Paediatric research sets new standards for therapy in paediatric and adult cholestasis

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Children with Alagille syndrome and progressive familial intrahepatic cholestasis (PFIC) experience debilitating pruritus, for which there have been few effective treatment options. In the past 2 years, the ileal bile acid transporter (IBAT) inhibitors maralixibat and odevixibat have been approved for the management of cholestatic pruritus in these individuals, representing an important step forward in improving their quality of life. Emerging data suggest these drugs might also improve event-free survival, therefore potentially altering the typical disease course currently seen in these disorders. This Review will discuss how genetic advances have clarified the molecular basis of cholestatic disorders, facilitating the development of new therapeutic options that have only been evaluated in children. We focus specifically on the newly licensed IBAT inhibitors for patients with Alagille syndrome 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.

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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 causes and include Alagille syndrome, 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, and diseases with unknown causes. Children with severe cholestatic disease experience multiple problems, including poor growth, fat-soluble vitamin deficiency, metabolic bone disease, disfiguring xanthomas in some cases, and debilitating pruritus. Management of these children has been challenging due to the small 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 that relieve cholestatic pruritus have been approved for use in young children with Alagille syndrome and PFIC, in some instances in children as young as 2 months. Emerging data also suggest that these drugs might improve event-free survival, and their benefits might therefore extend beyond the symptomatic alleviation of pruritus. These drugs—specifically, maralixibat and odevixibat of the ileal bile acid transporter (IBAT) inhibitor class—were approved for use in children with cholestatic disease before their specific approval for use in adults. This approval sets a new standard for drug development in hepatology, reversing the traditional paradigm in which 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.

Development of a molecular approach to cholestasis

Over the past three decades, our understanding of the causes of childhood cholestasis has been transformed by advances in molecular genetics that led to the delineation of the genetic basis of multiple cholestatic disorders that once had unclear causes (table). For example, Alagille syndrome is now known to be caused primarily by pathogenic genetic variants in *JAG1* and *NOTCH2*,[1,2]

Key messages

- Understanding the genetic causes of cholestasis in children has been fundamental in facilitating the identification of genetic causes of cholestasis in adults
- Alagille syndrome and progressive familial intrahepatic cholestasis are two genetically determined cholestatic disorders that present in childhood with severe cholestatic pruritus, which is refractory to current drug therapies
- Two new ileal bile acid transporter (IBAT) inhibitors (maralixibat for Alagille syndrome and odevixibat for progressive familial intrahepatic cholestasis) have been evaluated in paediatric clinical trials, with substantial improvements in pruritus, and have been approved for use in children
- IBAT inhibitors are being evaluated in trials for other paediatric and adult cholestatic disorders and could transform the management of cholestatic pruritus in both children and adults
- The approval of maralixibat and odevixibat are an important milestone for both children and adults with cholestasis, demonstrating that research into therapies for rare paediatric diseases can also benefit people with adult-onset diseases

	Clinical features	Inheritance	Typical age of disease onset	Gene and gene function
Alagille syndrome[1,2]	Hepatic: cholestasis, pruritus, and xanthomas (secondary to hypercholesterolemia); and extrahepatic: characteristic facial features, ocular abnormalities (eg, posterior embryotoxon), congenital heart disease (eg, peripheral pulmonary artery stenosis), skeletal abnormalities (eg, butterfly vertebrae), renal disorders (eg, renal dysplasia), noncardiac vascular lesions (eg, intracranial aneurysms and aortic aneurysms), and developmental delay	Autosomal dominant	Infancy* or childhood	*JAG1* encodes the Jagged1 protein, which acts as a ligand for receptors in the Notch signalling pathway; *NOTCH2* encodes the Notch2 receptor, which is part of a highly conserved signalling pathway involved in cell-cell signalling and cell fate determination
PFIC type 1 (might be referred to as FIC1 or ATP8B1 deficiency)[3]	Hepatic: low GGT cholestasis, jaundice, pruritus, and hepatic steatosis; and extrahepatic: secretory diarrhoea, short stature, sensorineural hearing loss, and pancreatitis	Autosomal recessive	Early infancy	*ATP8B1* encodes a flippase, which translocates aminophospholipids from the outer to the inner leaflet of the plasma membrane
BRIC type 1[3]	Recurrent episodes of cholestatic jaundice and pruritus	Autosomal recessive	First episode typically in adolescence and young adulthood	*ATP8B1* encodes a flippase, which translocates aminophospholipids from the outer to the inner leaflet of the plasma membrane
PFIC type 2 (might be referred to as BSEP deficiency)[4]	Low GGT cholestasis, jaundice, pruritus, and increased risk of hepatobiliary malignancy	Autosomal recessive	Early infancy	*ABCB11* encodes the BSEP required for transport of bile acids across the hepatocyte canalicular membrane
BRIC type 2[5]	Recurrent episodes of cholestatic jaundice and pruritus	Autosomal recessive	First episode typically in adolescence or young adulthood	*ABCB11* encodes the BSEP required for transport of bile acids across the hepatocyte canalicular membrane
PFIC type 3 (might be referred to as MDR3 deficiency)[6]	Cholestasis with elevated GGT, pruritus (generally less severe than in PFIC types 1 and 2), jaundice, and association with hepatobiliary malignancy	Autosomal recessive	Late infancy, childhood, or young adulthood	*ABCB4* encodes a flippase involved in biliary phospholipid secretion
TJP2 deficiency (might be referred to as PFIC type 4)[7,8]	Hepatic: low GGT cholestasis, jaundice, pruritus, and association with hepatobiliary malignancy; and extrahepatic: subdural haematomas and poorly characterised lung disease	Autosomal recessive	Most cases in infancy and childhood, with some reported cases in adolescence or young adulthood	*TJP2* encodes zona occludens 2 protein, which is involved in tight junction formation†
FXR deficiency (might be referred to as PFIC type 5)[9]	Low GGT cholestasis, early onset vitamin K-independent coagulopathy, and elevated serum alpha-fetoprotein	Autosomal recessive	Early infancy	*NR1H4* encodes the farnesoid X receptor, a nuclear bile acid receptor that regulates BSEP expression
OSTα deficiency (might be referred to as PFIC type 6)[10]	Hepatic: cholestasis with elevated GGT and liver fibrosis; and extrahepatic: congenital malabsorptive diarrhoea	Autosomal recessive	Infancy or childhood	*SLC51A* encodes the α subunit of the OSTα-OSTβ organic solute transporter, which facilitates transport of bile acids across the basolateral membrane enterocytes, hepatocytes, and cholangiocytes
USP53 deficiency (might be referred to as PFIC type 7)[11]	Hepatic: low GGT cholestasis, jaundice, and pruritus (can also present with a BRIC phenotype); and extrahepatic: hearing loss and hypocalcaemia	Autosomal recessive	Infancy to adolescence	*USP53* encodes a tight junction-associated protein that interacts with other tight junction proteins, including zona occludens 2
KIF12 deficiency (might be referred to as PFIC type 8)[12]	Hepatic: cholestasis with elevated GGT, jaundice, and pruritus (in some cases); and extrahepatic: mild renal pelvis abnormalities	Autosomal recessive	Infancy to adolescence	*KIF12* encodes a microtubule-associated motor protein involved in intracellular trafficking and establishing typical cell polarity
ZFYVE19 deficiency (might be referred to as PFIC type 9)[13]	Cholestasis with elevated GGT, jaundice, pruritus, congenital hepatic fibrosis, and sclerosing cholangiopathy (can also be considered a ciliopathy)	Autosomal recessive	Infancy or childhood	*ZFYVE19* encodes a protein involved in cytokinesis (and is thought to be involved in maintaining typical ciliary function)
MYO5B deficiency (might be referred to as PFIC type 10)[14]	Hepatic: low GGT cholestasis, jaundice, and pruritus (can also present with a BRIC phenotype); and extrahepatic: biallelic pathogenic variants in *MYO5B* are also associated with microvillus inclusion disease (a congenital diarrhoea); however, individuals with *MYO5B*-related cholestasis might or might not have concurrent intestinal disease	Autosomal recessive	Infancy or childhood	*MYO5B* encodes an actin-based motor protein involved in intracellular trafficking and plasma membrane localisation and might also help localise BSEP to the hepatocyte canalicular membrane
SEMA7A-related liver disease (might be referred to as PFIC type 11)[15]	Cholestasis with normal GGT and jaundice	Autosomal recessive	Infancy	*SEMA7A* encodes a membrane glycoprotein involved in integrin-mediated signalling; pathogenic variants might lead to reduced expression of canalicular membrane bile acid transporters
VPS33B-related liver disease (might be referred to as PFIC type 12)[16]	Hepatic: low GGT cholestasis, jaundice, and pruritus; extrahepatic: skin desquamation over joints, dextroscoliosis, and proteinuria; represents an attenuated or incomplete phenotype of arthrogryposis, renal dysfunction, and cholestasis syndrome in which cholestasis is the predominant manifestation	Autosomal recessive	Infancy or childhood	*VPS33B* encodes a vacuolar sorting protein involved in intracellular protein transport and maintaining cell polarity

