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CKJ REVIEW

Immune checkpoint inhibitors and their interaction with proton pump inhibitors–related interstitial nephritis

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ABSTRACT

Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy and outcomes, leading to an expanding use in millions of patients worldwide. However, they can cause a spectrum of immune-related adverse events (irAEs). Essentially, any organs can be affected by irAEs, which have emerged as therapy-limiting side effects. In the kidneys, ICI-associated acute interstitial nephritis (ICI-AIN) leads to acute kidney injury (AKI) in 2%–5% of patients on ICI therapy. AKI associated with ICI therapy pathologically presents with AIN in nearly 90% of the cases, but the pathophysiology of ICI-AIN remains to be defined. The generation of autoreactive T cells in patients receiving AIN-inducible drugs, such as proton pump inhibitors (PPIs), is one of the leading theories, supported by a higher incidence of ICI-AIN in patients on these AIN-inducible drugs. In this review, we will discuss our understanding of the incidence, potential pathophysiological mechanisms, clinical presentations, risk factors, diagnosis, and management of PPI-related AIN and its interaction with ICI therapy.

Keywords: acute kidney injury, immune checkpoint inhibitors, immune-related adverse events, interstitial nephritis, proton pump inhibitors

INTRODUCTION

Immune check point inhibitors (ICIs) are new anticancer drugs that act by blocking intrinsic down-regulators of the immune system, leading to empowerment of patients' own immune systems. Currently, four different classes of ICIs have been approved by the US Food and Drug Administration (FDA) for treatment of various cancers [1, 2], including anti-cytotoxic T lymphocyte–associated protein 4 (CTLA-4) (ipilimumab), anti-programmed cell death protein 1 (PD-1) (cemiplimab, nivolumab, and pembrolizumab), or PD-ligand 1 (PD-L1) (atezolizumab, avelumab, and durvalumab), and the most recent one antilymphocyte activation gene-3 (LAG-3) (relatlimab) [3–6]. Despite important benefits in cancer outcomes, ICIs can come with a myriad of adverse effects called immune-related adverse events (irAEs). Acute interstitial nephritis (AIN) is the most common type of renal irAE, being found in 80%–90% of patients who undergo kidney biopsy [7, 8]. Several risk factors have been identified in patients with ICI-associated AIN (ICI-AIN), including use of drugs such as proton pump inhibitors (PPIs) [9]. Gastrointestinal symptoms, such as "heartburn" or "stomach discomfort"' frequently caused by gastroesophageal reflux (GERD), are much more common in cancer patients. A large retrospective cross-sectional study reported that among cancer patients, up to 33% used acid-reducing agents, and PPIs were the most commonly prescribed drugs among this class of agents [10, 11]. In fact, the prevalence of PPI use is largely underestimated because of its over-the-counter use by millions of patients. Moreover, PPIs often fail to taper and/or discontinue, with a result of prolonged use. Although PPI use is generally safe, it has

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been demonstrated that PPI therapy is associated with a variety of adverse events, such as AIN causing acute kidney injury (AKI) [12–18]. Notably, the use of PPIs has been associated with worse outcomes in the setting of ICI therapy in some [19–21], although not in all studies [22]. As such, PPIs have been recognized as an important cause of drug-induced AIN both in the general population and in cancer patients receiving ICIs [4, 7, 17].

In the current review, we aim to discuss our understanding of the incidence, pathogenesis, clinical presentations, and risk factors to interpret a potential causal relationship between PPI and renal irAEs in the setting of ICI therapy. We also discuss the therapeutic strategies of PPI-related kidney injury based on the current evidence and understanding.

ICI and PPI-associated adverse events

ICI-related irAEs can occur in any organ at a substantially high frequency with a wide range from 59% to 85% overall [23], and with various degrees of severity from mild to life-threatening (Table 1). Unlike skin, gastrointestinal tract, and endocrine system, the kidneys are less frequently affected by irAEs [24]. AKI caused by AIN is the major type of ICI-related renal irAEs, being observed in nearly 90% of kidney biopsies [7]. However, it remains a challenge to distinguish ICI-related AKI (ICI-AKI) from other cause-related AKI due to lack of specific and reliable clinical characteristics and biomarkers. The presence of extrarenal irAEs such as rash, colitis, and thyroiditis in particular in those with ≥1 extrarenal irAEs may be an important hint in patients with suspected ICI-AKI [4, 7]. Other manifestations of ICI-related renal irAEs, such as electrolyte abnormalities (e.g. hyponatremia, hypokalemia, hyperkalemia, hypophosphatemia, and hypomagnesemia) and renal tubular acidosis also have been reported [4, 9, 25].

