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CHILDREN/ADOLESCENTS/YOUNG ADULTS AND ATHEROSCLEROSIS (D.P. WILSON, SECTION EDITOR)

The Role of Non-statin Lipid-Lowering Medications in Youth with Hypercholesterolemia

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Abstract

Purpose of Review Lifestyle modification is additive to lipid-lowering medications in the treatment of heterozygous familial hypercholesterolemia (HeFH), which does not respond sufficiently to statin therapy. While both are also important in homozygous familial hypercholesterolemia (HoFH), additional measures such as apheresis may be needed. The purpose of this review is to identify non-statin medications to lower cholesterol that are available for children and adolescents as adjunctive therapy.

Recent Findings Ezetimibe is commonly used as second-line pharmacotherapy for treatment of HeFH and HoFH. Colesevelam, a bile acid sequestrant, may be considered for adjunct therapy. Since 2015, the PCSK9 inhibitor evolocumab has been available for adolescents, and its FDA approval has now expanded to age 10 years. The ANGPTL3 inhibitor evinacumab has been approved for children age 12 years and older. A clinical trial for lomitapide is in progress.

Summary Approvals for PCSK9 and ANGPTL3 inhibitors have expanded opportunities for children and adolescents with HeFH and HoFH to achieve lower LDL-C levels.

Keywords Heterozygous familial hypercholesterolemia · Homozygous familial hypercholesterolemia · Cholesterol · Low-density lipoprotein · Pediatrics · Children

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide. Hypercholesterolemia is a significant predisposing factor, as elevated levels of low-density lipoprotein cholesterol (LDL-C) ranks third among modifiable risk factors that contribute to CVD [1]. The importance of early detection and treatment of hyperlipidemia cannot be overstated, as evidence suggests that the development of precursors of atherosclerotic cardiovascular disease (ASCVD) begins as early as childhood [2, 3]. In the setting of a high prevalence of obesity and worsening dietary practices among youth in the USA [4], the prevalence of at least one abnormal lipid level (total cholesterol, HDL-C, or non-HDL cholesterol) was reported to be 19.2% in 2013–2016. In youth less than 18 years of age, causes of dyslipidemia include unhealthy lifestyle, medication-related dyslipidemia, secondary dyslipidemia with an underlying medical condition, and genetic dyslipidemias (familial combined hyperlipidemia [5], familial severe hypertriglyceridemia, and familial hypercholesterolemia, (FH)).

Familial hypercholesterolemia is a common monogenic condition. The prevalence of heterozygous familial hypercholesterolemia (HeFH) is estimated to be 1 in 200–300 individuals [6, 7]. Homozygous FH (HoFH) is more rare with an estimated prevalence of 1 in 1 million in the US [8], or up to 1:300,000 to 1:400,000 worldwide [9]. FH is most often diagnosed clinically

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in youth with an elevated LDL-C > 190 mg/dl or > 160 mg/dl with family history [10, 11], while the presence of physical findings of hypercholesterolemia such as tendon xanthomas, and corneal arcus rarely occur [12]. Cascade screening is recommended, although a family history may often be inaccurate or incomplete. Universal childhood screening programs may identify 1.3 to 4.8 cases of FH per 1000 screened [13].

In the majority of individuals with FH, loss-of-function mutations in the gene for the LDL receptor (*LDLR*) lead to impaired clearance of LDL from the circulation, resulting in persistently high LDL-C levels. Less commonly, FH is caused by gain-of-function mutations in *PCSK9*, or mutations in *APOB*. In 2018, an expert consensus statement recommended genetic testing as part of the standard of care for patients clinically diagnosed or suspected to have FH along with their first- and second-degree relatives [14]. Since variations in LDL-C levels and receptor expression have been observed [15], information on the genotype can be instrumental in understanding the child's physiology in order to guide interpretation of response to therapy.

