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Evaluation of Transaminase Elevations in Subjects with Chronic Hepatitis C

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The opinions expressed by Dr. Carter in this presentation do not reflect official support or endorsement by the US Food and Drug Administration.

Determining DILI due to HCV DAA Therapy: Challenges

- Definitions used in non-HCV populations may not apply (Hy's Law)
- Liver biochemistries generally improve with DAA therapy
 - Should changes be evaluated from traditional x ULN, or baseline or nadir?
- Presentations vary based on multiple factors
 - Comorbidities, concomitant medications, stage of liver disease, host genetic factors etc.

Definitions and Management

- FDA DILI Guidance and Hy's Law
 - Not intended for patients with chronic HCV
 - Updates to guidance are in process
- What is the type of injury?
 - Immune related
 - Cholestatic
 - Drug-Drug interaction
- What discontinuation and follow-up criteria are appropriate in this population?
 - Based on what cut-offs?
 - Balance between safety and not having early discontinuation with loss of efficacy

Use of Multiple Investigational Agents

- Use of several unapproved products in a regimen makes attribution more difficult
 - Totality of data
 - Consideration of class
 - Protease inhibitors for treatment of HIV are known to have risk of hepatotoxicity
- What host factors are an issue?
 - Stage of disease; genetic predisposition, immune response to clearing of the virus (different without use of pegINF?)

OBSERVATIONS IN HEPATOTOXICITY

Drug-Induced Immunoallergic Hepatitis During Combination Therapy With Daclatasvir and Asunaprevir

Yohei Fujii, Yoshihito Uchida, and Satoshi Mochida

- Daclatasvir (DCV) – NS5A inhibitor
- Asunaprevir (ASV) – NS3/4A protease inhibitor
- Approved in Japan in combination for treatment of chronic hepatitis C

Hepatology. 2015 Jan;61(1):400-1.

DCV/ASV Immunoallergic Hepatitis

Case Report

- 57 year old male with GT1b CHC on a planned 24 week treatment with daclatasvir (DCV) and asunaprevir (ASV)
- At Day 15, developed fever and eosinophilia, ALT was normal and HCV RNA decreased to 50 IU/mL from 12.6 million IU/mL
- At Day 29: ALT was 609 U/L, Alk P 320 U/L and bilirubin 3.3 mg/dL and further increase in eosinophilia to 2,876 mm³ ; DCV and ASV were stopped
- Day 36 liver biopsy: interface hepatitis with bridging fibrosis and focal lobular necrosis with eosinophils, lymphocytes and plasma cells in the hepatic lobules and portal areas.
- Day 37 prednisone taper started with rapid resolution of liver biochemistry abnormalities

