Efficacy and Safety of Ileal Bile Acid Transport Inhibitors in Inherited Cholestatic Liver Disorders: A Meta-analysis of Randomized Controlled Trials

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Background: **Inherited cholestatic liver disorders such as progressive familial intrahepatic cholestasis (PFIC) and Alagille syndrome result in significant pruritus and increased serum bile acids, necessitating liver transplantation. This study aims to evaluate the efficacy and safety of Ileal bile acid transport inhibitors (IBATIs) in children with PFIC and Alagille syndrome.** ***Methods:*** **We conducted a comprehensive search across the databases to identify relevant randomized controlled trials (RCTs), and Covidence was used to screen eligible articles. All outcomes data were synthesized using risk ratios (RRs) or mean differences (MDs) with 95% confidence intervals (CIs) in RevMan 5.4. PROSPERO: CRD42024564270.** ***Results:*** **Four multicenter RCTs involving 215 patients were included. IBATIs were associated with a significant reduction in Itch Observer Reported Outcome (Itch (ObsRo)) score (MD: −0.90, 95% CI [−1.17, −0.63], $P < 0.01$), serum bile acids (MD: −119.06, 95% CI [-152.37, −85.74], $P < 0.01$), total bilirubin (MD: −0.73, 95% CI [-1.32, −0.15], $P = 0.01$), and increased proportion of patients achieving ≥1 score reduction in Itch (ObsRo) score (RR: 2.54, 95% CI [3.83, 1.69], $P < 0.01$) and bile acid responders (RR: 8.76, 95% CI [2.46, 31.23], $P < 0.01$) compared with placebo. No differences were observed in any treatment-emergent adverse events (TEAs) (RR: 1.02, 95% CI [1.12, 0.93], $P = 0.71$), TEAs leading to drug discontinuation (1.03, 95% CI [5.56, 0.19], any serious TEAs, or liver-related TEAs.** ***Conclusion:*** **IBATIs showed significant improvement in various cholestatic parameters with tolerable safety profile; however, future research on optimal dosage and long-term outcomes is needed. (J Clin Exp Hepatol 2025;15:102462)**

INTRODUCTION

Inherited cholestatic liver diseases are a group of rare and severe conditions that are predominantly diagnosed in children.[1] These conditions are characterized by impaired bile flow, leading to the accumulation of bile acids and other toxic substances in the liver and bloodstream.[2] Among the most common inherited cholestatic liver diseases are progressive familial intrahepatic cholestasis (PFIC), Alagille syndrome, and biliary atresia.[3,4] These disorders can lead to a considerable amount of morbidity and mortality, and liver transplantation may be required in some cases.[1] The cause of inherited cholestatic liver diseases comprises genetic mutations impacting bile acid transport, synthesis, or metabolism.[5] For example, mutations in the ATP8B1, ABCB11, and ABCB4 genes cause various types of PFIC by disrupting the normal transport of bile acids in liver cells.[6] Additionally, mutations in the JAG1 or NOTCH2 genes lead to Alagille syndrome, which affects the formation of bile ducts and other organs, resulting in a broad spectrum of clinical symptoms.[7] Bile acids in hepatocytes and cholangiocytes can lead to cell damage, inflammation, and the development of progressive liver fibrosis.[8]

Traditional management strategies have focused on supportive care, including nutritional support, fat-soluble vitamin supplementation, and symptomatic relief of pruritus.[9] However, these approaches fail to explain the fundamental processes that lead to the progression of the disease. Increasing evidence has focused on

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Abbreviations: ALT: alanine aminotransferase; ASBT: apical sodium-dependent bile acid transporter; AST: aspartate aminotransferase; CI: confidence interval; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; IBAT: ileal bile acid transporter; IBATI: ileal bile acid transporter inhibitor; Itch (ObsRo): Itch Observer Reported Outcome; MD: mean difference; PEBD: partial external biliary diversion; PFIC: progressive familial intrahepatic cholestasis; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT: randomized controlled trial; RR: risk ratio; TEA: treatment-emergent adverse event; UDCA: ursodeoxycholic acid
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interrupting the enterohepatic circulation of bile acids to treat cholestatic liver diseases.[10] Previously, surgical approaches have historically played a crucial role in managing cholestatic liver diseases, paving the way for the development of pharmacological interventions. Partial external biliary diversion and ileal bypass surgeries have successfully reduced serum bile acid levels and alleviated symptoms in patients with PFIC and other cholestatic conditions.[11,12] These surgical techniques effectively interrupt the enterohepatic circulation of bile acids, providing proof of concept for targeting this pathway.[13]

The ileal bile acid transporter inhibitors (IBATIs), including odevixibat and maralixibat, have been identified as promising drugs for treating cholestatic liver diseases.[14] The potential benefits of IBATIs are multifaceted. First, by interfering with the reabsorption of the bile acids in the enterohepatic circulation, they decrease the bile acid level in the blood, minimizing hepatocellular injury and progression of liver fibrosis.[1,15] Second, they may exhibit benefits in relieving pruritus, improving the quality of life of children affected with this condition.[16] Third, since ileal bile acid transporter (IBAT) blockers promote increased bile acid secretion, absorption of fat-soluble vitamins and other nutrients may be improved.[1]

A previous single-arm meta-analysis highlighted the efficacy of IBAT inhibitors across current trials but also noted a significant increase in alanine aminotransferase (ALT) levels by 40 U/L, suggesting potential liver enzyme elevation as a side-effect.[17] Individual placebo-controlled clinical trials have shown promising results, but the evidence remains fragmented.[18,19] Thus, this systematic review and meta-analysis aims to summarize the existing data regarding the effectiveness of IBAT blockers in treating inherited cholestatic liver diseases in pediatric patients.

