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Real-world experience with odevixibat in children with progressive familial intrahepatic cholestasis

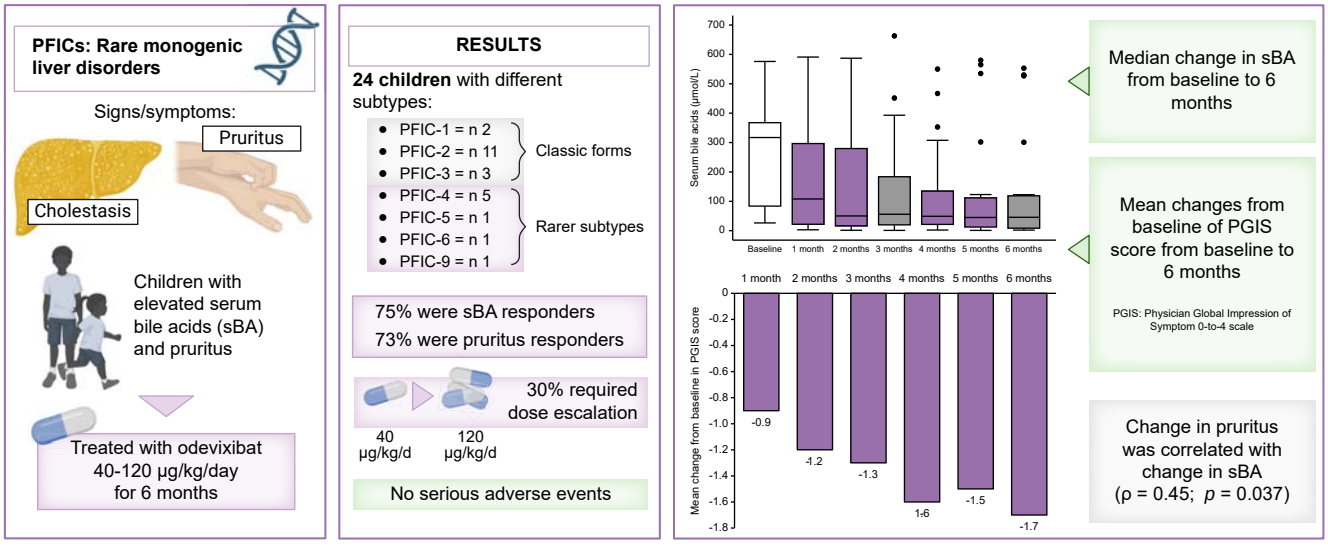
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Graphical abstract



Highlights:

- Children with PFIC have high sBA and clinically relevant pruritus.
- In a real-life scenario, outside strict eligibility criteria, odevixibat is effective in reducing sBA levels and improving pruritus.
- In a proportion of patients, dose escalation might be required to improve the response to treatment.
- Odevixibat should be considered in both patients with classic types of PFIC and rarer PFIC subtypes.

Impact and implications:

Published data on the use of odevixibat in a real-world scenario are lacking. We explored the effectiveness of odevixibat in a heterogenous cohort of children diagnosed with PFIC (including patients with classic as well as rarer types of PFIC, and with advanced liver disease and associated comorbidities). Our results demonstrate that odevixibat is effective for the treatment of cholestasis and pruritus in children with different PFIC subtypes in a real-life scenario. These results support the use of odevixibat in children with any type of PFICs, including those with different stages of liver disease and comorbidities.

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Research article

JHEP|Reports

Real-world experience with odevixibat in children with progressive familial intrahepatic cholestasis

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Background & aims: A previously published trial demonstrated that odevixibat is effective in the treatment of cholestatic pruritus of children with progressive familial intrahepatic cholestasis (PFIC). Real-world experience is necessary to confirm the results of registration trials with selective eligibility criteria. We present our 'real-life experience' of the effectiveness and safety of odevixibat in patients with different PFIC subtypes.

Methods: We carried out a multicenter prospective study of patients with PFIC treated with odevixibat (40 or escalated to 120 μg/kg/day). Pruritus was assessed by 'Physician Global Impression of Symptom' at baseline and monthly up to 6 months. Serum bile acids (sBA) responders were patients who achieved a reduction in sBA levels ≥70% from baseline (or a value <70 μmol/L) after 6 months; pruritus responders were patients who reported improvement in their pruritus score.

Results: In total, 24 patients (median age 6.6 years [3.7–12.1], male:female = 11/13) were enrolled; 16 (67%) had classic PFIC types (PFIC-1, 2; PFIC-2, 11; and PFIC-3, 3), whereas eight (33%) had rarer forms (PFIC-4, 5, PFIC-5, 1; PFIC-6, 1; and PFIC-9, 1). All had high sBA levels and 22/24 (92%) had pruritus. Four (17%) had associated comorbidities.
After 6 months of treatment, sBA decreased from a median of 317.1 μmol/L (range 82.3–369.0 μmol/L) to 45.6 μmol/L (range 7.2–120 μmol/L; p <0.001); the mean change in pruritus score was -1.7. Overall, 75% of patients were sBA responders, 73% were pruritus responders, and 30% required dose escalation. Reduced pruritus correlated significantly with reduced sBA (p <0.05). A cut-off value of sBA >333.5 μmol/L increased the risk of no response to odevixibat by 17-fold (p <0.001). No serious adverse events were recorded.

Conclusions: Odevixibat is effective and safe in reducing sBA levels and improving pruritus in a real-life scenario in both patients with classic PFIC types and in those with other rarer subtypes. Dose escalation is required in some patients to improve the response to treatment.