Management of FH involves significant challenges, as this condition requires pharmacotherapy in addition to a CHILD-2 low-fat diet (25–30% total calories from fat, < 7% saturated fat). The goal is to lower LDL-C by > 50% or to < 130 mg/dL in children [11]. While statins are approved for pediatric use as young as age 7–8 years, and follow-up studies confirm their safety [16], adjunctive therapy is sometimes necessary in order to achieve adequate lowering of cholesterol. In a 20-year follow-up study of FH individuals who initiated statin therapy between 8 and 18 years of age, the mean LDL-C level decreased by − 32% from baseline, and the data suggested fewer CVD events. However, only 20% of FH subjects reached LDL-C levels < 100 mg/dL [17].

For many years, the standard of care for FH included a statin, ezetimibe, and for those with HoFH, LDL apheresis [9]. However, statins in combination with ezetimibe are often insufficient to lower LDL-C to goal in HeFH, while apheresis significantly impacts quality of life if required in HoFH. One large Spanish cohort of FH patients reported that high-intensity statin plus ezetimibe lowered LDL-C to < 100 mg/dL in fewer than 10% of subjects [18] The purpose of this article is to review additional options for youth less than 18 years of age, especially newer therapies, such as inhibitors of PCSK9 and ANGPTL3 (see Table 1). We will discuss these medications, review the evidence regarding their lipid-lowering effects, and also highlight areas where further research is needed for pediatric use.

Medication Classes with at Least One Approved Indication for Pediatric Use

Ezetimibe — Selective Cholesterol-Absorption Inhibitor

Ezetimibe is an azetiadione that reduces intestinal cholesterol uptake from biliary and dietary sources through

Table 1 Lipid-lowering medications with approved indications for pediatric use

Class of medication and drug name	Approved pediatric age range	Approved pediatric indication	Clinical trial treatment duration	Clinical trial lipid outcome measure (% change from baseline)				Reference
				LDL-C	Apo B	TG	Lp(a)	
Selective cholesterol-absorption inhibitor								
Ezetimibe	10–17 years	HeFH	12 weeks	− 28%	− 22%	− 6%	NR	Kusters et al. [27]
Bile-acid sequestrant								
Colesevelam	10–17 years	HeFH	8 weeks, 3.75 mg	− 10.0%	− 6.2%	+ 17.4%	NR	Stein et al. [32]
PCSK9 inhibitor								
Evolocumab	10–17 years	HoFH and HeFH	12 weeks (TESLA-B)	–23·1%	–19·2%	–1·4%	–9·4%	Raal et al. [15]
			48 weeks (TAUSSIG), ± apheresis	–23.3%	–16.2%	NR	–11.9%	Raal et al. [36]
			24 weeks (HAUSER-RCT)	− 44.5%	− 34.9%	NR	− 7.4%	Santos et al. [37.••]
ANGPTL3 inhibitor								
Evinacumab	12–17 years	HoFH	24 weeks	− 47.1%	− 41.4%	− 55.0%	− 5.5%	Raal et al. [45.••]

This table lists the non-statin medications currently approved for use in pediatric patients, along with lipid outcome measures from select clinical trials that included subjects age 17 years or younger

HeFH heterozygous familial hypercholesterolemia, *HoFH* homozygous familial hypercholesterolemia, *NR* not reported, *RCT* randomized controlled trial, *LDL-C* low-density lipoprotein cholesterol, *Apo B* apolipoprotein B, *TG* triglyceride, *Lp(a)* lipoprotein(a), *PCSK9* proprotein convertase subtilisin/kexin type 9 serine protease, *ANGPTL3* angiopoietin-like 3

selective inhibition of the Niemann-Pick C1-Like 1 (NPC1L1) sterol transporter. Studies on adults originally reported that ezetimibe in combination with a statin reduced LDL-C by − 15% compared to statin alone [19–21], and later evidence supported a reduction of subsequent cardiovascular events after acute coronary syndrome [22], but no effect on lipoprotein(a) (Lp(a)) [23]. For children and adolescents, ezetimibe is currently approved for youth 10 years of age or older.

