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FULL REVIEW

Renal effects of immune checkpoint inhibitors

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ABSTRACT

Recent advances in immune checkpoint inhibitor (ICPI) development have led to major improvements in oncology patient outcomes. Cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) are two essential immune checkpoint receptors. Ipilimumab and tremelimumab (anti-CTLA-4-blocking antibodies) and pembrolizumab and nivolumab (antibodies targeting PD-1 receptors) have already been approved by US Food and Drug Administration in several malignancies. Two different forms of ICPI-induced renal damage have been identified, including acute (granulomatous) tubulointerstitial nephritis and immune complex glomerulonephritis. The observed acute renal damage can be reversed upon ICPI drug discontinuation and renal function can recover back to normal following the introduction of systemic corticosteroid treatment. Any delay in treating this complication could result in definitive and irreversible renal injury.

Keywords: checkpoint blockade, immunotherapy, ipilimumab, nivolumab, pembrolizumab

Immunotherapy has long been part of the standard treatment for early-stage cancers. The most well-known treatments include the intravesical bacillus Calmette–Guérin vaccine for non-muscle-invasive bladder cancer and topical imiquimod for superficial basal and squamous cell skin carcinomas. In addition, high-dose interleukin-2 can also be used for the metastatic stage in renal cell carcinoma and melanoma [1–3].

Over the past decade, the ability of cancer cells to evade immune destruction has been recognized as one of the hallmarks of tumour pathogenesis [4]. This understanding has favoured the development of novel therapeutic agents that can activate anti-tumour immune responses or reverse immunosuppressive mechanisms through which tumours escape immune-mediated rejection [4].

Nowadays, blockade of immune checkpoints has been identified as the most effective immunotherapy approach used to

Table 1. Current available immune checkpoint inhibitors

Agent	Class/clinical trial phase	Target	Indications
Currently FDA-approved immune checkpoint inhibitors			
Ipilimumab	IgG1, human	CTLA-4	Unresectable or metastatic melanoma
Pembrolizumab	IgG4, humanized	PD-1	Unresectable or metastatic melanoma[a]
Nivolumab	IgG4, human	PD-1	Unresectable or metastatic melanoma[a] Advanced NSCLC in PD-L1$^+$ tumours[b] BRAF V600 wild-type unresectable or metastatic melanoma in combination with ipilimumab Metastatic squamous and non-squamous NSCLC after failure of first-line platinum-based chemotherapy
New immune checkpoint inhibitors in the clinical pipeline			
Tremelimumab	Phase III	CTLA-4	Advanced melanoma
	Phase II		Mesothelioma
Pidilizumab	Phase II	PD-1	Haematologic or solid cancers
MPDL3280A	Phase III	PD-L1	NSCLC, urothelial bladder cancer
MEDI4736	Phase III	PD-L1	NSCLC, melanoma
Elotuzumab	Phase III	IDO-1	Multiple myeloma
INCB024360	Phase II	IDO-1	Solid cancers
Indoximod	Phase II	IDO-1	Breast cancer
Lirilumab	Phase II	KIR	Haematologic or solid cancers
IMP321	Phase II	LAG-3	Melanoma

[a]After failure of ipilimumab and, if BRAF V600 mutant-positive, failure of BRAF inhibitor therapy.
[b]After failure of first-line platinum-based chemotherapy and also, if epidermal growth factor receptor or anaplastic lymphoma kinase aberrations exist, after failure of agents targeting these pathways.
CTLA-4, cytotoxic lymphocyte-associated protein 4; FDA, US Food and Drug Administration; IDO-1, indoleamine 2,3-dioxygenase 1; Ig, immunoglobulin; KIR, killer cell immunoglobulin-like receptor; LAG-3: lymphocyte activation gene 3; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1.

fight cancer tolerance through the physiological downregulation of immune responses. Development of these antibodies, known collectively as immune checkpoint inhibitors (ICPIs), has contributed considerably to the improvement of patient outcomes in several malignancies (Table 1) [5, 6]. The potent activity of ICPIs results in inflammatory manifestations characterized as immune-related adverse events (irAEs) reported in a majority of patients receiving ipilimumab or pembrolizumab or nivolumab. Less than 20% of these patients experienced significant side effects (grades 3–5) [5, 7, 8].

