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BRIEF REPORT

Infliximab for the treatment of patients with checkpoint inhibitor–associated acute tubular interstitial nephritis

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ABSTRACT

Acute tubular interstitial nephritis (ATIN) is the most frequently reported pathology in patients with checkpoint inhibitor (CPI) induced acute kidney injury (AKI). Glucocorticoid (GC) therapy and discontinuation of CPI are the mainstay of treatment to prevent permanent renal dysfunction and dialysis. However, less than 50% of patients have complete kidney recovery and relapse of ATIN can occur. Infliximab is effective in treating other immune-related adverse events but its use for the treatment of CPI-ATIN is not well established. We report the first retrospective study examining the steroid-sparing potential of infliximab in achieving durable and complete renal recovery for patients with CPI-ATIN. Data were collected from medical records of patients diagnosed with CPI-AKI with a kidney biopsy or clinical diagnosis of ATIN that was managed with GC and infliximab. Infliximab-containing regimens were used to treat 10 patients with CPI-ATIN. Four patients relapsing after GC therapy achieved durable and complete renal recovery, four patients experienced partial renal recovery, and two patients showed no improvement in kidney function. This is the first study evaluating clinical outcomes using an infliximab-containing regimen for treatment of relapsed CPI-ATIN in patients or patients failing to achieve complete response after primary therapy. Our data suggest that infliximab may be a treatment option for achieving durable and complete renal recovery in this patient population and represents a potential steroid-sparing strategy in challenging cases of CPI-ATIN. Rigorous clinical studies are warranted to evaluate the risk-benefit analysis for infliximab usage in CPI-ATIN patients.

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Background

The most frequently described histopathological finding in checkpoint inhibitor (CPI) induced acute kidney injury (AKI) is acute tubular interstitial nephritis (ATIN).[1,2] Histologically, ATIN is characterized by the presence of inflammatory infiltrates within the renal cortical interstitium. Without prompt diagnosis and effective treatment, the inflammatory milieu triggers destructive fibrogenesis and consequently, permanent loss of kidney function. Progression to chronic kidney disease is a common consequence of ATIN,[3,4] and in patients with cancer, worsening kidney function can delay or limit cancer treatment. Discontinuation of the potential offending agent(s) and initiation of glucocorticoids (GC) are the mainstay of CPI-associated ATIN management.

Guidelines on GC therapy for CPI-ATIN are vague and treatment can last for months. Less than 50% of patients with ATIN will have complete recovery of kidney function.[2] In those with partial or no recovery of kidney function, there is no recommendation for additional treatment. Relapse of ATIN is also a challenge and associated with worse kidney prognosis.[5] Limited data on the use of steroid-sparing agents (i.e., mycophenolate mofetil or cyclosporin) in cases of steroid-resistant, drug-induced ATIN were successful but pose considerable challenges in cancer patients due to the associated risk of cancer progression and T cell suppression.[6,7] In cases of

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relapsed CPI-ATIN, GC are frequently re-dosed or reinitiated. Steroid-sparing agents (SSA) that can be used in lieu of or in conjunction with GC to facilitate durable renal recovery are desperately needed for patients with cancer.

Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine that mediates certain systemic inflammatory diseases. TNF-α has also been implicated in the etiology and responsiveness to treatment in CPI-induced irAEs including immune-related enterocolitis (irEC),[8] sarcoidosis-like reactions,[9] and severe arthritis.[10] The use of infliximab, a monoclonal antibody targeting TNF-α for treatment of ATIN is not considered a standard of care and has not previously been reported. Here we conducted the first retrospective review and report the clinical outcomes of infliximab treatment in a cohort of 10 patients with relapsed CPI-ATIN or as salvage therapy in previously treated CPI-ATIN patients with partial or no kidney recovery.

Material and methods

We retrospectively reviewed the medical records of all patients who received CPI treatment, developed AKI, and had a diagnostic kidney biopsy at The University of Texas MD Anderson Cancer Center (MDACC) from 2016 to 2020 (Supplemental Table 1). This retrospective study was approved by the MDACC Institutional Review Board in accordance with the Declaration of Helsinki. We identified 85 cases who had AKI from 2016 to 2020. Eight cases had biopsy-proven ATIN treated with GC (equivalent prednisone dose of at least 0.5 mg/kg) and infliximab (5 mg/kg). We collected two additional cases with presumed CPI-associated ATIN. Due to the high-risk potential for renal hemorrhage, kidney biopsy was deferred in two cases (Case 3 and 10). The patient in Case 3 had a solitary kidney and on anticoagulation (clopidogrel and aspirin) for a recent transient ischemic attack. The patient in Case 10 had a history of polycystic kidney disease. For all cases, we collected the following information: age, sex, cancer diagnosis, name and class of CPI, potential nephrotoxic medications, serum creatinine at baseline and during AKI, date of last follow-up, urine sediment, proteinuria, serological markers, kidney pathology findings, infliximab adverse effects, and tumor status.

All patients received either programmed cell death protein 1 (PD-1) inhibitors: pembrolizumab or nivolumab, programmed death-ligand 1 (PD-L1) inhibitors: atezolizumab or durvalumab or combined PD-1 with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors: ipilimumab. Dosing regimens were as follows: pembrolizumab 200 mg every 3 weeks, nivolumab 480 mg every 4 weeks or 1–3 mg/kg every 3 weeks, atezolizumab 1200 mg every 3 weeks or 840 mg every 2 weeks, durvalumab 10 mg/kg every 2 weeks, and ipilimumab 1–3 mg/kg every 3 weeks.

We defined AKI using Kidney Disease: Improving Global Outcomes (KDIGO) classification guidelines (increase in serum creatinine ≥0.3 mg/dL within 48 hours or ≥50% of baseline within 7 days).[11] Complete kidney function recovery was defined as post-AKI improvement in creatinine level to <0.35 mg/dL above baseline. Partial recovery was defined as creatinine level >0.35 mg/dL to less than the peak creatinine at the time of AKI diagnosis (based on at least two measurements). Each patient's kidney function was followed for at least 3 months after AKI diagnosis before determining kidney recovery status as complete, partial, or no recovery. One exception was made for Case 6, as the decision to transition to hospice was made 4 weeks after CPI-AKI diagnosis.

