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Editorial Comment

EDITORIAL COMMENT

Proton pump inhibitors and adverse kidney outcomes during immune checkpoint blockade: time to sound the alarm?

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ABSTRACT

Immune checkpoint inhibitors (ICIs) have significantly altered the treatment landscape for cancer in the last decade. However, their benefits are often offset by therapy-limiting immune-related adverse events (irAEs). Acute interstitial nephritis (AIN) is the most common renal irAE, but the exact mechanisms underlying its development are poorly understood. ICI-induced immune activation against drug-derived antigens, leading to an inflammatory response within the kidney interstitium, has been postulated, evidenced by current observations of a higher incidence of ICI-associated AIN in patients receiving AIN-inducing drugs such as proton pump inhibitors (PPIs). The role of PPIs in this specific context has garnered significant attention, given their ubiquitous use and sometimes misuse. In this issue of *CKJ* Miao *et al.* summarise and synthesize the best available evidence to clarify the interactions of PPIs with ICIs in the development of AIN and other adverse kidney outcomes. The sum of evidence provided appear to implicate PPIs in the development of clinically significant short- and long-term kidney-related adverse effects in patients on immune checkpoint blockade, although causality cannot be proven. In this editorial we discuss the key practical implications of these findings and emphasize the need for further quality studies to delineate the true relationship of ICIs and PPIs in the development of AIN.

Keywords: acute interstitial nephritis, immune checkpoint inhibitors, proton pump inhibitors

Immune checkpoint inhibitors (ICIs) have significantly altered the treatment landscape for cancer in the last decade and are now the standard of care for multiple cancers. Their widespread use has resulted in the emergence of a myriad of immune-mediated toxicities that can affect any organ system at variable time points during therapy and are collectively termed immune-related adverse events (irAEs). Acute interstitial nephritis (AIN) is the most frequently observed kidney irAE, with glomerular diseases and electrolyte/acid–base disturbances being increasingly reported [1, 2]. Exact mechanisms underlying the development of irAEs, including AIN occurring during ICI use are poorly defined. They are broadly understood to be off-target adverse effects caused by the ICI-induced disruption of homeostatic peripheral tolerance, a process normally regulated by the CTLA-4 and PD-1/PD-L1 pathways. This leads to consequent activation of the immune system towards itself and other non-tumour environmental antigens. Potential sources of the latter may include diet, viruses and, more importantly, drugs [3].

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In this issue of *Clinical Kidney Journal*, Miao *et al.* [4] review and summarise the evidence evaluating the link between PPIs and ICIs in the development of AIN and revisit the role of PPIs in adverse kidney outcomes. Growing evidence from observational studies appears to suggest a potential association between PPIs and ICI-associated AIN (ICI-AIN), evidenced by an increased risk of ICI-related acute kidney injury (AKI) [5–8] as well as a more rapid onset of AKI [9] in patients concurrently on PPIs and ICIs. Reported risk can be as significant as 3-fold and has been consistently reported in larger studies [5, 10]. Recurrence of ICI-AIN is also more likely when PPI is continued at the time of ICI rechallenge. More recently, a meta-analysis evaluating 27 studies has reported PPIs to be a significant risk factor for AKI in patients receiving ICIs {pooled odds ratio 2.23 [95% confidence interval (CI) 1.88–2.64], $P < .001$, $I^2 = 0.0\%$, $n = 8$ studies} [11]. Interestingly, adverse long-term kidney outcomes, defined as a composite of new-onset chronic kidney disease (CKD) or significant (>30%) estimated glomerular filtration rate (eGFR) decline sustained for >90 days, have also been reported in a single study of ICI-treated patients, where PPI was identified as the only other significant risk predictor besides age [12]. Although causality cannot be proven due to the observational nature of these studies, the sum of evidence provided by these findings implicates PPIs in the development of clinically significant short- and long-term kidney-related adverse effects in patients on immune checkpoint blockade.