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Introduction

Progressive familial intrahepatic cholestasis (PFIC) represents a heterogeneous group of rare genetic disorders. Classic forms include PFIC-1 (familial intrahepatic cholestasis 1 [FIC-1] deficiency), PFIC-2 (bile salt export pump [BSEP] deficiency), and PFIC-3 (multidrug resistance protein 3 [MDR3] deficiency); rarer forms are PFIC-4 (tight junction protein 2 [TJP2] deficiency), PFIC-5 (farnesoid X receptor [FXR] deficiency), PFIC-6 (myosin 5B [MYO5B] deficiency) and other subtypes.[1–3]

Clinical presentation varies from mild forms to severe chronic cholestasis manifesting with jaundice, untreatable pruritus, and failure to thrive; some patients might also present with extrahepatic manifestations.[2,3] Pruritus can cause self-mutilation, scarring, and sleep deprivation, and severely affects quality of life of patients and their family members.[3,4] Historically, treatment options for severe pruritus were limited to off-label symptomatic medications, which often failed to control symptoms.[4,5]

Recent research strategies identified new therapeutic molecules. Odevixibat, a selective inhibitor of the ileal bile acid transporter (IBAT), is a new agent that can pharmacologically interrupt the enterohepatic circulation of bile acids (BAs), leading to increased fecal BA excretion, reduced levels of sBA, and improvement in pruritus.[2,6] In two relevant clinical trials, PEDFIC 1 (randomized controlled trial [RCT]: NCT03566238) and PEDFIC 2 (open-label, single-arm trial: NCT03659916), investigators demonstrated the safety and efficacy of odevixibat for the management of cholestasis and pruritus in patients with PFIC-1 and PFIC-2.[7–9]

In both clinical trials, patients with mutations in *ABCB11* predicting a complete absence of functional BSEP protein were excluded because the complete loss of function in BSEP

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affects sBA secretion and its enterohepatic circulation, rendering IBAT inhibition at the ileum site ineffective.[7–9]

Although the inclusion criteria of the PEDFIC 2 study allowed the enrollment of patients with other forms of PFIC, patients with rarer subtypes were not included (there was only one patient with PFIC-6 in the entire cohort).[8]

RCTs are conducted on populations that have been selected according to inclusion and exclusion criteria. Consequently, patients with comorbidities or disease subtypes are often excluded. Thus, patients enrolled in RCTs do not truly represent the entire population and, therefore, results from RCTs require confirmation from clinical situations that are common in a real-world scenario.[10] Given that published data on real-world experience are lacking, we present here our experience of odevixibat use in patients with PFIC treated outside clinical trials, to add information on the characteristics of patients and response to treatment in a real-life scenario.

Methods

In March 2021, an Expanded Access Protocol (EAP) was launched with the aim to provide odevixibat to all patients diagnosed with PFIC not previously enrolled in an RCT. Based on this program, the Liver Disease Working Group of the Italian Society for Pediatric Gastroenterology, Hepatology and Pediatric Nutrition (SIGENP) led a prospective multicenter national study to collect data on patients in Italy with PFIC treated with odevixibat.

Patient selection

Patients diagnosed with PFIC at the age of 0–18 years were enrolled and treated with odevixibat according to inclusion criteria: (1) genetically confirmed diagnosis of PFIC; (2) body weight ≥5 kg; (3) elevated sBA (more than twice the upper limit of normal); (4) approval from the local ethics committee for each patient; and (5) informed consent provided by patient or their legal guardian.

Indications to treatment included high sBA with (or without) pruritus. Initially, odevixibat was supplied as capsules for oral administration, once daily (during breakfast), at a dosage of 120 μg/kg for all patients. However, in 2022, the protocol was modified to administer odevixibat at the initial dosage of 40 μg/kg once daily; after 3 months, the dose was increased to 120 μg/kg in patients with poor response to treatment, defined as 'no significant reduction in sBA levels (<70% from baseline, or a value >70 μmol/L) and no improvement in pruritus scale'; in patients without pruritus only, variation in sBA levels was considered to assess changes in dosage. Odevixibat was administered as whole capsules in older children or mixed with food (yogurt or jam) in younger ones.

Assessments and endpoints

Laboratory parameters were assessed at baseline and every month for 6 months (Months 0–6 of the study) including: full blood count, serum albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin (total and direct), gamma-glutamyl transferase (GGT), sBA, prothrombin time-international normalized ratio (INR), and fat-soluble vitamins. Pruritus was assessed by the Physician Global Impression of Symptom (PGIS) scale and scored from 0 to 4 points, where 0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe pruritus (Table S1).[7] Sleep disturbances were defined as 'difficulty in falling asleep and frequent nocturnal awakenings due to pruritus' and were scored as present or absent based on caregiver-reported information.

The endpoints of the study were: (1) reduction in sBA levels; and (2) improvements in pruritus, after 6 months of treatment compared with baseline. To assess the response to odevixibat, we considered the following definitions, which correspond to those adopted in previous clinical trials[7,8] (1) sBA responders: patients who achieved a reduction in sBA levels ≥70% from baseline, or a value <70 μmol/L, after 6 months of treatment[7]; and (2) pruritus responders: patients who reported any improvement in pruritus scale (at least -1 point PGIS score), compared with baseline, after 6 months of treatment.

Changes in pruritus and sBA levels were analyzed to see whether pruritus correlated with sBA concentrations at Months 3 and 6.

To identify baseline clinical or biochemical factors associated with poor response to odevixibat treatment, patients classified as responders and non-responders were divided into two groups and compared.

The study concluded after 6 months of treatment. In patients who did not respond to odevixibat, the treatment was discontinued. All adverse events, whether reported by the patient or observed by the physician, were recorded. This study was approved by the local ethics committee at Bergamo Hospital, Bergamo, Italy, which was the referral center for this study (Reg.187/21).

Statistical analysis

Continuous variables are reported as median and IQR and categorical ones as frequency and percentage. Wilcoxon–Mann-Whitney *U* tests were used for testing differences among continuous variables, and chi-squared test or Fisher's exact test (depending on the expected frequencies in the contingency tables) were used for categorical variables. Specifically, the chi-squared test was used when all expected cell counts were >5, whereas Fisher's exact test was used when the expected frequencies, in any cell, were <5.

