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ORIGINAL ARTICLE

Hepatology

Odevixibat as an adjunctive treatment for refractory pruritus in rare variants of cholestatic liver disease

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Abstract

Objectives: Odevixibat, a reversible ileal bile acid transport inhibitor, has been shown to reduce serum bile acids (sBA) and pruritus mostly in children with progressive familial intrahepatic cholestasis (PFIC) 1 and 2 in clinical trials and case reports. There are currently no published case reports or series describing its use in rare variants of cholestatic liver disease.

Methods: We describe three children with progressive cholestatic liver disease who developed refractory pruritus, who had a genotypic diagnosis of *AKR1D1*, *ABCB4* variant, and *PKHD1* and *PKHD2* variants; all being variants of unknown significance as per the American College of Medical Genetics and Genomics guidelines.

Results: On Odevixibat there was a significant improvement in sBA (absolute change from baseline: −196 and −393 μmol/L) and pruritus in two children with heterozygous *AKR1D1* and *ABCB4* mutations. The child with *ABCB4* variants was found to have features of sclerosing cholangitis along with a diagnosis of Crohn's disease, which represents the first reported usage of Odevixibat in such a case with good response. There was some reported improvement in the third child with *PKHD1* and *PKHD2* variants; however, we hypothesize that no sustained improvement could be due to severe and progressive nature of the disease. There were no side effects reported and it was well tolerated in all.

Conclusion: We suggest that Odevixibat may be used as an adjunctive drug in refractory pruritus and could be started early in the course of disease if clinically and phenotypically indicated.

KEYWORDS

bile acids, cholestasis, ileal bile acid transport, quality of life

1 | INTRODUCTION

Progressive familial intrahepatic cholestasis (PFIC) represents a heterogeneous group of rare genetic disorders characterized by cholestasis, elevated serum bile acids (sBA), intense pruritus, and progressive liver failure requiring liver transplantation during childhood.[1]

Pruritus associated with cholestasis can have a significant detrimental effect on patient and family quality of life (QoL). Treatment of pruritus in cholestatic liver disorders has been challenging historically with limited medical interventions, requiring the use of multiple drugs in severe cases with larger side-effect profiles. Surgical interventions to interrupt bile acid

Abbreviations: iBAT, ileal bile acid transport; IBD, inflammatory bowel disease; PFIC, progressive familial intrahepatic cholestasis; QoL, quality of life; sBA, serum bile acids; UDCA, ursodeoxycholic acid.

enterohepatic circulation such as partial external biliary diversion and ileal exclusion have been used with limited success.[2] Odevixibat, a reversible ileal bile acid transport (iBAT) inhibitor, decreases the bile acid uptake by disrupting the enterohepatic circulation, and has been approved in Europe for the sole or an add-on treatment of PFIC patients aged ≥6 months.[3] There is however limited clinical experience or data available for its use in rare subtypes of PFIC or other cholestatic liver disorders in children with no unifying genetic diagnosis.

In this study, we present our experience with the use of Odevixibat in three children with severe cholestasis and elevated sBA with genetic variants defined in *AKR1D1*, *ABCB4*, and *PKHD1* and *PKHD2* genes. Informed parental consent was obtained from in each case (see Figures 1–3 and Table 1).

What is Known

- Pruritus treatment in cholestatic liver disease is challenging.
- Odevixibat is approved as an add-on treatment for progressive familial intrahepatic cholestasis in patients ≥6 months.

What is New

- Improvement in pruritus with the use of Odevixibat in rare variants of cholestatic liver disease.
- Use of Odevixibat in a pediatric case of primary sclerosing cholangitis.

