Overview of Updated Practice Guidelines for Pediatric Nonalcoholic Fatty Liver Disease

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Abstract: Nonalcoholic fatty liver disease (NAFLD) is a form of chronic liver disease that is characterized by excessive fatty infiltration of the liver in the absence of significant alcohol consumption. As in the adult population, the etiology of NAFLD in children has been attributed to genetic predilection, insulin resistance, and obesity. The prevalence of NAFLD in the pediatric population has consistently increased over the past few decades, and it is currently considered the most common chronic liver disease in children. With increasing disease prevalence, NAFLD diagnosis and management have become more challenging. New guidelines for the management of pediatric NAFLD were published in 2017 by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. Additionally, the American Association for the Study of Liver Diseases updated their guidelines on NAFLD and included a section dedicated to the pediatric population. This article provides an overall description of the burden and natural history of pediatric NAFLD, with a focus on diagnosis and management in light of the recently updated guidelines.

Knowledge of the risk factors, pathophysiology, management, and prognosis of pediatric nonalcoholic fatty liver disease (NAFLD) has evolved since the disease was first identified in 1983.[1] The roles of insulin resistance and obesity as risk factors in the development of NAFLD have been well established.[2] Unfortunately, the prevalence of children who are overweight (body mass index [BMI] in the 85th-94.9th percentile), obese (BMI in the 95th-98.9th percentile), and severely obese (BMI in the 99th or higher percentile) is rising in the United States, contributing to the rapid ascent of NAFLD as the most common form of chronic liver disease in children. Genetic predilection and environmental triggers have also been implicated in the early onset of NAFLD, with a higher tendency for complications associated with adults who developed NAFLD in early childhood.[3] NAFLD is defined as

histologic evidence of at least 5% of hepatic steatosis in the absence of other causes of excessive fat accumulation in liver cells, such as alcohol abuse, chronic exposure to steatogenic agents, hereditary metabolic conditions, and viral hepatitis.[3] NAFLD has a histologic spectrum that ranges from simple fatty deposition in the hepatocyte (ie, nonalcoholic fatty liver) to the potentially progressive form of nonalcoholic steatohepatitis (NASH), which is characterized by lobular inflammation and hepatocyte injury in the form of ballooning and which leads to progression to fibrosis and possibly cirrhosis.[4] Interestingly, young children with NASH may show unique histologic features, including the presence of periportal inflammation and fibrosis without ballooning.[3] Of note, the onset of NAFLD and the progression to advanced fibrosis have been documented within the first decade of life.[5,6]

Despite advances in managing pediatric NAFLD over the past 3 decades, knowledge is lacking in regard to its natural history, screening strategies, and effective treatment.[7] This article reviews the most recent guidelines for the management of pediatric NAFLD as published by 2 professional medical societies in the United States, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the American Association for the Study of Liver Diseases (AASLD).[3,7] A comparison between the NASPGHAN and AASLD guidelines is provided in the Table. This article also evaluates pharmacologic agents that are in late-stage development in adult clinical trials, as they may soon be evaluated in the pediatric population.

Epidemiology

Currently, no studies accurately describe the true incidence of pediatric NAFLD[7]; however, research findings have shown the highest incidence of the disease to be among Hispanic children of Mexican descent.[8] Several studies have estimated the prevalence of pediatric NAFLD, with considerable variability.[7] Differences in prevalence estimates depend on a number of factors, principally the NAFLD diagnostic criteria (which are based on an elevation in liver enzymes, imaging studies, or liver histology) and the demographic characteristics of the sampled population. A recent analysis by Anderson and colleagues showed the prevalence ranging from 8% in nonobese children to as high as 34% in obese children.[9] Furthermore, the prevalence of NAFLD was found to be higher in male children and adolescents and positively correlated with BMI.[9,10] Other factors that are associated with a relatively high prevalence of NAFLD include Hispanic and Asian ethnicity; impaired glucose tolerance, prediabetes, or diabetes; panhypopituitarism; and obstructive sleep apnea.[3,7,9,10]

