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Transaminase Elevations in the Treatment of Heart Failure

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Drug-Induced Liver Injury Conference XV
Wednesday, March 18, 2015
Disclosure Slide

I have nothing to disclose, and the opinions expressed here are my own.
Objectives

• To review the effects of acute and chronic heart failure on acute and chronic liver injury, respectively.

• To discuss the challenges in assessing the potential for a drug product to cause drug-induced liver injury in the setting of heart failure.
Hepato-Cardiac Diseases

• Heart diseases affecting the liver
• Liver diseases affecting the heart
• Conditions affecting the heart and the liver at the same time
Heart Failure

Acute heart failure → Acute ischemic hepatitis (acute liver injury)

Chronic heart failure → Chronic congestive hepatopathopy (“nutmeg liver”)

*Goal is to treat the underlying heart disease*
Nutmeg + Liver
Liver Injury

• Acute (ischemic hepatitis)
• Chronic
Acute Liver Injury

• Occurs when hepatic blood flow is decreased and the liver can no longer protect itself from hypoxic damage → get hepatocellular injury
Acute Liver Injury

- Hypotension
- Hypoxemia
- Increased metabolic demand
Hypotension

• Acute myocardial infarction (AMI)
• Heart failure (HF)
  – Accounts for most cases of acute liver injury
• Pulmonary embolus
• Sustained arrhythmia (afib/flutter with RVR)
Hypoxemia

- Respiratory failure
- Obstructive sleep apnea
Increased Metabolic Demand

• Toxic/Septic Shock
Acute Liver Injury: Symptoms

• Asymptomatic; or
• Nonspecific Symptoms
  – Nausea/vomiting
  – Anorexia
  – Malaise
  – Right-upper quadrant pain
  – Jaundice
  – Oliguria
  – Flapping tremors
Acute Liver Injury: Laboratory Evaluation

• Sharp increases in ALT, AST, TB, ALP, LDH, PT, occasionally accompanied by renal impairment
  – Peak 1-3 days after the onset of the insult
  – Normalize within 5 to 10 days
• ALT/LDH ratio < 1.5
Acute Liver Injury: Pathophysiology

- Characterized by centrilobular necrosis of zone 3 hepatocytes
Histology
Liver Injury

• Acute (ischemic hepatitis)
• Chronic
Chronic Heart Failure and Hepatic Dysfunction

• Ischemic/nonischemic cardiomyopathies
• Pulmonary arterial hypertension
• Valvular heart disease
  – Mitral stenosis
  – Tricuspid regurgitation
• Constrictive pericarditis
• Fontan Procedure (postoperative consequences)
Chronic Liver Injury: Symptoms

- Mild, dull right upper quadrant pain
- Hepatomegaly
- Peripheral Edema
- Ascites
- Jaundice (uncommon)
Chronic Liver Injury: Laboratory Evaluation

• AST, ALT, LDH, GGT, and ALP 2-3x ULN
• Increased TB (direct and indirect)
  – Rarely exceeds 3 mg/dL
• Hypoalbuminemia
Chronic Liver Injury: Pathophysiology

- Hepatocyte atrophy
- Perisinusoidal edema
- Enhanced hepatic lymph formation
- Thrombosis within sinusoids, hepatic venules, and portal tracts (from stagnant flow)
- Zone 3 – alternating pattern of hemorrhage and necrosis
- Zones 1 and 2 – normal or slightly steatotic areas
<table>
<thead>
<tr>
<th>Etiology</th>
<th>ACUTE LIVER INJURY</th>
<th>CHRONIC LIVER INJURY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute heart failure</td>
<td>Chronic heart failure</td>
</tr>
<tr>
<td>Laboratory Data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB</td>
<td>Marked Increase (15-20 mg/dL)</td>
<td>Mild Increase (rarely &gt; 3 mg/dL)</td>
</tr>
<tr>
<td>ALT and AST</td>
<td>&gt; 10x</td>
<td>Normal/Mild Increase (2-3 x ULN)</td>
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<tr>
<td>LDH</td>
<td>Marked Increase</td>
<td>Normal/Mild Increase (2-3 x ULN)</td>
</tr>
<tr>
<td>ALP</td>
<td>Increased</td>
<td>Normal/Mild Elevation (2-3 x ULN)</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>Normal or Prolonged</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Albumin</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Benign and usually self-limited</td>
<td>Slowly progressive course</td>
</tr>
</tbody>
</table>
Severe Drug-Induced Liver Injury

- Hepatocellular injury
- Aminotransferase (AT) elevations (ALT, AST) > 3x ULN and TB > 2x ULN
- Normal ALP
- No other reasons to explain the combination of increased AT and TB (e.g., hepatitis, preexisting or acute liver disease, another drug capable of causing the observed injury, PK interactions)
- May not be dose-related or evident nonclinically (exception: acetaminophen)
- Idiosyncratic hepatotoxicity (e.g., bromfenac, troglitazone, ximelagatran)
Summary

- There is a mutual relationship between the heart and the liver.
- Acute heart failure can lead to acute liver injury (acute ischemic hepatitis).
- Chronic heart failure can lead to chronic liver injury (chronic congestive hepatopathy).
- Treat the underlying heart failure.
- In the setting of heart failure, it can be challenging to assess whether a drug product can cause drug-induced liver injury.
Back-Up Slides
Acute Liver Injury

• Hypotension
  – Acute myocardial infarction (AMI)
  – Heart Failure (HF)
    • Accounts for most cases of acute liver injury
  – Pulmonary embolus
  – Sustained arrhythmia (afib/flutter with RVR)

• Hypoxemia
  – Respiratory failure
  – Obstructive sleep apnea

• Increased metabolic demand
  – Toxic/septic shock