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# Long-term colestyramine treatment prevents cholestatic attacks in refractory benign recurrent intrahepatic cholestasis type 1 disease

Running head: Cholestyramine for long-term remission in BRIC 1

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## Introduction

Benign recurrent intrahepatic cholestasis (BRIC) is an autosomal recessive cholestatic disease characterized by intermittent cholestatic episodes of variable severity and duration. BRIC type 1 has been linked to gene mutations encoded in the hepatocanalicular transporter *ATP8B1.*[1] It has been suggested that ATP8B1 affects the regulation of the farnesoid X receptor, and thus ATP8B1 deficiency could lead to an imbalance between intestinal absorption of bile acids and hepatic secretion, causing bile acid accumulation.[2] The latter aggravates hepatocellular dysfunction leading to a vicious cycle.

The existing therapeutic strategies aim to relieve symptoms during the cholestatic episodes. Ursodeoxycholic acid (UDCA), rifampin, nasobiliary drainage and plasmapheresis have been used.[1] Limited experience is available for colestyramine, an anion-exchange resin that binds bile acids in the gastrointestinal tract, preventing their reabsorption.[3] We present a patient with severe BRIC, in whom colestyramine treatment successfully prevented the development of further cholestatic episodes.

## Case presentation

A 47-year-old German man presented to our department in February 2011 with a history of an uncommonly severe form of BRIC since the age of 17 with icteric attacks occurring nearly twice yearly and often lasting for several months, accompanied by excessive pruritus, fatigue and anorexia with significant weight loss, and followed by only short asymptomatic phases (Figure 1A). A liver biopsy performed in 1997 showed features of BRIC with no signs of liver fibrosis. Since 2000, the patient had been treated during the cholestatic attacks with Molecular Adsorbents Recirculating System albumin dialyses, and in 2007 he was evaluated for liver transplantation.

Upon presentation his blood tests, abdominal ultrasound, and liver stiffness were normal. Genetic testing identified the common mutation p.I661T in one allele of the *ATP8B1* gene. Notably, his sister had received a liver transplant in 2004 due to severe cholestatic liver disease.

In June 2011, we initiated a long-term treatment with colestyramine 4g daily divided into two doses along with UDCA 1g given separately. During follow-up, we noticed minor cholestatic flares with an

elevation of total bile acid (TBA) concentrations in serum accompanied by itching. Whenever pruritus appeared, or elevation of TBA was noted, the dose of colestyramine was increased up to 16g daily. Under this preemptive treatment, occasionally observed itching episodes in association with mildly increased TBA always turned to normal, followed by disappearance of pruritus, and bilirubin concentrations could be kept within the normal range throughout the whole observation period of up to nine years. The patient was taught to individually increase colestyramine dose at the time he noticed itch starting, and he experienced no more icteric flares thereafter (Figure 1A-B). No side effects were observed. In January 2014 he was signed off from the liver transplant list.

## Discussion

We present a patient with refractory BRIC type 1 successfully managed with colestyramine administered as long-term treatment along with dose adjustments to prevent cholestatic flares, as described above. Our therapeutic principle was based on the hypothesis that bile acid accumulation is the initiating event, which leads to dysfunction of the hepatobiliary transporters and, subsequently, bile acid retention. By administering colestyramine we intended to inhibit bile acid accumulation and interrupt this vicious cycle.

We cannot exclude the probability that the clinical remission is part of the natural course of the disease rather than the result of the therapy. However, the fact that the relief of pruritus and normalization of biochemical parameters were observed immediately after increasing colestyramine dose as well as the longstanding clinical remission make this scenario less likely.

Our case suggests that colestyramine might not only shorten icteric episodes in BRIC type 1 but also prevent their onset. This effect points to the critical role of bile acids in BRIC pathogenesis and implies a beneficial effect of colestyramine. Colestyramine was safe and well-tolerated and, thus, it may be considered as a long-term prophylactic treatment in BRIC patients with frequent and/or severe cholestatic attacks.

