Odevixibat therapy in patients with progressive familial intrahepatic cholestasis (PFIC) associated with MYO5B mutations: a retrospective case series

THU-336

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Introduction

- Progressive familial intrahepatic cholestasis (PFIC) is a heterogenous family of genetic, infantile-onset diseases characterised by impaired bile secretion and hepatocellular cholestasis, and severe pruritus [1, 2].
- Loss-of-function mutations in the MYO5B gene can cause both PFIC and microvillus inclusion disease (MVID) [3-5].
- PFIC associated with MYO5B mutations (PFIC10) is very rare, with less than fifty cases described to date worldwide.
- Odevixibat [6-8] is a small-molecule inhibitor of the ileal bile acid transporter which was licensed for the treatment of PFIC in Europe and the USA in July 2021 [6].
- Odevixibat was evaluated in the Phase 3 PEDFIC 1 study versus placebo in children with PFIC1 and PFIC2 and in the ongoing PEDFIC 2 open-label extension study that enrolled patients with all PFIC subtypes. The PEDFIC programme has demonstrated the potential of odevixibat to normalise serum bile acid levels and resolve pruritus, as well as its good tolerability profile [9].
- However, data on the utility of odevixibat in rarer forms of PFIC, notably associated with MYO5B mutations remain limited and it is important to obtain further information in the real-world treatment setting.

Objectives

- To describe outcome in five children with PFIC associated with MYO5B mutations treated with odevixibat.

Methods

- This was a retrospective study of children with PFIC associated with MYO5B mutations.
- Participants were identified because they had been enrolled either in the PEDFIC2 clinical trial (one child) or in the European compassionate use programme initiated by the manufacturers of odevixibat in July 2021.

Inclusion criteria

- Children with PFIC and documented MYO5B mutations.
- Intractable pruritus despite treatment with rifampicin and ursodeoxycholic acid.
- Initiation of treatment with odevixibat between March 2021 and July 2022

Follow-up

- The children were followed-up according to the centre's routine practice.
- Children attended at least quarterly visits at which a full clinical evaluation was performed. Blood samples were taken at most, but not all, visits for liver biochemistry.

Study variables

- Serum levels of bile acids
- Total bilirubin and ALAT
- Pruritus
  - rated on a four-point Likert scale: absent, mild, moderate or severe
- Sleep disturbances
  - rated on a four-point Likert scale: absent, mild, moderate or severe
- Digestive symptoms
- Treatments (odevixibat, ursodeoxycholic acid UDCA), rifampicin and vitamin supplementation)

Results

Patients

- Five children aged 2 - 10 years, 4 boys and 1 girl, were included from 4 European countries (DE, FR, IT and GB).
- The characteristics of the patients are presented in Table 1.
- Biallelic mutations in *MYO5B* were identified in all patients, except Patient 2.
- One boy (Patient 4) also had MVID and, for this reason, was fed parenterally for the first year of life.
- Patient 2 was on the waiting list for a liver transplant.
- In the year before starting odevixibat, all patients presented with moderate to severe pruritus.
- Four out of five had sleep disturbances due to pruritus.
- Prior to treatment, sBA levels were >150 µmol/L in all patients; total bilirubin was >25 µmol/L all children.
- Serum ALAT at baseline ranged from 37 IU/L (Patient 5) to 100 IU/L (Patient 3).

Treatment

- The initial dose of odevixibat ranged from 32.5–120 µg/kg/day.
- The dose was later increased from 32.5 to 65 µg/kg/day in Patient 3 and from 37.5 to 65 µg/kg/day in Patient 5, in the latter case to control itching).
- In two other patients, odevixibat treatment was temporarily interrupted due to an episode of infectious gastroenteritis. Both boys subsequently resumed the prior dose of odevixibat.
- In Patients 4 and 5, access to treatment was discontinuous for administrative reasons.
- Patient 5 was poorly compliant until a home care team was provided 8 months after treatment start.
- All patients had been treated previously with rifampicin, UDCA and vitamins; these treatments were continued under odevixibat at the same dose.
- After 6 months of odevixibat, Patient 2 discontinued concurrent treatment with no impact on sBA or bilirubin, or reappearance of symptoms.

Table 1. Patient characteristics

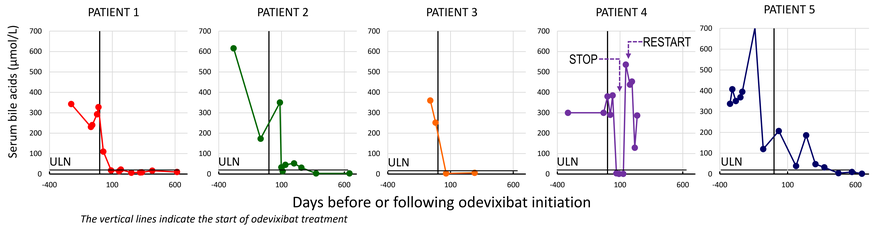
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	Boy	Girl	Boy	Boy	Boy
Age at first symptoms[1]	6 months	5 months	7 years	1 month	15 months
Age at PFIC diagnosis	18 months	15 months	7 years	9 month	25 months
Age at treatment initiation	9 years 11 mo	4 years	7 years 2 mo	15 months	3 years
***MYO5B* mutations**	c.356A>G homozygous	c.3190C>T heterozygous	c.244G>A homozygous	c.1361G>A ; c.1208C>A	c.1072C>G; del Exon 1-23
sBA prior to treatment	293 µmol/L	174 µmol/L	252 µmol/L	380 µmol/L	337 µmol/L
tBR prior to treatment	54 µmol/L	26 µmol/L	89 µmol/L	102 µmol/L	62 µmol/L
ALAT prior to treatment	41 IU/L	57 IU/L	58 IU/L	100 IU/L	37 IU/L
Prothrombin time/INR	97%	100%	1.0	97%	100%
Pruritus[2]	Moderate	Severe	Severe	Moderate	Severe
Sleep disturbances[2]	Mild	Severe	Severe	Severe	Moderate