PPIs are a class of medications used to suppress acid production by irreversibly binding to the H^+/K^+ ATPase pump on the secretory surface of the gastric parietal epithelial cells [26, 27]. Currently, the US FDA have approved six PPI drugs: omeprazole, esomeprazole, lansoprazole, lansoprazole, pantoprazole, and rabeprazole [28]. PPI is mainly used for treatment of acid-related disorders, such as peptic ulcer disease, GERD, erosive esophagitis, and Barrett's esophagus [29]. As one of the most frequently used classes of medications worldwide [30, 31], including among cancer patients [10], PPIs are generally thought to be safe, however, their use has been associated with a substantial adverse impact (Table 2). PPI-related kidney adverse effects including AIN and AKI have been reported [12–18]. Several large epidemiologic studies suggested that PPI use significantly increased the risk of incident chronic kidney disease (CKD), CKD progression, and kidney failure [32–35].

Advent of ICI therapy and its association with AKI, most caused by AIN in patients taking PPIs, makes the relationship stronger [4, 7, 8, 36].

PPI-related AIN in the setting of ICI therapy

Relatively, AIN is an uncommon cause of kidney disease. Data from analysis of kidney biopsy registers and several large case series suggested that only a small portion, ~2%–3%, developed AIN [28, 37–39]. But AIN is much more common in hospitalized patients with AKI, accounting for 10%–20% [40]. A large case series study including 133 patients with biopsy-proven AIN from 1993 to 2011 at the Mayo Clinic suggested that the most frequent cause of AIN was drugs (70%), followed by autoimmune disease (20%), and infections (4%) [41]. Antibiotics, non-steroidal inflammatory drugs (NSAIDs), and PPIs have been thought to be three major drug classes responsible for drug-induced AIN, accounting for 80%–90% overall [42]. To date, ICI-AIN is attracting more and more attention.

Table 1: ICI-related: adverse events.

Organ	irAEs
Skin	Pruritus
	Rash, dermatitis
Gastrointestinal tract system	Gastritis
	Colitis
	Pancreatitis
	Type 1 diabetes
Endocrine system	Hypophysitis
	Thyroiditis (e.g. hypothyroidism, hyperthyroidism)
	Adrenalitis
Heart	Myocarditis
	Pericarditis
	Heart failure
	Arrhythmia
Liver	Hepatitis
	Transaminitis
Lung	Pneumonitis
	Pleuritis
Blood	Thrombocytopenia
	Hemolytic anemia
	Neutropenia
Rheumatology	Vasculitis
	Arthritis
	Sarcoidosis
	Polymyalgia rheumatica
	Scleroderma
Nervous and muscular system	Neuropathy
	Demyelination
	Meningitis
	Encephalitis
	Myasthenia gravis
	Myositis
Kidney	AKI (AIN)
	Glomerular disease (e.g. pauci-immune crescentic GN, C3 GN, renal vasculitis, and podocytopathy)
	ATI/ATN
	Electrolyte abnormalities (e.g. hyponatremia, hypokalemia, hyperkalemia, hypophosphatemia, and hypomagnesemia, RTA)

irAEs: ICI-related adverse events; AIN: acute interstitial nephritis; GN: glomerulonephritis; C3: complement 3; ATI: acute tubular injury; ATN: acute tubular necrosis; RTA: renal tubular acidosis.

Currently, there is no precise data demonstrating prevalence and incidence of ICI-AIN and PPI-related AIN (PPI-AIN). Available data indicated that the incidence of AKI in patients receiving ICIs was ~17% [4, 9, 43–45]. However, the incidence of AKI directly related to ICI use was low, ranging from 0.8% to 5% [4, 7, 36, 46]. Some reports suggested that the second cause of drug-induced AIN was PPI use, accounting for 14%–64% [41, 47–51], and incidence of biopsy-proven AIN related to PPI has been increasing over the last decades [52].

PPIs are so often taken, even overdosed in cancer patients. Development of AKI in patients receiving ICIs who also take PPIs has become more evident. PPIs have been consistently shown to be a risk factor for AKI in ICI-treated patients [4, 7, 36, 46]. A

Table 2: PPI-related: adverse effects and potential mechanism.

	Association [89]	Potential mechanism
Adverse non-kidney effects		
Vitamin B_{12} deficiency	Likely causative	Increased gastric pH alters absorption of Vitamin B12 in the terminal ileum, potential for microbial overgrowth that utilizers cobalamin [89]
Cardiovascular disease (e.g. myocardial infarction)		Unknown; likely be related to impairment of endothelial nitric oxide synthase; drug interaction (e.g. increased cardiovascular risk in patients with concomitant use of PPI and clopidogrel) [96, 97]
Clostridioides difficile infection	Unclear	Alteration of gut microbiome [98, 99]
Community-acquired pneumonia	Unlikely	Alteration of gut microbiome [98, 100]
Dementia	Unclear	Increased production and degradation of amyloid and binding to tau. Decreased availability of other nutrients [89]
Small Intestine Bacterial Overgrowth	Likely causative	Alteration of gut microbiome [98, 99]
Gastric cancer		Hypergastrinemia, gastric atrophy and bacterial overgrowth in the stomach [101]
Osteoporotic fractures	Unclear	Reduction in calcium absorption due to increased gastric pH [98, 102]
Adverse kidney effects		
Hypomagnesemia	Likely causative	Increased gastric pH alters Mg transport and absorption; changes in the expression and activity of key transporters both the small intestine and the colon; reduced Mg^{2+} solubility in the intestinal lumen; alteration of gut microbiome [103]
AIN		Cell and humoral-mediated drug hypersensitivity [52, 62]
Acute kidney injury	Unclear	AIN [52]
CKD and kidney failure	Unclear	Subclinical AIN [28, 89]