In the present work, we review the renal adverse events (AEs) reported in patients receiving ICPIs.

CHECKPOINT SYSTEM AND IMMUNE CHECKPOINT BLOCKADE

The immune system plays a critical role in the control and eradication of cancer cells. The anti-tumour immune response, driven by T-lymphocytes, is tightly regulated through a complex and delicate balance between inhibitory checkpoints and activating signals [9–12].

Cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) are two important immune checkpoint receptors that belong to the immunoglobulin superfamily; their ligands are CD80/CD86 B7 and programmed cell death ligand 1 (PD-L1), respectively. Following binding of the receptors to their specific ligands, T-cell effectors are downregulated, leading to tumour cell tolerance.

CTLA-4 (also known as CD152) is expressed on the surface of T cells and plays a critical role in the maintenance of immunologic homeostasis. Mice genetically deficient in CTLA-4 develop a rapidly progressive, fatal lymphoproliferative disease, characterized by multiorgan T-cell infiltration, and die after only 3–4 weeks of life [13, 14]. CTLA-4 activation induces immune tolerance [15] by turning down CD4$^+$ T-helper cell activity and turning up CD4$^+$ T-regulatory (Treg) cell function [16]. The T-cell surface receptor PD-1 inhibits T-cell function upon binding to its ligands PD-L1 and PD-L2 [17]. PD-L1 is expressed on T cells, B cells, natural killer cells, dendritic cells, monocytes/macrophages, mast cells, and various tumour tissues where it is thought to play a role in tumour immune escape [18]. PD-1 expression is seen on T cells and some other immune cells specifically within the tumour microenvironment and various tumour tissues where it is thought to play a role in tumour immune escape [18].

CTLA-4 plays a significant role in early immune response, primarily occurring in lymphoid tissues, while PD-1, whose expression is upregulated after T-cell activation in peripheral tissues, is more involved in late immune response [19]. Blockade of these pathways by anti-CTLA-4, anti-PD-1 or anti-PD-L1 antibodies allows T cells to maintain their anti-tumour property and their ability to mediate tumour cell death [5, 6, 19].

Two CTLA-4-blocking antibodies are currently under clinical investigation—ipilimumab and tremelimumab [20, 21]. Ipilimumab (Yervoy®; Bristol-Myers Squibb, Princeton, NJ, USA) is a human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) targeting the co-inhibitory receptor CTLA-4, which is overexpressed in many cancers [5, 22, 23]. Ipilimumab obtained US Food and Drug Administration approval in 2010 for treating patients with metastatic or surgically unresectable melanoma lesions, following promising data emerged from

Table 2. Selected immune-related adverse event rates (%) associated with immune checkpoint inhibitors in advanced melanoma [8, 32, 33, 43]

	Ipilimumab (3 mg/kg 3 times weekly)		Nivolumab (3 mg/kg twice weekly)		Pembrolizumab (2 mg/kg twice and 3 times weekly)	
NCI CTC grade	All	3/4	All	3/4	All	3/4
Skin disorders	42–60	1–2	30–52	1–2	26–36	0
Gastrointestinal disorders	31–45	10–15	12–19	0–3	16–21	3–6
Pneumonitis	0–2	<1	1–2	<1	<1	<1
Endocrine disorders	5–10	3	7–13	<1	13–17	<1
Hepatitis	1–7	0–2	3–6	2–3	1–2	1–2
Renal and urinary disorders	<1	<1	1	<1	1	0

clinical studies that demonstrated an increase in overall survival from 6.4 to 10 months [6] and durable responses longer than 30 months in about 20% of the treated population [24, 25]. Subsequently, ipilimumab and tremelimumab have shown promising results in phase I–III clinical trials in several other cancer types [26].

