Kidney360

Is Rechallenge Appropriate in Patients that Develop Immune Checkpoint Inhibitor-Associated AKI?: COMMENTARY

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Over the past decade, immune checkpoint inhibitors (ICIs) have changed the paradigm of cancer treatment, from the use of cytotoxic therapies with indiscriminate effects on tumor and normal tissue, to targeted therapies that harness the host immune system to direct an antitumor response. Specifically, these drugs are IgG4 mAbs that are directed against cell-surface receptors found on T cells, such as programmed death protein-1 and cytotoxic lymphocyte antigen-4. These receptors, when activated by binding to ligands on antigen-presenting cells and parenchymal cells, initiate negative regulatory signaling pathways to prevent antigen-specific T-lymphocyte activation and function. From the evolutionary perspective, this is an adaptation to encourage immunologic self-tolerance. At the same time, tumor cells upregulate ligands such as programmed death ligand-1 that bind to these receptors and inhibit tumor-specific T cell immunity (1). ICIs were developed to counteract this inhibition and elicit a T cell tumor-targeted response. In clinical trials for cancers traditionally resistant to cytotoxic therapy, such as melanoma and renal cell carcinoma, these drugs including ipilimumab (anti-cytotoxic lymphocyte antigen-4), nivolumab, and pembrolizumab (anti-programmed death protein-1) showed effective and durable anti-tumor responses. Since then, these and other ICIs (including atezolizumab and durvalumab, which target programmed death ligand-1) have been approved for use in an increasing list of malignancies, with favorable outcomes for patients with advanced disease.

Although they are advancing clinical outcomes, ICIs also carry the risk of immune-related adverse events (irAEs) resulting in immune-mediated injury to various organs including the kidneys, where clinical presentation has been AKI and/or less commonly, proteinuria. While glomerular diseases including immune complex GN, FSGS, and minimal change disease have been reported, the majority of patients who have been biopsy proven have revealed acute tubulointerstitial nephritis (ATIN) with lymphocyte-predominant infiltrate with partial to complete response to withholding further ICI use and dosing with corticosteroids (1–4). This is in contrast to other irAEs, particularly colitis or rheumatologic disease, which often require additional immunosuppression, such as antagonism of TNF or IL-6 (5). The overall incidence for ICI-associated AKI has been reported as between 5% and 10%, with increased incidence for patients receiving dual ICIs (4). In summary, while there is a burden of AKI in patients receiving ICIs, the overall kidney prognosis is good. Although it is tempting to see this as a silver lining, the clinical conundrum that remains, particularly in those patients with exhausted treatment options, is whether redosing with ICIs is feasible. This critical question forms the basis of the debate in this issue of *Kidney360*.

On the CON side, Drs. Kanduri and Velez lay out the case that rechallenge with ICIs is associated with a significant risk of AKI recurrence that should give clinicians pause before dosing ICIs again. On this, they cite several reports, including the largest study to date on ICIs and AKI by Cortazar and colleagues, who undertook a retrospective multicenter analysis of 138 patients who developed AKI while on ICIs (3). Of these, 60% underwent kidney biopsy, with >90% of patients revealing ATIN on histopathology. Rechallenge was attempted in 31 patients, with only seven of those (22%) experiencing recurrent AKI. This is arguably a favorable outcome in that most patients did not have recurrent AKI, and has been replicated with other, mostly single-center, studies that provide recurrence rates of 7%–20% (6,7). The authors presenting the CON position rightly point out that most published cases of rechallenge did not have biopsy data with the first occurrence of AKI. This raises the question of whether recurrent AKI was not more common in published reports because the original AKI itself was not likely to have recurred, for example, acute tubular necrosis or ATIN from proton pump inhibitors that were stopped, or volume depletion from acute gastrointestinal symptoms. Thus, they suggest rechallenge should not be considered in patients with biopsy-proven ATIN resulting in high-grade kidney irAE clearly linked to ICI use, because the risk of recurrent AKI is likely higher. In patients who must receive ICIs due to a lack of alternative therapies, they

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suggest strategies that putatively reduce AKI recurrence risk, including: (*1*) co-dosing low-dose corticosteroids; (*2*) class-switching ICIs; (*3*) avoiding dual ICIs and agents associated with AIN; and (*4*) use of IL-6 inhibition.

On the PRO side, Dr. Hermann proposes an algorithmic approach that takes into account the presence of other, concurrent irAEs. Specifically, she suggests if there are irAEs with significant morbidity or mortality risk, such as myocarditis, rechallenge should not be undertaken. In contrast to Kanduri and Velez, she recommends that in all other patients, redosing should be considered once prior AKI has been treated to complete or partial response. For patients with higher-grade irAEs, there is considerable overlap with the recommendations from the CON side, including using low-dose immunosuppression if prior AKI did not implicate an alternate drug (nonsteroidal anti-inflammatory drugs, proton pump inhibitors) as potential etiology. Lastly, as with the CON side, there is advice on regular monitoring of kidney function, with drug discontinuation if there is recurrent AKI.