An international multicenter, randomized, double blind, placebo-controlled trial (RCT) on children age 6–11 years with HeFH showed that ezetimibe 10 mg plus simvastatin 40 mg/day resulted in a mean LDL-C reduction of 54.0% compared to 38.1% mean LDL-C reduction with simvastatin alone [24]. A small prospective [25] and a retrospective study [26] suggested LDL-C reductions could be achieved in children with hypercholesterolemia through monotherapy. Subsequently, a multicenter RCT of children with HeFH or non-familial hypercholesteromia showed that ezetimibe monotherapy for 12 weeks with dietary intervention led to − 28% LDL-C reduction [27] compared to − 1% reduction in the placebo group, along with reductions in total cholesterol (− 21.1% vs + 1.2%), non-HDL-C (− 25% vs + 0.3%), and apoB (− 22% vs − 1%) (Table 1). One subject demonstrated an ALT at least 3 × the upper limit of normal (ULN), while one of five subjects experienced treatment-related adverse events (5.4% of treated subjects).

Therefore, in clinical practice, ezetimibe provides a generally well-tolerated option for lipid-lowering therapy. It may be used as monotherapy for statin-intolerant patients (which, although possible, is rare in youth), or in combination with a statin.

Bile Acid Sequestrants

Sequestrants bind to bile acids, blocking the absorption of cholesterol and bile acids from the intestines. Various formulations are approved for treatment of hypercholesterolemia in adults. Although colestipol and cholestyramine have also been studied in children [28–31], colesevelam is the only agent in this class that has been approved by the FDA for pediatric patients age 10 years or older with HeFH [32]. In a RCT of 194 subjects age 10–17 years, significant LDL-C reductions of − 6.3% and − 12.5% difference from placebo were observed after 8 weeks at the lower (1.875 g/day) and higher (3.75 g/day) doses of colesevelam (Table 1), respectively. Bile acid sequestrants are available as a tablet, or as a powder to be dissolved in liquid. Challenges to adherence include lack of palatability and its gastrointestinal side effects, which may include nausea, vomiting, constipation, and gas. Absorption of ingested substances such as vitamins as well as medications may also be reduced with concurrent use. Therefore, bile acid sequestrants are recommended to be taken at least 4 h after all medications [33].

PCSK9 Inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are human monoclonal antibodies that lower LDL-C by inhibiting PCSK9-mediated degradation of the LDLR. The current evidence from long-term trials (> 48 weeks) indicate that the currently available PCSK9 monoclonal antibodies, evolocumab and alirocumab, are safe and effective when used as an add-on or, in adults, as monotherapy. Evolocumab was originally approved in 2015 for use in adults and adolescents with HoFH as young as 13 years of age. In 2021, expanded approval was granted beginning at 10 years of age for treatment of HeFH. Alirocumab was originally approved in 2015 for use in adults with CVD, HeFH, and HoFH; however, pediatric clinical trials are still in progress.

The unique functionality of genetic variants that cause FH in a child may be informative when using PCSK9 inhibitors, since residual LDL receptor (LDLR) function influences the lipid-lowering effect. Patients with homozygous null LDLR mutations (LDLR function < 2%) have demonstrated minimal lipid-lowering effects from PCSK9 inhibitor treatment in contrast to individuals with defective LDLR mutations, who may still respond due to residual LDLR function [15]. Thedrez and colleagues reported that lymphocytes from HoFH TESLA study subjects with defective/null mutations expressed lower flow cytometry LDLR levels than subjects with defective/defective mutations [34]. Therefore, understanding the patient's genotype may help set expectation of effect from PCSK9 inhibitors.

Evolocumab

The pivotal study of evolocumab was a phase 3 RCT of 901 adults with hypercholesterolemia and CV risk (DESCARTES). In addition to diet, evolocumab 420 mg was given every 4 weeks as monotherapy, or combined with atorvastatin 10 mg or 80 mg (with or without ezetimibe). The treated subjects showed a least square means reduction of ~ − 57% at week 12 maintained through week 52, while 82.3% of patients on evolocumab achieved LDL-C level < 70 mg/dL vs 6.4% on placebo [35].

