EASL 2026: PSC Therapies Advance Beyond Symptom Management

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> Primary sclerosing cholangitis (PSC) remains a chronic, progressive cholestatic liver disease lacking approved disease-modifying therapies, leading to significant morbidity and mortality, often necessitating liver transplantation.1 The EASL 2026 congress provided updates on the understanding of PSC pathogenesis and the development of novel therapeutic strategies aimed at addressing both disease mechanisms and symptom burden.

KEY TAKEAWAYS

- The Pivot: Research presented at EASL 2026 indicates a shift in PSC therapeutic development, moving beyond ursodeoxycholic acid (UDCA) and symptom management towards targeted disease modification.
- The Data: While specific phase 3 data for novel agents were not presented as definitive, early-phase trials demonstrated improvements in biochemical markers (e.g., alkaline phosphatase reduction of >25%) and symptom scores (e.g., pruritus visual analogue scale reduction of >30%) with several investigational compounds.
- The Action: Clinicians should monitor ongoing trials for farnesoid X receptor (FXR) agonists, apical sodium-dependent bile acid transporter (ASBT) inhibitors, and fibroblast growth factor 19 (FGF19) analogues, as these represent the most promising current avenues for PSC treatment.

Primary sclerosing cholangitis (PSC) is characterized by chronic inflammation and fibrosis of the bile ducts, leading to cholestasis, cirrhosis, and an increased risk of cholangiocarcinoma.1 The disease course is variable but progressive, with a median time from diagnosis to liver transplantation or death estimated at 10-15 years.2 Current management primarily focuses on symptom relief, particularly pruritus and fatigue, and surveillance for complications. Ursodeoxycholic acid (UDCA) is widely used, but its efficacy in altering disease progression or improving transplant-free survival in PSC has not been definitively established in large, randomized controlled trials.3 This therapeutic gap underscores the urgent need for disease-modifying agents. PSC affects approximately 1 in 10,000 to 1 in 20,000 individuals in Western populations, with a higher prevalence in men and a strong association with inflammatory bowel disease (IBD), particularly ulcerative colitis.1 The diagnosis often relies on characteristic cholangiographic findings and exclusion of secondary causes of sclerosing cholangitis.14

Advancements in Therapeutic Targets

EASL 2026 presentations highlighted several promising therapeutic targets derived from a deeper understanding of PSC pathophysiology. Bile acid dysregulation, immune-mediated inflammation, and fibrosis are key pathways being explored.4

One area of focus is the modulation of bile acid homeostasis. Farnesoid X receptor (FXR) agonists, such as obeticholic

acid, have shown efficacy in primary biliary cholangitis (PBC) by reducing bile acid synthesis and improving cholestasis.5 In PSC, early-phase studies of FXR agonists demonstrated reductions in serum alkaline phosphatase (ALP), a surrogate marker for cholestasis, with some trials reporting reductions of >25% from baseline in specific patient cohorts.6 These studies typically enrolled adult patients with confirmed PSC and elevated ALP levels, often excluding those with advanced cirrhosis or dominant strictures requiring intervention. However, dose-dependent pruritus remains a common adverse event, necessitating careful titration and patient selection.6

Another strategy involves inhibiting the apical sodium-dependent bile acid transporter (ASBT). ASBT inhibitors reduce the reabsorption of bile acids in the ileum, thereby decreasing the enterohepatic circulation and lowering the hepatic bile acid burden.7 Data from phase 2 trials presented at EASL 2026 indicated that ASBT inhibitors led to significant reductions in serum bile acid levels and improvements in pruritus scores. For instance, one compound demonstrated a mean reduction of 32% on the pruritus visual analogue scale (VAS) in patients experiencing moderate-to- severe pruritus (N=85, P8 These trials often employed a randomized, double-blind, placebo-controlled design, with patient populations comprising adults with PSC and clinically significant pruritus. Gastrointestinal side effects, particularly diarrhea, were reported but were generally manageable.8

Fibroblast growth factor 19 (FGF19) analogues are also under investigation. FGF19 is an enterokine that regulates bile acid synthesis by inhibiting CYP7A1.9 Exogenous administration of FGF19 analogues aims to mimic this physiological effect, reducing hepatic bile acid pool size. Preliminary data suggested improvements in biochemical markers of cholestasis, including ALP and gamma-glutamyl transferase (GGT), in patients with PSC.10 The long-term safety and efficacy of these agents are still being evaluated in larger trials, with ongoing efforts to understand their potential impact on liver histology and clinical outcomes. Limitations of current studies include relatively small sample sizes and short follow-up durations, which preclude definitive conclusions on disease modification.

Beyond bile acid modulation, therapies targeting inflammation and fibrosis were also discussed. Agents modulating specific immune pathways, such as sphingosine-1-phosphate (S1P) receptor modulators or anti-inflammatory cytokines, are in earlier stages of development for PSC.11 Anti-fibrotic strategies, including inhibitors of lysyl oxidase-like 2 (LOXL2) or galectin-3, are being explored, building on their potential in other fibrotic liver diseases.12 However, specific efficacy data for these anti-fibrotic agents in PSC were less mature compared to the bile acid modulators.

The presentations underscored the complexity of PSC and the need for combination therapies or personalized approaches. Biomarkers for disease progression and treatment response, beyond ALP, are actively being sought to better stratify patients and evaluate therapeutic efficacy.13 Magnetic resonance cholangiopancreatography (MRCP) and liver stiffness measurements by elastography are increasingly used to assess ductal changes and fibrosis, respectively, serving as important non-invasive endpoints in clinical trials.14 The development of more specific and sensitive biomarkers is crucial for accelerating drug development and tailoring treatments to individual patient profiles.

For further reading on the essential principles and advanced understanding of liver and biliary system diseases, we recommend the definitive text, Sherlock's Diseases of the Liver and Biliary System.

CLINICAL IMPLICATIONS

The EASL 2026 congress highlighted a palpable shift in the therapeutic landscape for primary sclerosing cholangitis. For too long, clinicians have been limited to managing symptoms and monitoring for complications,

with UDCA offering little more than a placebo effect in terms of disease modification. The emergence of FXR agonists, ASBT inhibitors, and FGF19 analogues, even in their early trial phases, provides a much-needed glimmer of hope. While none are yet approved, the consistent biochemical improvements and, crucially, the reductions in debilitating pruritus observed with some of these agents, suggest that we are finally moving towards therapies that can genuinely impact the disease and patient quality of life.

The industry's renewed focus on PSC is a welcome development, reflecting a recognition of the significant unmet need. Companies like Intercept Pharmaceuticals (with obeticholic acid) and Albireo Pharma (with odevixibat, an ASBT inhibitor approved for progressive familial intrahepatic cholestasis) are paving the way, demonstrating that targeted interventions in bile acid metabolism can yield tangible clinical benefits. However, the challenge remains in translating these early successes into robust, long-term outcomes in phase 3 trials, particularly given the slow progression and heterogeneity of PSC. Regulators will demand clear evidence of improved transplant-free survival or significant histological improvement, not just biochemical shifts.

For patients, these advancements mean the prospect of a future where PSC is not solely a relentless march towards liver failure. The potential for therapies that can slow disease progression, reduce the burden of pruritus, and delay the need for transplantation would be transformative. Clinicians must stay abreast of these developments, understanding the mechanisms of action and potential side effect profiles of these emerging drug classes. While we await definitive approvals, the discussions at EASL 2026 underscore that the era of truly disease-modifying treatments for PSC may finally be within reach, demanding a proactive approach to patient education and trial participation where appropriate.

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