Several pathomechanisms have been postulated in AIN occurring during ICI use. These include the perturbation of immune tolerance to self or haptenized kidney antigens as a result of checkpoint inhibition, reactivation of latent drug-specific T cells, production of kidney-specific autoantibodies and induction of inflammatory cytokines, all of which may occur in combination or isolation [13]. Although the direct contributions of PPIs and their interactions with these mechanisms in ICI-AIN remain speculative and have yet to be addressed by quality basic or translational studies, several observations from published reports lend reasonable support to the hypothesized interaction between drug-derived antigens, drug-specific T cells primed to these antigens and the broader role of immune tolerance in the pathogenesis of AIN. The presence of circulating T cells demonstrating reactivity to the PPI lansoprazole has been seen using the drug lymphocyte stimulation test in the context of ICI-AIN, supporting the existence of drug-specific T cells, although it is understood that their presence alone does not automatically equate to disease [14]. However, when the immune activation threshold is consequently lowered by checkpoint inhibition, antigenic rechallenge could conceivably trigger reactivation of these drug-specific T cells, best evidenced by anecdotal reports of AIN recurring with inadvertent PPI re-exposure in both ICI- [8] and non-ICI-treated patients [15].

Miao *et al.* [4] reviewed and found few clinical or histological features that reliably distinguish between classic AIN induced by non-steroidal anti-inflammatory drugs (NSAIDs) and/or antibiotics, PPI-AIN and ICI-AIN, perhaps owing to the non-specific clinical presentation of AIN in general. Of note, perceived differences relating to the timing of onset of AKI in relation to drug exposure has been described among classic AIN, PPI-AIN and ICI-AIN [16], but overlap appears to exist. Reasons for this heterogeneity in temporality are presently unaddressed by available studies. However, the highly variable onset of ICI-AIN ranging from hyperacute to delayed presentations [10, 17, 18], together with our understanding of immune checkpoint inhibition, would argue against a direct tubulointerstitial toxic effect of ICIs. Several translational studies have since indicated the role of chemokine C-X-C motif ligand (CXCL9) in promoting kidney tubulointerstitial inflammation in various settings [19, 20], including those occurring during ICI use [21–23]. More recently, Moledina *et al.* [24] observed significantly higher urine CXCL9 levels in patients with biopsy-confirmed AIN of diverse aetiologies, including those induced by drugs (antibiotics, NSAIDs, PPIs, ICIs), compared with non-AIN controls. Patients exhibiting higher levels of urine CXCL9 were also more likely to have received ICI. Although comparison of CXCL9 levels between different drug classes was regrettably not performed in this study due to limited sample size, these data taken in aggregate suggest that AINs, regardless of aetiology, are likely to share fundamental similarities in disease biology.

Consistent with this hypothesis, Adam *et al.* [23] found significant molecular overlap in the gene expression signatures of ICI-AIN, ICI-associated T cell–mediated rejection and drug-induced AIN and, interestingly, with a predominant hypersensitivity fingerprint in these entities. We postulate that all AINs have both unique and shared immunologic origins and are caused by cumulative pathological 'hits', with the loss of immune tolerance playing a central role in their pathogenesis. However, unlike in ICI-AIN, where the breach of immune tolerance can be reasonably attributed to checkpoint inhibition, the origins of the loss of renal tolerance may be less readily identified in other forms of AIN, including PPI-AIN. The diversity of kidney irAEs, which includes *de novo* glomerular diseases [1, 25], further supports the presence of an underlying systemic immune dysregulation unmasking their development.

The emerging association of PPI with ICI-AIN and the extensive use of PPI makes its potential for theoretical harm in the context of ICI use difficult to disregard, although it is unclear how the evidence presented should inform clinical practice. The risk of kidney irAEs may theoretically be lessened by avoiding implicated external antigens such as PPIs. As pointed out by the authors, current evidence is insufficiently robust to recommend a complete avoidance of PPIs. As any PPI exposure may hypothetically result in the sensitization and development of drug-specific T cells, this risk exposure may be difficult to modify unless the drug is strictly avoided during ICI use. As AIN-inducing medications are not limited to PPIs alone, it is neither feasible nor practical for cancer patients to avoid all classes of AIN-inducing drugs indefinitely. However, as PPIs are more frequently associated with inappropriate use or overuse compared with NSAIDS and antibiotics, emphasizing their rational use in cancer patients receiving ICIs remains a sensible approach to mitigating the risk of adverse kidney outcomes while maximising benefits.