Wilcoxon signed-rank test or Sign test were used for paired comparisons of continuous variables, and the McNemar test was used for paired comparisons of categorical variables. Spearman rank correlation was used to evaluate correlations between continuous variables. Receiver operating characteristic (ROC) curves with corresponding AUCs were used to identify the most predictive variables for a non-response outcome. The Liu method was used to identify the best cut-off for each variable. A univariate logistic regression model was performed to estimate the odds ratio (OR) of non-response outcome along with the corresponding 95% CI.

A two-sided p value ≤0.05 was considered significant for all tested hypotheses. The analysis was performed using Stata Software, release 16.1 (StataCorp LP, College Station, TX, USA).

Results

A total of 24 patients (median age 6.6 years [3.7–12.1]; median weight 20.6 kg [12.8–34.0]; male/female = 11/13), from 12 centers, were prospectively enrolled and treated with

odevixibat between 2021 and 2023; 16/24 patients had classic forms of PFIC (PFIC-1 = 2; PFIC-2 = 11; and PFIC-3 = 3) and eight of 24 had rarer subtypes, including five patients with PFIC-4, one with PFIC-5, one with PFIC-6, and one with zinc finger protein 9 deficiency (PFIC-9).[1,11–14] For convenience, we named all forms (both classic and rarer) as 'PFIC'.

At the time of treatment, all patients were older than 6 months. All but two patients were under 18 years of age and two patients were 22 and 28 years old, both of whom were diagnosed with PFIC-2 during childhood and were in follow-up at pediatric centers.

Diagnosis was genetically confirmed in all patients (homozygous mutation in 13 patients; biallelic compound heterozygous in 11); two of 11 patients with PFIC-2 had a homozygous mutation producing a truncated protein (one female, aged 4.8 years; one male, aged 6.3 years) (Table S2).

One patient with PFIC-1 (female) underwent cholecystojejunocolonic anastomosis (partial internal biliary diversion) at 18 months of age because of intractable pruritus. The second patient with PFIC-1 (male) underwent liver transplantation (LT) at the age of 1 year and re-LT plus total internal biliary diversion (TIBD) at the age of 5 years because of severe steatosis and graft dysfunction.

All patients had high sBA levels (median = 317 μmol/L, range 82.3–369.0) without clinical jaundice (total bilirubin was 0.2–2.5 mg/dl); only one patient with PFIC-6 (aged 1.4 years) had high bilirubin levels (total bilirubin 5.9 mg/dl, conjugated bilirubin 4.9 mg/dl). Twenty-two of 24 (92%) patients had pruritus, scored as 'severe' (grade 3) in eight of 22 (36%) and 'very severe' (grade 4) in 14/22 (64%); sleep disturbances were recorded in 16/24 patients (67%).

Seven patients (29%; three with PFIC-2, one with PFIC-4; two with PFIC-3; and one with PFIC-9) had clinical manifestations of portal hypertension (PH, namely splenomegaly and hypersplenism, with no gastroesophageal varices on endoscopy). Liver synthetic function was preserved in all patients.

Four patients had associated comorbidities: one patient (with PFIC-2, aged 9.7 years) had severe psoriasis unresponsive to medical treatment (ustekinumab); one patient (with PFIC-2, aged 13 years) had developmental delay and facial dysmorphisms; one patient (with PFIC-2, aged 4.8 years) had coeliac disease; and one patient (with PFIC-4, aged 9.4 years) was misdiagnosed with biliary atresia and underwent Kasai portoenterostomy at the age of 65 days.

Five out of 24 patients received odevixibat at a starting dose of 120 μg/kg/day and 19/24 patients at 40 μg/kg/day. All patients were receiving medication for the treatment of pruritus and cholestasis, including ursodeoxycholic acid (UDCA; n = 24/24); rifampicin (n = 13/24); and antihistamines (n = 6/24). The co-administration of BA-binding resins was not allowed. During the study period, neither was the introduction of new antipruritic agents allowed, and pre-existing medication had to be maintained at the same dose. Patient characteristics are reported in Table 1.

Table 1. Demographic, clinical and laboratory characteristics at baseline in 24 patients with PFIC treated with odevixibat.

Characteristics	Patients (n = 24)
Age (years)	6.6 (3.7–12.1)
Weight (kg)	20.6 (12.8–34.0)
Sex	
Female	13 (54)
Male	11 (46)
Type of PFIC	
FIC-1 deficiency (PFIC-1)	2 (8)
BSEP deficiency (PFIC-2)	11 (46)
MDR3 deficiency (PFIC-3)	3 (13)
TJP2 deficiency (PFIC-4)	5 (21)
FXR deficiency (PFIC-5)	1 (4)
MYO5B deficiency (PFIC-6)	1 (4)
ZFYVE19* (PFIC-9)	1 (4)
Type of mutation†	
Homozygous	13 (54)
Bi-allelic compound heterozygous	11 (46)
Medications	
UDCA	24 (100)
Rifampicin	13 (54)
Antihistamines	6 (25)
Pruritus (PGIS score)	
None	2 (8)
Mild	4 (17)
Moderate	4 (17)
Severe	6 (25)
Very severe	8 (33)
Sleep disorders	
Yes	16 (67)
No	8 (33)
Laboratory	
sBA (μmol/L)	317.1 (82.3–369.0)
AST (U/L)	76 (49–123)
ALT (U/L)	54 (27–85)
Total bilirubin (mg/dl)	1.3 (0.8–2.2)
GGT (U/L)	24 (15–46)
ALP (U/L)	498 (346–576)
INR	1.0 (0.9–1.0)
Albumin (g/dl)	4.0 (3.8–4.3)
Hemoglobin (g/dl)	12.8 (11.9–13.6)
WBC (mm^3)	6,830 (4,465–9,855)
Platelets (mm^3)	246,500 (97,500–442,000)
Splenomegaly‡	7 (25)

Data are presented as median (IQR) or n (%).
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSEP, bile salt export pump; FIC1, familial intrahepatic cholestasis 1; FXR, farnesoid X receptor; GGT, gamma-glutamyl transferase; INR, international normalized ratio; MDR3, multidrug resistance protein 3; MYO5B, myosin 5B; PGIS, physician global impression of symptom; sBA, serum bile acids; TJP2, tight junction protein 2; UDCA, ursodeoxycholic acid; WBC, white blood cells.
*Zinc finger five-type containing 19.
†In two patients with PFIC-2, genetic mutation produced premature termination codons with protein truncation.
‡Detected on liver ultrasound.

