Real-world Experience of Odevixibat▼ in Adults With Genetic Disorders of Cholestasis

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Introduction

- Genetic disorders of cholestasis, including progressive familial intrahepatic cholestasis (PFIC), typically present in infancy or early childhood[1,2]
  - Patients with PFIC often have elevated serum bile acid levels and severe pruritus associated with impaired quality of life (QoL)[1,2]
- Odevixibat is a potent, selective inhibitor of the ileal bile acid transporter that effectively reduced bile acids and pruritus in patients with PFIC in the phase 3 PEDFIC 1 and PEDFIC 2 studies[3,4]
  - Bylvay is approved for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older in the United Kingdom[5]
- In this real-world case series, we evaluated the efficacy and safety of odevixibat in adult patients with genetic disorders of cholestasis

Methods

Data Collection and Analysis

- Patients included in the study were adults harbouring suspected or confirmed genetic variants associated with cholestasis who initiated odevixibat treatment at age >16 years
- Patient data were collected through 31 January 2023 using standardised case report forms that included fields for demographic, clinical, and treatment information
- Details on the patient's medical history and symptoms before initiating odevixibat were recorded, as well as data on serum bile acid levels, hepatic parameters (ie, total bilirubin and alanine aminotransferase [ALT]), pruritus severity, and sleep disturbance before and after the initiation of odevixibat
  - Median changes from pre-treatment levels of serum bile acids and hepatic parameters to the last available assessment after the initiation of odevixibat were analysed using Wilcoxon signed-rank tests
- Safety assessments included treatment-emergent adverse events

Results

Patients

- Data from 10 patients across 8 treatment centres (50% male; age range at diagnosis: 6 months–35 years; age range at data collection: 22–48 years) were analysed; patient characteristics are presented in **Table 1**
  - Of these 10 patients, 6 were diagnosed in adulthood (patients 1–6)

Table 1. Demographic and Disease Characteristics of Adult Patients With Genetic Disorders of Cholestasis

	Age at Diagnosis	Age at Data Collection	Sex	Affected Gene(s)
Patients 1–6: diagnosed in adulthood				
Patient 1	35 years	38 years	F	*ABCB4*[a]
Patient 2	34 years[b]	48 years	M	*ABCB11*[c]
Patient 3	32 years	32 years	M	ND[d]
Patient 4	26 years	41 years	F	*ABCB11*[c]
Patient 5	18 years	29 years	F	*ABCB11*[e]
Patient 6	18 years	23 years	M	*ABCB11*[f]
Patients 7–10: diagnosed in childhood				
Patient 7	11 years	33 years	M	*ATP8B1, ABCB11, ABCB4*[g]
Patient 8	9 years	32 years	F	*ABCB11*[h]
Patient 9	4 years	22 years	F	ND[i]
Patient 10	6 months	25 years	M	ND[j]

[a]Heterozygous c.1445T>C variant. [b]Patient was symptomatic for many years prior to diagnosis. [c]Common variant in *ABCB11* (c.1331T>C). [d]Clinical presentation compatible with PFIC. [e]Homozygous c.1331T>C, heterozygous c.149T>C, and heterozygous c.1568C>G variants. [f]Homozygous c.1546T>C, heterozygous c.3148C>T, and heterozygous c.2599C>T variants. [g]Homozygous *ATP8B1* variant (p.R952Q), heterozygous *ABCB11* variants (p.A444V and c.3084A>G), and heterozygous *ABCB4* variant (c.787A>T). [h]Heterozygous c.1723>T and heterozygous c.1139delT variants. [i]Diagnosis of PFIC type 1. [j]Demonstrated similar haplotype to known patients with recurrent episodic cholestasis.
F, female; M, male; ND, not determined; PFIC, progressive familial intrahepatic cholestasis.

