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Novel Targets in Rare Liver Diseases in Childhood

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ABSTRACT

Rare liver diseases are highly diverse and driven by multiple mechanisms that are not well understood. Classifying these diseases is challenging, but the European Reference Network (ERN) on rare liver diseases has proposed categorizing them as autoimmune, infectious, genetic/hereditary, vascular, neoplastic, and others with unknown causes. Despite the difficulties in studying these diseases due to limited access to large series and biological samples, they have significant translational value. Rare liver diseases can serve as unique models for understanding liver pathophysiological responses and mechanisms of disease progression. In monogenic conditions, the impact of a single faulty gene on homeostatic mechanisms can be studied under well-established experimental conditions. Therefore, rare liver diseases can be seen as a roadmap for understanding core mechanisms that may also be relevant for more common chronic liver diseases. There are numerous rare liver diseases in newborn and childhood, with some of the more common ones being Alagille syndrome, biliary atresia, primary bile disorders, a group of 9 gene defects with correlating enzyme defect of the two different bile synthesis pathways, primary biliary cholangitis, primary sclerosing cholangitis and progressive familial intrahepatic cholestasis (PFIC). Going into detail all these have any genetic background in children, which will be evaluated closely in this manuscript.

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Introduction

Liver diseases in children and adolescents are rare and they are not in the public eye [1,2]. Other diseases in children, such as cancer or heart disease, receive a lot of attention in the public eye, but liver diseases in children do not. However, it is important to diagnose these diseases as early as possible [3]. Left untreated, most of the over 100 different liver diseases in children can become chronic and lead to the long-term development of liver cirrhosis. This scarring of the liver can also result in the loss of vital functioning liver cells in children. If a child experiences increasing liver dysfunction, a liver transplant may be necessary [4]. Today, liver transplants can be performed as a life-saving therapy with good and lasting success, even in small children. There are liver diseases in children and adolescents that have symptoms similar to those in adults, but most of these liver health deficits in children have different origins. The course of liver diseases in children often differs from those in adults as well. Liver diseases in children and adolescents are divided into three major groups. The first group includes congenital malformations of the bile ducts, bile duct obstruction, and other bile duct diseases. The second group encompasses all metabolic diseases, and the third group includes liver inflammations. Diagnosing liver diseases in children and adolescents is often difficult, as they may have few symptoms or the symptoms may be so nonspecific that they resemble harmless conditions. Prolonged symptoms such as fatigue, loss of appetite, and growth disorders should always prompt a visit to the pediatrician to check liver function tests. As with other diseases, early diagnosis is often important for successful therapies in liver diseases. Many childhood liver diseases can be well treated with timely diagnosis. Novel examination and treatment methods, from which children and adolescents also benefit, are in development. The common yellowing of the skin that often occurs in newborns is usually the harmless neonatal jaundice. Only if this yellowing of the skin lasts longer than two weeks should a blood test be done to determine if it is a liver disease or, for example, a bile duct obstruction. Some of the most common liver diseases in children and adolescents include biliary atresia, various metabolic diseases, and autoimmune diseases.

Alagille Syndrome

The syndrome was first described by Daniel Alagille (1925–2005), a French professor of pediatrics at the University of Paris-Sud [5-14]. The Alagille syndrome (ALGS; also known as Alagille-Watson syndrome or arteriohepatic dysplasia) is a very rare genetic disease that is inherited in an autosomal dominant manner [5,14]. The exact frequency of the disease is not known, but it is estimated to be 1 in 70,000 to 1 in 100,000. The inheritance pattern is autosomal dominant, with a penetrance of 100% and variable expressivity or phenotype [6]. There are two subtypes described, one with a mutation in the JAG1 gene on chromosome 20p12.2 (ALGS1) and the other with a mutation in the NOTCH2 gene on chromosome 1p13-p11 (ALGS2) [9,11,12,14]. The rate of new mutations is estimated to be over 50%. A publication described five cases of 20p deletion to the 10 cases published. Four had craniofacial, vertebral, ocular, and cardiovascular features of Alagille syndrome, which adds weight to the assignment of this

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disorder to the short arm of chromosome 20. Included in this study is the first report of familial transmission of a 20p deletion [14,15]. The syndrome is characterized by cholestasis with prominent jaundice in newborns, caused by rarefaction of the bile ducts leading to complete biliary atresia in some cases, typical facial features (broad forehead, deep-set eyes, hypertelorism, narrow chin) and skeletal abnormalities (butterfly vertebrae, short distal phalanges, clinodactyly, shortened ulna); eye and optic nerve disorders (embryotoxon, drusen on the optic nerve) and heart disease, especially pulmonary artery stenosis and other cardiac defects. Treatment is symptomatic, and in severe cases, a liver transplant may be necessary. Recent research focus on ileal bile acid transporters inhibitors (IBAT). Despite elevated alanine aminotransferase (ALT) levels, ileal bile acid transporter (IBAT) inhibitors have favorable outcomes in patients with Alagille syndrome [13]. Further trials may consider adjusting the dosing frequency to reduce gastrointestinal side effects while maintaining positive effects on pruritus and sBAs.

