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Reply to: "Managing PFIC 7 with odevixibat: Alleviation of pruritus and biochemical response"

Odevixibat in progressive familial intrahepatic cholestasis subtypes: Insights from emerging real-world evidence

To the Editor:

I read with great interest the recent letter by Ala and colleagues describing the first genetically confirmed case of progressive familial intrahepatic cholestasis (PFIC) type 7 (USP53 deficiency) successfully treated with an ileal bile acid transporter (IBAT) inhibitor (odevixibat), which resulted in rapid resolution of pruritus and sustained biochemical response.[1] This report confirms the efficacy of IBAT inhibitors for the treatment of patients with rare PFIC subtypes, and it raises key questions on how to extend the evidence generated in pivotal trials to the broader PFIC spectrum encountered in daily practice.

The clinical development of odevixibat was primarily supported by two trials: PEDFIC 1 (randomized controlled trial [RCT]: NCT03566238) and PEDFIC 2 (open-label, single-arm trial: NCT03659916).[2,3] Both trials demonstrated the efficacy and safety of this IBAT inhibitor in children with PFIC. However, the study populations were restricted almost exclusively to patients with PFIC-1 and PFIC-2.[2,3] As a result, a gap emerged between the trial evidence (limited to PFIC-1 and PFIC-2) and clinical practice, where the increasingly widespread use of genetic testing is identifying additional PFIC subtypes for which no robust evidence is available.[4]

In this context, real-world data play a critical role in bridging the knowledge gap. Recently, a multicenter prospective study evaluated the efficacy of odevixibat in 24 children with PFIC, including both classic (types 1, 2, and 3) and rarer subtypes. In this cohort, eight patients had PFIC-4 (tight junction protein 2 [TJP2] deficiency, n = 5), PFIC-5 (farnesoid X receptor [FXR] deficiency, n = 1), PFIC-6 (myosin 5 B [MYO5B] deficiency, n = 1), and PFIC-9 (zinc finger protein 9 deficiency [ZFYVE19] deficiency, n = 1). All eight responded well to treatment, with reductions in serum bile acid (sBA) levels and improvement of pruritus without severe adverse events[5] (Table).

Further support comes from the retrospective case series by Roquelaure *et al.*, who reported five children with PFIC-6 (MYO5B deficiency) treated with odevixibat. In four patients, sBA normalized within 6 months, accompanied by resolution of pruritus and improvement in sleep quality. The only exception was a child with poor adherence and concomitant gastrointestinal complications, in whom treatment interruption blunted the therapeutic effect. Tolerability was overall good, with just one hospitalization for diarrhea[6] (Table 1).

Real-world data are relevant for several reasons. First, these studies demonstrate that efficacy and safety of odevixibat extend beyond the classic PFIC-1 and PFIC-2 forms, encompassing a broader spectrum of genetic subtypes.[1,5–8] Therefore, early recognition and treatment of these rare conditions with IBAT inhibitors should be encouraged, even in the absence of strong evidence from large randomized trials.

Second, real-world data may help support the expansion of the therapeutic indication for IBAT inhibitors. At present, in some countries, access to odevixibat remains limited to the classic forms (PFIC-1 and PFIC-2), thereby excluding patients with rarer subtypes, for whom treatment is either unavailable or considered off-label.[9,10] In this context, real-world evidence is essential to bridge the current knowledge gap and to support broader access to the drug by extending its availability beyond the classic forms to include rarer subtypes. Nevertheless, additional studies are needed to expand the cohort of treated patients and to validate these initial findings.

An important question that remains unanswered is why these rare PFIC subtypes show such a favorable response to IBAT inhibitors, as the pathogenetic mechanisms underlying this sensitivity are still poorly understood. It can be postulated that, despite impaired bile acid secretion and transport, a significant proportion of bile acids may still reach the terminal ileum, where the drug can effectively block their reabsorption, thereby enhancing fecal excretion and resulting in a marked reduction in sBA levels. This hypothesis, however, requires confirmation through further studies.

In conclusion, real-world experience provides valuable insights beyond pivotal trials, demonstrating efficacy and safety in genetic subtypes not represented in controlled studies. These findings should encourage clinicians to consider odevixibat as a valuable therapeutic option in rarer PFIC subtypes. While confirmation in larger cohorts is still required, the accumulating real-world data are highly encouraging and may represent a turning point in the management of these rare diseases.

Table 1. Real-world studies of children with rare subtypes of PFIC treated with odevixibat.

Real-world studies	Patients	Subtypes of PFIC (age at treatment)	Response to treatment at 6 months		Symptoms related to treatment
			Reduction in sBA levels	Improvements of pruritus scale	
AS. Ala *et al.*[1]	1	PFIC-7 (21 months)	Yes*	Yes	None
B. Roquelaure *et al.*[6]	5	PFIC-6 (between 15 months and 10 years)	Yes** (in 4/5 pts, 80%)	Yes (in 4/5, 80%)	Diarrhea in 2 patients
Di Giorgio *et al.*[5]	8	n = 5 PFIC-4 n = 1 PFIC-5 n = 1 PFIC-6 n = 1 PFIC-9 (between 1.4 years and 11.2 years)	Yes*** (in 8/8 pts, 100%)	Yes (in 8/8 pts, 100%)	Temporary diarrhea in 2 patients

sBA, serum bile acid.
*Response to treatment defined as "sBA within the range of 10–20 μmol/L".
**Response to treatment defined as "sBA close to or within the normal range, <10 μmol/L); late response to treatment was recorded in one patient due to low adherence to treatment.
***Response to treatment defined as "patients who achieved a reduction in sBA levels >70% from baseline, or a value <70 μmol/L".

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Supplementary data

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