Although it has been suggested that the decision to discontinue PPIs should be based on the lack of an indication for continued PPI use, rather than on the sole concern for PPI-associated adverse events [26], in specific high-stakes situations like ICI rechallenge, it may be prudent to avoid PPIs, along with other AIN-associated medications. A gastroenterology consult should be obtained for patients with definitive indications for long-term use of PPIs for consideration of suitable alternatives. Otherwise, we propose that PPI use and indication should be routinely reviewed in all ICI-treated patients at each clinical opportunity, with dose and duration limited to the minimum required for those with indications, and PPIs should be actively deprescribed when deemed non-essential, in accordance to current best practices [26]. Benefits of indicated use arguably outweigh the potential risks of ICI-AIN given the relative rarity of kidney irAEs, with short courses with rapid taper or on-demand use additionally justified, as the risk of AIN appears to be graded according to the

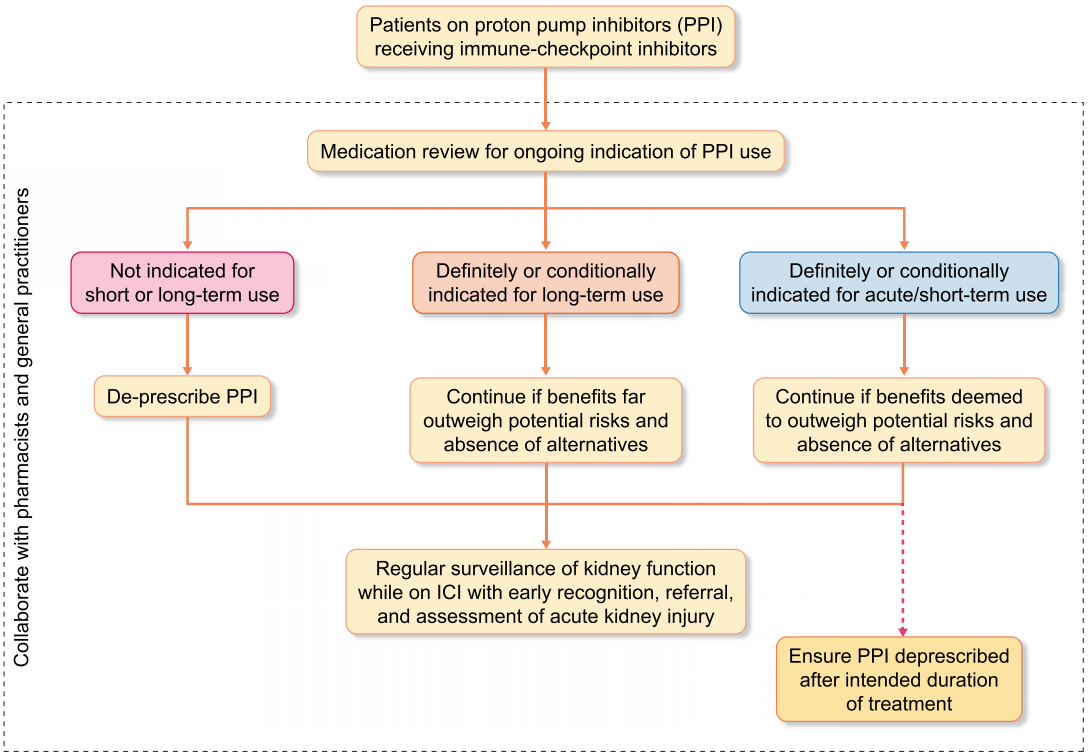

Figure 1: Suggested work flow on promoting responsible use of PPIs in patients treated with ICIs.

dose and duration of PPI use [27]. Whether merits of these proposed strategies outweigh the alternative use of H2 antagonists in reducing ICI-AIN is unknown.

