When ‘Well-Controlled’ PBC Doesn’t Mean Itch-Free:

Rethinking Pruritus in Clinical Practice

Allysa Saggese, NP



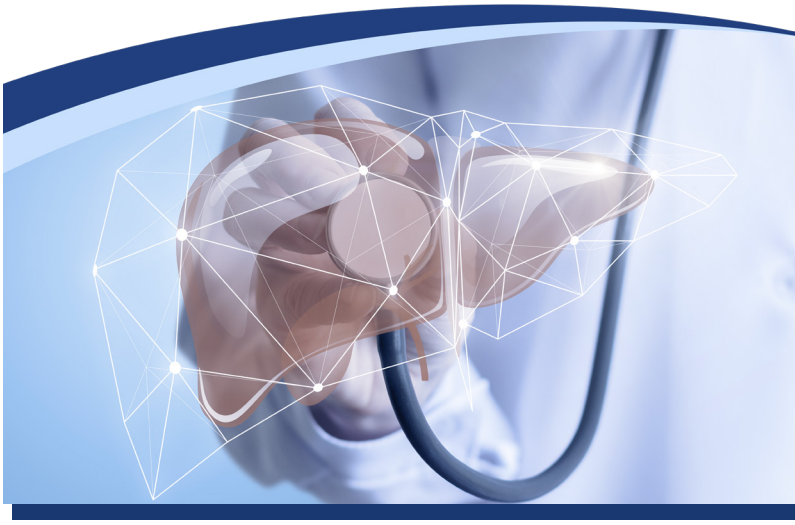
Primary biliary cholangitis (PBC) is traditionally taught as a biliary disease diagnosed by an abnormal alkaline phosphatase (ALP) level, a positive antimitochondrial antibody (AMA) test, with or without a positive liver biopsy, and usually has accompanying symptoms of pruritus (itch) and fatigue. Patients are started on ursodeoxycholic acid (UDCA) (also known as ursodiol) and in as early as 6 months, an ALP, or biochemical, response may be seen after administration of this first-line treatment. With reassuring labs, there may be no further changes to the treatment plan. What is often left unassessed is whether patients' symptoms improve as their ALP levels normalize—specifically, whether pruritus improved. In many cases, it has not.

UDCA, the first-line treatment for PBC, is a synthetic bile acid that reduces naturally produced bile acids, increases the production and uptake of hydrophilic bile acids, and reduces the autoimmune action of PBC. Thus, providers see a response as ALP levels decrease. However, for all the good it can do, it does not treat pruritus.[1] Patients can experience pruritus at any ALP level, fibrosis stage, or point in the course of PBC, despite a reduction or normalization of ALP with first- or second-line medications. Studies show that up to 89% of patients report pruritus, with about 34% experiencing it frequently or all the time.[1,2,3]

Pruritus has typically been difficult to both manage and monitor. There are no validated blood tests that correlate reliably with itch severity. Several potential biomarkers and pathways have been studied, including IL-31, serum bile acids, and the autotaxin (ATX)/lysophosphatidic acid (LPA) pathway. IL-31 is understood to be a known pruritogen through atopic dermatitis studies, and has a possible connection to pruritus in liver disease.[4] Bile and bile acids are often elevated in cholestatic diseases and are thought to activate G protein-coupled receptors on sensory neurons.[1] The ATX/LPA pathway may contribute to pruritus through increased levels of ATX, an enzyme involved in producing LPA, and LPA itself, a lipid-signaling molecule that activates itch-sensing neurons.[1] Even with these candidate biomarkers and pathways identified, there is still no single reliable blood test that accurately reflects pruritus in patients with cholestatic disease; therefore, pruritus assessments rely on patient reports or questionnaires.

Understanding the potential pathways of pruritus can help explain why ALP levels do not reliably correlate with itch severity in patients with PBC. ALP monitoring alone may consequently fail to capture the substantial quality-of-life burden associated with pruritus. Routine symptom assessment should therefore be part of regular clinical care. Current liver society guidelines recommend a stepwise approach to treating pruritus; however, the therapies traditionally listed in these guidelines were not specifically approved for PBC-associated pruritus.[5] Currently, not only are several treatments that target these biomarkers and pathways being evaluated in clinical trials, but the United States has also approved the first and only medication for pruritus in PBC: linerixibat.

Linerixibat is the first medication indicated for the treatment of cholestatic pruritus associated with PBC in adult patients. As an ileal bile acid transporter (IBAT) inhibitor, it works by reducing intestinal bile acid reabsorption and increasing bile acid excretion in the feces.[6] Currently, there are two other IBAT inhibitors on the market; however, both are indicated for rare pediatric liver diseases and are not indicated for pruritus in PBC. Linerixibat was approved following the GLISTEN trial, conducted from December 2021 to May 2024, a randomized, multicenter, double-blind, placebo-controlled Phase 3 trial in patients with PBC with moderate-to-severe pruritus.[6] The trial outcomes showed that participants taking linerixibat compared with those taking placebo had a significant overall improvement in their pruritus over 24 weeks of treatment, with some patients experiencing significant improvement as early as week 2.[6] Notably, about half of the participants had an ALP of < 1.67 × ULN, a level that is currently considered serologically "controlled" PBC, meaning that these participants had moderate-to-severe pruritus despite low or normal ALP levels. There is a clear distinction between ALP levels and symptoms in patients with PBC, highlighting the need for treatments, like linerixibat, that specifically address pruritus in this population.



In treating patients with PBC, providers are urged to recognize that the full scope of the disease includes not only laboratory results but also symptoms. Patients with a biochemical response to first and/or second-line medications may still experience moderate-to-severe pruritus, regardless of their ALP level, fibrosis stage, or disease duration. With the FDA approval of linerixibat, patients now have access to the first FDA-approved medication specifically indicated for PBC-associated pruritus. The approval of linerixibat highlights the growing recognition of the burden of PBC symptoms, the need for targeted treatments, and the importance of assessing symptoms alongside biochemical markers when evaluating disease control in PBC.

Sources

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