Biliary Atresia

Biliary atresia (BA) is a rare disease characterized by the closure of the bile ducts, which occurs exclusively in the neonatal period [16-45]. The cause is still unclear [16-45]. In developed countries, biliary atresia is the most common cause of the need for liver transplantation in infants [20,21,23,36,37,45,46,]. The prevalence at birth varies worldwide between 1 in 20,000 and 1 in 3,100 live births, with a higher incidence observed in Asia and the Pacific region [16-45]. In Western Europe, approximately one child out of 18,000 is affected within the neonatal period. Girls are slightly more affected than boys. About one-tenth of cases are associated with additional congenital malformations (e.g., heart defects, polysplenia) and are classified as syndromic forms. The isolated occurrence of bile duct obstruction is referred to as non-syndromic form. Internationally, the subdivision between extrahepatic and intrahepatic forms is no longer made, as the disease affects the entire liver and all bile ducts. The etiology of biliary atresia is largely unknown [17,22,24,26,39]. Various clues, such as changes in the ultrasound structure of the liver in utero, suggest that the narrowing of the bile ducts begins early in pregnancy [26,39]. Extensive studies on the influence of viral infections have suggested a link to cytomegalovirus, respiratory syncytial virus, Epstein-Barr virus, and human papillomavirus [17,22,24,26,39]. It is rarely found in association with Kabuki syndrome [24]. Increased urinary dipeptidyl peptidase IV activity in extrahepatic biliary atresia was found in a study published in 1995 [42]. Genetic influences also seem to play a role: individual studies report familial and ethnic (in the Pacific region or parts of the USA) clusters, and certain HLA types (HLA-B12; haplotype A9-B5; haplotype A28-B35) have been found to be more common in affected children [16-45]. Microscopic examination of the tissue reveals inflammatory damage to the bile ducts with proliferation of connective tissue (sclerosis) and narrowing to the point of obstruction of the bile ducts. Fibrosis in biliary atresia is rapidly progressive within a short time and is significantly correlated to SOX9 and HPCs. Assessment of targeting SOX9 and HPCs on fibrosis progression is warranted [46]. Patients with biliary atresia show significant ultrastructural abnormalities in the canaliculi, particularly in their microvilli, which were found to be correlated with the lack of villin protein as shown by immunostaining of liver tissue sections and western blot analysis [43]. Moreover, there was a marked reduction or absence of villin mRNA [43]. Differentiation between neonatal hepatitis and biliary atresia by measuring serum-alpha-fetoprotein was found in early studies [44]. After birth, children develop prolonged jaundice, which is predominantly caused by water-soluble "direct" bilirubin, unlike normal neonatal jaundice [16-45]. They pass pale stools, acholic stools, and their urine turns brown [16-45]. A third characteristic symptom is enlargement of the liver. There is often an association with facial dysmorphia, eye malformations, heart defects, and skeletal malformations. The general condition of the children is initially good, and even their growth is not affected in the first few months. Weight loss and increasing irritability only occur later. Signs of increased pressure in the portal vein of the liver (portal hypertension) eventually include splenomegaly and accumulation of fluid in the abdominal cavity [16-45]. Due to the impaired bile flow, insufficient bile acids reach the intestine, leading to impaired fat digestion and absorption of fat-soluble vitamins, especially vitamin K, which can cause a tendency to bleed. In any child with neonatal jaundice lasting longer than two weeks, biliary atresia must be actively ruled out due to the particular prognostic significance of an early diagnosis. The first step is a laboratory differentiation of bilirubin into the water-soluble, conjugated direct and the water-insoluble, unconjugated indirect form [16-45]. An ultrasound examination after a four- to twelve-hour fasting period confirms the suspicion if the gallbladder is not visible or shrunken, if there is increased echogenicity of the liver hilum, or if there is a cyst in the liver hilum. If the gallbladder appears normal on ultrasound and the suspicion persists, the anatomical structure and patency of the bile ducts must be investigated with a contrast X-ray examination, a cholangiography. Any remaining diagnostic uncertainties can be clarified, if necessary, by a liver biopsy. Untreated, the disease leads to a gradual fibrous transformation of the liver with cirrhosis and death within the first few years of life. In order to temporarily restore bile flow, affected children initially undergo a Kasai operation, a hepatoportoenterostomy [36,45]. During this procedure, the altered bile ducts, including the connective tissue between the right and left portal vein branches in the liver, are removed [36,45]. Subsequently, a loop of intestine is sewn onto the open portal vein in the liver so that the bile fluid can flow directly into the intestine from the portal vein [36,45]. Additional medical treatment with anti-inflammatory drugs to slow down the progressive transformation of liver tissue, or with substances that can improve bile flow, is sometimes recommended, but is controversial due to a lack of evidence of long-term benefit. If bile flow improves after the Kasai operation, this is reflected in a decrease in jaundice and increasing brown coloration of the stool [36,45]. However, even if this favorable situation occurs, two-thirds of patients develop liver cirrhosis caused by bile stasis. This or primary failure of the Kasai operation necessitates a liver transplantation [20,21,23,36,37,45]. The organ is usually transplanted in the second year of life, but may be necessary as early as six months of age. Due to the development of new transplantation procedures (liver splitting, living donation), the availability of this treatment method has increased in recent times. Survival with one's own liver into adulthood is observed in only about one-tenth of patients. Nevertheless, nowadays, approximately 90% of all affected individuals can hope for survival

with largely normal quality of life. Biliary atresia accompanied by additional spleen malformations generally has a worse prognosis. Similarly, the prospect of successful treatment decreases as the changes in the bile ducts extend further into the liver. The success rate for the Kasai operation also decreases with increasing age of the children, which is why early diagnosis is of particular importance. The overall prognosis improves with the availability of liver transplantation. In the Hamburg Transplantation Center, the survival rate of children who received a liver transplant in infancy was 87% after two years.

The exact mechanism of progressive injury in BA is not fully understood. Recent research has focused on matrix metalloproteinase-7 (MMP-7) as a potential biomarker for diagnosing BA [47]. MMPs play a role in extracellular matrix turnover and have other functions beyond the ECM. The involvement of MMP-7 and other MMPs in liver fibrosis is still being explored [47]. Studies have shown that measuring serum MMP-7 levels can accurately diagnose BA in cholestatic patients, and hepatic MMP-7 expression is linked to BA-related liver fibrosis [47]. While the specific role of MMP-7 in the pathophysiology of BA is not clear, research has examined its role in other fibrotic conditions like renal and idiopathic pulmonary fibrosis [47]. MMP-7 is known to be involved in Wnt/β-catenin signaling, promoting inflammation and fibrosis through mechanisms like shedding of E-cadherin and activation of osteopontin (OPN) and TNF-α [47]. It also appears to play a role in angiogenesis. MMP-7 could play a role as potential prognostic biomarker for BA and suggest new avenues for therapeutic and research exploration in the future [47]. Hes1 might contribute to the maturation and the cellular structure organization of biliary epithelial cells, which provides new insight into understanding the pathology of biliary atresia [48]. Expression of the Hes1 transcriptional co-regulator, RBP-Jκ was also reduced in this study [48]. The prognostic predictors of biliary atresia (BA), including total bile acid (TBA), reactive ductular cells (RDCs), and fibrosis, were linked to the development of liver progenitor-like cells (LPLCs). LPLCs expressing both SOX9 and HNF4A rarely co-stained with markers of portal hepatic progenitor cells (portal-HPCs) such as CK19, CK7, EPCAM, PROM1 (CD133), TROP2, and AFP. Under conditions of cholestasis, LPLCs exhibited enhanced proliferation and resistance to senescence compared to hepatocytes [49]. Additionally, LPLCs formed pseudo-rosette structures transitioning from the periportal parenchyma to the portal region, suggesting differentiation towards RDCs during cholestasis progression [49]. LPLCs are linked to disease progression and prognostic factors in BA. Their bipotent characteristics differ from those of portal-HPCs. As cholestasis advances, LPLCs demonstrate increased proliferation and anti-senescence properties, continuing to differentiate into RDCs.