Facilitating these practice changes would ultimately require onconephrologists to raise community awareness and provide practical guidance on why and how responsible use of PPIs should be encouraged in this context. This should be performed in tandem with stakeholder engagement with the oncology and other relevant medical communities for effective dissemination and sustained implementation. Practically, these medication interventions may be integrated into the medication reconciliation and review process as potential quality initiatives [27] (Fig. 1) and supported or led by oncology pharmacists, who are increasingly recognised as integral members of multidisciplinary oncological care teams [28]. Meanwhile, continued efforts should be made to evaluate the real-world incidence of AIN in patients on concurrent ICI and PPI therapy, as well as the role of PPI in the pathogenesis of ICI-AIN. This is undoubtedly challenging due to the relative paucity of high-quality, prospectively controlled studies, as well as animal models to replicate human disease seen in kidney irAEs. Experimental models of AIN exist [29] but have not been formally investigated in the setting of ICI. Nonetheless, the collection of detailed drug exposure inclusive of ever and current exposure of AIN-inducing drugs in ICI users, together with detailed, longitudinal blood and organ immune analyses such as drug-specific T cells and/or other relevant biomarkers collected at various time points of treatment and at the time of kidney irAEs and T cell subsets within kidney interstitial infiltrates, may help to clarify the relationship between ICI-AIN, PPI-AIN and AIN-inducing medications. These may be facilitated through the use of well-designed ICI patient registries and biobanking and championed by concerted, multi-institutional efforts.

While pending further quality studies to clarify the interaction of PPIs with ICIs in AIN development, multidisciplinary approaches that focus on early recognition, referral and assessment of all AKIs occurring in the context of ICIs remain crucial for optimal outcomes. Poorer kidney prognosis seen in PPI-AIN without concurrent ICI therapy may be related to delayed diagnosis due to a lack of active surveillance, leading to chronic interstitial inflammation and fibrosis. Conversely, the regular surveillance of kidney function in patients on ICI therapy, together with heightened awareness of irAEs, may allow earlier recognition and treatment, and consequently better outcomes. The ability to rapidly diagnose ICI-AIN with the use of non-invasive, point-of-care diagnostics is highly desirable and may be possible in the future should promising biomarkers such as urinary CXCL9 become sufficiently validated for routine use. Despite the lack of randomised controlled studies, corticosteroids have been utilised successfully to treat ICI-AIN occurring with or without concurrent PPI, especially when commenced in a timely fashion, and are accepted as first-line treatment [10]. In cases of ICI-AIN where PPI has been implicated, rechallenge with the same or a different PPI is understandably discouraged, especially if ICI rechallenge is considered [30]. However, there remains a paucity of data guiding the safety and use of other AIN-predisposing medications in the setting of ICI-AIN, with trimethoprim–sulfamethoxazole being a drug of particular relevance, being the most common option for *Pneumocystis carinii* pneumonia prophylaxis during prolonged steroid therapy. Its avoidance has been suggested in this specific setting [4] on the basis of AIN-risk minimisation in general rather than a recommendation rooted in evidence.

The epidemiological evidence presented in the review by Miao *et al.* [4] signals yet another potential association of PPIs with adverse kidney outcomes, with emerging data from a specific population of cancer patients receiving ICIs. Prospective studies are warranted to delineate the true relationship of ICIs and PPIs in the development of AIN, but careful and appropriate use of PPI in ICI-treated patients should be strongly encouraged on the basis of precautionary principles. Future studies looking at the long-term effectiveness in reducing AIN and adverse kidney outcomes in this subpopulation and sustainability of this proposed strategy are additionally required.

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AUTHORS' CONTRIBUTIONS

Authors contributed equally to the article.

CONFLICT OF INTEREST STATEMENT

B.S. is a member of the *CKJ* editorial board.

(See related article by Miao and Herrmann. Immune checkpoint inhibitors and their interaction with proton pump inhibitors–related interstitial nephritis. *Clin Kidney J* (2023) 16: 1834–1844.)

