

Cholestatic Pruritus: Current Management Approach and Emerging Therapies – Mini Review

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Abstract

Cholestatic Pruritus is a phenomenon that occurs in disease processes that impair bile flow. This condition poses significant challenges to quality of life and is often underdiagnosed and undertreated. While the direct cause of cholestatic pruritus remains unclear, it likely involves a complex interplay between multiple biochemical pathways. Due to recent advances in diagnostic tools, more biochemical pathways of cholestatic pruritus have been discovered. As a result, exciting new therapies such as the Ileal Bile Acid Transporter (IBAT) inhibitors and peroxisome proliferator-activated receptor (PPAR) agonists are emerging as effective therapies. In this article, we provide a brief biochemical summary of the various pathways as candidate causes of cholestatic pruritus and examine the evidence behind each of the current available therapeutic options. Additionally, we will discuss emerging therapies and examine the evidence behind their use. Finally, we will provide our recommended stepwise approach to treating a patient with cholestatic pruritus in both the inpatient and outpatient settings.

Keywords: Cholestatic Pruritus, Management, Emerging therapies

Introduction

Cholestasis is the reduction of bile flow through intrahepatic canaliculi due to the gradual destruction of epithelial cells or through the obstruction of large ducts of the biliary tree. This obstruction can lead to a sensation of itch, also called pruritus. This pruritus can be severe and significantly alter a patient's quality of life and ability to function socially [1]. In some rare cases, it can even be a reason why a patient undergoes a liver transplant [2]. Cholestatic pruritus is seen in the following conditions: Primary Sclerosing Cholangitis (PSC), Primary Biliary Cholangitis (PBC), Biliary obstructions, Alagille Syndrome, Progressive Familial Intrahepatic Cholestasis (PFIC) and Benign Recurrent Intrahepatic Cholestasis (BRIC). Each of these conditions result in pruritus due to cholestasis. In PSC, there is stricturing of intra and extra hepatic bile ducts which results in cholestasis. In PBC there is autoimmune destruction of the small and medium sized bile ducts leading to cholestasis. Alagille syndrome is a genetic condition that causes decreased bile duct development which causes

cholestasis. PFIC is another genetic condition that results in defects in bile production and secretion causing cholestasis. Finally, BRIC is a rare genetic condition that alters bile salt transport resulting in cholestasis.

Patients with cholestatic pruritus can suffer severe impairments. This was highlighted in the TARGET-PBC study, a longitudinal observational study of 211 patients with PBC. In this study, three patient-reported outcome questionnaires were used for patients to score their functional impairments. These were the PBC-40, 5-D Itch and the PROMIS fatigue score. In all three of these questionnaires, the median score indicated significant impairment from cholestatic pruritus. In fact, the median PROMIS fatigue score was a 4, indicating that patients with PBC were "worn out, so tired I had to force myself to do things I needed to do, if I was busy one day, I needed at least another day to recover, and I had to pace myself for day-to-day things". The TARGET-PBC study also found that 81% of patients still had pruritus, with only 52% feeling that they had received any treatment for their pruritus [1].

The TARGET-PBC study underscores the negative impact of cholestatic pruritus on patients.

It also highlights the need for providers to recognize this symptom and do a better job in managing it. Ultimately, any diseases impact on quality of life is the most important factor to a patient and the TARGET-PBC study highlights the gap that exists between how much the pruritus affects a patient and the symptom relief they achieve.

The reason for this care gap is likely two-fold. One reason is the fact that there is no one known definitive cause/pathway for cholestatic pruritus and the other reason is due to limited, effective therapeutic options [3]. Through this review, we aim to briefly touch on the various pathways that are involved in pruritus and also discuss current and emerging therapies for cholestatic pruritus.

Pathways

The etiology of cholestatic pruritus is complex and likely involves a dynamic interplay between various pathways. The earliest theories for cholestatic pruritus suspected Bile Acids as the main driver of cholestatic pruritus. This is due to a 1974 study where bile acids were directly injected into human skin and induced pruritus [4]. Additional studies were also done in 2013 with transmembrane G-protein coupled receptor 5 (TGR5) (itch-encoded sensory neuron receptor) knockout mice and found that mice with the knocked out TGR5 gene did not experience pruritus but mice with the TGR5 gene did have pruritus when bile acids were injected into their skin [5]. While this did show bile acids were involved in pruritus, it was unclear if this was due to the bile acid itself or downstream effects of bile acid. Subsequent studies also found that the degree of elevation of bile acid did not correlate with the degree of pruritus [6].