Natural History and Outcomes

Although the exact time of onset of pediatric NAFLD is unknown, some studies provide evidence of disease onset during the perinatal period in children of mothers with diabetes mellitus. A retrospective cohort study showed a significantly higher percentage of hepatic steatosis, assessed by magnetic resonance imaging, in neonates of obese mothers with gestational diabetes mellitus compared to neonates of normal-weight, nondiabetic mothers.[11] Other studies have shown increased hepatic steatosis in infants of mothers with a high BMI and in stillborn infants of mothers with diabetes mellitus, providing further evidence of disease onset in the perinatal period.[12,13]

Little is known about the natural history and outcomes of pediatric NAFLD due to a lack of prospective studies evaluating children over a long period of time; hence, disease prognosis remains uncertain. However, it is well documented that the entire spectrum of NAFLD, from hepatic steatosis to NASH to fibrosis and even cirrhosis, may occur during childhood. A long-term, retrospective, cohort study followed 66 children for 20 years to assess pediatric NAFLD progression and prognosis.[4] In this study, children with NAFLD had 14 times the risk of progression to severe liver disease or death when compared to children without NAFLD.[4] Hepatocellular carcinoma (HCC) is considered part of the NAFLD spectrum in adult patients. HCC in pediatric patients with NAFLD is exceedingly rare, although it has been reported by Nobili and colleagues, who identified the presence of HCC in a 7-year-old boy who was previously diagnosed with NAFLD.[14] The need for liver transplantation to treat children and young adults with NAFLD-related end-stage liver disease is well known and might be on the rise.[15,16] These findings demonstrate that pediatric NAFLD may progress to severe disease (ie, cirrhosis, end-stage liver disease, HCC) with fatal outcomes or the need for liver transplantation. However, larger prospective studies are required to validate these findings and to better understand the natural history of pediatric NAFLD.

A significant aspect of pediatric NAFLD is its association with multiple extrahepatic manifestations, such as hypertriglyceridemia, hypertension, premature atherosclerosis, obstructive sleep apnea, polycystic ovarian syndrome, and other comorbidities that have been reviewed in detail by Selvakumar and colleagues.[17]

Screening Children for Nonalcoholic Fatty Liver Disease

Children with NAFLD often do not present with symptoms, and health care providers may miss opportunities to screen for NAFLD in at-risk children.[3,18] As a result,

Table. Summary of the NASPGHAN and AASLD Guidelines on the Diagnosis and Management of Pediatric NAFLD

	AASLD Guideline (2017)	NASPGHAN Guideline (2017)
Screening for NAFLD	No recommendation regarding screening in overweight and obese children due to paucity of evidence	• Screen with ALT levels using sex-specific upper limits of normal in all obese children and in overweight children with other risk factors starting at the age of 9-11 years. • Recommends against using routine ultrasound due to low sensitivity
Diagnosis/Workup	• Rule out other causes of chronic liver diseases. • Additional consideration to be given to monogenic causes of chronic liver disease such as inborn errors of fatty acid metabolism, peroxisomal disorders, and lysosomal storage disorders in very young or nonoverweight children	• Exclude alternative etiologies for elevated ALT levels and/or hepatic steatosis. • Investigate the presence of coexisting chronic liver diseases.
Liver Biopsy	Consider: • when diagnosis is unclear • in the presence of high titers of autoantibodies in association with high globulin (to rule out autoimmune hepatitis) • when multiple disorders are possible • before starting potentially hepatotoxic medications • in order to establish a diagnosis of NASH prior to starting pharmacotherapy for NASH.	• Consider for the assessment of NAFLD in children who have an increased risk of NASH and/or advanced fibrosis, such as patients with higher ALT levels (>80 U/L), splenomegaly, and AST/ALT >1. • Known clinical risk factors for NASH and advanced fibrosis include panhypopituitarism and type 2 diabetes.
Noninvasive Tests to Diagnose NASH and Stage Fibrosis	Further validation studies are required before noninvasive tests can be applied in the clinic.	Further validation studies are required before noninvasive tests can be applied in the clinic.
Treatment	• Intensive lifestyle modifications should be the first-line treatment. • Metformin (500 mg twice daily) should not be prescribed as a NASH-specific therapy. • Vitamin E may be used to treat pediatric NASH, but the risks and benefits should be discussed with each patient, given that long-term safety of high-dose vitamin E in children is unknown.	• Lifestyle modifications to improve diet and increase physical activity are recommended as first-line treatments. • Avoid sugar-sweetened beverages. • Increase moderate- to high-intensity physical activity and limit screen time activities to <2 hours per day. • No currently available medications or supplements are recommended to treat NAFLD because none have been proven to benefit the majority of patients with NAFLD.

AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NASPGHAN, North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition.

pediatric NAFLD may be undetected in a significant proportion of the population. Routine liver function tests and imaging studies of the abdomen often lead to incidental findings of pediatric NAFLD.[3] Given that NAFLD may progress during childhood and that lifestyle modification with weight reduction has been shown to effectively reverse the course of early disease, it is logical to consider screening for NAFLD in children at risk.[7] Clinicians should take into account certain risk factors when deciding whether or not to screen for NAFLD, such as a BMI classified as overweight or obese (in the 85th percentile or higher), insulin resistance, prediabetes or diabetes, dyslipidemia, obstructive sleep apnea, or a family history of NAFLD.[7,19] In fact, the NASPGHAN practice guideline recommends screening for NAFLD beginning between ages 9 and 11 years for all obese and overweight children with additional risk factors. An earlier screening age was suggested for patients at higher risk, such as children with severe obesity or panhypopituitarism. The recommended screening test is alanine aminotransferase (ALT) using sex-specific upper limits of normal (females, 22 U/L; males, 26 U/L).[7] The guideline recommends

against using routine ultrasound as a screening test due to inadequate sensitivity and specificity. However, this is a controversial point, as many children with evidence of NAFLD on ultrasound may have normal ALT levels and because advanced fibrosis has been well documented in children with normal liver enzymes. Due to the lack of data on the long-term benefits and cost-effectiveness of screening for NAFLD, the AASLD did not make a recommendation regarding screening in overweight and obese children.

Establishing the Diagnosis of Pediatric Nonalcoholic Fatty Liver Disease

Before arriving at a diagnosis of NAFLD, clinicians should exclude other causes of elevated transaminases and hepatic fatty infiltration, such as viral hepatitis, autoimmune liver disease, metabolic diseases, Wilson disease, and hepatotoxic medications.[7] When elevated transaminases occur in a setting of high autoantibody titers, especially in association with high globulins or a high total-protein-to-albumin ratio, it is important to histologically exclude autoimmune hepatitis.[3,7] Of note, low serum titers of autoantibodies are common in children with NAFLD and should not trigger a liver biopsy by themselves. After excluding other causes of chronic liver disease, the diagnosis of suspected NAFLD is typically established; however, liver biopsy remains the gold standard for the diagnosis of definitive NAFLD and for determining disease severity, including the presence of NASH and fibrosis. Prior to performing a liver biopsy, clinicians should have a discussion with the child and the family to ensure that they understand the benefits and risks of the procedure.[3] Some of the risks associated with liver biopsy include bleeding, pain, leakage of bile, formation of arteriovenous fistulas, pneumothorax, and death.[20]

Noninvasive Assessment of Severity

The severity of steatosis can be determined using special magnetic resonance imaging–based technologies such as magnetic resonance spectroscopy and proton density fat fraction, although these modalities may not be readily available.[21-23] Controlled attenuation parameter (CAP) is another noninvasive tool that can be used for assessing the severity of steatosis, and is based on a radiofrequency ultrasound signal acquired by a transient elastography device (FibroScan, Echosens). CAP is an estimate of the ultrasonic attenuation coefficient at 3.5 MHz, and is feasible in older children, operator-independent, and easily reproducible.[24] Recent findings from a study conducted at the Boston Children's Hospital demonstrated that CAP was able to identify the presence or absence of steatosis as well as discriminate between different grades of steatosis with reasonable accuracy in comparison to liver biopsy.[25]

