Immunotherapy induced DILI

Session: Hepatology

Audrey Coilly, MD, PhD
Centre Hepato-Biliaire
Paul Brousse Hospital, Villejuif France
Paris-Sud, Paris Saclay University
Disclosures

In connection with the talk

Ipsen
Others
Astellas
Abbvie
BMS
Intercept
Gilead
Novartis
Mr F., 52 years

Kidney carcinoma: nephrectomy in 2013

Pulmonary metastases in October 2014
• Treatment with SUNITINIB: tumor progression

Feb 2016 → Nivolumab (anti-PD1) administration. Overall 10 injections
5 months after Nivolumab initiation – Immune-related AE

Allergic rhinitis

Cutaneous manifestations (grade I)
- erythematous eruption eczema-like
- skin photosensitivity

Rise in liver tests (grade II-III)
- ALT 3.5ULN, AST 2ULN, GGT 5ULN, AlkP 3ULN,
- Bilirubine and PT were normal
Diagnostic work up

Clinical: asymptomatic

Viral serology and PCR: hepatitis A, E, B, C, HHV6, CMV, EBV negatives

Immunology: IgG normal, ANA 1:80 speckled, ASMA 1:80 no anti-actin

Doppler Ultrasound: steatosis

Liver biopsy: marked lobular hepatitis, moderate portal and peri-portal activity, inflammatory infiltration made by lymphocytes and macrophages
Corticosteroids 0.5mg/kg/day

AST
ALT

12-Jul 14-Jul 16-Jul 18-Jul 20-Jul 22-Jul 24-Jul 26-Jul

0 50 100 150 200 250 300 350

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« Auto-immune-like » hepatitis induced by immunotherapy

Steroids response
Favorable outcome regarding liver injury
Continuation of nivolumab
Agenda

1. Toxicity of immunotherapy

2. How to diagnose immunotherapy induced DILI?

3. How to manage immunotherapy induced DILI?
1. Toxicity of immunotherapy

2. How to diagnose immunotherapy induced DILI?

3. How to manage immunotherapy induced DILI?
Paradigm shift in cancer therapy

Historical Paradigm: Targeting Tumor Cells

New Paradigm: Targeting Immune Cells

Tumor Cell

Lymphocyte
Adaptive immune system helps controlling and eliminating cancer

CHECK-POINTS

Adapted from Pardoll, Nat Rev Cancer 2012
The blockade of immune checkpoints in cancer immunotherapy

Several have been approved

Anti-CTLA4
ipilimumab

Anti-PD1
pembrolizumab, nivolumab

Anti-PDL1
avelumab, durvalumab and atezolizumab
Adaptative anti-tumor immunity leads to survival benefits

Long duration responses

Which translates into OS benefits

Screening  Week 12  Week 14  Week 72

Hodi et al. Abstract #3008 ASCO 2008

Anti-CTLA4

Overall Survival (proportion)

Time (months)

0 12 24 36 48 60 72 84 96 108 120

Ipilimumab

Pembrolizumab Bladder

Pembrolizumab Chemo

43.9%

30.7%

Bellmunt SITC 2016

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Spectrum of toxicity of immune checkpoint blockade agents

New kind of toxicities - IRAE

Agenda

1. Toxicity of immunotherapy

2. How to diagnose immunotherapy induced DILI?

3. How to manage immunotherapy induced DILI?
Mrs S., 45 years

- Hodgkin lymphoma stage IV
- Administration of Pembrolizumab (anti-PD1)

After 29 injections:

<table>
<thead>
<tr>
<th></th>
<th>12/06/15</th>
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<tr>
<td>AST, IU/L</td>
<td>690</td>
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<tr>
<td>ALT, IU/L</td>
<td>1386</td>
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<tr>
<td>Alk P, IU/L</td>
<td>136</td>
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<tr>
<td>T Bili, μmol/L</td>
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</table>
Mrs S., 45 years

- Hodgkin lymphoma stage IV
- Administration of Pembrolizumab (anti-PD1)

After 29 injections:

<table>
<thead>
<tr>
<th>Test</th>
<th>12/06/15</th>
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<tr>
<td>AST, IU/L</td>
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<td>136</td>
</tr>
<tr>
<td>T Bili, μmol/L</td>
<td>10</td>
</tr>
</tbody>
</table>