Bile acids have two pathways for synthesis, the classical and alternative pathways. In both, cholesterol is broken down into bile acids, but each involves a different rate-limiting enzyme [7]. In the classical pathway, bile acids are produced and bind to the farnesoid X receptor (FXR) which will then activate the Small Heterodimer Partner (SHP), a regulatory nucleotide receptor which stimulates liver receptor homolog (LRH-1), an inhibitor of the classical pathway [8]. Peroxisome proliferator-activated receptor (PPAR) is another receptor that is activated by FXR and is known to decrease bile acid synthesis and increase bile acid uptake into hepatocytes [9]. FXR is also known to increase levels of IL-31, a known interleukin that causes pruritus, skin inflammation and hypersensitivity [10].

Lysophosphatidic acid (LPA) is a phospholipid that has been found to be a mediator of cholestatic pruritus through the activation of TRPA1 and TRPV1, which are known pruritogenic agents [11]. Interestingly, TRPV1 also increases IL-21 and IL-17, two other interleukins that are associated with pruritus

[12]. Furthermore, Autotoxin (ATX) is the rate-limiting enzyme for LPA and has found to be increased in cholestatic pruritus [13]. Given these findings, LPA and ATX have been studied as therapeutic targets in cholestatic pruritus. Of note, serotonin is also thought to play a part in this pathway by increasing TRPV1, resulting in increased pruritus [14].

Finally, endogenous opioids are thought to be involved in pruritus due to the overactivation of Mu-opioid receptor or deactivation of the kappa-opioid receptor, which can increase itching [15]. However, a small cross-sectional study looking at levels of endogenous opioids quantified through ELISA found that there was no relation between endorphin levels and Pruritus [16]. Given this, it is still unclear exactly how opioids factor into the regulation of cholestatic pruritus.

As evident by the number of pathways involved in cholestatic pruritus, each with substantial evidence, this process is multifactorial. It likely involves a dynamic interplay between all these pathways, making it hard to develop therapeutics to target cholestatic pruritus.

Therapies

Currently the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) have guidelines for cholestatic pruritus. Both start with identifying and resolving a reversible cause such as a stricture or obstruction. If no reversible cause is found, both guidelines recommend using cholestyramine as the first line agent. After this, rifampin, naltrexone or sertraline are second line agents. EASL then recommends using Bezafibrate (approved in the European Union) but AASLD recommends advanced therapies such as plasmapheresis, molecular adsorbent recirculating system (MARS) and even transplant [17,18]. Here, we will discuss the various treatment options and the evidence behind each.

Cholestyramine, a bile acid resin, is the first line therapy for cholestatic pruritus. This agent binds bile acids and prevents their resorption through the ileum. As a result, bile acids are excreted as waste and not reabsorbed into serum, decreasing pruritus. The evidence for cholestyramine comes from two randomized control trials done in 1984 that showed that cholestyramine at a three gram and four-gram dosage was superior to placebo [19]. Interestingly, a randomized control trial done in 2010 using Colesevelam, another bile acid resin, did not decrease pruritus compared to placebo [20]. However, due to the evidence from 1984 and long-term use in clinical practice, it continues to be the first line medication. The use of this medication does present significant challenges in that it decreases the absorption of other oral medications and can cause patients significant bloating and constipation. As a result, in cases where this medication is not tolerated, second line agents are used.

Rifampin is a second line agent that works by activating PXR, which decreases ATX in hepatocytes which in turn decreases LPA, so that TRPA1 and TRPV1 are not stimulated and pruritus is decreased [21]. The evidence behind Rifampin includes three randomized control trials and one meta-analysis. The meta-analysis showed that 77% of patients that used rifampin had a decrease in pruritus [22]. The side effects of Rifampin are hepatotoxicity in 7.3% of patients and it requires a slow up-titration over two weeks. Given the side effect of hepatotoxicity, the use of Rifampin is limited to patients with a normal AST or ALT [23].