METHODOLOGY

Ethics approval and consent to participate

Not applicable.

Protocol Registration

Our review procedure was registered and published in PROSPERO with the ID: CRD42024564270. We conducted a systematic review and meta-analysis sincerely guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[20] and the Cochrane Handbook of Systematic Reviews and Meta-Analysis.[21] The PRISMA 2020 checklist is illustrated in (Table S1).

Data Sources and Search Strategy

Web of Science, Scopus, PubMed (MEDLINE), and Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched by two reviewers (M.I., M.A.) from inception until May 30, 2024. No search filters were used. The detailed search approach and results are outlined in (Table S2).

Eligibility Criteria

We included the randomized controlled trials (RCTs) with the following PICO criteria: population (P); patients′ age< 18 years, both genders, having inherited cholestatic liver disorders including PFIC and Alagille syndrome; intervention (I); IBATIs such as maralixibat and odevixibat regardless of the dose, frequency, and duration; comparator (C); placebo; outcome (O); the primary outcome of this review was change from baseline in Itch Observer Reported Outcome (Itch(ObsRo)) score and proportion of patients achieving equal to or greater than one score reduction in Itch (ObsRo) score (pruritis responders). Our secondary outcomes included the efficacy outcomes, including the change from baseline in serum bile acids, total bilirubin, cholesterol, aspartate aminotransferase (AST) and ALT, bile acid responders, and safety outcomes, including any treatment-emergent adverse events (TEAs), any serious TEAs, TEAs leading to drug discontinuation, and liver-related TEAs.

Study Selection

Search results from all the databases were imported to Covidence.org, and duplicates were removed automatically. Four authors screened the remaining records independently (M.E., M.S.T., A.M.M., and S.A.), and any conflict between them was resolved by another author (M.I.). The screening was done in two steps: (i) title and abstract screening to determine the study′s relevance for this meta-analysis, and (ii) full-text screening according to the inclusion criteria for the final eligibility for qualitative and quantitative analysis.

Data Extraction

Data were collected independently by four review authors (M.E., M.S.T., A.M.M., and S.A.) and extracted into a uniform data extraction Excel sheet. The extracted data included characteristics of the included studies, including first author name, year of publication, National Clinical Trial (NCT) ID, country, study design, total participants, intervention detail such as drug, dose, duration, type of inherited cholestatic liver disease, inclusion criteria, primary outcome, and follow-up duration; participants′ baseline characteristics, including the number of participants, mean age, gender, race, baseline serum bile acid, itch (ObsRo) score, ASL, ALT, bilirubin, and concomitant drugs such as rifaximin and ursodeoxycholic acid; and outcome measures as previously described across the intervention and comparator group. Any disagreements were resolved by consensus.

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Risk of Bias and Certainty of Evidence

Four reviewers (M.E., M.S.T., A.M.M., and S.A.) independently assessed the included studies' quality using the Cochrane RoB 2.0 tool.[22] The domains that were evaluated included the risk of bias resulting from the randomization process, the risk of bias due to deviation from the intended intervention, the risk of bias due to missing outcome data, the risk of bias in the measuring of outcomes, and the risk of bias in selecting the reported results.

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) recommendations[23] were followed, considering inconsistency, imprecision, indirectness, publication bias, and risk of bias. The evaluation was carried out for each outcome, and the decisions were justified and documented. Any discrepancies were settled through discussion.

Statistical Analysis

Statistical analysis was conducted using RevMan v5.4 software. We utilized risk ratios (RRs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes, both reported with 95% confidence intervals (CIs) under the initial framework of the fixed-effects model. However, in cases of significant heterogeneity, as determined by the χ^2 test ($P < 0.1$) or substantial heterogeneity indicated by the I^2 test (values between 50% and 100%), we applied the random-effects model to account for variability. On significant heterogeneity, a leave-one-out sensitivity analysis was also conducted. Also, a subgroup analysis based on the type of inherited cholestatic liver disorder was conducted for the outcomes reported in all the studies.

RESULTS

Search Results and Study Selection

The search result yielded 398 articles. After duplication removal (n = 194) and reviewing the titles and abstracts (n = 204) for the relevance of the studies, sixty-seven studies were chosen for full-text review. Four of these studies met the inclusion criteria for our systematic review and meta-analysis. Our search findings are displayed in the PRISMA flow diagram (Figure 1).

Characteristics of Included Studies

This study involves four[18,19,24,25] multicenter RCTs with 215 children with PFIC and Alagille syndrome. Two studies used maralixibat,[19,24] and two used odevixibat,[18,25] and the treatment period ranged from 13 to 26 weeks. Further detailed characteristics of the included studies and participants' baseline characteristics are outlined in Tables 1 and 2, respectively.

Risk of Bias and Certainty of Evidence

The overall risk of bias was low in the included trials. All the included RCTs showed a low risk of bias in the randomization process, the risk of bias due to deviation from the intended intervention, the risk of bias due to missing outcome data, the risk of bias in the measuring of outcomes, and the risk of bias in selecting the reported results (Fig. S1). A GRADE evidence profile outlines the certainty of evidence (Table 3).