Response to odevixibat

All but two patients (92%) received odevixibat for 6 months, with two receiving it for 3 months. Among the latter, one patient (with PFIC-2, aged 1.8 years) did not respond to odevixibat and their parents decided to discontinue the treatment after 3 months; one patient (with PFIC-6, aged 1.4 years) responded well to odevixibat (sBA reduced from 299 μmol/L at baseline to 10 μmol/L, after 3 months), but follow-up visits were interrupted at Month 3.

Changes in sBA

At 6 months, median sBA levels were significantly reduced compared with baseline (45.6 μmol/L [7.2–120] *vs.* 317.1 μmol/L [82.3–369]; p <0.001) (Fig. 1; Table S3).

At 6 months, 18 patients were sBA responders (75%; n = 1 with PFIC-1; n = 6 with PFIC-2, n = 3 with PFIC-3, n = 5 with PFIC-4, n = 3 with PFIC-5/PFIC-6/PFIC-9 [one each]). This

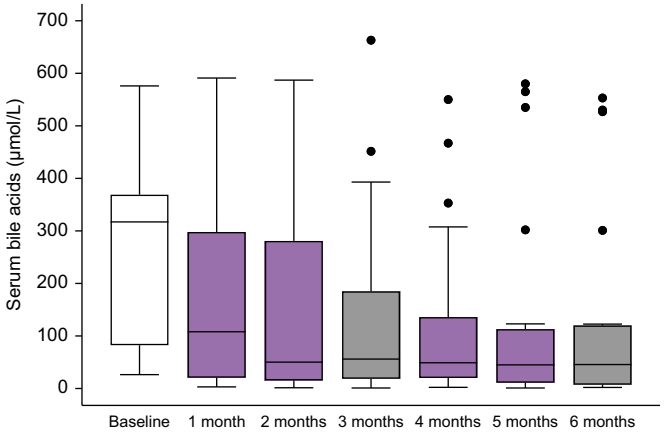


Fig. 1. Median change in sBA from baseline to 6 months. Box plots represent the distribution of sBA concentrations at baseline and at each monthly follow-up time point (1–6 months). The boxes show the IQR, with the line inside each box representing the median. White colum indicates the baseline study period; violet columns indicate the follow-up visits; grey columns (months 3 and 6) indicate the time to assess the respond to treatment. Whiskers extend to 1.5 times the IQR from the box edges, and individual dots represent outliers. sBA, serum bile acids.

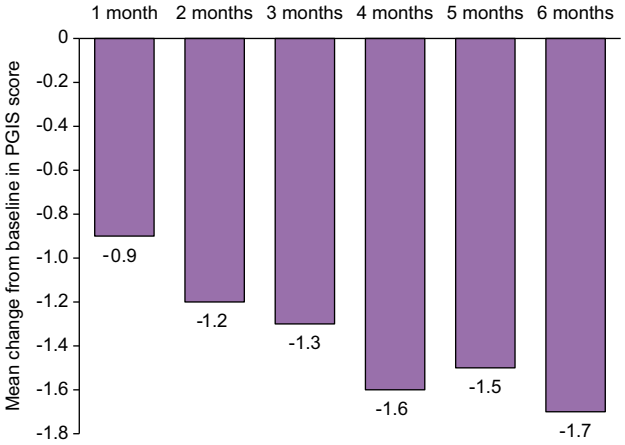


Fig. 3. Mean changes from baseline of PGIS score from baseline to 6 months. PGIS, physician global impression of symptoms.

percentage was higher compared with that recorded at the 3-month follow-up (54%; Fig. 2).

Percentages of sBA responders by type of PFIC were: n = 1/2 with PFIC-1, 50%; n = 6/11 with PFIC-2, 55%; n = 3/3 with PFIC 3, 100%; n = 5/5 with PFIC-4, 100%; and n = 3/3 with PFIC-5, PFIC-6, and PFIC-9, 100%. Percentages of sBA responders among seven patients with PH was 71% (n = 5/7). In one patient with PFIC-2 and severe psoriasis, sBA levels decreased from 365 µmol/L (at baseline) to 48 µmol/L (at 6 months) and pruritus resolved. Surprisingly, while the treatment for psoriasis remained unchanged, all psoriatic plaques completely disappeared.

Changes in pruritus

The mean change in PGIS score from baseline was -1.3 at Month 3 and -1.7 at Month 6 (Fig. 3). Percentages of pruritus responders at 3 and 6 months were 63% and 73% respectively, including those with severe and very severe pruritus (Fig. 4). Mean PGIS score decreased from 3.6 (SD 1.3) at baseline to 2.3 (SD 1.4) at Month 3 and to 1.9 (SD 1.3) at Month 6 (Fig. S1). Sleep disturbances completely resolved in all pruritus responders. A reduction in sBA levels (<70 µmol/L) without improvement in pruritus was only observed in one patient (with PFIC-3, aged 1.3 years). Correlation between absolute change in pruritus and sBA levels at 3 and 6 months reached statistical significance (Month 3, p = 0.016; Month 6, p = 0.023; Fig. 5).

