Paediatric research sets new standards for therapy: a milestone for paediatric and adult cholestasis

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Abstract

Children with Alagille syndrome (ALGS) and progressive familial intrahepatic cholestasis (PFIC) experience debilitating pruritus, for which there have been few effective treatment options. The recent approval of the ileal bile acid transporter (IBAT) inhibitors maralixibat and odevixibat to manage cholestatic pruritus in these patients is a significant step forward in improving their quality of life. Emerging data suggest these drugs may also improve event-free survival, therefore potentially altering the typical disease course currently seen in these disorders. This review will discuss how advances in genetics have clarified the molecular basis of cholestatic disorders, which has facilitated the development of new therapeutic options that were only evaluated in children. We focus specifically on the newly licensed IBAT inhibitors for patients with ALGS and PFIC and explore the next steps for these drugs in relation to other paediatric and adult cholestatic disorders, recognising that they have the potential to benefit a wider group of patients with gastrointestinal and liver disease.

Key messages

- Understanding the genetic causes of cholestasis in children has been fundamental in facilitating the identification of genetic causes of cholestasis in adults.
- ALGS and PFIC are two genetically determined cholestatic disorders which present in childhood with severe cholestatic pruritus that is refractory to current drug therapies.
- Two new IBAT inhibitors (maralixibat and odevixibat for ALGS and PFIC respectively) have been evaluated in paediatric clinical trials, with significant improvements in pruritus, and have been specifically approved for use in children.
- IBAT inhibitors are currently being evaluated in trials for other paediatric and adult cholestatic disorders and may transform the management of cholestatic pruritus in both children and adults.
- The approvals of maralixibat and odevixibat are a significant milestone for both children and adults with cholestasis, demonstrating that research into therapies for rare paediatric diseases may benefit adult-onset diseases as well.

1. Introduction

Cholestatic disease in childhood is rare but serious. Causes are wide-ranging with biliary atresia being the most common. Genetic and inherited metabolic diseases are the next most common cause and include Alagille syndrome (ALGS), progressive familial intrahepatic cholestasis (PFIC), cystic fibrosis, alpha-1 antitrypsin deficiency, galactosemia, tyrosinemia type 1 and citrin deficiency among many other conditions. Other causes include congenital

and developmental anomalies, infection, immune-mediated disease, drugs and parenteral nutrition, hypopituitarism, biliary sludge, prematurity as well as diseases of currently unknown aetiology. Children with severe cholestatic disease experience multiple problems, including poor growth, fat soluble vitamin deficiency, metabolic bone disease, disfiguring xanthomas in certain cases, and debilitating pruritus. Management of these children has been challenging due to the limited number of licensed therapeutic options to control pruritus and delay the onset of liver failure. Eventually, children with chronic cholestasis who develop liver failure require liver transplantation, which comes with its own limitations and risks. Cholestatic disease remains the leading indication for liver transplantation in the paediatric age group.

Management of children with cholestatic disease is now changing. For the first time, new drugs which relieve cholestatic pruritus have been specifically approved for use in young children with ALGS and PFIC. Emerging data also suggest that these drugs may improve event-free survival and their benefits may thus extend beyond symptomatic alleviation of pruritus. It is notable that these drugs – specifically, maralixibat and odevixibat of the ileal bile acid transporter (IBAT) inhibitor class – have been approved for use in children with cholestatic disease before approval in adults. This sets a new standard for drug development in hepatology, reversing the traditional paradigm where drugs are evaluated and approved first in adults. In this review, we discuss how advances in molecular genetics led to an understanding of the pathophysiology of rare cholestatic diseases in children, which facilitated new therapeutic approaches that will benefit both children and adults.

2. The development of a molecular approach to cholestasis

Over the past three decades, understanding of the causes of childhood cholestasis has been transformed by advances in molecular genetics that led to delineation of the genetic basis of multiple cholestatic disorders with a once unclear aetiology (Table 1). For example, ALGS is now known to be caused primarily by pathogenic genetic variants in *JAG1* and *NOTCH2* (1, 2), which encode the Notch ligand Jagged1 and the Notch2 receptor respectively. The Notch pathway is a highly conserved signalling pathway involved in cell fate determination in various organ systems, including the biliary system. In ALGS, there is therefore abnormal biliary development and a paucity of intrahepatic bile ducts with onset of cholestatic disease in early infancy or childhood. PFIC is now recognised as a heterogenous group of disorders caused by biallelic (homozygous or compound heterozygous) pathogenic variants in various genes (e.g. *ATP8B1, ABCB11, ABCB4, TJP2, NR1H4, USP53, MYO5B)*, with the list of implicated genes continuing to expand with the increasing availability and use of sequencing technology (Table 1). While the exact causative gene may differ, the PFIC disorders involve failure of intrahepatic bile synthesis, secretion or flow, leading to chronic cholestasis that can progress to cirrhosis in childhood. The range of genetic cholestatic diseases has led to the use of gene panels as part of the diagnostic work-up of paediatric cholestasis and a reduction in the proportion of cases with an unknown cause.

