


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

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Introduction

Immune checkpoint inhibitors (ICIs) are a promising new therapeutic class of drugs that has achieved remarkable progress among patients with hematologic and solid organ malignancies. They block the inhibitors of T lymphocytes, impair the survival of regulatory T cells, and thereby potentiate the immune system to fight against cancer cells. With increased use of ICIs, patients developing immune-related adverse events (irAEs) are proportionately rising. The overall incidence of ICI-related irAEs ranges from 60% to 85%; the skin, gastrointestinal tract, lungs, and liver are the most commonly affected organs (1). The incidence of kidney injury from irAEs is estimated to be 2%–5%, where the risk with monotherapy is around 2%, and combination therapy accounts for <5% (2,3). The true incidence is likely higher, given the lack of kidney biopsies in patients with mild AKI and the potential masking effects of steroids when used for treatment of other irAEs. Acute interstitial nephritis and acute tubular necrosis are the most common injury patterns associated with irAEs.

In the study by Cortazar *et al.* (4) including 138 patients with ICI-AKI, at a median of 14 weeks after ICI initiation, 43% experienced stage 2 AKI, 57% sustained stage 3 AKI, and 9% were dependent on RRT. Although complete recovery of ICI-AKI is noted among 40% of the patients and partial recovery among 45%, 15% had no recovery of kidney function. In the subgroup analysis of patients with ICI-AKI who required RRT, seven out of 13 (54%) had no recovery of renal function, indicating patients with ICI-AKI sustain a complicated clinical course, especially if they have RRT dependency. Additionally, steroids are the mainstay of treatment for ICI-associated irAEs and are frequently associated with multiple adverse effects, including fluid retention, weight gain, cushingoid features, and glucose intolerance (5,6).

On the basis of the grade and severity of irAEs, ICI therapies are typically held while battling with adverse effects. Rechallenging ICIs after a period of temporary discontinuation could potentially improve overall survival of patients with resistant cancers, although putting them at risk of recurrent irAEs. Among patients with severe grade 3 or higher kidney

toxicity (SCr >3× baseline, or >4 mg/dl or need for RRT), the American Society of Clinical Oncology and the National Comprehensive Cancer Network recommended permanent discontinuation of ICIs (7–9). Among patients with lower-grade kidney toxicities, there is no clear consensus on appropriate timing of rechallenge, although some studies suggest holding ICI until the AKI episode is almost completely resolved (9,10).

Although no randomized controlled studies have explored this area, a few shed some light on the clinical course of patients who were rechallenged with ICI therapies. In a study by Isik *et al.* (11) including 37 patients, rechallenge of ICI was attempted in 16 patients who sustained ICI-AKI at a median of 2 months after the initial AKI episode. Recurrence of AKI was noted in three of 16 patients who were rechallenged (19%). One remained on RRT and none achieved complete kidney recovery after a recurrent AKI episode. The authors also reported a favorable survival trend among patients who were not rechallenged with ICI compared with rechallenged patients. However, this observation could be biased because patients who were rechallenged likely necessitated chemotherapy to combat active cancer, although that might not have always been the case for the nonre-challenged group. A significant number of patients (81%) were on lower doses of corticosteroids at the time of rechallenge and the majority received the same ICI regimen. In a study by Manohar (10), rechallenge was attempted among four out of 14 patients, and one sustained AKI recurrence (25%). Rechallenge was attempted after the serum creatinine neared the baseline. In the multicenter study by Cortazar *et al.* (4), 31 patients were rechallenged at a median of 1.8 months after the initial ICI-AKI episode. Although most of them were rechallenged with the same ICI agent, the recurrence of AKI was observed in 23%. A shorter latency between the initial AKI episode and rechallenge was identified as one of the major risk factors associated with recurrent AKI. Furthermore, a recent study by Allouchery *et al.* (12) demonstrated that among patients with ICI rechallenge, 39% experienced at least one grade ≥2 irAE, and ICI rechallenge should be considered with caution among patients

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with grade 4 irAE. Moreover, in study by Simonaggio *et al.* (13), out of 40 patients who were rechallenged with the same ICI, 55% encountered same or a different irAE. Subsequently, a trend towards a higher recurrence rate was noted on rechallenging the patient after more severe initial irAE. Lastly, in a multicenter study by Abu-Sbeih *et al.* (14), the recurrence of immune-mediated colitis was reported to be higher in patients with anti-cytotoxic T-lymphocyte antigen 4 (CTLA4) (44%) as compared with those receiving anti-programmed cell death 1 or ligand 1 (PD1/PDL1) (32%).

Summarizing the above-mentioned studies, the overall risk of irAE after rechallenge with ICI is high and ranges from 28% to 55% (12–14), whereas the risk of ICI-AKI after rechallenge is reported to vary between 19% and 25% (4,10,11). Further, in most available case series, it is left to the treating physician to decide whether the AKI episode is ICI induced without the need for a biopsy. Therefore, it is possible that in patients without recurrence after ICI reintroduction, the initial AKI episode was not ICI induced (because most AKI episodes in patients who are ICI treated are of prerenal origin), emphasizing the importance of kidney biopsies in patients experiencing AKI under ICI treatment without another obvious explanation. Hence, we propose that ICI rechallenge should not be attempted among patients with biopsy-proven ICI-AKI.

