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

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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? PRO

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Introduction

Immune checkpoint inhibitors (ICIs) target two seminal negative feedback loops in T cells, which are in place to avoid overactivation and uncontrolled immune responses including those against self-antigens: cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 pathway (PD-1)/programmed death ligand 1 (PD-L1). Reversing this break and enabling tumor-directed immune activity has remarkably improved survival rates for various malignancies, including for those historically considered to have a very poor prognosis. Despite their proven efficacy across a wide range of malignancies, ICI can cause a unique spectrum of autoimmune toxicities known as immune-related adverse events (irAEs). These irAEs can affect virtually any organ, including the kidneys as ICI-associated acute kidney injury (AKI), and can emerge as therapy-limiting side effects for ICIs.

Patients with cancer who developed severe irAEs, Grade 3 or 4 by the Common Terminology Criteria for Adverse Events (CTCAE), are at risk of developing these very same toxicities upon rechallenging with ICIs.¹ Understandably, the medical team in charge of these patients can be quite hesitant to rechallenge with ICI even if a therapeutic benefit is seen. With the expanding use of ICI, the outlined problem will continue to become more frequent. ICI associated AKI (ICI-AKI) occurs in 2-5% of patients receiving immunotherapy, but the incidence differs depending on the agent administered as well as the dose of the agent, with the highest incidences reported for anti-CTLA-4/anti-PD-1/PD-L1 combination therapy.² ³ Among ICI-AKIs, acute interstitial nephritis (AIN) is the most common pathological finding and it tends to respond quite promptly in the majority of cases by withholding ICI therapy and timely administration of corticosteroids. Rechallenge with ICI becomes a point of discussion for the multidisciplinary care team at the point resolution of AKI, weighing the risks and benefits. Initially, in clinical trials, when patients developed severe toxicity, resumption of ICI therapy was usually not allowed if disease progressed. As these drugs became more broadly available in real-world scenarios, centers with more experience learned to identify and manage ICI-AKI with declining fear of rechallenge, especially when an alternative anti-
cancer therapy is not available. There are a few relevant studies that have looked at rechallenging patients who developed ICI-AKI (Table 1). One of the first studies was performed by our group, a retrospective observational cohort study of 1173 were 14 patients were deemed to have ICI-AKI and 4 patients underwent rechallenge. This study was further extended by Isik et al. which reported on 37 patients who developed ICI-AKI. All of them had their ICI therapy held and 92% were treated with corticosteroids. Rechallenge was attempted in 16 (43%) of the 37 patients approximately 2 months after the AKI event. Fifteen (97%) of these patients were rechallenged with the same ICI agent (PD-1 inhibitor) implicated in the initial AKI episode, and in 3 (20%) patients, nivolumab ICI therapy was reduced from combination therapy with ipilimumab to monotherapy. There was only 1(6%) patient who switched drugs (pembrolizumab to atezolizumab). A total of 13 (81%) patients were on corticosteroids at rechallenge. Recurrent ICI-AKI occurred in 3 (19%) of the rechallenged patients and there was no difference of latency period between the initial AKI episode and rechallenge between those who developed or not recurrent AKI. As use of AIN-inducible drugs, such as proton pump inhibitors (PPIs) and non-steroidal anti-inflammatory drugs (NSAIDs) have been implicated in increased risk to develop ICI-AKI, we looked at AIN drug subtype at rechallenge and no significant difference was found in patients with recurrent AKI and those without a recurrent AKI as well as no difference in the dose of corticosteroids.

The above study findings were corroborated in a larger multicentre retrospective study by Cortazar et al. In this multicenter study with a total of 138 patients with ICI-AKI, 31 (22%) patients were rechallenged approximately 1.8 months after the diagnosis of ICI-AKI. Recurrence of ICI-AKI was noted in 7 patients (23%). Most of patients (85%) had partial (PR) or complete response (CR) after treatment. Like other studies discussed previously, most of the patients (87%) were rechallenged with the same ICI treatment received at initial AKI episode, and around 40% were still treated with corticosteroids at the time of rechallenge.
Based on the results of the studies performed to date rechallenge is feasible and associated with a risk of recurrent ICI-AKI of approximately 20%. Importantly, Isik et al. did not find survival differences between patients rechallenged versus those not rechallenged with ICI therapy.\textsuperscript{6} An explanation for these results could be related to potential bias towards treating patients with more aggressive malignancies with ICI again due to lack of an alternative treatment with other conventional therapies and potentially decreasing survival benefit. Given the relative low incidence of recurrent ICI-AKI, it seems reasonable to consider rechallenge in patients who present with tumour treatment response while on immunotherapy.