Medical History and Symptoms Prior to Odevixibat Initiation

- Across patients, common presenting features included pruritus, jaundice, impaired sleep and attention, and diminished QoL (**Table 2**)
  - Pruritus was a primary indication for treatment with odevixibat in 9 of 10 patients (patients 2–10)
- At the last available assessment prior to odevixibat initiation, median serum bile acids, total bilirubin, and ALT values were 138 μmol/L, 18 μmol/L, and 56 U/L, respectively (**Table 2**)

Table 2. Medical History and Laboratory Values Prior to Odevixibat Initiation in Adult Patients With Genetic Disorders of Cholestasis

	Presenting Features	Prior Disease-Related Surgeries and Procedures	Laboratory Values at the Last Available Assessment Prior to Odevixibat Initiation		
			Serum Bile Acids, μmol/L	Total Bilirubin, μmol/L	ALT, U/L
Patient 1	• No pruritus • Impaired QoL due to fever and abdominal pain	Gallbladder resection	10	6	23
Patient 2	• Pruritus • Recurrent jaundice	NA	69	36	65
Patient 3	• Persistent pruritus • Jaundice • Abdominal pain	NA	96	177	56
Patient 4	• Pruritus • Recurrent jaundice	NA	84	11	39
Patient 5	• Pruritus	Nasobiliary drain	48	4	7
Patient 6	• Pruritus • Jaundice	NA	214	9	145
Patient 7	• Recurrent pruritus, jaundice, and liver dysfunction • Impaired QoL • Psychological distress	Bilirubin adsorption (10 cycles)	260	412	57
Patient 8	• Pruritus	NA	284	24	46
Patient 9	• Pruritus • Poor QoL and attention • Fatigue • Short stature	Small bowel resection	>180	266	ND
Patient 10	• Persistent pruritus • Intermittent cholestasis • Anorexia • Sleep and attention disorders	NA	386	12	138

ALT, alanine aminotransferase; NA, not applicable; ND, not determined; QoL, quality of life.

Treatment With Odevixibat

- Median exposure to odevixibat was 3.4 months (range: 0.9–25.5 months; **Table 3**)
  - Treatment was ongoing at the time of data collection in 9 of 10 patients
  - Patient 7 discontinued treatment with odevixibat after 1.8 months due to significant improvement of symptoms, as well as normalized blood values and liver function

Clinical Outcomes After Odevixibat Initiation

Pruritus and Other Symptoms of Interest

- Overall, 9 of 10 patients experienced improvement in pruritus with odevixibat, with 8 patients reporting complete absence of pruritus at the last available assessment (**Table 3**)
- Improvements in sleep, mood, and QoL were also observed with odevixibat (**Table 3**)

Table 3. Clinical Outcomes With Odevixibat in Adult Patients With Genetic Disorders of Cholestasis

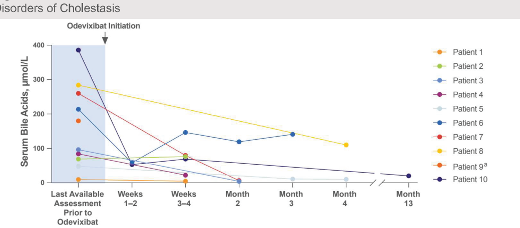
	Odevixibat Dosage at Data Collection, μg/day	Exposure to Odevixibat, months	Outcomes With Odevixibat
Patient 1	2400	1.7	• No changes in pruritus or sleep
Patient 2	2400	1.3	• Improved pruritus (no itch within 1 month)
Patient 3	3600	4.6	• Improved pruritus (VAS=7 to VAS=0 by month 2) • Improved sleep and increased energy for daily life routine
Patient 4	2400	0.9	• Improved pruritus (no itch within 1 month) • First time patient was symptom-free
Patient 5	2400	4.8	• Improved pruritus (no itch by month 2) • Able to care for child
Patient 6	2400	3.5	• Improved pruritus (no itch within 3 months) • No waking up at night
Patient 7	2400	1.8	• Improved pruritus (absent by month 2) • Improved jaundice • Positive psychological impact
Patient 8	2400	4.3	• Improved pruritus (no itch by month 3) • Better mood
Patient 9	1600	3.4	• Improved pruritus (~20% reduced) • Eyes are less yellow • More engaged in activities of daily living
Patient 10	2400 and 1200, alternating	25.5	• Improved pruritus (no itch by month 3) • Continued sleep for first time in life

VAS, visual analogue scale.