Major risk factors are associated with AKI after rechallenge, although not consistent across the reported studies, include shorter latency to rechallenge, combination therapies, and persistence of underlying AKI. Rechallenging increases risk of recurrent AKI, hospitalizations, RRT dependency, severe CKD, and recurrence of irAEs in other organs. Therefore, ICI-AKI should not be seen as a simply treatable condition (Table 1).

The precise mechanism of AKI after ICI rechallenge remains unclear, but is likely similar to the mechanisms that precipitated the initial bout of AKI. We hypothesize that on rechallenging, there could be an increased immunologic activation of effector T cells that were primed during initial ICI exposure, intensifying autoimmune response. The tubular and interstitial injury after initial AKI episode could be indolent even after cessation of ICI therapy and on reinitiation, the underlying disease process could be revamped with more severe injury. Additionally, long-lived memory T cells that were activated during previous AKI episode could trigger turbulent inflammatory response with release of cytokines and inflammatory markers, accelerating the tubular injury (15). Recurrent AKI episodes may result in eventual loss of kidney function, with a subsequent negative effect on clinical outcomes.

Table 1. CONS of rechallenging with immune checkpoint inhibitors

1	Recurrence of AKI
2	Potential RRT dependency
3	Increased hospitalizations
4	Accelerated progression to severe CKD
5	Increased health care utilization
6	Risk of irAE in other organs

irAE, immune-related adverse effects; RRT, renal replacement therapy.

Considering the high recurrence rates of irAEs and ICI-AKI on rechallenge and the lack of data on long-term effects of rechallenging ICIs, rechallenging should be discouraged and considered as a last resort, especially among patients who sustained severe grade kidney irAE on initial administration. Among the subset of patients who are at risk of developing severe irAE and who must receive ICI as essential component of anticancer therapy, the following measures should be considered while reinitiating ICIs to reduce AKI from irAE: (1) rechallenge after near resolution of initial AKI episode, (2) use of single ICI instead of combination therapy, (3) rechallenge while patients are still on low-dose corticosteroids, (4) increase the latency between the initial AKI episode and rechallenge, (5) use of PD1/PDL1 inhibitors if possible, as compared with CTLA4 inhibitors, (6) avoidance of concomitant agents that could cause acute interstitial nephritis, (7) use of Interleukin (IL)-6 inhibitor, tocilizumab for patients with severe grade >3 kidney toxicity in combination with ICI use (16), and (8) a multidisciplinary team approach (Figure 1).

In conclusion, multiple factors play a part in the decision to rechallenge a patient with ICIs and we believe this decision should be individualized considering the availability of alternative therapies, severity, and grade of initial irAE, tumor response, and coexisting comorbid conditions. Further, it is essential to identify risk factors associated with severe irAE and consider necessary preventive strategies while reintroducing ICI therapies in an attempt to reduce the risk of kidney injury and severity of CKD.

Disclosures

J. Velez reports consulting for Bayer and Mallinckrodt Pharmaceuticals; reports being on the advisory board for Mallinckrodt

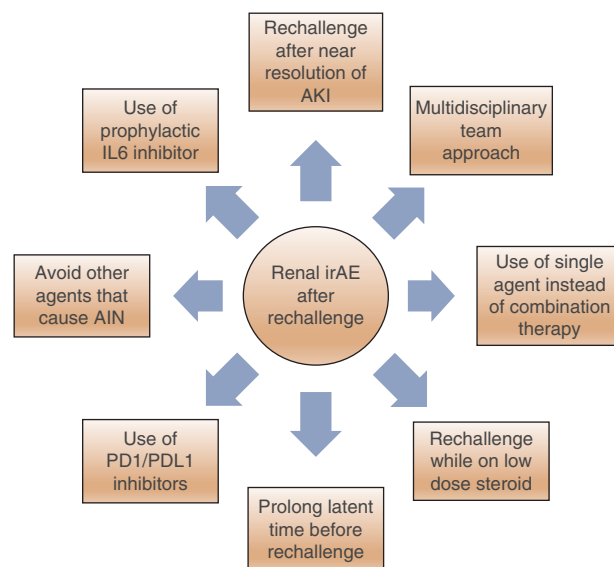


Figure 1. | Recommended measures to potentially decrease the risk of recurrent AKI from immune-related adverse events on rechallenge with immune checkpoint inhibitors. irAE, immune-related adverse events; PD1, programmed cell death protein 1; PDL1, programmed death ligand 1; AIN, acute interstitial nephritis.

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Author Contributions

J. Velez provided supervision, reviewed and edited the manuscript; S. Kanduri conceptualized the study, was responsible for the visualization and wrote the original draft.

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