2 | CASE DESCRIPTION

2.1 | First case

A now 14-year-old male born to nonconsanguineous parents in Nigeria, with unremarkable birth history and no family history of liver disease, was referred by his local hospital at the age of 12 years due to a history of high gamma-glutamyl transpeptidas conjugated jaundice with dark urine and hepatosplenomegaly for the last 2 years. There were no bleeding complications, but he was suffering from intense pruritus affecting his sleep, energy levels, and overall QoL. His liver ultrasound scan (USS)

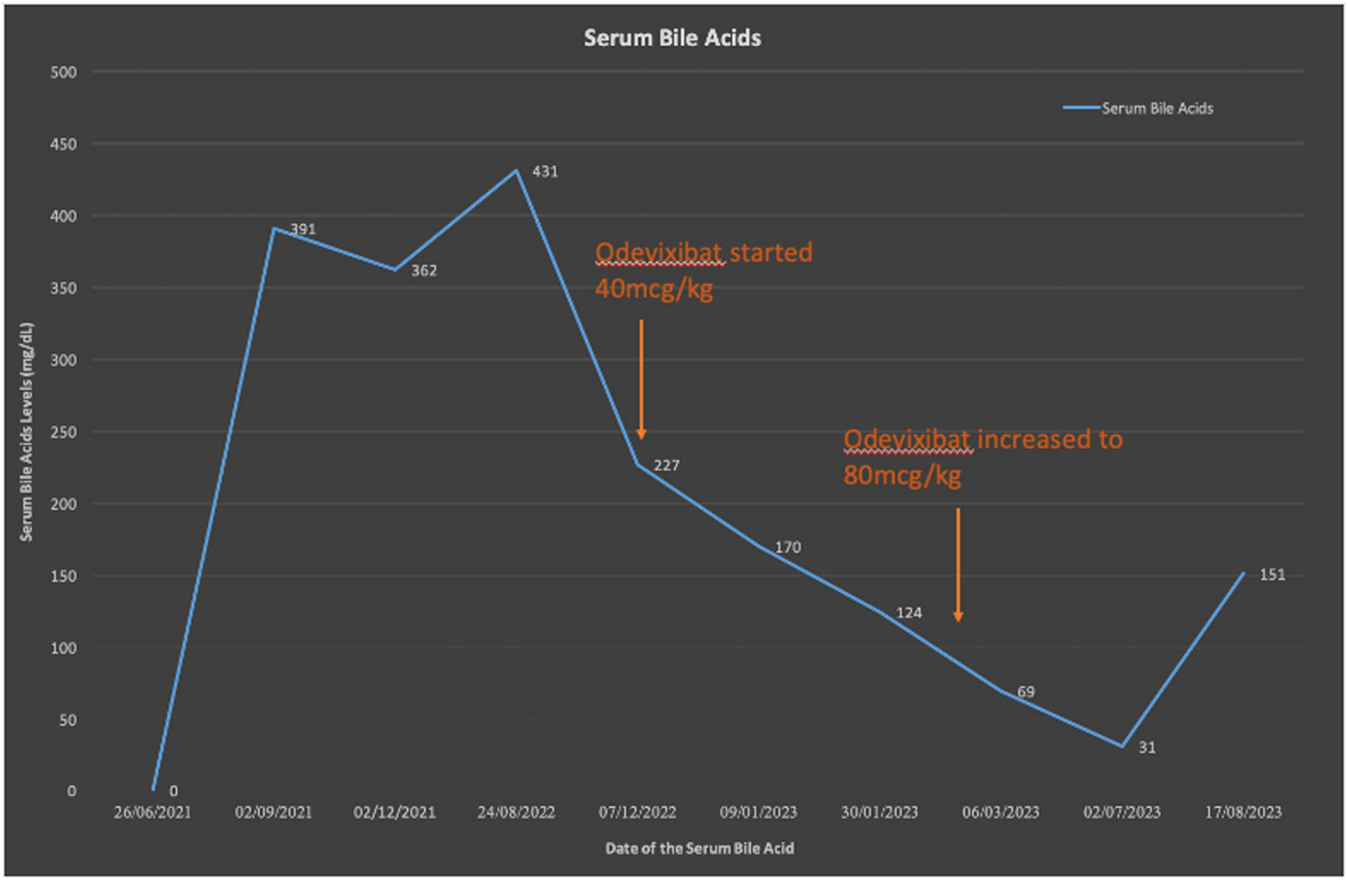

FIGURE 1 Patient 1; Serum levels of bile acids before and after the start of Odevixibat treatment. Arrows indicate the time when Odevixibat was introduced.