Relapsed CPI-ATIN was defined as AKI that occurred after completion of GC therapy or during GC taper that was attributed to ATIN, excluding other potential secondary causes of kidney impairment. A repeat kidney biopsy was obtained if the relapse could have been attributed to an etiology other than ATIN. Repeat kidney biopsies were obtained for Case 8 and 9.

Case summaries

Herein we present individual case patient histories aggregated by kidney functional outcome followed by a summary of findings.

Cases with complete kidney recovery:

Case 1

A 69-year-old White female with stage III breast cancer receiving nanoparticle albumin-bound (nab)-paclitaxel and atezolizumab (anti-PD-L1 monocolonal antibody) presented with fevers and was found to have AKI with a serum creatinine (Cr) level of 4.03 mg/dL (baseline Cr 0.70 mg/dL) (Figure 1a). Urinalysis was notable for hematuria, pyuria, and albuminuria (Tables 1 and 2). Her creatinine peaked at 7.47 mg/dL and she was initiated on dialysis. Kidney biopsy revealed ATIN, focal tubular microabscesses, tubulitis (Figure 2a and b), and acute tubular injury (ATI). Her creatinine rapidly improved to 1.09 mg/dL with GC therapy. One week after therapy completion, her AKI recurred (Cr 5.70 mg/dL) accompanied by pyuria (>182WBC/HPF). Serum cytokine levels revealed a tumor necrosis factor-alpha (TNF-α) of 136 pg/mL (Ref: 0–22 pg/mL). Due to this recurrence of CPI-ATIN, she was reinitiated on a short 2-week course of prednisone, and infliximab was added this time; her creatinine responded quickly and fell to 1.09 mg/dL. Her creatinine has remained stable at 1.05 mg/dL 5 months post infliximab infusion. She has had a complete pathologic response with no residual cancer.

Case 2

A 67-year-old White male with a history of stage IV metastatic melanoma receiving combination therapy with ipilimumab (anti-CTLA4) and pembrolizumab (anti-PD1) was admitted for altered mental status and AKI. He was diagnosed with CPI-induced autoimmune encephalitis and methylprednisolone 1 g IV daily was initiated. His serum creatinine peaked at 3.54 mg/dL (baseline 0.93 g/dL). No biopsy was obtained since his creatinine had improved. Two weeks after he completed a five-week course of GC treatment, he again recurred with AKI, Cr 2.26 mg/dL (from Cr 1.01 mg/dL). Kidney biopsy confirmed ATIN with focal non-caseating granuloma (negative for acid-fast and fungal stains) (Figure 2c) and ATI (acute tubular injury). Due to relapsed CPI-ATIN, he was reinitiated on a shortened course of prednisone and infliximab and experienced complete renal recovery achieving baseline

Table 1. Timeline and outcome of patients with acute kidney injury secondary to checkpoint inhibitor–related interstitial nephritis treated with glucocorticoids and infliximab.

Case Ref.	CPI Treatment duration prior to 1st AKI	1st AKI; Cr change[a] TNF-α level	Days from AKI diagnosis until GC	Management of 1st AKI Kidney response after starting the therapy	Duration from discontinuation of GC or infliximab until 1st relapse Cr change TNF-α level	Management of 1st relapse Kidney response after starting therapy	Infliximab Side effects[b]	Kidney outcome	PFS Overall survival
Case 1	Atezolizumab 3 months	Cr 0.70 > 7.47 requiring hemodialysis TNF-α 39	18 days	CPI was d/c GC for 15 days Cr 2.90, day 7 Cr 1.09, day 15	1 week off GC Cr 1.09 > 5.70 TNF-α 136	GC for 15 days Infliximab at day 4 Cr 1.09, week 3 TNF-α 0, week 1	N/A	Complete recovery	PFS, no evidence of disease at 6 months
Case 2	Pembrolizumab + Ipilimumab 3 months	Cr 0.93 > 3.54 TNF-α 489	2 days	CPI was d/c GC for 5 weeks Cr 0.89, day 6	2 weeks off GC Cr 1.01 > 2.26 TNF-α 48	GC for 15 days Infliximab at day 12 Cr 1.11, week 2 Cr 0.97, week 14 TNF-α 9, week 8	URTI	Complete recovery	PFS, no evidence of disease at 9 months
Case 3	Nivolumab 12 months	Cr 1.29 > 2.29 TNF-α 10	1 day	Already off CPI for 5 months GC for 5 weeks Cr 1.64, week 2	Week 3 while on GC Cr 1.60 > 1.67 TNF-α N/A	GC for additional 3 weeks Infliximab at week 3 Cr 1.34, week 7 TNF-α N/A	N/A	Complete recovery	PFS, no evidence of disease at 20 months.
Case 4	Nivolumab + Ipilimumab 7 months	Cr 1.07 > 2.43 TNF-α N/A	10 days	CPI was d/c GC for 3 weeks Cr 1.48, week 3	10 days off GC Cr 1.48 > 1.78 TNF-α of 12	Infliximab at week 2 off GC Cr 1.24, day 14 TNF-α N/A	N/A	Complete recovery	PFS, no evidence of disease at 9 months.
Case 5	Nivolumab 4 months	Cr 0.61 > 3.27 TNF-α 24	5 days	CPI was d/c GC for 8 weeks Cr 1.83, week 7	1 week off GC No change in kidney function, Cr 1.93	2 doses of Infliximab at week 2 and 4 weeks off GC Cr 1.51, week 4 after last infliximab dose TNF-α N/A	N/A	Partial recovery	PFS, stable disease at 9 months
Case 6	Atezolizumab 4 months	Cr 1.64 > 5.88 requiring hemodialysis TNF-α 36	22 days	CPI was d/c GC for 21 days Infliximab, day 17 Cr 3.20, day 30 (off hemodialysis)	N/A	N/A	N/A	Partial recovery	PFS, 8 months OS, 10 months
Case 7	Pembrolizumab 6 months	Cr 1.18 > 3.36 TNF-α 39	8 weeks	CPI was held for 4 weeks after AKI GC for 5 weeks Cr 2.09, week 5	4 weeks off GC Restarted on CPI Cr 2.06 > 2.78 TNF-α 38	CPI was held for 12 weeks, restarted due to disease progression Infliximab at week 10 and 16 Cr 2.09, week 15 TNF-α 17, week 15	N/A	Partial recovery	PFS, 11 months OS, alive

(*Continued*)

Table 1. (Continued).