Primary Bile Acid Synthesis Disorders (BAS)

Inherited defects in bile acid synthesis are rare genetic disorders that can present as neonatal cholestasis, neurological issues, or deficiencies in fat-soluble vitamins. There are nine recognized defects in bile acid synthesis, including deficiencies in oxysterol 7α-hydroxylase, Δ4-3-oxosteroid-5β-reductase, 3β-hydroxy-Δ5-C27-steroid dehydrogenase, cerebrotendinous xanthomatosis (sterol 27-hydroxylase deficiency), α-methylacyl-CoA racemase, and Zellweger syndrome (cerebrohepatorenal syndrome). These conditions are characterized by the inability to produce normal bile acids and an accumulation of abnormal bile acids and bile acid intermediates. Individuals with inherited defects in bile acid synthesis typically have normal or low serum bile acid levels, normal γ-glutamyl transpeptidase levels, and no itching. Failure to diagnose these conditions can lead to liver failure or chronic liver disease. Early identification can lead to significant clinical improvement with oral bile acid therapy. Inborn errors of bile acid synthesis are rare genetic disorders that make up 1–2% of cases of neonatal cholestasis, which is characterized by conjugated or direct hyperbilirubinemia in the first few months of life. Most patients with inborn errors of bile acid synthesis respond well to oral bile acid therapy. Cholic acid and chenodeoxycholic acid, the primary bile acids, are produced through enzymatic modifications to cholesterol involving at least 14 enzymes, multiple subcellular compartments, and two chemical pathways. The classic 'neutral' pathway is the main route for bile acid synthesis, producing cholic acid and chenodeoxycholic acid in equal amounts. The rate-limiting step in this pathway is the modification of the steroid nucleus by cholesterol 7α-hydroxylase. The farnesoid X receptor (FXR) regulates CYP7A1 through bile acids. FXR is a ligand-activated transcription factor that acts on target genes as a monomer or heterodimer with RXR. Bile acids are natural ligands for FXR, with chenodeoxycholic acid being the most potent activator. FXR activation leads to upregulation of SHP, which inhibits LRH-1's ability to activate CYP7A1. LRH-1 is crucial for SHP gene expression, as the SHP–LRH-1 complex reduces SHP expression, decreasing the negative feedback signal. An alternative 'acidic' pathway involves C27-hydroxylation of cholesterol by sterol 27-hydroxylase, followed by C7α-hydroxylation by oxysterol 7α-hydroxylase, resulting in primarily chenodeoxycholic acid production. Side-chain modification occurs after steroid nucleus modification in both pathways, with C27-hydroxylation in mitochondria and further side-chain modification in peroxisomes. The final step in primary bile acid synthesis is the conjugation of cholic acid and chenodeoxycholic acid to taurine or glycine. Deficiencies in genes encoding enzymes involved in bile acid synthesis pathways can cause liver disease by reducing canalicular bile acid secretion and accumulating potentially hepatotoxic bile acid precursors. These disruptions typically present as cholestasis in infants, resembling other neonatal liver diseases like biliary atresia. The exact prevalence of bile acid synthesis (BAS) defects is not well-established, but estimates suggest it may be around 1-9 per 1,000,000 individuals, excluding cerebrotendinous xanthomatosis. Inborn errors in BAS likely contribute to 1-2% of cases of unexplained liver disease in infants, children, and adolescents. The age at which these defects are diagnosed can vary. Symptoms may manifest in infancy with liver cholestasis, in childhood with unexplained liver disease, or in adulthood with neurological issues. Infants and children with BAS defects may experience complications due to fat malabsorption and deficiencies in fat-soluble vitamins, leading to conditions such as rickets, bleeding disorders, neuroaxonal dystrophy, and night blindness. There are seven known inborn errors of BAS that can cause liver cholestasis, including deficiencies in various enzymes. Diagnosis is typically based on analyzing hepatic

enzyme and bilirubin levels, as well as using specialized techniques like liquid secondary ionization mass spectrometry (LSIMS) and gas chromatography-mass spectrometry (GC-MS) on urine, serum, and bile samples. Early detection and treatment are crucial for a favorable outcome, as many BAS defects are treatable if identified promptly. Treatment usually involves primary bile acid therapy, with different types of bile acids used depending on the specific defect. Prognosis varies depending on the type of defect, with untreated cases potentially leading to progressive liver disease or other serious complications. Early intervention can lead to long-term survival and clinical improvement.

Primary Biliary Cholangitis (PBC)