Naltrexone is another second line agent that works by blocking the mu-opioid receptor to alleviate pruritus. The evidence behind Naltrexone is the most robust as there are five different randomized control trials in support of Naltrexone. These involve a 1988 study of 11 PBC patients, three clinical trials in the 1990s and one randomized control trial from 2006. Of the current guideline agents, Naltrexone has the most recent randomized trial data [24].

After these established therapies for cholestatic pruritus, there are numerous emerging therapies involving the PPAR-agonists and IBAT Inhibitors.

PPAR-agonists involve three main classes: alpha, gamma and delta. Alpha is found in skeletal muscle tissues and the liver and is a known agent in bile acid metabolism. Gamma is found in fatty tissue and colonic tissue and Delta is found to be active in fatty acid oxidation. In a mouse model, it was found that the injection of PPAR-alpha into mouse tissue caused decreased bile acid synthesis, which is where the notion of its involvement in bile acid metabolism comes from. PPAR-alpha works by decreasing bile acid synthesis and increases bile acid excretion [25].

The following medications are included in this class: Bezafibrate, Fenofibrate, Elafibrinor, and Seladelpar. Bezafibrate is currently approved for use in the European Union and is used in clinical trials in the United States. However, the other PPAR-agonists are still pending approval.

The evidence for Bezafibrate comes from two major trials, the BEZURSO study and the FITCH study. The BEZURSO Study is a phase three trial evaluating the use of Bezafibrate in PBC patient's refractory to ursodeoxycholic acid (UDCA). In this patient population, there was a normalization of alkaline phosphatase (ALP) in 67% of patients. In addition, there was a significant improvement in pruritus, fatigue, and liver stiffness in these patients but no improvement in quality-of-life scores [26]. The FITCH study is a double-blinded placebo-controlled trial of PSC and PBC patients with moderate itching and found that patients treated with bezafibrate had decreased morning and evening itching and decreased 5-D itch scores. The FITCH trial had a primary endpoint of 50% reduction in pruritus that was seen in 45% of patients versus only 11% in the placebo

group, giving a p-value of 0.003. It also showed a reduced serum ALP by 35% suggesting reduced biliary damage [27]. Based on these studies, the evidence behind Bezafibrate is strong and suggests that this is another useful therapy for cholestatic pruritus.

Elafibrinor, a PPAR-alpha and gamma agonist is another emerging therapy, FDA approved for treatment of PBC in July 2024. Currently, it has a phase 2 clinical trial (NCT03124108) and a phase three clinical trial (ELATIVE trial). The NCT03124108 trial studies PBC patients that are refractory to UDCA and has found that these patients have decreased pruritus over a twelve-week period of using Elafibrinor [28]. In the ELATIVE trial, Elafibrinor normalized ALP in 15% of the treatment group compared to 0% in the control group. Furthermore, at the 52-week mark, patients had a PBC-40 reduction with p-value of 0.0070 and 5D itch score reduction p-value of 0.0199. As with any medication, there are side effects to Elafibrinor which include abdominal pain, nausea, vomiting. However, when compared to UDCA using a least-square mean analysis there was no difference [29].

The other recently FDA approved drug for treatment of PBC is Seladelpar, a PPAR-delta agonist, with multiple recent trials. The two most prominent trials are the ENHANCE and RESPONSE trials. The ENHANCE trial is a phase three, double blind, randomized and placebo-controlled trial that followed 240 patients over 1 year. Patients were divided into placebo, 5 mg and 10 mg dose groups and at the 10 mg dose, 27.3% of patients had normalization of ALP compared to 0% in the placebo group. There was also a decrease of 3.14 in the Numerical Rating Scale (NRS) for pruritus in the 10 mg population and a 2.01 decrease in NRS for the 5 mg population compared to 1.55 in the placebo group. Most impressively, the 10 mg group had 78.2% of patients that had normalization of total bilirubin, decrease in ALP to $<1.5 \times \text{ULN}$ and $>15\%$ ALP decrease. 15% of patients also had normalized ALP at the end of the RCT vs. 0% in the placebo group [30].