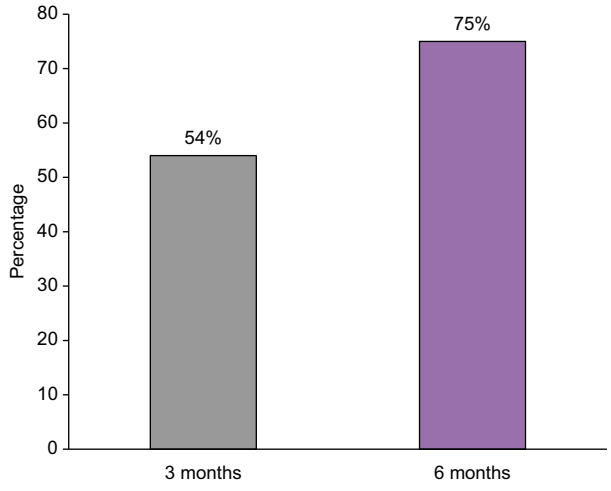


Fig. 2. Percentage of sBA responders (defined as reduction in sBA levels ≥70% from baseline, or a value <70 µmol/L) in 24 patients with PFIC treated with odevixibat for 6 months. PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid.

Other biochemical parameters

Median values of liver enzymes, total bilirubin, and platelet count did not change significantly from baseline to 6 months' follow-up (p >0.05; Table S4). However, in one patient with PFIC-2 (treated at a dosage of 120 µg/kg), AST levels increased from 72 IU/L (at baseline) to 121 IU/L (at 1 month), and then decreased to 54 IU/L at Month 3. In two patients (one with PFIC-1 and one with PFIC-4; both treated at a dosage of 40 µg/kg) ALT levels increased from 50 IU/L (at baseline) to 140 IU/L (at 1 month) and from 25 IU/L to 99 IU/L, respectively.

Based on these results, we decided that there was no need to reduce the dosage of odevixibat for this mild increase in ALT, and this increase was eventually observed to be transient.

Similarly, an increase in total bilirubin was recorded in one patient with PFIC-2, from 1.4 mg/dl (at baseline) to 3.2 mg/dl (at 1 month), which then decreased to 1.9 mg/dl (at Month 3). Overall, liver enzymes and bilirubin returned to baseline within 3 months.

Remarkably, in one patient with PFIC-6, high total bilirubin levels recorded at baseline (5.9 mg/dl) completely normalized at by Month 3 (0.8 mg/dl); the same occurred in one patient with PFIC-2 (total bilirubin 2.8 mg/dl at baseline, which normalized to 0.4 mg/dl); both were sBA responders. A more prolonged value of INR at Month 6 was reported in two patients, one with PFIC-4 (INR 1.0 at baseline and 1.4 at Month 6) and one with PFIC-1 (INR 1.3 at baseline and 1.5 at Month 6). Splenomegaly was reported at baseline in seven patients (29%) and no changes in spleen size were recorded at 6 months.

Escalation dose of odevixibat

At Month 3, seven of 19 patients (37%) had a dose escalation of odevixibat (from 40 to 120 µg/kg/day). Five out of seven

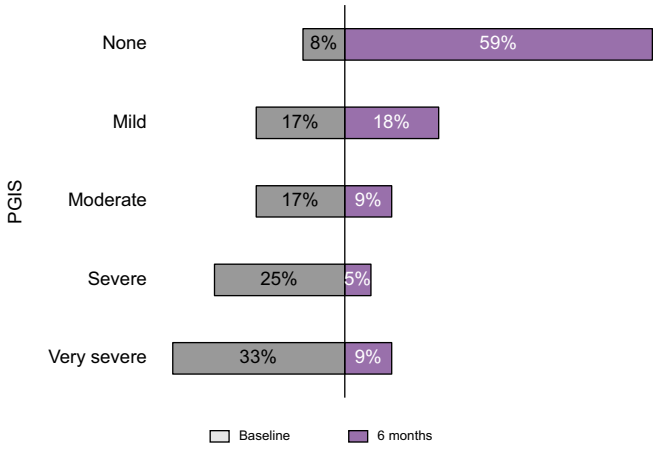


Fig. 4. Percentages of patients with pruritus (according to PGIS) at baseline and at Month 6. PGIS, physician global impression of symptoms.

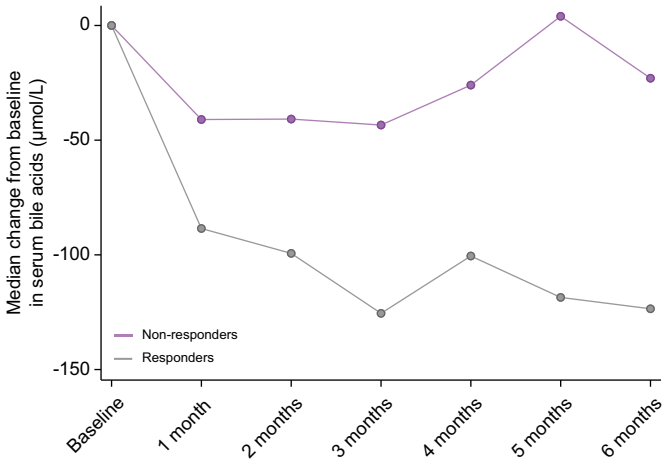


Fig. 6. Median change in serum bile acids from baseline to 6 months in responders (n = 18) and non-responders (n = 6).

patients had a partial reduction in sBA levels (defined as reduction >30% but <70% compared with baseline value; partial responders).[7,8]

After dose escalation, we observed a further reduction in sBA levels and improvement in pruritus in four of seven patients (57%, one with PFIC-2, two with PFIC-4; and one with PFIC-5; all responders). By contrast, no changes were observed in the other three patients (one with PFIC-1, one with PFIC 2; and one with PFIC-3).