Epidemiologic studies have reported varying incidence rates of 0.33 to 5.8 per 100,000 inhabitants per year and prevalence rates of 1.9 to 40.2 per 100,000 inhabitants [50,51]. Prevalence rates have shown some increase in recent decades, likely due to improved diagnostic tools, increased disease awareness, and improved survival [13,52]. PBC has been described worldwide, with North America and Northern Europe showing the highest incidence and prevalence rates. The prevalence of PBC is much higher in some areas of the US and UK compared to South America or Africa, possibly due to better recognition in the US and UK. First-degree relatives may have up to a 500times increase in prevalence, but the debate continues on whether this risk is greater in the same-generation relatives or the following generation. The first report of the disease dates back to 1851 by Addison and Gull, who described a clinical picture of progressive jaundice in the absence of mechanical obstruction of the large bile ducts. Ahrens et al. in 1950 published the first detailed description of 17 patients with this condition and coined the term "primary biliary cirrhosis". In 1959, Dame Sheila Sherlock reported a further series of PBC patients and recognized that the disease could be diagnosed in a precirrhotic stage. She proposed the term "chronic intrahepatic cholestasis" as a more appropriate description of the disease, but this nomenclature failed to gain acceptance, and the term "primary biliary cirrhosis" remained in use for decades. In 2014, international liver associations agreed to rename the disease "primary biliary cholangitis" to correct the inaccuracy and remove the social stigmata of cirrhosis, as well as the misunderstanding, disadvantages, and discrimination associated with the previous name. PBC is a prime example of female preponderance in autoimmunity, with a female to male ratio of up to 9:1, although some recent data suggest an increasing male prevalence. Major defects of sex chromosomes, such as enhanced monosomy X in female patients and enhanced Y chromosome loss in male patients, have been described and may explain the greater female predisposition to develop PBC. An association of a greater incidence of PBC at latitudes more distant from the Equator is similar to the pattern seen in multiple sclerosis. Cases have been reported in patients as young as 15. Primary biliary cholangitis (PBC), previously known as primary biliary cirrhosis, is an autoimmune liver disease characterized by the slow, progressive destruction of the small bile ducts, leading to the accumulation of bile and toxins in the liver, a condition known as cholestasis. This can result in liver damage, scarring, fibrosis, and eventually cirrhosis. Common symptoms of PBC include fatigue, itching, and in more advanced cases, jaundice. It is more prevalent in women, with a sex ratio of at least 9:1 female to male. The reasons for this gender disparity are not fully understood, but may involve the impact of sex hormones such as estrogen on the immune system. PBC has been recognized since at least 1851 and was previously referred to as "primary biliary cirrhosis" until patient advocacy groups proposed changing its name to "primary biliary cholangitis" in 2014. People with PBC may experience fatigue, dry skin, dry eyes, and itching, which can be intermittent and worse at night. More severe cases may also present with jaundice, impaired bone density, and increased risk of fractures. Additionally, skin lesions around the eyes, known as xanthelasma, may be present due to increased cholesterol levels. Primary biliary cholangitis (PBC) can progress to cirrhosis of the liver, leading to various symptoms and complications, including fluid retention in the abdomen (ascites), an enlarged spleen, esophageal varices, and hepatic encephalopathy. Additionally, individuals with PBC may also exhibit symptoms of associated extrahepatic autoimmune disorders such as thyroid disease, rheumatoid arthritis, or Sjögren's syndrome. PBC is classified as an autoimmune disorder and is characterized by the slow, progressive destruction of the small bile ducts of the liver. Most people with PBC have antimitochondrial antibodies (AMAs) against pyruvate dehydrogenase complex (PDC-E2), an enzyme complex found in the mitochondria. There is also evidence of a genetic predisposition to the disease, with cases of PBC occurring in family members and a genetic association with other autoimmune diseases. Research has identified specific genetic regions and genes involved in cytokine regulation that are important in the development of PBC. A study of over 2,000 patients has identified a gene, POGLUT1, that seems to be linked to this condition. Previous studies have also indicated the potential involvement of this gene. An environmental Gram-negative Alphaproteobacterium called Novosphingobium aromaticivorans has been linked to this disease, with several reports suggesting a potential role for this organism in causing the condition. The mechanism appears to involve a cross-reaction between the proteins of the bacterium and the mitochondrial proteins of the liver cells. The gene encoding CD101 may also contribute to host susceptibility to this disease. A failure of immune tolerance against the mitochondrial pyruvate dehydrogenase complex (PDC-E2) is a primary cause, with the shedding of the antigen into apoptotic bodies or "apotopes" leading to the anatomic localization. Similar autoreactivity may also occur with other proteins, including the gp210 and p62 nuclear pore proteins. Gp210 has increased expression in the bile duct of anti-gp210 positive patients, and these proteins may be associated with prognosis. Most patients are currently diagnosed when asymptomatic, having been referred to the hepatologist for abnormal liver function tests (mostly raised GGT or alkaline phosphatase) performed for annual screening blood tests. Other frequent scenarios include screening of patients with nonliver autoimmune diseases, rheumatoid arthritis, or investigation of elevated cholesterol, evaluation of itch or unresolved cholestasis postpartum. Diagnosing PBC is generally straightforward. The basis for a definite diagnosis are abnormalities in liver enzyme tests are usually present and elevated gamma-glutamyl transferase and alkaline phosphatase are found in early disease. Elevations in bilirubin occur in advanced disease. Antimitochondrial antibodies are the characteristic serological marker for PBC, being found in 90–95% of patients and only 1% of controls. PBC patients have

AMA against pyruvate dehydrogenase complex (PDC-E2), an enzyme complex that is found in the mitochondria. Those people who are AMA negative but with disease similar to PBC have been found to have AMAs when more sensitive detection methods are employed. Other auto-antibodies may be present antinuclear antibody measurements are not diagnostic for PBC because they are not specific, but may have a role in prognosis. Anti-glycoprotein-210 antibodies, and to a lesser degree anti-p62 antibodies, correlate with the disease's progression toward end-stage liver failure. Anti-gp210 antibodies are found in 47% of PBC patients. Anti-centromere antibodies often correlate with developing portal hypertension. Anti-np62 and anti-sp100 are also found in association with PBC. An abdominal ultrasound, magnetic resonance cholangiopancreatography, or a CT scan is typically done to rule out blockage in the bile ducts. This may be necessary to exclude a condition that causes secondary biliary cirrhosis, such as other biliary duct disease or gallstones. A liver biopsy may be helpful, and if there is still uncertainty in some patients, an endoscopic retrograde cholangiopancreatography, which is an endoscopic investigation of the bile duct, may be performed. Liver biopsy is not necessary for the diagnosis of PBC due to the high specificity of serological markers. However, it is still necessary when PBC-specific antibodies are absent, or when co-existent autoimmune hepatitis or nonalcoholic steatohepatitis is suspected. Liver biopsy can be useful for staging the disease for fibrosis and ductopenia. Finally, it may also be appropriate in the presence of other extrahepatic comorbidities. PBC is characterized by chronic, nonsuppurative inflammation on microscopic examination of liver biopsy specimens, which surrounds and destroys interlobular and septal bile ducts. The histopathologic findings in primary biliary cholangitis include: Inflammation of the bile ducts, characterized by intraepithelial lymphocytes, periductal epithelioid granulomas and proliferation of bile ductules. The Ludwig and Scheuer scoring systems have historically been used to stratify four stages of PBC, with stage 4 indicating the presence of cirrhosis. In the new system of Nakanuma, the stage of disease is based on fibrosis, bile duct loss, and features of cholestasis, i.e. deposition of orcein-positive granules, whereas the grade of necroinflammatory activity is based on cholangitis and interface hepatitis. The accumulation of orcein-positive granules occurs evenly across the PBC liver, which means that staging using the Nakanuma system is more reliable regarding sampling variability. Liver biopsy for the diagnosis and staging of PBC lost favor after the evidence of a patchy distribution of the duct lesions and fibrosis across the organ. The widespread availability of noninvasive measures of fibrosis means that liver biopsy for staging of PBC is somewhat obsolete. Liver biopsy does, however, remain useful in certain settings. The main indications are to confirm the diagnosis of PBC when PBC-specific antibodies are absent and confirm a diagnosis of PBC with AIH features (overlap PBC-AIH). Liver biopsy is also useful to assess the relative contribution of each liver injury when a comorbid liver disease is present, such as non-alcoholic steatohepatitis. In patients with inadequate response to UDCA, liver biopsy may provide the explanation and could undoubtedly inform risk stratification. For example, it may identify a previously unsuspected variant syndrome, steatohepatitis, or interface hepatitis of moderate or greater severity. It is also useful in AMA and ANA-specific antibody negative cholestatic patients to indicate an alternative process, sarcoidosis, small duct PSC, adult idiopathic ductopenia.

