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

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Background

- Alagille syndrome (ALGS) is a rare, debilitating, autosomal dominant disorder that presents with a broad range of clinical manifestations.[1]
  - The key clinical manifestations include cholestasis, failure to thrive, xanthomas, and progressive liver disease, all of which can lead to liver transplant or death.[1]
- A uniquely burdensome manifestation of ALGS is the presence of xanthomas in 24%-42% of patients. Xanthomas are thought to result from impaired bile acid excretion from the liver.[1-4]
- Xanthomas can be debilitating and disfiguring and are an indication for liver transplantation in approximately half of transplant recipients with ALGS.[2,5]
- Maralixibat (MRX), an ileal bile acid transporter (IBAT) inhibitor, is approved for the treatment of cholestatic pruritus in patients with ALGS ≥2 months of age in the EU, and ≥3 months of age in the US (Fig.1).[6,7]
- Patients with ALGS treated with MRX showed substantial improvement and resolution of xanthomas across multiple clinical trials.[5,8]

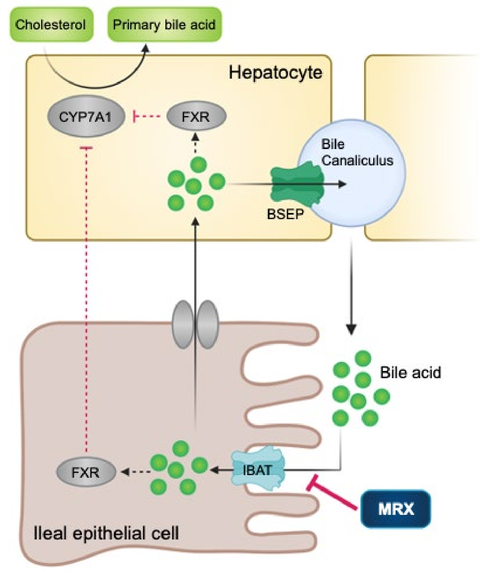
Objective

- To report the use of MRX for the treatment of severe xanthomas in 2 children with ALGS

Methods

- Chart reviews were performed for 2 children with ALGS complicated by cholestatic pruritus and xanthomas from 2 different institutions.

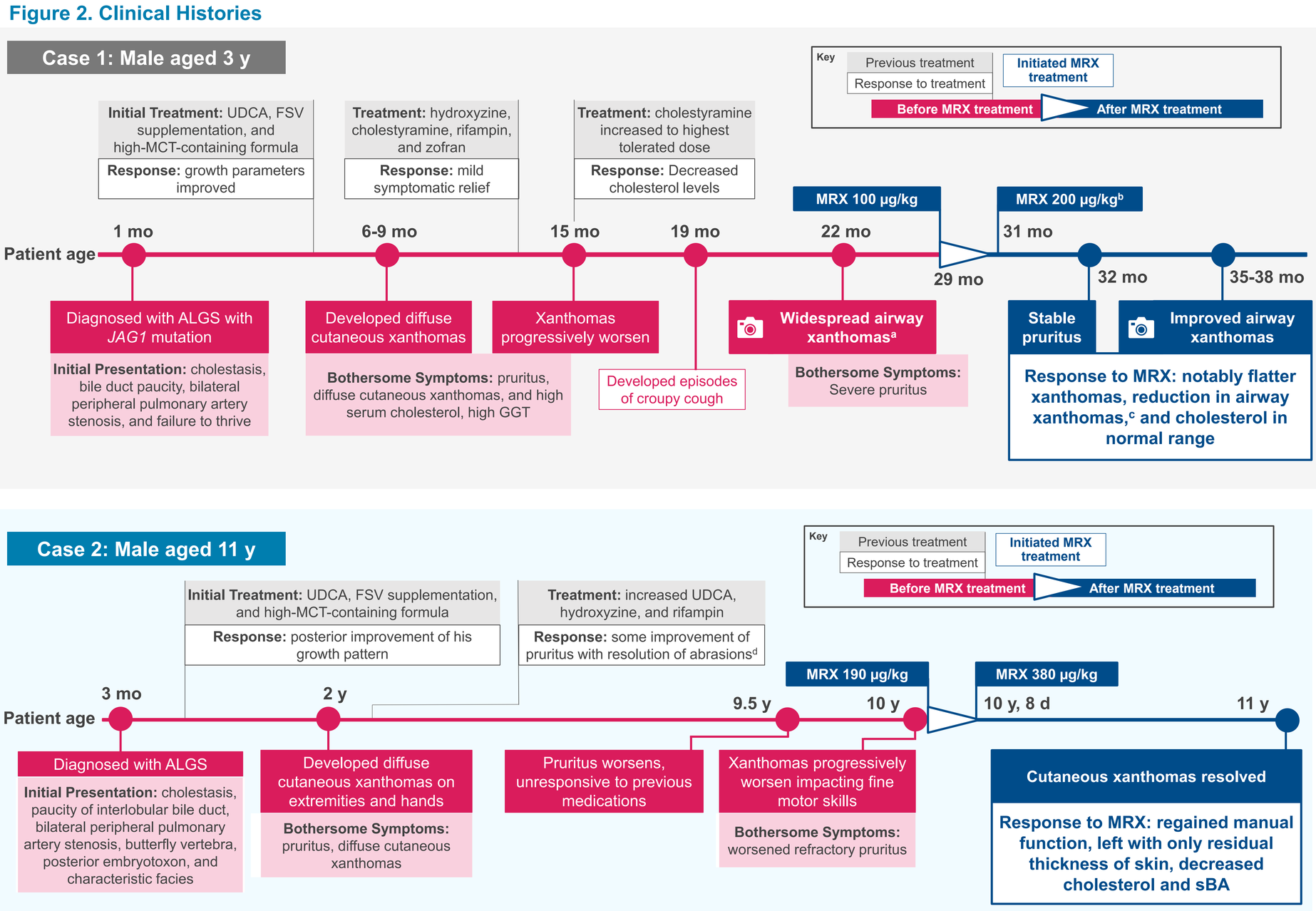
Figure 1. Cholesterol Conversion to Bile Acids