Non-responders

Six of 24 patients did not respond to odevixibat treatment (25%; five with PFIC-2, including two patients with truncated protein; and one with PFIC-1) and maintained high sBA levels (Fig. 6). At the end of the study, four of these patients (all with PFIC-2; aged 1.8, 2.4, 8.0, and 13.1 years) were listed for LT, whereas two patients (one aged 6.3 years, with PFIC-2; one aged 2.4 years, with PFIC-1 and TIBD) remained on off-label medication. On univariate logistic regression model analysis, the only factor associated with poor response to treatment was baseline sBA level. A cut-off value >333.5 µmol/L increased the risk of no response to odevixibat treatment by 17 fold (OR 17.5; 95% CI, 1.56–196.3; p <0.001) (Table S5).

Growth parameters

Median values of weight and height increased from baseline to 6 months without reaching statistical significance (median weight 20.7 kg [13.6–35 kg] at baseline *vs*. 23.4 kg [15.3-45.8 kg] at Month 6; median height 117 cm [93–141] at baseline *vs*. 122 cm [106–154] at Month 6). Similarly, mean weight and mean height Z-scores did not change significantly from baseline (weight: -0.68, SD 1.08; height: -0.80, SD 1.24) to 6 months' follow-up (weight: -0.82, SD 1.26; height: -1.11, SD 1.37) (Fig. S2).

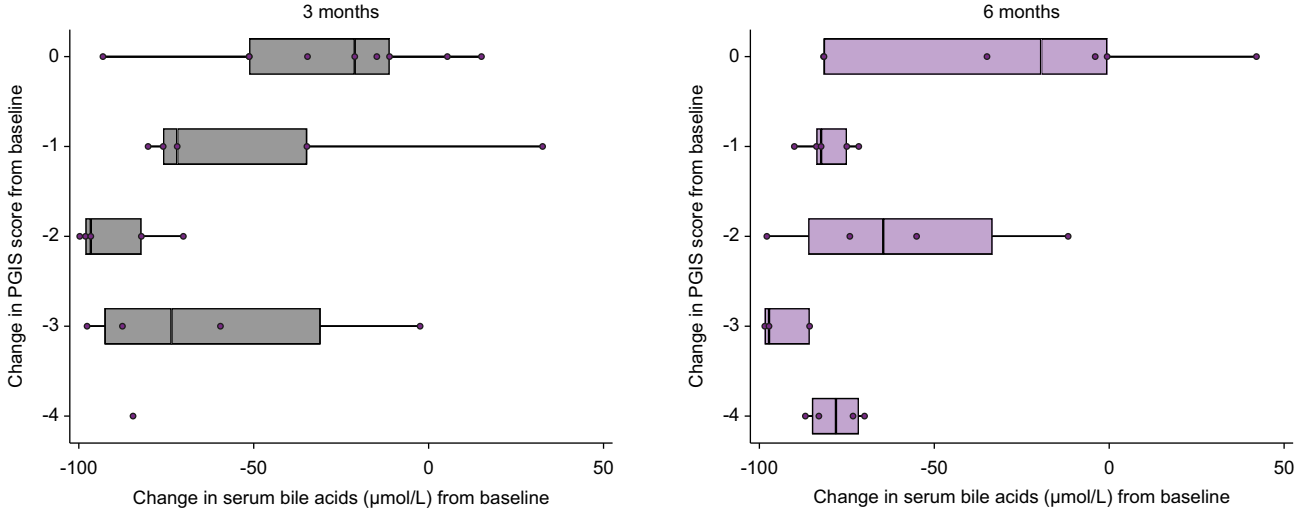


Fig. 5. Correlation between absolute change in PGIS from baseline and percent change in serum bile acids from baseline at 3 months and at 6 months. The graph shows box plots of the distribution of the relative change in serum bile acids from baseline to 3/6 months for each category of change in PGIS score. The boxes show the IQR, with the line inside each box representing the median. Whiskers extend to XX times the IQR from the box edges, and individual dots represent outliers. Spearman's test indicates a statistically significant correlation at both time points (3 months: Spearman's rho = 0.54; p = 0.007; 6 months: Spearman's rho = 0.45; p = 0.037). PGIS, physician global impression of symptoms.

All patients received fat-soluble vitamin supplements as standard of care during the study period; 11/24 patients (46%) at baseline and 12/24 patients (50%) at 6 months' follow-up still showed a deficiency in at least one fat-soluble vitamin (A, D, or E). Fat-soluble vitamin deficiency was not regarded as related to odevixibat treatment by the investigators.

Adverse event

No serious adverse events were recorded during the study period, including those unrelated to the study drug. Temporary diarrhea and abdominal pain were recorded in four of 24 patients (17%; two with PFIC-2 and two with PFIC-4); one patient (with PFIC-3) complained of nausea and lack of appetite. Symptoms spontaneously resolved in all patients within 3 months.

Discussion

In this multicenter prospective study, we report our real-life experience of odevixibat use in patients with PFIC. This cohort has different characteristics compared with those reported in previous studies.[7,8] We believe that this study strongly supports the results obtained in RCTs in a group of patients that truly represents the population of a real-life scenario.

In our experience, odevixibat was effective in reducing sBA levels and improving pruritus in most of the treated patients. Treatment of cholestatic pruritus is the main goal of therapy, as shown in PEDFIC 1, a placebo-controlled trial of 62 children with PFIC-1 and 2 who experienced a significant reduction in sBA and improvement in pruritus in 33% (*vs*. none in the placebo group) and 55% of patients (vs. 30% in the placebo group), respectively.[7] A subsequent study suggested that reduction in sBA and pruritus also results in improvement of native liver survival.[8] However, a more prolonged follow-up is required to establish whether odevixibat can change the trajectory of the disease in patients with PFIC.