Table 1: Genetic architecture of Alagille syndrome and the progressive familial intrahepatic cholestasis (PFIC) disorders

Disorder	Clinical features	Inheritance	Typical age of disease onset	Gene	Gene function	Reference

Alagille syndrome	**Hepatic:** cholestasis, pruritus, xanthomas (secondary to hypercholesterolemia) **Extrahepatic:** characteristic facial features, ocular abnormalities (e.g. posterior embryotoxon), congenital heart disease (e.g. peripheral pulmonary artery stenosis), skeletal abnormalities (e.g. butterfly vertebrae), renal disorders (e.g. renal dysplasia), noncardiac vascular lesions (e.g. intracranial aneurysms, aortic aneurysms), developmental delay	Autosomal dominant	Infancy or early childhood	*JAG1, NOTCH2*	*JAG1:* encodes the Jagged1 protein that acts as a ligand for receptors in the Notch signalling pathway *NOTCH2:* encodes the Notch2 receptor that is part of a highly conserved signalling pathway involved in cell fate determination	(1, 2)
PFIC type 1	**Hepatic:** low GGT cholestasis, jaundice, pruritus, hepatic steatosis **Extrahepatic:** secretory diarrhoea, short stature, sensorineural hearing loss, pancreatitis	Autosomal recessive	Early infancy	*ATP8B1*	Encodes a flippase that translocates aminophospholipids from the outer to the inner leaflet of the plasma membrane	(3)
BRIC type 1	Recurrent episodes of cholestatic jaundice and pruritus	Autosomal recessive	First episode typically in adolescence or young adulthood	*ATP8B1*	Encodes a flippase that translocates aminophospholipids from the outer to the inner leaflet of the plasma membrane	(3)
PFIC type 2 (may be referred to as BSEP deficiency)	Low GGT cholestasis, jaundice, pruritus, increased risk of hepatobiliary malignancies	Autosomal recessive	Early infancy	*ABCB11*	Encodes the BSEP that is required for transport of bile acids across the hepatocyte canalicular membrane	(4)
BRIC type 2	Recurrent episodes of cholestatic jaundice and pruritus	Autosomal recessive	First episode typically in adolescence or young adulthood	*ABCB11*	Encodes the bile salt export pump that is required for transport of bile acids across the hepatocyte canalicular membrane	(5)
PFIC type 3	Cholestasis with elevated GGT, pruritus (generally less severe than in PFIC types 1 and 2), jaundice, association with hepatobiliary malignancy	Autosomal recessive	Late infancy, early childhood or young adulthood	*ABCB4*	Encodes a floppase involved in biliary phospholipid secretion	(6)

PFIC type 4	**Hepatic:** low GGT cholestasis, jaundice, pruritus, association with hepatobiliary malignancy **Extrahepatic:** subdural haematomas and poorly characterised lung disease have been reported Note: a particular homozygous variant in *TJP2* has been found in some patients with familial hypercholanemia, which is characterised by fluctuating but generally high serum bile acid levels, pruritus without jaundice, as well as malabsorption of fat and fat-soluble vitamins	Autosomal recessive	Majority of cases in infancy, with some reported cases in childhood and late adolescence /early adulthood	*TJP2*	Encodes the zona occludens 2 protein involved in tight junction formation	(7, 8)
PFIC type 5	Low GGT cholestasis, early onset vitamin K-independent coagulopathy, elevated serum alpha-fetoprotein	Autosomal recessive	Early infancy	*NR1H4*	Encodes the farnesoid X receptor, a nuclear bile acid receptor that regulates BSEP expression	(9)
OSTα deficiency (may be referred to as PFIC type 6)	**Hepatic:** cholestasis, liver fibrosis **Extrahepatic:** congenital malabsorptive diarrhoea	Autosomal recessive	Childhood	*SLC51A*	Encodes the α subunit of the OSTα-OSTβ organic solute transporter which facilitates transport of bile acids across the basolateral membrane of enterocytes and hepatocytes	(10)
USP53-related cholestasis (may be referred to as PFIC type 7)	**Hepatic:** Low GGT cholestasis, jaundice and pruritus. May also present with a BRIC phenotype. **Extrahepatic:** sensorineural hearing loss	Autosomal recessive	Infancy, childhood or adolescence	*USP53*	Encodes a tight junction-associated protein that interacts with other tight junction proteins, including zona occludens 2	(11)
KIF12-related cholestasis (may be referred to as PFIC type 8)	**Hepatic:** cholestasis, jaundice, pruritus (in some cases) **Extrahepatic:** mild renal pelvic abnormalities have been reported	Autosomal recessive	Infancy, childhood or adolescence	*KIF12*	Encodes a microtubule-associated motor protein involved in intracellular trafficking and establishing normal cell polarity	(12)
ZFYVE19-related cholestasis (may be referred to	Cholestasis, jaundice, pruritus, congenital hepatic fibrosis	Autosomal recessive	Infancy or childhood	*ZFYVE19*	Encodes a protein involved in cytokinesis and thought to be involved in maintaining	(13)

