Maralixibat for the Treatment of Severe Xanthomas in 2 Children With Alagille Syndrome

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Introduction

Alagille syndrome (AGUS) is a rare, disabling, extracranial dominant disorder that presents with a broad range of clinical manifestations.1

- The classic clinical triad of features includes cholangiopathy, facial or bony syndactyly, and progressive liver disease, all of which result from liver transplantation or death.1

- A recently elucidated mechanism of AGUS is the presence of defects in 24%–42% of patients. Xanthomas are thought to result from impaired bile acid excretion from the liver.1

- Xanthomas can be disabling and disfiguring and are an indicator for liver transplantation in the appropriate high-risk transplant patient with AGUS.1

- Maralixibat (MRL) is a minimally absorbed bile acid transporter (BICAT) inhibitor that prevents enterohepatic bile acid circulation and is approved for the treatment of cholestatic pruritus in patients with AGUS 13 months of age in the US and 12 months of age in the EU.1

- Following AGUS treatment with maralixibat showed substantial improvement and resolution of xanthomas across a diverse clinical trial.1

![Figure 1. Cholesteryl Conversion to Bile Acids](image)

Cholesteryl is converted to primary bile acids in the liver by CYP7A1. Bile acids excreted by the liver are taken up by liver cells, converted into secondary bile acids, and then returned to the liver through the portal vein.1 Bile acids and cholesterol, bile acids bind to FXR, which reinforces the activity of CYP7A1.1 Maralixibat is a novel, minimally absorbed, orally administered IBAT inhibitor that interrupts the enterohepatic circulation of bile acids leading to increased bile acid excretion in feces.1

![Figure 2. Clinical Histories](image)

- Case 1: Male, aged 11 y
- Case 2: Male, aged 3 y

Objective

- To report the use of maralixibat for the treatment of severe xanthomas in 2 children with AGUS.

Methods

- Case reports were performed for 2 children with AGUS complicated by cholestatic pruritus and xanthomas from different clinical trials.

![Figure 3. Laboratory Assessment Values](image)

Table 1. Laboratory Assessment Values

<table>
<thead>
<tr>
<th>Case</th>
<th>Test</th>
<th>Before MRL</th>
<th>After MRL</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>Total cholesterol</td>
<td>212 mg/dL</td>
<td>177 mg/dL</td>
<td>0.01</td>
</tr>
<tr>
<td>Case 2</td>
<td>Total cholesterol</td>
<td>278 mg/dL</td>
<td>190 mg/dL</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Conclusions

- The 2 cases of patients with AGUS reported here demonstrate resolution of severe, debilitating xanthomas and extrachromosomal xanthomas upon treatment with MRL.

- Case 1 may be the first case in the literature reporting upper and lower xanthoma resolution in a child with AGUS secondary to cholestatic liver disease and associated complications improved 8 months after initiation of medical treatment.

- Case 2 demonstrates the resolution of severe cutaneous xanthomas 12 months after initiation of medical treatment, resulting in reduced pruritus.

- These clinical cases support the potential for maralixibat to have a positive impact on the management of AGUS beyond cholestatic pruritus.