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Resolution of Pruritus in a Child With Alagille Syndrome Treated With Maralixibat for Seven Years: Durable Response and Discontinuation of Other Medications

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Abstract: Intractable pruritus is one of the most prominent and debilitating features of Alagille syndrome. Maralixibat is the first US Food and Drug Administration-approved drug for the treatment of cholestatic pruritus in children with Alagille syndrome aged 3 months and older. Clinical trials of maralixibat have reported follow-up to 4 years and reported a ≥1-pt reduction using the Itch-Reported Outcome (Observer) (ItchRO[Obs]) instrument (0–4 scale), as this decrease was previously defined as a clinically meaningful improvement in pruritus; participants in clinical trials were expected to be maintained on stable doses of antipruritic agents. We report on a patient with 3 notable features: (1) complete resolution of her pruritus; (2) durability of this response for over 7 years; and (3) ability to discontinue all other antipruritic medications.

Key Words: Alagille syndrome, IBAT inhibitor, cholestasis

INTRODUCTION

Alagille syndrome (ALGS) is a rare, autosomal dominant condition characterized predominantly by complications of cholestasis secondary to ductopenia as well as congenital cardiac malformations (1,2). One of the hallmarks of ALGS is anicteric cholestasis that leads to significantly elevated bile acids and is thought to contribute to intractable pruritus observed in the majority of patients (2). In 2021, maralixibat, an ileal bile acid transporter inhibitor, became the first drug approved by the US Food and Drug Administration for the treatment of cholestatic pruritus in children with ALGS aged 3 months and older (3). Approval was supported by 3 clinical trials with long-term extension studies that defined a clinically meaningful change as ≥1-point reduction in the Itch-Reported Outcome (Observer) (ItchRO[Obs]) instrument (4–6). Published data from ICONIC (NCT02160782) reported follow-up to 4 years whereas data from the ITCH (NCT02057692) and IMAGO trials and extensions (IMAGINE II: NCT02117713; IMAGINE: NCT02047318) reported follow-up to 72 weeks (4,5,7). All studies allowed for stable doses of concomitant antipruritic drugs.

In this report, we provide a case history of a patient who has been on maralixibat with several notable features: (1) complete resolution of her pruritus; (2) durability of this response for over 7 years; and (3) ability to discontinue other antipruritic medications.

CASE REPORT

The patient is currently a 9-year-old female, born at full term following an uncomplicated pregnancy and early post-partum period. At 1 month of age, she was noted to have cholestatic jaundice by her pediatrician and was referred for evaluation, including consideration of biliary atresia and the need for hepatoportoenterostomy. During her evaluation, she had persistent evidence of cholestatic jaundice, and additional testing identified cardiac, renal, and facial characteristics of ALGS. Based on these findings and confirmatory genetic testing that identified a *JAG1* mutation (c.672 G>A which is a nonsense mutation p.Trp224Stop [W224X]), she was diagnosed with ALGS. At discharge, she was prescribed ursodeoxycholic acid (UDCA), a choloretic agent, at 10 mg/kg 2 times daily as well as an ADEK multivitamin.

At 3 months of age, the patient developed severe, unrelenting pruritus. In clinic, the child was noted to be visibly uncomfortable, with signs of excoriations from persistent scratching as well as bloody clothing (Fig. 1). She was initially prescribed hydroxyzine, an antihistamine, at night with minimal effect on pruritus though some improvement in sleep; additional doses were available as needed during the day but were also of little benefit. At 8 months of age, she was prescribed cholestyramine, a bile-acid sequestrant, at 3 g 3 times daily with little relief, and at 18 months of age, she was started on rifampin, a pregnane X receptor agonist, at 50 mg twice daily. The combination of these 4 medications failed to alleviate her symptoms.

The patient was enrolled in the ITCH trial of maralixibat in May 2015 at 2 years of age; UDCA and cholestyramine were discontinued before starting the trial given no perceived benefit, though she remained on rifampin and hydroxyzine. At screening/baseline, she was documented to have a Clinician Scratch Scale (CSS) of 4, indicating cutaneous mutilation, and an ItchRO(Obs) of 2.57, indicating moderate-to-severe pruritus (Table 1). Notable baseline labs included total bilirubin 1.0 mg/dL, direct bilirubin 0.6 mg/mL, and alanine aminotransferase 173 IU/mL.

ITCH was a randomized, blinded trial for 13 weeks, and the mother reported no significant change in her pruritus during this study; after unblinding, the patient was noted to be on placebo. After 13 weeks, she rolled over to the open-label long-term extension study (IMAGINE II) and received maralixibat, readily tolerating the maximum dose of 266 μg/kg per day throughout the clinical trial. After 10 days of maralixibat, the mother reported a significant reduction in pruritus and documented an ItchRO(Obs) score of 0 by week 4 of therapy. Throughout the open-label phase, her ItchRO(Obs) and CSS scores were in nearly all instances 0, except if she had a concurrent infection. At approximately 1 month after starting maralixibat, she discontinued rifampin with only rare use of hydroxyzine, and she has

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H. Lin is accepting full responsibility for the case report and had access to the data and control of the decision to publish.