Cholesterol is converted to primary bile acids in the liver by cholesterol 7-α-hydroxylase (CYP7A1). Bile acids secreted by the liver are taken up by ileal epithelial cells through IBATs and then returned to the liver through the portal vein. In ileal cells and hepatocytes, bile acids bind to the farnesoid X receptor (FXR) which represses the activity of CYP7A1. MRX is a novel, minimally absorbed, orally administered IBAT inhibitor that interrupts the enterohepatic circulation of bile acids leading to increased bile acid excretion in faeces.[5,9] BSEP, bile salt export pump.

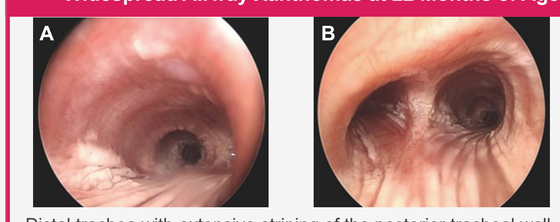
Results

Figure 2. Clinical Histories



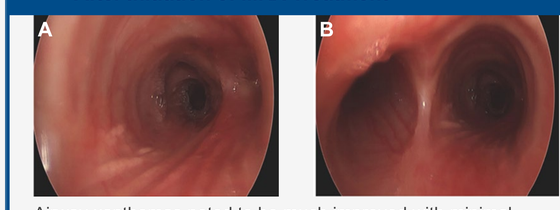
FSV, fat-soluble vitamin; GGT, gamma-glutamyl transferase; MCT, medium chain triglyceride; MRX, maralixibat; sBA, serum bile acid; UDCA, ursodeoxycholic acid. [a]Seen with rigid bronchoscopy. [b]After 1 week at 100 µg/kg MRX, dose was increased to 200 µg/kg. Dose was reduced to 100 µg/kg after 4 weeks due to persistent diarrhoea. After 2 weeks at 100 µg/kg, diarrhoea subsided, and the dose was again increased to 200 µg/kg. [c]The patient was noted to have 4+ adenoids and 2-3+ tonsils and underwent adenoidectomy and tonsillectomy with improvement in cough noted postoperatively. [d]By 9.5 years of age, his pruritus had worsened and was unresponsive to his previous medications.

