Immune Checkpoint Inhibitor Debate: Biopsy vs. No Biopsy

The PRO Argument!

Mark A. Perazella, MD, FASN
Professor of Medicine
Section of Nephrology
Yale University School of Medicine
New Haven and West Haven VAMC
Mark A. Perazella, MD, MS

- New York Medical College
- Medicine Residency at Yale Primary Care Program
- Nephrology Fellowship at Yale University/Yale-New Haven Hospital
- Professor of Medicine at Yale University School of Medicine
  - Clinician Educator: Drug nephrotoxicity, AIN, Onco-Nephrology, HIV-related kidney disease
Disclosures

**Employer:**
Yale University School of Medicine

**Honoraria:**
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Learning Objectives

• Describe that immune-checkpoint inhibitor associated AKI is a rare but important IRAE
• Recognize that knowledge of the kidney lesion (AIN vs. ATI) causing AKI is important to direct appropriate management and avoid unnecessary complications
• Recognize that clinical and laboratory data are inadequate non-invasive diagnostic tools for AIN, making kidney biopsy required in most cases to differentiate AIN from ATI
Case 1

- **HPI:** 72 year old man with metastatic melanoma was seen in nephrology consultation for acute kidney injury
- **PMH:** mild asthma, GERD, HTN, and chronic low back pain
- **Medications:** aspirin, albuterol inhaler, omeprazole, tramadol, losartan, no herbals or OTC meds; ipilimumab and nivolumab were being utilized for advanced melanoma (on therapy for 8 weeks)
- **Examination:** BP 145/92 mmHg, conjunctival pallor, trace ankle edema, and no skin rash

- **Labs:** WBC 10.5 (2% eos), serum Cr 5.9 mg/dl (baseline 1.2 mg/dl)
- **Urinalysis:** SG 1.012, 1+ protein, 1+ blood, 1+ LE
- **Urine sediment:** 5-10 isomorphic RBCs/HPF, 5-10 WBCs/HPF, and 3-5 RTECs/HPF, 1-3 RTEC casts/LPF and 1-3 granular casts/LPF
• The patient undergoes kidney biopsy to make a diagnosis

Light Microscopy

Acute Interstitial Nephritis

• Diffuse infiltration of interstitium with inflammatory cells
• Interstitial edema and tubular injury with tubulitis, no granuloma
Case 2

• **HPI:** 67 year old woman with **non-small cell lung cancer** was seen in nephrology consultation for **acute kidney injury.** Recently noted to have **colitis** and **dermatitis** (treated with course of steroids).

• **PMH:** fibromyalgia, DJD knees, HTN, former cigarette smoker

• **Medications:** aspirin, naproxen, tramadol, lisinopril, no herbals or OTC meds; **ipilimumab** and **pembrolizumab** were being utilized for **NSCLC** (on therapy for 12 weeks)

• **Examination:** BP 115/78 mmHg, crackles left lung base, no ankle edema, and faint rash on chest and back

• **Labs:** WBC 9.1 (3% eos), serum Cr 4.8 mg/dl (baseline 0.9 mg/dl)

• **Urinalysis:** SG 1.015, 1+ protein, 1+ blood, 1+ LE

• **Urine sediment:** 5-10 RBCs/HPF, 6-10 WBCs/HPF, 4-6 RTECs/HPF, 1-3 waxy casts and 1-3 finely granular casts/LPF
• The patient undergoes kidney biopsy to make a diagnosis

**Light Microscopy**

**Acute Tubular Injury**

- Dilated tubular lumens, interstitial *edema* and tubular injury
- Apical blebbing, tubular cell vacuolization, flattening and dropout
### Immune Checkpoint Inhibitor-associated AKI

#### Case 1
- 72 year old man with metastatic melanoma
- Ipilimumab + nivolumab (8 weeks)
- AKI alone, no associated IrAEs
- Omeprazole, losartan
- No skin rash
- Serum Cr 3.9 mg/dL
- U/A: 1+ protein, 1+ blood, 1+ LE
- Urine sediment: RBCs, WBCs, RTECs, RTEC and granular casts
- Biopsy: **Acute interstitial nephritis**