as PFIC type 9)					normal ciliary function	
MYO5B-related cholestasis (may be referred to as PFIC type 10)	**Hepatic:** Low GGT cholestasis, jaundice, pruritus. May also present with a BRIC phenotype. **Extrahepatic:** Biallelic pathogenic variants in *MYO5B* are also associated with microvillus inclusion disease (a congenital diarrhoea); however patients with *MYO5B*-related cholestasis may or may not have concurrent intestinal disease.	Autosomal recessive	Infancy or early childhood	*MYO5B*	Encodes an actin-based motor protein involved in intracellular trafficking and plasma membrane localisation; may also help localise BSEP to the hepatocyte canalicular membrane	(14)
SEMA7A-related cholestasis (may be referred to as PFIC type 11)	Cholestasis with normal GGT, jaundice	Autosomal recessive	Infancy	*SEMA7A*	Encodes a membrane glycoprotein involved in integrin-mediated signalling. Loss of function may lead to reduced expression of canalicular membrane bile acid transporters	(15)
VPS33B-related cholestasis (may be referred to as PFIC type 12)	**Hepatic:** low GGT cholestasis, jaundice, pruritus **Extrahepatic:** skin desquamation over joints, dextroscoliosis and proteinuria have been reported. Represents an attenuated or incomplete phenotype of arthrogryposis, renal dysfunction and cholestasis (ARC) syndrome in which cholestasis is the predominant manifestation.	Autosomal recessive	Infancy of early childhood	*VPS33B*	Encodes a vacuolar sorting protein involved in intracellular pro tein transport and maintaining cell polarity	(16)

Abbreviations: GGT, gamma-glutamyl transferase; BRIC, benign recurrent intrahepatic cholestasis; BSEP, bile salt export pump. Note that this list includes all PFIC subtypes listed in the Online Mendelian Inheritance in Man catalogue as of June 2023 but is not an exhaustive list of genes implicated in monogenic paediatric inherited cholestatic disorders. Also note that clinical diagnostic testing may not be offered for all of these genes (e.g. SLC51A and SEMA7A).

The prognosis for patients with these rare diseases has changed dramatically over the past few decades, as liver transplantation is an effective treatment for children with acute and chronic liver failure who would otherwise die in childhood. However, liver transplantation is associated with lifelong risks of graft failure, rejection and biliary and vascular complications. Post-transplant immunosuppression confers risks of infection, malignancy, delayed growth and chronic kidney disease. Organ availability is a limiting factor, and paediatric liver transplantation is not available in certain regions of the world. Although outcomes post liver transplantation in children with ALGS have improved over time (17), the multi-system nature of the condition – particularly if severe cardiac, vascular or renal manifestations are present

– can affect liver transplant candidacy, compound the risks of major surgery or necessitate adjustments to standard management protocols (18-21). Therefore, if indeed IBAT inhibitors reduce the need for liver transplantation in these patients, it would be beneficial. Currently, patients with PFIC are not completely curable with liver transplantation. Recurrent disease post liver transplantation is an issue with PFIC type 1 (caused by pathogenic variants in *ATP8B1*) due to the development of graft steatohepatitis, persistent (and sometimes worsened) diarrhoea and variable catch-up growth (22). In addition, patients with PFIC type 2, who have pathogenic variants in the *ABCB11* gene encoding the bile salt export pump (BSEP), can develop a recurrent PFIC phenotype after transplantation. This is thought to be mediated by the development of anti-BSEP antibodies in patients with severe *ABCB11* variants that lead to absent BSEP in the native liver and a lack of tolerance to BSEP in the transplanted liver (23, 24). These limitations underscore the need for new therapeutic strategies which delay or prevent liver transplantation and are informed by a molecular understanding of cholestasis.

International collaborative studies enabling large-scale natural history and genotype-phenotype correlation in these rare diseases have been crucial to the development of new therapeutic strategies. The NAtural Course and Prognosis of PFIC and Effect of Biliary Diversion (NAPPED) consortium, which includes tertiary referral centres around the world, found that PFIC type 2 patients with more severe *ABCB11* variants had shorter native liver survival and a higher frequency of hepatocellular carcinoma compared to patients with less severe *ABCB11* variants (25). This prognostically important information can guide management decisions. Additionally, the Global ALagille Alliance (GALA) database includes patients from 29 different countries and has provided valuable real-world data that can serve as a comparator arm when evaluating new therapies (26). By pooling data from around the world, global databases provide an opportunity to study the effect of new therapies in rare diseases and promote inclusivity and fairer representation in research.

The impact of these new therapies will extend beyond the paediatric population. The identification of genes associated with severe paediatric cholestatic disease has shed light on the genetic contribution to cholestatic diseases affecting adults. For instance, homozygous variants in *ATP8B1* and *ABCB11*, the genes associated with PFIC types 1 and 2 respectively, are also associated with benign recurrent intrahepatic cholestasis (BRIC) types 1 and 2. BRIC is characterised by recurrent episodes of cholestasis but, by definition, does not progress to biliary cirrhosis. Heterozygous variants in *ABCB4*, the gene associated with PFIC type 3, have also been associated with low phospholipid-associated cholelithiasis (27-29). Both *ABCB11* and *ABCB4* variants have been reported in patients with drug-induced liver injury (30, 31), while heterozygous *ATP8B1*, *ABCB11* and *ABCB4* variants have been reported in patients with intrahepatic cholestasis of pregnancy (ICP) (32). Recognition of the shared genetic determinants of paediatric and adult cholestasis will lead to the identification of further genetic causes for cholestasis in adults, who could benefit from drugs targeting similar molecular pathways.