REFERENCES

1. Kitchlu A, Jhaveri KD, Wadhwani S *et al*. A systematic review of immune checkpoint inhibitor-associated glomerular disease. *Kidney Int Rep* 2021;**6**:66–77. https://doi.org/10.1016/j.ekir.2020.10.002
2. Uppal NN, Workeneh BT, Rondon-Berrios H *et al*. Electrolyte and acid-base disorders associated with cancer immunotherapy. *Clin J Am Soc Nephrol* 2022;**17**:922–33. https://doi.org/10.2215/CJN.14671121
3. Mangan BL, McAlister RK, Balko JM *et al*. Evolving insights into the mechanisms of toxicity associated with immune checkpoint inhibitor therapy. *Br J Clin Pharmacol* 2020;**86**:1778–89. https://doi.org/10.1111/bcp.14433
4. Miao J, Herrmann SM. Immune checkpoint inhibitors and their interaction with proton pump inhibitors-related interstitial nephritis. *Clin Kidney J* 2023;sfad109. https://doi.org/10.1093/ckj/sfad109
5. Seethapathy H, Zhao S, Chute DF *et al*. The incidence, causes, and risk factors of acute kidney injury in patients receiving immune checkpoint inhibitors. *Clin J Am Soc Nephrol* 2019;**14**:1692–700. https://doi.org/10.2215/CJN.00990119
6. Gupta S, Short SAP, Sise ME *et al*. Acute kidney injury in patients treated with immune checkpoint inhibitors. *J Immunother Cancer* 2021;**9**:e003467. https://doi.org/10.1136/jitc-2021-003467
7. Gérard AO, Barbosa S, Parassol N *et al*. Risk factors associated with immune checkpoint inhibitor-induced acute kidney injury compared with other immune-related adverse events: a case–control study. *Clin Kidney J* 2022;**15**:1881–7. https://doi.org/10.1093/ckj/sfac109
8. Shirali AC, Perazella MA, Gettinger S. Association of acute interstitial nephritis with programmed cell death 1 inhibitor therapy in lung cancer patients. *Am J Kidney Dis* 2016;**68**:287–91. https://doi.org/10.1053/j.ajkd.2016.02.057
9. Isik B, Alexander MP, Manohar S *et al*. Biomarkers, clinical features, and rechallenge for immune checkpoint inhibitor renal immune-related adverse events. *Kidney Int Rep* 2021;**6**:1022–31. https://doi.org/10.1016/j.ekir.2021.01.013
10. Cortazar FB, Kibbelaar ZA, Glezerman IG *et al*. Clinical features and outcomes of immune checkpoint inhibitor-associated AKI: a multicenter study. *J Am Soc Nephrol* 2020;**31**:435–46. https://doi.org/10.1681/ASN.2019070676
11. Liu C, Wei W, Yang L *et al*. Incidence and risk factors of acute kidney injury in cancer patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *Front Immunol* 2023;**14**:1173952. https://doi.org/10.3389/fimmu.2023.1173952
12. Chute DF, Zhao S, Strohbehn IA *et al*. Incidence and predictors of CKD and estimated GFR decline in patients receiving immune checkpoint inhibitors. *Am J Kidney Dis* 2022;**79**:134–7. https://doi.org/10.1053/j.ajkd.2021.05.012
13. Sprangers B, Leaf DE, Porta C *et al*. Diagnosis and management of immune checkpoint inhibitor-associated acute kidney injury. *Nat Rev Nephrol* 2022;**18**:794–805. https://doi.org/10.1038/s41581-022-00630-8
14. Koda R, Watanabe H, Tsuchida M *et al*. Immune checkpoint inhibitor (nivolumab)-associated kidney injury and the importance of recognizing concomitant medications known to cause acute tubulointerstitial nephritis: a case report. *BMC Nephrol* 2018;**19**:48. https://doi.org/10.1186/s12882-018-0848-y
15. Assouad M, Vicks SL, Pokroy MV *et al*. Recurrent acute interstitial nephritis on rechallenge with omeprazole. *Lancet* 1994;**344**:549. https://doi.org/10.1016/S0140-6736(94)91945-3
16. Draibe JB, García-Carro C, Martinez-Valenzuela L *et al*. Acute tubulointerstitial nephritis induced by checkpoint inhibitors versus classical acute tubulointerstitial nephritis: are they the same disease? *Clin Kidney J* 2021;**14**:884–90. https://doi.org/10.1093/ckj/sfaa027
17. Tawhari I, Fenton SE, Sosman JA *et al*. Hyperacute onset of Immune checkpoint inhibitor-related acute interstitial nephritis. *Kidney Int Rep* 2020;**5**:2084–8. https://doi.org/10.1016/j.ekir.2020.08.002
18. Cortazar FB, Marrone KA, Troxell ML *et al*. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. *Kidney Int* 2016;**90**:638–47. https://doi.org/10.1016/j.kint.2016.04.008
19. Menke J, Zeller GC, Kikawada E *et al*. CXCL9, but not CXCL10, promotes CXCR3-dependent immune-mediated kidney disease. *J Am Soc Nephrol* 2008;**19**:1177–89. https://doi.org/10.1681/ASN.2007111179
20. Hricik DE, Nickerson P, Formica RN *et al*. Multicenter validation of urinary CXCL9 as a risk-stratifying biomarker for kidney transplant injury. *Am J Transplant* 2013;**13**:2634–44. https://doi.org/10.1111/ajt.12426
21. Singh S, Long JP, Tchakarov A *et al*. Tertiary lymphoid structure signatures are associated with immune checkpoint inhibitor related acute interstitial nephritis. *JCI Insight* 2022;e165108. https://doi.org/10.1172/jci.insight.165108
22. Nuñez NG, Berner F, Friebel E *et al*. Immune signatures predict development of autoimmune toxicity in patients with cancer treated with immune checkpoint inhibitors. *Med* 2023;**4**:113–29.e7. https://doi.org/10.1016/j.medj.2022.12.007
23. Adam BA, Murakami N, Reid G *et al*. Gene expression profiling in kidney transplants with immune checkpoint inhibitor-associated adverse events. *Clin J Am Soc Nephrol* 2021;**16**:1376–86. https://doi.org/10.2215/CJN.00920121