TESLA-B was a phase 3 RCT that included 8 children with HoFH as young as 13 years of age in a cohort of 50 subjects [15] (Table 1). In this study, the 49 subjects, who completed 420 mg evolocumab every 4 weeks for 12 weeks, showed relative reductions of − 30.9% for LDL-C − 23.1% for apoB compared with placebo. No significant changes were observed in Lp(a) or TG. An open-label phase 3 trial (TAUSSIG) included 14 children age 12 or older out of 106 total subjects with or without apheresis. The total

cohort showed LDL-C reductions of − 20.6% at week 12, and − 23.3% at week 48 [36].

Evolocumab has also been evaluated in HeFH patients age 10–17 years. A phase 3 RCT (HAUSER-RCT) was conducted in which 104 children received evolocumab and 53 received placebo. At week 24, the evolocumab group showed a reduction in LDL-C percent change from baseline of − 44.5%, compared to − 6.2% in the placebo group [37.••, 38].

Adverse effects, such as flu-like symptoms and injection-site reactions, have been reported in both adult and pediatric study subjects. Muscle-related effects were more common among adults with a history of statin-intolerance [39, 40]. In the HAUSER pediatric study, adverse events that occurred > 1% in the evolucomab group included symptoms such as headache, flu-like symptoms, upper respiratory tract infection, and constipation, but there were no reports of myalgia or muscle spasm.

Evolocumab is delivered by injection via pre-filled syringe, auto-injector device, or for HoFH, in a disposable, single-use infusion device. Evolocumab is dosed at 140 mg every 2 weeks for HeFH, while HoFH patients receive 420 mg monthly.

Alirocumab

The safety and efficacy of alirocumab was established in the ODYSSEY COMBO I study, comprised of 316 adults with hypercholesterolemia at high risk of CVD. After treatment for 24 weeks, there was a mean difference from baseline LDL-C of − 45.9% with alirocumab 75 mg given every 2 weeks, while 75% of patients achieved LDL-C < 70 mg/dL in alirocumab group compared to 9% in the placebo group [41].

A phase II trial evaluating the efficacy and safety of alirocumab in youth with HeFH has been published (ODYSSEY KIDS) [42]. A total of 42 patients age 8–17 years were enrolled and evaluated in four cohorts defined by weight-based dosing (30 mg < 50 kg or 50 mg ≥ 50 kg every 2 weeks; 40 mg < 50 kg or 75 mg ≥ 50 kg every 2 weeks; 75 mg < 50 kg or 150 mg ≥ 50 kg every 4 weeks; 150 mg < 50 kg or 300 mg ≥ 50 kg every 4 weeks). The results showed reductions in LDL-C of − 46% among subjects in the cohort receiving the highest dosage. ApoB was also reduced by ~ − 38% in two of the four cohorts.

The types of adverse effects are generally similar in adult and pediatric trials. In ODYSSEY KIDS, the most common adverse effects were nasopharyngitis (14%), upper respiratory tract infection (12%), viral gastroenteritis (12%), and diarrhea (12%). While the adult trial [41] reported musculoskeletal and connective tissue symptoms in 23.7% of alirocumab-treated subjects (vs 21.5% in the placebo group), ODYSSEY KIDS reported a few muscle-related complaints, and if present, did not impact continuation in the study. The following were reported by only one subject each: muscle spasms, myalgias, flank pain, arthritis, and tendon pain.

Angiopoietin-Like Protein 3 Inhibitor

Evinacumab is a monoclonal antibody that inhibits angiopoietin-like protein 3 (ANGPTL3). Evinacumab received FDA approval in 2021 to treat HoFH as add-on therapy, including youth age 12 years and older. Angiopoietin-like 3 (ANGPTL3) is a protein that inhibits lipoprotein and endothelial lipase, resulting in higher levels of TG and other lipids. Loss-of-function mutations in ANGPTL3 lead to low LDL-C and TG, and is associated with a 41% lower risk of CAD [43, 44]. The effects of ANGPTL3 inhibition on lipid levels appear to be independent of LDL receptor function, and therefore, this class of medication may be a viable option for HoFH patients with null/null LDLR genotype who might not respond sufficiently to PCSK9 therapy.