In our experience, 50% of patients with classic forms of PFIC responded well to treatment; a similar percentage was reported in the PEDFIC 1 study.[7] We also enrolled and treated a child with PFIC-2 and severe psoriasis not responding to ustekinumab as a result of the Koebner phenomenon.[15] After treatment with odevixibat and resolution of cholestatic pruritus, we observed complete healing of the psoriatic plaques, confirming that cholestatic pruritus had contributed to maintaining and worsening psoriatic lesions.

Data on the efficacy of odevixibat in patients with rarer forms of PFIC are scant; only two patients with PFIC-6 have been reported in two different cohorts.[8,16] We previously reported the successful treatment with odevixibat in patients with PFIC-4 and PFIC-9, included in the current cohort, and provide a longer follow-up contributing to confirm those preliminary results.[17,18] In the current cohort, one-third of patients had rarer forms of PFIC (types 4, 5, 6, and 9), all of whom responded well to odevixibat treatment. This suggests that underlying pathogenetic mechanisms of cholestasis render these forms of PFIC particularly responsive to novel treatments with IBAT inhibitors. Surprisingly, a patient with PFIC-4 found to have a homozygous mutation predicting a truncating protein (male, aged 9.4 years) responded well to odevixibat, suggesting that the type of mutation in PFIC-4 is less relevant compared with those in patients with PFIC-2.[7,17] Interestingly, we treated a female patient with PFIC-5 (aged 5.3 years; homozygous NR1H4 mutation) presenting with high sBA, mild pruritus, and incomplete cirrhosis on histology. Patients with PFIC-5 progress rapidly to end-stage liver disease,[19] and the pathogenetic mechanisms of cholestasis likely do not benefit from odevixibat treatment. However, we decided to start treatment with the hope of slowing down disease progression. The patient responded well (sBA normalized and pruritus solved), although a more prolonged follow-up is required to best assess the long-term benefits on native liver survival in this PFIC subtype.

We also observed a valuable response to treatment in a small group of patients who had clinical features of PH; 72% of them (n = 5/7) were sBA and pruritus responders. Furthermore, on statistical analysis, parameters of PH were not associated with poor response to treatment. Odevixibat treatment reduced sBA and alleviated pruritus in an adult patient (aged 35 years) with advanced, icteric cholestatic liver disease and cirrhosis who was listed for LT with a model of end-stage liver disease (MELD) score of 20 points.[20] These results strongly suggest that even patients with advanced liver disease should be treated with odevixibat before becoming candidates for LT.

Defining the minimum threshold of sBA to start treatment with IBAT inhibitors in children without pruritus is challenging. However, the presence of associated symptoms suggesting disease progression or the absence of valuable treatment options to manage post-LT complications could support the decision to start treatment even in patients with a mild increase in sBA levels. In this study, two patients had mild cholestasis in the absence of pruritus, associated with clinical features of PH (one patient with PFIC-3) and diarrhea (one transplanted patient with PFIC-1); in both patients, sBA normalized after treatment with odevixibat, with disappearance of diarrhea in the latter patient.

Percentages of sBA and pruritus responders at Month 6 were higher compared with Month 3; this might be partially caused by escalation dose, which could have contributed to improve the response rate.

In our cohort, 80% of patients (n = 4/5) who, after an increased dosage, became responders at 6 months were partial responders at 3 months, suggesting that a partial response at 3 months predicts the full response after dose escalation.

Similarly, in the PEDFIC 2 study, the authors reported a better response to treatment over time and further improvements in pruritus responses after dose escalation.[8] In the study by Baumann *et al.*,[16] a reduction in sBA and improvements in pruritus were observed with all doses of odevixibat (from 10 to 200 μg/kg/die). In a phase 1 study of healthy subjects, odevixibat dose-dependently reduced sBA levels.[21]

The correlation between sBA levels and pruritus remains an open issue.[22,23] In our study, we found a statistically significant correlation between pruritus and sBA levels. In a phase 2 study including patients with PFIC, the authors demonstrated a significant correlation between pruritus and sBA levels.[16] Although sBA are unlikely to be directly responsible for pruritus, these results confirm that, in patients with PFIC, pruritus severity is often associated with sBA levels, and reduction in sBA levels after treatment correlates with pruritus improvement.

Before initiation of odevixibat, most patients had elevated liver enzymes because of the underlying liver disease. Median values of biochemical parameters did not significantly change during the study period. In the PEDFIC 1 study, there was no significant reduction in ALT levels in patients treated with

odevixibat compared with the placebo group. Persistence of high transaminases despite treatment with an IBAT inhibitor suggests an incomplete resolution of cholestasis, but this hypothesis should be better explored in studies with a longer follow-up period.

Three patients in this cohort had a temporary increase in transaminase levels that normalized spontaneously by Month 3. This suggests that there is no need to discontinue the treatment in the presence of mild/moderate changes in liver enzymes.

The pathogenetic mechanisms leading to elevation of transaminase levels remain unknown. Similarly to previous studies, we also observed an increase in liver enzymes at different doses, suggesting that there is no correlation between the utilized dosage and the alteration in serum transaminases.[7,8,16]

Treatment with IBAT inhibitors could reduce post-transplant diarrhea in PFIC-1 disease. Ohlendorf and co-authors described a child with PFIC-1 (aged 2 years and 8 months) who developed severe post-LT diarrhea negatively impacting their quality of life. After 6 months of odevixibat treatment, the patient showed less stool output, weight and height gain, and improved physical energy.[24] Similar results were reported in three children with PFIC-1 (aged 6, 9, and 13 years) and post-LT diarrhea; all patients had less-frequent and/or firmer stools as well as improvements in daily quality of life after starting odevixibat treatment.[25] None of these four patients showed features of liver disease progression during the study.

A different result was reported in one child included in our cohort who was treated with odevixibat because of chronic diarrhea and mild cholestasis. After having received two liver transplants, they continued to have recurrence of severe graft dysfunction and a severe bowel distension and dysmotility; therefore, the patient was listed for a combined liver-intestinal transplantation. This suggests that management of patients with PFIC-1 after LT remains challenging even in the era of IBAT inhibitors.