Primary Sclerosing Cholangitis (PSC)

Primary sclerosing cholangitis (PSC) is a chronic liver and gallbladder disease characterized by inflammation and scarring of the bile ducts, which hinders the normal flow of bile from the gallbladder. This condition can lead to liver damage and failure, as well as an increased risk of various cancers, including liver cancer and colorectal cancer. The exact cause of PSC is unknown, but factors such as genetic susceptibility, immune system dysfunction, and gut flora composition may play a role. PSC is often associated with inflammatory bowel disease (IBD), particularly ulcerative colitis. Liver transplant is the most definitive treatment for PSC, but disease recurrence can occur in some cases. PSC is rare and most commonly affects individuals with IBD, typically diagnosed in their 30s or 40s. Men are more commonly affected than women, and individuals of Northern European ancestry are at higher risk. Symptoms of PSC can vary, with some individuals experiencing no symptoms while others may have severe itching, fatigue, abdominal pain, and jaundice. Complications of PSC include bile duct infections, malabsorption of nutrients, and liver enlargement. The pathogenesis of PSC is complex and not fully understood, involving inflammation, scarring of the bile ducts, and impaired bile flow. Recent research has highlighted the role of intestinal microbiota and cellular senescence in the development of PSC. Overall, PSC is a challenging condition to manage, and ongoing research is needed to improve understanding and treatment options for affected individuals. CT scan findings in a case of primary sclerosing cholangitis. PSC is typically diagnosed by meeting at least two of three clinical criteria after ruling out other causes of sclerosing cholangitis: [•Serum alkaline phosphatase (ALP) levels > 1.5x the upper limit of normal for over 6 months. Cholangiography showing biliary strictures or irregularities consistent with PSC. Liver biopsy confirming PSC (if available).

In the past, a cholangiogram would be done through endoscopic retrograde cholangiopancreatography (ERCP), revealing "beading" of the bile ducts. Currently, magnetic resonance cholangiopancreatography (MRCP) is preferred for diagnostic cholangiography due to its noninvasive and accurate nature. MRCP offers high spatial resolution and can visualize the biliary tract in small animal models of PSC. Most individuals with PSC show evidence of autoantibodies and abnormal immunoglobulin levels [14]. For instance, around 80% of PSC patients have perinuclear antineutrophil cytoplasmic antibodies (P-ANCA). However, these immunoglobulin findings are not specific to PSC and their clinical significance is unclear. Antinuclear antibodies and anti-smooth muscle antibody are present in 20-50% of PSC cases, but they are not disease-specific and may indicate an overlap with autoimmune hepatitis (PSC-AIH overlap syndrome). The differential diagnosis may include primary biliary cholangitis, drug-induced cholestasis, cholangiocarcinoma, IgG4-related disease, post-liver transplantation nonanastomotic biliary strictures, and HIV-associated cholangiopathy. Primary sclerosing cholangitis and primary biliary cholangitis have distinct differences in liver tissue damage location, associations with inflammatory bowel disease, treatment response, and disease progression risks.

Primary sclerosing cholangitis is typically categorized into three subgroups based on the affected bile ducts: classic PSC, small-duct PSC and PSC associated with autoimmune hepatitis. There is no FDA-approved pharmacologic treatment for PSC. Some experts suggest a trial of ursodeoxycholic acid to lower liver enzyme levels, although its impact on liver histology and survival is uncertain. Supportive treatment focuses on symptom relief, such as using antipruritics for itching, antibiotics for cholangitis, and vitamin supplements for deficiencies in fat-soluble vitamins. Liver transplantation is the only long-term treatment for PSC, with indications including recurrent cholangitis, cirrhosis, hepatocellular carcinoma, and portal hypertension complications. Survival prediction models exist, but their clinical utility is limited. Surveillance for PSC-associated cancers is crucial due to the increased risk of cholangiocarcinoma in PSC patients. Similarly, individuals who are newly diagnosed with primary sclerosing cholangitis are advised to undergo a screening colonoscopy due to their significantly increased risk of colorectal cancer compared to the general population. Primary sclerosing cholangitis is closely linked to inflammatory bowel disease, particularly ulcerative colitis and to a lesser extent Crohn's disease. Up to 5% of patients with inflammatory bowel disease are also diagnosed with primary sclerosing cholangitis, and around 70% of individuals with primary sclerosing cholangitis have inflammatory bowel disease. The presence of colitis is associated with a higher risk of liver disease progression and the development of bile duct cancer (cholangiocarcinoma), although the exact relationship is not well understood. Regular monitoring of individuals with primary sclerosing cholangitis is crucial. Primary sclerosing cholangitis has a male-to-female ratio of 2-3:1 and can affect individuals of any age, although it is typically diagnosed in the fourth decade of life, often in conjunction with inflammatory bowel disease. The progression of primary sclerosing cholangitis is slow and often asymptomatic, leading to delayed diagnosis and clinical consequences. Data on the prevalence and incidence of primary sclerosing cholangitis are limited, with varying rates reported in different countries. In the United States, an estimated 29,000 individuals have primary sclerosing cholangitis. While there is no known curative treatment for primary sclerosing cholangitis, ongoing clinical trials are exploring options to slow disease progression. Obeticholic acid and simtuzumab are being investigated for their potential therapeutic effects on primary sclerosing cholangitis.