PCR HEV : +
DO NOT forget we are gastroenterologist

3 steps approach
3-steps approach

1. Exclude another cause of hepatitis

Special attention to:
Viruses – needs PCR
Other medication

Of importance:
Could lead to stop a beneficial treatment

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### 3-steps approach

**2. Predict whether liver damage can be attributed to immunotherapy**

<table>
<thead>
<tr>
<th></th>
<th>WHO 4 Levels</th>
<th>Naranjo 4 Levels</th>
<th>RUCAM 5 Levels</th>
<th>M &amp; V 5 Levels</th>
<th>DILIN 5 Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Level 1 [Certain]</td>
<td>Definite</td>
<td>Highly Probable</td>
<td>Definite</td>
<td>Definite and Highly Likely</td>
</tr>
<tr>
<td></td>
<td>Level 2 [Probable]</td>
<td>Probable</td>
<td>Probable</td>
<td>Probable</td>
<td>Probable</td>
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<tr>
<td></td>
<td>Level 3 [Possible]</td>
<td>Possible</td>
<td>Possible</td>
<td>Possible</td>
<td>Possible</td>
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<tr>
<td></td>
<td>Level 4 [Unlikely]</td>
<td>Doubtful</td>
<td>Not Likely and Excluded</td>
<td>Not Likely and Excluded</td>
<td>Unlikely</td>
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</tbody>
</table>
RUCAM: Roussel-UCLAF Causality Assessment Method

RUCAM Causality Assessment

<table>
<thead>
<tr>
<th>Drug:</th>
<th>Initial ALT:</th>
<th>Initial AK P:</th>
<th>R ratio = [ALT ULN] + [AK P ULN]:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Assessment**

1. **Time to onset**

   - **From the beginning of the drug:**
     - **Suggestive**
     - **Compatible**
     - **Inconclusive**

   - **From cessation of the drug:**
     - **Compatible**

<table>
<thead>
<tr>
<th>Hepatocellular Type</th>
<th>Cholestatic or Mixed Type</th>
<th>Score (check one only)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** If reaction begins before starting the medication or >15 days after stopping (hepatocellular), or >30 days after stopping (cholestatic), the injury should be considered unrelated and the RUCAM cannot be calculated.

2. **Course**

   - **Change in ALT between peak value and ULN**
   - **Change in AK P (or total bilirubin) between peak value and ULN**

<table>
<thead>
<tr>
<th>After stopping the drug:</th>
<th>Score (check one only)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. **Risk Factors:**

   - **Ethanol**
   - **Ethanol or Pregnancy (either)**
   - **Age**

<table>
<thead>
<tr>
<th>Score (check one for each)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

© LSG. 2019
### RUCAM: Roussel-UCLAF Causality Assessment Method

<table>
<thead>
<tr>
<th>4. Concomitant drugs:</th>
<th>Score (check one only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- None or no information or concomitant drug with incompatible time to onset</td>
<td>0</td>
</tr>
<tr>
<td>- Concomitant drug with suggestive or compatible time to onset</td>
<td>1</td>
</tr>
<tr>
<td>- Concomitant drug known to be hepatotoxic with a suggestive time to onset</td>
<td>2</td>
</tr>
<tr>
<td>- Concomitant drug with clear evidence for its role (positive rechallenge or clear link to injury and typical signature)</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Exclusion of other causes of liver injury:</th>
<th>Score (check one only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (6 causes):</td>
<td></td>
</tr>
<tr>
<td>- Acute viral hepatitis due to HAV (IgM anti-HAV), or</td>
<td></td>
</tr>
<tr>
<td>- HBV (HbsAg and/or IgM anti-HBc), or</td>
<td></td>
</tr>
<tr>
<td>- HCV (anti-HCV and/or HCV RNA with appropriate clinical history)</td>
<td></td>
</tr>
<tr>
<td>- Bilary obstruction (by imaging)</td>
<td></td>
</tr>
<tr>
<td>- Alcoholism (History of excessive intake and AST/ALT ≥ 2)</td>
<td></td>
</tr>
<tr>
<td>- Recent history of hypotension, shock or ischemia (within 2 weeks of onset)</td>
<td></td>
</tr>
<tr>
<td>Group II (2 categories of causes):</td>
<td></td>
</tr>
<tr>
<td>- Complications of underlying diseases such as autoimmune hepatitis, sepsis, chronic hepatitis B or C, primary biliary cirrhosis or sclerosing cholangitis, or</td>
<td></td>
</tr>
<tr>
<td>- Clinical features or serologic and virologic tests indicating acute CMV, HSV, or HSV</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. Previous information on hepatotoxicity of the drug:</th>
<th>Score (check one only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Reaction labeled in the product characteristics</td>
<td>0</td>
</tr>
<tr>
<td>- Reaction published but unreported</td>
<td>1</td>
</tr>
<tr>
<td>- Reaction unknown</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. Response to readministration:</th>
<th>Score (check one only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Positive</td>
<td>Doubling of ALT with drug alone</td>
</tr>
<tr>
<td>- Compatible</td>
<td>Doubling of the ALT with the suspect drug combined with another drug which had been given at the time of onset of the initial injury</td>
</tr>
<tr>
<td>- Negative</td>
<td>Increase of ALT but less than ULN with drug alone</td>
</tr>
<tr>
<td>- Not done or not interpretable</td>
<td>Other situations</td>
</tr>
</tbody>
</table>