3. Treatment of pruritus, a significant unmet need in children with cholestasis

Historically, off-label prescribing has been common in paediatric practice, with frequent extrapolation of data from adult cohorts, partly because of the difficulties in performing

clinical trials in children. However, the need for high-quality medicines for children is increasingly important as children with once fatal conditions live longer with advances in care and develop new and unique clinical needs. For example, the cholestatic pruritus experienced by patients with ALGS and PFIC can be especially severe, sometimes to the point of being mutilating, and significantly impacts quality of life. Treatment of pruritus includes ursodeoxycholic acid, cholestyramine, antihistamines, rifampicin, sertraline, and opioid antagonists. Not only are these drugs not licensed to manage pruritus in these disorders but even when used in combination, they may fail to control this distressing symptom. Surgical interventions to interrupt the enterohepatic circulation and reduce serum bile acids include partial external biliary diversion (PEBD), partial internal biliary diversion (PIBD) and ileal exclusion (33). While these interventions may be effective in some patients, they are invasive, carry the risk of cholangitis (particularly in the case if PIBD) and may involve creation of an external stoma (in the case of PEBD) with its associated complications, including impact on young patients' body image and confidence. Moreover, from NAPPED data, only 54% of patients with PFIC who underwent surgical biliary diversion actually experienced a sustained improvement in pruritus (25). The use of other non-pharmacological interventions to control pruritus such as nasobiliary drainage, plasmapheresis and albumin dialysis using the molecular adsorbent recirculation system has been reported but is not common (34-36).

Intractable pruritus is a frequent indication for liver transplantation in ALGS and PFIC, even in the absence of significant fibrosis or progressive liver failure. In fact, intractable pruritus was listed as an indication for transplantation (either in isolation or in combination with other factors) in almost 50% of transplanted ALGS patients with a history of neonatal cholestasis (37). Paediatric patients with severe cholestatic disease thus represent a group with a high unmet clinical need.

4. The development of ileal bile acid transport (IBAT) inhibitors

The underlying pathogenesis of pruritus in cholestasis is not entirely clear but likely multifactorial. Bile acids and endogenous opioids are among the proposed responsible pruritogens; however, there is no clear correlation between the levels of these substances and the presence or severity of pruritus (38, 39). More recently, it has been suggested that lysophosphatidic acid and autotaxin may be responsible (40, 41). However, further research is needed to clarify the mechanism by which lysophosphatidic acid and autotaxin become upregulated in cholestatic disease and might subsequently trigger pruritus.

Despite uncertainty over the exact pathogenesis of cholestatic pruritus, trials of small molecule IBAT inhibitors in young patients with ALGS and PFIC have confirmed their ability to improve pruritus based on observer-reported pruritus assessment scores (42). This has been accompanied by clinically meaningful improvements in quality of life and family impact scores in treatment responders (43).

IBAT inhibitors work by interrupting the enterohepatic circulation of bile acids. This process refers to the biliary excretion of bile acids into the small intestine, followed by intestinal re-uptake of bile acids and return to the liver via the portal venous system. The IBAT (also known as the apical sodium-dependent bile acid transporter or ASBT) is located at the enterocyte brush border in the terminal ileum and is responsible for reabsorption of bile acids.

Pharmacological agents that inhibit the IBAT therefore lead to increased faecal bile acid excretion and lower levels of bile acids returning to the liver (Figure 1).

Both IBAT inhibitors recently licensed for use in children (maralixibat and odevixibat, Figure 2) are orally administered and minimally absorbed. Gastrointestinal side effects such as abdominal pain and diarrhoea are not unexpected based on their mechanism of action, due to the increased bile acid load delivered to the colon. Fat-soluble vitamin deficiency is also a possible concern. It is therefore recommended that levels of fat-soluble vitamins are checked prior to commencement of IBAT inhibitors and monitored during treatment. Increases in liver enzymes have been reported, although it is not clear whether this is related to drug treatment or fluctuation or progression of the underlying liver disease.

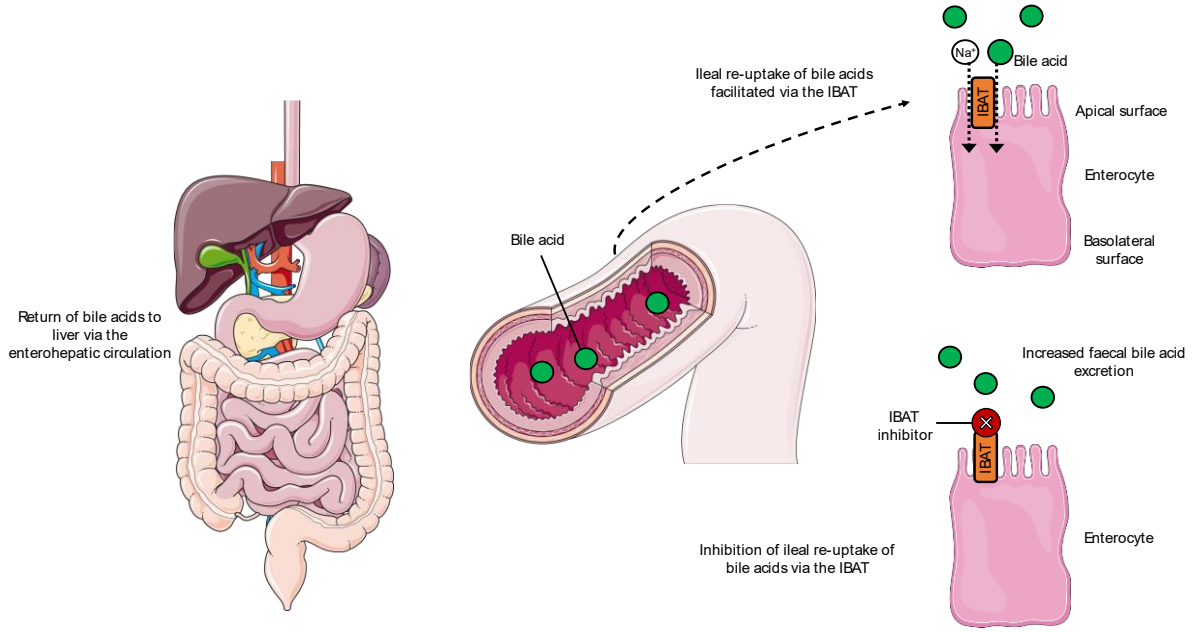
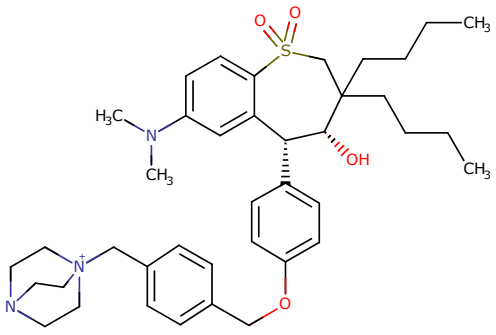