Progressive Familial Intrahepatic Cholestasis (PFIC)

Progressive familial intrahepatic cholestasis (PFIC) is a group of familial cholestatic conditions caused by defects in biliary epithelial transporters. The clinical presentation typically begins in childhood with progressive cholestasis, leading to issues such as failure to thrive, cirrhosis, and the potential need for liver transplantation. The types of progressive familial intrahepatic cholestasis include: Type 1 (OMIM #211600), also known as Byler disease; Type 2 (OMIM #601847), also known as ABCB11 deficiency or BSEP deficiency; Type 3 (OMIM #602347), also known as ABCB4 deficiency or MDR3 deficiency and Type 4 (OMIM #615878), caused by mutations in TJP2. The disease typically manifests before the age of 2, but cases have been diagnosed in adolescence. PFIC-1 usually presents at an earlier age, with symptoms like cholestasis, jaundice, and failure to thrive. Intense pruritus is a common feature, and in adolescent patients, it has been associated with suicide. Patients may also experience fat malabsorption, leading to deficiencies in fat-soluble vitamins and complications like osteopenia. PFIC is inherited in an autosomal recessive pattern. PFIC-1 is caused by mutations in ATP8B1, a gene responsible for phospholipid translocation across membranes. PFIC-2 is caused by mutations in ABCB11, which codes for the bile salt export pump (BSEP). PFIC-3 is caused by mutations in ABCB4, which encodes multidrug resistance protein 3 (MDR3). Liver biopsies typically show evidence of cholestasis, duct hypoplasia, hepatocellular injury, and fibrosis. Treatment involves supportive care, including medications like ursodeoxycholic acid, cholestyramine, rifampin, and naloxone in refractory cases. Surgical procedures like partial external biliary diversion (PEBD) may be considered. Patients should receive fat-soluble vitamin supplementation and may require liver transplantation in cases of significant liver dysfunction. Family members should undergo testing for PFIC mutations to assess the risk of transmission. Without liver transplantation, PFIC can progress to fulminant liver failure and death in childhood. Hepatocellular carcinoma may develop in PFIC-2 at a young age, with consanguinity considered a major risk factor. Similar mutations in transport proteins may increase the risk of intrahepatic cholestasis of pregnancy.

New Therapy Options

Medical Therapy of PBC by New Targets

The first-line therapy for PBC is ursodeoxycholic acid, with obeticholic acid being introduced for those with residual cholestasis [50]. Future licensed therapies for PBC may include peroxisome proliferator-activated receptor (PPAR) pathway agonists like seladelpar, elafibrinor, and saroglitazar, as well as NOX inhibitors for liver fibrosis [50]. Symptom management is crucial, with PPAR agonists showing promise in reducing itch and IBAT inhibitors like linerixibat being explored for pruritus [50]. The evolving landscape of PBC therapy aims for proactive, individualized approaches to achieve normal serum tests, improve quality of life, and prevent end-stage liver disease [50]. UDCA improves liver enzyme levels, slows down histological progression, and improves liver transplant-free survival. UDCA also reduces the need for liver transplantation. UDCA should be taken at a dose of 13 to 15 mg per kg of body weight per day, usually in two divided doses each day. Liver chemistries usually improve within a few weeks of starting UDCA, and 90% of any benefit is observed after 6–9 months of therapy. Liver chemistries should be re-evaluated after 1 year of treatment. UDCA is usually continued lifelong. Up to 40% of people do not respond to treatment with UDCA. Patients with PBC who have an inadequate response to UDCA or those few (less than 3%) who are intolerant to UDCA are candidates for second-line therapies. Obeticholic acid (OCA) is FDA-approved for the treatment of PBC in individuals intolerant or unresponsive to UDCA. OCA is a farnesoid X receptor agonist, and results in increased bile flow. OCA is started at 5 mg daily, and liver chemistries should be rechecked after 3 months of treatment. If the liver chemistries remain elevated, then the dose of OCA may be increased to 10 mg per day. The most common side effect of OCA is pruritus. Fibric acid derivatives, or fibrates, are agonists of the peroxisome proliferator activator receptor (PPAR), a

nuclear receptor involved in several metabolic pathways. While fibrates are approved for the treatment of hypertriglyceridemia, they exert anticholestatic effects and have been studied for the treatment of PBC. Among the fibrates, bezafibrate and fenofibrate, PPAR-alpha selective agonists, have been extensively studied as therapeutic agents because of their potential ability to decrease bile acid synthesis and bile acid-related hepatic inflammation. A randomized, controlled trial in 2018 showed its efficacy in patients with inadequate response to UDCA. While fibrates can be considered as off-label treatment for PBC that does not respond to UDCA, they should not be used in decompensated cirrhosis. Several additional medications have been investigated as potential treatments for PBC, and found to be ineffective as single agents (monotherapy), including: chlorambucil, colchicine, cyclosporine, corticosteroids, azathioprine, malotilate, methotrexate, mycophenolate mofetil, penicillamine, and thalidomide. Budesonide may be used as an off-label treatment for PBC, although its efficacy is controversial. Seladelpar, a PPAR-delta receptor agonist, is being studied for treatment of PBC. Pruritus is a common symptom in people with PBC. First-line treatment of pruritus consists of anion-exchange resins, such as cholestyramine, colestipol, or colesevalam. These anion-exchange resins are nonabsorbed, highly positively charged substances that bind bile acids, which are negatively charged anions. Anion-exchange resins relieve itching caused by excess bile acids in circulation by binding bile acids in the gut and facilitating elimination. Bloating or constipation may occur with anion-exchange resins. Cholestyramine may affect absorption of UDCA; if cholestyramine is necessary, it should be taken at least 60 minutes before or 4 hours after UDCA is taken. Treatment options for pruritus that does not improve with anion-exchange resins include: rifampicin, naltrexone, or sertraline. Rifampicin may rarely cause drug induced liver injury and should be avoided if serum bilirubin is elevated (greater than 2.5 mg/dL). Liver enzymes should be monitored after starting rifampin. Rifampicin induces enzymes, resulting in numerous potential drug-drug interactions. Opioid antagonists may cause a self-limited opioid withdrawal like reaction, with abdominal pain, elevated blood pressure, tachycardia, goose bumps, nightmares, and depersonalization. To avoid such reactions, the dose should start low and gradually be increased. Other treatments. Fatigue is a common symptom in PBC, and there are currently no licensed therapies for its management. However, a structured approach to addressing fatigue, quantifying its impact, and supporting patients to cope with its effects has been found to be effective. Disease-specific tools such as the PBC-40 quality-of-life measures can be used to assess the impact of fatigue. Coenzyme Q and rituximab have been shown to be ineffective, while a graded exercise program has been found to help some individuals. Patients with PBC may have poor absorption of oil-soluble vitamins (A, D, E, and K) due to impaired lipid-dependent absorption. Supplementation is recommended when bilirubin levels are elevated. Individuals with PBC are at an increased risk of developing osteoporosis compared to the general population and those with other liver diseases. Screening and treatment of osteoporosis is an important part of PBC management. Liver transplant is the only curative therapy for patients with advanced liver disease. Five-year patient survival rates following liver transplant are better than for most other indications for LT (80–85%). The introduction of UDCA has significantly altered the course of the disease. Numerous studies have demonstrated its efficacy in improving liver biochemistry, histological progression, and transplant-free survival. Among patients treated with UDCA, the degree of liver biochemistry improvement, or UDCA-response, can help identify patients with different long-term prognoses. Patients without cirrhosis who experience an improvement in liver enzymes to the normal range while on UDCA treatment have excellent survival rates, similar to the general population. However, survival is significantly reduced in those with abnormal liver biochemistry while on treatment. Alkaline phosphatase and total bilirubin are the two most important parameters for evaluating response to UDCA. Qualitative and quantitative definitions of UDCA-response have been developed based on changes in bilirubin, transaminases, and ALP after 6 to 24 months of treatment with UDCA at 13–15 mg/kg/day. Patients can be risk-stratified at diagnosis based on the likelihood of UDCA-response. This can help identify patients who may be eligible for second-line therapies before waiting for treatment failure under UDCA, potentially impacting the disease course. Hepatocellular carcinoma (HCC) is rare in PBC. Recent large-scale cohort studies have shown that the lack of UDCA-response after 12 months of therapy and male sex are associated with an increased risk of developing HCC in PBC. After liver transplant, the recurrence of disease may be as high as 18% at five years and up to 30% at 10 years. Risk factors for disease recurrence are not well-established.