Case Ref.	CPI Treatment duration prior to 1st AKI	1st AKI; Cr change[a] TNF-α level	Days from AKI diagnosis until GC	Management of 1st AKI Kidney response after starting the therapy	Duration from discontinuation of GC or infliximab until 1st relapse Cr change TNF-α level	Management of 1st relapse Kidney response after starting therapy	Infliximab Side effects[b]	Kidney outcome	PFS Overall survival
Case 8	Nivolumab + Ipilimumab 4 months	Cr 1.31 > 1.94 TNF-α N/A	10 weeks	Ipilimumab was d/c GC for 1 week followed by maintenance dose for adrenal insuff. Cr 1.52, day 7	2 weeks Cr 1.52 > 2.36 TNF-α N/A	Nivolumab was d/c GC for 4 days followed by maintenance dose Cr 1.7–1.9 week 2–19 Infliximab week 20 Cr 1.57, week 3 post infliximab TNF-α N/A	URTI	No	recovery
PFS, no	evidence of disease at 19 months								
Case 9	Durvalumab 3 months	Cr 1.74 > 5.86 TNF-α N/A	8 days	CPI was d/c GC for 17 days Cr 2.55, day 17	4 weeks off GC Cr 2.45 > 8.56 requiring hemodialysis TNF-α 85	Delayed till week 13 of relapse GC for 3 weeks Infliximab at day 4 Cr 8.33, week 2 TNF-α 0, week 2	N/A	No	recovery
PFS,	20 months OS, alive								
Case 10	Pembrolizumab 30 months	Cr 1.22 > 1.83 TNF-α N/A	10 days	CPI was d/c GC for 4 weeks Cr 1.36, week 4	2 weeks Cr 1.28 > 1.60 TNF-α 21	Infliximab, 3 weeks off GC Cr 1.75 day 11 Cr 1.73 week 8 TNF-α 0, week 3	N/A	No	recovery
PFS,	stable disease at 32 months.								

CPI, checkpoint inhibitor; AKI, acute kidney injury; Cr, serum creatinine (mg/dl); TNF-α, tumor necrotic factor-alpha (pg/ml); GC, glucocorticoids; W, white; H, Hispanic; M, male; F, female; d/c, discontinued; N/A, not available; PFS, progression-free survival; OS, overall survival; insuff.; insufficiency; URTI, upper respiratory tract infection.

[a]peak serum creatinine

[b]within 8 weeks post infliximab dose. all URTIs were treated with oral antibiotic as outpatient