previous study suggested that ICI-AKI in patients who also took PPIs occurred earlier and had a three-times higher rate than those with other causes-related AKI during immunotherapy [36]. Similarly, two major studies have shown that PPI use was significantly associated with ICI-AKI both with a hazard ratio (HR) of 2.85 (95% CI 1.34–6.08 and 95% CI 1.81–4.48, respectively) [4, 7]. In addition, a largest retrospective cohort study showed that PPI use, especially in those with a history of prior or concomitant extrarenal irAEs, was associated with an increased risk of ICI-AKI [8]. These studies suggested that ICI-AKI appears to be more common in patients who use PPI compared to those who do not.

Pathophysiological mechanism

Currently, the precise mechanisms of ICI-AKI remain unclear. The CTLA-4 and PD-1/PD-L1 axis plays a crucial role in maintaining normal immune response and self-tolerance. In the setting of ICI therapy, CTLA-4 inhibitor targets CTLA-4 highly expressed on T cells, then blocks its binding to CD80/CD86 mainly expressed on antigen-presenting cells. This allows interaction of CD28 and CD80/CD86, resulting in T-cell activation [53]. Blocking interaction of PD-1 and PD-L1 with anti-PD-1 or anti-PD-L1 monoclonal antibodies, respectively, promotes tumor cell apoptosis/death but also activates T cells or suppress their deactivation [54] (Fig. 1). Aberrant activation of self-reactive T cells initiated by ICIs can reduce or disturb immune tolerance against renal antigens [55]. Recently, it has been shown that the abundance of specific immune cells (e.g. $CD4^+$ memory T cells, T helper, and dendritic cells) was significantly increased in kidney tissues of patients with ICI-AIN [56]. These findings suggested that dendritic cell-T-cell interaction within ICI-AIN and the subsequent T-cell activation may contribute to the underlying pathophysiology. These occurs in the setting of elevated proinflammatory cytokines detected in the urine of patients with ICI-AIN, specifically TNF-α, suggesting that ICI-induced inflammation involves the pathogenesis of kidney injury [56].

Mechanistically, exposure to drugs such as PPIs, NSAIDs, and antibiotics could trigger a drug-specific T-cell-mediated immune reaction. ICIs then reactivate these drug-specific latent T cells, leading to loss of tolerance [5]. It is hypothesized that administration of drugs that potentially increase the risk of AIN may initiate the immune reaction triggered by drug-specific T cells in the setting of immunotherapy [5, 57, 58]. The precise pathogenesis of PPI-AIN has not been defined; several immunologic mechanisms would most likely be involved (Fig. 1). Drug-induced AIN is mainly a cell-mediated immune response, supported by the findings that the predominant lymphocytes are T cells in kidney biopsies [59]. A positive stain of either $CD4^+$ or $CD8^+$ T cells also has been revealed in kidney interstitial tissue [57, 60]. Similar to other drug-induced AIN, one of the most suggested mechanisms is that PPI may act as a hapten, resulting in a formation of complex by binding to proteins through covalent links either locally or peripherally [52, 61, 62]. Locally, the drug can bind to kidney specific tubulointerstitial proteins. Peripherally, the drug-formed haptens are transported to kidney, where they are filtered, endocytosed, and metabolized by tubular epithelial cells [61]. The resultant metabolites are presented to dendritic cells that are located in kidney interstitial tissue, leading to subsequent T-cell-mediated immune response [62]. Cytotoxic T-cell-mediated damage is mainly involved in the pathogenesis of drug-induced AIN. Yet, kidney injury driven by antibody-mediated immune reaction is also possible in some