#### Case 2
- 67 year old woman with NSCLC
- Ipilimumab + pembrolizumab (12 weeks)
- AKI with IrAEs- colitis and dermatitis
- Naproxen, lisinopril
- Faint rash on chest and back
- Serum Cr 4.3 mg/dL
- U/A: 1+ protein, 1+ LE
- Urine sediment: WBCs, RTECs, waxy and granular casts
- Biopsy: **Acute tubular injury**

#### Treatment: ICPIs, omeprazole and losartan held; prednisone 60 mg/day given
- Outcome: Recovered from AKI; ICPIs not re-started (but they should probably be with close monitoring for recurrence)

#### Treatment: Naproxen and lisinopril held prior to biopsy, but no corticosteroids given
- Outcome: ICPIs restarted before AKI recovery with close monitoring; AKI did not develop following rechallenge
Approaching the Patient with Immune Checkpoint Inhibitor-associated AKI

Dr. Glezerman,
What would you recommend for our patients that develop AKI in the setting of immune-checkpoint inhibitor therapy?

You guys are putting too much thought into this. Just give them some prednisone.

Medical team

Dr. Glezerman
# Oncology Guidelines for Immune Checkpoint Inhibitor-associated AKI

<table>
<thead>
<tr>
<th>ASCO</th>
<th>NCCN</th>
<th>SITC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Limited Diagnostic Work-up</strong></td>
<td>Routine U/A not necessary</td>
<td>Obtain spot urine protein/creatinine ratio</td>
</tr>
<tr>
<td><strong>Recommendation for Kidney Biopsy</strong></td>
<td>Proceed directly to corticosteroids if no alternative cause identified</td>
<td>Consider biopsy if G1 toxicity; otherwise, proceed directly to corticosteroids</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>Hold ICPI and start 0.5–1 mg/kg/day prednisone equivalents. Increase to 1–2 mg/kg/day if no improvement. Permanently discontinue in 2017 toxicities</td>
<td>Hold ICPI and start 0.5–1 mg/kg/day prednisone equivalents. Increase to 1–2 mg/kg/day if no improvement. Permanently discontinue in 2017 toxicities. Add additional immunosuppression if G2 after 1 week</td>
</tr>
<tr>
<td><strong>Nephrology Consultation</strong></td>
<td>Recommended for G2 toxicity</td>
<td>Recommended for G2 toxicity</td>
</tr>
<tr>
<td><strong>ICPI Re-challenge</strong></td>
<td>Consider if no recurrence of AKI or chronic renal insufficiency</td>
<td>Consider on resolution of ICPI-AKI to G5.1 with or without corticosteroids. For G2, consider rechallenge at least 2 months after holding ICPI</td>
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Moss E, Perazella MA. Frontiers Nephrol, 2022
Immune Checkpoint Inhibitor-associated AKI
Diagnostic and Management Issues

- Can a diagnosis of AIN be made definitively with clinical information and lab tests?
- Does making an accurate diagnosis of ICPI-associated AKI matter?
- Can kidney biopsy be performed safely in these patients?
- Are corticosteroids a benign therapy that can be given to cancer patients without a legitimate indication?
- Is it helpful to know the cause of AKI when rechallenging with ICPIs?
Immune Checkpoint Inhibitor-associated AKI
Diagnostic Issues

- Can a diagnosis of AIN be made definitively with clinical information and lab tests?
  - Are clinical findings (rash, fever) or lab tests (serum/urine eos, pyuria) useful?

Immune Checkpoint Inhibitor-associated AKI

Diagnostic Issues

- Does making an accurate diagnosis of ICPI-associated AKI matter?
  - For example, is it important to distinguish AIN from ATI?

**ICPI-AKI Kidney Biopsy**

**AIN**
- Stop ICPI(s)
- Administer corticosteroids
- Observe response

**ATI**
- Address ATI causes
- Continue ICPI(s)
- Do not administer corticosteroids
Immune Checkpoint Inhibitor-associated AKI
Diagnostic Issues

- Does making an accurate diagnosis of ICPI-associated AKI matter?
  - Does histology provide prognostic information to guide management?

