if starting corticosteroids - PJP prophylaxis recommended for patients on prednisone ≥20 mg for ≥4 weeks[a] - Start calcium + vitamin D for bone prophylaxis if on long term steroids	- Avoid nephrotoxic drugs, and review hydration status - Rule out alternative etiologies of AKI	- Rule out alternative etiologies of AKI - Discontinue ATIN-associated medications: PPIs, antibiotics, NSAIDs	- Rule out alternative etiologies of AKI - Discontinue ATIN-associated medications: PPIs, antibiotics, NSAIDs - Can consider re-challenge with ICI for those patients with complete renal recovery, or for those with incomplete recovery whose other cancer-targeted therapies are limited after risk-benefit discussion with the patient and team - Re-challenge contra-indicated in patients with life threatening irAEs

[a]New guidelines under development currently.
[b]Consider starting PJP prophylaxis if still steroid-dependent after 2 weeks. Avoid atovaquone due to risk of diarrhea, and dapsone due to risk of hemolytic anemia.
Cr: creatinine; CrCl: creatinine clearance; IV: intravenous; IVF: IV fluid; H2RB: Histamine 2 Receptor Blocker.

Table 3: Creatinine-based criteria for AKI as defined by CTCAE (AKI grade) and KDIGO (AKI stage).

Grade/stage	Serum creatinine by CTCAE criteria	Serum creatinine by KDIGO criteria
1	>1–1.5 × baseline	>1.5–1.9 × baseline OR ≥0.3 mg/dL increase
2	>1.5–3 × baseline	>2–2.9 × baseline
3	>3–6 × baseline	>3 × baseline OR ≥4 mg/dL OR RRT start
4	>6 × baseline	N/A

RRT: renal replacement therapy; N/A: not applicable.

that infliximab use does not impact tumor response, with the potential exception of genitourinary cancers [65–68]. Infliximab has been used for the treatment of multiple irAEs including ATIN, colitis, pneumonitis, hepatitis, myocarditis and myositis [68, 69]. There is case-series evidence that suggests it is effective in the treatment of steroid-refractory or dependent ICI-ATIN [60]. Our local practice is to maintain the prednisone dose at a therapeutic level (for relapsing disease) until the patient receives the first dose of infliximab 5 mg/kg, after which further faster steroid taper to discontinuation can be resumed, with weekly monitoring of the creatinine initially. We trend a cytokine panel prior to each infliximab infusion to monitor TNF-α levels as these are often initially elevated and may correlate with response. The infusions are administered monthly, with one to two infusions needed based on our experience 36].

Mycophenolate

Mycophenolate exerts its immunosuppressive effect by impeding lymphocyte proliferation. In solid organ transplant patients, it has not been shown to increase the risk of post-transplant malignancies, unlike azathioprine and cyclosporine [70]. In keeping, a recent retrospective cohort study including 11 patients on mycophenolate for steroid refractory ICI-associated hepatitis showed no negative impact on tumor response [71]. Limited data exist on the use of mycophenolate for steroid-dependent or -refractory ICI-associated ATIN. In Gupta *et al.*'s multicenter retrospective trial, 5/11 patients receiving mycophenolate mofetil (MMF) demonstrated renal recovery, of whom 2 non-responders had biopsy-proven ATIN and 1 responder had biopsy-proven ATIN [11]. In Cortazar *et al.*'s case–control study, four patients with biopsy-proven, steroid-refractory ATIN received MMF, of whom all had partial renal responses [12]. While an optimal dose has not been established, a dose of 1 g twice daily (BID) of MMF for 10 days concomitantly administered with a slow steroid taper has been reported as successful [72].

Tocilizumab

Tocilizumab is a monoclonal antibody inhibiting IL6, an inflammatory cytokine that has been implicated in both irAEs as well as decreased tumor response to ICI therapy [61]. As a result, there is increasing interest in the use of anti-IL6 therapy for the prophylaxis of irAE and for the treatment of corticosteroid-refractory irAEs, with multiple prospective clinical trials underway. To date, we do not have any substantial clinical evidence guiding tocilizumab use in steroid-refractory ATIN, though this may change as more data become available.