Figure 1. Mechanism of action of ileal bile acid transport (IBAT) inhibitors. The ileal re-uptake of bile acids at the apical surface of the enterocyte is coupled with sodium uptake. Normally, bile acids are re-absorbed in the ileum via the IBAT and returned to the liver via the portal venous system as part of the enterohepatic circulation of bile acids. IBAT inhibitors (e.g. maralixibat, odevixibat) interfere with the re-uptake of bile acids, thereby interrupting the enterohepatic circulation and increasing faecal bile acid excretion. Note: the figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

(A)



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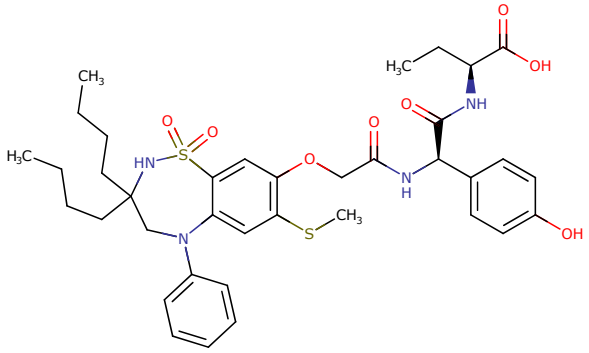

Figure 2. (A) The chemical structure of maralixibat ($C_{40}H_{56}N_3O_4S$) and **(B)** the chemical structure of odevixibat ($C_{37}H_{48}N_4O_8S_2$). Source: DrugBank Online (44). Note: images of chemical structures from DrugBank Online used under a Creative Commons Attribution-NonCommercial 4.0 international public license.

4.1. Maralixibat

Maralixibat was approved in September 2021 in the USA for the treatment of cholestatic pruritus in patients with ALGS who are over one year of age, and in December 2022 in the European Union (EU) for the treatment of cholestatic pruritus in patients with ALGS aged two months and older. The ICONIC trial, a placebo−controlled, double-blind phase 2b study with a randomised withdrawal period and subsequent open-label extension, was a key investigation (45). This was the first trial of an IBAT inhibitor in cholestatic disease to meet its primary efficacy endpoint, which was a statistically significant mean change in serum bile acid levels during the randomised drug withdrawal period in participants who had previously achieved a serum bile acid reduction of at least 50%. Statistically significant improvements in pruritus were also noted with maralixibat. Clinical xanthoma scores and height Z-scores were better in the patients followed up to week 204 as part of the long-term extension (n=15). Notably, the trial used higher doses of maralixibat than previous studies which failed to meet their efficacy endpoints. All ALGS patients in this study had *JAG1* pathogenic variants, although ALGS may be caused by *NOTCH2* pathogenic variants in approximately 2.5% of cases. However, despite possible differences in the frequency of cardiac, vertebral and facial manifestations between ALGS patients with *JAG1* versus *NOTCH2* variants (46), there is currently no known difference in the liver phenotype between these groups and no specific reason to suspect a differential response to maralixibat.

The drug was generally well-tolerated, with gastrointestinal disorders occurring in 15% of maralixibat-treated patients during the randomised drug withdrawal period (compared to 19% with placebo). During the open-label extension, ALT increases were noted in 17% of patients on maralixibat.

An analysis using real-world data from the GALA database as a control arm to assess outcomes over six years in 84 children treated with maralixibat found that maralixibat-treated patients had improved event-free survival (defined as surgical biliary diversion, hepatic decompensation, liver transplantation or death) compared to control patients from the GALA database (47). Longer-term follow-up is needed to understand how maralixibat changes the usual disease course in ALGS.