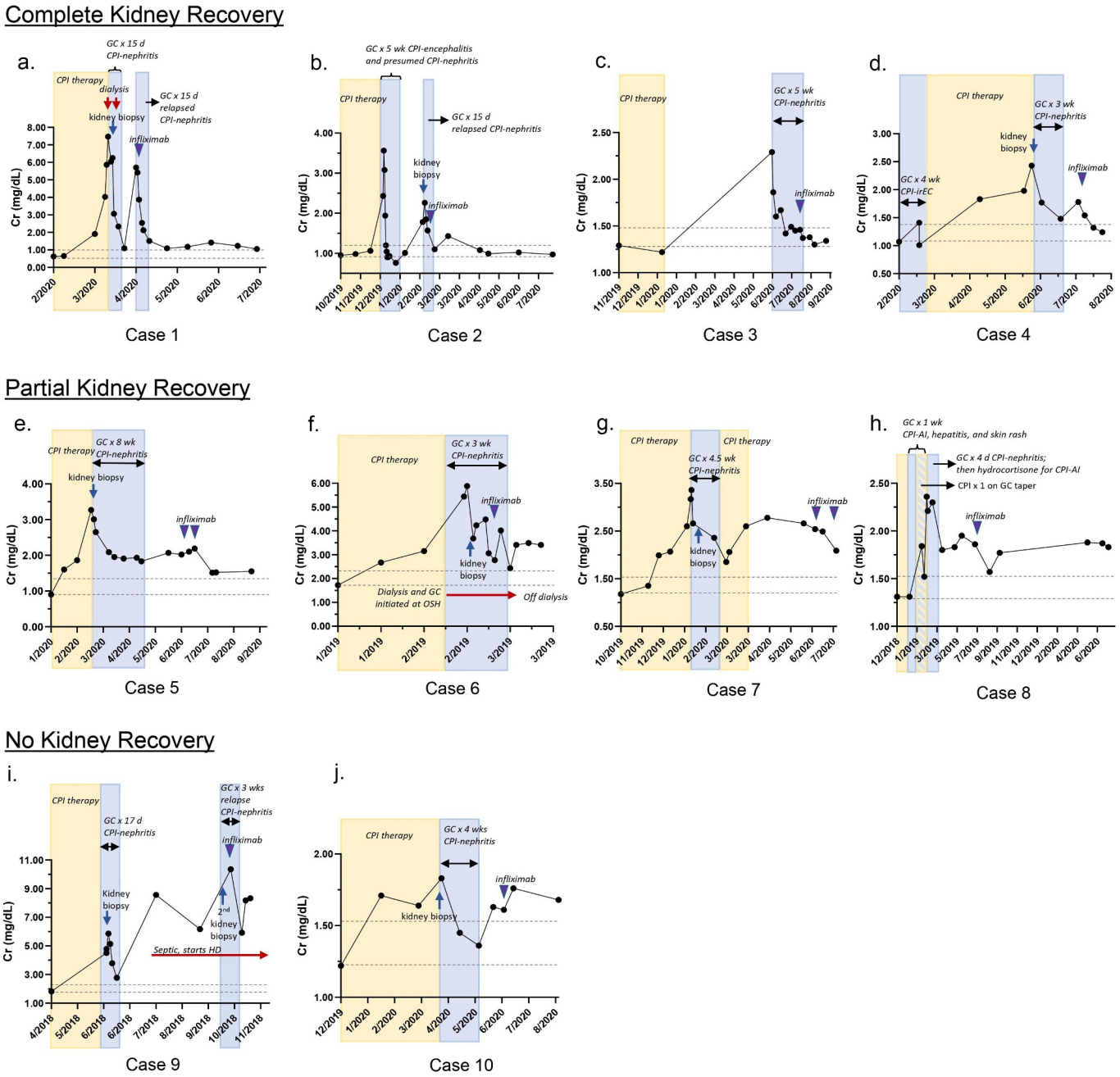

Figure 1. Time course of events and response to treatment. Panels A-D: Cases 1–4 with complete kidney recovery. Panels E-H: Cases 5–8 with partial kidney recovery. panels I-J: Cases 9–10 no kidney recovery. yellow: checkpoint inhibitor (CPI) therapy. CPI dosing regimens are provided in Table 1. Blue: glucocorticoid (GC) therapy. Purple triangle: infliximab (5 mg/kg IV). Dotted black line represents creatinine level to < 0.35 mg/dL above baseline; complete renal recovery.

function with a Cr 0.97 mg/dL. He has no evidence of cancer recurrence and continues to be followed.

Case 3

A 77-year-old White female with stage 3 chronic kidney disease (CKD, baseline Cr 1.29 mg/dL), stage II malignant melanoma with anorectal primary was treated with adjuvant nivolumab (anti-PD1). Five months after completing her last cycle of nivolumab, labs revealed AKI (Cr 2.29 mg/dL) and pyuria (Figure 1c). CPI-associated ATIN was suspected. Due to her recent transient ischemic attack requiring anticoagulation with clopidogrel and aspirin, renal biopsy was deferred. She was started on prednisone with initial improvement in her serum creatinine. However, her serum creatinine failed to improve past 1.60 mg/dL and repeat labs showed an increased Cr of 1.67 mg/dL. Due to concern for relapsed CPI-ATIN, prednisone was increased back to 40 mg daily. After 21 days of failed GC taper, she received infliximab. Within a week she was off steroids and her creatinine remained stable at 1.34 mg/dL. There is no evidence of cancer recurrence from follow-up scans.

Case 4

A 76-year-old White male with insulin-dependent diabetes mellitus, Barret's esophagus, stage I adenocarcinoma of the gastroesophageal (GE) junction, and stage IV metastatic malignant melanoma of the distal esophagus was treated with combination therapy with ipilimumab and nivolumab. His