This list includes all PFIC subtypes 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. The characterisation and nomenclature of the PFIC disorders is constantly evolving and subject to discussion. Clinical diagnostic testing might not be offered for all these genes (eg, *SLC51A* and *SEMA7A*) due to limited evidence. ATP8B1=ATPase, class I, type 8B, member 1. BRIC=benign recurrent intrahepatic cholestasis. BSEP=bile salt export pump. FIC1=Familial intrahepatic cholestasis 1. FXR=Farnesoid X receptor. GGT=gamma-glutamyltransferase. KIF12=Kinesin family member 12. MDR3=Multidrug resistance protein 3. MYO5B=Myosin VB. OSTα=Organic solute transporter-α. PFIC=progressive familial intrahepatic cholestasis. TJP2=Tight junction protein 2. USP53=Ubiquitin specific peptidase 53. ZFYVE19=Zinc finger FYVE-type containing 19. *Defined as younger than 12 months. †One homozygous variant in *TJP2* has been found in some individuals with familial hypercholanemia, which is characterised by fluctuating but generally high serum bile acid concentrations, pruritus without jaundice, and malabsorption of fat and fat-soluble vitamins.

Table: **Genetic architecture of Alagille syndrome and the PFIC disorders**

which encode the Notch ligand Jagged1 and the Notch2 receptor, respectively. The Notch pathway is a highly conserved signalling pathway involved in cell-cell signalling and cell fate determination in various organ systems, including the biliary system. In Alagille syndrome, abnormal biliary development and a paucity of intrahepatic bile ducts therefore lead to the 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 (eg, *ATP8B1*, *ABCB11*, *ABCB4*, *TJP2*, *NR1H4*, *USP53*, and *MYO5B*), with the list of implicated genes continuing to expand with increasing availability and use of sequencing technology (table). Although the exact causative gene might differ between PFIC disorders, they all involve the 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 investigation of paediatric cholestasis and a subsequent reduction in the proportion of cases with an unknown cause.

The prognosis for patients with these rare diseases has changed substantially 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 some regions of the world. Although outcomes after liver transplantation in children with Alagille syndrome have improved over time,[17] the multisystem 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, IBAT inhibitors would be beneficial if they do indeed reduce the need for liver transplantation in these individuals. PFIC is not completely curable with liver transplantation. Recurrent disease after 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 phenotypic recurrence is thought to be mediated by the development of anti-BSEP antibodies in some patients with severe *ABCB11* variants that lead to absent BSEP in the native liver and immunological intolerance when exposed to BSEP in the transplanted liver.[23,24] These limitations underscore the need for new therapeutic strategies to delay or prevent liver transplantation that are informed by a molecular understanding of cholestasis.

International collaborations enabling large-scale natural history and genotype–phenotype correlation studies 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 48 tertiary referral centres around the world (in both high-income and low-income countries), found that individuals with PFIC type 2 and more severe *ABCB11* variants had shorter native liver survival and a higher frequency of hepatocellular carcinoma compared with individuals with less severe *ABCB11* variants.[25] This prognostically important information can guide management decisions. Additionally, the Global Alagille Alliance (GALA) database includes patients from 32 countries (including high-income and low-income countries) and has provided valuable real-world data that can serve as a comparator group when evaluating new therapies.[26] By pooling data, 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 people with drug-induced liver injury,[30,31] whereas heterozygous *ATP8B1*, *ABCB11*, and *ABCB4* variants have been reported in people with intrahepatic cholestasis of pregnancy.[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.