Figure 3. Case 1: Rigid Bronchoscopy Demonstrating Widespread Airway Xanthomas at 22 Months of Age



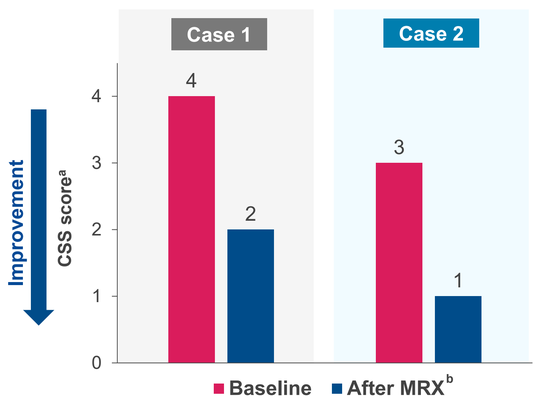
Distal trachea with extensive striping of the posterior tracheal wall with streaks of xanthomas (A) extending into both mainstems at the carina (B).

Figure 4. Case 1: Repeat Bronchoscopy 8.5 Months After Initiation of MRX Treatment



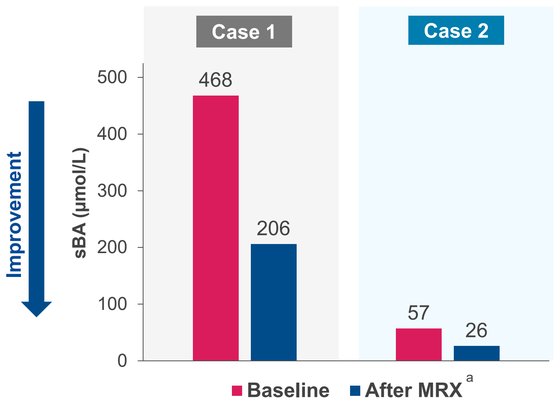
Airway xanthomas noted to be much improved with minimal streaking in the left and right mainstem (A), completely patent subglottis, no vocal cord lesions, and an almost clear trachea (B). MRX, maralixibat.

Figure 5. CSS Scores



CSS, Clinician Scratch Scale; MRX, maralixibat. [a]CSS, 0 = none, 1 = rubbing or mild scratching when undistracted, 2 = active scratching without abrasions, 3 = abrasions, and 4 = cutaneous mutilations, haemorrhage, scarring.[5] [b]At time of reporting, treatment duration for case 1 was 6 months, and for case 2 was 12 months.

Figure 6. sBA Values



MRX, maralixibat; sBA, serum bile acid. [a]At time of reporting, treatment duration was 12 months.

Table 1. Laboratory Assessment Values

	Case 1		Case 2	
Laboratory assessment	Baseline	After MRX (duration)	Baseline	After MRX (12 mo)
Cholesterol (mg/dL)	404	389 (11 mo)	525[a]	271
Total bilirubin (mg/d/L)	4.4	5.3	0.3	0.1
ALT (U/L)	111	90 (8 mo)	103	58
AST (U/L)	103	116 (8 mo)	111	64

ALT, alanine transaminase; AST, aspartate transaminase; GGT; gamma-glutamyl transferase; MRX, maralixibat; NA, not available. [a]Baseline assessment for case 2 was at 10 years of age.

Conclusions

- The 2 cases of patients with ALGS reported here demonstrate resolution of severe, debilitating xanthomas and extracutaneous xanthomas upon treatment with MRX.
  - Case 1 may be the first case in the literature reporting upper and lower airway xanthomas in a child with ALGS secondary to cholestatic liver disease and hypercholesterolaemia, which were markedly improved 9 months after initiation of MRX.
  - Case 2 demonstrates the resolution of severe cutaneous xanthomas 12 months after initiation of MRX resulting in regained manual function.
- These clinical cases support the potential for MRX to have a positive impact on the management of ALGS beyond cholestatic pruritus.

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Disclosures

GB reports no conflicts of interest. Q-T RE, and BV are consultants for Mirum Pharmaceuticals, Inc. DBM is a full-time employee of and shareholder in Mirum Pharmaceuticals, Inc.

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