References:

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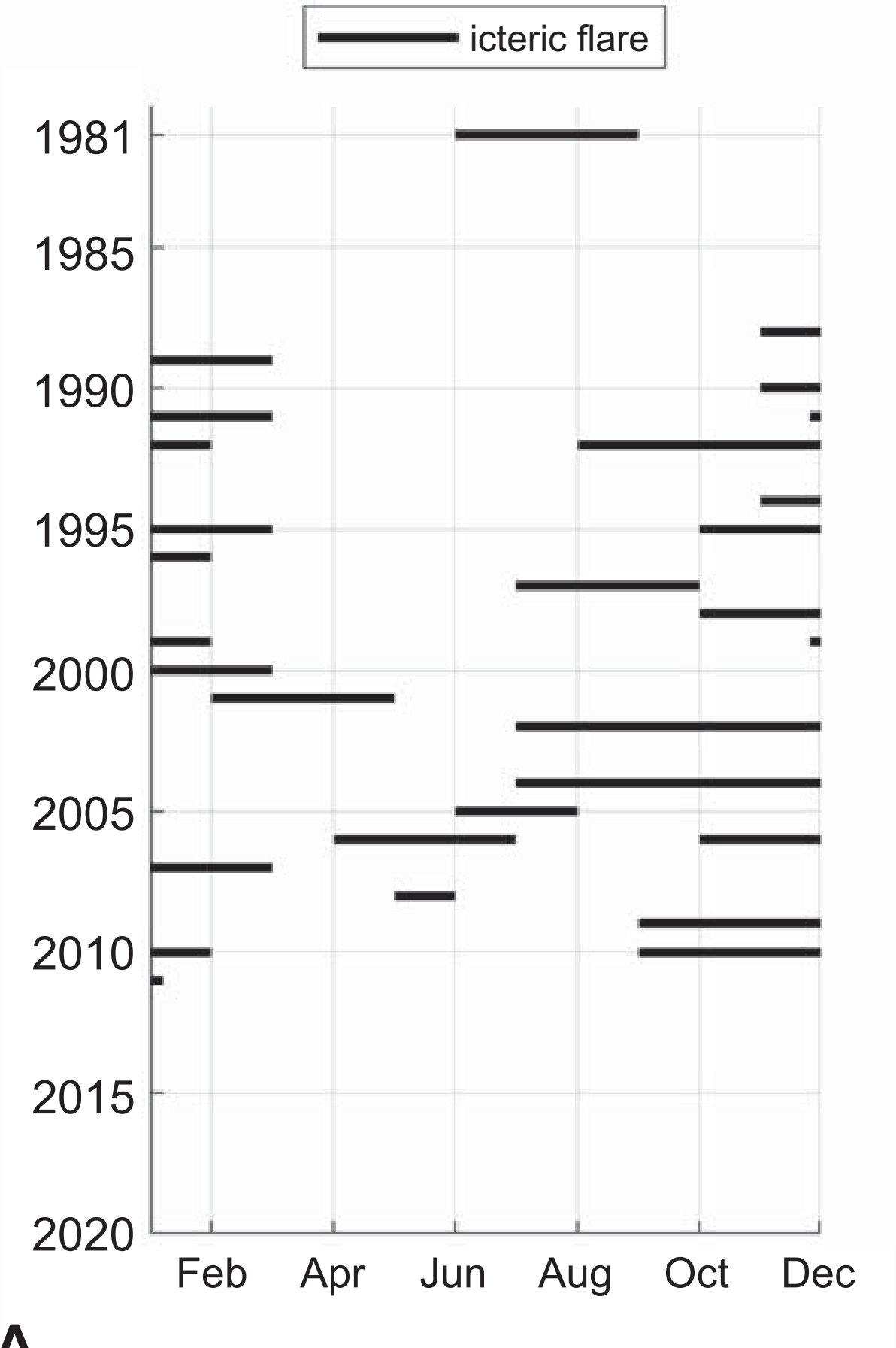
Figure legends