Peroxisom-Proliferator-Activated Receptors (PPAR)-Agonists

Peroxisome Proliferator-Activated Receptors (PPARs) are intracellular receptors that are activated by a physiological or pharmacological ligand and regulate the expression of a variety of genes as transcription factors. They belong to a group of receptors located in the cell nucleus. Three PPAR subtypes (α, β/δ, γ) have been identified in the human body. These subtypes differ not only in their local expression but also in their gene expression patterns and the biological function of the genes they regulate. PPARα is highly expressed in the liver, kidney, intestine, and heart. Activation of PPARα primarily affects blood lipid levels, including reducing circulating triglycerides, synthesizing Apo A1, increasing free fatty acid uptake, enhancing fatty acid oxidation, and increasing HDL while reducing LDL levels. PPARα activation also has anti-inflammatory effects. PPARβ (also known as PPARδ) is present in almost all tissues of the human body. The β/δ receptor primarily regulates genes involved in lipid metabolism and plays a central role in cell proliferation. Activation of PPARβ/δ in obese animals has shown improvements in various metabolic parameters and weight reduction. PPARγ is ubiquitously expressed and activation improves glucose metabolism, insulin sensitivity, free fatty acid uptake, adipocyte and macrophage differentiation, and has anti-inflammatory effects. Activation of PPARγ has also been associated with a reduced risk of atherosclerosis. PPARs can be activated by both physiological and pharmacological ligands. After activation, PPARs bind to an activated Retinoid-X-Receptor (RXR), forming a complex that binds to a specific DNA sequence, the PPAR response element (PPRE), inducing specific gene transcription patterns. Due to their influence on various metabolic processes in the human body, there is a growing interest in therapeutically modulating PPARs. Different

substances that act through PPAR activation are already in use or in clinical trials. These PPAR agonists have distinct gene activation and deactivation patterns, making classification of PPAR agonists based on their specific effects challenging. Fibrates are pharmacological ligands for PPARα primarily used as lipid-lowering agents to treat lipid metabolism disorders (e.g., Bezafibrate, Gemfibrozil). They notably reduce blood triglyceride levels and slightly increase HDL cholesterol. Lanifibranor, an indole-sulfonamide, is a pan-PPAR agonist currently undergoing clinical trials. It improves insulin sensitivity, macrophage activation, and reduces the expression of inflammatory genes more effectively than single or dual PPAR agonists. Initial results from the randomized NATIVE study on Lanifibranor's potential to reduce liver fibrosis in NASH (non-alcoholic fatty liver disease) are promising, with a Fast-Track approval application submitted to the FDA. Thiazolidinediones/ Glitazones are pharmacological substances that predominantly activate PPARγ, enhancing insulin sensitivity and preventing hyperinsulinemia. They are known as insulin sensitizers and are used to treat patients with diabetes mellitus (e.g., Pioglitazone). Glitazars are dual PPAR agonists that interact with both PPARα and PPARγ receptors, potentially influencing various metabolic processes favorably. By activating PPARγ, they improve peripheral tissue insulin sensitivity, while PPARα activation enhances lipid profile parameters (e.g., increasing HDL cholesterol, reducing LDL cholesterol). PPARα/γ agonists are considered promising options for cardiovascular risk prevention in patients with type 2 diabetes. However, early representatives like Muraglitazar and Tesaglitazar failed to meet expectations due to side effects, halting their development. Aleglitazar, a PPARα/γ agonist in clinical trials, binds to PPARα and PPARγ receptors with nearly equal affinity, resulting in a specific gene activation and deactivation pattern distinct from other glitazars. Phase II clinical data show favorable effects on glucose levels, lipid profile, blood pressure, and inflammatory markers, suggesting Aleglitazar's potential to reduce cardiovascular risk in patients with type 2 diabetes. A Phase III endpoint study was conducted to investigate this hypothesis, but in 2013, Swiss pharmaceutical company Roche halted the study due to safety concerns and lack of efficacy.