ICPI-AKI Kidney Biopsy

AIN
- IFTA < 50%
  - Diffuse infiltrate
  - Stop ICPI(s)
  - Administer corticosteroids
  - Observe response

ATI
- IFTA > 50-75%
  - Stop (or continue) ICPI(s)
  - No corticosteroids (or short course?)
  - Address ATI causes
  - Continue ICPI(s)
  - Do not administer corticosteroids
Immune Checkpoint Inhibitor-associated AKI

Diagnostic Issues

- Can kidney biopsy be performed safely in these patients?
  - Is the complication rate (bleeding, death) of kidney biopsy too high?

What are the complications associated with native kidney biopsy?

<table>
<thead>
<tr>
<th>Complication</th>
<th>Rate</th>
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<tbody>
<tr>
<td>Bleeding requiring transfusion</td>
<td>1.6%</td>
</tr>
<tr>
<td>Bleeding requiring intervention</td>
<td>0.3%</td>
</tr>
<tr>
<td>Death</td>
<td>0.06% or 1 in 1,667</td>
</tr>
</tbody>
</table>

Kidney Biopsy Complications

N=52,138 (2010-2018) France

- Bleeding requiring transfusion: 5%
- Bleeding requiring intervention: 0.4%/0.1%
- Death: 1%

Other Recent Publications

Halimi J-M, et al. CJASN. 2020

Kidney Biopsy Complications

- Bleeding requiring transfusion: <0.5%, 4.3%, 5.7% (3 studies)
- Bleeding requiring intervention: 0.6% (4 studies)
- Death: 0.00006 (3 studies)

**Immune Checkpoint Inhibitor-associated AKI Management Issues**

- Are corticosteroids a benign therapy that can be given to cancer patients without a legitimate indication?
  - Do corticosteroid cause significant adverse effects?
  - Do corticosteroids reduce the efficacy of the anti-cancer treatment?


- CS for irAEs in NSCLC were associated with shorter progression free survival (Mouri A, et al. J Clin Med. 2021)

- CS AEs: glycemic control, weight gain, fluid retention, sleep disturbance, disruption in mood, HTN, and risk of opportunistic infections

- 6 days of CS were associated with diabetes mellitus, sepsis, venous thromboembolism, and fractures (Waljee AK, et al. BMJ. 2017)
Immune Checkpoint Inhibitor-associated AKI
Management Issues

- Is it helpful to know the cause of AKI when rechallenging with ICPIs?
  - Will knowing the initial ICPI-associated AKI was due to AIN help with surveillance and therapy?

**Recurrent ICPI-associated AKI**

- Treat as AIN?

  - Stop ICPI(s)
  - Administer corticosteroids
  - Observe response
Immune Checkpoint Inhibitor-associated AKI
Diagnostic and Management Issues

• **BIOPSY (CON):**
  1) Most AKI is AIN, thus doesn’t change management
  2) Avoids potential biopsy complications
  3) Early CS Rx is associated with better AIN recovery
  4) Empiric CS Rx is associated with similar rates of complete or partial recovery in the absence of kidney biopsy

• **BIOPSY (PRO):**
  1) Allows accurate diagnosis of AKI (ATI vs. AIN vs. other)
  2) Allows directed management of AKI
  3) Provides prognostic information if AIN is found
  4) Avoids adverse effects of CS if ATI is observed
  5) Allows continued ICPI if AIN is not seen (avoiding the negative impact of ICPI D/C)
Immune Checkpoint Inhibitor-associated AKI

References

• Poggio ED, et al. What are the complications of kidney biopsy? *CJASN*. 2021
• Perazella MA, Sprangers B. Checkpoint inhibitor therapy-associated acute kidney injury: time to move on to evidence-based recommendations. *CKJ*. 2021
• Perazella MA, Shirali AC. Immune checkpoint inhibitor nephrotoxicity: what do we know and what should we do? *Kidney Int*. 2020
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