Treatment of pruritus—a crucial unmet need

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 involving children. However, the need for high-quality medicines for children is increasingly important as children with once-fatal conditions live longer due to advances in care and

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develop new and unique clinical needs. For example, the cholestatic pruritus experienced by individuals with Alagille syndrome and PFIC can be especially severe to the extent of being mutilating, thereby severely affecting 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 do not always control this distressing symptom. Surgical interventions to interrupt enterohepatic circulation and reduce serum bile acids include partial external biliary diversion, partial internal biliary diversion, and ileal exclusion.[33] Although these interventions can be effective in some individuals, they are invasive, carry the risk of cholangitis (particularly in the case of partial internal biliary diversion), and can necessitate an external stoma an external stoma (in the case of partial external biliary diversion) with its associated complications, including negative effects on young people's body image and confidence. Moreover, from NAPPED data, only 54% of individuals with PFIC who had surgical biliary diversion experienced a sustained improvement in their pruritus.[25] The use of other non-pharmacological interventions to control pruritus, such as nasobiliary drainage, plasmapheresis, and albumin dialysis through the molecular adsorbent recirculation system, has been reported but is not common.[34–36]

Intractable pruritus is a frequent indication for liver transplantation in people with Alagille syndrome and PFIC, even in the absence of substantial 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 individuals with Alagille syndrome and a history of neonatal cholestasis.[26] Paediatric patients with severe cholestatic disease thus represent a group with a high unmet clinical need.

Development of IBAT inhibitors

The underlying pathogenesis of pruritus in cholestasis is not entirely clear but is probably multifactorial. Bile acids and endogenous opioids are among the proposed responsible pruritogens; however, there is no clear correlation between concentrations of these substances and the presence or severity of pruritus.[37,38] In the past 10 years, lysophosphatidic acid and autotaxin have been suggested as triggers of pruritis.[39,40] However, further research is needed to clarify the mechanism through which lysophosphatidic acid and autotaxin become upregulated in cholestatic disease and potentially subsequently trigger pruritus.

Despite uncertainty over the exact pathogenesis of cholestatic pruritus, trials of small-molecule IBAT inhibitors in children with Alagille syndrome and PFIC have confirmed their ability to improve pruritus on the

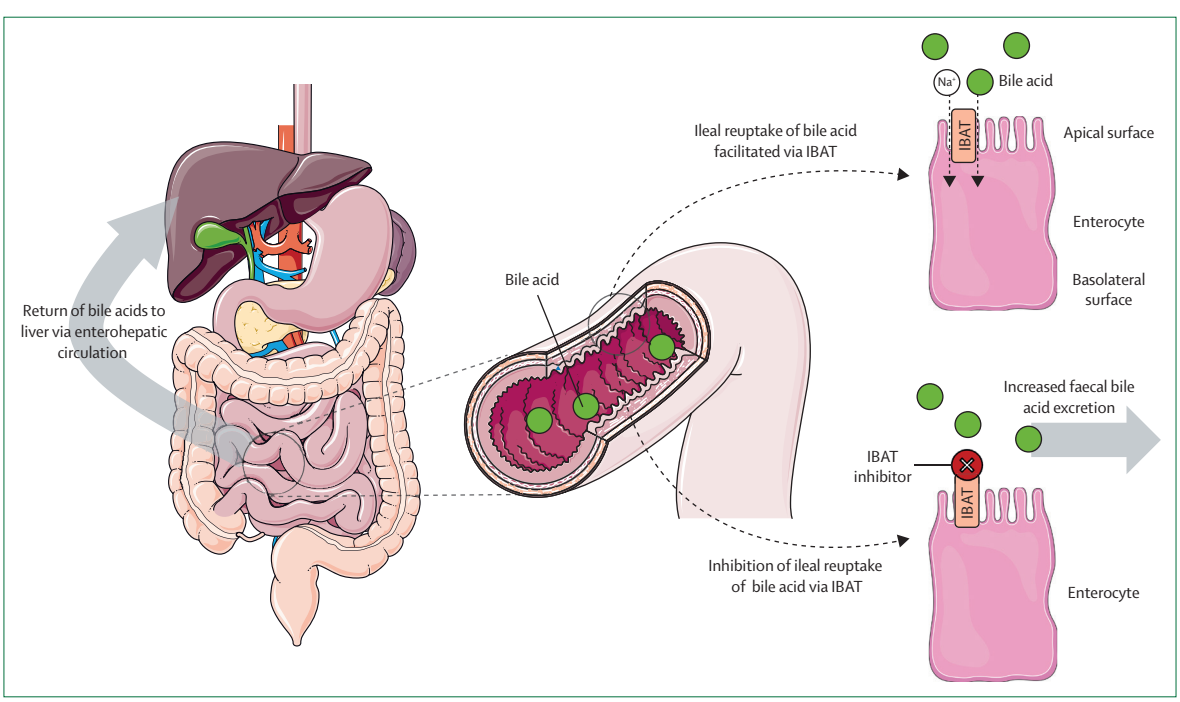

Figure 1: **Mechanism of action of IBAT inhibitors**
The ileal reuptake of bile acids at the apical surface of the enterocyte is coupled with sodium uptake. Normally, bile acids are reabsorbed in the ileum via the IBAT and returned to the liver via the portal venous system as part of the enterohepatic circulation of bile acids. IBAT inhibitors (eg, maralixibat and odevixibat) interfere with the reuptake of bile acids, thereby interrupting enterohepatic circulation and increasing faecal bile acid excretion. The figure was partly generated with Servier Medical Art, licensed under a CC BY 3.0 unported license. IBAT=ileal bile acid transporter.

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basis of observer-reported pruritus assessment scores.[41] This improvement in pruritus assessment scores has been accompanied by clinically meaningful improvements in quality of life and family impact scores among treatment responders.[42]

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 the intestinal reuptake of bile acids and their return to the liver via the portal venous system. The IBAT (also known as the apical sodium-dependent bile acid transporter [ASBT]) is located at the enterocyte brush border in the terminal ileum and is responsible for the reabsorption of bile acids. Pharmacological IBAT inhibitors therefore increase faecal bile acid excretion and lower levels of bile acids returning to the liver (figure 1).

Two IBAT inhibitors 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 given their mechanism of action, as increased bile acid is delivered to the colon. Fat-soluble vitamin deficiency is also a possible concern. Patients' concentrations of fat-soluble vitamins should therefore be checked before starting treatment with IBAT inhibitors and then be monitored during treatment. Increases in liver enzymes have been reported, although whether related to drug treatment, or fluctuations in or progression of the underlying liver disease is unclear.