Other agents

Tofacitinib, an inhibitor of the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway, has been successfully used in only one case report for the treatment of corticosteroid-dependent ICI-ATIN in a patient who had already received infliximab [73]. We recommend cautious use of this agent as it has been associated with adverse cardiovascular outcomes and secondary cancers [74]. We do not recommend the use of azathioprine, cyclosporine or cyclophosphamide for the treatment of ICI-associated ATIN, despite their inclusion as treatment options in the NCCN and ASCO guidelines, due to limited supporting data [49, 50].

Glomerular renal irAEs

A subset of patients develop glomerular lesions, or systemic vasculitis as irAEs. In certain cases, it may be difficult to discern whether the glomerular lesion is ICI-associated or whether it represents a paraneoplastic syndrome. In other cases, a patient may experience recurrence of prior glomerulopathy post-ICI initiation, though only one case has been reported to date [75]. Regardless, these patients require immunosuppressive therapy tailored to their presenting lesions. While specific treatment recommendations for this patient population are beyond the scope of this review, it is worth highlighting a recent systematic review by Kitchlu *et al.* This review included 45 patients with glomerular disease as renal irAE, with a renal response rate of 73% [14]. The majority of patients were treated with corticosteroids (98%), and a subset of patients with proliferative lesions received concomitant cyclophosphamide or rituximab. Three patients with renal recovery were re-challenged, of which two had recurrent disease.

ICI re-challenge for ICI-associated ATIN

Oncology guideline recommendations regarding re-challenge vary, with the 2021 ASCO guidelines calling for permanent ICI cessation for KDIGO stage 3 or CTCAE grade 3 AKI, the updated 2024 NCCN guidelines suggest re-challenge is a possibility for KDIGO stage 3 or CTCAE grade 3 AKI as long as the AKI resolves to less than stage 1/grade 1, and the Society for Immunotherapy of Cancer (SITC) and European Society for Medical Oncology (ESMO) guidelines offer no clear recommendations on re-challenge [3, 49–51].

Currently, the data favor re-challenge upon resolution of ICI-AKI, regardless of initial AKI stage, with most large retrospective studies reporting a recurrence rate of 15%–25%, and smaller studies reporting recurrence rates of 0%–25% with most patients re-challenged using the same ICI [8, 11, 12, 55, 76–78]. Notably, an association between initial ICI-AKI stage and risk of recurrent AKI post-re-challenge has not been demonstrated [11]. There is significant heterogeneity in the included patients; most patients do not have biopsy-proven ATIN but have presumed ATIN, and some patients are re-challenged while on ATIN-associated drugs whereas others are not. The use of secondary prophylaxis at the time of re-challenge with a median dose of prednisone 10 mg has been used to varying degrees (40%–80%), although Gupta *et al.* did not find a difference in outcomes between the two groups, revealing a need for prospective studies, especially for those patients whose initial ICI-AKI occurred while on an ATIN-associated drug [8, 11, 12]. A trend toward a shorter latency period with re-challenge is noted, with a median time to recurrence of

Table 4: Immunosuppression strategies, dosing recommendations, major adverse effects and precautions.

