Background

- Familial Hypercholesterolemia (FH) is an under-recognized autosomal dominant disease with a prevalence of 1:250 in the general population.
- Homozygous FH (HoFH), the more severe subtype, is a rare, 1:160,000-300,000 disease, traditionally felt to be due to the complete absence of the LDL-receptor on the hepatocyte, and now recognized to be secondary to a number of possible biallele or compound mutations across various genes, including LDL-R, ApoB, and PCSK9.
- Traditional treatment includes the use of statins, bile acid sequestrants, niacin, and ezetimibe.
- More recently anti-sense and monoclonal antibody therapies have been developed, but accounts of their simultaneous use have not yet been reported in the literature.

Objective

- We report the first known case, to our knowledge, of the simultaneous use of the combination of mipomersen and evolocumab in a patient with HoFH.

Case Presentation

- A 41 year-old Hispanic woman presented to the Bellevue Hospital Lipid Clinic after recent hospitalization for angina.
- PMH: HIV (on HAART, CD4 656) and “hyperlipidemia.”
- Medications: daily rosuvastatin 40mg, ezetimibe 10mg, aspirin 81mg and twice daily cholestyramine.
- Never-smoker.
- Fam Hx: +HLD in father, paternal grandmother, and in multiple siblings
- As a 7 year-old child in Mexico she had developed subcutaneous nodules on her elbows and ankles.

Table 1: Cholesterol Response to Medications

<table>
<thead>
<tr>
<th></th>
<th>Tot Chol (mg/dL)</th>
<th>LDL (mg/dL)</th>
<th>HDL (mg/dL)</th>
<th>TG (mg/dL)</th>
<th>Non-HDL (mg/dL)</th>
<th>ApoB (mg/dL)</th>
<th>% LDL Reduction from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index admission*</td>
<td>419</td>
<td>360</td>
<td>30</td>
<td>147</td>
<td>389</td>
<td>288</td>
<td>--</td>
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<td>First Lipid Clinic visit*</td>
<td>397</td>
<td>331</td>
<td>31</td>
<td>193</td>
<td>366</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>S/p 3 doses mipomersen</td>
<td>287</td>
<td>238</td>
<td>33</td>
<td>83</td>
<td>254</td>
<td>--</td>
<td>28</td>
</tr>
<tr>
<td>S/p 2 doses evolocumab</td>
<td>108</td>
<td>62</td>
<td>38</td>
<td>40</td>
<td>70</td>
<td>48</td>
<td>74</td>
</tr>
</tbody>
</table>

Case Presentation Cont.

- After three doses of mipomersen her LFTs were unchanged and her LDL-C was 238mg/dL.
- At that time the FDA approved a novel injectable PCSK9 inhibitor for treatment of FH and the patient was empirically trialed on evolocumab on top of background therapy. After two doses, LDL-C was 62mg/dL.

Discussion

- This is the first known case of a HoFH patient simultaneously treated with traditional and recently-approved medications, including the anti-sense drug mipomersen and a PCSK9 inhibitor.
- The patient’s dramatic 74% reduction in LDL-C with PCSK9 inhibition is 2.5-fold greater than previously reported responses in HoFH patients (TESLA).
- Her response to medical therapy informs the clinician of her genotype; namely, her dramatic response to PCSK9 inhibition excludes the “traditionally” conceived null-null LDL-R genotype of classic HoFH.
- In this case, treatment with mipomersen and evolocumab on top of standard therapies, was not only safe and highly efficacious in reducing cholesterol burden, but also avoided the need for additional therapy, including apheresis.

Table 1: Cholesterol Response to Medications

- "on daily: rosuvastatin 40mg, ezetimibe 10mg; and cholestyramine twice daily
- For top of baseline medications
- For top of baseline medications and mipomersen

References