The RESPONSE trial is a phase three placebo-controlled trial that also looked at Seladelpar 10 mg and found a decrease in the NRS by 3.2 in the 10 mg group and 1.7-point decrease in the placebo group at six months ($p < 0.005$). They also found that at the twelve-month mark, 61.7% of patients had a normalization of total bilirubin, decrease in ALP to $<1.67 \times \text{ULN}$ and $>15\%$ ALP decrease compared to 20% in the placebo group ($p < 0.0001$). Twenty-five percent of the participants also had at normalized ALP at 54 weeks vs, 0% in the placebo group [31].

IBAT inhibitors are also an emerging therapy, but are still early in development. These agents prevent the absorption of bile acids at the ileum. There are four therapies in this class: maralixibat, odevixibat, linerixibat, and volixibat. Malalixibat is still under investigation and has a phase two study for pruritus in PBC patients. For PFIC and Alagille syndrome, it has recently

been approved [32]. Odevixibat is another agent approved for Alagille syndrome patients older than 12 months. It has predominantly been studied in PFIC and Alagille patients with a phase 3 clinical trial published in 2022 [33]. Linerixibat is an IBAT that is being studied in patients with PBC. The GLISTEN study is currently in phase 3, with published data from its phase 2 study (GLIMMER) that showed doses of linerixibat at 40 mg, 90 mg, and 180 mg daily significantly decreased itch over the 12-week treatment period from patients with moderate to severe itching (NRS >4/10) in all quality-of-life domains in the PBC-40 questionnaire [34]. Finally, Volixibat is also being studied in PSC and PBC patients and has phase 2 randomized double-blind placebo- controlled studies, called VANTAGE for PBC and VISTAS for PSC, which are actively enrolling patients [35].

While no clinical trials are currently ongoing, IL-31 inhibitors provide a new and exciting therapeutic option. In a recent study by Xu *et al.*, published in *Hepatology*, IL-31 was found to be involved in cholestatic pruritus [36]. Furthermore, the ENHANCE trial found that patients treated with Seladelpar had decreased levels of IL-31 [37]. Given these studies, it is possible that IL-31 is the end product that causes pruritus. Given the number of agents that have emerged to inhibit IL-17 and IL-21 in conditions like psoriasis and allergic dermatitis, the development of agents targeting IL-31 may provide a modality to target the end product and trigger of cholestatic pruritus.

Conclusion

Cholestatic pruritus presents a complex challenge to patients and providers, and it continues to be undertreated and underrecognized. While current guideline-directed therapies are present with cholestyramine, rifampin, naltrexone and sertraline, there are many emerging therapies (**Table 1**) to aid in the treatment of this pathology. Of these agents, Bezafibrate is currently approved in Europe and has shown excellent results. Seladelpar is another agent, which not only helps improve pruritus but also improves liver biochemistries that are elevated due to intrahepatic bile duct injury caused by PBC. In addition to these two new and exciting agents, the IBAT inhibitor class of medications is also emerging. As it continues to be studied in PBC and PSC patients, it may provide more therapies to use for cholestatic pruritus. Finally, the recent discovery of IL-31's involvement in pruritus may provide a unique downstream pruritogen to target. With the emergence of these therapies, we suggest a step-wise approach that starts with first-line agent Cholestyramine and then advancing to second-line agents such as Naltrexone, Rifampin, and Sertraline as currently mentioned in guidelines. If second line agents fail, then proceeding to Bezafibrate and if the patient fails fibrate therapy, trialing Seladelpar. If all these agents fail, approaches such as plasmapheresis, MARS and transplant may need to be considered.

Table 1. New and Emerging Therapies.

IBAT – Inhibitors	Marilixibat Odevixibat Linerixibat Volixibat IBAT inhibitor 4250
Fibrate	Bezafibrate Fenofibrate
PPAR - Agonist	Seladelpar Elafibrinor
FXR – Agonist	Tropifexor
Mu - Opioid Receptor Partial Agonist – Antagonist	Butorphanol

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