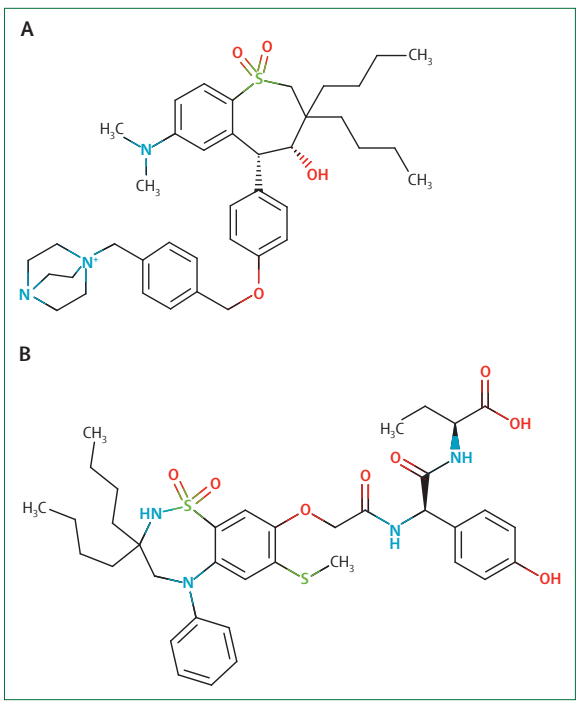

Figure 2: **Chemical structures of IBAT inhibitors**
The chemical structure of (A) maralixibat ($C_{40}H_{56}N_2O_4S$) and (B) odevixibat ($C_{37}H_{48}N_4O_8S_2$). The structures were obtained from DrugBank Online[43] and published under a CC BY-NC 4.0 international public license. IBAT=ileal bile acid transporter.

Maralixibat

Maralixibat was approved in September, 2021, in the USA for the treatment of cholestatic pruritus in individuals with Alagille syndrome older than 1 year, and in December, 2022, in the EU for the treatment of cholestatic pruritus in individuals with Alagille syndrome aged 2 months and older.

The ICONIC trial,[44] a placebo-controlled, double-blind phase 2b study of 31 patients with Alagille syndrome with a randomised withdrawal period and subsequent open-label extension, was a key investigation. ICONIC 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 participants followed up to week 204 as part of the long-term extension (n=15; 48%). Notably, ICONIC tested higher doses of maralixibat than previous studies that did not meet efficacy endpoints. All participants with Alagille syndrome in the ICONIC trial had *JAG1* pathogenic variants, although Alagille syndrome is caused by *NOTCH2* pathogenic variants in approximately 2·5% of cases. Despite possible differences in the frequency of cardiac, vertebral, and facial manifestations between individuals with Alagille syndrome with *JAG1* versus *NOTCH2* variants,[45] 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 patients treated with maralixibat during the randomised drug withdrawal period (compared with 19% with the placebo). During the open-label extension, alanine transaminase increases were noted in 17% of participants on maralixibat.

In an analysis of 6-year outcomes among 84 individuals given maralixibat (with control data from the GALA database), maralixibat was associated with improved event-free survival, where an event was defined as surgical biliary diversion, hepatic decompensation, liver transplantation, or death.[46] Longer term follow-up is needed to understand how maralixibat changes the usual disease course in Alagille syndrome.

The phase 3 MARCH-PFIC trial (NCT03905330) studied maralixibat in individuals with several types of PFIC. Although the trial data are unpublished, publicly available topline data suggest a statistically significant decrease in pruritus in individuals with PFIC type 2 (primary endpoint) and individuals with a range of PFIC types (a secondary endpoint).[47] In the open-label phase 2

INDIGO study of maralixibat,[48] none of the participants with PFIC type 2 and truncating *ABCB11* variants achieved a serum bile acid response, whereas 37% of participants with PFIC type 2 and non-truncating *ABCB11* variants did. Further data on how PFIC type and specific genotype influence responses to IBAT inhibitors could facilitate precision medicine approaches to cholestasis.

Odevixibat

Odevixibat was approved in July, 2021, in the EU for the treatment of PFIC in individuals aged 6 months and older, and in the USA for the treatment of pruritus in individuals with PFIC aged 3 months and older. Results from the PEDFIC 1[49] and PEDFIC 2 (NCT03659916) trials were key to these approvals.

PEDFIC 1 was a randomised, double-blind, phase 3 study in 62 participants with PFIC types 1 and 2.[49] Individuals treated with odevixibat experienced statistically significant improvements in observer-reported pruritus compared with individuals given the placebo over 24 weeks of treatment. Additionally, the percentage of participants with a serum bile acid response was higher in the odevixibat group than in the placebo group (33% *vs* 0%). With respect to safety and tolerability, 31% of patients in the odevixibat group had treatment-emergent diarrhoea or frequent bowel motions. 14% of participants had treatment-emergent increases in alanine transaminase.

PEDFIC 2 is an open-label extension of PEDFIC 1 and includes participants with other types of PFIC. All 69 participants in PEDFIC 2 received odevixibat. A pooled analysis of data from both PEDFIC 1 and PEDFIC 2 trials at the interim data cut-off point (in July, 2020) found that participants treated with odevixibat continued to experience improvements in pruritus and serum bile acid levels over time.[50] Among participants 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 these pooled data at a later data cut-off point (in January, 2022) found that a 70% or larger decrease in serum bile acid concentration or an absolute concentration of 70 µmol/L or less in participants with PFIC at 6 months of odevixibat treatment was associated with native liver survival at 3 years.[50] Long-term follow-up will clarify the durability of the treatment effects and establish how long native liver survival might be extended, particularly as NAPPED data show that only 32% of individuals with PFIC type 2 currently survive to adulthood (ie, age 18 years) with their native liver.[25]

Odevixibat has also been evaluated in 52 individuals with Alagille syndrome (with 17 given the placebo and 35 given the intervention) in the phase 3 ASSERT trial (NCT04674761). Topline data show that the trial met its primary endpoint of improvement in pruritus and secondary endpoint of a reduction in serum bile acids.[51] In June, 2023, odevixibat received approval in the USA for the treatment of cholestatic pruritus in individuals with Alagille syndrome aged 12 months and older. In July, 2023, the European Medicines Agency's Committee for Medicinal Products for Human Use followed with a positive opinion for the use of odevixibat to treat cholestatic pruritus in individuals with Alagille syndrome aged 6 months or older. There are currently no direct treatment comparisons between maralixibat and odevixibat in either Alagille syndrome or PFIC; the aforementioned GALA (for Alagille syndrome) and NAPPED (for PFIC) databases could provide an opportunity to understand differences between these IBAT inhibitors in each condition in the future.