**TOTAL (add the checked figures):**

---

**Abbreviations used:** ALT, alanine aminotransferase; AR, alkaline phosphatase; ULN, upper limit of the normal range of values

**Modified from:** Donat G and Benichou C. J Clin Epidemiol 1993; 46: 1329-30

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## RUCAM: Roussel-UCLAF Causality Assessment Method

4. Concomitant drug(s):
- None or no information or concomitant drug with incompatible time to onset: 0
- Concomitant drug with suggestive or compatible time to onset: +1
- Concomitant drug known to be hepatotoxic with a suggestive time to onset: +2
- Concomitant drug with clear evidence for its role (positive rechallenge or clear link to injury and typical signature): +3

5. Exclusion of other causes of liver injury:
   - Group I (6 causes):
     - Acute viral hepatitis due to HAV (IgM anti-HAV), or: +2
     - HBV (IgM anti-HBc), or: +1
     - HCV (anti-HCV and/or HCV RNA with appropriate clinical history): +3
     - Biliary obstruction (by imaging): +0
     - Alcoholism (history of excessive intake and AST/ALT > 2): 0
     - Recent history of hypotension, shock or ischemia (within 2 weeks of onset): 0
   - Group II (2 categories of causes):
     - Complications of underlying disease(s) such as autoimmune hepatitis, sepsis, chronic hepatitis B or C, primary biliary cirrhosis or sclerosing cholangitis: -3
     - Clinical features or serologic and virologic tests indicating acute CMV, EBV, or HSV: -2

6. Previous information on hepatotoxicity of the drug:
   - Reaction labeled in the product characteristics: +2
   - Reaction published but unlabeled: +1
   - Reaction unknown: 0

7. Response to readministration:
   - Positive: +3
   - Compatible: +1
   - Negative: -2
   - Not done or not interpretable: 0

Scores (check one only):
- 0 < drug is excluded
- 1-2 = unlikely
- 3-5 = possible
- 6-8 = probable
- >8 = highly probable

**Scores (check one only):**
- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8

**Total (add the checked figures):**

Abbreviations used: ALT, alanine aminotransferase; AKP, alkaline phosphatase; U/L, upper limit of the normal range of values

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3-steps approach

3. Histological assessment
Several reported series: « AIH-like »

Clinical features of 11 patients with acute hepatitis using Ipilimumab – anti CTLA4

