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Ileal bile acid transport inhibitors - A new future in treatment of cholestatic diseases

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Keywords: Progressive familial intrahepatic cholestasis type 1 (PFIC1). ATP8B1 deficiency. ileal bile acid transporter inhibitor (IBAT). Liver transplantation.

Dear Editor,

Odevixibat, a selective inhibitor of ileal bile acid transporter is the first drug approved for symptomatic treatment of progressive familial intrahepatic cholestasis (PFIC) in patients over three months.

We present a 14-year-old male with PFIC1 who required double liver transplant at five years old. Subsequently, liver function normalized, nevertheless, bowel habits and intestinal malabsorption worsened (10–12 daily and nocturnal stools, Bristol 6–7), with severe dehydration that required multiple hospitalizations, associating malnutrition and failure to thrive that required daily home parenteral nutrition(PN). At 14 years old, Odevixibat (40 mcg/kg/day) was initiated, leading to a marked improvement in bowel habits by the second day (1–2 daily stools, Bristol 2) and progressive weight gain, which allowed after 40 days of treatment discontinue PN following seven years.

According to safety guidelines monitoring liver and bile profiles were conducted. After two months, transaminase levels increased (AST 532 U/L, ALT 776 U/L) (Table 1), with minimal improvement after dose reduction to half. IBAT was temporary discontinued, with the consequent liver profile normalization, leading to clinical deterioration, recurrence of diarrhea, and reinstatement of daily PN.

Odevixibat was restarted at progressively increasing doses, from 5 mg/kg/day to 12 mg/kg/day, currently well tolerated. After one year of treatment, cholestasis and liver parameters remain stable at the upper normal limit, with significant clinical improvement in bowel habits and overall quality of life for the patient and family, without the need for parenteral nutrition.

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In PFIC1, due to ATP8B1 expression in multiple organs, extrahepatic symptoms may worsen after liver transplantation, with chronic diarrhea as consequence of bile acid synthesis dysregulation and enterohepatic circulation[1,2]. IBATs are an innovative non-surgical alternative for interruption of enterohepatic bile acid circulation that have demonstrated improve severe post-transplant diarrhea[1]. Odevixibat has been a turning point in disease management, given the clinical improvement and enhanced quality of life for both the patient and their family. However, hepatotoxicity is a frequent adverse effect[3]. Given the early favourable response, temporary drug suspension was considered, followed by reintroduction after liver profile normalization, with dose escalation to the minimal effective dose, without adverse effects.

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Table 1. Evolution of clinical and laboratory values before and during treatment.

Laboratory values	**Prior IBAT**	**1 month IBAT**	**2 months IBAT**	**3 months IBAT**	**4 months IBAT**	**5 months IBAT**	**6 months IBAT**	**9 months IBAT**	**12 months IBAT**
ALT (U/L)	172	109	392	565	173	776	111	94	82
AST (U/L)	77	49	372	438	90	532	52	45	46
GGT (U/L)	154	102	296	350	114	259	36	42	33
Total bilirubin (mmol/L)				1,16		2,09	1,41	1,69	1,32
Direct bilirrubin (mmol/L)						0,57		0,41	
Bile acids (mmol/L)	53,36	26	231,69	30,53	-	123,67	26,87	147,93	11,87
INR	1,26	1,23	1,18	1,46	1,26	1,31	1,37	1,29	1,22
Daily stools (nº)	8-10	2-3	2-3	2-3	2-3	6-8	2-3	2-3	2-3
Bristol	6-7	3-4	3-4	3-4	3-4	6-7	3-4	3-4	4-5
Weight (kg – SD)	44,9 (-1,23)			46.2 (-0,91)				50,5 (-1)	49 (-1,24)
Waterlow weight index (%)	68,81			79,29				77,39	71,49
Waterlow height index (%)	103,25			105,64				101,37	101,99
Odevixibat dosaje (mg/kg/day)	-	40	20	20	20	STOP	5	10	12

ALT: alanine

aminotransferase. AST: aspartate aminotransferase. GGT: Gamma-Glutamyl Transferase. IBAT: ileal bile acid transporter inhibitor. INR: international normalized ratio. Kg: kilograms. L: liter. Mg: milligrams. Mmol: millimole. Nº: number. SD: standard deviation. U: units.