Both pembrolizumab (Keytruda®; Merck & Co., Inc., Whitehouse Station, NJ, USA) and nivolumab (Opdivo®; Bristol-Myers Squibb) are two approved IgG4-k mAb targeting PD-1 receptors expressed on T cells, resulting in disinhibition of tumour-specific immune responses [27, 28]. More recently, anti-PD-1 and anti-PD-L1 mAbs have shown unprecedented rates of durable clinical responses, with a response rate from 10 to 45% in a non-preselected group of patients diagnosed with advanced solid tumours [29–31]. Their efficacy reaches around 40% in some melanoma studies [32, 33] and in selected patients with bladder cancer [34]. Positive results may reach up to 20% in non-small-cell lung cancer (NSCLC) [35, 36], renal cell carcinoma and diffuse large B-cell lymphoma [30, 37].

Toxicities associated with ICPIs are related to their immunologic effects, termed irAEs [38]. These irAEs affect over two-thirds of patients (Table 2) [38–42]. Based on results of published trials using the National Cancer Institute CTCAE to classify irAEs, PD-1 blockade appears to be better tolerated and has a lower frequency of irAEs than CTLA-4 blockade [28].

The most common irAEs (Table 2) [38–42] are fatigue and dermatologic toxicities, which manifest early on, followed by endocrinopathies (thyroid dysfunction). Other rare irAEs that have been reported include uveitis, pancreatitis, neuropathies, pneumonitis, myocarditis and renal disorders.

Renal irAEs

To assess the incidence and nature of renal irAEs in oncology patients receiving ICPIs, a systematic search of literature up to January 2016 was performed. Kidney injury can be divided into creatinine impairment and renal parenchymal damages.

CREATININE LEVEL IMPAIRMENT

Renal involvement remains rare and elevated creatinine is uncommon (0–4%) [33, 36, 43–48].

In a retrospective study summarizing unexpected and rare ipilimumab-induced AEs, only two cases of acute kidney injury (AKI) out of 120 patients were reported [49]. The time taken to develop renal impairment appeared to vary from 6 to 12 weeks. Renal failure was preceded by, or accompanied by, a rash in half of the cases [50].

The highest rate of renal impairment that has been reported was 4% in a phase II lung cancer trial, in which patients were treated with nivolumab 3 mg/kg every two weeks (q2w) [36, 45], but no higher-grade events have been reported. In patients treated with pembrolizumab 2 mg/kg every three weeks (q3w), 10 mg/kg q3w and 10 mg/kg q2w, all grades of renal and urinary disorders were reported in <1, 1.4 and 3% of the study population, respectively [51]. The onset median time of renal-selected events is highly variable, ranging from 6 [52] to 10.5 weeks [53], and up to 30 weeks for the different pembrolizumab regimens [54]. The resolution time-frame of grade 3–4 renal AEs is 4.7 weeks (3–6 weeks) [48]. The resolution median time of renal-selected events in nivolumab pivotal trials in squamous NSCLC is 5.9 weeks, ranging from 0.7 to 37.6 weeks. Based on pooled pivotal studies [51, 55, 56], renal events were resolved in 71, 61 and 100% of affected patients on nivolumab 3 mg/kg q2w (melanoma, CA209017/-063) [51, 53, 56], nivolumab 3 mg/kg q2w (sq NSCLC, CA209037/-066) [52, 55] and pembrolizumab (melanoma, all regimen P001/-002) [51, 54], respectively. From 3695 patients treated with ICPIs and in phase II/III clinical trials, Cortazar *et al.* [57] estimated an overall incidence of AKI of 2.2%, with severe or grade III/IV AKI incidence of 0.6%.

Therefore, increased creatinine values must be recognized because renal failure is the most common renal event in clinical practice and it is a biomarker of distinct pathological mechanisms.

RENAL PARENCHYMAL DAMAGES

Two different forms of ICPI-induced renal parenchymal damage have been reported thus far: acute (granulomatous) tubulointerstitial nephritis (ATIN) and immune complex glomerulonephritis (Table 3). Taken together, these reports confirm that ICPIs are associated with immune renal injury. This highlights the requirement of renal biopsy for patients with renal failure and/or nephrotic-range proteinuria and treated with ICPIs. Early detection of this condition is vital, so steroid treatment can be initiated as soon as possible to obtain a complete recovery of renal function [23].