The severity of liver fibrosis in patients with NAFLD is potentially the most important prognostic factor for long-term outcomes, and having a reproducible noninvasive method to assess it is paramount. Imaging techniques such as transient elastography (using FibroScan) and magnetic resonance elastography have been proven to be accurate in adults; however, these technologies are still being validated in the pediatric population and show promising results.[7] Serologic tests based on biomarkers of liver fibrosis, such as the Enhanced Liver Fibrosis (ELF; Siemens) test, have been evaluated in children and have shown reasonable accuracy, although external validation is warranted before these tests can be implemented in routine clinical practice.[26] The fibrosis biomarkers that are included in the ELF test are tissue inhibitor of metalloproteinase-1, hyaluronic acid, and amino-terminal propeptide of type III procollagen. Additional fibrosis scores that use readily available clinical variables to predict the presence or severity of fibrosis have been developed in children, but their reproducibility has been questioned. A detailed review of fibrosis biomarkers and imaging studies in the context of pediatric NAFLD was recently published.[27]

Treatment of Nonalcoholic Fatty Liver Disease in Children

Several clinical trials have been conducted to assess the different approaches to managing pediatric NAFLD. However, these trials have limitations, including small sample size, short duration of intervention, different primary endpoints, and insufficient knowledge about the natural history of the disease.[7] Treatment modalities may be broadly classified into lifestyle modification and pharmacotherapy. The decision on which treatment modality to use depends on disease severity and the safety of treatment (Figure). Bariatric surgery, although not recommended as a treatment for pediatric NAFLD, may be considered in severely obese children with advanced NAFLD who have other serious comorbidities, such as type 2 diabetes mellitus, idiopathic intracranial hypertension, and debilitating sleep apnea.[7] The goal of treatment is to reduce the burden of disease and improve long-term outcomes, and efficacy is considered to be achieved when there is a reduction in hepatocyte fat content, decreased hepatocyte inflammation, absence of fibrosis, and a reduction of transaminases to within normal levels.[3,7]

Lifestyle Modification

Dietary restriction and exercise are recommended as first-line treatments for all obese children with NAFLD