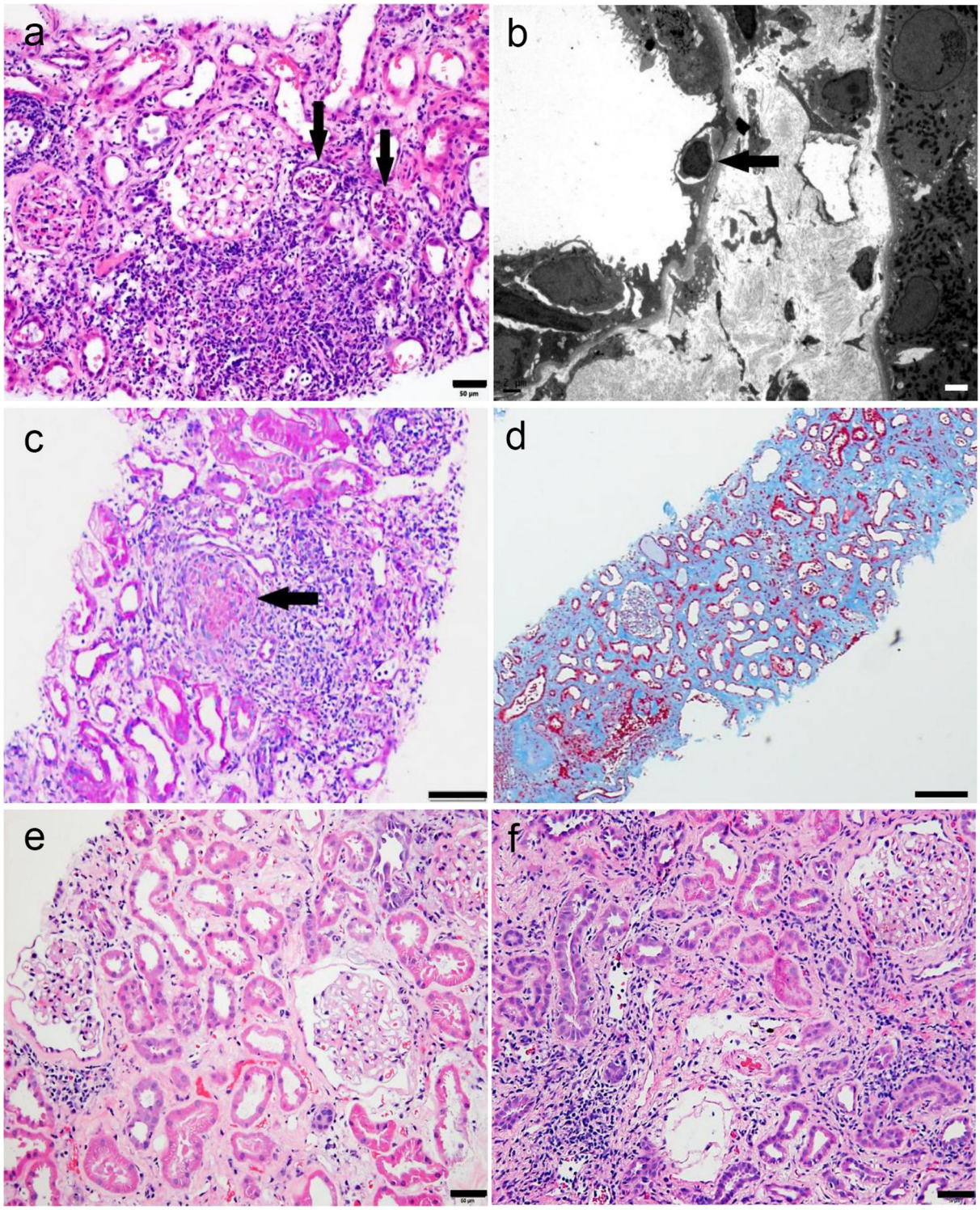

Figure 2. Representative images of CPI-induced AKI A. Case 1. hematoxylin and eosin (H&E) stain: moderate to severe tubulointerstitial inflammation with lymphocytes, neutrophils, and tubular microabscesses (arrows). scale bar 50 µm. B. Case 1. Electronic micrograph (EM) of tubule with flattened epithelial cells and intraepithelial lymphocyte (tubulitis, arrow). Scale bar 2 µm. C. Case 2. Periodic acid-Schiff (PAS) stain with acute tubulointerstitial inflammation and focal granuloma with associated tubular basement membrane break (arrow). Scale bar 100 µm. D. Case 7. Masson's trichrome stain with diffuse moderate interstitial fibrosis. Scale bar 200 µm. E. Case 9, first biopsy. H&E stain: mild to moderate tubulointerstitial inflammation with lymphocytes, plasma cells, and occasional eosinophils. Scale bar 50 µm. F. Case 9, second biopsy. H&E stain: diffuse moderate tubulointerstitial inflammation with lymphocytes, plasma cells, and neutrophils. Scale bar 50 µm.

treatment course was complicated by irEC and AKI (creatinine increased to 1.41 mg/dL from baseline of 1.07 mg/dL). He was started on prednisone with a taper over 4 weeks for CPI-irEC. Upon completion of GC therapy, his renal function fully recovered. Follow-up labs 1 month later, however, showed AKI with Cr of 2.43 mg/dL. Kidney biopsy revealed CPI-ATIN, ATI, 16% global sclerosis, and 10% interstitial fibrosis and tubular atrophy (IFTA). GC therapy with prednisone 60 mg daily was initiated and complicated by hyperglycemia and insomnia. His creatinine improved to 1.48 mg/dL, but

follow-up labs 10 days later showed an increase to 1.78 mg/dL. GC therapy was not reinitiated due to side effects. Instead he received infliximab. His kidney function improved and has remained stable at a Cr of 1.32–1.24 mg/dL for the last 3 months. His melanoma and esophageal adenocarcinoma remain in remission.

Cases with partial kidney recovery:

Case 5

A 64-year-old White female with stage IV adenocarcinoma of the stomach was started on folinic acid, fluorouracil, and oxaliplatin (FOLFOX) with nivolumab. One month after her last chemo-immunotherapy cycle, she presented with AKI, creatinine peak of 3.27 mg/dL (baseline Cr 0.61 mg/dL), and pyuria (Figure 1e, Table 1). Kidney biopsy revealed ATIN and ATI. After 8 weeks of GC therapy, she had partial recovery of her kidney function (Cr 1.93 mg/dL). She came to MDACC for a second opinion on cancer therapy and the multidisciplinary tumor board deemed that the kidney risks were too high for further treatment. In an attempt to further improve her kidney function, she was given two treatments of infliximab and within 2 weeks of her second dose, her creatinine subsequently improved to 1.51 mg/dL and has been stable for the last 5 months. She is now on folinic acid, fluorouracil, and irinotecan (FOLFIRI) with stable disease.

Case 6

A 72-year-old White male with a history of hypertension, diabetes mellitus, CKD stage 3 (baseline 1.64 mg/dL), and stage IV anaplastic thyroid cancer on atezolizumab (anti-PD-L1)

Table 2. Clinical characteristics of patients with acute kidney injury associated with checkpoint inhibitor–related interstitial nephritis treated with glucocorticoids and infliximab.

Case Ref.	Malignancy Age/race/sex	Co-morbidities	ATIN associated Medications prior to AKI[a]	Concurrent chemotherapy	Urinalysis UPCR at time of initial AKI	Renal pathology at the time of AKI IFTA	Other irAE	Repeat urinalysis UPCR at time of 1st relapse or lack of kidney recovery with GC
Case 1	Breast cancer 69/W/F	Hypertension	Omeprazole Ciprofloxacin	Nab-paclitaxel	36 RBC/HPF >182 WBC/HPF 3.16 g/g	ATIN and ATI 0% IFTA	N/A	15 RBC/HPF >182 WBC/HPF 2.07 g/g
Case 2	Melanoma 67/W/M	N/A	N/A	N/A	6 RBC/HPF 12 WBC/HPF 1 g/g	ATIN and ATI 20% IFTA	Encephalitis Adrenal insufficiency	17 RBC/HPF 8 WBC/HPF 0.4 g/g
Case 3	Melanoma 77/W/F	CKD	Omeprazole	N/A	0–1 RBC/HPF 3 WBC/HPF < 0.14 g/g	No biopsy	Hypothyroidism Skin rash	Negative dipstick
Case 4	Melanoma 76/W/M	Hypertension Diabetes	Omeprazole	N/A	0 RBC/HPF 0 WBC/HPF 0.42 g/g	ATIN and ATI 10% IFTA	Colitis Hepatitis	Negative dipstick 0.4 g/g
Case 5	Gastric carcinoma 64/W/F	Hypertension	Omeprazole	FOLFOX	0–3 RBC/HPF 11–30 WBC/HPF N/A	ATIN and ATI N/A	hypothyroidism	Negative dipstick
Case 6	Anaplastic thyroid cancer 72/W/M	Hypertension Diabetes CKD	N/A	Cobimentinib	4 RBC/HPF 18 WBC/HPF 0.62 g/g	ATI and focal ATIN 30% IFTA	Skin rash	N/A
Case 7	Adenocarcinoma of the lung 77/H//M	Diabetes CKD	Pantoprazole	Pemetrexed + Carboplatin	55 RBC/HPF 1 WBC/HPF 0.75 g/g	ATI with mild focal CTIN Moderate fibrosis	N/A	Negative dipstick 0.38 g/g
Case 8	Melanoma 52/W/M	Hypertension PCKD CKD	N/A	N/A	1 RBC/HPF 3 WBC/HPF 0.01 g/g	No kidney biopsy	Hepatitis Pneumonitis Skin rash Adrenal insufficiency	Negative dipstick 0.1 g/g
Case 9	Squamous cell lung cancer 77/W/M	Hypertension CKD	Pantoprazole	N/A	3–5 RBC/HPF 11–25 WBC/HPF N/A	1st; ATIN and ATI 30% IFTA 2nb; AIN, CTIN and ATI 40% IFTA[b]	Pneumonitis	6–10 RBC/HPF 21–50 WBC/HPF 0.31 g/g
Case 10	Adenocarcinoma of the lung 52/W/F	CKD	N/A	Pemetrexed	18 RBC/HPF 1 WBC/HPF 0.10 g/g	CTIN 70% IFTA	N/A	1 RBC/HPF 1 WBC/HPF 0.74 g/g