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Risk Factors for Liver Disease</th>
<th>Medication History</th>
<th>Doses of Ipilimumab</th>
<th>Peak ALT (U/L); AST (U/L); TB (mg/dL); AP (U/L)*</th>
<th>Predominant Histologic Pattern of Liver Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>M</td>
<td>None</td>
<td>Amlodipine, lisinopril, carbidopa, ropinirole, lorazepam, odanetron</td>
<td>3</td>
<td>467/975/6.1/436</td>
<td>Panlobular hepatitis</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>M</td>
<td>Obese</td>
<td>Capecitabine, BRAF inhibitor</td>
<td>3</td>
<td>715/767/15.6/453</td>
<td>Panlobular hepatitis</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>M</td>
<td>None</td>
<td>None</td>
<td>4</td>
<td>3075/1293/4.6/302</td>
<td>Panlobular hepatitis</td>
</tr>
<tr>
<td>4</td>
<td>71</td>
<td>M</td>
<td>Hemochromatosis carrier</td>
<td>Nivolumumab</td>
<td>2</td>
<td>416/560/1.1/315</td>
<td>Panlobular hepatitis</td>
</tr>
<tr>
<td>5</td>
<td>47</td>
<td>M</td>
<td>None</td>
<td>Nivolumumab</td>
<td>3</td>
<td>189/67/0.6/81</td>
<td>Panlobular hepatitis</td>
</tr>
<tr>
<td>6</td>
<td>53</td>
<td>M</td>
<td>None</td>
<td>+/− Nivolumumab†</td>
<td>3</td>
<td>185/201/0.6/185</td>
<td>Panlobular hepatitis</td>
</tr>
<tr>
<td>7</td>
<td>69</td>
<td>M</td>
<td>None</td>
<td>None</td>
<td>2</td>
<td>629/365/0.8/129</td>
<td>Zone 3 hepatitis</td>
</tr>
<tr>
<td>8</td>
<td>47</td>
<td>F</td>
<td>None</td>
<td>+/− Nivolumumab†</td>
<td>4</td>
<td>384/163/0.4/79</td>
<td>Zone 3 hepatitis</td>
</tr>
<tr>
<td>9</td>
<td>33</td>
<td>M</td>
<td>Alcohol</td>
<td>Levetiracetam, vemurafenib</td>
<td>3</td>
<td>575/220/0.6/48</td>
<td>Zone 3 hepatitis</td>
</tr>
<tr>
<td>10</td>
<td>83</td>
<td>M</td>
<td>None</td>
<td>Dutasteride, alendronic acid, hydrocortisone, ketoconazole, metaclopamidine, nilutamide</td>
<td>2</td>
<td>377/143/0.4/374</td>
<td>Cholangitis/portal inflammation</td>
</tr>
<tr>
<td>11</td>
<td>65</td>
<td>M</td>
<td>Obese</td>
<td>Amlodipine, atenolol, rosuvastatin, aspirin fluticasone, gabapentin, omeprazole, quinapril, dexamethasone</td>
<td>1</td>
<td>550/340/0.7/134</td>
<td>Steatohepatitis</td>
</tr>
</tbody>
</table>

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1 clinical case, patient with glioblastoma treated with Nivolumab – anti-PD1

Hepatocyte clarification and macrovacuolar steatosis
Suggesting mitochondrial toxicity

Lobular hepatitis: polymorphic infiltration
No plasmocytes

Simonelli, Immunotherapy 2016
2 patients treated with Ipilimumab + Nivolumab

Small fibrin ring granuloma with central lipid vacuole

Trichrome staining highlights the fibrin ring in the granuloma
Patients with immune-mediated hepatitis from Paul Brousse/IGR

536 patients treated with immunotherapy 2015-2017

19 (1.3%) acute hepatitis

3 patients excluded:
1 = absence of histology
1 = PCR HEV+
1 = hepatic tumor infiltration

16 (1%) immune-mediated hepatitis

9 anti-PD1/PDL1

7 anti-CTLA4 +/- anti-PD1

De Martin, … Coilly, … Samuel, J Hepatol 2018
Anti-CTLA4 Ipilimumab: histological features

Centrilobular necrosis with fibrin ring granulomas

Sinusoidal inflammatory infiltrates with activated lymphocytes and histiocytes

De Martin, … Coilly, … Samuel, J Hepatol 2018
1. Toxicity of immunotherapy

2. How to diagnose immunotherapy induced DILI?

3. How to manage immunotherapy induced DILI?
3 questions to address

1. What is the severity/prognosis?

2. Is there useful treatment?

3. Could we rechallenge patient with immunotherapy?
Immunotherapy induced DILI is uncommon

Thousands of patients using immunotherapy

Prevalence of hepatitis: 1-5%

<10 case-reports of severe ALF

De Martin, J Hepatol 2018, Larkin, NEJM 2015
Fulminant/severe hepatitis

Efficacy and safety of ipilimumab monotherapy in patients with pretreated advanced melanoma: a multicenter single-arm phase II study