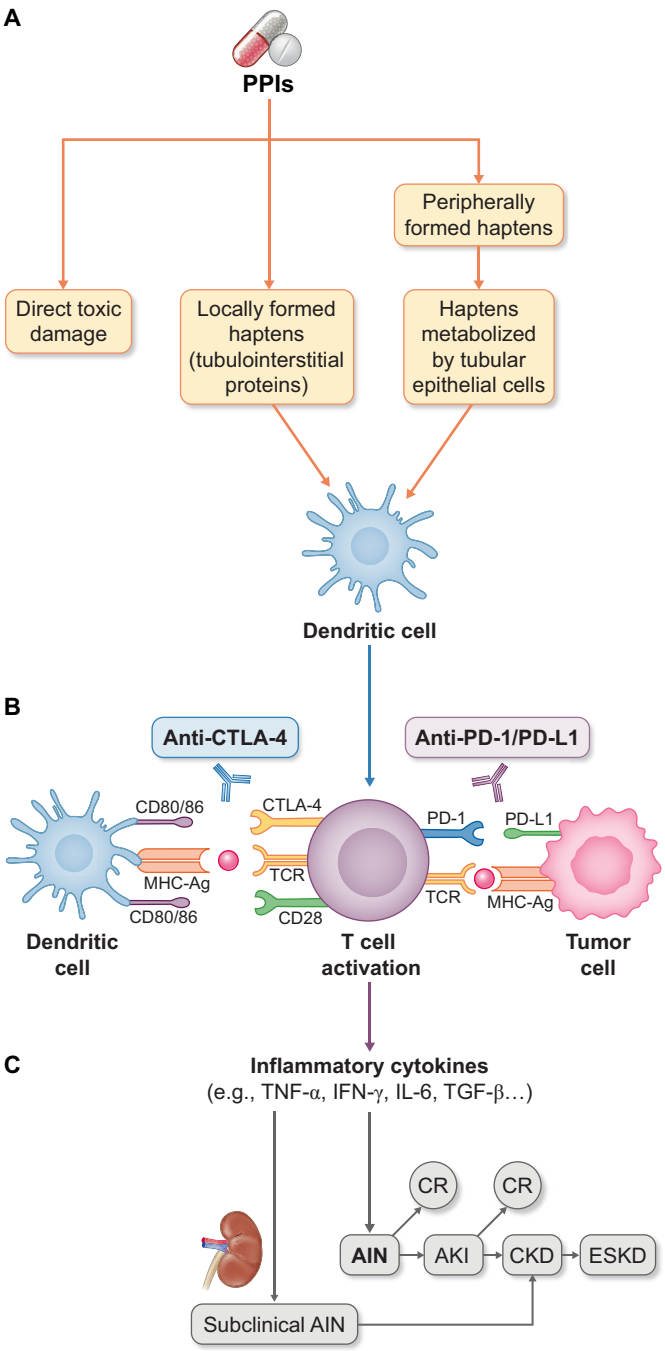

Figure 1: Proposed major pathophysiological mechanisms of PPI-related kidney adverse outcomes in the setting of ICI therapy. **(a)** In addition to the direct toxic damage, one of the most suggested mechanisms is that PPI may act as a hapten. In kidney, PPI can bind to kidney specific tubulointerstitial proteins. The peripherally drug-formed haptens are transported to kidney, and metabolized by tubular epithelial cells. The resultant antigen–antibody complex and/or metabolites are presented to dendritic cells located in kidney interstitial tissue, leading to subsequent T-cell-mediated immune response. **(b)** In the setting of ICI therapy, anti-CTLA-4 (i.e. ipilimumab) can induce T-cell activation mainly by blocking CD80/CD86 binding to the CTLA-4 receptor, which allows CD28 binding. Blocking PD-L1 binding to PD-1 with anti-PD-1 or anti-PD-L1 monoclonal antibodies (i.e. nivolumab and atezolizumab) promotes tumor cell killing but also activates T cells or suppresses deactivation of T cells. **(c)** Injured cells produce proinflammatory chemokines and cytokines, which can recruit inflammatory cells and induce fibroblast proliferation related to tubular cell damage (i.e. AIN or subclinical AIN) and further kidney injury (AKI, CKD, and ESKD). CTLA-4: cytotoxic T-lymphocyte–associated antigen 4; PD-1: programmed death 1; PD-L1: PD-ligand-1; CR: complete remission or recovery; EKSD: end-stage kidney disease.

cases, supported by the finding of deposits of antigen–antibody complexes in the kidneys [62]. Additionally, drugs can cause direct toxic damage to tubular cells. Similar to superantigen stimulations, some drugs may directly interact with the T-cell receptor or the major histocompatibility peptide complex, leading to T-cell activation [63]. Overall, injured cells produce proinflammatory chemokines and cytokines, which can recruit inflammatory cells and induce fibroblast proliferation, which

are thought to be related to tubular cell damage and kidney damage [37, 64].

Kidney histology

Kidney biopsy is generally required for the definitive diagnosis of AIN. Under a light microscope, it is generally characterized by extensive interstitial infiltration, mainly caused by monocytes and lymphocytes. Presence of eosinophils, plasma cells, and polymorphonuclear cells is of varying degrees. Glomerular and vascular parts are usually normal [42, 62]. The characteristics of chronic interstitial nephritis, such as interstitial fibrosis and tubular atrophy, can develop with the progression of the disease [42, 62]. Usually, immune deposits are not observed on immunofluorescence staining, but some cases can have fibrinogen deposits in interstitial tissue.

AIN is the most common histopathological finding in ICI-AKI. However, other patterns that occur either alone or in conjunction with AIN also have been described, including various glomerular diseases and acute tubular injury or acute tubular necrosis though with a low incidence of <10% of all cases [9]. Glomerular diseases reported in ICI-AKI have pauci-immune crescentic glomerulonephritis, anti-glomerular basement membrane disease, C3 glomerulonephritis, IgA and membranous nephropathy, and amyloid A amyloidosis [7, 8, 65]. Additionally, minimal change disease, focal segmental glomerulosclerosis (FSGS), lupus nephritis, and renal vasculitis after ICIs therapy have been reported in several case reports [66–68].