Therefore, the decision on whether or not to rechallenge patients after an episode of ICI-AKI will depend on a variety of considerations. These including the severity of renal irAE and if other risk factors were present at the time of development of ICI-AKI, such as use of ICI combination therapy or the use of AIN-inducible drugs, as these can be discontinued. Although robust evidence is lacking, clinicians may consider secondary prevention by use of corticosteroids when there is absence of other therapeutic alternatives even for patients with more severe kidney toxicities such as Grade 3 or higher.

With all these factors in mind, there are few scenarios where rechallenge can be feasible and ICI therapy can be resumed as safely as possible and independent of the severity of the initial renal irAE once PR or CR is accomplished with immunosuppression therapy.

**Rechallenge with switching of the class of ICI therapy**

For the patients who developed irAE and who responded to ICI therapy, one alternative is to consider switching ICI classes, but only when appropriated after discussion with oncological team, as some ICI classes may not be approved for the specific type cancer. Some organs seem to be affected by one class more than by another. Patients on anti-CTLA-4 agents may experience more colitis and hypophysitis, while patients on PD-1 blockade may develop
more pneumonitis. One study reported on an incidence of ICI-AKI of less than 1% with PD-L1 blockade compared to an incidence of 2-5% with other classes. This may be due to the lack of impairment of the PD-1/PD-L2 pathway. This approach can henceforth be considered in a number of cases, especially in the hands of an experienced team and in the absence of other available treatment options.

**Rechallenge using the same class of ICI therapy**

The use of combination ICI therapy increases the risk of ICI-AKI, therefore rechallenge with de-escalation to monotherapy is recommendable in this setting. Many times, anti-CTLA-4 therapy is discontinued, and anti-PD-1 monotherapy is resumed. As shown in the outlined retrospective studies, rechallenge is mostly done with the same ICI, and recurrence of ICI-AKI occurred in 1 in 5 patients in most of the studies. Close monitoring remains important in all patients undergoing rechallenge for early detection of AKI so that severe AKI events could be avoided.

**Rechallenge with ICI therapy concomitantly or without immunosuppressive therapy**

Concomitantly immunosuppressive therapy is a common scenario as outlined in the aforementioned retrospective studies. After the initial episode of ICI-AKI, immunotherapy is resumed after AKI resolution concomitantly with low dose steroids (usually 10-20 mg daily depending on other factors such as severity of AKI and concomitant extra renal irAEs) this secondary prevention can be maintained for the first month or cycle 1-2 after resumption ICI therapy before attempting tapering; recurrence of ICI-AKI in this setting is seen in 5-25%. Even though counterintuitive, the concomitant administration of corticosteroids and ICI therapy does not necessarily lead to poorer clinical cancer outcomes. Date supporting secondary prevention with corticosteroids are not as robust yet, but corticosteroids can be considerate in conjunction with ICI in the absence of other
therapeutic alternatives. On the contrary, observations have shown that for some patients after resolution of ICI-AKI, once potential culprit drug (e.g. PPI/NSAIDs) at the time of development of ICI-AKI is discontinued, these patients may not require secondary prevention with immunosuppression if kidney function remains is stable. On Figure 1 a proposed algorithm for secondary prevention of ICI-AKI during rechallenge after thorough multidisciplinary discussion.

It is important to note that the correlation of development of irAE and response to therapy has been consistently reported in different types of cancer. Given the reasonable risk profile, the benefit of resuming ICI therapy in selected patients despite initial nephrotoxicity can be quite attractive and should be considered, especially when it is the only therapy option left.