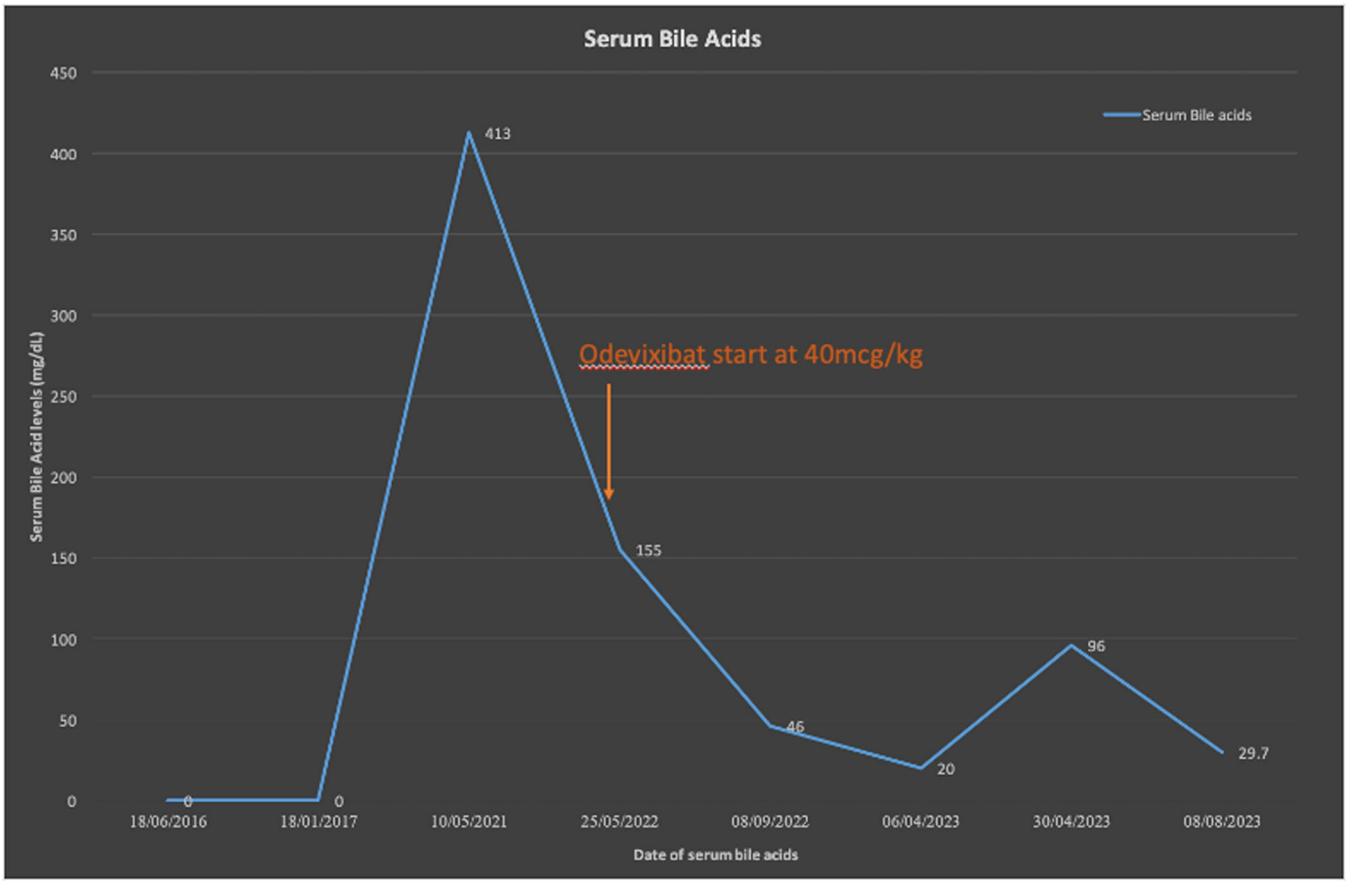

FIGURE 2 Patient 2; Serum levels of bile acids before and after the start of Odevixibat treatment. Arrows indicate the time when Odevixibat was introduced.