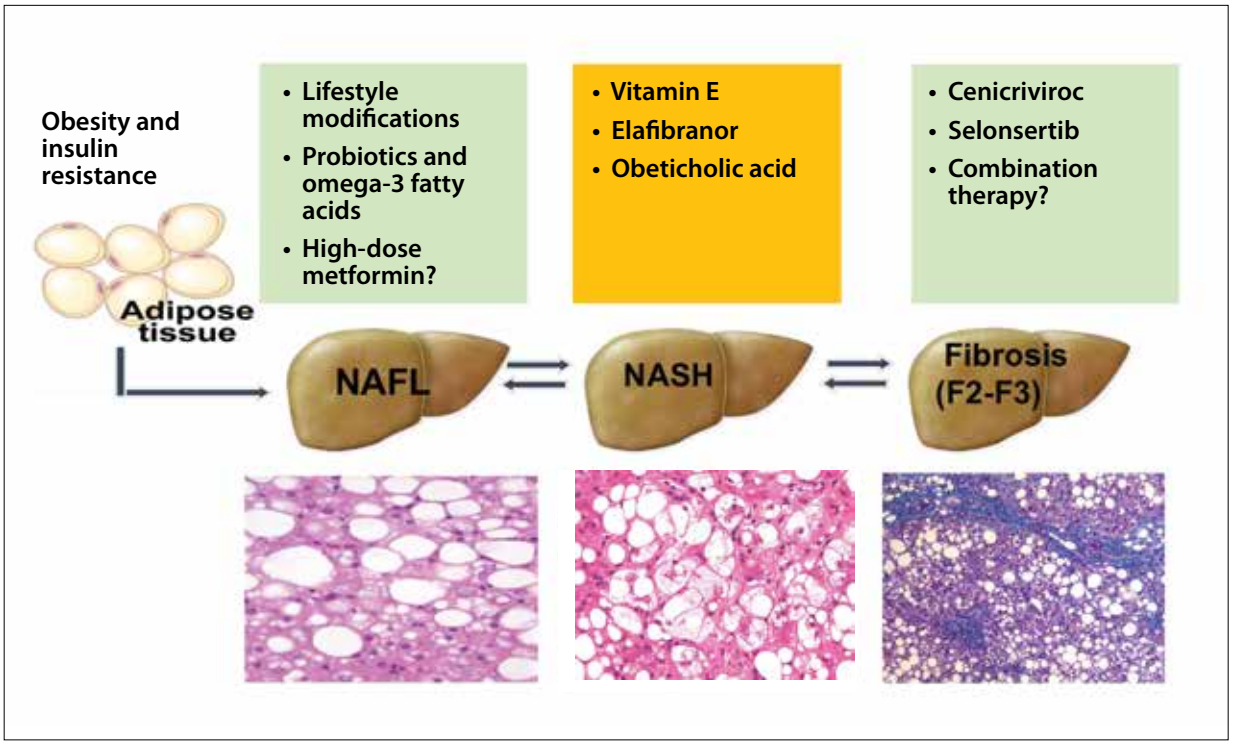

Figure. Treatment of pediatric nonalcoholic fatty liver disease based on disease severity. Patients with early disease or nonalcoholic fatty liver (NAFL) should focus on weight loss through lifestyle modifications; safe medications such as probiotics and omega-3 fatty acids could also be considered. Children with nonalcoholic steatohepatitis (NASH) may benefit from medications with antioxidant or anti-inflammatory effects. Patients with NASH-induced fibrosis may need medication with antifibrotic effects.

and have been endorsed by both the NASPGHAN and AASLD practice guidelines.[7,28] In general, the success of dietary restriction and weight loss alone in the management of NAFLD has been low, but there is literature suggesting that lifestyle modification does work. A study that was conducted in Italy by Nobili and colleagues showed a reduction in serum ALT and hepatic steatosis in children who lost approximately 20% of their body weight over a 12-month period.[28] Reportedly 94% of children were able to achieve this goal, but it has not been our experience or the experience of other large NAFLD programs in the United States. In general, multifaceted approaches to weight management have been successful in improving liver enzymes. These approaches consist of frequent contacts (a minimum of 26 hours within a 6-month period), dietary modifications (eg, avoidance of sugary drinks, consumption of balanced diets), daily moderate- to high-intensity physical activity, reduced screen time (<2 hours per day), and family engagement.[29] Although bariatric surgery may be performed to achieve significant weight loss, it is not currently recommended as a specific treatment for pediatric patients with NAFLD.[7]

In the adult literature, most studies have demonstrated that only 5% to 10% of patients have been able to lose 10% of their body weight, leaving the majority of patients in need of other interventions to treat NAFLD. More pediatric studies need to be conducted in order to standardize the amount of weight loss required to achieve treatment goals.[3] Furthermore, future research should focus on identifying specific diets that are beneficial for either halting or reversing disease progression.[3,30,31]

Pharmacotherapy

Insulin Sensitizers Insulin resistance plays a prominent role in the development and progression of NAFLD; therefore, insulin sensitizers have shown promise in the treatment of NAFLD. Pioglitazone is a peroxisome proliferator-activated receptor (PPAR) γ agonist that boosts insulin sensitivity. A large randomized clinical trial in adults with NASH who were treated with 30 mg of pioglitazone daily showed a reduction in serum transaminases as well as in hepatic steatosis, inflammation and ballooning, and resolution of NASH.[32,33] Some of the side effects of pioglitazone include weight gain, worsening of cardiac failure, and a potentially increased risk of bladder cancer.[34]

Therefore, pioglitazone is not expected to gain widespread use in the treatment of pediatric NAFLD. Metformin also increases insulin sensitivity and is approved to be used in children with diabetes. However, the TONIC (Treatment of NAFLD in Children) trial was unable to establish the superiority of metformin (500 mg twice daily) over placebo in reducing serum transaminase levels or improving NAFLD histology.[35] Based on the results of this trial, both the NASPGHAN and AASLD guidelines do not recommend using metformin to specifically treat NAFLD or NASH. The major limitations of the TONIC trial were the low dose of metformin used and the lack of significant improvement in insulin sensitivity. The effects of higher doses of metformin in pediatric NAFLD are unknown, but this treatment can be administered in clinical practice in patients who have evidence of prediabetes and NAFLD given its known long-term safety and low cost. However, clinicians should be aware that metformin-associated hepatotoxicity has been described, and that metformin should not be used in patients with end-stage liver disease.