Primary Outcome

The meta-analysis showed a significant reduction in Itch (ObsRo) score (mean difference [MD]:-0.90, 95% CI [−1.17, −0.63], $P < 0.01$) and a more significant proportion of patients achieving ≥1 score reduction in Itch (ObsRo) score (RR: 2.54, 95% CI [3.83, 1.69], $P < 0.01$) with IBATIs compared with placebo (Figure 2).

The result was homogenous for the change in Itch (ObsRo) score ($I^2 = 0\%$, $P = 0.53$) and the proportion of patients achieving equal to or greater than one score reduction in Itch (ObsRo) score ($I^2 = 0\%$, $P = 0.87$). Also, the test for subgroup analysis based on the type of inherited cholestatic liver disease was not significant for mean itch (ObsRo) score ($P = 0.35$) and proportion of patients achieving ≥1 score reduction in Itch (ObsRo) score ($P = 0.81$) (Figs. S2–S3).

Secondary Outcomes

Efficacy Outcomes

The meta-analysis showed that the IBATIs were associated with a significant reduction in serum bile acids (MD: −119.06, 95% CI [−152.37, −85.74], $P < 0.01$) and a more significant proportion of bile acid responders (RR: 8.76, 95% CI [2.46, 31.23], $P < 0.01$) compared with placebo (Figure 3). Also, a reduction in total bilirubin (MD: −0.73, 95% CI [−1.32, −0.15], $P = 0.01$) and serum cholesterol (MD: −1.97, 95% CI [−3.64, −0.31], $P = 0.02$) was significant with IBATIs compared with placebo (Fig. S4). However, there were no differences in change in ALT (MD: 17.99, 95% CI [−19.32, 55.30], $P = 0.34$) and AST (MD: 9.27, 95% CI [−44.17, 62.71], $P = 0.73$] between the two groups (Fig. S5).

The results were homogenous for change in serum bile acids ($I^2 = 40$, $P = 0.17$), bile acid responders ($I^2 = 0\%$, $P = 0.66$), change in total bilirubin ($I^2 = 0\%$, $P = 0.55$), serum cholesterol ($I^2 = 0\%$, $P = 0.84$); however, heterogeneous for change in ALT ($I^2 = 84\%$, $P < 0.01$) and AST ($I^2 = 89\%$, $P < 0.01$). The leave out one sensitivity analysis is shown in (Fig. S6).

The test for subgroup analysis based on the type of inherited cholestatic liver disease was not significant for the change in bile acid ($P = 0.08$), total bilirubin ($P = 0.31$), and ALT ($P = 0.06$) (Figs. S7–9).

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Safety Outcomes

No differences were observed in any treatment-emergent adverse events (TEAs) (RR: 1.02, 95% CI [1.12, 0.93], P = 0.71), TEAs leading to drug discontinuation (1.03, 95% CI [5.56, 0.19], P = 0.97], any serious TEAs (RR: 0.82, 95% CI [0.39, 1.71], P = 0.30), and liver-related TEAs (RR: 1.03, 95% CI [0.70, 1.54], P = 0.54) between the two groups (Fig. S10).

The result was homogenous for any TEAs (I^2 = 47%, P = 0.13), TEAs leading to drug discontinuation (I^2 = 0%, P = 0.96), any serious TEAs (I^2 = 18%, P = 0.30), and liver-related TEAs (I^2 = 0%, P = 0.54).

