Monitoring and Management of GI/Hepatic Immune-Related Adverse Events Associated with Immune Checkpoint Inhibitor Therapy

By Dr. Arndt Vogel

Key principles of hepatic and GI immune-related adverse events (irAEs)

- Immune checkpoint inhibitors (ICIs) can cause **colitis and hepatitis**; rates are ~10%–20% with single-agent ICIs and ≥30% with dual-agent ICIs
- **Toxicities usually occur early**, especially hepatitis (often in the first 4–6 weeks), so early and frequent lab monitoring is important
- **Always consider other causes** before attributing to ICIs
- Most patients can be restarted on ICI treatment after irAE resolution

Best practices checklist

- Baseline and routine labs for all ICI patients
  - CBC, creatinine, electrolytes, ALT, AST, ALP, GGT, total bilirubin, albumin (± CRP)
  - Repeat LFTs regularly (~before each cycle) and increase frequency if abnormal
- If new diarrhea (suspected colitis)
  - Think infection first and review meds that affect the gut
  - Use fecal inflammatory markers and endoscopy as needed (see **colitis** section)
- If abnormal LFTs (suspected hepatitis)
  - Look at pattern and **trend**, and think obstruction, hepatotoxic drugs/supplements, viral hepatitis, and liver metastases.
  - Use ultrasound ± further imaging and serology as guided by the **hepatitis** section
- Factor in any comorbidities, such as existing IBD, viral hepatitis, NAFLD, and known liver metastases when interpreting symptoms and labs
- Act and refer early: escalate steroids and involve GI/hepatology early for ≥grade 2 colitis/hepatitis, diagnostic uncertainty, or steroid-refractory disease

Colitis: recognition and first steps

- Symptoms
  - New/worsening diarrhea; grade by extra bowel movements/day over baseline
    - Grade 1: ≤4; Grade 2: 4–7; Grade 3: >7; Grade 4: life-threatening
- Diagnostic workup: stool studies (bacteria, parasites, viruses), review other meds (PPIs, antibiotics, probiotics)
  - CT abdomen/pelvis if concern for perforation, severe pain or bleeding
  - Colonoscopy with biopsy if symptoms are prolonged, diagnosis is unclear, or to assess for ulcers predicting steroid-refractory disease
- Management
  - Grade 1: Symptomatic (low-fibre diet, loperamide); continue ICIs with close follow-up
  - Grade 2: Hold ICIs; start oral prednisone ~1 mg/kg/day (often ~60 mg). Taper based on clinical response over at least 4-6 weeks
  - Grade 3–4: Hospitalize; IV methylprednisolone ~1 mg/kg/day; **always involve gastroenterology**. If no clear improvement in ~3–5 days, treat as steroid-refractory and consider rescue (e.g. infliximab)

Hepatitis: recognition and first steps

- Key labs: ALT, AST, ALP, GGT, total bilirubin, albumin
- Diagnostic workup
  - Is there biliary obstruction (metastases, stones)?
    - Liver ultrasound
    - Review medications and supplements
  - Is there baseline chronic liver disease (HBV, HCV, NAFLD)?
  - Liver biopsy if steroid-refractory or other diagnoses suspected
- Grade 1–2 (AST/ALT >ULN to ≤5× ULN; bilirubin ≤3× ULN)
  - Grade 1: continue ICI with closer LFT monitoring (e.g., every 1–2 weeks); evaluate for other causes (meds, metastases, viral hepatitis)
  - Grade 2 or a clear upward trajectory (ALT/AST approaching 3–5× ULN): hold ICI; check LFTs every 2–3 days; start prednisone ~1 mg/kg/day if values are sustained/increasing. Don't wait for very high levels if the trend is worsening
- Grade 3–4 (AST/ALT >5× ULN and/or bilirubin >3× ULN or liver dysfunction)
  - Hold/discontinue ICIs
  - Admit; start IV methylprednisolone ~1 mg/kg/day; expect LFT improvement within ~3–5 days
  - If no clear downward trend, treat as steroid-refractory (15%–20% are refractory) and add MMF; increasing steroids above 1 mg/kg does not add benefit
  - **Urgent hepatology consult for grade 3 with worrisome trajectory and all grade 4/decompensated cases**
  - **Rising bilirubin that is not clearly obstructive is particularly concerning for impending liver failure and requires urgent hepatology input**

When to consult gastroenterology/hepatology

- Urgent
  - Grade 3–4 colitis (or any concern for perforation, severe bleeding, or systemic toxicity)
  - Rapidly rising ALT/AST, bilirubin increase, or clinical concern for impending liver failure
- Early/semi-urgent
  - Any ≥grade 2 colitis or hepatitis not clearly explained by infection, medications, or progression
  - Uncertain diagnosis
  - Steroid-refractory cases where infliximab (for colitis) or MMF (for hepatitis) may be needed, or where liver biopsy is being considered

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; CRP, C-reactive protein; CT, computed tomography; GGT, gamma-glutamyl transferase; GI, gastrointestinal; HBV, hepatitis B virus; HCV, hepatitis C virus; IBD, inflammatory bowel disease; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; LFT, liver function test; MMF, mycophenolate mofetil; NAFLD, non-alcoholic fatty liver disease; PPI, proton pump inhibitor; ULN, upper limit of normal.

1. Dolladille et al. *JAMA Oncology*. 2022. 2. Li et al. JNCCN.org. 2023. 3. Martins F et al. *Nature Reviews Clinical Oncology*. 4. Postow MA et al. *N Engl J Med*. 2018;378:158–168.
5. Riveiro-Barciela et al. *Clinical Gastroenterology and Hepatology*. 2023.