revealed a finely heterogeneous liver parenchyma with nodularity and splenomegaly of 14.9 cm. His liver biopsy showed porto-portal bridging fibrosis with focal nodule formation and cholangiopathic features with retained multidrug resistance protein 3 (MDR3) canalicular expression. Genetic studies revealed that he was compound heterozygous for two variants in *ABCB4*: c.2800G>A p.(Ala934Thr) and *ABCB4*: c.2717T>G p.(Val906Gly) both of unknown significance as per the American College of Medical Genetics and Genomics guidelines. *ABCB4* variants are known to be associated with increased risk of both progressive cholangiopathy and hepatobiliary malignancy. He was initially treated with ursodeoxycholic acid (UDCA) (500 mg BIS-IN-DIE (BD), 10 mg/kg BD) for his symptoms and was followed up regularly. On review in February 2022, he was noted to have itchy skin lesions which were treated with steroids. Magnetic resonance cholangiopancreatography showed intrahepatic cholangiopathy on the background of cirrhosis and portal hypertension with splenic varices and lieno-renal shunting. A further review 6 months later did not show any improvement with his pruritus, and in December 2022, he was started on Odevixibat at 40 µg/kg. A follow-up after 4 weeks showed improvement in sBA and symptoms of itching. The dose of Odevixibat was further increased to 80 µg/kg in February 2023 with follow-up showing further improvement in his symptoms and further reduction in sBA. He continues to be on UDCA and currently, he has good sleep quality and reports minimal itching and overall improved QoL. There were no reported side effects.

2.2 | Second case

A now 7-year-old boy born to non-consanguineous parents with unremarkable birth history was initially referred from Gibraltar in 2016 at 9 weeks of life USS showing normal gallbladder and a liver biopsy demonstrating changes of giant cell hepatitis with canalicular cholestasis. Genetic analysis revealed a heterozygous mutation in *AKR1D1* gene for c.149G>A p.(Arg50Gln) and homozygosity for the common modifier in *ABCB11* gene c.1331T>C p.(Val444Ala), not known to be causally associated with cholestasis and/or neonatal hepatitis. He was therefore classified as having Idiopathic neonatal hepatitis and was followed up by his local hospital in Gibraltar until 2021, when at the age of 5 years, he returned due to persistently elevated liver enzymes and itching which was now affecting his