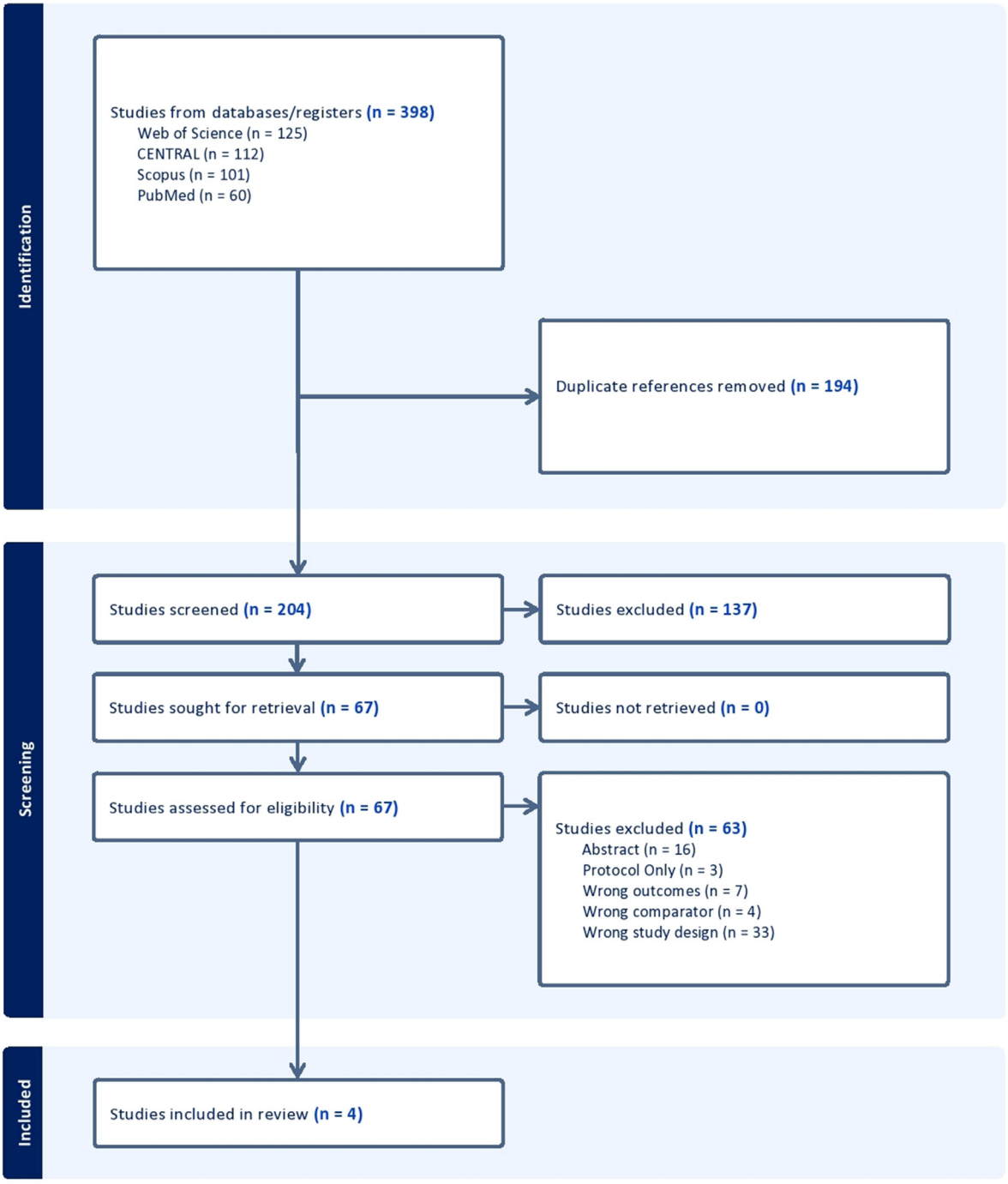

Figure 1 PRISMA flow chart of the screening process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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Table 1 Characteristics of the Included RCTs.

Study ID	Study design	NCT ID	Country	Total number of participants	Type of inherited cholestatic liver disease	Main inclusion criteria	Intervention			Primary outcome	Follow-up
							Drug	Dose	Duration		
Miethke et al. 2024 (MARCH-PFIC)[21]	Multicentre, double-blinded, phase III RCT	NCT03905330	Lebanon, Brazil, Mexico, Colombia, Poland, Italy, the USA, Argentina, Austria, Belgium, Canada, France, Germany, Singapore, Türkiye, and the UK	64	PFIC	Participants aged 12 months or older and younger than 18 years with a clinical diagnosis of PFIC with persistent (>6 months) pruritus and biochemical abnormalities, pathological evidence of progressive liver disease, or both with an average morning pruritus severity score by Itch-ReportedOutcome (Observer; ItchRO[Obs]) of 1·5 or higher during the last 4 consecutive weeks of screening	Maralixibat	Starting dose 142·5 μg/kg, then escalated to 570 μg/kg	26 weeks	The mean change in average morning ItchRO (Obs) severity score	26 weeks
Ovchinsky et al. 2024 (ASSERT)[22]	Multicentre, double-blinded, phase III RCT	NCT04674761	Belgium, France, Germany, Italy, Malaysia, the Netherlands, Poland, Türkiye, the UK, and the USA	52	Alagille syndrome	Individuals of any age with a genetically confirmed diagnosis of Alagille syndrome (i.e., a documented mutation in JAG1 or NOTCH2), a history of significant pruritus as determined by the investigator, an average observer reported scratching score or a patient-reported pruritus score for those aged 18 years and older (not reported since no patients aged ≥18 years were enrolled), of 2 or more, as measured by the PRUCISION instrument, and elevated serum bile acid concentrations (i.e. more significant than the upper limit of normal [ULN] by patient age)	Odevixibat	120 μg/kg per day	24 weeks	Change from baseline in the averaged morning and evening ObsRO caregiver scratching scores.	24 weeks

(*Continued on next page*)

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Table 1 (*Continued*)

Study ID	Study design	NCT ID	Country	Total number of participants	Type of inherited cholestatic liver disease	Main inclusion criteria	Intervention			Primary outcome	Follow-up
							Drug	Dose	Duration		
Thompson et al. 2022 (PEDFIC-1)[15]	Multicentre, double-blinded, phase III RCT	NCT03566238	USA, Canada, Europe, Australia, and the Middle East.	62	PFIC	Children (aged 0.5–18 years) with a clinical diagnosis of PFIC1 or PFIC2 and genetic confirmation of biallelic pathogenic mutations in the ATP8B1 (i.e. PFIC1) or ABCB11 (i.e. PFIC2) genes, elevated serum bile acids (≥100 μmol/L), history of significant pruritus as determined by the investigator, and an average caregiver reported observed scratching score of 2 or greater (calculated from daily electronic diary [eDiary] entries) in the 14 days preceding randomization	Odevixibat	40 μg/kg & 120 μg/kg	24 weeks	The proportion of the patients with improvement in pruritis of at least 1 point and serum bile acid equal to or > 70 % reduction from baseline	24 weeks
Shneider et al. 2018 (ITCH)[16]	Multicenter, double-blinded phase IIb RCT	NCT02057692	USA, Canada	37	Alagille syndrome	Children aged 1 year to 18 years who had cholestasis and pruritus caused by ALGS, confirmed by JAGGED1 or NOTCH2 genotyping, presence of significant pruritus determined by ItchRO observation of child reported by parent/guardian/care-giver (Obs) and an average daily ItchRO (Obs) score of ≥2 for 2 consecutive weeks.	Maralixibat	70, 140, 280 μg/kg/day	13 weeks	Change in pruritus as measured by the ItchRO (Obs)	13 weeks

PFIC: progressive familial intrahepatic cholestasis; Itch (ObsRo): itch observer reported outcome; RCT, randomized controlled trial; UNL: upper normal limit.