ATIN

Acute interstitial nephritis induced by ICPIs is related to severe inflammatory cell infiltrates with or without granuloma.

Table 3. Renal adverse events associated with ICPIs

References	Onset (week after starting ICPI)	Renal presentation	Kidney biopsy	Treatment	Outcome
Case reports					
Anti-CTLA-4					
Beck *et al.* [39]	NA	Nephritis	Not performed	Steroid	NA
Fadel *et al.* [58]	6	NS	Lupus MN	Steroid	Resolved at 12 months
Forde *et al.* [59]	12	Oliguric AKI	Not performed	Steroid	Resolved at 1 week (SCr from 4.75 to 0.7 mg/dL)
Voskens *et al.* [49]	8	AKI	Not performed	Steroid	Resolved
Izzedine *et al.* [50]	6	AKI	Granulomatous AIN	Steroid	Resolved
	6	AKI	Granulomatous AIN	Steroid	Resolved
Anti-PD-1					
Vandiver *et al.* [60]	48 h after initial infusion	AKI	Not performed	Steroid	Resolved within 3 days (SCr from 1.94 to 0.9 mg/dL)
Combination (ipilimumab + nivolumab)					
Murakami *et al.* [61]	3	AKI	AIN	Steroid + MMF	No RF improvement. Fatal septic shock
Case series					
Cortazar *et al.* [57] Ipilimumab, 6 pts Nivolumab, 1 pt Pembrolizumab, 2 pts Combination, 4 pts	3–35	AKI, 13 pts Oliguric AKI, 2 pts HT, 2 pts Pyuria, 8 pts Low-grade Pu, 9 pts	12/13: AIN (three with granuloma formation) 1/13: TMA	Steroid, 10 pts No steroid, 2 pts (ipilimumab)	Complete RF improvement, 2 pts Partial RF improvement, 7 pts Acute HD, 4 pts; chronic HD, 2 pts No improvement in RF
Shirali *et al.* [62] Nivolumab, 4 pts Pembrolizumab, 2 pts	12–72	AKI, 6 pts Leukocyturia, 2 pts Low-grade Pu, 2 pts	Diffuse (3 pts) or focal (3 pts) AIN without granuloma formation	Steroid, 5 pts	Complete RF improvement No patient required haemodialysis Recurrent AKI following ICPI rechallenge

AIN, acute interstitial nephritis; CTLA-4, cytotoxic T-lymphocyte antigen 4; HD, haemodialysis; HT, hypertension; ICPI, immune checkpoint inhibitor; MMF, mycophenolate mofetil; MN, membranous nephropathy; NA, not available; NS, nephrotic syndrome; PD-1, programmed cell death protein 1; pt(s): patient(s); Pu, proteinuria; RF, renal function; SCr, serum creatinine; TMA, thrombotic microangiopathy.

The mechanism of injury is assumed to involve cell-mediated immunity.

Previous literature review revealed five cases in patients with metastatic melanoma treated with ipilimumab 3 mg or 10 mg/kg [39, 49, 58, 59] and one non-biopsy-proven case with nivolumab 3 mg/kg [60]. Renal disease manifested as AKI related to acute interstitial nephritis (two with granuloma formation) associated or not with acute tubular necrosis. The development time for renal parenchymal abnormalities appeared to vary from 6 to 12 weeks. Treatment consisted of discontinuing the attributable drugs and initiating corticosteroids. Interestingly, patients fully recovered without fatal outcomes, relapses and chronic renal failure. It has been shown that, despite immunosuppressive effects of corticosteroid therapy, the anti-tumour response to ipilimumab did not decrease [63] . Regarding nivolumab, the reported case is a 58-year-old woman with stage IV metastatic melanoma, who presented with severe hyponatraemia (117 mmol/L) and AKI (serum creatinine 2.48 mg/dL) following an initial infusion of nivolumab 3 mg/kg [60]. The obtained diagnosis was immune nephritis (kidney biopsy not performed) secondary to nivolumab administration and the patient was treated with prednisone (50 mg orally twice daily). After 2 weeks of steroids, serum creatinine normalized to 0.91 mg/dL and sodium levels increased to nearly 134 mEq/L [60]. One patient (unpublished personal case) experienced AKI (creatinine 300 µmol/L) due to acute granulomatous interstitial nephritis, which occurred after 18 months of treatment with pembrolizumab 10 mg/kg/21 days for metastatic melanoma and fluindione for venous thrombosis. Kidney function recovered back to normal following the interruption of both molecules associated with corticosteroid treatment.