Six patients (25%, all with classic forms of PFIC) did not respond to odevixibat treatment, four of whom were listed for LT. Factors predicting the response to odevixibat are currently unclear.[26] In a recent study on patients with PFIC-2, the authors demonstrated that odevixibat might induce hepatobiliary BA secretion in responsive patients with PFIC-2 and could lead to improved prognostic serum BA parameters of liver health.[27] We found that a sBA cut-off value >333.5 μmol/L increased the risk of no response to treatment by 17 fold (p <0.001), suggesting a poor response in children with very severe cholestasis. It is likely that a residual biliary BA excretion allows odevixibat to divert a sufficient amount of BA in the stool to accomplish a negative balance between synthesis and elimination, ending up with a reduction of the BA pool. This would not be the case in patients with a complete loss of function of the defective protein. Indeed, three patients with PFIC-2 and genetic mutations producing a truncated protein (two from this study and one from Baumann *et al.*'s cohort) were treated with odevixibat unsuccessfully, confirming that the presence of unfavorable genetic mutations predicting complete absence of function is a factor associated with no response to treatment.[16]

Defining the correct timing for starting treatment with odevixibat is crucial. In our cohort, a genetically confirmed diagnosis of PFIC was required to be enrolled in this study. However, in clinical practice, when the clinical phenotype strongly supports the diagnosis of PFIC, it is recommended not to delay the initiation of the treatment while awaiting the results of genetic testing.[28]

Odevixibat was well tolerated in all patients. A small proportion complained of gastrointestinal symptoms, including diarrhea and abdominal pain, which occurred within the first 4 weeks of treatment and lasted less than 2 months; no serious adverse events were recorded in this cohort. In Baumann *et al.*'s study, the authors reported no treatment-related serious adverse events, apart from a temporary increase in transaminase levels.[16] In Thompson *et al.*'s study, the most common adverse events were diarrhea or frequent bowel movements; serious adverse events occurred in three of 42 (7%) odevixibat-treated patients and in five of 20 (25%) placebo-treated patients; three patients experienced drug-related increase in ALT, AST, and total bilirubin levels, which also resulted in interruption of study drug administration.[7]

Odevixibat can affect absorption of fat-soluble vitamins.[7,8] However, in our cohort, no patients experienced new or worsening fat-soluble vitamin deficiency during the study period.

Similarly, to the PEDFIC 1 study,[7] we did not detect any significant changes in mean weight and height Z-scores in our cohort. A different result was reported in PEDFIC 2 study, suggesting that a more prolonged follow-up is required to assess improvements in growth parameters.[8]

Although PFIC is a rare disease and the 24 patients reported here represent 57% of the entire cohort of treated patients who were included in PEDFIC 1,[7] the small sample size could be considered a limitation of this study. Another limitation is that we reported early data on a cohort of pediatric patients treated with odevixibat and followed for only 6 months; although such an on-therapy period is considered sufficient to evaluate the response to treatment, these results will need to be confirmed in a study with a larger sample size and a longer follow-up.

The strengths of this study are its prospective, real-life design, and the characteristics of this cohort of participants, which allowed us to add information on response to odevixibat treatment in patients with different PFIC subtypes in daily clinical practice. In the future, a larger cohort and a prolonged follow-up would allow us to make further analysis, including a comparison between the long-term outcome of responders versus partial responders.[8]

In conclusion, in a real-life scenario, odevixibat is effective in reducing sBA levels and improving pruritus in patients with different subtypes of PFIC. The drug is well tolerated overall, an escalation dose might be required to achieve a better response to treatment. Severity of pruritus also correlates with sBA levels.

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Abbreviations

ALT, alanine-aminotransferase; AST, aspartate aminotransferase; BA, bile acids; BSEP, bile salt export pump; EAP, Expanded Access Protocol; FIC-1, familial intrahepatic cholestasis 1; FXR, farnesoid X receptor; GGT, gamma-glutamyl transferase; IBAT, ileal bile acid transporter; INR, international normalized ratio; LT, liver transplantation; MDR3, multidrug resistance protein 3; MELD, model of end-stage liver disease.MYO5B, myosin 5B; OR, odds ratio; PFIC, progressive familial intrahepatic cholestasis; PGIS, physician global impression of symptom; PH, portal hypertension; RCT, randomized controlled trial; ROC, receiver operating characteristic; sBA, serum bile acids; SIGENP, Italian Society of Gastroenterology, Hepatology and Nutrition; TIBD, total internal biliary diversion; TJP2, tight junction protein 2; UDCA, ursodeoxycholic acid.

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Conflicts of interest

ADG, MS, MC, PC, GI, CM, EN are members of the advisory board for Ipsen and Mirum. AL is a consultant for Advanz Pharma, AlfaSigma, Takeda, Ipsen, and GSK; received speaker fees from Gilead, GSK, AbbVie, MSD, Advanz Pharma, AlfaSigma, GSK, and Incyte; and received travel support from Ipsen. FN: member of advisory board for Ipsen pharma. LD is a consultant or member of the advisory board of Mirum, Albireo/Ipsen, Alexion, Intercept/Advanz Pharma, Astra Zeneca, Vivet, Selecta, Spark, Tome, and Genespire. MF, SG, AM, FN, CZ, GC, AG declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceived and planned study: ADG. Writing: first draft: ADG. Draft reviewed: LD, MS, MF, PC, MC, AL, SG, GI, AM, CM, FN, CZ, EN. Statistical analysis: GC, AG. Interpretation of results and critical revision of manuscript for important intellectual content: ADG, LD, MS, MF, PC, MC, AL, SG, GI, AM, CM, FN, CZ, EN. Each author approved the submission of this version of the manuscript and takes full responsibility for the manuscript.

Data availability statement

The data that support the findings of this study are available from the corresponding authors, upon reasonable request.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101309.

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