Management of Chronic Hepatic Itch

Miriam M. Düll, MD, Andreas E. Kremer, MD, PhD, MHBA*

KEYWORDS

• Autotaxin • Bile salt • Cholestasis • Liver • Lysophosphatidic acid • Management • Pruritus

KEY POINTS

- The palms and soles are predilection sites for itching specific to the immune-mediated disorders primary biliary cholangitis and primary sclerosing cholangitis; however, pruritus often generalizes.
- Autotaxin activity correlates with itch intensity in patients with hepatic pruritus.
- Cholestyramine is the only drug licensed to treat hepatic itch.
- Rifampicin at a dosage between 150 and 600 mg/d strongly attenuates hepatic itch.
- Bezafibrate at a dosage of 400 mg/d may represent a valuable alternative treatment option for hepatic itch.

INTRODUCTION

Various hepatobiliary disorders are frequently accompanied by chronic pruritus, particularly if cholestasis is an inherent feature of the underlying disease.[1] In these hepatic disorders, cholestasis can be caused by different mechanisms[2]:

- Hepatocellular cholestasis: impaired hepatocellular secretion
  For example, intrahepatic cholestasis of pregnancy (ICP), benign recurrent intrahepatic cholestasis, progressive familial intrahepatic cholestasis type, toxin-induced or drug-induced cholestasis, acute or chronic viral hepatitis
- Cholangiocellular cholestasis: intrahepatic bile duct damage
  For example, primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and secondary sclerosing cholangitis (SSC), or Alagille syndrome
- Obstructive cholestasis: obstruction of the intrahepatic or extrahepatic bile duct
  For example, gallstone disease, biliary atresia, enlarged lymph nodes, cholangiocellular adenoma or carcinoma, or pancreatic head carcinoma.

Pruritus is frequently observed in all these conditions and significantly reduces the quality of life of these patients and affects their sleep. In some patients, itching became so severe that liver transplantation was considered, even in absence of liver failure.[3] Several pruritogens, including bile salts, endogenous opioids, histamine, serotonin, progesterone metabolites, and lysophosphatidic acid (LPA),[4] have been hypothesized to be involved in the pathogenesis of hepatic itch; however, the definite mechanisms have not yet been revealed. Management involves a stepwise approach that tends to be insufficient in some patients. This review summarizes state-of-the-art treatment, demonstrates alternative regimens

Disclosure Statement: The authors have nothing to disclose.
This work was supported by a grant from the Deutsche Forschungsgemeinschaft (KR4391/1-1) and grants E20 and E27 of the IZKF in Erlangen to A.E. Kremer.
Department of Medicine 1, Friedrich-Alexander-University Erlangen-Nürnberg, Ulmenweg 18, Erlangen 91054, Germany
* Corresponding author.
E-mail address: andreas.kremer@uk-erlangen.de

Dermatol Clin ■ (2018) ■–■
https://doi.org/10.1016/j.det.2018.02.008

in patients who are difficult to treat, and summarizes current clinical trials that may represent future treatment options.

CLINICAL ASPECTS OF HEPATIC PRURITUS

Prevalence

Epidemiologic data on hepatic pruritus are scarce. Pruritus is commonly observed in hepatobiliary disorders with cholestatic features, albeit to different extents depending on the underlying condition. Approximately 70% of patients with PBC, PSC, or SSC report on pruritus at some point during their course of disease.[5,6] The prevalence of pruritus in PBC patients in an extensive online survey of 577 participants was as high as 56% (A.E. Kremer and colleagues, unpublished, 2018). In women with ICP, pruritus is even part of the definition criteria of the condition. Obstruction of intrahepatic or extrahepatic biliary tracts is less commonly associated with hepatic itch, with 45% of affected patients with malignant obstruction, such as carcinoma of the pancreatic head, and 16% of affected patients with benign biliary obstruction, such as choledocholithiasis.[7] Between 5% and 15% of untreated patients with chronic hepatitis C virus infections reported itching.[8] In contrast, hepatic itch is rarely observed in patients with chronic hepatitis B virus infections, alcoholic or nonalcoholic fatty liver disease, or alcoholic or nonalcoholic steatohepatitis (NASH), even in case of cholestasis.[9]

Clinical Picture

In immune-mediated hepatobiliary diseases such as PBC and PSC, hepatic pruritus often initially presents at the limbs, particularly at the palms and soles,[5] before itching spreads over other body parts. A circadian rhythm has been conclusively shown by displaying the scratch activity in patients with PBC using piezoelectric electrode attached to the fingernail.[10] The highest rating of itch intensity is commonly reported in the evening and early at night,[11] although this is an usual pattern in chronic pruritus that is often aggravated by warmth and limited sensory input during the night. Patients with hepatic itch do not present with primary lesions of the skin; however, enduring scratching may result in secondary skin alterations; for example, excoriations and prurigo nodularis. These phenomena might cause difficulties in distinguishing hepatic itch from a primary dermatologic condition. Pruritus can have a burdensome impact on the quality of life of patients with hepatic disorders, among other consequences, by inducing sleep deprivation and resulting in exhaustion, fatigue, and depression.[12] Finally, women suffering from hepatic itch show increased symptoms before menstruation, as well as during late pregnancy or hormone replacement therapy.

Pathogenesis of Hepatic Pruritus

Despite the extensive itch research in animals, the underlying pathogenetic mechanisms of chronic pruritus in humans remain largely elusive. This also holds true for the pathogenesis of chronic hepatic itch, although several potential mediators have been controversially discussed to be involved in cholestatic disorders, such as bile salts, histamine, serotonin, endogenous opioids, and progesterone metabolites. LPA, a small phospholipid, was recently identified as a novel candidate pruritogen in hepatobiliary disorders.[13]

Bile Salts

More than 2000 years ago the Greek physician Aretaeus the Cappadocian already suggested “prickly bilious particles” as cause for pruritus in jaundiced patients. Even today his theory still holds true, at least in part: removing bile from the human body; for example, by nasobiliary or transcutaneous drainage, is often very effective in attenuating severe and long-lasting hepatic itch.[14] Bile salts and certain subspecies, which are present in bile in high concentrations, have long been suggested as potential pruritogens. This bile salt hypothesis has recently experienced clinical support by the observation that the novel semisynthetic bile salt obeticholic acid induced or worsened pruritus in PBC and NASH subjects in clinical trials. GSK2330672, a novel inhibitor of the ileal bile acid transporter (IBAT), prevents the reuptake of bile salts in the ileum and strongly improves hepatic itch. Nevertheless, several observations argue against bile salts as direct pruritogens in cholestasis because no correlation was observed between the intensity of cholestatic pruritus and the levels of bile salts in serum, urine, or skin.[15,16] Women with ICP show only slightly increased total serum bile salt (TBS) levels yet suffer from pruritus. Obstructive cholestasis linked with increased TBS is much less commonly associated with pruritus and the anion exchange resin colesevelam diminished TBS levels by approximately 50% without being superior to placebo in ameliorating pruritus.[17] Thus, bile salts or certain subspecies might instead represent indirect pruritogens in hepatobiliary disorders.