Recently, two clinical reports of ipilimumab-, nivolumab- and pembrolizumab-related adverse renal effects have been reported [58, 63]. Based on a listing of 13 patients who reported ICPI-induced AKI, described by Cortazar *et al.* [57], the median time for AKI development was 3 months (21–245 days). Renal features included pyuria in eight patients, low-grade proteinuria (median 0.48 g/g; 0.12–0.98 g/g) and median peak serum creatinine 4.5 mg/dL (3.6–7.3 mg/dL). AKI events (4.9%) were more commonly observed in patients on combined ICPI therapy, compared with those on ICPI monotherapy (ipilimumab 2.0%, nivolumab 1.9% and pembrolizumab 1.4%). ATIN was observed in 12 patients (three with granuloma formation and one with thrombotic microangiopathy). Among the 12 patients with ATIN, glucocorticoid treatment of 10 patients resulted in a complete (2 patients) or partial (7 patients) recovery of renal function. Four patients required haemodialysis despite treatment with glucocorticoids, of whom only two required chronic dialysis. No improvement in renal function was seen in the remaining two patients with ATIN, who did not receive glucocorticoid treatment.

Shirali *et al.* [62] reported six cases of biopsy-proven ATIN developed between 3 and 18 months following therapy with nivolumab and pembrolizumab for lung cancer. Similar to the

observations described by Cortazar *et al.* [57], renal function improved back to baseline level following discontinuation of the ICPIs and potential co-offending drugs, combined with the introduction of steroid treatment in five out of six patients. No patient required haemodialysis. One patient developed recurrent AKI following ICPI rechallenge [62].

Murakami *et al.* [61] described the first case of biopsy-proven severe ATIN following two doses of combined nivolumab and ipilimumab therapy. Unlike previous cases where patients responded well to steroid therapy, this patient relapsed 2 weeks after steroid therapy had been started, despite high doses being used, and subsequently the patient developed fatal septic shock.

Finally, a trial in melanoma patients treated with ICPIs identified that, based on autopsy results, four of the 12 treated patients developed interstitial nephritis, including one patient with granuloma [64].

These studies highlight the variable, and often prolonged, time course between drug exposure [2 weeks to 8 months; and, in some cases, extending beyond drug cessation (2 months)] and the development of renal injury [48, 50, 58, 61, 62]. Immunosuppressive treatment, often initially using steroids, without discontinuing the immunotherapy agent has been suggested by a few authors for cases of mild irAEs [65].

It is believed that cell-mediated immunity is implicated in the mechanism of renal injury. ICPI therapy may promote, via speculative aberrant pathways listed below, a permissive environment for the migration of T-cell effector(s) into the kidneys, thus initiating an inflammatory response that could clinically lead to ATIN [66].

(i) ICPIs may reactivate exhausted drug-specific T cells previously primed by nephritogenic drugs, and consequently, due to loss of tolerance, memory T cells are activated against the drug. It is noteworthy that 14 out of the 19 patients reported by Cortazar *et al.* [57] and Shirali *et al.* [62] were on culprit drugs associated with ATIN (proton pump inhibitors and non-steroidal anti-inflammatory drugs) [65]. Alternatively, ICPIs could synergistically potentiate antigen recognition and T-cell proliferation at lymph nodes and provoke untethered cytotoxic T-cell effects in the periphery, not only against the tumour, but also against normal tissues [61].