**Figure 1 A. Icteric flares of a patient with severe benign recurrent intrahepatic cholestasis type 1 disease since 1981.** Icteric episodes are marked as black lines. The patient had been suffering nearly twice yearly from severe prolonged episodes of jaundice, which were accompanied by excessive pruritus, fatigue and anorexia with significant weight loss, and were followed by only short asymptomatic periods. The cholestatic episodes required hospitalization. Since the initiation of the prophylactic treatment with colestyramine in June 2011, no icteric episodes have been observed. **B. Clinical course of the disease after initiation of treatment with colestyramine.** Shown are the curves of total bile acids (blue line) and total bilirubin (orange line) since the first presentation of the patient to our department. Dotted blue and orange lines indicate the upper limits of normal for total bile acids and total bilirubin, respectively. A colestyramine therapy with 16g daily was administered in March 2011, when elevated levels of total bile acids and pruritus were noticed (green arrow). The patient received also ursodeoxycholic acid (UDCA-white bar). The treatment was repeated in April, May and June 2011. We then decided to initiate a long-term treatment with colestyramine 4g daily (green bar). The dose of colestyramine was increased up to 16g daily, whenever elevation of total bile acids was noted (green arrows). Since 2014, the patient individually increased colestyramine dose at the time he noticed itch starting and regulated accordingly the duration (usually 3-5 days). The patient experienced yearly 2-3 itch episodes, which required increase of the dose, usually in the spring and fall. Under this therapy, no more icteric flares appeared and total bilirubin remained at very low levels.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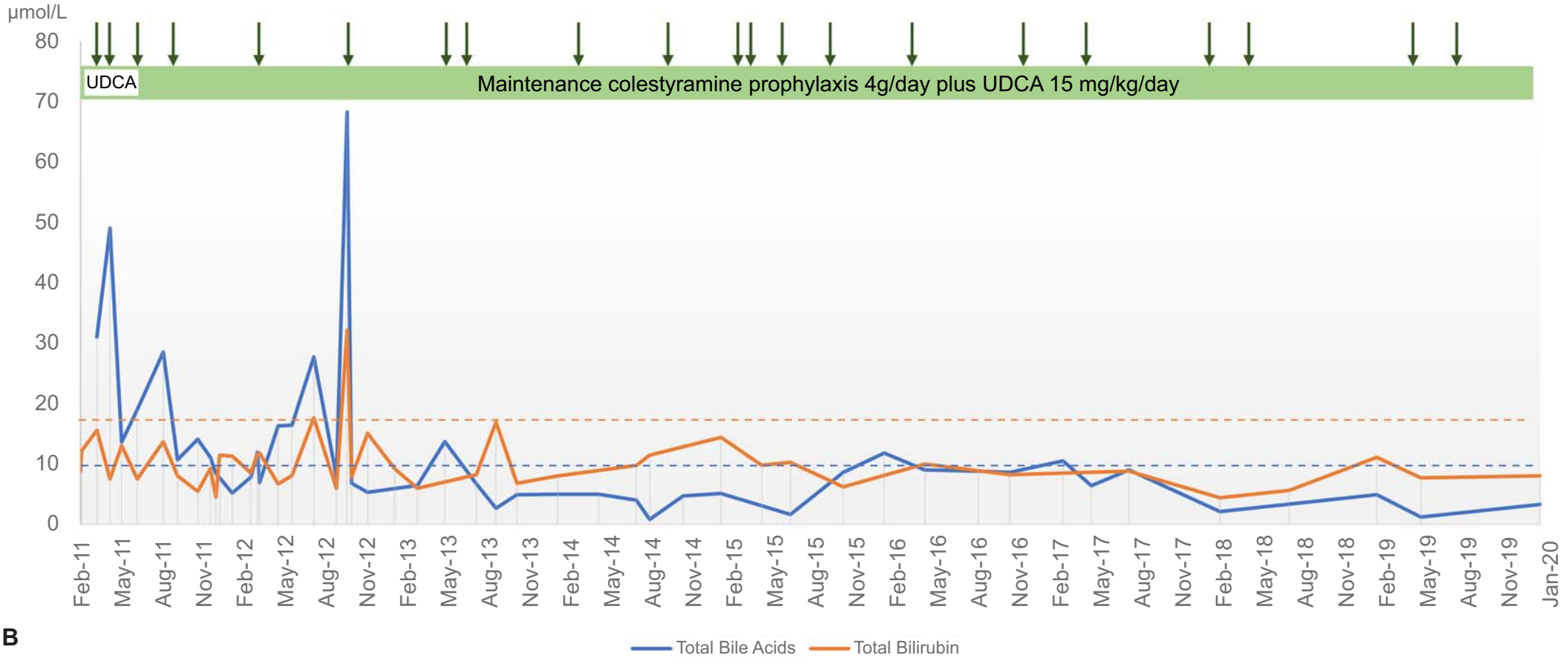
µmol/L
80
70
60
50
40
30
20
10
0
UDCA
Maintenance colestyramine prophylaxis 4g/day plus UDCA 15 mg/kg/day
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Aug-19
Nov-19
Jan-20
Total Bile Acids
Total Bilirubin

**B**