ALAT: alanine aminotransferase; PFIC: progressive familial intrahepatic cholestasis;sBA:serum bile acids; tBR: total bilirubin.
[1]First documentation, actual date of first symptoms unknown. [2]Reported at the visit preceding the start of odevixibat treatment.

Serum bile acids

- sBA fell rapidly 1-3 months following initiation of odevixibat and reached the normal range (or close) within six months in 4/5 children (Figure 1).
- The response was less rapid in Patient 5, who was poorly compliant during the first months of treatment.
- On-treatment sBA levels remained within or close to the normal range throughout the follow-up, which now extends to >2 years in 2 patients.
- In Patient 4, treatment was interrupted after four months due to a gastrointestinal infection, whereupon sBA levels rapidly returned to above pre-treatment levels. Once treatment was reinstated, sBA levels decreased again.
- In Patients 4 and 5, access to treatment was discontinuous, which may explain the fluctuations in sBA levels observed.

Figure 1. Change in sBA levels over time.

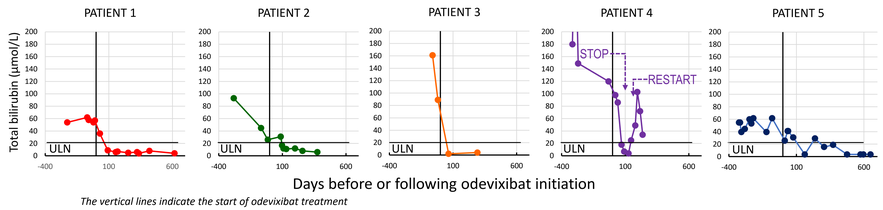


The vertical lines indicate the start of odevixibat treatment

Bilirubin

- Following initiation of odevixibat treatment, total bilirubin levels descended into the normal range within three months in all patients (Figure 2).
- Patient 4 experienced a delayed and transitory increase in bilirubin to pre-treatment levels following interruption of treatment.
- The other children all maintained normal bilirubin levels throughout the follow-up period.

Figure 2. Change in serum bilirubin levels over time.

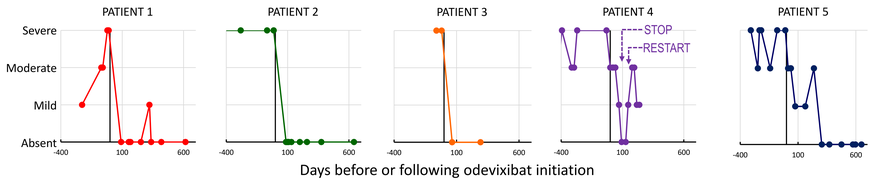


The vertical lines indicate the start of odevixibat treatment

Pruritus and sleep

- In four children, pruritus had resolved at the first follow-up visit following treatment initiation (1 to 3 months).
- In general, symptoms remained controlled throughout the on-treatment follow-up period (Figure 3).
- In Patient 5, mild pruritus persisted under odevixibat 37.5 µg/kg/day but resolved completely after a dose increase to 65 µg/kg/day.
- In Patient 4, moderate pruritus returned when odevixibat treatment was interrupted due to gastroenteritis.
- Sleep disturbances improved in parallel with the resolution of pruritus in all children.
- Patient 2 has been withdrawn from the waiting list for liver transplantation due to symptomatic remission and her stable clinical state over two years of follow-up.

Figure 3. Change in pruritus score over time.



Safety

- Digestive tolerability of odevixibat was good.
- Two patients reported an episode of infectious diarrhoea (adenovirus in Patient 1 and enteropathogenic *E. coli* in Patient 4) not deemed to be related to odevixibat treatment.
- In Patient 4, the episode was followed by transient paralytic ileus.
- Diarrhoea did not recur following resumption of odevixibat treatment in either patient.
- No new or worsening gastrointestinal symptoms were observed in the other children.
- No adverse events were documented that were considered potentially related to odevixibat.

CONCLUSIONS

- Treatment with odevixibat led to rapid normalisation of sBA and bilirubin within 1 – 3 months in 4/5 patients.
- Once sBA had normalised, the response was maintained throughout odevixibat treatment.
- Pruritus and sleep improved as soon as four weeks after starting treatment.
- The absence of tolerability or safety signals with odevixibat is reassuring with respect to the requirement for long-term treatment with odevixibat.
- Continuity of treatment and adherence is important to obtain a sustained response.
- The findings provide the first evidence for the efficacy and safety of odevixibat in PFIC associated with MYO5B mutations.

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