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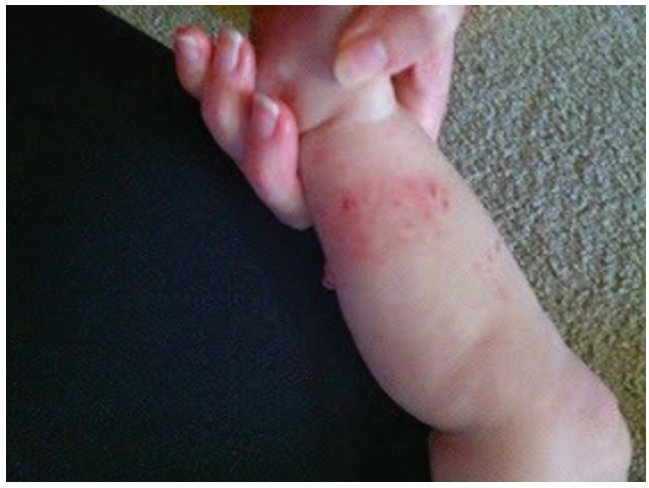

FIGURE 1. Evidence of excoriations prior to starting maralixibat treatment.

TABLE 1. Clinician Scratch Scale and ItchRO(Obs)

Score	Clinician Scratch Scale	ItchRO(Obs)
0	None	None
1	Rubbing or mild scratching when undistracted	Mild
2	Active scratching without abrasions	Moderate
3	Abrasions	Severe
4	Cutaneous mutilations, hemorrhage, scarring	Very severe

ItchRO(Obs), Itch-Reported Outcome (Observer).

not required the hydroxyzine for several years. She has also had a significant increase in growth, with a height z-score at baseline of −2.17 to −1.07 at her most recent visit and a weight z-score at baseline of −1.65 to −0.87 at her most recent visit (ie, 7 years of therapy). She has had no evidence of increased abdominal pain, diarrhea, or other adverse events thought to be related to the drug. At her last clinic visit, her total and direct bilirubin were stable from before starting therapy, and alanine aminotransferase has been elevated at 480 IU/mL without clinical sequelae and within observations seen in the natural history (6). Additional notable labs include albumin of 4.0 g/dL and international normalized ratio (INR) of 1.0 indicating good synthetic function, as well as platelets of 219 K/mL indicating no evidence of portal hypertension; total serum bile acids, which were 43.6 μmol/L at baseline, have fluctuated from this level to as low as 11.6 μmol/L.

Overall, she has been without pruritus for 7 years, including 6 years at the clinical trial dose of 266 μg/kg/day and most recently at the commercial dose of 380 μg/kg/day. She has no need for additional concomitant antipruritic medication. She has been on a stable dose of a daily vitamin supplement containing cholecalciferol (3000 IU) and K2 (75 μg) for several years.

DISCUSSION

Here, we highlight a patient with ALGS that has 3 notable features beyond what has been previously reported: (1) complete resolution of her pruritus (ie, a 4-point reduction in CSS to 0); (2) durability of this response for over 7 years; and (3) ability to discontinue all other antipruritic medications. Pruritus is one of the most debilitating symptoms in ALGS, and before maralixibat, there were no Food and Drug Administration-approved therapies for this devastating symptom experienced by the majority of children with ALGS (6). Our case highlights the durable impact of maralixibat on pruritus for children with ALGS. Although prior studies have identified a ≥1-point reduction in ItchRO(Obs) as clinically meaningful, this patient was able to experience complete resolution of pruritus and, correspondingly, able to have significant improvement in her quality of life, including the ability to pursue all the activities that should be available to a child her age (6). Consistent with previous reports, she has had a significant gain in height with a documented increase in height z-score of more than one standard deviation (4). We acknowledge that each child with ALGS can be expected to have a different response to maralixibat, including variations in effectiveness and safety. But we are pleased to see that the patient represents the possibility that at least some children may show a complete response, in this case, a 4-point reduction, as well as long-term resolution of her pruritus, an important complication in this challenging disease.

Another worthwhile observation is that the patient was able to discontinue the other medications she used for the management of ALGS: UDCA, cholestyramine, rifampin, and hydroxyzine. Medication burden can be a significant challenge for children with ALGS as most children are on UDCA, multiple antipruritic therapies, one or more vitamins, and potentially may be on medications to control the cardiac disease as well. Therefore, physicians should be cognizant of the medication burden and pursue opportunities to eliminate medications with little benefit. In this patient's case, we were able to reduce 4 other medications while adding maralixibat.

Intractable pruritus is one of the most common indications for liver transplant in children with ALGS, with a recent publication reporting pruritus as an indication in 69% of children (8). The degree of improvement, and 7 years of durability of response in symptoms experienced by the patient after treatment with maralixibat, indicate that a subset of patients may exist for whom transplant would otherwise have been pursued, but now instead have a pharmacologic option to mitigate this debilitating problem.

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