Serum Bile Acids

- At the last available assessment after initiation of odevixibat, the median (quartile 1, quartile 3) reduction in serum bile acids from pre-odevixibat levels was –73 (–174, –38) μmol/L (P=0.012); serum bile acid levels over time in individual patients are shown in **Figure 1**
  - In the patient with the longest duration of exposure (patient 10), decreases in serum bile acids were sustained with continued treatment

Figure 1. Serum Bile Acids Prior to and After Odevixibat Initiation in Adult Patients With Genetic Disorders of Cholestasis

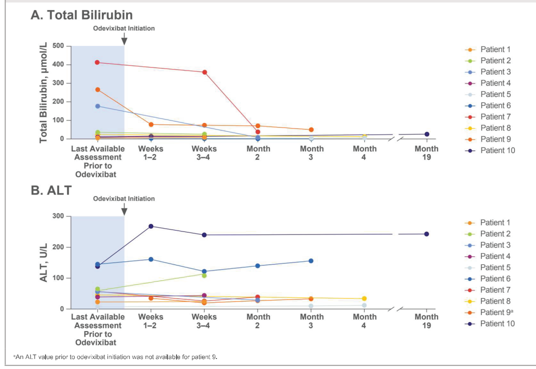


ªA serum bile acid value after odevixibat initiation was not available for patient 9.

Hepatic Parameters

- No significant median changes from pre-odevixibat values in total bilirubin or ALT values were observed at the last available assessment after the initiation of odevixibat (P≥0.16); total bilirubin and ALT levels over time in individual patients are shown in **Figure 2**

Figure 2. Total Bilirubin and ALT Prior to and After Odevixibat Initiation in Adult Patients With Genetic Disorders of Cholestasis



ªAn ALT value prior to odevixibat initiation was not available for patient 9.

Safety and Tolerability

- Gastrointestinal adverse events were reported in 2 of 10 patients (mild diarrhoea modifiable with dietary changes in patient 1; increased defecation that resolved with dosage adjustment in patient 10)
- No new safety signals were reported during treatment with odevixibat

CONCLUSIONS

- In adult patients with genetic disorders of cholestasis, odevixibat treatment was associated with improvements in pruritus and reductions in serum bile acids
- There were no new safety signals with odevixibat treatment in this real-world cohort of adult patients
- These initial findings help expand our understanding of treatment options for adults with genetic disorders of cholestasis and warrant further study in larger cohorts or registries

Plain Language Summary

- Cholestasis is a condition in which bile flow from the liver is reduced
- Patients with genetic disorders of cholestasis often experience symptoms beginning in infancy or early childhood, including a feeling of extremely itchy skin called pruritus
- Odevixibat is a medication that has proven effective in reducing symptoms in children with these genetic disorders
- In this study, odevixibat was given to a small group of adult patients and made symptoms of pruritus less intense

Abbreviations

ALT, alanine aminotransferase; NA, not applicable; ND, not determined; PFIC, progressive familial intrahepatic cholestasis; QoL, quality of life; VAS, visual analogue scale.

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5. Bylvay Summary of Product Characteristics (UK)

Disclosures: P. Trivedi: The Wellcome Trust, the Medical Research Foundation, Guts UK, PSC Support, LifeArc, NIHR, Gilead Sciences, Bristol Myers Squibb – Grant support; Intercept, Dr. Falk Pharma – Grant support, lecture and advisory board/consultancy fees; Albireo, Ipsen – Advisory board/consultancy fees; GlaxoSmithKline – Grant support and advisory board/consultancy fees; **A. Borghi:** AbbVie – Travel grant and consultant; **C. Engelmann:** Albireo – Writing, advisory, lecture fees; Intercept – Lecture fee; Novartis – Writing fee; Hepyx Ltd – Shareholder; **V. S. Hegade:** Nothing to disclose, **S. Hohenester:** Albireo – Consultant; AbbVie – Travel grant; Intercept – Lecture fee; **D. Joshi:** Boston Scientific, Intercept, Albireo – Advisory board/consultancy fees; **J. Monkelbaan:** Nothing to disclose; **A. Morgando:** Nothing to disclose; **P. Nagraj, V. Valcheva:** Albireo – Employment

Presented at the Annual Meeting of the European Association for the Study of the Liver (EASL): The International Liver Congress | Vienna, Austria | 21–24 June 2023

Acknowledgments: The authors thank the patients who contributed data to this case series.

Medical Writing Support: The authors thank Peloton Advantage, LLC (Parsippany, NJ, USA), an OPEN Health company, for providing medical writing and editorial support, which was industry sponsored in accordance with Good Publication Practice guidelines (GPP3).

This study was sponsored by Albireo, an Ipsen company.

BYL-UK-000243
December 2024