Next steps

Approval of maralixibat and odevixibat represents a milestone in the treatment of cholestatic disease, with substantial benefits for quality of life in patients with Alagille syndrome and PFIC. Their licensing for cholestatic pruritus reverses the typical chronology in which 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 older than 6 months[52] but is still considering whether maralixibat can be approved for Alagille syndrome.[53]

Since the intrahepatic retention of bile acids can cause liver injury, the association of IBAT inhibitors with reductions in serum bile acid levels in subsets of patients might indicate a longer-term protective effect on the liver through prevention of disease progression. Ultimately, sustained reductions in bile acid load might offer a possibility of delaying the need for liver transplantation in many young patients, but longer term studies are required to confirm this.

IBAT inhibitors in other paediatric and adult cholestatic disorders

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 the drugs prove effective in delaying transplantation in this progressive liver disease, it will be substantially beneficial for these children.[54]

The PEDFIC 2 study of odevixibat included a small number of individuals with PFIC who were older than 18 years. Clinical trials of maralixibat also included individuals with Alagille syndrome who were older than 16 years, and early data from 14 participants (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.[55] Moreover, improvements in pruritus were maintained in patients transitioning to early adulthood.[55] In adults, safety in pregnancy and breastfeeding are important considerations. Although 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 substantial fetal exposure during pregnancy.[56,57] Animal data suggest that treatment with odevixibat during pregnancy might cause fetal cardiovascular malformations.[58,59] The low systemic absorption of maralixibat and odevixibat at recommended doses in parents is not expected to result in substantial exposure to breastfeeding infants; however, there are no data on whether these drugs are present in human milk or not. More data and experience with the use of IBAT inhibitors in adult patients with Alagille syndrome and PFIC will be available in the future.

IBAT inhibitors and other novel drugs are currently in clinical development for the treatment of cholestatic diseases affecting adults, such as primary biliary cholangitis and primary sclerosing cholangitis (appendix). From questionnaire studies, up to 70–80% of patients with primary biliary cholangitis experience pruritus at some point in their disease course,[60,61] and 38% of patients with primary sclerosing cholangitis report pruritus.[62] However, pruritus in primary biliary cholangitis and primary sclerosing cholangitis can be difficult to control with available drugs. Although ursodeoxycholic acid and obeticholic acid are licensed for use in primary biliary cholangitis, they have little effect on pruritus, and obeticholic acid can even induce or exacerbate pruritus in primary biliary cholangitis. Cholestyramine is licensed for pruritus in partial biliary obstruction and primary biliary cholangitis but might not provide adequate relief in patients with moderate-to-severe pruritus. Other drugs used for pruritus in these individuals are off label and of variable benefit.[63]

There might be a potential role for IBAT inhibitors in BRIC and intrahepatic cholestasis of pregnancy, as pruritus is a major feature of these conditions, and individuals can have the same pathogenic gene variants as in PFIC. However, clinical trials in intrahepatic cholestasis of pregnancy face particular challenges; the phase 2 OHANA trial (NCT04718961) evaluating the IBAT inhibitor volixibat in adults with intrahepatic cholestasis of pregnancy was terminated due to enrolment feasibility in the setting of high-risk pregnancy.

IBAT inhibitors might also have a role in non-cholestatic liver diseases. For example, they improve metabolic and histological parameters and gut microbiota dysbiosis in mouse models of metabolic dysfunction-associated steatotic liver disease and metabolic dysfunction-associated steatohepatitis.[64,65] In one mouse model of metabolic dysfunction-associated steatohepatitis, fewer liver tumours were observed in mice treated with an IBAT inhibitor compared with untreated mice.[66] However, a phase 2 trial of volixibat in metabolic dysfunction-associated steatohepatitis was terminated due to poor efficacy at the 24-week interim analysis, despite evidence of target engagement.[67] A3907 is an oral systemic drug that inhibits IBAT in the intestine, kidneys (preventing bile acid reuptake from urine), and liver (preventing reuptake from bile).[68] A3907 also improved biochemical and histological markers of metabolic dysfunction-associated steatohepatitis in a mouse model.[69] It has entered a phase 2 clinical study in adults with primary sclerosing cholangitis (NCT05642468; appendix p 1) but is not being trialled for other liver diseases at present. The role of systemic IBAT inhibitors in both cholestatic and non-cholestatic liver disease remains to be proven, and their safety, tolerability, and efficacy compared with luminally restricted IBAT inhibitors need clarification.

Beyond liver disease, elobixibat (the first-in-class IBAT inhibitor) has been approved in Japan[70] and Thailand[71] 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.

See Online for appendix

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

Although IBAT inhibitors are transformative in some patients, not everyone with Alagille syndrome and PFIC responds to this treatment. In PFIC, this might be because the underlying pathogenic variant is truncating or non-truncating. Additionally, PFIC is a heterogeneous category of disorders, and few data support the use of IBAT inhibitors in rarer types of PFIC (table). Long-term studies are required to clarify when IBAT inhibitors are indicated in these rarer types of PFIC and 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 recessive disorder caused by pathogenic variants in *UGT1A1*) can lead to substantial 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). Data published in 2023 showed that three adult patients treated with the higher dose of GNT0003 experienced an encouraging reduction in serum bilirubin, enabling cessation of phototherapy from week 16 after vector administration up to at least week 78 after vector administration.[72] AAV-based gene therapy and lipid nanoparticle-encapsulated mRNA therapy have also been explored in mouse models of PFIC type 3, in which they have improved clinical and histological markers of disease.[73–75] 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 for PFIC type 2 and VTX-803 for PFIC type 3).[76]

Conclusion

The IBAT inhibitors mark a new era in the management of paediatric cholestasis, with the prospect of improving

Search strategy and selection criteria

References for this Review were identified through searches of PubMed and Google Scholar with the search terms "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", "volixibat", "elobixibat", "linerixibat", and "A3907" from database inception until June 20, 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 when 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 selected on the basis of originality, quality, and relevance to the broad scope of this Review.

pruritus, quality of life, and transplant-free survival in individuals with Alagille syndrome and PFIC. The initial clinical trials of these drugs highlight the importance of evaluating new therapies in rare paediatric diseases, not only so that children can 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 in Alagille syndrome and PFIC, particularly in relation to the indications for and timing of liver transplantation. Paediatric research has thus set a new standard for the treatment of cholestatic disease in both children and adults.