Regarding PPI-AIN, no specific histologic findings are detected. A study from Australian teaching hospitals, including 18 patients with biopsy-proven AIN, showed classic findings of AIN either with focal or with diffuse interstitial infiltrates. Kidney biopsy revealed presence of eosinophils in 83% (15 out of 18) of patients [49]. Kidney biopsies of patient with ICI-AIN have similar pattern, but may present with other findings such as FSGS, vasculitis, and, at times, granulomatous sarcoid-like lesions [36, 66, 69, 70].

In summary, the histopathological patterns of ICI-AIN can be heterogenous. Kidney biopsy is important and sometimes required in patients with a highly suspected ICI-AKI particularly in those who also take PPIs.

Clinical presentations

A multicenter study found that most patients with ICI-AKI presented with non-nephrotic proteinuria, almost half had sterile pyuria, and ~21% had eosinophilia [7]; a similar finding was reported by other studies [8, 65, 71], However, these clinical manifestations lack specificity and are not enough to distinguish the ICI-AKI from other causes including drugs (e.g. PPI)-related AKI.

PPI-related kidney adverse effects present with a wide spectrum of renal manifestations, ranging from subclinical kidney damage, AKI with a variety of severities, to delayed occurrence of incident CKD and ESKD. Regarding PPI-AIN, it has been reported that fever presents in less than half patients, rash in <10%, and eosinophilia in about one-third [28]. The classical triad of systemic hyperallergic reactions, composed of fever, rash, and eosinophilia, is rare and only presents in <10% of patients [72]. By contrast, a study showed that nonspecific symptoms were more common, including fatigue and nausea (39%, $n = 7/18$), and weight loss (22%, $n = 4/18$) [49]. Notably, many patients do not have or only present with mild symptoms. Similar to NSAIDs, patients with PPI-AIN less commonly have the classical triad compared to other drugs [62]. Nearly every drug-induced AIN presents with non-oliguric AKI, if AKI occurs [62]. Some cases present with hypokalemic and hyperchloremic metabolic acidosis, indicating that the tubulointerstitial tissue is the potential site of kidney damage [25, 62, 73]. Approximately 90% of patients with drug-induced AIN have tubular non-nephrotic level proteinuria, but a study suggested that older patients more likely had higher degree of proteinuria [74].

Additionally, the time from initiation of PPI use to development of clinical AIN is very variable. AIN related to antibiotics such as β-lactams and cephalosporins usually presents with a short interval (several days or weeks), but PPI- and NSAID-related AIN often have a longer drug exposure duration (PPIs, generally 1 week to 9 months; NSAIDs, 6–18 months) prior to AIN [62]. Rechallenge with a PPI in patients who previously had PPI-AIN may more rapidly develop a new AIN [75–77]. A case series study showed that within 12 hours of re-exposure to pantoprazole, a patient developed symptoms of another episode of AIN [16]. A population-based study in the Ontario region reported that 59% of patients with PPI-AIN discharged from hospital received a further prescription of a PPI; among these rechallenged patients, 7.5% were readmitted for AKI in the ensuing 120 days [14].

A study compared ICI-AIN to other drugs (e.g. NSAIDs, fluoroquinolones, β-lactams, and PPIs)-related AIN, and found that biopsy-proven ICI-AIN presented with a larger latency period after ICI initiation (197±185 vs 114 ± 352 days, $P = 0.006$), lower creatinine at diagnosis (3.8 ± 1.0 vs 6.0 ± 4.2 mg/dl, $P = 0.007$), and higher urinary leucocyte counts (263.2 ± 418.0 vs 133.6 ± 284.6, $P = 0.048$), as well as lower slope of decreasing creatinine over time during follow-up ($P = 0.023$, 0.014 and 0.004 at months 1, 3, and 6, respectively) [78]. However, among patients with other drugs-related AIN, most were on NSAIDs (19.4%) and only a small fraction (2.9%) were on PPIs, with no information about how many were on PPIs in the ICI group [78]. A multicenter study also showed a longer interval from ICI initiation to AKI, with a median 14 weeks (interquartile [IQR] 6–47 weeks) [7], similar to the findings from other studies [65, 71]. But it should be noted that ICI-AKI can occur at any time after ICI initiation, ranging from a couple of days to >10 weeks [7].

In summary, data about clinical features in patients with ICI-AKI, particularly in those who also take PPIs, remain limited and this needs to be further addressed.

Risk factors

Several studies have reported that PPI-AIN was more frequent in the elderly patients. The study from the Mayo Clinic showed that patients with PPI-AIN tended to be older compared with antibiotic- or NSAID-related AIN [41]. The New Zealand population-based nested case-control study suggested a 10-times greater risk for AIN in current PPI use ≥60 years compared to younger users aged 15–49 years (20 vs 2 per 100 000 patient-years) [17]. The Ontario population-based study of 290 592 individuals aged ≥65 years showed a three-times greater risk for AIN among elderly patients recently beginning PPI therapy compared to the propensity matched controls (0.32 vs 0.11 per 1000 person-years) [14]. A recent meta-analysis including nine studies showed that among 2.6 million patients enrolled, 20% were PPI users, and the PPI use significantly increased the risk of AIN (relative risk ratio, 3.61; 95% CI, 2.37–5.51) [79]. Additionally, PPI-AIN is far more common in hospitalized patients and in those with a burden of comorbid disease [37, 51]. Patients using high dose of PPI for prolonged duration may have a higher risk for AIN [38]. A longer drug exposure and longer delay in starting steroid therapy was correlated with poor recovery [41].