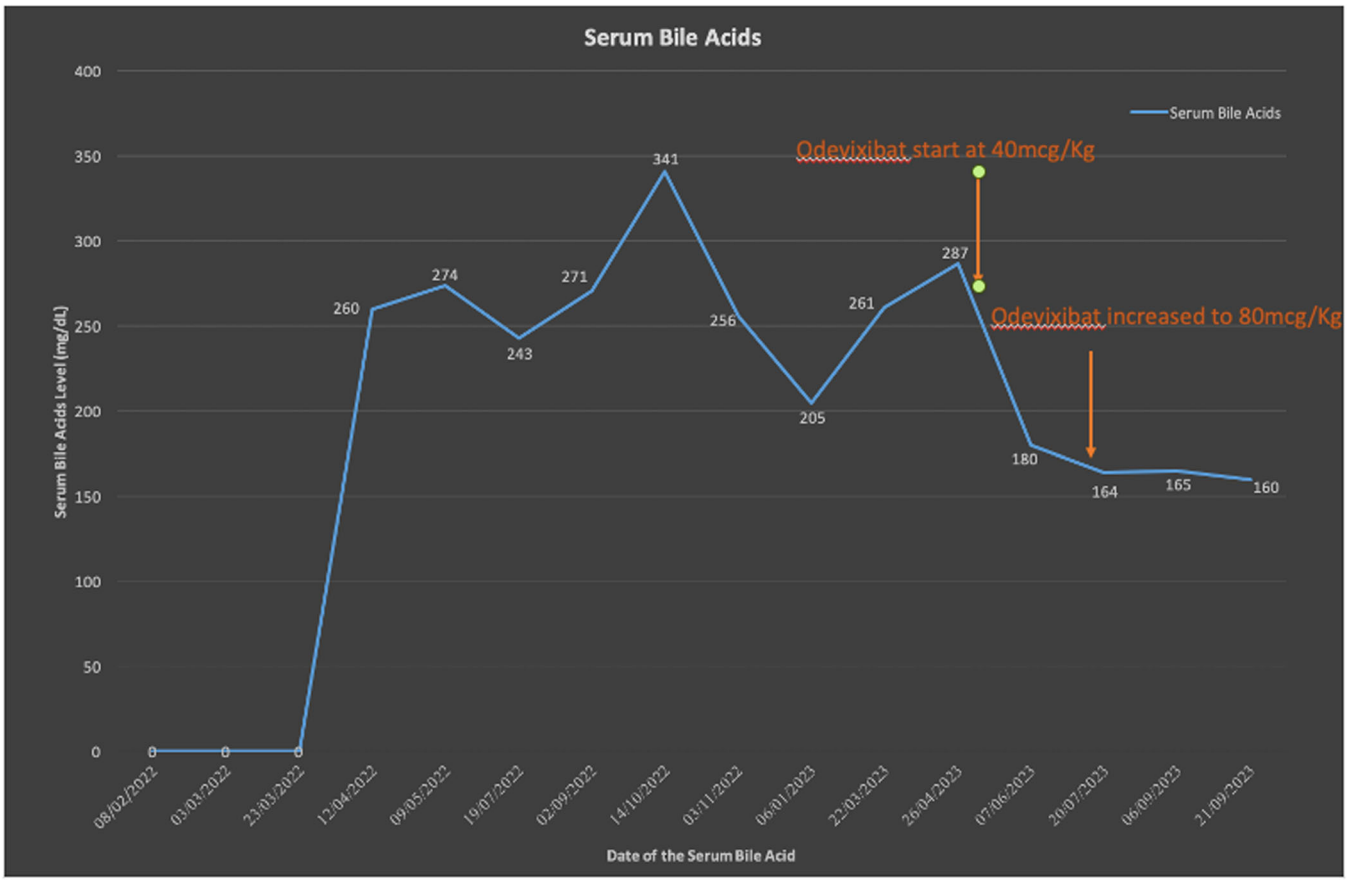

FIGURE 3 Patient 3; Serum levels of bile acids before and after the start of Odevixibat treatment. Arrows indicate the time when Odevixibat was introduced.

sleep and overall QoL. His USS showed a heterogeneous liver parenchyma with mild dilatation of the left bile duct and splenomegaly of 12 cm. He underwent a repeat liver biopsy showing porto-portal bridging fibrosis with partial nodularity and cholangiopathic features, suggestive of sclerosing cholangitis. The patient was already on UDCA (10 mg/kg BD), cetirizine (5 mg BD), and rifampicin (5 mg/kg OD) were added in May 2021 due to troubling pruritus affecting his sleep. On review, he continued to have troubling pruritus and nose bleeds. In February 2022, he underwent axial imaging which did not show any evidence of intra or extrahepatic cholangiopathy. His upper gastrointestinal endoscopy and colonoscopy revealed grade I esophageal varix with erythema in rectum, ascending colon, cecum, and ileocecal valve (ICV), hence he was diagnosed with inflammatory bowel disease (IBD) with histological confirmation of active chronic proctocolitis, active ileitis, erosive active inflammation in the ICV. He was started on sulphasalazine for his IBD. However, the pruritus continued to worsen, and he was started on Odevixibat at a dose of 40 μg/kg per day in May 2022. sBA levels were repeated after 2 weeks on treatment which showed significant reduction along with improvement in pruritus, sleeping pattern, and quality of life. He has been followed up jointly since then by our and the local team. He has continued to show a persistent improvement in his pruritus and his sBA have consistently been low. There were no reported side effects.