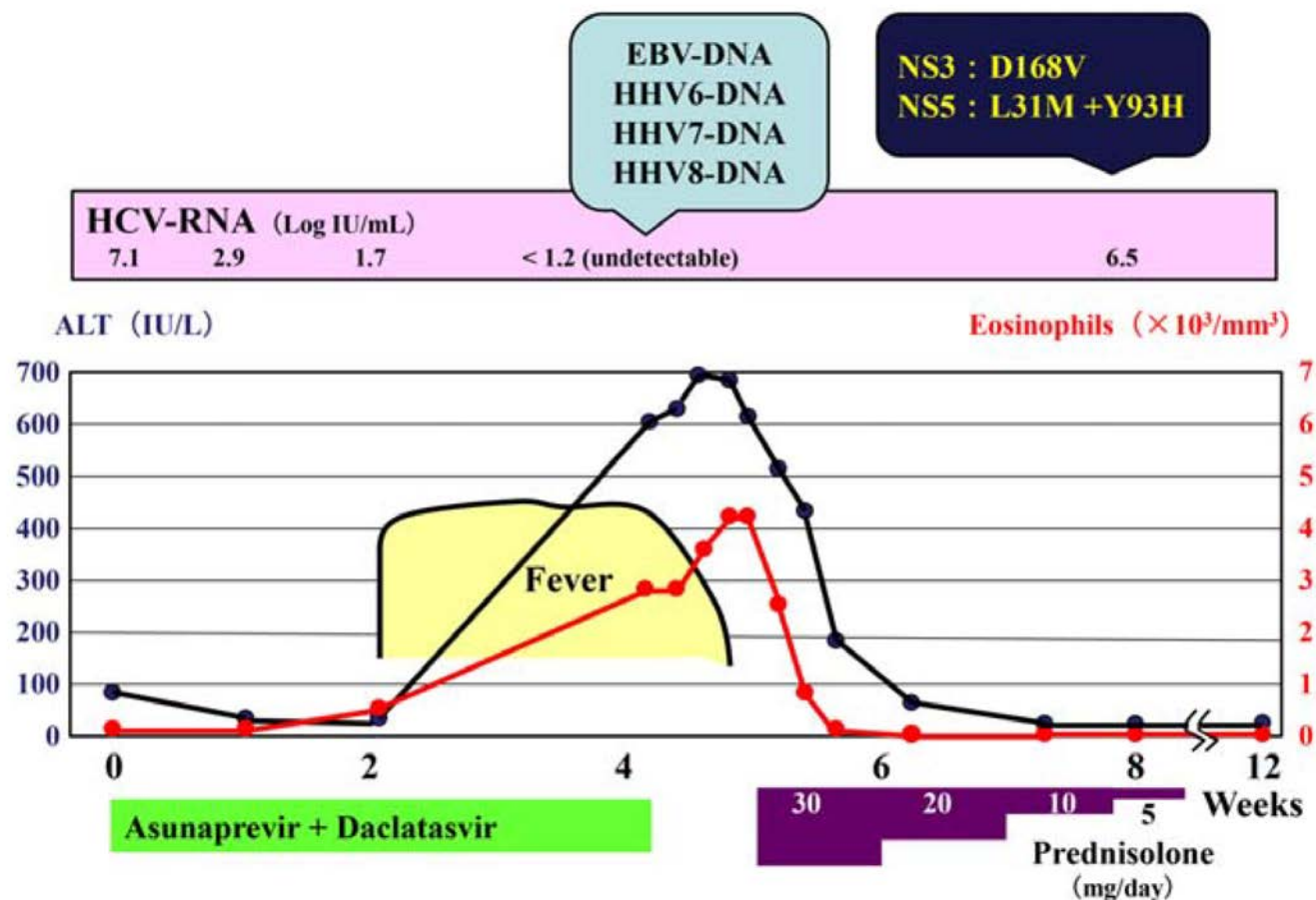


Fig. 1. Clinical course of a patient with immunoallergic liver injury during therapy with daclatasvir and asunaprevir.

Genetic Component to Syndrome and/or DILI?

- Authors state overall clinical syndrome was typical of drug fever or drug-hypersensitivity syndrome rather than DRESS (drug rash with eosinophilia and systemic signs)
- In the Japanese DCV/ASV trial, 16% of subjects had ALT elevations and 9% had ALT above 5x ULN
 - This syndrome as well as ALT elevations/fever appeared more frequently in Japanese than in US/EU trials
- Authors suggest genetic basis for liver findings

Impact of Stage of Disease

- Unknown how more advanced disease states of CHC may respond to many of the new DAA regimens
- Few have large safety databases of more advanced cirrhotic subjects at approval
- More advanced patients are also in most need for treatment
- Leads to compassionate use

Sofosbuvir and Simeprevir



- Sofosbuvir (nucleotide analog NS5B polymerase inhibitor) and simeprevir (NS3/4A protease inhibitor)
- Recommended as an option in treatment guidelines (off label) prior to approval of this regimen on November 5, 2014
- Was often used in patients with advanced disease and limited pegINF/RBV free treatment options
 - Simeprevir label: not recommended for severe hepatic impairment (Child-Pugh Class C)

Hepatic Decompensation Likely Attributable to Simeprevir in Patients with Advanced Cirrhosis

Jonathan G. Stine · Nicolas Intagliata · Neeral L. Shah ·
Curtis K. Argo · Stephen H. Caldwell · James H. Lewis ·
Patrick G. Northup

- 2 case reports of DILI leading to hepatic decompensation in patients with advanced HCV cirrhosis treated with Simeprevir and Sofosbuvir on a compassionate basis.
- Both patients developed marked hyperbilirubinemia out of proportion to their aminotransferases, despite clearance of HCV RNA.
- Authors point to **possible impaired metabolism from under-expression of hepatic transporters OATP1B1 and MRP2**, which are known to be reduced in advance liver disease and cirrhosis
- Authors argue that SMV be used with great caution, if at all, in CPT Class B or C patients (await newer DAAs- NS5As are referenced)

Viekira Pak



- Approved December 19, 2014
- Ombitasvir (NS5A inhibitor), paritaprevir (NS3/4A protease inhibitor), ritonavir (CYP3A inhibitor) fixed dose combination tablets copackaged with dasabuvir (non-nucleoside NS5B polymerase inhibitor) tablets.

Factors complicating evaluation of potential DILI with Viekira Pak

- ALT elevations observed in estrogen-containing oral contraceptive DDI trial in healthy volunteers
- Risk of elevations of ALT in females using systemic estrogen containing medications seen in phase 3 trials was higher than overall population (9% vs. 1%)
- Paritaprevir is a known inhibitor of the bilirubin transporter OATP1B1, which leads to asymptomatic elevations of predominantly indirect bilirubin levels.
- Viekira Pak is combined with Ribavirin for all GT1a subjects and for GT1b subjects with cirrhosis
- Hemolytic anemia caused by ribavirin increases indirect bilirubin levels

Source: Clinical Review available online at Drug@FDA

Summary of Potentially Confounding Issues

- DAAs concentrate and are metabolized in the liver and have various transporter affects (DDIs)
- Patients have various stages of disease and may have very different presentations (asymptomatic to obvious decompensation)
- Genetic factors may play a role for some drugs
- Class affects may be important

Issues that FDA Reviewers Continue to Grapple With!

- How often should patients be monitored for abnormalities of liver biochemistries?
- What level of change warrants modification to the monitoring plan and/or discontinuation (balancing safety with efficacy)?
 - Increase from baseline, or nadir value or ULN?
- Are there “at risk” patients that need enhanced monitoring or should avoid certain drugs/classes?
 - This could include race or other host or viral factors