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Table 2 Baseline Characteristics of the Included Participants.

Study ID	Number of participants		Age		Gender, Male		Race								Baseline disease clinical parameters parameters										Baseline laboratory parameters										Concomitant Medications			
	IBATIs						IBATIs				Placebo				Pruritis (Itch(Ro)) score		Sleep Disturbance EDQ		Z score of height		Z score of Weight		Presence of Xanthoma		Serum bile acids		Total Bilirubin		Serum ALT		ALP		Cholesterol		UDCA		Rifampicin	
	IBATs	Placebo	IBATIs	Placebo	IBATIs	Placebo	White	Black	Asian	Others	White	Black	Asian	Others	IBATIs	Placebo	IBATIs	Placebo	IBATIs	Placebo	IBATIs	Placebo	IBATIs	Placebo	IBATIs	Placebo	IBATIs	Placebo	IBATIs	Placebo	IBATIs	Placebo	IBATIs	Placebo	IBATIs	Placebo	IBATIs	Placebo
Miethke et al. 2024 (MARCH-PFIC)	33	31	4·9 (4·1)	4·4 (3·6)	17 (52 %)	13 (42 %)	24 (73 %)	1 (3 %)	3 (9 %)	3 (9 %)	19 (61 %)	2 (6 %)	0	6 (19 %)	2·9 (0·9)	2·7 (0·9)	3·7 (0·8)	3·7 (1·0)	−2·08 (1·29)	−2·06 (1·48)	−1·75 (1·29)	−1·28 (1·33)	NR	NR	254 (140)	272 (147)	4·12 (3·80)	4·04 (4·46)	88 (62)	127 (104)	630 (286)	518 (290)	NR	NR	27 (82 %)	30 (97 %)	18 (55 %)	15 (48 %)
Ovchinsky et al. 2024 (ASSERT)	35	17	6·1 (3·4–8·8)	4·2 (1·5–9·2)	21 (60 %)	6 (35 %)	30 (86 %)	2 (6 %)	2 (6 %)	1 (3 %)	13 (76 %)	2 (12 %)	1 (6 %)	1 (6 %)	2·8 (0·5)	3·0 (0·6)	NR	NR	NR	NR	NR	NR	9 (26 %)	2 (12 %)	237 (115)	246 (121)	52 (43)	62 (57)	186 (83)	149 (84)	NR	NR	8·0 (2·0)	9·2 (4·8)	30 (86 %)	16 (94 %)	NR	NR
Thompson et al. 2022 (PEDFIC-1)	42	20	3·2 (1·3–6·1)	2·8 (0·8–4·5)	19 (45 %)	12 (60 %)	35 (83 %)	2 (5 %)	1 (2 %)	4 (10 %)	17 (85 %)	0 (0 %)	1 (5 %)	2 (10 %)	3·0 (2·5–3·1)	3·0 (2·7–3·3)	NR	NR	NR	NR	NR	NR	NR	NR	221 (160–351)	255 (168–329)	2·2 (0·8–3·3)	1·8 (0·6–4·3)	70 (39–105)	56 (37–85)	NR	NR	NR	NR	32 (76 %)	18 (90 %)	24 (57 %)	17 (85 %)
Shneider et al. 2018 (ITCH)	25	12	7.5 (4.55)	5.5 (4.19)	15 (60 %)	6 (50 %)	20 (80 %)	3 (12 %)	1 (4 %)	1 (4 %)	9 (75 %)	3 (17 %)	0 (0 %)	0 (0 %)	3.0 (0.63)	2.8 (0.53)	NR	NR	-1.71 (1.365)	-1.43 (0.753)	-1.35 (1.168)	-1.21 (0.931)	NR	NR	221.7 (223.1)	204.9 (162.5)	4.7 (5.95)	6.4 (6.77)	144.6 (81.28)	188.1 (93.05)	570.0 (179.5)	685.4 (305.7)	372.2 (271.1)	475.6 (392.0)	22 (88 %)	9 (75 %)	17 (68 %)	8 (67 %)

Data reported in mean (standard deviation), median (interquartile range) or number (percentage). IBATis: ileal bile acid transport inhibitors; Itch (Ro): Itch observer reported outcome; UDCA: ursodeoxycholic acid; ALT: alanine aminotransferases; AST: aspartate aminotransferases; ALP: Alkaline phosphatase.

