



Effectiveness of Ileal Bile Acid Transporter Inhibitors (IBAT) in Treating Pruritus in Progressive Familial Intrahepatic Cholestasis: A Meta-Analysis

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Introduction

- Progressive familial intrahepatic cholestasis (PFIC) is a rare genetic disorder with severe pruritus primarily affecting the hepatic system through a reduction in the ability of the liver to eliminate waste products, in particular bile acid, via defective bile transporters [1].
- There is no gold standard pharmacological treatment for the disease with many off-label treatment options failing to provide adequate relief [2].
- Surgical techniques, such as biliary diversion, are an option when medical intervention has failed but this comes with its own safety risks and one in four patients failing to achieve improvements [3].
- In 2021, the FDA approved odevixibat, an ileal bile acid transporter inhibitor (IBAT), as one of the first treatment options for pruritus in patients living with PFIC. A prior meta-analysis in 2022 of IBAT use in Alagille syndrome reported a significant reduction of pruritus, but no current analysis has been performed for PFIC [4].

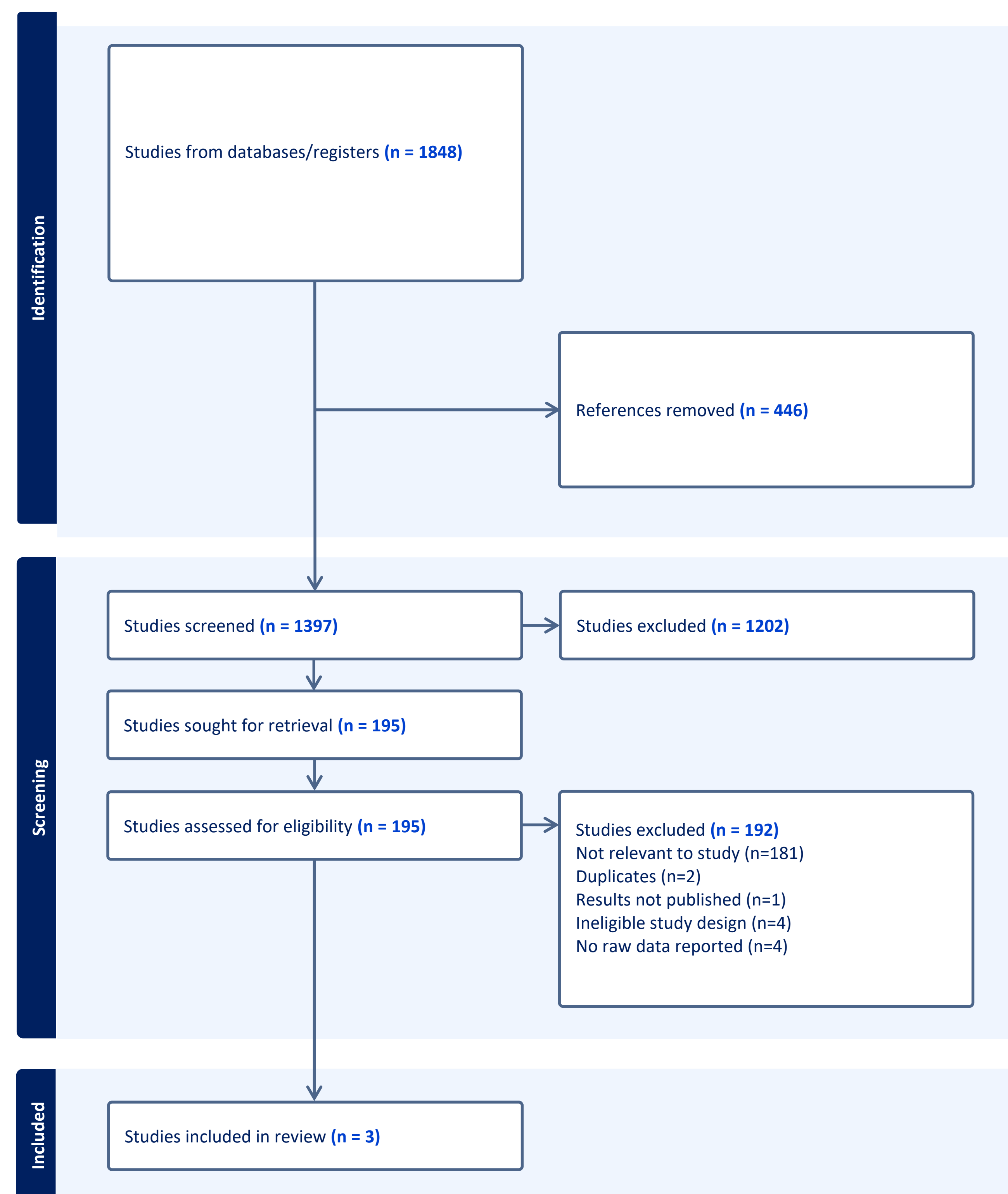
Objective

- Evaluate clinical trials in the literature to determine effectiveness of IBAT usage in itch and bile acid reduction in PFIC.

Methods

- A systematic review was performed to further evaluate IBAT inhibitor's efficacy, specifically, maralixibat and odevixibat, on pruritus (PROSPERO ID: CRD42023437275, Table 1) in PFIC.
- The following databases were searched for articles up to June 28, 2023, with no restriction imposed on publication date: PubMed, MEDLINE, Embase, Scopus, LILACS, Cochrane, CINAHL, and GREAT. We also searched the trial register ClinicalTrials.gov.
- Inclusion criteria: any clinical trial utilizing IBAT inhibitors in PFIC; with or without a comparator; primary outcomes include outcomes such as itch severity and bile acid serum levels reported as raw data.
- Exclusion criteria: no report of any primary outcome with raw data; secondary research (review or meta-analysis); gray literature (dissertation, conference abstract, letter, review, commentary, editorial, note); language other than English. No language or date restrictions were applied.

Figure 1: PRISMA Guidelines



Results

- The pooled analysis revealed a significant reduction in pruritus (ItchRO) among PFIC patients (n=70), with an average mean reduction of 1.105 and a standard mean difference of 0.78 (95% CI: [0.28-1.29], I² = 52%, p = 0.002).
- ItchRO is a Likert scale (1-4) with reductions >= 1 being clinically significant [5].
- Simultaneously, a substantial decrease in serum bile acid levels was observed with an average mean reduction of 103.98 and a standard mean difference of 0.78 (95% CI: [0.46-1.10], I² = 0%, p < 0.00001).
- Visual inspection of the funnel and forest plots showed no signs of asymmetry, indicating a lack of publication bias. Furthermore, the quality of included studies was generally high, contributing to the robustness of our findings.

Findings

- The results from this study further support prior interventions suggesting that the disruption of bile acid circulation cycles has a positive correlation with reducing serum bile acid levels and leading to reductions in patient-reported itch, possibly through decreased stimulation of bile-acid activated MRGPRX4 receptors for cholestatic itch [6,7].
- A prior case report in 2020 noted that a patient receiving 4 weeks of odevixibat therapy whose symptoms returned after ceasing IBAT usage showed similar bile acid and pruritus improvements as on odevixibat use upon eventual partial external biliary diversion [8].
- While monitored clinical trials with large sample sizes and head-on comparators between the interventions should be explored, the results suggest that IBAT usage might be an effective alternative to more invasive surgical interventions for patients experiencing severe pruritus with PFIC.
- Future studies should continue to implement standardized patient outcome metrics (e.g. ItchRO) to further facilitate comparative analysis.

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Figure 2: Pooled Analysis for IBAT on (a) Serum Bile, (b) ItchRo