ATIN, acute tubulointerstitial nephritis; CTIN, chronic tubulointerstitial nephritis; AKI, acute kidney injury; Cr, creatinine; irAE, immune-related adverse event; GC, glucocorticoids; Nab, protein bound; N/A, not available; CKD, chronic kidney disease; PCKD, polycystic kidney disease; UPCR urine protein to creatinine ratio; RBC, red blood cell; WBC, white blood cell; ATI, acute tubular injury; IFTA, interstitial fibrosis with tubular atrophy FOLFOX, leucovorin calcium, fluorouracil, and oxaliplatin

[a]ATIN associated medications within 4 weeks prior to initial AKI

[b]2nd kidney biopsy was done at the time of relapse

and cobimetinib was admitted to an outside hospital (OSH) with complaints of fatigue. He was found to have AKI on presentation with a Cr of 5.88 mg/dL and initiated on dialysis (Figure 1f). Urine studies were significant for pyuria, hematuria, and proteinuria. After the coordination of care, the patient was started on GC for potential CPI-associated nephritis. He was discharged on dialysis. One week later he fell at home and was admitted to MDACC. Serum TNF-α level was 36 pg/mL. Kidney biopsy revealed focal ATIN and ATI. Since the biopsy still showed evidence of ATIN, infliximab was added to his GC regimen. One week later, he was off dialysis with a creatinine of 3.20 mg/dL. Unfortunately, 1 month after hospital discharge the patient suffered a severe ischemic stroke and was transitioned to hospice.

Case 7

A 77-year-old Hispanic male was diagnosed with stage IV adenocarcinoma of the right lung treated with carboplatin, pemetrexed, and pembrolizumab and continued on maintenance pemetrexed and pembrolizumab. He was admitted to the hospital with AKI (Figure 1g). His serum creatinine peaked at 3.36 mg/dL (baseline Cr 1.18 mg/dL) and urine studies indicated significant hematuria. He was initiated on methylprednisolone 180 mg IV daily due to concern for CPI-induced AKI. A kidney biopsy was performed 4 days after steroid initiation which showed ATI, focal chronic interstitial nephritis, moderate IFTA, and 14% global glomerulosclerosis (Figure 2d). He completed a four-week course of GC with creatinine improvement to 2.09 mg/dL. Due to cancer progression, he was restarted on pembrolizumab and had repeat AKI with a creatinine of 2.78 mg/dL (Table 2). Due to his worsening kidney function, two doses of infliximab were administered. While the creatinine improved to 2.09 mg/dL, follow-up restaging scans showed evidence of cancer progression.

Case 8

A 52-year-old White male with a history of polycystic kidney disease, stage 2 CKD (baseline Cr 1.30 mg/dL), stage IV malignant melanoma on ipilimumab and nivolumab was admitted for fatigue. He was diagnosed with CPI-induced adrenal insufficiency (AI), hepatitis, and skin rash (Figure 1h). Labs also showed AKI (Cr of 1.94 mg/dL). He was started on GC treatment for non-kidney related irAEs and his kidney function simultaneously improved to Cr of 1.52 mg/dL. He received an additional cycle of nivolumab and had repeat AKI (Cr of 2.36 mg/dL). Due to his history of PCKD, a renal biopsy was deferred. For presumed CPI-AKI, he was restarted on prednisone with improvement to Cr 1.75 mg/dL. After 4 days of prednisone, the patient had severe mood side effects and stopped his GC therapy. With only partial recovery of his kidney function, infliximab was administered with a transient improvement in his serum creatinine to 1.50 mg/dL. His creatinine remained stable at 1.70–1.80 mg/dL for over a year, and he has had no evidence of cancer.

Cases with no kidney recovery:

Case 9

A 77-year-old White male with stage IV squamous cell lung cancer of the right upper lobe was on adjuvant durvalumab (anti-PD-L1). After three cycles of durvalumab, he was admitted for AKI with a Cr of 5.86 mg/dL (baseline 1.74 mg/dL) (Figure 1i). He underwent a kidney biopsy which revealed ATIN and ATI (Figure 2e). He was started on GC and his creatinine improved to 2.55 mg/dL. One month later, he was admitted to an OSH with fevers and hypotension. Labs showed a Cr of 8.56 mg/dL. He was initiated on dialysis and remained dialysis-dependent on discharge. He returned to MDACC 4 months later. Due to an unclear reason for his kidney failure, he underwent a repeat biopsy which showed chronic and active ATIN and ATI (figure 2f). Since there was continued CPI-associated nephrotoxicity, he was re-challenged with GC and infliximab. Due to his underlying chronic obstructive pulmonary disease and increased risk of severe lung infection, no further treatment of irAE nephritis was attempted and he remained on dialysis. Twenty months after initiation of CPI therapy, the patient had a disease relapse.