Contributors

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

Declaration of interests

DK has received consulting fees from Albireo, Anylam, Mirum, Intercept, Takeda, Freeline, GSK, Orphalan, and AstraZeneca; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, and educational events from Mirum and Albireo; and grants for clinical trials from Albireo, AbbVie, Gilead Sciences, Mirum, and Intercept. RJ and ERM declare no competing interests.

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References

1 Li L, Krantz ID, Deng Y, et al. Alagille syndrome is caused by mutations in human *Jagged1*, which encodes a ligand for Notch1. *Nat Genet* 1997; **16:** 243–51.
2 McDaniell R, Warthen DM, Sanchez-Lara PA, et al. *NOTCH2* mutations cause Alagille syndrome, a heterogeneous disorder of the notch signaling pathway. *Am J Hum Genet* 2006; **79:** 169–73.
3 Bull LN, van Eijk MJ, Pawlikowska L, et al. A gene encoding a P-type ATPase mutated in two forms of hereditary cholestasis. *Nat Genet* 1998; **18:** 219–24.
4 Strautnieks SS, Bull LN, Knisely AS, et al. A gene encoding a liver-specific ABC transporter is mutated in progressive familial intrahepatic cholestasis. *Nat Genet* 1998; **20:** 233–38.
5 van Mil SW, van der Woerd WL, van der Brugge G, et al. Benign recurrent intrahepatic cholestasis type 2 is caused by mutations in *ABCB11*. *Gastroenterology* 2004; **127:** 379–84.
6 de Vree JM, Jacquemin E, Sturm E, et al. Mutations in the *MDR3* gene cause progressive familial intrahepatic cholestasis. *Proc Natl Acad Sci USA* 1998; **95:** 282–87.
7 Sambrotta M, Strautnieks S, Papouli E, et al. Mutations in *TJP2* cause progressive cholestatic liver disease. *Nat Genet* 2014; **46:** 326–28.
8 Carlton VE, Harris BZ, Puffenberger EG, et al. Complex inheritance of familial hypercholanemia with associated mutations in *TJP2* and *BAAT*. *Nat Genet* 2003; **34:** 91–96.
9 Gomez-Ospina N, Potter CJ, Xiao R, et al. Mutations in the nuclear bile acid receptor FXR cause progressive familial intrahepatic cholestasis. *Nat Commun* 2016; **7:** 10713.
10 Gao E, Cheema H, Waheed N, et al. Organic solute transporter alpha deficiency: a disorder with cholestasis, liver fibrosis, and congenital diarrhea. *Hepatology* 2020; **71:** 1879–82.
11 Maddirevula S, Alhebbi H, Alqahtani A, et al. Identification of novel loci for pediatric cholestatic liver disease defined by KIF12, PPM1F, USP53, LSR, and WDR83OS pathogenic variants. *Genet Med* 2019; **21:** 1164–72.
12 Ünlüsoy Aksu A, Das SK, Nelson-Williams C, et al. Recessive mutations in *KIF12* cause high gamma-glutamyltransferase cholestasis. *Hepatol Commun* 2019; **3:** 471–77.
13 Luan W, Hao CZ, Li JQ, et al. Biallelic loss-of-function *ZFYVE19* mutations are associated with congenital hepatic fibrosis, sclerosing cholangiopathy and high-GGT cholestasis. *J Med Genet* 2021; **58:** 514–25.
14 Gonzales E, Taylor SA, Davit-Spraul A, et al. *MYO5B* mutations cause cholestasis with normal serum gamma-glutamyl transferase activity in children without microvillous inclusion disease. *Hepatology* 2017; **65:** 164–73.
15 Pan Q, Luo G, Qu J, et al. A homozygous R148W mutation in *Semaphorin 7A* causes progressive familial intrahepatic cholestasis. *EMBO Mol Med* 2021; **13:** e14563.
16 Qiu YL, Liu T, Abuduxikuer K, et al. Novel missense mutation in *VPS33B* is associated with isolated low gamma-glutamyltransferase cholestasis: attenuated, incomplete phenotype of arthrogryposis, renal dysfunction, and cholestasis syndrome. *Hum Mutat* 2019; **40:** 2247–57.
17 Black K, Ziogas IA, Thurm C, et al. Pediatric liver transplant survival in Alagille syndrome is comparable to biliary atresia—a linked database analysis. *J Pediatr Gastroenterol Nutr* 2022; **75:** 257–63.
18 Mainwaring RD, Felmly LM, Collins RT, Hanley FL. Impact of liver dysfunction on outcomes in children with Alagille syndrome undergoing congenital heart surgery. *Eur J Cardiothorac Surg* 2022; **63:** ezac553.
19 Luong R, Feinstein JA, Ma M, et al. Outcomes in patients with Alagille syndrome and complex pulmonary artery disease. *J Pediatr* 2021; **229:** 86–94.
20 Kohaut J, Pommier R, Guerin F, et al. Abdominal arterial anomalies in children with Alagille syndrome: surgical aspects and outcomes of liver transplantation. *J Pediatr Gastroenterol Nutr* 2017; **64:** 888–91.
21 Valamparampil JJ, Reddy MS, Shanmugam N, Vij M, Kanagavelu RG, Rela M. Living donor liver transplantation in Alagille syndrome—single center experience from south Asia. *Pediatr Transplant* 2019; **23:** e13579.
22 Okamoto T, Sonoda M, Ogawa E, et al. Long-term outcomes of living-donor liver transplantation for progressive familial intrahepatic cholestasis type 1. *J Pediatr Gastroenterol Nutr* 2021; **72:** 425–29.
23 Kubitz R, Dröge C, Kluge S, et al. High affinity anti-BSEP antibodies after liver transplantation for PFIC-2—successful treatment with immunoadsorption and B-cell depletion. *Pediatr Transplant* 2016; **20:** 987–93.
24 Stindt J, Kluge S, Dröge C, et al. Bile salt export pump-reactive antibodies form a polyclonal, multi-inhibitory response in antibody-induced bile salt export pump deficiency. *Hepatology* 2016; **63:** 524–37.

