JHEP Reports

Odevixibat treatment in an adult patient with advanced icteric progressive cholestatic liver disease

To the Editor:

Ileal bile acid transporter (IBAT) inhibitors, such as odevixibat, are promising new therapeutic options for the treatment of pruritus and the reduction of elevated serum bile acid levels, a potential driver of liver injury progression in patients with cholestatic liver disease.[1] Evidence is accumulating for the efficacy and safety of odevixibat in pediatric patients and in patients with compensated liver disease,[2–8] but data are limited for adults in an advanced icteric state. Herein, we present a case of stabilized liver function and reduction of severe pruritus during a 30-week treatment course with odevixibat followed by rapid deterioration requiring liver transplantation after cessation of treatment in an adult patient with advanced icteric cholestatic liver disease.

A 35-year-old patient presented to our outpatient clinic with cirrhosis stage Child-Pugh B7 after a 10-year history of progressive cholestatic liver disease of unknown origin characterized by rarefied intrahepatic bile ducts, strongly elevated serum bile acid levels and severe pruritus. Diabetes mellitus type 1 with good glycemic control with continuous subcutaneous insulin infusion and a bicuspid aortic valve were pre-existing clinical conditions. Previous diagnostics included comprehensive but negative autoimmune and viral serology (Table S1), liver histology showing alterations of intrahepatic bile duct walls and ductal proliferation indicating cholangiopathy but without typical histological features of primary biliary cholangitis, primary sclerosing cholangitis, or IgG4-related disease, and cholangiography demonstrating multiple strictures with highly rarefied intrahepatic bile ducts (Fig. 1A). Colonoscopy with step biopsies revealed no evidence of inflammatory bowel disease. The patient had no family history of liver disease. Laboratory parameters upon presentation are presented in Table S1. The patient was under long-term treatment with ursodeoxycholic acid (1,000 mg/day) and bezafibrate (400 mg/day), and had undergone multiple endoscopic retrograde cholangiographies with balloon dilations, but with progressive disease despite all therapeutic efforts. Antipurinergic treatment with cholestyramine (16 g/day) and rifampicin (300 mg/day) had no relevant clinical effect. The patient was listed for liver transplantation with a current model of end-stage liver disease (MELD) score of 20 points.

Upon presentation in our outpatient clinic, the patient was included in the national HiChol registry for the systematic evaluation of patients with cholestatic liver disease, and a comprehensive genetic work-up was initiated, as recommended in cases of unclear cholestasis.[9] However, whole-exome sequencing revealed only a heterozygous c.17_18del variant in *NOTCH2*, which is a common polymorphism with unknown pathogenetic relevance. As severe pruritus and strongly elevated serum bile acid levels were the leading features in our patient and are hallmarks of progressive familial intrahepatic cholestasis (PFIC), we decided for an add-on therapy with odevixibat. Treatment was initiated at a dose of 2,400 μg odevixibat per day (∼30 μg/kg bodyweight/day) for 16 weeks with a subsequent dose increase to 7,200 μg/day (∼100 μg/kg bodyweight/day) for another 14 weeks in addition to ursodeoxycholic acid, bezafibrate and rifampicin. Serum bile acid levels decreased by a maximum of 57% compared to baseline within the first 8 weeks of treatment but rose back to baseline levels in the further course, despite increasing the dose of odevixibat (Fig. 1B). Pruritus slightly worsened in the first 8 weeks after treatment initiation, but improved strongly in the further course, from 6 out of 10 on a visual analogue scale at baseline to a minimum of 1/10 after 16 weeks of therapy, with strong improvement of previously disturbed night sleep. Serum bilirubin levels and cholestasis parameters remained fluctuating at similar serum levels compared to the pre-treatment situation, without improvement under therapy (Fig. 1B and Table S1). Parameters of liver synthesis and MELD score remained stable. The patient reported diarrhea and abdominal discomfort for 3 days after the start of therapy, and after increasing the dose of odevixibat. Notably, daily insulin demand increased during the treatment period from 70 to 150 units per day, without change of appetite, food intake, glycated hemoglobin levels, or body weight, and reached pre-treatment levels after cessation of odevixibat therapy.

Treatment with odevixibat was stopped after 30 weeks, as liver function did not show improvement under therapy. However, after cessation of therapy, serum bile acid levels and pruritus strongly increased, and liver function rapidly worsened (Fig. 1B). MELD score increased from 19 to 27 points within 11 weeks after end of treatment, and a deceased donor liver transplantation was successfully performed in week 11 after the end of odevixibat treatment.