One treatment-related death by liver failure occurred in a patient who did not promptly receive systemic steroids. For

Case Report

Acute Liver Failure from Anti-PD-1 Antibody Nivolumab in a Patient with Metastatic Lung Squamous Cell Carcinoma

Mortality due to immunotherapy related hepatitis

O’Day, Annals of Onco 2010

Sarmen, Austin Oncol 2016

Bhave, J Hepatol 2018
**Common Toxicity Criteria for Adverse Events: CTCAE**

Cancer Therapy Evaluation Program of the National Cancer Institute (NCI) of the National Institutes of Health

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>Grade 0</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Life-threatening</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>Grade 4</td>
<td>Grade 4</td>
</tr>
<tr>
<td>ALT</td>
<td>Normal</td>
<td>&gt;1.0-2.5</td>
<td>&gt;2.5-5.0</td>
<td>&gt;5.0-20</td>
<td>&gt;20</td>
</tr>
<tr>
<td>AST</td>
<td>Normal</td>
<td>&gt;1.0-2.5</td>
<td>&gt;2.5-5.0</td>
<td>&gt;5.0-20</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>Normal</td>
<td>&gt;1.0-2.5</td>
<td>&gt;2.5-5.0</td>
<td>&gt;5.0-20</td>
<td>&gt;20</td>
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<tr>
<td>GGT</td>
<td>Normal</td>
<td>&gt;1.0-2.5</td>
<td>&gt;2.5-5.0</td>
<td>&gt;5.0-20</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Normal</td>
<td>&gt;1.0-1.5</td>
<td>&gt;1.5-3.0</td>
<td>&gt;3.0-10</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>
### Common Toxicity Criteria for Adverse Events: CTCAE

Cancer Therapy Evaluation Program of the National Cancer Institute (NCI) of the National Institutes of Health

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>Grade 4</th>
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<tbody>
<tr>
<td>ALT</td>
<td>&gt;20</td>
</tr>
<tr>
<td>AST</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>&gt;20</td>
</tr>
<tr>
<td>GGT</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>

#### Mild, Moderate, Severe

- **Overestimation of severity**
- **Not following experience of ALF**

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>Normal</th>
<th>&gt;1.0-1.5</th>
<th>&gt;1.5-3.0</th>
<th>&gt;3.0-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>Normal</td>
<td>&gt;1.0-1.5</td>
<td>&gt;1.5-3.0</td>
<td>&gt;3.0-10</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT/AST ULN</td>
<td>Steroids</td>
<td>Immunotherapy</td>
<td></td>
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<tr>
<td>------------------</td>
<td>--------------------------------</td>
<td>----------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>No</td>
<td>Continue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT/AST≤3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>0.5-1mg/Kg/day</td>
<td>Hold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3&lt;ALT/AST≤5</td>
<td>Start 4–6 week steroid taper</td>
<td>Continue once resolved to ≤grade 1 and off corticosteroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>when G1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>1-2mg/Kg/day</td>
<td>Hold; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5&lt;ALT/AST≤20</td>
<td>Start 4–6 week steroid taper</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>when G1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>If no improvement in 2–3 days,</td>
<td>Discontinue immunotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT/AST&gt;20</td>
<td>add additional/alternative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>immune suppressant</td>
<td></td>
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</tbody>
</table>
### Consensus of Society for Immunotherapy of Cancer Toxicity Management Working Group

<table>
<thead>
<tr>
<th>ALT/AST ULN</th>
<th>Steroids</th>
<th>Immunotherapy</th>
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<td>Hold Continue once resolved to ≤grade 1 and off corticosteroids</td>
</tr>
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<td>Grade 3 5&lt;ALT/AST≤20</td>
<td>1-2mg/Kg/day Start 4–6 week steroid taper when G1</td>
<td>Hold; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy</td>
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<td>Grade 4 ALT/AST&gt;20</td>
<td>If no improvement in 2–3 days, add additional/alternative immune suppressant</td>
<td>Discontinue immunotherapy</td>
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37 Immunotherapy induced DILI 

Spain L, Cancer Treatment Review 2016, Puzanov I, J Immunother Cancer. 2017
## Consensus of Society for Immunotherapy of Cancer Toxicity Management Working Group