The phase 3 MARCH-PFIC trial (NCT03905330) studied maralixibat in patients with several types of PFIC. While formal data has not yet been published, publicly available topline data suggested a statistically significant decrease in pruritus in patients with PFIC type 2 (primary endpoint) as well as patients with a range of PFIC types (a secondary endpoint) (48). It is worth noting that in the open-label phase 2 INDIGO study, none of the PFIC type 2 patients with truncating *ABCB11* variants achieved a serum bile acid response while 37% of PFIC type 2 patients with non-truncating *ABCB11* variants did (49). Further data on how the PFIC type and specific genotype influence the response to IBAT inhibitors could pave the way for precision medicine approaches to cholestasis.

4.2. Odevixibat

Odevixibat was approved in July 2021 in the EU for the treatment of PFIC in patients aged 6 months and older, and in the USA for the treatment of pruritus in patients with PFIC aged 3 months and older. Results from the PEDFIC 1 and PEDFIC 2 trials were key to these approvals.

PEDFIC 1 was a randomised, double-blind, phase 3 study in patients with PFIC types 1 and 2 (50). It showed that patients treated with odevixibat experienced statistically significant improvements in observer-reported pruritus compared to placebo over 24 weeks of treatment. Additionally, the percentage of patients with a serum bile acid response was higher in patients treated with odevixibat (33% in the odevixibat group versus 0% in the placebo group). With respect to safety and tolerability, treatment-emergent diarrhoea or frequent bowel motions occurred in 31% of patients in the odevixibat group. Treatment-emergent increases in ALT occurred in 14%.

PEDFIC 2 (NCT03659916) is an open-label extension of PEDFIC 1 and includes patients with other types of PFIC. All patients in PEDFIC 2 received odevixibat. A pooled analysis of the data from both PEDFIC 1 and PEDFIC 2 trials at the interim data cut-off point (in July 2020) found that patients treated with odevixibat continued to experience improvements in pruritus and serum bile acid levels over time (51). In patients who received odevixibat in both PEDFIC 1 and PEDFIC 2, growth parameters had also improved at week 48 of treatment. Ad hoc supplementary analysis of this pooled data at a later data cut-off point in January 2022 found that a ≥70% decrease in serum bile acid levels or an absolute level of ≤70 µmol/L at 6 months of odevixibat treatment in PFIC patients was associated with native liver survival at 3 years (51). Long-term follow-up will clarify the durability of the treatment effects and just how long native liver survival might be extended, particularly as NAPPED data shows that only 32% of PFIC type 2 patients currently survive to adulthood (18 years) with their native liver (25).

Odevixibat has been evaluated in patients with ALGS in the phase 3 ASSERT trial (NCT04674761), where announced topline data showed that it met its primary endpoint of improvement in pruritus and secondary endpoint of a reduction in serum bile acids (52). There are currently no direct treatment comparisons between maralixibat and odevixibat in ALGS or PFIC; the aforementioned GALA (for ALGS) and NAPPED (for PFIC) databases may provide an opportunity to understand differences between these IBAT inhibitors in each condition in the future.

5. The next steps

The approvals of maralixibat and odevixibat represent a milestone in the treatment of cholestatic disease with significant benefits for quality of life in ALGS and PFIC respectively. Their licensing for cholestatic pruritus reverses the typical chronology where drugs are approved for use in adults before being adapted to the paediatric population. In the UK, the National Institute for Health and Care Excellence approved odevixibat in February 2022 for children with PFIC aged over 6 months (53), but are still considering whether maralixibat can be approved for ALGS (54).

Since the intrahepatic retention of bile acids may cause liver injury, the association of IBAT inhibitors with reductions in serum bile acid levels in subsets of patients may indicate a

longer-term protective effect on the liver through prevention of disease progression. Ultimately, sustained reductions in the bile acid load may offer a possibility of delaying the need for liver transplantation in many of these young patients, but longer-term studies are required to confirm this.

5.1. IBAT inhibitors in other paediatric and adult cholestatic disorders

Currently, maralixibat (in the phase 2b EMBARK trial, NCT04524390) and odevixibat (in the phase 3 BOLD trial, NCT04336722) are being evaluated in children with biliary atresia post-Kasai portoenterostomy. If they prove effective in delaying transplantation in this progressive liver disease, it will be of significant benefit to these children (55).

It is worth noting that the PEDFIC 2 study of odevixibat included a small number of PFIC patients over 18 years of age. Clinical trials of maralixibat also included patients with ALGS over 16 years of age and early presented data from 14 patients (11 started maralixibat before 16 years of age and three started maralixibat after 16 years of age) suggest that maralixibat is safe and well-tolerated in this cohort (56); moreover, improvements in pruritus were maintained in patients transitioning to early adulthood (56). In adults, safety in pregnancy and breastfeeding are important considerations. While the safety of maralixibat in these contexts has not been established, no adverse effects have been observed in animal studies and the low systemic absorption of the drug is not expected to lead to significant foetal exposure during pregnancy (57, 58). Odevixibat during pregnancy may cause foetal cardiovascular malformations based on animal data (59, 60). The low systemic absorption of maralixibat and odevixibat at recommended doses in the parent is not expected to result in significant exposure to the breastfeeding infant; however, there are no data on whether these drugs are present in human milk or not. Increasing data and experience with the use of IBAT inhibitors in adult patients with ALGS and PFIC will be available in the future.