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Table 3 GRADE Evidence Profile.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%) With [placebo]	Study event rates (%) With [IBATs]	Relative effect (95% CI)	Anticipated absolute effects Risk with [placebo]	Anticipated absolute effects Risk difference with [IBATs]
Itch (ObsRo) score change											
215 (4 RCTs)	Not serious	Not serious	Not serious	Serious[a]	none	⨁⨁⨁◯ Moderate	80	135	–	80	MD **0.9 lower** (1.17 lower to 0.63 lower)
Patients achieving Itch (ObsRo) score reduction of >/ = 1											
211 (4 RCTs)	Not serious	Not serious	Not serious	Serious[b]	none	⨁⨁⨁◯ Moderate	19/76 (25.0%)	84/135 (62.2%)	**RR 2.54** (1.69–3.83)	19/76 (25.0%)	**385 more per 1000** (from 173 more to 708 more)
Serum bile acids change											
214 (4 RCTs)	Not serious	Not serious	Not serious	Serious[c]	Strong association	⨁⨁⨁⨁ High	80	134	–	80	MD **119.06 lower** (152.37 lower to 85.74 lower)
Bile acids responders											
120 (2 RCTs)	Not serious	Not serious	Not serious	Extremely serious[d]	none	⨁◯◯◯ Very low	2/48 (4.2%)	29/72 (40.3%)	**RR 8.76** (2.46–31.23)	2/48 (4.2%)	**323 more per 1000** (from 61 more to 1000 more)
Serum total bilirubin change											
195 (4 RCTs)	Not serious	Not serious	Not serious	Serious[c]	none	⨁⨁⨁◯ Moderate	71	124	–	71	MD **0.73 lower** (1.32 lower to 0.15 lower)
Serum cholesterol change											
89 (2 RCTs)	Not serious	Not serious	Not serious	Very serious[a]	none	⨁⨁◯◯ Low	29	60	–	29	MD **1.97 lower** (3.64 lower to 0.31 lower)
AST change											
214 (4 RCTs)	Not serious	Very serious[e]	Not serious	Serious[c]	none	⨁◯◯◯ Very low	80	134	–	80	MD **17.99 higher** (19.32 lower to 55.3 higher)
ALT change											
159 (3 RCTs)	Not serious	Very serious[e]	Not serious	Serious[c]	none	⨁◯◯◯ Very low	59	100	–	59	MD **9.27 higher** (44.17 lower to 62.71 higher)
Treatment-emergent adverse events											
244 (4 RCTs)	Not serious	Not serious	Not serious	Serious[b]	none	⨁⨁⨁◯ Moderate	84/95 (88.4%)	130/149 (87.2%)	**RR 1.02** (0.93–1.12)	84/95 (88.4%)	**18 more per 1000** (from 62 fewer to 106 more)
Serious treatment-emergent adverse events											
244 (4 RCTs)	Not serious	Not serious	Not serious	Serious[b]	none	⨁⨁⨁◯ Moderate	10/95 (10.5%)	14/149 (9.4%)	**RR 0.82** (0.39–1.71)	10/95 (10.5%)	**19 fewer per 1000** (from 64 fewer to 75 more)

CI: confidence interval; MD: mean difference; RCT, randomized controlled trial; RR: risk ratio.

Explanations:

[a]A wide confidence interval that does not exclude the appreciable harm/benefit, with a low number of participants (<400 participants).

[b]A low number of events (<300 events).

[c]A low number of participants (<400 participants).

[d]A wide confidence interval that does not exclude the appreciable harm/benefit, with a low number of events (<300 events).

[e]I^2 > 75%.

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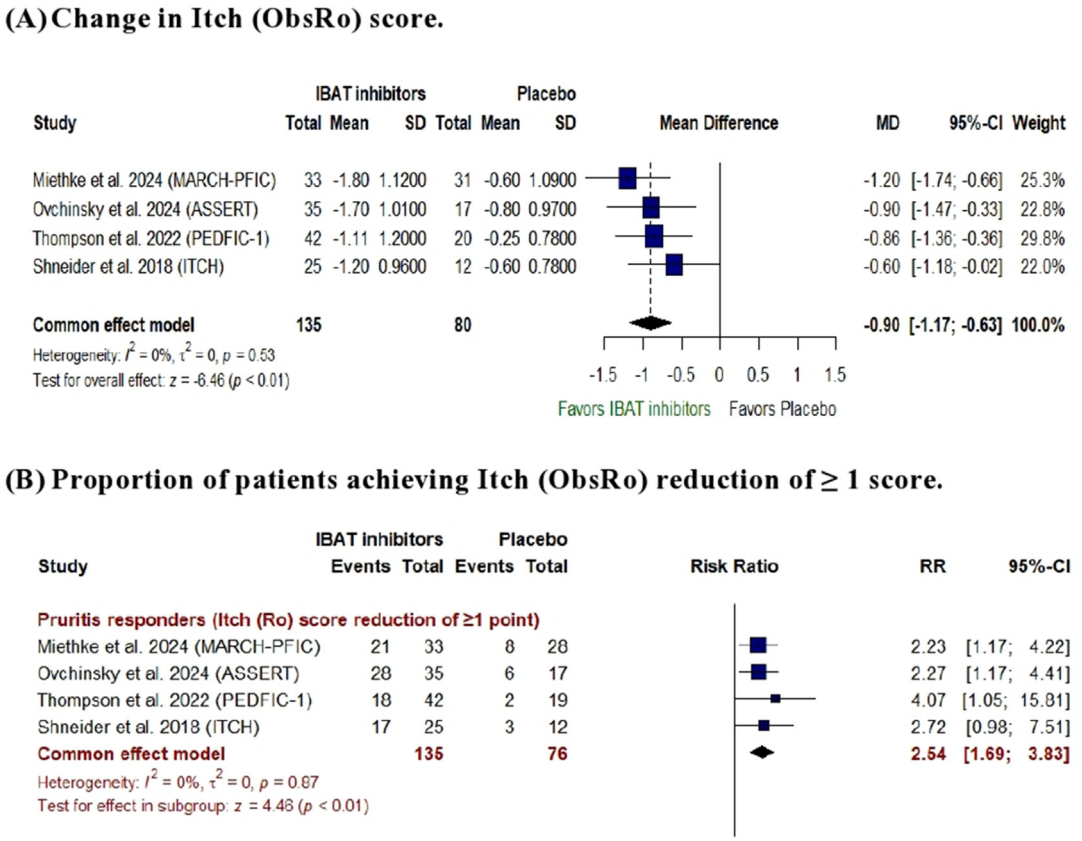