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ALT/AST≤3         | No                                | Continue                                           |
| Grade 2
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Start 4–6 week steroid taper when G1 | Hold
Continue once resolved to ≤grade 1 and off corticosteroids |
| Grade 3
5<ALT/AST≤20        | 1-2mg/Kg/day
Start 4–6 week steroid taper when G1 | Hold; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy |
| Grade 4
ALT/AST>20         | If no improvement in 2–3 days, add additional/alternative immune suppressant | Discontinue immunotherapy |

**ALT/AST ULN**: Upper Limit of Normal

**Steroids**

- Grade 1: No
- Grade 2: 0.5-1mg/Kg/day
- Grade 3: 1-2mg/Kg/day
- Grade 4: If no improvement in 2–3 days, add additional/alternative immune suppressant

**Immunotherapy**

- Continue
- Hold
- Hold; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy
- Discontinue immunotherapy
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*ALT/AST ULN: Upper Limit of Normal for ALT and AST.*

39 Immunotherapy induced DILI

*Spain L, Cancer Treatment Review 2016, Puzanov I, J Immunother Cancer. 2017*
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Possible efficacy of budesonide  
Ziemer, J Hepatol, 2016

Possible increase with other immunosuppressive agents (ATG, mycophenolate)  
Chmiel, J of Clinical Oncol 2011  
De Martin, J Hepatol, 2018

Spain L, Cancer Treatment Review 2016, Puzanov I, J Immunother Cancer. 2017
Steroids use is debatable

De Martin, J Hepatol 2018
Rechallenge? Avoid anti-CTLA4

• 76-year-old patient with an ovarian cancer → grade 2 hepatitis on Nivolumab improved by corticosteroids.

• Introduction of Ipilimumab due to cancer progression → development of fulminant hepatitis.

• Resolution with plasma exchange.

HE: hepatic encephalopathy

Prothrombin time (%)

11-oct

0 2 4 6 8 10 12 14

0 2 4 6 8 10 12 14

Riveiro-Barcela, J Hepatol 2018
• 80 patients treated with combination therapy.

• All discontinued immunotherapy due to irAEs, 29 (36%) for hepatitis, 19 (24%) grade 3 or 4.

• All patients resumed anti-PD1 therapy and 50% experienced a toxicity.

• 5 (17%) patients had hepatitis recurrence.

Percentage of patients with toxicities with combination therapy and after resuming anti-PD1 therapy.

43 Immunotherapy induced DILI – Audrey Coilly

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Pollack, Ann Oncol 2018
• 73-year-old patient with metastatic melanoma → grade 3 hepatitis after 2 cycle of Nivolumab.

• No hepatitis recurrence after immunotherapy reintroduction on budesonide prophylaxis.

Evolution of AST, ALT and GGT

Last scenario: anti-PD1 alone + steroids... The trend

Methylprednisolone, starting dose 1 mg/kg body weight (72 mg/d), stopped at the time of restart nivolumab

Ursodeoxycholic acid 2 x 500 mg

N-acetylcysteine 3 x 1200 mg (dose reduced to 3 x 600 mg on day 90)

Budesonide 3 x 3 mg (dose reduced to 2 x 3 mg on day 162)
Multidisciplinary approach is absolutely required

Oncologist
Hepatologist
Immunologist
Pharmacist
Pathologist
Virologist, radiologist
Management proposition of hepatic immune-toxicity

- Cytolysis and cholestasis grade ≥ 3
- Liver biopsy
- Rule out common causes of acute hepatitis

- Hepatic tumor infiltration
- Immune-mediated hepatitis
- Other findings

Based on severity of liver injury (bilirubin ≥ 2.5 mg/dL and/or INR ≥ 1.5 and histology)

- Surveillance
- Corticosteroids 0.5-1 mg/kg/d
- Corticosteroids 2 mg/kg/d +/- 2nd immunosuppressive drug

* the biopsy is not recommended if viral hepatitis
In summary

Immune-mediated hepatitis due to immune checkpoint inhibitors for metastatic cancer is rare

The diagnosis requires the exclusion of all causes of acute hepatitis

Liver histology helps to:

1. Confirm the diagnosis
2. Evaluate the severity of the hepatic injury

Corticosteroid therapy needs to be patient oriented according to the biological and histological severity of liver injury, with a multidisciplinary decision