The potential role of PK-based drug interactions in FAERS-reported rhabdomyolysis cases in patients receiving a DAA regimen and a Statin

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The opinions expressed in this presentation are the presenter’s and do not necessarily reflect the official views of the United States Food and Drug Administration (FDA)
Introduction

• **Statins (HMG-CoA Reductase Inhibitors)**
  – Approved to manage dyslipidemia and reduce the risk of cardiovascular events
  – Statins are commonly used in adults in the US
    > 20% adults age 40 and over use statins
  – Generally safe, but associated with myotoxicity

• **Statin-associated rhabdomyolysis**
  – Rapid breakdown of skeletal muscles, leading to the release of toxic breakdown products into plasma
  – Rare but can be life threatening
  – Risk factor: ↑ age, renal impairment, uncontrolled hypothyroidism, genetic factors, and certain concomitant medications

Introduction

• The use of statins in patients with chronic hepatitis C (HCV) infection
  – Expected to be common considering the average age of HCV patients\(^2\)
  
  – Some DAAs have the potential to increase the exposures of statins by inhibiting metabolism/transport of statins
  
  – Several cases of rhabdomyolysis associated with the use of HCV DAA regimens in combination with statins have been reported to the FDA Adverse Event Reporting System (FAERS)

## Clinical drug interactions between HCV direct-acting antivirals and statins

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Atorvastatin</th>
<th>Fluvastatin</th>
<th>Lovastatin</th>
<th>Pitavastatin</th>
<th>Pravastatin</th>
<th>Rosuvastatin</th>
<th>Simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daclatasvir</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>SI</td>
<td>N</td>
</tr>
<tr>
<td>Elbasvir/grazoprevir</td>
<td>SI</td>
<td>N</td>
<td>N</td>
<td>SN</td>
<td>SN</td>
<td>SI</td>
<td>N</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir/dasabuvir</td>
<td>CI*</td>
<td>N</td>
<td>CI</td>
<td>N</td>
<td>SI</td>
<td>SI</td>
<td>CI</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir</td>
<td>CI*</td>
<td>N</td>
<td>CI</td>
<td>N</td>
<td>SI</td>
<td>N</td>
<td>CI</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>SI</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>SI</td>
<td>SI</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Sofosbuvir/ledipasvir</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>SN</td>
<td>SI</td>
<td>N</td>
</tr>
</tbody>
</table>

N: Not studied *in vivo* (may or may not have the potential for significant interaction)  
CI: Not studied but contraindicated due to the expected significant interaction (*: recently added)  
SI: Studied *in vivo*, interactions that may be clinically relevant were observed  
SN: Studied in vivo, no significant interaction was observed  

Data source: U.S prescribing information
Objective

To evaluate each rhabdomyolysis case reported to FAERS and determine if there is a mechanistic basis for a PK-based drug interaction that would lead to increased exposure of the statin
Methods

• The FAERS database was searched for cases of rhabdomyolysis associated with the use of currently marketed FDA approved DAA regimens from approval to 2017*
  - FAERS: over 13 million spontaneous reports submitted to FDA by healthcare professionals, consumers, and drug manufacturers

• Case definition: any report of a clinical diagnosis of rhabdomyolysis temporally associated with DAA therapy, with or without use of a statin

• For cases associated with statin use, the potential for drug interactions between DAA regimens and statins was assessed
  - Based on available in vivo drug interaction information in the respective US prescribing information (USPI) or
  - Predicted based on metabolic enzyme/transporter-mediated interaction potential

*FAERS search end date: February 28, 2017 for sofosbuvir or simeprevir containing regimens and August 2, 2016 for other DAA regimens
Methods

• **Scope of Research**
  o To determine if a PK-based drug interaction could be playing a role in rhabdomyolysis cases
  o However, the research is not intended to:
    • Determine whether rhabdomyolysis is caused by a DAA regimen itself
    • Determine the incidence of rhabdomyolysis in patients receiving statins with each DAA regimen (higher number of cases may reflect drug utilization patterns)

• **Limitations**
  o General limitations of FAERS analysis
    • No definitive causality
    • Incomplete information
    • Reporting bias
    • Cannot be used to capture incidence due to under-reporting
  o Many patients also had at least one other contributing factor that could increase the risk of statin-associated rhabdomyolysis (e.g., advanced age, renal impairment, other conditions known to increase the risk of rhabdomyolysis)
Results