2.3 | Third case

A now 21-month-old girl born to nonconsanguineous parents with unremarkable perinatal history and no significant family history was born at 38 weeks' gestation with a low birth weight of 2.6 kg. She was investigated for congenital adrenal hyperplasia soon after birth due to possible clitoromegaly but was found to have a normal karyotype. She was then referred to our center due to conjugated hyperbilirubinemia and pale stools. She underwent abdominal USS which showed normal gall bladder. Due to pale stools, she underwent an endoscopic retrograde cholangiopancreatography that showed normal and patent extrahepatic bile ducts but abnormal intrahepatic bile ducts. A cholestasis gene panel was performed that did not identify any known genetic associations. She continued to have raised liver enzymes and her sBAs were

JPGN REPORTS

TABLE 1 Serum levels in Patients 1, 2, and 3 of liver enzymes, serum bile acids, INR, and platelets.

Laboratory parameters Patient 1	26/06/2021	02/09/2021	02/12/2021	24/02/2022	24/08/2022	07/12/2022	09/01/2023	30/01/2023	06/03/2023	02/07/2023	17/08/2023
ALT (U/L)	256	154	186	151	110	151	146	125	148	199	165
AST (U/L)	269	163	158	156	120	190	165	156	188	276	247
GGT (U/L)	1638	669	829	638	567	668	NA	427	437	691	329
Total bilirubin (μmol/L)	106	103	64	71	49	62	71	75	96	138	136
Direct bilirubin (μmol/L)	NA	NA	NA	NA	40	44	NA	NA	NA	NA	NA
Serum bile acids (μmol/L)	NA	391	362	NA	431	227	170	124	69	31	151
INR	1.1	1	1	1	1	1	NA	NA	NA	NA	1.2
Albumin (g/L)	44	42	42	39	40	42	42	40	41	41	38

Laboratory parameters Patient 2	18/06/2016	18/01/2017	10/05/2021	25/05/2022	08/09/2022	01/02/2023	06/04/2023	30/04/2023	08/08/2023
ALT (U/L)	287	151	219	191	156	126	122	156	106
AST (U/L)	274	163	271	186	NA	NA		NA	NA
GGT (U/L)	151	655	279	274	216	252	221	249	202
Total bilirubin (μmol/L)	112	7	10	17	18	18	16	18	27
Direct bilirubin (μmol/L)	67	3	NA	NA	7	7	5	8	11
Serum bile acids (μmol/L)	NA	NA	413	155	46	NA	20	96	29.7
INR	1.2	1	0.9	1.1	1	1.1	1	1.1	1.1
Albumin (g/L)	40	44	44	42	43	41	44	43	42
Platelets ($\times 10^9$)	454	NA	159	227	173	196	182	156	152

Laboratory parameters Patient 3	08/02/2022	03/03/2022	23/03/2022	12/04/2022	09/05/2022	19/07/2022	02/09/2022	14/10/2022	03/11/2022	06/01/2023	22/03/2023	26/04/2023	07/06/2023	20/07/2023	06/09/2023	21/09/2023
ALT (U/L)	22	65	75	89	106	134	108	89	65	93	188	186	191	154	176	204
AST (U/L)	54	124	130	149	172	227	195	165	118	145	201	201	224	193	227	242
GGT (U/L)	1288	1024	1114	1361	1115	838	604	580	482	758	908	943	982	812	979	980
Total bilirubin (μmol/L)	143	89	119	117	107	83	57	52	54	70	116	168	182	191	258	234
Direct bilirubin (μmol/L)	60	67	90	96	84	65	42	37	38	54	91	115	135	154	NA	712

TABLE 1 (Continued)

Laboratory parameters Patient 3	08/02/2022	03/03/2022	23/03/2022	12/04/2022	09/05/2022	19/07/2022	02/09/2022	14/10/2022	03/11/2022	06/01/2023	22/03/2023	26/04/2023	07/06/2023	20/07/2023	06/09/2023	21/09/2023
Serum bile acids (μmol/L)	NA	NA	NA	260	274	243	271	341	256	205	261	287	180	164	165	160
INR	1.1	1.2	1.1	1	1.1	1.1	1.2	1.1	1.1	1.2	1.2	1.1	1.2	1.3	1.1	1.2
Albumin (g/L)	42	38	38	40	36	34	34	37	39	36	42	39	38	40	38	38
Platelets (10^9)	117	452		407	330	190	121	134	140	76	89	89	101	95	105	103