25 van Wessel DBE, Thompson RJ, Gonzales E, et al. Genotype correlates with the natural history of severe bile salt export pump deficiency. *J Hepatol* 2020; **73:** 84–93.

26 Vandriel SM, Li LT, She H, et al. Natural history of liver disease in a large international cohort of children with Alagille syndrome: results from the GALA study. *Hepatology* 2023; **77:** 512–29.

27 Dong C, Condat B, Picon-Coste M, et al. Low-phospholipid-associated cholelithiasis syndrome: prevalence, clinical features, and comorbidities. *JHEP Rep Innov Hepatol* 2020; **3:** 100201.

28 Poupon R, Rosmorduc O, Boëlle PY, et al. Genotype–phenotype relationships in the low-phospholipid-associated cholelithiasis syndrome: a study of 156 consecutive patients. *Hepatology* 2013; **58:** 1105–10.

29 Avena A, Puggelli S, Morris M, et al. *ABCB4* variants in adult patients with cholestatic disease are frequent and underdiagnosed. *Dig Liver Dis* 2021; **53:** 329–44.

30 Ulzurrun E, Stephens C, Crespo E, et al. Role of chemical structures and the 1331T→C bile salt export pump polymorphism in idiosyncratic drug-induced liver injury. *Liver Int* 2013; **33:** 1378–85.

31 Lang C, Meier Y, Stieger B, et al. Mutations and polymorphisms in the bile salt export pump and the multidrug resistance protein 3 associated with drug-induced liver injury. *Pharmacogenet Genomics* 2007; **17:** 47–60.

32 Dixon PH, Sambrotta M, Chambers J, et al. An expanded role for heterozygous mutations of *ABCB4, ABCB11, ATP8B1, ABCC2* and *TJP2* in intrahepatic cholestasis of pregnancy. *Sci Rep* 2017; **7:** 11823.

33 Hüpper MN, Pichler J, Huber WD, et al. Surgical versus medical management of progressive familial intrahepatic cholestasis—case compilation and review of the literature. *Children* 2023; **10:** 949.

34 Jannone G, Stephenne X, Scheers I, et al. Nasobiliary drainage prior to surgical biliary diversion in progressive familial intrahepatic cholestasis type II. *Eur J Pediatr* 2020; **179:** 1547–52.

35 Kronsten V, Fitzpatrick E, Baker A. Management of cholestatic pruritus in paediatric patients with Alagille syndrome: the King's College Hospital experience. *J Pediatr Gastroenterol Nutr* 2013; **57:** 149–54.

36 Heerkens M, Dedden S, Scheepers H, et al. Effect of plasmapheresis on cholestatic pruritus and autotaxin activity during pregnancy. *Hepatology* 2019; **69:** 2707–10.

37 Koofy NE, Yassin N, Okasha S, William H, Elakel W, Elshiwy Y. Evaluation of the role of bile acids and serotonin as markers of pruritus in children with chronic cholestatic liver disease. *Arab J Gastroenterol* 2021; **22:** 199–202.

38 Düll MM, Wolf K, Vetter M, Dietrich P, Neurath MF, Kremer AE. Endogenous opioid levels do not correlate with itch intensity and therapeutic interventions in hepatic pruritus. *Front Med* 2021; **8:** 641163.

39 Kremer AE, Gonzales E, Schaap FG, Oude Elferink RP, Jacquemin E, Beuers U. Serum autotaxin activity correlates with pruritus in pediatric cholestatic disorders. *J Pediatr Gastroenterol Nutr* 2016; **62:** 530–35.

40 Hegade VS, Pechlivanis A, McDonald JAK, et al. Autotaxin, bile acid profile and effect of ileal bile acid transporter inhibition in primary biliary cholangitis patients with pruritus. *Liver Int* 2019; **39:** 967–75.

41 Ebhohon E, Chung RT. Systematic review: efficacy of therapies for cholestatic pruritus. *Therap Adv Gastroenterol* 2023; **16:** 17562848231172829.

42 Kamath BM, Goldstein A, Howard R, et al. Maralixibat treatment response in Alagille syndrome is associated with improved health-related quality of life. *J Pediatr* 2022; **252**: 68–75.

43 Wishart DS, Feunang YD, Guo AC, et al. DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Res* 2018; **46:** D1074–82.

44 Gonzales E, Hardikar W, Stormon M, et al. Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomised phase 2 study. *Lancet* 2021; **398:** 1581–92.

45 Kamath BM, Bauer RC, Loomes KM, et al. *NOTCH2* mutations in Alagille syndrome. *J Med Genet* 2012; **49:** 138–44.

46 Hansen BEVS, Vig P, Garner W, et al. Maralixibat-treated patients with Alagille syndrome demonstrate improved event-free survival in a natural history comparison with patients from the gala database: application of real-world evidence analytics. North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) Annual Meeting; Oct 4–7, 2023. *Frontline Gastroenterol* 2023; **14:** A5–6.

47 Mirum Pharmaceuticals. Positive topline data announced from Mirum's LIVMARLI phase 3 MARCH study in progressive familial intrahepatic cholestasis (PFIC). Mirum Pharmaceuticals, Oct 24, 2022. https://ir.mirumpharma.com/news-events/News/news-details/2022/Positive-Topline-Data-Announced-from-Mirums-LIVMARLI-Phase-3-MARCH-Study-in-Progressive-Familial-Intrahepatic-Cholestasis-PFIC/default.aspx (accessed May 12, 2023).

48 Loomes KM, Squires RH, Kelly D, et al. Maralixibat for the treatment of PFIC: long-term, IBAT inhibition in an open-label, phase 2 study. *Hepatol Commun* 2022; **6:** 2379–90.

49 Thompson RJ, Arnell H, Artan R, et al. Odevixibat treatment in progressive familial intrahepatic cholestasis: a randomised, placebo-controlled, phase 3 trial. *Lancet Gastroenterol Hepatol* 2022; **7:** 830–42.

50 Thompson RJ, Artan R, Baumann U, et al. Interim results from an ongoing, open-label, single-arm trial of odevixibat in progressive familial intrahepatic cholestasis. *JHEP Rep Innov Hepatol* 2023; **5:** 100782.

51 Albireo. Albireo reports positive topline data from phase 3 trial of Bylvay® (odevixibat) in Alagille syndrome. GlobeNewswire, Oct 11, 2022. https://ir.albireopharma.com/node/14856/pdf (accessed May 12, 2023).