A Phase 3 RCT, the Evinacumab Lipid Studies in Patients with Homozygous Familial Hypercholesterolemia (ELIPSE HoFH), examined the effect of evinacumab in addition to other lipid-lowering medications in 65 subjects, including 2 between 12 and 17 years of age. After 24 weeks, LDL-C was reduced by − 47.1% in the treatment group (LDL-C + 1.9% in placebo group) (Table 1) [45.••]. A post hoc analysis of 8 subjects with null/null mutations (LDLR activity < 2%) showed LDL-C reduction of − 53.5% in treated subjects at 24 weeks (LDL + 18.8% in placebo group).

Evidence regarding evinacumab's precise mechanism of action in lowering lipoproteins is emerging. A small stable isotope tracer study [46] examining lipoprotein kinetics of apoB in four adult subjects demonstrated that evinacumab increased the fractional clearance rate of intermediate-density lipoprotein (IDL) (616 ± 504%) and LDL (113 ± 14%), while reducing LDL-C levels (− 59 ± 2%). Regarding the effect of evinacumab on VLDL apoB, only 2 out of 4 subjects showed lower production rates.

Evinacumab is delivered as an intravenous injection 15 mg/kg every 4 weeks. Side effects may include flu-like symptoms, and elevation in transaminases has been observed. Adolescent and adult females of child-bearing age should be informed about the potential teratogenic effects of evinacumab based on data from animal studies. Female patients are recommended to be tested for pregnancy prior to starting therapy, and if sexually active, to use an effective method of contraception during treatment until 5 months after the last dose of evinacumab [47].

Medications Approved for Use in Adults, but Not in Children (Table 2)

Niacin

Nicotinic acid (niacin) has been used for the treatment of hypercholesterolemia in adults, but has not been approved for pediatric use. Niacin promotes apoB degradation and reduces VLDL (and thus LDL-C) production [48]. A retrospective study based on off-label use in children reported that doses of niacin higher than 1000 mg per day in 8 children lowered total cholesterol (−23%) and LDL-C (−30%) [49], with no significant changes in HDL-C or TG. The reported side effects were similar to those among adults, including flushing, headache, and elevated liver enzymes. While niacin was previously used commonly as adjunctive pharmacologic therapy among adults

Table 2 Pediatric studies on lipid-lowering medications with approved indications for adult use only

Class of medication and drug name	Age range of children studied	Indication studied in children	Duration of treatment	Reported lipid outcome measures (% change from baseline)				Reference
				Total cholesterol	LDL-C	TG	HDL-C	
Vitamin B3								
Niacin	4–14 years	Hypercholesterolemia, retrospective study, $n=20$	~8 months	−12.6%	−16.8%	+13.2%	+3.6%	Colletti et al. [49]
Fibrates								
Bezafibrate	4–15 years	HeFH, crossover study, $n=14$	6 months	−16%	NR	−33%	+15%	Wheeler et al. [54]
Bezafibrate (after sitosterol)	5.3–10.8 years	HeFH, crossover study, $n=7$	3 months	−18%	−28%	-41%	+14.6%	Becker et al. [57]
Fenofibrate	4–19 years	Hyperlipidemia, $n=17$	3 months	−22%	NR	−39%	NR	Steinmetz et al. [55]
Gemfibrozil	mean age 14 years	Metabolic syndrome, retrospective study, $n=47$	~8 months	−14%	+6%	−57%	+20%	Smalley and Goldberg [56]
MTP Inhibitor								
Lomitapide	3–16 years	HoFH, case series, $n=11$	20 months	NR	-58.4%	NR	NR	Ben-Omran T et al. [69]
Omega-3 Fatty Acids								
EPA + DHA	10–19 years	Hypertriglyceridemia, RCT, $n=25$	6 months	− 1.7%	+6.8%	− 27.0%	+0.6%	de Ferranti et al. [75]
EPA + DHA + lifestyle	10–16 years	Obesity with hypertriglyceridemia, RCT, $n=65$	12 weeks	− 5.6%	NR	− 44.1%	+2.0%	Huang et al. [76]
EPA + DHA	10–16 years	Hypertriglyceridemia, RCT, $n=130$	12 weeks	− 2.9%	NR	− 39.1%	+3.8%	Del-Rio-Navarro et al. [77]
Small interfering RNA targeting hepatic PCSK9								
Inclisiran	12–17 years	HeFH, 1 year RCT, 1 year OLE, $n = 150$	2 years	Study is currently in progress				Clinicaltrials.gov [79]

