Advances in Pathogenesis and Treatment of Pruritus

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KEYWORDS

• Cholestasis • Itch • Autotaxin • Lysophosphatidate • Pruriception • Bile salts

KEY POINTS

- The pathogenesis of itch in cholestatic hepatobiliary disorders remains unclear. Proposed pruritogenic factors include increased serum autotaxin activity and subsequent lysophosphatidate formation, hyperexcitability of sensory neurons, female steroid hormones, and altered enterohepatic pruritogen (biotrans)formation.
- Stepwise treatment of cholestatic pruritus with anion exchanger resins (cholestyramine), pregnane X receptor agonists (rifampicin), opioid antagonists (naltrexone, naloxone), and serotonin reuptake inhibitors (sertraline) is recommended in guidelines.
- In patients with severe pruritus, unresponsive to standard treatment, experimental approaches including UV-B phototherapy, extracorporeal albumin dialysis, and nasobiliary drainage need to be considered. Liver transplantation represents the last option in the most desperate cases.

INTRODUCTION

Pruritus is a common symptom in patients suffering from various hepatobiliary disorders. The common denominator, cholestasis, can have its origin at different levels of the biliary tree: (1) hepatocellular secretory failure (eg, in intrahepatic cholestasis of pregnancy (ICP), progressive familiar intrahepatic cholestasis, benign recurrent intrahepatic cholestasis, and various examples of drug-induced cholestasis); (2) intrahepatic bile duct abnormalities (eg, in primary biliary cirrhosis [PBC], primary sclerosing cholangitis [PSC], Alagille syndrome); as well as (3) extrahepatic, obstructive cholestasis caused by gallstones, benign strictures (eg, primary or secondary sclerosing cholangitis) or tumor growth (eg, cholangiocarcinoma, pancreatic carcinoma, or hilar lymph node metastasis). Itch is also reported in some patients with (4) chronic hepatitis C.[1,2]

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Generalized pruritus determines quality of life of patients to a great extent, leading to sleep deprivation, depression, and, anecdotally, suicidal ideation.[3] The pathogenesis of this intruding symptom has been under investigation for decades, but the molecular mechanism is still largely unclear. Concordantly, treatment options proposed in current evidence-based guidelines (**Table 1**) do not yet provide relief for all patients. Consequently, experimental therapeutic approaches are increasingly applied, broadening insight in the possible molecular targets involved in cholestatic itch. However, desperate cases of severe cholestatic pruritus, refractory to any treatment modalities mentioned earlier, represent an indication for liver transplantation often performed in the precirrhotic stage.[4]

STUDYING ITCH IN CHOLESTASIS

In the clinical setting, itch intensity is mostly evaluated in cholestatic patients by visual analogue scales (VAS) or comparable scores.[5,6] Two decades ago, devices to objectify scratching activity were proposed to evaluate itch intensity in an objective manner and were regarded as a golden diagnostic standard to prove efficacy of novel therapies.[7] However, limited availability and the considerable costs of these devices as well as the undervalued subjective component of the symptom itch have questioned these devices as a golden diagnostic standard in the community. Therefore, use of VAS together with validated quality-of-life questionnaires has become an accepted method to adequately evaluate novel therapeutic approaches. However, it remains essential to include adequate placebo controls in all therapeutic trials because placebo treatment alone has consistently improved pruritus in about 30% of tested patients in various trials.[5]

Cholestatic experimental animals barely develop itch. Thus, animal studies are being severely hampered by the ongoing search for a proper rodent model of cholestatic pruritus. Estradiol-induced cholestasis in rats may be an exception.[8] In general, animal itch studies describe acute models, in which intracutaneous injection of pruritogens

Table 1
Stepwise treatment of itch in cholestatic liver disease according to current guidelines.[16] Ursodeoxycholic acid (UDCA) is regarded as standard treatment of ICP and PBC,[16] but consistently alleviates pruritus only in ICP.[16] A comparable antipruritic effect of UDCA has not been reported in other cholestatic disorders

Step	Intervention	Remarks
1	Cholestyramine (up to 4 times 4 g daily)	Alternate with intake of other oral medication with time intervals of at least 4 h; monitor fat-soluble vitamins
2	Rifampicin (150 mg, increase up to 600 mg daily)	Monitor serum liver tests because of risk of hepatotoxicity
3	Naltrexone (25 mg, increase up to 50 mg daily)	Possible withdrawallike symptoms at initiation
4	Sertraline (50 mg, increase up to 75 mg daily)	
5	Experimental approaches (eg, UV-B therapy, extracorporeal albumin dialysis, nasobiliary drainage)	Refer to specialized center
6	Liver transplantation	

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