Understanding and Treating Pruritus in Primary Biliary Cholangitis

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KEYWORDS

• Cholestasis • Itch • Refractory • Intractable • Therapy

KEY POINTS

- Pruritus is reported by up to 80% of patients with primary biliary cholangitis (PBC) during long-term follow-up.
- Pathophysiological mechanisms of pruritus in PBC include the accumulation of pruritogenic bile acids and bile salts, modulation of itch pathways through autotaxin-lysophosphatidic acid, an imbalance between different types of receptors for endogenous opioids, and modulation of the perception of pruritus by serotonin and substance P.
- Bile acid–binding resins such as cholestyramine are first-line therapy. Rifampin has a large body of evidence supporting its efficacy as a second-line agent but it must be used cautiously due to risk of hepatotoxicity and multiple drug–drug interactions.
- Opioid antagonists and sertraline are useful alternatives.
- Invasive therapeutic strategies for patients with debilitating pruritus include plasmapheresis, nasobiliary drainage, and filtration using the molecular adsorbent recirculating system where available.

Primary biliary cholangitis (PBC) is the most common chronic cholestatic liver disease in adults in the United States and is characterized by inflammation targeting cholangiocytes of the interlobular and septal bile ducts.[1] Although most patients currently diagnosed with PBC are asymptomatic (60%), fatigue and pruritus are the most common symptoms reported over long-term follow-up. For instance, pruritus is only present in 19% of patients at the time of initial diagnosis of PBC but is reported by up to 80% of those followed up for 10 years after establishing the diagnosis.[2] The reported

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risk of developing pruritus in patients with untreated PBC without this symptom is 27% per year; however, the natural history of pruritus in PBC is highly variable and improvement or resolution may also occur in up to 23% of patients per year.[3]

Pruritus in PBC is characteristically generalized and intermittent; however, in some patients it may be persistent and occasionally even debilitating. It is usually more severe in the limbs, particularly in soles of feet and palms of hands; it is exacerbated by heat, pressure, or contact to wool. Similar to fatigue, the severity of pruritus does not correlate with histologic progression of PBC and may actually improve during advanced stages in certain patients. Circadian variation of the severity of pruritus is frequently reported, with worsening of this symptom in the late evenings and at night.[4]

PATHOPHYSIOLOGY OF PRURITUS IN PRIMARY BILIARY CHOLANGITIS

A brief review of the pathophysiology of pruritus in PBC is necessary to better understand currently available and investigational therapeutic options (**Table 1**). Transduction of an itch into neural signals begins with activation of a peripheral receptor. There are 2 major classes of peripheral itch receptors: transient receptor potential (TRP) and G protein-coupled receptors. Itch receptors can be found on unmyelinated peripheral neurons known as C-fibers, which can be subdivided into mechanoinsensitive histamine-responsive and mechanosensitive histamine-unresponsive subtypes. The ascending pruritic neural pathway can be summarized as follows: sensory itch signals

Table 1
Mechanisms of action of various therapeutic interventions for pruritus in pruritus in primary biliary cholangitis

Mechanism of Action	Agents	Comments
Interference with enterohepatic circulation of bile acids	Cholestyramine	First-line therapy
	Colesevelam	Not recommended for patients who previously failed cholestyramine
	Colestipol	No data on PBC
	Maralixibat	Investigational
	GSK2330672	Investigational
	Nasobiliary drainage	Invasive
PXR agonist, decreases LPA and autotaxin levels	Rifampin	Important drug–drug interactions
Endogenous opioid antagonists	Naltrexone	Possible opioid withdrawal symptoms
	Naloxone	Intravenous
	Nalfurafine hydrochloride	Available in Japan
Modulation of serotonin	Sertraline	Short-lasting effect
	Ondansetron	Short-lasting effect
Activation of PPAR-α	Bezafibrate	May also lead to normalization of alkaline phosphatase, although independently of its effect on pruritus
	Fenofibrate	
Substance P or NK-1 modulation	Aprepitant	Not enough data on PBC
Modulation of nonspecific nociceptive pathways	Dronabinol	Only 1 small case series reported efficacy

Abbreviations: LPA, lysophosphatidic acid; NK-1, neurokinin-1; PPAR, peroxisome proliferator-activated receptor; PXR, pregnane X receptor.