IBAT inhibitors are currently in clinical development for the treatment of cholestatic diseases affecting adults, such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), along with other novel drugs (Supplementary Table 1). From questionnaire studies, up to 70–80% of patients with PBC experience pruritus at some point in their disease course (61, 62), while 38% of patients with PSC report pruritus (63). However, pruritus in PBC and PSC can be difficult to control with current drugs. While ursodeoxycholic acid and obeticholic acid are licensed for use in PBC, they have a limited effect on pruritus and in fact, obeticholic acid may induce or exacerbate pruritus in PBC. Cholestyramine is licensed for pruritus in partial biliary obstruction and PBC but may fail to provide adequate relief in patients with moderate to severe pruritus. Other drugs used for pruritus in these patients are off-label and of variable benefit (64).

There may be a potential role for IBAT inhibitors in BRIC and ICP as pruritus is a major feature in these conditions and patients can have pathogenic variants in the same genes that are affected in PFIC. Clinical trials in ICP face particular challenges, however. The phase 2 OHANA trial (NCT04718961) evaluating the IBAT inhibitor volixibat in adult patients with ICP was terminated due to enrolment feasibility in the setting of high-risk pregnancy.

IBAT inhibitors may also have a role in non-cholestatic liver diseases. For example, they improve metabolic and histological parameters as well as gut microbiota dysbiosis in mice models of metabolic dysfunction-associated steatotic liver disease and metabolic dysfunction-associated steatohepatitis (MASH) (65, 66); in one mouse model of MASH, fewer liver tumours were observed in mice treated with an IBAT inhibitor (67). However, a phase 2 trial of volixibat in MASH was terminated due to lack of efficacy at the 24-week interim analysis despite evidence of target engagement (68). A3907 is an oral systemic ASBT inhibitor that inhibits ASBT in the intestine, kidneys (preventing bile acid re-uptake from urine) and liver (preventing re-uptake from bile) (69). A3907 also improved biochemical and histological markers of MASH in a mouse model (70). It has entered phase 2 clinical study in adults with PSC (NCT05642468, see Supplementary Table 1) but not other liver diseases at present. The role of systemic ASBT inhibitors in both cholestatic and non-cholestatic liver disease remains to be proven and their safety, tolerability and efficacy compared to luminally restricted IBAT inhibitors need clarification.

Beyond liver disease, elobixibat (the first-in-class IBAT inhibitor) has been approved in Japan and Thailand for the treatment of chronic constipation as the increased bile acid load delivered to the colon increases colonic secretion of water and electrolytes and colonic motility.

Supplementary Table 1: Other drugs being studied for cholestasis and/or cholestatic pruritus.

Agent	Condition	Age range	ClinicalTrials.gov identifier
Minimally absorbed IBAT (or ASBT) inhibitors			
Linerixibat	PBC	18 years to 80 years	NCT04167358
Linerixibat	PBC	18 years to 80 years	NCT04950127
Linerixibat	PBC	18 years to 80 years	NCT02966834
Volixibat	PBC	18 years and older	NCT05050136
Volixibat	PSC	16 years and older	NCT04663308
Systemic ASBT inhibitor			
A3907	PSC	18 years to 65 years	NCT05642468
Fibrates (PPAR-α agonists)			
Fenofibrate	Chronic cholestatic liver disease	6 months to 18 years	NCT03586674
Fenofibrate	PBC	18 years to 75 years	NCT05749822
Fenofibrate	PBC	18 years to 70 years	NCT02823353
Fenofibrate	PBC	18 years to 70 years	NCT02823366
Fenofibrate with UDCA	PBC	18 years to 75 years	NCT05751967
Bezafibrate	PSC	18 years to 75 years	NCT04309773
Bezafibrate	PBC	18 years to 99 years	NCT04514965
Fibrates in combination with obeticholic acid			
Bezafibrate alone and with obeticholic acid	PBC	18 years and older	NCT05239468
Bezafibrate with obeticholic acid	PBC	18 years and older	NCT04594694
PPAR-γ agonists and dual PPAR-α/γ agonists			

Seladelpar	PBC	18 years to 75 years	NCT04620733
Seladelpar	PBC	18 years to 75 years	NCT03602560
Seladelpar	PBC	18 years to 80 years	NCT04950764
Seladelpar	PBC	18 years to 75 years	NCT03301506
Seladelpar	PBC	18 years to 75 years	NCT02955602
Saroglitazar magnesium	PBC	18 years to 75 years	NCT05133336
Saroglitazar magnesium	PBC	18 years to 75 years	NCT03112681
Elafibranor	PBC	18 years to 75 years	NCT03124108
Elafibranor	PBC	18 years to 75 years	NCT04526665
Farnesoid X receptor agonists (apart from obeticholic acid)			
CS0159 (linafexor)	Healthy subjects	18 years to 55 years	NCT05624294
Tropifexor	PBC	18 years and older	NCT02516605
ASC42	PBC	18 years to 75 years	NCT05190523
EDP-305	PBC	18 years to 75 years	NCT03394924
MRGPRX4 antagonists			
EP547	Cholestatic or uremic pruritus	18 years to 80 years	NCT04510090
EP547	PBC or PSC	18 years to 80 years	NCT05525520
NADPH oxidase inhibitors			
Setanaxib	PBC	18 years and older	NCT05014672
Setanaxib	PBC	18 years to 80 years	NCT03226067
Other agents			
Probiotics (lacto-B)	Chronic cholestasis	29 days to 215 months	NCT04787419
Berberine ursodeoxycholate	PBC	8 years to 75 years	NCT04604652
CNP-104 (nanoparticle-encapsulated PDC-E2 peptide)	PBC	18 years to 75 years	NCT05104853
Emtricitabine/tenofovir disoproxil and raltegravir	PBC	18 years and older	NCT03954327
Nalfurafine hydrochloride	PBC	18 years and older	NCT02659696
Sublimated mare milk	PBC	18 years to 75 years	NCT03665519
OP-724 (CREB-binding protein/β-catenin inhibitor)	PBC	20 years to 74 years	NCT04047160