Figure 2 Forest plot of the (A) change in Itch (ObsRo) score, (B) proportion of patients with equal to or greater than 1 score reduction in the Itch (ObsRo) score. RR: risk ratio, CI: confidence interval. Itch (ObsRo), Itch Observer Reported Outcome.

DISCUSSION

Our meta-analysis demonstrates that IBATIs significantly improve critical outcomes in patients with inherited cholestatic liver disorders. The primary outcome showed a substantial reduction in the Itch (ObsRo) score and a higher proportion of patients achieving clinically meaningful itch reduction with IBATIs compared with placebo. Also, secondary efficacy outcomes such as reduction in serum bile acids, total bilirubin, serum cholesterol, and a greater proportion of bile acid responders were significant with the IBATIs, with tolerable safety profile as no difference observed in any TEAs, serious TEAs, TEAs leading to drug discontinuation, and liver-related TEAs.

Reducing pruritus is particularly important given the profound impact of chronic itching on patients' quality of life, affecting sleep, mood, social interactions, and overall well-being.[26] The mechanism of action of IBATIs involves inhibiting the IBAT, also known as the apical sodium-dependent bile acid transporter.[15] By preventing bile acid reabsorption in the terminal ileum, IBATIs effectively reduce systemic bile acid levels, increase fecal bile acid excretion, and potentially modulate bile acid signaling pathways.[27] This mechanism alleviates pruritus and improves other biochemical parameters associated with cholestasis as evidenced by reduced total bilirubin and serum cholesterol levels.[28]

Interestingly, our analysis did not show significant differences in ALT and AST levels between IBATI and placebo groups; however, significant heterogeneity was observed in the pooled analysis. This heterogeneity suggests that the impact of IBATIs on liver enzymes may vary considerably among patients. Several factors could contribute to this variability, including differences in underlying disease mechanisms and complex pathophysiology of cholestatic liver diseases, where multiple factors contribute to liver enzyme elevations, genetic factors, or varying stages of disease progression among study participants. The lack of significant changes in liver enzymes suggests that while IBATIs effectively manage symptoms and specific biomarkers, they may need to be combined with other therapies to address all aspects of cholestatic liver diseases comprehensively.

The safety profile of IBATIs appears favorable, with no significant differences in treatment-emergent adverse events, serious adverse events, or liver-related adverse events compared with placebo. This favorable safety profile, combined with their efficacy, positions IBATIs as a potential first-line or early second-line treatment option for

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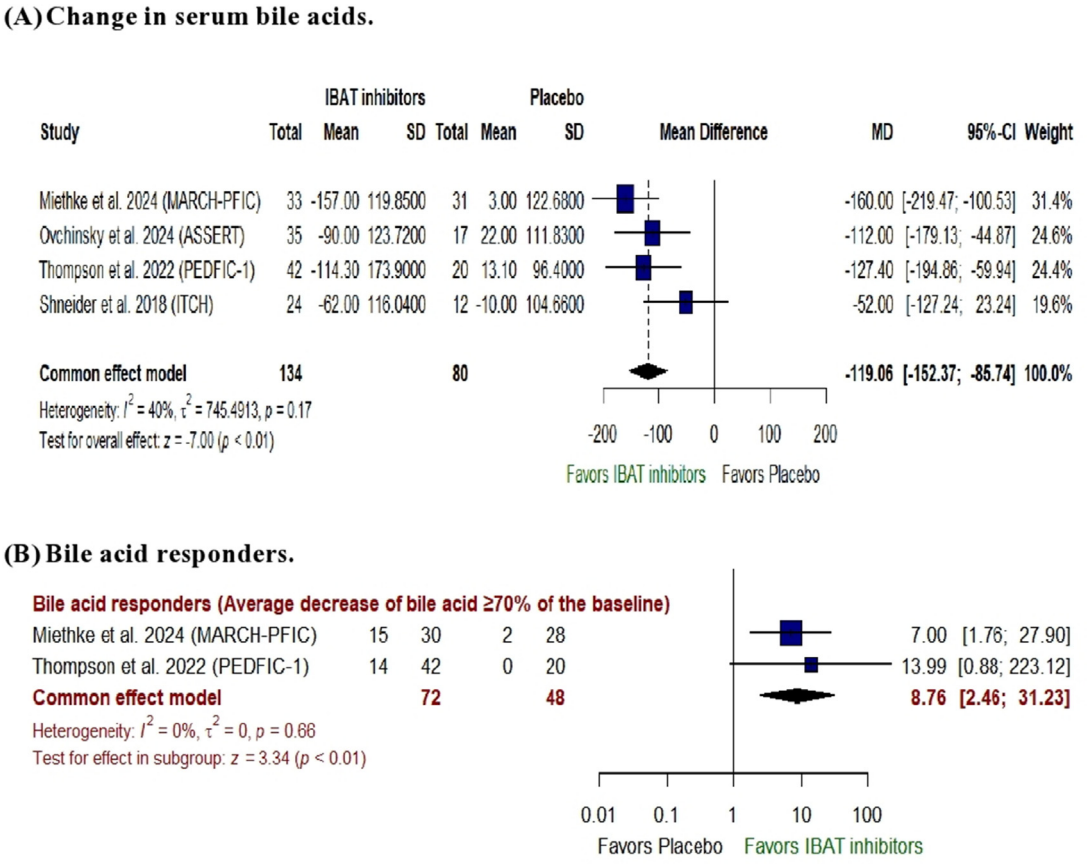