This table lists non-statin medications that have been FDA-approved for use in adults, and may have been studied in children but are not currently approved for age < 18 years. Included are lipid outcome measures from studies that included subjects age 17 years or younger

Percent change from baseline is presented. Please see references for outcomes relative to placebo

HeFH heterozygous familial hypercholesterolemia, *HoFH* homozygous familial hypercholesterolemia, *NR* not reported, *RCT* randomized controlled trial, *LDL-C* low-density lipoprotein cholesterol, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol, *MTP* microsomal triglyceride transfer protein, *EPA* eicosapentaenoic acid, *DHA* docosahexaenoic acid

with hypercholesterolemia, the FDA withdrew its approval for use in combination with statins in 2016 [50].

Fibrates

Fibrates are peroxisome proliferator-activated receptor alpha (PPARα) agonists that reduce triglyceride, LDL-C, and total cholesterol levels. Fibrates are FDA-approved to treat adults with hypertriglyceridemia, but not children. Among adults age 50–95 years, fenofibrate treatment over 5 years reduced total CVD events compared to placebo (FIELD study) [51]. Fenofibrate add-on therapy to statins has also been shown to reduce the risk of hypertriglyceridemia and low-HDL-C, but did not significantly impact cardiovascular events (ACCORD-lipid trial) [52]. Extended-release fenofibrate and gemfibrozil are not recommended for co-administration with statins, the latter due to risk of muscle-related toxicity [53].

The data for use of fibrates among children with hypercholesterolemia is limited with a few small studies published over the past four decades [54–57]. These studies on bezafibrate, fenofibrate, and gemfibrozil suggested a potential benefit in lowering of total cholesterol and LDL-C. Additional studies have examined use of fibrates in the setting of other chronic conditions such as nephropathy [58] and neuronal ceroid lipofuscinosis [59]. Efforts are underway to develop safer and more effective fibrates, such as pemafibrate [60], that minimally impact liver and kidney function through selective PPARα modulation (SPPARM) [61].

Lomitapide

Lomitapide is an oral MTP (microsomal triglyceride transfer protein) inhibitor approved by the FDA in 2012 for use in adults with HoFH, but not yet in children. MTP is an enzyme that is highly expressed in the endoplasmic reticulum of hepatocytes and enterocytes, and plays a key role in the production of chylomicrons and VLDL. In a phase 3 open label study of 29 adults, treatment with lomitapide in addition to standard lipid-lowering therapy, with or without apheresis, resulted in a mean reduction of LDL-C of − 50% after 26 weeks [62], with apoB and TG reductions of − 49% and − 45%, respectively. Seventeen subjects in the extension trial maintained LDL-C reduction (− 45.4%) at 126 weeks [63], and such benefits have since been confirmed in further studies [64]. An extension study of 19 subjects suggested cardioprotective benefits of lomitapide, with only 2 major adverse CVD events after 126 weeks (1 cardiac death and 1 coronary artery bypass graft). This is equivalent to a CVD event rate of 1.7 events per 1000 months on treatment, compared to the background rate in HoFH individuals at 21.7 events per 1000 months [65]. The LOWER registry [66] reported on 5-year data of long-term follow-up from 187 adults, noting that the median dose was only 10 mg, with mean LDL-C reductions of − 30.3%, and side effects were consistent with those previously reported. 58.4% of study subjects showed at least a 50% LDL-C reduction. An LDL-C reduction to < 100 mg/dL was attained at any time point by 65.4% of subjects, and LDL-C < 70 mg/dL was attained 41.4%.