- Number of rhabdomyolysis cases reported to FAERS in patients receiving a DAA regimen (with or without statin use): n=42

- Number of cases associated with the use of a DAA regimen and a statin: n=14 (33%)
  - Is there a mechanistic basis for a PK-based interaction (DAA increases statin exposures) that increases the risk of rhabdomyolysis?
Results

• Scenario 1: Significant increases in statin plasma concentrations are known or anticipated due to drug interactions
  - Four cases were reported in patients receiving contraindicated combinations in USPI
    • Ombitasvir/paritaprevir/ritonavir/dasabuvir and simvastatin
  - Five cases were reported in patients receiving combinations where a statin dose cap is recommended in the DAA’s USPI
    • Ombitasvir/paritaprevir/ritonavir/dasabuvir and pravastatin (n=1)
    • Daclatasvir containing regimen and rosvustatin (n=1)
    • Simeprevir/sofosbuvir and atorvastatin (n=2)
    • Simeprevir/sofosbuvir and rosvustatin (n=1)
    • For cases reported with the statin dose (n=2): all of those patients were taking recommended statin doses per DAA USPI (e.g., the maximum allowed dose of atorvastatin with simeprevir is 40 mg)
Results

• Scenario 2: A drug interaction resulting in an increase in statin plasma concentrations is anticipated but no specific dosing recommendation is available in USPIs at the time of event (2 cases)
  – Ombitasvir/paritaprevir/ritonavir/dasabuvir and atorvastatin (n=1)
  – Simeprevir/sofosbuvir/daclatasvir and atorvastatin (n=1)

• Scenario 3: No significant interaction is expected based on in vitro or in vivo study results (3 cases)
  – Sofosbuvir/ledipasvir and atorvastatin (n=3)
  – These patients were previously clinically stable on atorvastatin (40 mg or 80 mg) prior to addition of sofosbuvir/ledipasvir ± ribavirin
  – It cannot be determined whether statin exposure alone or changes in statin exposure could precipitate rhabdomyolysis in these cases
Discussion

• Drug interactions observed between a statin and a DAA regimen are mediated by
  – Inhibition of CYP3A4 (by ritonavir)
  OR
  – Inhibition of hepatic (± intestinal) transporters by NS3/4 protease inhibitors

Rhabdomyolysis cases

<table>
<thead>
<tr>
<th>DAA regimens NOT including a NS3/4 protease inhibitor or ritonavir</th>
<th>DAA Regimens including a NS3/4A protease inhibitor (± ritonavir)</th>
</tr>
</thead>
<tbody>
<tr>
<td># of total cases: 25</td>
<td># of total cases: 17</td>
</tr>
<tr>
<td># of cases with statin: 3 (12%)</td>
<td># of cases with statin: 11 (65%)</td>
</tr>
</tbody>
</table>
Discussion

- Can drug interaction results be different in healthy volunteers versus patients? **Yes**
- What is the key difference between healthy volunteers and patients with HCV infection? *Hepatic function (some patients may have diagnosed cirrhosis, others may have fibrosis)*

**Potential impact of impaired hepatic function on the magnitude of interaction between DAA regimens and Statins**

- **Perpetrator concentrations**
  - Protease inhibitors ↑

- **Victim concentrations**
  - atorvastatin ↑ ↑
  - rosuvastatin, fluvastatin, pitavastatin, pravastatin ↑
  - lovastatin, simvastatin – not studied

**Changes in physiology**
- Reduced expression level of hepatic uptake transporters (OATP1B1/3)
Summary

- Fourteen cases of rhabdomyolysis have been reported to FAERS in patients receiving a DAA regimen and a statin.
- For most cases (11/14), there is a mechanistic basis for a PK-based interaction, thus increased statin exposures caused by a DAA regimen could potentially have increased the risk of rhabdomyolysis.
- For cases involving hepatic transporter mediated interactions with protease inhibitors, the magnitude of the interaction is potentially higher in comparison to the magnitude of the interaction observed in healthy volunteers due to the underlying disease condition.
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