Figure 3 Forest plot of (A) change in serum bile acid, (B) Bile acid Responders. RR: risk ratio, CI: confidence interval.

cholestatic pruritus, particularly in patients who have not responded adequately to other treatments such as bile acid sequestrants or rifampicin 27.

Moreover, our meta-analysis underscores the need for personalized medicine approaches to manage cholestatic pruritus.[29] Given the variability in liver enzyme responses, tailoring treatments based on individual patient characteristics, including genetic factors and disease etiology, could optimize therapeutic outcomes and minimize adverse effects.[30] Future studies should investigate biomarkers that predict response to IBATIs and explore their efficacy in different subgroups of patients with cholestatic liver diseases. Moreover, the long-term effects of IBATI treatment remain vital for future research. While our meta-analysis demonstrates short-term efficacy and safety, the potential long-term benefits, such as sustained symptom relief and possible effects on disease progression, must be balanced against any potential risks associated with prolonged alteration of bile acid metabolism.[27]

Comparison with previous meta-analyses provides additional context for our findings. A meta-analysis focused on patients with Alagille syndrome showed significant reductions in ItchRO scores and serum bile acids with IBATI treatment, similar to our results.[17] However, that analysis found an increase in ALT levels, contrasting with our finding of no significant change in liver enzymes. This discrepancy highlights the potential variability in responses among different patient populations and underscores the need for further research to understand the underlying mechanisms.

Implications for Future Research

The results of our meta-analysis have several important implications for clinical practice and future research. The significant improvement in pruritus scores and bile acid levels suggests that IBATIs could be considered a valuable treatment option for cholestatic pruritus. Their favorable safety profile may lead to increased adoption in clinical practice, potentially improving the quality of life for many patients suffering from this debilitating symptom. Future research directions should include long-term efficacy and safety studies, investigation of combination therapy approaches, identification of predictive biomarkers, and exploration of the impact of IBATIs on disease progression and long-term outcomes. Additionally, studying the effects of IBATIs on bile acid-dependent signaling pathways could provide insights into their broader physiological impacts and potential applications beyond cholestatic pruritus.

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Strengths and Limitations

Our study has several strengths, including a comprehensive analysis of efficacy and safety outcomes, focusing specifically on IBATIs. Including multiple clinically relevant endpoints provides an exhaustive overview of the impact of these drugs on cholestatic pruritus and associated parameters. The low heterogeneity observed in the outcomes suggests the generalizability and robustness of our findings. Also, we included well-designed multicenter RCTs involving patients with both PFIC and Alagille syndrome. Finally, incorporating the most recent clinical trials, our meta-analysis presents an up-to-date synthesis of the available evidence on IBATIs. However, some limitations should be acknowledged. The number of studies included in the meta-analysis was relatively small, which may limit the generalizability of our findings.

Additionally, other parameters such as patients' reported quality of life, lipid profile, and change in height or weight scale could not be assessed due to limited data given in the included trials to pool in this regard. Similarly, the long-term efficacy and safety of IBATIs were not assessed due to the limited duration of the included studies. There may also be heterogeneity in the baseline characteristics of the included participants across studies, including variations in underlying liver diseases, disease severity, and liver enzymes. Additionally, we excluded the acquired cholestatic disorders to ensure a homogeneous study population. These conditions differ from inherited cholestatic disorders in etiology (autoimmune), age of onset, and severity, potentially introducing heterogeneity, focusing solely on inherited disorders aimed to strengthen the reliability of our findings.

IBATIs significantly reduced the itch intensity, serum bile acid, total bilirubin, and cholesterol with a tolerable safety profile in patients with inherited cholestatic liver disorders. Future research should focus on long-term outcomes, optimal dosage, combination therapies, and larger populations to further elucidate the role of IBATIs in managing inherited cholestatic liver diseases.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

M.A. conceived the idea and M.I. designed the research workflow. M.I. and M.A. searched the databases. M.E., M.S.T., A.M.M., and S.A. screened the retrieved records, extracted relevant data, assessed the quality of evidence, and M.I. resolved the conflicts. A.A.I. performed the analysis. M.I., A.B.E., S.K., and M.A. wrote the final manuscript. M.A. supervised the project. All authors have read and agreed to the final version of the manuscript.

DECLARATION OF COMPETING INTEREST

We declare that there are no conflicts of interest associated with this manuscript. We have no financial or personal relationships with any individuals or organizations that could inappropriately influence our work or its interpretation. All sources of financial support for this research are disclosed, and there are no potential conflicts of interest related to employment, consultancies, patents, or any other relevant affiliations. We affirm that this submission is free from any bias or undue influence, and the findings presented are solely based on the merits of the research.

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AVAILABILITY OF DATA AND MATERIALS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jceh.2024.102462.

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