Antioxidants Oxidative stress and the production of reactive oxygen species are thought to be involved in fatty liver disease progression to NASH and advanced fibrosis.[36] Therefore, antioxidants have been identified as possible therapeutic candidates in the management of NAFLD and NASH. Clinical trials have been conducted to assess the effects of vitamin E as an antioxidant on fatty liver disease. The best evidence for the use of vitamin E to treat NASH in children comes from the multicenter TONIC trial, in which the administration of 800 IU daily significantly reduced the NAFLD activity score, with resolution of NASH in 58% of subjects.[35] However, the primary endpoint of sustained ALT reduction was not attained, and there was no improvement in liver fibrosis.[35,37] Despite the promising outcomes of vitamin E in the treatment of fatty liver disease, the effects of its long-term use are still being investigated owing to the potential to increase the risk of prostate cancer and all-cause mortality.[38,39] Given the results of the TONIC trial, the AASLD guideline suggested that vitamin E may be used to treat children with biopsy-proven NASH, but the risks and benefits should be discussed with each patient before committing to treatment.[3] In contrast, the NASPGHAN guideline does not recommend the use of vitamin E in children with NASH or NAFLD.[7]

Omega-3 Fatty Acids Omega-3 fatty acids (eg, docosahexaenoic acid [DHA] and eicosapentaenoic acid) may help in improving liver histology in patients with NAFLD by promoting fatty acid oxidation and inhibiting de novo lipogenesis. Studies on the efficacy of omega-3 fatty acids in NAFLD have shown inconclusive results. A randomized, controlled trial of DHA (250 and 500 mg/day) for 6 months in children with biopsy-proven NAFLD found significant reduction in hepatic steatosis as demonstrated by ultrasonography compared to placebo.[40] A limitation to these findings is that ultrasonography has low accuracy in predicting changes in hepatic steatosis. On the contrary, a more recent randomized trial of DHA in obese and/or overweight children with NAFLD (ALT ≥30 U/L and ultrasound evidence of steatosis) showed no effect on ALT, steatosis, or insulin resistance.[41] Regardless of the controversial evidence of the efficacy of DHA in improving liver histology, its reasonable safety profile makes it a viable choice for the treatment of pediatric NAFLD.

Probiotics Strong evidence suggests that gut microbiota play a role in the development of obesity and its complications, including NAFLD. The obese microbiome has been shown to increase the yield of energy from food by harvesting inaccessible nutrients. Therefore, manipulation of gut microbiota with probiotics might prove to be an effective treatment strategy to halt the development and progression of NAFLD. Studies have evaluated the use of probiotics in adults and children with NAFLD. In a randomized, controlled trial involving 20 children with elevated transaminases and evidence of steatosis on ultrasound, 8-week treatment with the probiotic *Lactobacillus rhamnosus* GG (12 billion colony-forming units/day) led to significant improvement in ALT levels compared to placebo independent of changes in BMI.[42] Additionally, Alisi and colleagues demonstrated significant improvement in ultrasound-based steatosis in children after 4 months of treatment with VSL#3 compared to placebo.[43] More recently, a randomized, placebo-controlled trial of a probiotic for 12 weeks showed improvement in liver enzymes and lipid profiles in obese children.[44] These results, along with minimal cost and side effects, make probiotics a promising future treatment option for pediatric patients with NAFLD; however, randomized, controlled trials with larger sample sizes, long-term follow-up, and assessment of efficacy based on liver histology are warranted.

Novel Investigational Medications for Adult Nonalcoholic Fatty Liver Disease Several commonly used medications in adults, such as statins, glucagon-like peptide-1 agonists, and angiotensin receptor blockers, have shown some promising effects on the severity of NAFLD in adults, but there are no data to support their use in children.

