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**Key Points:**

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**Abstract:**

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Is rechallenge appropriate in patients that develop immune checkpoint inhibitor-associated AKI? CON

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Introduction

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

In the study by Cortezar et al (4) including 138 patients with ICI-AKI (Immune checkpoint inhibitor associated acute kidney injury), at a median of 14 weeks after ICI initiation, 43% experienced stage 2 AKI, 57% sustained stage 3 AKI and 9% were dependent on kidney replacement therapy (KRT). While 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 sub group analysis of ICI- AKI patients who required KRT, seven out of thirteen patients (54%) had no recovery of renal function indicating patients with ICI-AKI sustain a complicated clinical course especially those with KRT.
dependency. Additionally, steroids are the main stay 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).

Based on 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 while putting them at risk of recurrent irAEs. Among patients with severe grade 3 or higher kidney toxicity (SCr >3x baseline, or >4 mg/dl or need for RRT), the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) recommended permanent discontinuation of ICIs (7-9). Among patients with lower grade kidney toxicities, there are no clear consensus on appropriate timing of rechallenge, although some studies suggest to hold ICI until AKI episode is near completely resolved (9, 10).

While no randomized controlled studies have explored this area, few studies shed some light on clinical course of patients who were rechallenged with ICI therapies. In a study by Herrmann 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 initial AKI episode. Recurrence of AKI was noted in 3 of 16 rechallenged patients (19%). One remained on KRT and none achieved complete kidney recovery after recurrent AKI episode. Authors also reported a favorable survival trend among patients who were not rechallenged with ICI compared to rechallenged patients. However, this observation could be biased because patients who were rechallenged likely necessitated chemotherapy to combat
active cancer whereas that might have not been always the case for the non-rechallenged group. Significant number of patients (81%) were on lower doses of corticosteroids at the time of rechallenge and majority received the same ICI regimen. In study by Manohar et al (10), rechallenge was attempted among 4 out of 14 patients and one sustained AKI recurrence (25%). Rechallenge was attempted after the serum creatinine reached near baseline. In the multicenter study by Cortezar et al (12), 31 patients were rechallenged at a median of 1.8 months after initial ICI-AKI episode. While most of them were rechallenged with same ICI agent, the recurrence of AKI was observed in 23%. Shorter latency between 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 (13) 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 with grade 4 irAE. Moreover, in study by Simonaggio et al (14), out of 40 patients who were rechallenged with the same ICI, 55% encountered same or a different irAE. Subsequently, a trend towards higher recurrence rate was noted upon rechallenging the patient after more severe initial irAE. Lastly, in a multicenter study by Abu-Sbieh et al (15), the recurrence of immune mediated colitis was reported to be higher in patients with anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) (44%) as compared to those receiving anti–programmed cell death 1 or ligand 1 (PD-1/L1) (32%).

Summarizing the above-mentioned studies, the overall risk of irAE after rechallenge with ICI is high and it ranges from 28% to 55% (13-15) while the risk of ICI- AKI after rechallenge is reported to vary between 19% to 25 % (10-12). Further, in most available
case series, it is left to the treating physician whether the AKI episode is ICI-induced or not without the need of a biopsy. Therefore, it is possible that in the cases without recurrence after ICI reintroduction, the initial AKI-episode was not ICI-induced (as most AKI episodes in ICI treated patients are of prerenal origin) emphasizing the importance of kidney biopsies in patients experiencing AKI under ICI treatment without obvious other explanation. Hence, we propose that ICI rechallenge should not be attempted among patients with biopsy proven cases of ICI- AKI.

Major risk factors associated with AKI after rechallenge, even though 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, KRT dependency, severe chronic kidney disease and recurrence of irAEs in other organs. Therefore, ICI-AKI should not be taken lightly 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 upon rechallenging, there could be an increased immunological 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 upon re initiation, 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 (16).
Recurrent AKI episodes may result in eventual loss of kidney function with subsequent negative impact on clinical outcomes.

Considering the high recurrence rates of irAEs and ICI-AKI upon rechallenge and 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 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 initial AKI episode and rechallenge, 5) use of PD1/ PDL1 inhibitors if possible, as compared to CTLA4 inhibitors, 6) avoidance of concomitant agents that could cause AIN, 7) use of IL6 inhibitor, tocilizumab for patients with severe > grade 3 kidney toxicity in combination with ICI use(17), 8) multidisciplinary team approach (Figure 1).

In conclusion, multiple factors play into the decision to rechallenge a patient with ICIs and we believe that this decision should be individualized considering the availability of alternative therapies, severity and grade of initial irAE, tumor response and co-existing co morbid 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 chronic kidney disease.

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Table 1

| Potential CONS of rechallenging with ICI |
|----------------------------------------|
| 1                                      | Recurrence of AKI                      |
| 2                                      | Potential KRT dependency               |
| 3                                      | Increased hospitalizations              |
| 4                                      | Accelerated progression to severe CKD  |
| 5                                      | Increased health care utilization       |
| 6                                      | Risk of irAE in other organs           |

Table. 1 CONS of rechallenge with ICI. ICI - Immune Check Point Inhibitors, AKI- acute kidney injury, CKD- chronic kidney disease, KRT- kidney replacement therapy, irAE- immune related adverse effects.

FIGURE LEGEND

Figure 1: Recommended measures to potentially decrease the risk of recurrent AKI from Immune related adverse events upon rechallenge with Immune checkpoint Inhibitors
Renal irAE after rechallenge

- Rechallenge after near resolution of AKI
- Multidisciplinary team approach
- Use of single agent instead of combination therapy
- Use of prophylactic IL6 inhibitor
- Avoid other agents that cause AIN
- Use of PD1/PD-L1 inhibitors
- Prolong latent time before rechallenge
- Rechallenge while on low dose steroid

AKI - Acute Kidney Injury, irAE – Immune related adverse events, PD1- programmed cell death protein 1, PD-L1 – programmed death ligand 1, AIN – Acute interstitial nephritis, IL6-Interleukin-6.