Disclosures

S. Herrmann reports the following: Patents and Inventions: Pfizer, but this is not related to the current research.

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Author Contributions
Sandra Herrmann: Conceptualization; Formal analysis; Investigation; Writing - original draft; Writing - review and editing.
References:

<table>
<thead>
<tr>
<th>Study</th>
<th>N° of patients with initial kidney irAE</th>
<th>N° of patients rechallenged</th>
<th>ICI treatment rotation</th>
<th>% of patients on IS at the time of rechallenge</th>
<th>% of ICI-AKI recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isik et al.⁶</td>
<td>37</td>
<td>16</td>
<td>Combination to anti-PD-1 Anti-PD-1 to same Anti-PD-1 to anti-PD-L1</td>
<td>81%</td>
<td>N=3 (19%)</td>
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<td>33% Stage 1</td>
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<td>33% Stage 2</td>
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<td>33% Stage 3</td>
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<tr>
<td>Cortazar et al.⁷</td>
<td>138</td>
<td>31</td>
<td>Most patients were rechallenged with the same ICI agent. Mostly anti-PD-1.</td>
<td>39%</td>
<td>N=7 (23%)</td>
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<tr>
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<td>29% Stage 3</td>
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<td></td>
<td></td>
<td>71% Stage ≤2</td>
</tr>
<tr>
<td>Dolladiille et al.¹</td>
<td>276</td>
<td>78</td>
<td>Informative rechallenges mostly done with an Anti–PD-1/PD-L1 monotherapy</td>
<td>N/A</td>
<td>N=4 (5.1%)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Stage N/A</td>
</tr>
<tr>
<td>Hultin et al.¹²</td>
<td>23</td>
<td>5</td>
<td>Four received anti-PD-1 monotherapy One patient received</td>
<td>60% (40% N/A)</td>
<td>No recurrence of renal irAE</td>
</tr>
</tbody>
</table>
• No, number; %, percentage; irAE, immune-related adverse event; ICI, immune checkpoint inhibitor; AKI, acute kidney injury; IS, immunosuppression. N/A, not available.

• Acute kidney injury stage according to Kidney Disease: Improving Global Outcomes clinical practice guidelines: 1.5–1.9 fold from baseline serum creatinine (SCr) (AKI stage 1); 2–2.9 fold from baseline SCr (AKI stage 2); and over threefold from baseline SCr (AKI stage 3).

**Figure Legend:**

**Figure 1: Proposed flow chart approach for secondary prevention during immune checkpoint inhibitor rechallenge after initial nephrotoxicity:** IrAE, immune-related adverse event; ICI, immune checkpoint inhibitor; AKI, acute kidney injury; IS, immunosuppression; ATN, acute tubular necrosis; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor.
Figure 1

**Biopsy-proven ATN or highly suspicion ICI-AKI** → Yes → **ICI therapy-associated AKI**

**IS treatment with corticosteroids taper until AKI resolves***

Is it safe to rechallenge with ICI?

Yes → **ICI plus concomitant IS therapy (usually initial dose of Prednisone during rechallenge is 10-20 mg daily) unless special consideration**

No → Biopsy-proven ATN or non-irAE renal pathology

Safe to resume ICI therapy once AKI unrelated to ICI resolves and no concomitant major extra-renal irAEs (e.g., Colitis/Myocarditis)

If history of life-threatening irAEs (e.g., myocarditis, cytokine release syndrome)

* Taper corticosteroids until equivalent prednisone dose of 10 mg daily. Rechallenge can be attempted at this time if lack of other alternative therapy due to tumor progression. Otherwise, consider rechallenge when corticosteroid is completely tapered off and no recurrence of AKI.

** If patient had ICI-AKI while on combination therapy or had an obvious trigger (e.g., NSAIDs/PPIs/Antibiotics) and this is discontinued. Rechallenge with ICI monotherapy could be considered without secondary prevention, once AKI resolves and patient is off IS (usually 8 weeks ± 2 weeks depending ICI half-life) assuming response to steroid and stable kidney function prior rechallenge.

**ICI-AKI recurrence**

Yes → Stop ICI treatment per guidelines and treat as indicated with IS

No → Continue concomitant IS treatment for the next 1-2 ICI cycles based on patient tolerance and if no recurrence of ICI-AKI or other unacceptable toxicity, attempt taper of IS for secondary prevention.