In conclusion, odevixibat treatment significantly alleviated severe pruritus in an adult patient with advanced, icteric cholestatic liver disease and cirrhosis, despite fluctuating serum bile acid levels. The concurrence in time of treatment cessation and worsening of the patient's condition might indicate a stabilizing effect of odevixibat on liver function in this case. The unexpected increase of the daily insulin demand might have resulted from decreased bile acid-induced intestinal production of glucagon-like peptide-1, with decreased stimulation of residual endogenous insulin secretion.[10] This case suggests the potential of odevixibat not necessarily to improve but rather to maintain liver function in adult patients with advanced cirrhosis, with the crucial benefit of pruritus relief.

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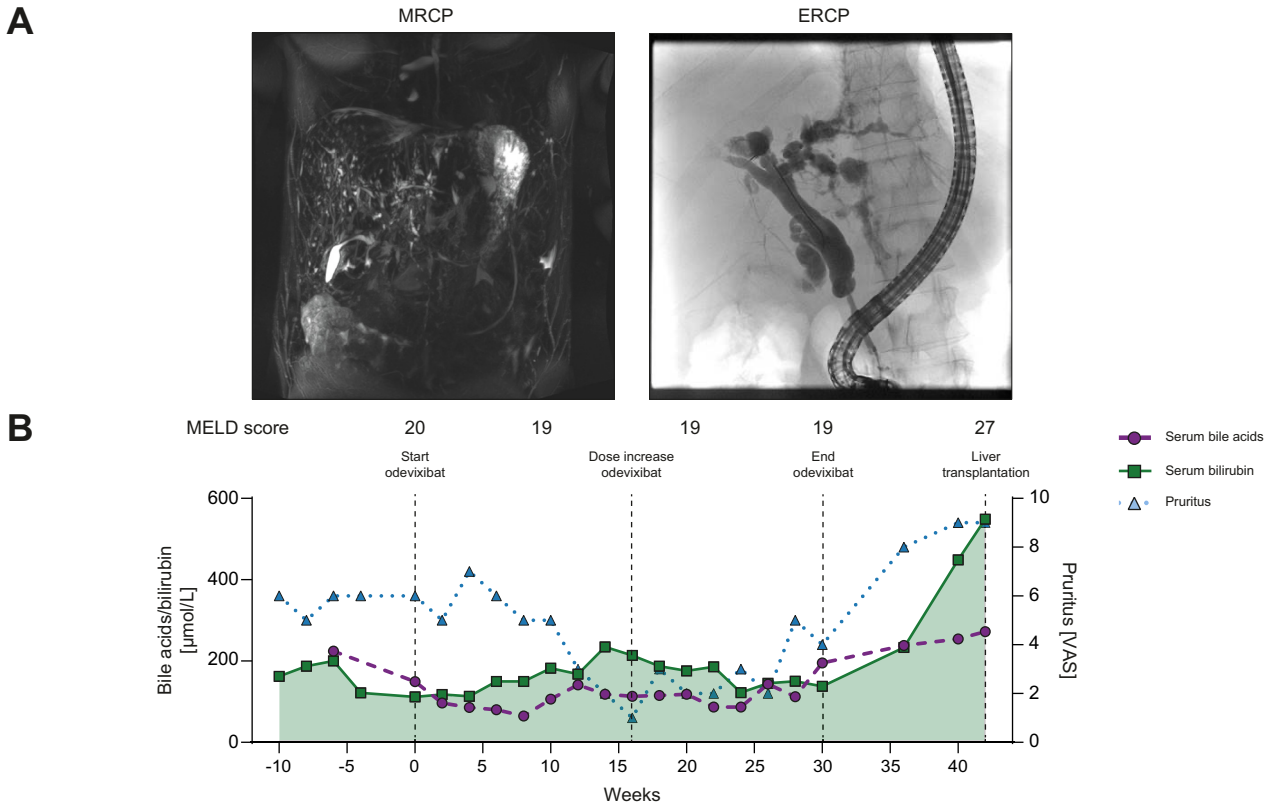

Fig. 1. Cholangiography and course of pruritus and laboratory parameters. (A) Cholangiography before start of treatment with odevixibat. (B) Course of serum bile acids (green line), serum bilirubin levels (red line), and pruritus (blue line) before, during, and after treatment with odevixibat. ERCP, endoscopic retrograde cholangiopancreatography; MELD, model of end-stage liver disease; MRCP, magnetic resonance cholangiopancreatography; VAS, visual analogue scale.

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Conflict of interest
VK has received speaker's honoraria from Albireo, Mirum and Falk Foundation. TH has received consultant honoraria and travel expense support from Albireo. All other authors declare no conflict of interest with regard to this work.

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

Authors' contributions
TH, AH and TB were involved in patient's care and sample collection. CD and VK performed genetic testing. TH prepared the figure. TH and TB wrote the manuscript. All authors revised and approved the final manuscript.

Data availability statement
Clinical data and further laboratory values are available from the corresponding author, upon reasonable request.

Informed consent
Written informed consent was obtained from the patient before submitting the manuscript.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2023.100978.

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