Immunosuppressive therapies	Dose and duration	Therapeutic drug monitoring	Markers of response	Drug toxicities	Precautions
Corticosteroids [11, 53, 54]	Prednisone equivalent: 0.8–1 mg/kg, max 60–80 mg. Taper by 10 mg per week until 20 mg, then taper by 5 mg per week to off		Monitor renal function weekly for the first 1–2 weeks. If Cr is decreasing then can decrease monitoring to every 2 weeks until end of therapy If Cr starts to rise with corticosteroid taper, this may indicate corticosteroid-dependent ICI-AKI	Opportunistic infections, hyperglycemia, osteopenia, hypertension, psychiatric side-effects	For prednisone doses ≥20 mg, PJP prophylaxis with inhaled pentamidine, dapsone or atovaquone is recommended as Bactrim is an ATIN-associated drug Atovaquone should be avoided in cases of concurrent colitis due to diarrhea as side effect Start vitamin D, calcium for osteopenia-prophylaxis
Infliximab [60]	5 mg/kg per infusion Dosed monthly Typically 1–3 infusions needed for initial ICI-AKI Start concomitantly with corticosteroids (typically at least 20 mg daily), then taper corticosteroids 5 mg per week after first infusion	Can monitor serum TNF-α levels for response prior to each infusion	For corticosteroid-dependent or -refractory AKI Cr should decrease within 1–2 weeks of initiation. Monitor Cr every 2 weeks, if Cr noted to be rising at the end of the month, this indicates benefit of additional doses	Infusion reactions, hepatotoxicity, TB or HBV re-activation, disseminated fungal infection, bacterial and viral infections. Formation of auto-antibodies with associated systemic or dermatologic auto-immune manifestations	Check Quantiferon and hepatitis B serology prior to infliximab start Monitor liver enzymes prior to each infusion
Mycophenolate [11, 12, 72]	1–2 g daily, administered in divided doses BID Trial for 1–2 weeks, then taper[a]		For corticosteroid-dependent or -refractory AKI Cr should decrease within 1–2 weeks of initiation	Bone marrow suppression with leukopenia and neutropenia, gastrointestinal side-effects including severe diarrhea, increased risk of viral infection, i.e. CMV	Check weekly CBC with therapy initiation

[a] Dosing recommendations adapted from management of non-ICI associated ATIN, with reduced duration of therapy.
Cr: creatinine; TB: tuberculosis; HBV: hepatitis B virus; CBC: complete blood count; CMV: cytomegalovirus.

Table 5: Clinical scenarios in which ICI re-challenge may be considered.

Responsive to corticosteroids [79]		
Patient on ATIN-associated drug at time of ICI-AKI diagnosis	**No ATIN-associated drug at time of ICI-AKI diagnosis**	**Refractory to treatment**
Suggest proceeding with re-challenge once:	Suggest proceeding with re-challenge once:	From a renal perspective, re-challenge is contra-indicated, especially for KDIGO stage 2–3 AKI
• AKI resolved • Patient on ≤10 mg prednisone daily • Permanent cessation of ATIN-associated drug if feasible	• AKI resolved • Patient on ≤10 mg prednisone daily	However, multi-disciplinary, patient-centered decision making will be required In the absence of alternative, effective treatments for the patient's cancer, a decision to continue with ICI therapy despite the risk of requiring long-term renal replacement therapy may be made
Re-challenge protocol[a]: • Can consider re-challenge without prophylactic steroids if ATIN-associated drug discontinued • Consider prophylactic Prednisone 10 mg daily for first 2 cycles, with subsequent tentative taper to off in the absence of recurrent AKI	Re-challenge protocol[b]: • Consider prophylactic dose Prednisone 10 mg daily for more than 2 cycles • If no recurrent AKI, can trial tapering Prednisone to off with close monitoring of renal function with weekly labs for the first 2 weeks, then every 2–4 weeks	

[a]These scenarios assume that there are no other, severe extra-renal irAEs that would preclude re-challenge. For all scenarios, we recommend close monitoring, with labs within the first week of re-challenge, and if renal function remains stable, subsequent labs every 2–4 weeks thereafter.
[b]In this scenario, without an identifiable culprit, these patients maybe at a higher risk of recurrence with taper of corticosteroid therapy to off.

6–10 weeks reported in two large retrospective studies [11, 12]. Time to re-challenge post-initial ICI-AKI has been reported at around 2 months [8, 11, 12]. In Table 5 we identify four potential clinical situations in which re-challenge may be considered. These scenarios assume that there are no other, severe extra-renal irAEs that would preclude re-challenge. For all scenarios, we recommend close monitoring, with labs within the first week of re-challenge, and if renal function remains stable, subsequent labs every 2–4 weeks thereafter.