Abbreviations: IBAT, ileal bile acid transport inhibitor; ASBT, apical sodium-dependent bile acid transporter; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid; PPAR, peroxisome proliferator-activated receptors; MRGPRX4, Mas-related G protein-coupled receptor X4; PDC-E2, E2 component of the pyruvate dehydrogenase complex; CREB, cyclic AMP response element-binding protein.

Search strategy for Table 1: We searched ClinicalTrials.gov from database inception to March 2023 for interventional studies where 'cholestasis' was the condition or disease of interest. We included studies that were recruiting, active but not recruiting, enrolling by invitation or completed in the last 5 years. We excluded trials that focused on parenteral nutrition-associated cholestasis or on symptoms apart from pruritus (e.g. fatigue, hypercholesterolaemia, reduced bone density), trials where the intervention was an immunosuppressive agent, and trials for PBC where the sole intervention was obeticholic acid (as obeticholic acid is licensed as a second-line agent in PBC and can potentially exacerbate pruritus). To identify trials of systemic ASBT inhibitors, we then searched ClinicalTrials.gov for interventional studies where 'ASBT inhibitor', 'IBAT inhibitor', 'apical sodium-dependent bile acid transporter inhibitor' or 'ileal bile acid transporter inhibitor' was the intervention/treatment of interest; this led to inclusion of one trial of a systemic ASBT inhibitor in the table for completion.

5.2. Non-responders to IBAT inhibitors and the potential of other novel therapies

Although transformative in certain patients, not all patients with ALGS and PFIC respond to this treatment. In PFIC, this may be because the underlying pathogenic variant is truncating or non-truncating. Additionally, PFIC is a heterogenous category of disorders and there are few data supporting IBAT inhibitor use in rarer PFIC types. Long-term studies are required to clarify differences in response.

In addition to small molecule IBAT inhibitors, novel nucleic acid-based therapies are being explored for genetically determined liver disease. Crigler-Najjar syndrome, an autosomal recessively inherited disorder caused by pathogenic variants in the *UGT1A1* gene, can lead to significant unconjugated hyperbilirubinaemia and dependence on phototherapy to reduce the risk of irreversible neurological dysfunction and death. GNT0003, an adeno-associated virus (AAV) vector carrying the *UGT1A1* transgene, has entered early-phase clinical study to evaluate safety and efficacy in patients with severe Crigler-Najjar syndrome (NCT03466463). Recently published data showed that three adult patients treated with the higher dose of GNT0003 experienced a significant reduction in serum bilirubin, enabling cessation of phototherapy from week 16 after vector administration up to at least week 78 after vector administration (71). AAV-based gene therapy and lipid nanoparticle-encapsulated messenger RNA therapy have also been explored in mouse models of PFIC type 3, where they have improved clinical and histological markers of disease (72-74). Mirum Pharmaceuticals, which developed maralixibat, will lead clinical development and commercialisation of two gene therapy programmes for PFIC initiated by Vivet Therapeutics (namely VTX-802 and VTX-803 for PFIC2 and PFIC3, respectively) (75).

6. Conclusion

The IBAT inhibitors have ushered in a new era in the management of paediatric cholestasis, with the prospect of improving pruritus, quality of life and transplant-free survival in patients with ALGS and PFIC. The initial clinical trials of these drugs highlight the importance of evaluating new therapies in rare paediatric diseases, not only so children have access to suitable drugs but also to pave the way for new therapies for adult conditions. Long-term follow-up is needed to understand how IBAT inhibitors will change the clinical trajectories currently seen in ALGS and PFIC, particularly in relation to the timing and indication for liver transplantation. Paediatric research has thus set a new standard for the treatment of cholestatic disease in both children and adults.

Search strategy

References for this Review were identified through searches of PubMed and Google Scholar with search terms such as “Alagille syndrome”, “progressive familial intrahepatic cholestasis OR PFIC”, “maralixibat”, “odevixibat”, “ileal bile acid transport inhibitor OR IBAT inhibitor OR apical sodium-dependent bile acid transporter inhibitor OR ASBT inhibitor” from database inception until June 2023. References were also identified through searches of the reference lists of included articles and through searches of the authors’ own files. Conference presentations, topline data from clinical studies and product label information are referenced where necessary to provide the most up-to-date developments in this rapidly moving field. Only references in English were reviewed. The final reference list was determined on the basis of originality, quality and relevance to the broad scope of this Review.

Authors' contributions

DK conceived of the review. RJ wrote the first draft with further review, editing and finalisation by RJ, EM and DK. All authors read and approved the final version for submission.

Conflict of interest statement

The authors declare no conflict of interest.

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Ethics committee approval

Not applicable.

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