24. Moledina DG, Obeid W, Smith RN *et al*. Identification and validation of urinary CXCL9 as a biomarker for diagnosis of acute interstitial nephritis. *J Clin Invest* 2023;**133**:e168950. https://doi.org/10.1172/JCI168950
25. Mamlouk O, Selamet U, Machado S *et al*. Nephrotoxicity of immune checkpoint inhibitors beyond tubulointerstitial nephritis: single-center experience. *J Immunother Cancer* 2019;**7**:2. https://doi.org/10.1186/s40425-018-0478-8
26. Targownik LE, Fisher DA, Saini SD. AGA clinical practice update on de-prescribing of proton pump inhibitors: expert review. *Gastroenterology* 2022;**162**:1334–42. https://doi.org/10.1053/j.gastro.2021.12.247
27. Al-Aly Z, Maddukuri G, Xie Y. Proton pump inhibitors and the kidney: implications of current evidence for clinical practice and when and how to deprescribe. *Am J Kidney Dis* 2020;**75**:497–507. https://doi.org/10.1053/j.ajkd.2019.07.012
28. Vulaj V, Hough S, Bedard L *et al*. Oncology pharmacist opportunities: closing the gap in quality care. *J Oncol Pract* 2018;**14**:e403–11. https://doi.org/10.1200/JOP.2017.026666
29. Wilson CB. Study of the immunopathogenesis of tubulointerstitial nephritis using model systems. *Kidney Int* 1989;**35**:938–53. https://doi.org/10.1038/ki.1989.78
30. Herrmann SM. Is rechallenge appropriate in patients that develop immune checkpoint inhibitor-associated AKI?: PRO. *Kidney360* 2022;**3**:799–802. https://doi.org/10.34067/KID.0003962021

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