Case 10

A 52-year-old White female with lung adenocarcinoma on maintenance pemetrexed and pembrolizumab was found to have AKI. Her creatinine increased from 1.22 to 1.83 mg/dL (Figure 1j). She underwent a kidney biopsy that revealed chronic tubulointerstitial inflammation and 70% IFTA. She was started on GC treatment, and her kidney function improved to 1.36 mg/dL. Unfortunately, she had severe GC side effects including insomnia, fluid retention, skin bruising, and irritability. Two weeks after the completion of GC, she was admitted with fevers, new lung infiltrates, and AKI (Cr 1.60 mg/dL). COVID-19, respiratory viral panel, legionella, fungal cultures, acid-fast stain, pneumocystis jirovecii, and cytomegalovirus testing were negative. The patient's fever and respiratory symptoms improved with supportive management, but her kidney function remained elevated. Infliximab was administered prior to discharge for potential cytokine-mediated AKI or relapse CPI-ATIN. Her kidney function remained stable at ~1.75 mg/dL. Her last restaging scans in July 2020 revealed stable disease and is in observation.

Summary of cases

Infliximab-containing regimens were used for 10 patients with CPI-ATIN. Four patients relapsing after GC therapy achieved durable and complete renal recovery, four patients experienced partial renal recovery, and two patients showed no improvement in kidney function. Detailed timeline and outcome of patients and clinical characteristics associated with CPI-ATIN are provided in Tables 1 and 2. In line with previously published studies,[1] the initial clinical and histologic features of CPI-ATIN of pyuria and sub-nephrotic range proteinuria were present in the majority of the patients (9 out of 10, Table 2). Time from CPI initiation to diagnosis of CPI-AKI ranged between 3 and 30 months. The median duration of GC therapy for the initial episode of AKI-associated ATIN was 3.5 weeks (range of 1–8 weeks) and all relapsed CPI-ATIN were reported within 4 weeks of GC cessation (Supplemental Table 2). Extra-renal irAEs were also common. Seven out of the 10 patients had extra-renal irAE (Table 2). Four out of the 10 cases had a diagnosis of malignant melanoma. There was no difference in kidney recovery between single-agent CPI versus combination CPI therapy or class of CPI. There was also no

relationship between the severity of AKI based on serum creatinine change and kidney recovery. Seven out of 10 cases had stable or no evidence of cancer progression. Three patients (Cases 6, 7, and 9) had disease progression with progression-free survival of 8 to 20 months. In these three cases, two had partial kidney recovery and one had no kidney recovery.

Discussion

To our knowledge, this is the first reported case series on the use of infliximab for CPI-associated ATIN. Infliximab was used for relapsed CPI-ATIN, or as salvage therapy for GC treated CPI-ATIN patients with partial or no recovery of kidney function. Of the 10 cases described, all 4 patients who had complete kidney recovery following infliximab therapy and discontinuation of GC therapy experienced complete tumor regression and/or progression-free survival at the last follow-up.

Etiologies for ATIN are known to be diverse and are most commonly associated with drugs (e.g., proton pump inhibitors (PPIs), non-steroidal anti-inflammatory drugs, antibiotics, etc.), but can also be seen in autoimmune disorders (i.e., sarcoidosis and systemic lupus nephritis) and infections (*Legionella, Leptospira, Streptococcus*, etc.).[12] ATIN is believed to be triggered by an immune response to exogenous antigens processed by renal tubular cells or endogenous nephritogenic antigens. These same mechanisms may also be responsible for CPI-ATIN. CPI therapy can lower the activation threshold of drug-specific T cells,[13,14] and potentially of cross-reactive T cells to kidney tissue-associated epitopes. In two cases of CPI-myocarditis, select clonal T cell populations infiltrating the myocardium were identical to those in the tumor and skeletal muscle.[15] However, an alternative hypothesis for this observation may be associated with the differential upregulation of cytokines (e.g., CXCL9, 10, 11, and 13) observed in cases of irAEs[16] thus recruiting T cells into the tissue indiscriminately, leading to identical T cell clones in tumor and inflamed tissue. Out of the 10 cases presented, six of the patients were concurrently receiving drugs associated with ATIN (Table 2),[17] and none had a previous diagnosis of autoimmune disease or infection associated with CPI-ATIN. Only one patient (Case 4) elected to continue PPI therapy due to medical necessity in the setting of Barrett's esophagus and GE adenocarcinoma.

Early intervention in ATIN is critical. Profibrotic cytokines and growth factors trigger rapid transformation of these inflammatory lesions to fibrogenesis that can be detected within 7 days of interstitial inflammation.[18] Thus, the probability of kidney recovery has been speculated to be associated with two main factors: duration of kidney failure and degree of interstitial scarring (i.e. IFTA).[19–23] Our observations suggest this as well. Within the first 2 months of CPI-AKI diagnosis, six patients (Cases 1–4, 6, and 10) received infliximab after initial GC treatment. Cases 1–4 had complete recovery of kidney function and Case 6 was able to come off dialysis with partial kidney recovery. In the four cases (Cases 5 and 7–9) where infliximab was given over 2 months after a diagnosis of CPI-AKI and initial GC treatment, three had partial kidney recovery and one had no kidney recovery. Usage of infliximab did improve some patient's serum creatinine levels, but not by definition of KDIGO kidney recovery. In Case 5 the creatinine improved from 1.93 mg/dL to 1.51 mg/dL which allowed for continued cancer treatment. Case 7 also had an improvement in creatinine from 2.78 mg/dL to 2.09 mg/dL. The degree of IFTA might have been a key factor in response to treatment. In Cases 9 and 10 (patients who had no recovery of kidney function), both had a previous diagnosis of CKD and had ~40% IFTA on biopsy. In the cases with complete or partial kidney recovery, most had minimal to no IFTA. Duration of kidney failure and preexisting degree of renal fibrosis may be most predictive of the renal response to treatment.