In the last 5 years, a number of clinical trials have assessed the safety and efficacy of different novel medications to treat NAFLD in the adult population. Several

drugs are in phase 3 development for adult patients with NAFLD and may receive approval by the US Food and Drug Administration by the year 2020. It is likely that some of these medications will be tested in the pediatric population after their efficacy has been established in adults.

Obeticholic acid (OCA; Ocaliva, Intercept Pharmaceuticals) is a synthetic analogue of chenodeoxycolic acid and is a potent activator of farnesoid X receptor, which is a nuclear receptor that exists in the liver and modulates bile acid, lipid, and glucose metabolism. In the FLINT (Farnesoid X Nuclear Receptor Ligand Obeticholic Acid for Noncirrhotic, Nonalcoholic Steatohepatitis) trial—a multicenter, double-blind, placebo-controlled, randomized study—OCA given at a dose of 25 mg daily for 72 weeks showed histologic improvement in 45% of patients compared to 21% in the placebo arm (P=.0002), with significantly higher rates of fibrosis regression.[45] The safety and long-term effects of OCA are being evaluated in a phase 3 trial.

Elafibranor (GFT505, Genfit) is an insulin sensitizer that is being evaluated as a candidate for NAFLD treatment. It is a PPAR agonist that exerts its effect on PPAR-α and PPAR-δ receptors, leading to potential improvement in hepatic steatosis, inflammation, and fibrosis. Elafibranor was evaluated in patients with NASH without cirrhosis. A dose of 120 mg for 52 weeks showed significantly higher rates of NASH resolution compared to the placebo group.[46] A phase 3 trial[47] is underway to assess the effect of 120 mg daily on NASH resolution after 72 weeks of treatment, with long-term follow-up to evaluate the development of liver-related complications.

Selonsertib (GS-4997, Gilead Sciences) is an apoptosis signal-regulating kinase 1 inhibitor that modulates hepatocyte apoptosis and liver fibrosis. Selonsertib was evaluated in a phase 2 trial and showed improvement in fibrosis on biopsy, liver stiffness measured by magnetic resonance elastography, and fat content in patients with moderate to severe liver fibrosis (F2 or F3).[48] Two phase 3 trials are currently assessing the efficacy of selonsertib in adult patients with NASH-associated advanced fibrosis or cirrhosis.[49,50]

Cenicriviroc is a dual antagonist of C-C chemokine receptor types 2 and 5. Activation of these chemokine receptors causes fibrogenesis by monocyte and macrophage recruitment to the inflamed tissue and activation of hepatic stellate cells. These receptors are upregulated in obese patients with NASH. The CENTAUR phase 2b trial evaluated cenicriviroc in noncirrhotic NASH patients with fibrosis.[51] Improvement in fibrosis by at least 1 stage was met in significantly more patients on cenivriviroc than on placebo (20% vs 10%; P=.02), leading to the advancement of this compound to a phase 3 trial that is currently recruiting patients.[52]

Conclusion

Pediatric NAFLD is a prevalent cause of chronic liver disease in children with potentially serious complications that may manifest in adolescents and young adults. The 2017 publications of practice guidelines by both the NASPGHAN and the AASLD is a step forward in providing clinicians with the necessary tools to optimize clinical care.

Further research is needed to understand the natural history of this disease and to provide accurate prognostic information to patients at the time of diagnosis, which will help in identifying risks for aggressive disease and in predicting disease progression. Establishing the cost-effectiveness and impact on long-term outcomes of different screening strategies for pediatric NAFLD is especially important in reducing the societal burden of this epidemic. The ideal screening test will be inexpensive, with high sensitivity and specificity. Effective screening will ensure early treatment, thereby preventing irreversible liver injury and improving quality of life. Liver biopsy remains the gold standard for diagnosing the presence of NASH and for determining the stage of liver fibrosis. Identifying and validating other noninvasive biomarkers or imaging modalities that accurately diagnose NASH and fibrosis are urgently needed to minimize the risks associated with performing liver biopsies in children.

Although lifestyle modifications (ie, diet and exercise) are recommended as first-line approaches in the management of pediatric NAFLD, it is expected that promising therapeutic agents for NAFLD will transform the way clinicians care for children with this disease.

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