Box 1. Strategies on how to personalize treatments

- Patients who develop ICI-ATIN while on ATIN-associated drugs benefit from permanent cessation of these drugs as well as initiation of corticosteroid therapy. However, upon renal recovery, re-challenge can be considered without secondary corticosteroid prophylaxis with close monitoring, as long as they remain off ATIN-associated drugs. In our practice we suggest a small dose of prednisone (10 mg daily) at least for the first two cycles
- In patients with stage 2 AKI or greater who have no other plausible AKI etiologies, it is reasonable to start empiric corticosteroids while awaiting biopsy results to avoid significant delays if two or more of the following features are present:
  - history of prior or concurrent extra-renal irAEs
  - sub-nephrotic-range proteinuria
  - sterile pyuria
  - evidence of RTA
  - elevated CRP and urine RBP/Cr ratio
  - serum IL2R >1.75 ULN (in the absence of other non-renal irAEs)
- The above holds for patients who have contra-indications to renal biopsy as well
- Some patients on ICI agents with longer half-lives (i.e. pembrolizumab) may benefit from longer corticosteroid tapers (8–10 weeks)
- For those patients with corticosteroid-dependent or -refractory ICI-ATIN, a serum cytokine panel may help elucidate which steroid-sparing therapy may provide more benefit, with elevated TNF-α suggesting a trial of infliximab
- We suggest considering secondary prophylaxis for ICI-re-challenge with prednisone 10 mg daily in selected patients, particularly those with severe initial ICI-AKI or within 2–4 months from the initial ICI-AKI. Additional evidence is required to guide clinical decision-making
- We recommend PJP prophylaxis for patients on corticosteroid therapy (dose ≥20 mg daily) for over 2–4 weeks using preferably non-ATIN inducible drugs such as pentamidine or atovaquone if no contraindications

SUMMARY

As the indications for ICI use in cancer therapy grow, our experience in managing renal irAEs will expand. We continue to rely on renal biopsy as the gold standard for the diagnosis of ICI-AKI, though there are several promising non-invasive biomarkers that would benefit from clinical validation including the product of CRP and urine RBP/Cr ratio, soluble IL2R, urinary TNF-α and, more recently, urinary CXCL9 for the diagnosis of ATIN [8, 23, 39, 41]. While corticosteroid therapy remains the standard of care for ICI associated ATIN, with early initiation shown to correlate with improved renal outcomes, we need prospective studies to determine the optimal dosing and duration of therapy, as well as to better elicit the role of promising steroid-sparing therapies like infliximab and tocilizumab [11, 61]. We advocate for ICI re-challenge after AKI recovery, with permanent cessation of ATIN-associated medications, and with consideration for prophylactic low-dose corticosteroids for the first two cycles, especially

if no ATIN associated drug was implicated in the initial AKI [79]. However, we would benefit from prospective studies which include patients with biopsy-proven ATIN to determine the role and optimal duration of secondary prophylaxis in patients with ICI-AKI undergoing re-challenge. Currently, prospective studies to determine the role of primary prophylaxis of irAE with agents that have shown potential for synergistic anti-tumor effects with ICI therapy, such as IL6- and TNF-α-inhibitors, are underway. The role of primary prophylaxis will be especially relevant as our ability to better predict those who may be at increased risk of developing renal irAE improves.

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E.-B.B. and S.M.H. were mutually involved in the planning, outline and writing. E.-B.B. wrote the original manuscript and designed the graphics. S.M.H. reviewed and edited all the revisions of the manuscript. A.K. reviewed and edited all revisions of the manuscript.

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No new data were generated or analyzed in support of this research.

CONFLICT OF INTEREST STATEMENT

No conflicts of interest to declare.

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