TNF-α is a pleiotropic cytokine that directly participates in the maintenance of immune homeostasis and has been proposed to be a therapeutic target. In rheumatoid and psoriatic arthritis and inflammatory bowel diseases, blockade of TNF-α can successfully lead to clinically beneficial immune suppression.[24–26] In CPI-induced irEC, Johnson *et al.* demonstrated that short-term use of infliximab improved symptom resolution, time to GC taper, and did not compromise overall survival.[8] In tumor immunology, the paradoxical role of TNF-α as both a pro- and anti-tumor mediator is well recognized. In addition to its role as an effector molecule in cytotoxic T lymphocyte triggered cancer cell death, TNF-α is also involved in promoting immune suppression of regulatory T and B lymphocytes and myeloid-derived suppressor cells. In a preclinical study, TNF-α blockade was shown to significantly enhance tumor immunity and overcome resistance to anti–PD1 and adoptive T cell therapy.[27]

Experience in the use of infliximab or TNF-α blockade to treat inflammatory kidney diseases is limited.[28] In a few case reports of sarcoid and granulomatous interstitial nephritis, treatment with infliximab was shown to be successful.[29,30] In cases of CPI-ATIN, others have reported elevated serum TNF-α levels.[31] In pre-clinical models of ATI, elevated TNF-α levels were associated with cytokine-induced tubular damage.[32,33] While some of our patients had elevated serum levels of TNF-α, baseline levels were not checked and this was not observed in all cases. This discrepancy may be due to the difficulty of measuring serum cytokines. The half-life of cytokines is short (usually less than 10 min), leading to brief peak levels in blood. Additionally, the potential for dilutional effect if only one organ system is inflamed as opposed to active systemic inflammatory disease may lower the overall level detected. Measuring the local and paracrine activity of cytokines in body fluids may allow for easier detection. Moledina, *et al.* noted that urinary IL-9 and TNF-*α* were independently predictive of drug-induced ATIN.[34] Changes in TNF-α level are likely easier to detect at the cellular or tissue level. In cases of CPI-ATIN or cytokine-mediated ATI, further investigation for urine as biological fluid for cytokine detection could be considered.

Benefits of anti-TNF-α treatments in kidney inflammation caused by autoantibodies such as ANCA-associated vasculitis or systemic lupus erythematosus have also been previously investigated and not found to be significant.[35,36] Induction of CPI-associated vasculitis and glomerulonephritis has been reported by our group and others.[37–39] In general, we would

not recommend infliximab for treatment in these cases.[40] Infliximab should be used with caution. All patients should be screened for tuberculosis and hepatitis B as TNF-α is a potent immunity cytokine in these diseases. Additionally, long-term use of infliximab in rheumatoid arthritis was shown to be associated with de novo formation of autoantibodies to antinuclear antibodies, anti-double-stranded DNA antibodies, and anti-cardiolipin antibodies.[41,42] In our case series, most patients had limited exposure to infliximab and no obvious side effects. More rigorous clinical studies are necessary to understand the risk-benefit analysis for infliximab usage in ATIN.

In six of these cases, an infliximab-containing regimen led to sustained renal response and kidney recovery (where previous GC therapy alone had failed), and further prevented re-initiation of protracted GC treatment, GC associated metabolic consequences, and delay in cancer treatment. While data is limited, in patients who have relapsed CPI-ATIN, cannot tolerate GC side effects, or experience partial or no recovery of kidney function, these studies suggest a possible steroid-sparing alternative that involves the administration of an infliximab-containing regimen and a short course of GC (1–2 weeks). Labs should be checked at 1 and 2 weeks after initial infliximab treatment. If improvement is observed, then labs can be followed on a monthly basis. Due to the known side effects of infliximab, we recommend limiting the use of infliximab to 1–3 doses. Due to the lack of randomized trials, we would not recommend infliximab as first-line therapy in ATIN at this time.

Infliximab use for the treatment of CPI-associated ATIN and ATI is novel, but this study has several limitations. First, this is a retrospective, single-center study with only 10 cases. Second, GC therapy for CPI-associated ATIN treatment duration was variable. The median GC treatment duration after the initial CPI-AKI diagnosis was approximately 4 weeks; longer GC therapy may have prevented CPI-ATIN relapse. Third, the administration of infliximab was varied – infliximab was given with and without GC. There was no standardization in the timing of infliximab. Fourth, kidney biopsies revealed different degrees of inflammation, immune cell infiltrates, and fibrogenesis. The significance of this is unknown, and more research is needed to understand the specific utility of targeting TNF-α in ATIN or ATI. Nevertheless, it should be noted that in each case when infliximab was added following initial treatment, renal recovery in patients responding to infliximab was long-lasting and accompanied by only a short course of GC, potentially life-extending therapy with CPI could be re-initiated, and in several cases, led to durable anti-tumor responses.

Conclusion

Currently, there is no available experience or recommendation on the use of infliximab in the treatment of CPI-ATIN. While not all patients responded to GC and infliximab, infliximab may be effective in patients with relapsed CPI-ATIN, severe GC side effects, or as salvage therapy in cases of CPI-ATIN with partial or no kidney recovery. For those patients who failed GC, infliximab represents a potential steroid-sparing option. This study supports the design of a trial to prospectively evaluate the role of infliximab in the treatment of CPI-associated ATIN and ATI.

Declarations

Ethics approval and consent to participate: This study was approved by the institutional review board in accordance with the principles of the Declaration of Helsinki.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Competing interests: The authors declare that they have no competing interests.

Authors' contributions: The idea was conceived by AA. Data acquisition was performed by JSL, OM, and AA. AT and WFG performed the histological examination of the kidney biopsies and contributed in writing the pathology section of the manuscript. The manuscript was prepared by JSL, OM, CY, and AA and edited by US, AT, WFG, RAS, RML, RD, MA, NA, and AD. All the authors contributed to the quality control data, analysis, interpretation of data, and writing and final proof of paper. All authors read and approved the final manuscript.

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