Drug-related liver injury due to immune-checkpoint inhibitors and drugs used in the therapy of autoimmune hepatitis

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Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Ipilimumab</td>
<td>CTLA-4</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin’s lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency</td>
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<tr>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>Melanoma, non–small-cell lung cancer, classic Hodgkin’s lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high microsatellite instability or mismatch-repair deficiency</td>
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<tr>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>Non–small-cell lung cancer, urothelial carcinoma</td>
</tr>
<tr>
<td>Avelumab</td>
<td>PD-L1</td>
<td>Merkel-cell carcinoma, urothelial carcinoma</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>PD-L1</td>
<td>Urothelial carcinoma</td>
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* CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed cell death 1, and PD-L1 programmed cell death ligand 1.

Immune-checkpoint inhibitors

These drugs reverse the inactivation of Antigen Presenting Cells and T cells enhancing the immune response to tumours.
Possible Mechanisms Underlying Immune-Related Adverse Events.

Organs Affected by Immune Checkpoint Blockade.

- Encephalitis, aseptic meningitis
- Hypophysitis
- Uveitis
- Thyroiditis, hypothyroidism, hyperthyroidism
- Dry mouth, mucositis
- Pneumonitis
- Rash, vitiligo
- Thrombocytopenia, anemia
- Myocarditis
- Hepatitis
- Pancreatitis, autoimmune diabetes
- Adrenal insufficiency
- Colitis
- Nephritis
- Enteritis
- Vasculitis
- Neuropathy
- Arthralgia

immune-related Adverse Events (irAEs):

Site

• More common sites:
  1. skin
  2. gastro-intestinal system
  3. liver
  4. endocrine system

• Less common sites:
  1. lung
  2. kidney
  3. etc.
immune-related Adverse Events (irAEs):
Frequency

Dose dependent
Commoner with more than 1 drug
immune-related Adverse Events: Timing

1. skin: 2-3 weeks
2. gastro-intestinal tract: 4-7 weeks
3. liver: 4-8 weeks
4. endocrine: 9 weeks

1/3rd of patients with liver involvement have preceding or concurrent involvement of other sites
immune-related Adverse Events: Patterns of liver damage

1. Panlobular hepatitis (70%)
2. Isolated zone 3 necrosis (20%)
3. Granulomatous hepatitis (5%)
4. Bile duct damage (1%)
5. Others e.g. fatty liver hepatitis (5%)

Journal of Clinical Pathology 2018;71:665-671
Seminars in Diagnostic Pathology,
https://doi.org/10.1053/j.semdp.2019.07.009
Patterns of Liver Damage:

1. Panlobular Hepatitis

• **Portal tract changes:** Mild
  1. Lymphocytic infiltrate – interface hepatitis, if severe
  2. Ductular reaction

• **Lobules:** Marked
  1. Focal necrosis and apoptosis
  2. Mainly lymphocytes - eosinophils may be prominent
  3. Activated macrophages – may form microgranulomas
  4. Regenerative hepatocyte changes
  5. Endothelialitis
Patterns of Liver Damage:
1. Panlobular Hepatitis
Patterns of Liver Damage:
1. Panlobular Hepatitis
Patterns of Liver Damage:
2. Isolated Zone 3 necrosis
Differences between Checkpoint inhibitor hepatitis and Auto-immune hepatitis

1. Low levels of auto-antibodies
2. No HLA association
3. Less portal and interface inflammation.
4. Plasma cells not conspicuous, eosinophils less common
5. Infiltration mainly be CD3+ CD8+ T-lymphocytes
   (as compared with CD20+ B cells and CD3 + CD4+ T lymphocytes in AIH)
6. Confluent necrosis, rosettes, emperipolesis and bile plugs less common

EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY 2019, VOL. 15, NO. 3, 231–244
Patterns of Liver Damage:

3. Granulomas

- Seen with ipilimumab +/- nivolumab.
Fibrin Ring Granulomas in Checkpoint Inhibitor-induced Hepatitis.
Everett, Jamie; Srivastava, Amitabh; Misdraji, Joseph
DOI: 10.1097/PAS.0000000000000759

FIGURE 2. Case 2: A, Small fibrin ring granuloma (arrow). B, Trichrome stain highlights the red fibrinous ring (arrow) within the fibrin ring granuloma. Note the presence of steatosis in hepatocytes around the fibrin ring granuloma.
Patterns of Liver Damage:

4. Bile duct damage

• Intrahepatic and extrahepatic bile ducts may be involved.
• PSC and PBC – like histology has been described
• Pattern of inflammation seen similar to that described in panlobular hepatitis

Investigational New Drugs. 2017 Aug 1;35(4):529-36
Intern Med 58: 1747-1752, 2019
Seminars in Diagnostic Pathology, https://doi.org/10.1053/j.semdp.2019.07.009
Patterns of Liver Damage 4. Bile duct damage: PBC – like pattern
Patterns of Liver Damage:
4. Bile duct damage

Patterns of Liver Damage 4. Others: Vascular damage
Patterns of Liver Damage 4. Others: Unmasking underlying liver disease

• **Auto-immune hepatitis**
  
  case report rare
  

• **Underlying viral hepatitis in patients with HCC**
  
  must be very uncommon
Patterns of Liver Damage 4. Others: Potentiating liver injury

- Viral infections?
- Drug Induced liver Injury?
Paracetamol induced liver damage in a mouse model - 72 hours

Control

Checkpoint inhibitor treated
Role of Liver Biopsy

Patients should have regular monitoring of their liver function tests. Consultation with a hepatologist be considered for any patient who develops grade 2 hepatotoxicity or greater.
Role of Liver Biopsy: Grading of liver injury

Table 3. Grading for hepatotoxicity is according to the Common Terminology Criteria for Adverse Events (CTCAE).

<table>
<thead>
<tr>
<th>Grade of Liver Injury</th>
<th>Definitions</th>
</tr>
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<tbody>
<tr>
<td>Grade 1</td>
<td>ALT/AST &lt; 3x ULN; TBili &lt; 1.5x ULN</td>
</tr>
<tr>
<td>Grade 2</td>
<td>AST/ALT 3-5x ULN; TBili 2-3x ULN</td>
</tr>
<tr>
<td>Grade 3</td>
<td>AST/ALT 5-20x ULN; TBili &gt;3x ULN</td>
</tr>
<tr>
<td>Grade 4</td>
<td>AST/ALT &gt; 20x ULN</td>
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<tr>
<td>Grade 5</td>
<td>Death due to hepatotoxicity</td>
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</table>
Role of Liver Biopsy

Liver biopsy can be useful in establishing the diagnosis.

Liver biopsy may be useful in a subset of patients to identify those with less severe inflammation (Grade 1 and 2) who may be able to avoid steroids.
Treatment

- Corticosteroids
- Limited data available on additional/alternative agents (e.g. tacrolimus)
- Guidelines from multiple groups agree on the need permanent discontinuation of immune checkpoint inhibitor therapy for grade 4 injury
Can other immunosuppressive drugs cause liver damage?
Can corticosteroids cause liver damage?

Effect of corticosteroids on the liver

Side effects are more common with long-term and/or high dose

1. Fatty change (which may include a fatty liver hepatitis) and/or glycogenosis
2. **Exacerbate underlying disease:**
   - non-alcoholic steatohepatitis.
   - chronic viral hepatitis.
   - autoimmune hepatitis
3. High doses of intravenous corticosteroids have been associated with acute liver injury