(ii) PD-1 checkpoint knockout mice developed glomerulonephritis, thus supporting the importance of PD-1 signalling in minimizing T-cell-mediated renal inflammation [67].

Lupus-like immune complex glomerulonephritis

One patient with nephrotic syndrome and preserved renal function on treatment with ipilimumab (for melanoma) [58] has been reported. The time taken for nephrotic syndrome to develop varied from 6 to 12 weeks. Treatment consisted of stopping the toxic drug and initiating corticosteroids. Again, the patient fully recovered, without fatal outcomes, relapses or chronic renal failure. A renal biopsy revealed lupus-related membranous nephropathy with both circulating anti-double-stranded DNA antibodies and glomerular IgG, C3 and C1q deposits [58]. Mice treated with anti-CTLA-4 antibodies also displayed similar results [68]. The pathogenesis of this adverse reaction may involve $CD25^{+}CD4^{+}$ Treg cells. Indeed, Treg cells express high levels of membranous CTLA-4, and both mice and patients with IPEX (immune dysfunction, polyendocrinopathy, enteropathy and X-linked inheritance) syndrome lacking Treg cells have shown autoimmune disease [69–71]. Moreover, CTLA-4-specific autoantibodies have been found in sera of patients with various autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, Behçet's disease and Sjögren's syndrome [72]. Future CTLA-4 polymorphism studies in patients on ipilimumab treatment are necessary to address this question.

SUGGESTED MANAGEMENT OF IMMUNE-RELATED RENAL TOXICITIES

Based on data from a small number of patients, we propose the following recommendations:

(i) In most cases, early detection of these reversible events is key to successful management:
  (a) In the case of a grade 1 renal event, the physician can continue the treatment under strict (twice weekly) monitoring of creatinine values, while promoting hydration and cessation of nephrotoxic drugs (i.e. aminoglycosides, contrast agents, etc.).
  (b) If the renal function has worsened to grade 2–3 renal toxicity, treatment should be postponed until creatinine values decrease to at least grade 1, and a renal biopsy should be performed. Prednisolone 0.5–1 mg/kg daily should be given.
  (c) If the renal function has worsened to grade 4 renal toxicity, treatment must be stopped, a renal biopsy performed and methylprednisolone dosed at 1–2 mg/kg daily should be given.

(ii) The use of glucocorticoids is the mainstay of irAE treatment. Overall, prognosis is excellent and *restitutio ad integrum* is the most common outcome [38]. Steroids should be reduced carefully over a month at least. In case of persistence, additional immunosuppressive regimens should be considered [48]. As a rescue option in situations where symptoms continue to worsen despite the introduction of steroid therapy.

(iii) For non-renal AEs, non-steroidal immunosuppressants may serve as a rescue option in situations where symptoms continue to get worse despite the introduction of steroid treatment (e.g. infliximab in colitis) [48]. It is noteworthy that, after the occurrence of an irAE, ICPI therapy may be delayed or even stopped in certain situations [48]. After resolution of the events or their improvement, a rechallenge with ICPI treatment should be proposed, whenever possible, due to their impressive clinical activity [48]. Overall survival, response rate and the median time to disease response or to disease progression were not affected by irAEs or treatment with systemic glucocorticoids of patients on ipilimumab [73, 74] or nivolumab [75].

CONCLUSIONS

Due to increased interest in ICPI treatment, clinicians should be aware of the potentially severe dual renal complications. Even though the vast majority of cases are acute interstitial nephritis, clinicians should keep in mind the possibility of an immune complex glomerulonephritis as a complication of these treatments, especially in the presence of glomerular proteinuria. It is important to continue reporting all cases using a register, to obtain more robust data that will allow estimation of ICPI-associated AKI incidence and to determine the best approach of diagnosis and treatment of ICPI-induced AKI. Early detection and close clinical renal monitoring are essential for successful management.

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CONFLICT OF INTEREST STATEMENT

None declared.

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