After considering both of the well-argued PRO and CON positions, I favor the PRO position, with some qualifiers. As the authors of the PRO and CON positions do, I acknowledge there are benefits but also risks with immunotherapy rechallenge (Table 1). Yet, what I have seen in most patients with ICI-associated AKI that I have evaluated at my institution's onco-nephrology clinic is stabilization of advanced malignancy by immunotherapy. Although optimization of kidney function is our charge as nephrologists, the zeal for that should not deprive the patient of potentially life-prolonging therapy. So, I agree that if life-threatening non-kidney irAEs are coexistent with kidney irAEs, then restarting ICIs is contraindicated. But, regardless of the severity of kidney irAEs, if that is the only irAE and the oncology team would otherwise rechallenge, I advise in favor of it. It should be noted that oncology guidelines, including those from the National Comprehensive Cancer Network, suggest permanent discontinuation of ICIs for Grade 3 or 4 AKI (8). Thus, this remains a decision primarily driven by the treating oncologist, although I often weigh in with data on recurrent kidney iRAEs. For patients for whom the oncologist does decide on rechallenge, I do not routinely advise use of prophylactic corticosteroids to prevent recurrent AKI from ICI-associated ATIN, because there are no data to support its use and there are conflicting reports on the effect of steroids on efficacy of ICIs (9,10). I am intrigued by the suggestion of the "CON" authors for use of IL-6 inhibition (with mAbs such as tocilizumab) as an alternate prophylactic against recurrent kidney irAEs. This has been suggested in the nonkidney literature for steroid-refractory irAEs, or for steroid avoidance when control of irAEs may require months of steroids (11). An added benefit for this may be a potential antitumor role for IL-6 inhibition (12). But IL-6 inhibition is not established as treatment for ATIN, so any role for it as a preventive measure is highly speculative.

Advising or decision making regarding ICI rechallenge requires in-depth conversations with oncology that go beyond our standard nephrology knowledge base, including understanding how well the patient in question responded to ICI therapy, what future response is expected, and the potential for alternate therapies. It also requires honest conversations with patients about their perceptions of life expectancy with advanced cancer and how they wish to spend those days. For some patients, when the choice is between added months to years of progression-free survival, even at the expense of severe AKI that could require dialysis, they will take the risk of kidney disease. For others, dialysis represents invasive treatment that is a disproportionate burden when faced with oncologic disease, particularly when performance status is poor. Finally, weight patients' options also requires difficult questions of us as providers. Some of these questions are similar to those raised in patients with other serious, chronic diseases such as advanced heart failure: what are the ethics and costs in offering renal replacement therapy to patients with likely terminal illness. Beyond this, rechallenge with ICIs is a particular dilemma. The physician is charged with Hippocrates' dictum: *primum, non nocere*. If ICIs represent a potentially life-prolonging therapy for a patient but with risk for kidney injury that may be severe enough to require RRT, which is the greater

Table 1. Benefits versus risks of drug rechallenge in patients with prior immune checkpoint inhibitor–associated acute kidney injury

Benefits of Rechallenge	Risk of Rechallenge
Data suggest risk of recurrence 7%–20%, on par with or better than AKI recurrence rates for other oncology drugs, including platinum drugs	Recurrence of AKI, including >Grade 3
Risk-minimizing strategies exist: class switching, prophylactic corticosteroids	Side effects of prophylactic corticosteroids
Potential for increased progression-free survival and overall mortality with ongoing use of immunotherapy	With recurrent AKI, options down the line for other therapy (including targeted small molecules and chemotherapy) may be limited
Avoidance of other therapy with greater nephrotoxic potential	Potential need for RRT with severe AKI
Apart from irAEs, better side effect profile of immunotherapy	Healthcare system burden with potential increase in severe AKI requiring RRT
No dose adjustments for patients with CKD (or ESKD)	Recurrent AKI may lead to increased morbidity and mortality
Dosing schedule generally less frequent than chemotherapy, allowing improved QOL for patients	AKI may result in prolonged hospitalization, impeding on patients' desire to be at home

irAE, immune-related adverse events; QOL, quality of life.

harm—preventing or allowing rechallenge? The answer to that question demands principled debate, as the authors of this issue of *Kidney360* demonstrate.

Disclosures

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Author Contributions

A.C. Shiral conceptualized the study, was responsible for the formal analysis and investigation, wrote the original draft, and reviewed and edited the manuscript.

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See related debates "Is Rechallenge Appropriate in Patients that Develop Immune Checkpoint Inhibitor-Associated AKI?: PRO," and "Is Rechallenge Appropriate in Patients that Develop Immune Checkpoint Inhibitor-Associated AKI?: CON," on pages 799–802 and 803–805, respectively.