A prospective epidemiologic study using the Atherosclerosis Risk in Communities database in the USA suggested a 31% increase of the risk for PPI-AIN in patients taking twice-daily dosages of PPIs compared to a single daily dosage [34].

Notably, as a new cause of AIN, ICIs have attracted more and more attention [46, 62, 80]. Several risk factors have been reported to be related to ICI-AKI, including lower estimated glomerular filtration rate (eGFR) at baseline, combination therapy of ICIs, and co-presence of extrarenal irAEs, as well as other concomitant drug uses (e.g. NSAIDs, antibiotics, and PPIs) [4, 7, 8]. In particular, PPI use is a remarkable predictor for ICI-AKI. Two large retrospective studies suggested that PPI use caused a roughly 3-fold increase of the risk for ICI-AKI [4, 7]. Patients with recurrent AKI after ICI rechallenge often had a concomitant use of PPI [7, 46]. Regarding the interval between ICI initiation and AKI development, our study found that it was shorter in ICI-AKI patients compared with non-ICI-AKI patients undergoing ICI therapy (median 4 vs 8.5 months, $P = 0.026$) [36]. Patients with ICI-AKI had higher rates of PPI use within 14 days before AKI occurrence compared to those with non-ICI-AKI (68% vs 23%, $P = 0.009$). Similar to other reports [4], our results confirmed that PPI use was significantly associated with ICI-AKI. We also found that use of PPI or other AIN-associated drugs led to a more rapid onset of AKI [36], suggesting that when PPIs are prescribed at the initiation of ICI therapy, these patients should be followed particularly closely for AKI events; however, larger prospective studies are needed to validate this finding.

In summary, older age (>60 years), higher dosage, longer exposure, and concomitant use of kidney offending drugs (e.g. NSAIDs and antibiotics) are proposed risk factors for PPI-AIN in the setting of ICI therapy.

Diagnosis

As mentioned before, PPI-AIN lacks specific symptoms and signs for diagnosis. Most cases with AIN can have abnormal urinary analysis findings, such as hematuria, sterile pyuria, eosinophilia, and casts (e.g. white blood cell). The retrospective study from Australian teaching hospitals found that eosinophiluria and eosinophils in the interstitial tissue presented in 61% (11 out of 18) and 83% (15 out of 18) cases, respectively [49]. Whereas these are highly suggestive of AIN, they can only be used to support the diagnosis. Owing to the lack of specific clinical features and reliable noninvasive tests, kidney biopsy is generally required to make a diagnosis. The possibility of PPI-AIN or AKI should be considered in patients who are receiving PPI therapy and encounter a gradual rise in serum creatinine over weeks to months with no reasonable explanation. To prevent or avoid progression of PPI-AIN to CKD, it is important but also a great challenge for clinicians to diagnose subclinical AIN in a timely fashion, particularly in those with nonspecific manifestations or those without symptoms. Thus, a careful and detailed investigation of clinical presentation, medication history, and kidney function test is important in recognizing these patients. Kidney biopsy should be considered to make the diagnosis in patients with highly suspected AIN.

Recently, urinary TNF-α and IL-9 have been suggested as independent predictors of AIN. A study showed that patients with AIN had consistently higher levels of urine TNF-α and IL-9 than those with other kidney disease (e.g. acute tubular injury, glomerular diseases, and diabetic kidney disease). Compared to the clinician's prebiopsy suspicion of AIN, as well as available standard clinical tests, urinary TNF-α and IL-9 plus clinical tests remarkably improved AIN prediction model performance (area under the curve, 0.84 vs 0.62 vs 0.69, respectively) [81]. These findings have been validated more recently in a prospective pilot study showing that in patients with ICI-AIN, urine TNF-α was significantly elevated with a strong discriminatory ability [56]. Another study demonstrated that tertiary lymphoid structure signatures and urine chemokine markers can differentiate ICI-AIN from other cause-related AIN [82].