Ileal Sodium/Bile Acid Cotransporter (ASBT/IBAT/NTCP)

Ileal sodium/bile acid cotransporter, also known as apical sodium–bile acid transporter (ASBT) and ileal bile acid transporter (IBAT), are proteins that are encoded by the SLC10A2 gene in humans. ASBT/IBAT is primarily expressed in the ileum on the brush border membrane of enterocytes. Its main function is the initial uptake of bile acids, especially conjugated bile acids, from the intestine as part of their enterohepatic circulation. Several medications are being developed to inhibit IBAT, such as elobixibat for constipation and irritable bowel syndrome, and volixibat for nonalcoholic steatohepatitis. The sodium/bile acid cotransporter, also known as Na+-taurocholate cotransporting polypeptide (NTCP) or liver bile acid transporter (LBAT), is a protein encoded by the SLC10A1 gene in humans. NTCP is an integral membrane glycoprotein with 349 amino acids and a mass of 56 kDa. It plays a role in the enterohepatic circulation of bile acids, along with another homologous transporter involved in bile acid reabsorption. NTCP binds two sodium ions and one conjugated bile salt molecule to facilitate hepatic influx of bile salts, as well as transport of steroid hormones, thyroid hormones, and xenobiotics. NTCP also acts as a cell surface receptor for hepatitis B and hepatitis D virus entry, which can be inhibited by various substances. NTCP deficiency in individuals can lead to elevated bile salt levels in plasma, but the phenotype is not always clear. Some individuals with a specific NTCP polymorphism are protected against HBV infection. NTCP-deficient mice show reduced hepatic bile salt uptake and some protective effects against high-calorie diet-related issues and liver damage in cholestasis, although these effects have not been fully replicated in humans.

Bile Acids and Farnesoid X Receptor Modulators

Bile acids (BAs) are evolutionally conserved molecules synthesized in the liver from cholesterol and have been shown to be essential for lipid homeostasis. BAs regulate a variety of metabolic functions viamodulating nuclear and membrane receptors. Farnesoid X receptor (FXR) is the most important nuclear receptor for maintaining BA homeostasis. FXR plays a tissue-specific role in suppressing BA synthesis and promoting BA enterohepatic circulation. Disruption of FXR in mice have been implicated in liver diseases commonly occurring in humans, including cholestasis, non-alcoholic fatty liver diseases, and hepatocellular carcinoma. Strategically targeting FXR activity has been rapidly used to develop novel therapies for the prevention and/or treatment of cholestasis and non-alcoholic steatohepatitis. This review provides an updated literature review on BA homeostasis and FXR modulator development. Bile acids (BAs) serve critical physiological functions, including elimination of cholesterol, absorption of fat and fat-soluble vitamins, regulation of the gut microbiome, and serving as important signaling molecules. BAs are endogenous ligands of farnesoid X receptor (FXR), Takeda G protein receptor 5 (TGR5), and sphingosine-1-phosphate receptor 2 (S1PR2). In the liver and intestine, BAs suppress their own synthesis, regulate glucose and lipid homeostasis, and inhibit inflammation and fibrogenesis. Disruption of BA homeostasis leads to severe pathological outcomes, including cholestasis, hepatic steatosis, fibrosis, and liver tumors. Regulating BA pathways has become a novel strategy to treat cholestasis and non-alcoholic steatohepatitis (NASH).

Conclusion

The liver plays a key role in protein and lipid metabolism, and diseases affecting hepatocytes can have widespread effects on various organs and systems. Hepatic conditions often involve the production of faulty or ineffective proteins, leading researchers to explore traditional gene therapy methods to boost protein levels by introducing transgenes. However, recent advancements in genome editing have opened up new possibilities for correcting genetic defects at the DNA level. This review explores the latest developments in using genome editing tools, particularly base editors, to develop therapeutic approaches for rare liver disorders, providing an update on the most recent strategies in the field.

Rare liver diseases encompass a diverse group of conditions that can impact various organs in addition to the liver due to the

multifunctional nature of hepatocytes. Liver cell abnormalities can lead to the development of various diseases characterized by the accumulation of proteins or toxic substances, resulting in systemic damage. Liver transplantation remains the primary curative option for most rare liver diseases, especially in pediatric patients, although it is limited by factors such as organ availability, post-operative complications, and immunosuppressive therapy-related side effects. The majority of rare hereditary liver diseases are caused by loss-of-function mutations or reduced gene expression, making them potential targets for traditional and innovative gene therapy strategies.

Traditional hepatic gene therapy aims to enhance the expression of deficient proteins by delivering therapeutic genes to hepatocytes, typically using recombinant adeno-associated viruses (rAAV). While rAAV-based approaches have shown efficacy in animal models and clinical settings, they are associated with limitations such as vector immunogenicity and pre-existing immunity in humans. Lipid nanoparticles (LNPs) have emerged as an alternative for transgene delivery to the liver, offering biodegradability and good tolerability. Recent advancements in genome editing technologies have shifted the focus towards correcting genetic mutations directly. Various genome editing platforms, including.

CRISPR-associated nucleases, have revolutionized targeted genomic manipulation by enabling precise modifications to DNA sequences. These platforms rely on nucleases that induce double-strand breaks (DSBs) in DNA, triggering repair mechanisms such as non-homologous end joining (NHEJ) or homology-directed repair (HDR). To improve the efficiency of correction without introducing random indels, researchers have developed base editing tools that enable the direct conversion of one DNA base to another without the need for DSBs. Cytosine and adenine base editors have been engineered to facilitate targeted substitutions with high efficiency and minimal off-target effects. While base editing technologies hold promise for therapeutic applications, concerns regarding off-target effects and fidelity remain [45]. Other genome editing techniques are advancing towards clinical translation, with a focus on rare genetic liver diseases, metabolic disorders, hemophilia, and hypercholesterolemia [45].

Genome editing is entering a new practical era that will gradually reveal more about the safety and effectiveness of these therapeutic approaches in humans. The liver has been a target for traditional gene therapy for some time, demonstrating its suitability for such treatments, but also showing that outcomes can vary depending on its regenerative capacity, which can lead to dilution of episomal transgenes through cell division, particularly in younger patients. Engineered nuclease-based approaches are expected to provide more definitive and sustained benefits. Additionally, the recent development of base editors represents a significant advancement towards precise single nucleotide correction. However, this technology is still in its early stages and further efforts are needed to minimize off-target effects and refine the system for clinical application in these extreme rare liver diseases in childhood.

Peroxisom-proliferator-activated receptors (PPAR)-agonists, ileal sodium/bile acid cotransporter (ASBT/IBAT/NTCP) and Farnesoid X receptor modulators could play an important role in the future to reduce the degree of cholestasis and later liver fibrosis in these extreme rare liver diseases. Further research must focus on higher study populations to analyze the long-term efficacy of the upper mentioned drugs in rare liver diseases in childhood.

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