52 National Institute for Health and Care Excellence. Odevixibat for treating progressive familial intrahepatic cholestasis. National Institute for Health and Care Excellence, 2022. https://www.nice.org.uk/guidance/hst17 (accessed June 22, 2023).

53 National Institute for Health and Care Excellence. Maralixibat for treating cholestatic pruritus in Alagille syndrome ID3941. National Institute for Health and Care Excellence, 2021. https://www.nice.org.uk/guidance/indevelopment/gid-ta10832 (accessed June 22, 2023).

54 Laue T, Baumann U. Odevixibat: an investigational inhibitor of the ileal bile acid transporter (IBAT) for the treatment of biliary atresia. *Expert Opin Investig Drugs* 2022; **31:** 1143–50.

55 Hirschfield G, Mogul D, Baek M, Vig P, Kamath BM. Impact of maralixibat on cholestatic pruritus in adults aged 16 years and older with Alagille syndrome. European Association for the Study of the Liver Congress; 2023 (poster WED-257). https://mirumpharma.com/wp-content/uploads/2023/06/Kamath-BM-EASL-2023-Impact-of-MRX-on-cholestatic-pruritus-in-adults-aged-16-years-and-older-with-ALGS.pdf (accessed Sept 11, 2023).

56 US Food and Drug Administration. Full prescribing information on livmarli (maralixibat). US Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214662s000lbl.pdf (accessed Sept 15, 2023).

57 European Medicines Agency. Summary of product characteristics for livmarli. European Medicines Agency. https://www.ema.europa.eu/en/documents/product-information/livmarli-epar-product-information_en.pdf (accessed Sept 15, 2023).

58 US Food and Drug Administration. Full prescribing information on bylvay (odevixibat). US Food and Drug Administration, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215498s000lbl.pdf (accessed Sept 15, 2023).

59 European Medicines Agency. Summary of product characteristics for bylvay. European Medicines Agency. https://www.ema.europa.eu/en/documents/product-information/bylvay-epar-product-information_en.pdf (accessed Sept 15, 2023).

60 Hegade VS, Mells GF, Fisher H, et al. Pruritus Is common and undertreated in patients with primary biliary cholangitis in the United Kingdom. *Clin Gastroenterol Hepatol* 2019; **17:** 1379–1387.e3.

61 Mayo MJ, Carey E, Smith HT, et al. Impact of pruritus on quality of life and current treatment patterns in patients with primary biliary cholangitis. *Dig Dis Sci* 2023; **68:** 995–1005.

62 van Munster KN, Dijkgraaf MGW, Oude Elferink RPJ, Beuers U, Ponsioen CY. Symptom patterns in the daily life of PSC patients. *Liver Int* 2022; **42:** 1562–70.

63 Düll MM, Kremer AE. Evaluation and management of pruritus in primary biliary cholangitis. *Clin Liver Dis* 2022; **26:** 727–45.

64 Matsui M, Fukunishi S, Nakano T, Ueno T, Higuchi K, Asai A. Ileal bile acid transporter inhibitor improves hepatic steatosis by ameliorating gut microbiota dysbiosis in NAFLD model mice. *MBio* 2021; **12:** e0115521.

65 Yamauchi R, Takedatsu H, Yokoyama K, et al. Elobixibat, an ileal bile acid transporter inhibitor, ameliorates non-alcoholic steatohepatitis in mice. *Hepatol Int* 2021; **15:** 392–404.

66 Sugiyama Y, Yamamoto K, Honda T, et al. Impact of elobixibat on liver tumors, microbiome, and bile acid levels in a mouse model of nonalcoholic steatohepatitis. *Hepatol Int* 2023; published online Sept 4. https://doi.org/10.1007/s12072-023-10581-2.

67 Newsome PN, Palmer M, Freilich B, et al. Volixibat in adults with non-alcoholic steatohepatitis: 24-week interim analysis from a randomized, phase II study. *J Hepatol* 2020; **73:** 231–40.

68 Caballero-Camino FJ, Rodrigues PM, Wångsell F, et al. A3907, a systemic ASBT inhibitor, improves cholestasis in mice by multiorgan activity and shows translational relevance to humans. *Hepatology* 2023; **78:** 709–26.

69 Åkerblad P, Lindström E, Mattsson JP, et al. A3907, a novel, orally available inhibitor of the apical sodium-dependent bile acid transporter, improves key clinical markers of non-alcoholic steatohepatitis in obese diet-induced and biopsy-confirmed mouse models. International Liver Congress; June 23–26, 2021 (poster PO-1849).

70 Nakajima A, Fujimaki M, Arai Y, Emori K. Safety and efficacy of elobixibat, an ileal bile acid transporter inhibitor, in elderly patients with chronic idiopathic constipation according to administration time: interim analysis of post-marketing surveillance. *J Neurogastroenterol Motil* 2022; **28:** 431–41.

71 MIMS Thailand. Goofice (elobixibat)—full prescribing info. https://www.mims.com/thailand/drug/info/goofice?type=full (accessed Nov 2, 2023).

72 D'Antiga L, Beuers U, Ronzitti G, et al. Gene therapy in patients with the Crigler-Najjar syndrome. *N Engl J Med* 2023; **389:** 620–31.

73 Wei G, Cao J, Huang P, et al. Synthetic human *ABCB4* mRNA therapy rescues severe liver disease phenotype in a BALB/c*Abcb4*$^{-/-}$ mouse model of PFIC3. *J Hepatol* 2021; **74:** 1416–28.

74 Weber ND, Odriozola L, Martínez-García J, et al. Gene therapy for progressive familial intrahepatic cholestasis type 3 in a clinically relevant mouse model. *Nat Commun* 2019; **10:** 5694.

75 Aronson SJ, Bakker RS, Shi X, et al. Liver-directed gene therapy results in long-term correction of progressive familial intrahepatic cholestasis type 3 in mice. *J Hepatol* 2019; **71:** 153–62.

76 Vivet Therapeutics. Mirum Pharmaceuticals and Vivet Therapeutics enter into exclusive worldwide option and license agreement for Vivet's PFIC gene therapy programs. Vivet Therapeutics, March 12, 2021. https://www.vivet-therapeutics.com/mirum-pharmaceuticals-and-vivet-therapeutics-enter-into-exclusive-worldwide-option-and-license-agreement-for-vivets-pfic-gene-therapy-programs/ (accessed June 30, 2023).