In addition, our recent study showed that at time of AKI diagnosis, compared to non-ICI-AKI, serum C-reactive protein (CRP) was increased in ICI-AKI patients (median [IQR] 54.0 [33.7, 90.0] vs 3.5 [3.0, 7.9] mg/L, $P < 0.001$), and urine retinol binding protein to urine creatinine ratio was also significantly elevated (median [IQR] 1927 [1174, 46 522] vs 233 [127, 989] μg/g creatinine, $P = 0.013$) in patients with ICI-AKI [36]. Furthermore, systemic soluble interleukin-2 receptor (sIL-2R) has been found to be elevated in patients with ICI-AIN compared to ICI-treated controls and hemodynamic AKI controls (median 2.5-fold upper limit of normal vs 0.8- and 0.9-fold, $P < 0.001$ and $P = 0.008$, respectively) [83]. In this study, a sIL-2R cut-off point of 1.75-fold-upper limit of normal was suggested to be maximal specificity (100%) and optimal sensitivity (81%) in differentiating ICI-AKI from ICI-treated controls and hemodynamic AKI controls [83]. However, sIL-2R did not differ significantly in ICI-treated patients with extrarenal irAE (such as pneumonitis and colitis), suggesting that another extrarenal inflammatory process may also increase its levels as it does with CRP. The diagnostic value of these noninvasive biomarkers in detecting ICI-AIN or AKI in particular in those with concomitant use of PPIs remains uncertain and needs be further investigated.

PPI and the risk of AKI, CKD and ESKD in the setting of ICI therapy

Data from the Ontario population-based study indicated a ~2.5-fold increase of AKI risk (13.49 vs 5.46 per 1000 person-years) among patients receiving PPIs compared to controls [14]. Just recently, data from the large post-marketing surveillance indicated that compared to the histamine H2-receptor antagonists (H2RAs), patients who received PPIs without other reported concurrent medications had a four-fold increase in the frequency of AKI (odds ratio [OR], 4.2; 95% CI, 2.8–6.3), and those who received the following PPIs as monotherapy also significantly increased the AKI frequency: lansoprazole (OR, 10.8; 95% CI, 7–17), omeprazole (OR 5.8; 95% CI, 3.8–8.9), esomeprazole (OR, 3.3; 95% CI, 2.2–5), and pantoprazole (OR, 1.8; 95% CI, 1.01–3.3) [84]. These findings strongly suggested that PPI use is a significant predictor for AKI.

In the setting of AIN, the acute inflammation and damage of the tubulointerstitial tissue may become chronic interstitial fibrosis and scar over time, particularly in those whose AIN diagnosis is missed or not recognized as subclinical AIN. Ultimately, chronic interstitial inflammation leads to CKD and kidney failure in some severe cases. The case series study from Australia, including 18 patients with biopsy-proven PPI-AIN, indicated that in most patients, renal function was recovered at least partially by 3 months after AIN diagnosis and PPI discontinuation. However, the eGFR remained significantly reduced both at 3 and 6 months after initial presentation when compared with the baseline, with a median reduction of 15.9 and 11.5 ml/min per 1.73 cm^2, respectively [49]. Another case series study including 15 patients with PPI-AIN observed that serum creatinine concentration was significantly higher (1.57 vs 0.94 mg/dl) at 3–18 months after PPI withdrawal than baseline [50]. Therefore, CKD development could be a long-term consequence of PPI use.

A cohort study including 173 321 new PPI users and 20 270 H2RAs new users, both with normal renal function at baseline, indicated that compared to H2RAs, PPI significantly increased the risk of incident CKD, doubling of serum creatinine level, eGFR decline >30%, and ESKD development by 28%–96% [32]. Consistently, a meta-analysis including five studies with 536 902 participants showed that compared to H2RAs, the risk of CKD development in PPI users was increased by 29% (pooled RR, 1.29; 95% CI, 1.22–1.36) [85]. Despite withdrawal of PPI and steroid therapy, it is possible that after AIN and/or AKI, residual CKD may be left in some patients. It is also possible that the development of CKD may result from subclinical or undiagnosed AIN. However, these studies excluded patients with eGFR <60 ml/min/1.73 m^2. Therefore, the effect of PPI use on CKD progression remains unknown in these populations. Recently, a graded association between cumulative PPI exposure and risk of CKD progression was revealed [86], suggesting that PPI use was significantly associated with high risk for both development and progression of CKD, and this association was more prominent in those taking high doses with long exposure.

Moreover, the population-based case-control study showed that PPI use increased the risk of ESKD by 88%, with the highest adjusted OR of esomeprazole (1.69; 95% CI, 1.45–1.98) and pantoprazole (1.63; 95% CI, 1.39–1.90), followed by rabeprazole (1.36; 95% CI, 1.02–1.81), lansoprazole (1.23; 95% CI, 1.09–1.4), and omeprazole (1.14; 95% CI, 1.02–1.26) [87]. A potential dose–response correlation was also detected between PPI use and risk for ESKD [87].

In the setting of ICI therapy, induction of subclinical AIN, ICI-induced immune activation causing accelerated progression of pre-existing kidney disease, or recurrent AKI episodes contribute to CKD progression. A recent large retrospective study showed that ICI-treated patients with rapid eGFR decline (1.4 vs 3.7 ml/min/1.73 m^2 per year average decline before vs after ICI, $P = 0.01$) was common, and new-onset CKD or significant (>30%) eGFR decline sustained for >90 days occurred in 20% of survivors who lived at least 5 years [88]. Moreover, age and use of PPIs were identified as important risk factors for new-onset CKD and sustained 30% eGFR decline, with an adjusted HR of 1.13 (95% CI 1.10–1.73) and 1.38 (95% CI 1.10–1.73, respectively [88]. In another study, the kidney function over time dropped significantly at 1 year follow-up from median (IQR) eGFR of 77.9 (62.6, 85.6) ml/min/1.73 m^2 at baseline before ICI therapy down to 57.1 (38.6, 69.9) ml/min/1.73 m^2 [36].