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; INR, international normalized ratio; NA, not available; sBA, serum bile acids.

elevated (260 μmol/L) at 3 months of age. She underwent a liver biopsy at 6 months of life, which showed broad porto-portal bridging fibrosis with nodularity, cholangiopathic features with intraductal bile plugs, microlithiasis, and foci of cholangitis. With regard to her imaging, her initial USS at 6 months showed heterogeneous liver parenchyma with splenomegaly. A repeat USS at 9 months of life showed atrophied right liver lobe with no detectable portal flow into that lobe. An abdominal computed tomography scan showed a coarsely heterogeneous liver with attenuated right portal vein. It was noted that she had developed portal hypertension with evidence of portosystemic shunting. She had developed itching by 6 months of age and was started on UDCA (10 mg/kg BD), which did not manage her symptoms, followed by rifampicin (5 mg/kg OD) at 9 months of life. Further molecular genetic testing showed she was heterozygous for a variant in the *PKHD1* gene c.275G>A p.(Arg92Gln) and for a variant in the *PKHD2* gene c.1130G>A p.(Ser377Asn), both variants of uncertain significance.

She remained deeply jaundiced with elevated sBA with pruritus affecting her quality of life, hence she was started on Odevixibat 40 μg/kg at 14 months of life for symptomatic relief, in May 2023. Her sBA decreased within 2 weeks of starting treatment and her itching improved slightly. However, on follow up her sBA and pruritus showed no further improvement and hence the dose was increased to 80 μg/kg in July 2023 with minimal further effect. There were no reported side effects. She is currently listed for liver transplantation.

3 | DISCUSSION

Odevixibat, a critical regulator of enterohepatic circulation of bile acids, has been shown to reduce intense pruritus and sBAs in patients with PFIC.[4,5] Recent case reports have described its use in children with newer subtypes of PFIC and Alagille syndrome.[6–8] We report here three children, in whom Odevixibat was used, as an adjunctive treatment for refractory pruritus in rare variants of cholestatic liver disease.

Odevixibat was effective in improving the overall QoL and pruritus along with biochemical reduction in sBA in two children with genetic diagnosis of compound heterozygous *ABCB4* gene mutations and heterozygous *AKR1D1* gene mutation. There was some symptomatic relief in itching in the third child with genetic diagnosis of heterozygous *PKHD1* and *PKHD2* gene variants with just over 50% reduction (160/341 mg/dL) in sBA but without sustained improvement. We hypothesize that the reason for this could be due to the very advanced nature of liver disease with highly raised sBA within the first 3 months of life and pruritus in the first 6 months in one child. The earlier clinical

trials did not include children with very advanced liver disease and only included children with genotypic diagnosis of PFIC.[4,5] The genetic study in children described here had genotypes of unknown significance but all children had a severe phenotype with cholestasis.[9] Hence, it is difficult to prove that genotype has a role in the response to Odevixibat in our cohort.

iBAT inhibitors have been shown to reduce sBA and pruritus in adults with primary sclerosing cholangitis as described by Bowlus et al.[10] We describe the use of Odevixibat in a child for the first time with a diagnosis of sclerosing cholangitis and IBD reflecting the effective use of drug in children with cholestatic disorders with varied clinical and phenotypical profiles. All children were started on a minimum dose of 40 μg/kg of Odevixibat, two children needed dose increment to 80 μg/kg and remained on a low dose as supported by the clinical trials and previous case reports. Odevixibat was well tolerated in all our patients with no reported side effects.

4 | CONCLUSION

To conclude, the addition of Odevixibat has proven to be an effective add-on drug in selective children with cholestasis and severe pruritus who do not fit within strict PFIC diagnostic criteria. The choice of treating children with cholestasis suffering from troubling pruritus was made on their phenotypic profile. Further large-scale studies are needed to confirm the effectiveness in other rare/undefined forms of cholestatic liver disorders, including the effects of starting earlier in the disease course, the results of which could widen patient eligibility for treatment.

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CONFLICT OF INTEREST STATEMENT

Dr. Tassos Grammatikopoulos: Consultancy-Albireo. The remaining authors declare no conflict of interest.

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