Overall, some observational studies including meta-analyses supported the association of PPI use with increased risks for AKI, incident CKD, CKD progression, and kidney failure, including among patients treated with ICI. But we should interpret this association cautiously as, currently, evidence from randomized controlled trials (RCTs) is lacking. The current evidence cannot demonstrate a strong causal relationship between PPI use and adverse kidney effects because the results could be affected by some confounding factors.

Management of AIN in the setting of PPI-ICI therapy

In the general population, current evidence suggests that initiation of and cumulative exposure to PPIs are associated with a risk of adverse renal outcomes. However, due to the uncertain causal relationship based on current evidence, no specific recommendations have been suggested for monitoring renal function in patients receiving particular long-term PPI therapy [89]. As for other drug-induced AIN, early recognition and diagnosis of PPI-AIN and discontinuation or dosage adjustment of PPI use in these cases are crucial for renal function recovery [42, 90, 91]. Current reports showed inconsistent results on treatment with corticosteroids (variable courses and doses) for PPI-AIN without ICI therapy [12, 92]. The benefits of corticosteroids treatment are only supported by case reports and small, retrospective studies. In a multicenter retrospective study of 61 patients with biopsy-proven drug-induced AIN (mostly on antibiotics and NSAIDs), serum creatinine was lower in those treated with steroids; therefore, prompt treatment after diagnosis of AIN would avoid subsequent interstitial fibrosis and an incomplete recovery of renal function [93]. The conclusive evidence supporting the therapeutic efficacy of corticosteroids remain lacking and RCTs are needed.

However, ICIs should be withheld in patients with ICI-AKI. PPI or any other AIN-related drugs should also be discontinued. Like PPI-AIN, there are no RCTs regarding the best treatment for ICI-AIN, but corticosteroids are considered the first line of treatment. The usual initial dose is 0.8–1 mg/kg/day for a period of 8–12 weeks, but shorter courses have been suggested [8, 46]. It has been shown that duration of corticosteroids of 28 days or less is safe and has similar efficacious compared to longer durations for patients with ICI-AKI [8]. However, these data require confirmation by larger studies and, ideally, RCTs that include patients with biopsy-proven ICI-AIN as a rebound of AIN can occur with a shorter duration of corticosteroid therapy. Until the association of PPI and ICI-AIN is better clarified, it is reasonable to monitor serum creatinine and/or eGFR with each ICI dose, based on CKD guidelines for monitoring patients taking medications with potential nephrotoxicity [89, 94]. Finally, rechallenge even with another PPI drug class is not suggested. PPI rechallenge may lead to another incident AIN, likely with a result of only partial recovery, then leaving a possibility of progression of kidney damage to advanced CKD. When necessary, it is suggested to switch to H2RAs. This is particularly important when PPI or another AIN-associated drug is used in the setting of rechallenge with ICI therapy [95].

CONCLUSION

Taken together, PPIs have been recognized and considered as one of the most frequent causes of drug-induced AIN, and PPI-related adverse kidney effects are potentially present, and we need be aware of them in practice even though current evidence is weak. The fact that AIN is the most common pathological finding in kidney biopsies of patients with ICI-AKI who also took PPI during ICI therapy provides further evidence. Currently, RCTs are lacking but are needed to consolidate a causal relationship between PPI use and its kidney adverse outcomes, including among patients receiving ICI therapy. Second, PPI-AIN has a lack of specific clinical manifestations or often presents with non-allergic symptoms. To prevent progression of PPI- AIN to CKD and kidney failure, it is important but also a great challenge for clinicians to quickly diagnose and recognize the subclinical AIN. Kidney biopsy should be considered in patients with highly suspected AIN, especially during ICI therapy, as its interruption may affect patient outcomes. Reliable noninvasive biomarkers are needed to help diagnosis of AIN in patients who cannot undergo a kidney biopsy, but their accessibility and validity may be limited. Third, at present no specific recommendations are proposed for treatment and management of PPI- AIN, but it is important to review the need for PPIs and to discontinue and/or make dose adjustment in every patient. Therapeutic effects with steroids are clear in patients with ICI-AIN, but duration still needs be investigated. Finally, rechallenge, even

with another PPI, is not suggested in those who have had an episode of PPI-AIN.

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CONFLICT OF INTEREST STATEMENT

All the other authors report no relevant disclosures.

DATA AVAILABILITY STATEMENT

No new data were generated or analyzed in support of this research.

(See related article by Tan and Sprangers. Proton pump inhibitors and adverse kidney outcomes during immune checkpoint blockade: time to sound the alarm? *Clin Kidney J* (2023) 16: 1709–1713.)

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