An international clinical trial for use in children is currently in progress [67]. Until data becomes available, the available pediatric literature on lomitapide is limited to case reports. Compassionate use in a child with HoFH, who was already receiving atorvastatin and ezetimibe, was published in 2019 [68]. With a baseline LDL-C of 428 mg/dL at age 7 years, the patient experienced − 37% LDL-C reduction over the next 4 years (lowest LDL-C 231 mg/dL, lomitapide dose up to 20 mg daily). In 2020, a case series was published on off-label use of lomitapide among 11 patients from 10 countries who had received the medication through patient access programs or via a named-patient basis from the pharmaceutical company [69]. These children, age 3–16 years old, had been on statins and ezetimibe with or without apheresis, before starting lomitapide. The mean reduction in LDL-C was − 58.4 ± 6.8%, from a mean baseline LDL-C of 419.9 ± 74.6 mg/dL to a mean nadir of 176.7 ± 46.3 mg/dL over an average of 20 months of treatment, and mean dose of 24.5 ± 4.3 mg. Six of the patients achieved LDL-C levels of < 100 mg/dL at least once while on treatment.

Lomitapide is available in doses ranging from 5 to 60 mg. Caution is advised during dose escalation in patients taking simvastatin and lovastatin due to metabolism through the cytochrome P450 CYP3A4 isoenzyme. The recommended maximum lomitapide dose in these patients is 30 mg daily. Accumulation of TG in the enterocytes, decreased chylomicron production, and impaired absorption of dietary fat contribute to gastrointestinal side effects. Hepatic steatosis may occur, and one study reported an increase of hepatic fat from 1% at baseline to 6% following treatment on lomitapide [62]. Omega-3 and omega-6 fatty acids are recommended as supplements (200 linoleic acid, 110 mg EPA, 220 ALA, and 80 mg DHA), along with vitamin E [70].

Due to the risk of hepatotoxicity, prescribing lomitapide involves Risk-Evaluation and -Mitigation Strategies (REMS) to closely monitor liver function and reduce risk of adverse effects. This requires that physicians become certified through an online training program in order to prescribe lomitapide, with vigilance to the frequent monitoring and dose titration strategy [70].

Bempedoic acid

Bempedoic acid is an adenosine triphosphate-citrate lyase inhibitor, which was approved by the FDA for use in adults with HeFH or established cardiovascular disease in addition

to maximally tolerated statin therapy. It is not currently approved for use in children or adolescents. Bempedoic acid suppresses cholesterol synthesis upstream of HMG-CoA reductase. Two phase 3 clinical trials in adults with HeFH or cardiovascular disease receiving maximally tolerated statins [71, 72] showed that adding bempedoic acid 180 mg daily resulted in LDL-C reduction at 12 weeks of − 18.1% and − 17.4% (respectively) relative to placebo, along with apoB reductions of − 11.1% and − 13.0%. One of the trials showed that the reductions appeared to be sustained at 52 weeks [71]. Among the side effects, increased blood uric acid levels may occur. Data from another clinical trial supports LDL-C-lowering benefits when added to statin therapy in combination with ezetimibe [73]. As of the writing of this review article, no clinical trials on its use in pediatrics have been registered with ClinicalTrials.gov.

Omega-3 Fatty Acids

Formulations of omega-3 fatty acids such as ethyl esters and icosapent ethyl have been approved to treat hypertriglyceridemia in adults, but not children (omega-3 ethyl esters, and icosapent ethyl). In the setting of hypercholesterolemia, these agents may decrease TG as an additional CVD risk factor, but they do not reduce LDL-C [74]. In the pediatric literature, variable effects on triglycerides have been reported [75, 76]. A RCT among youth age 10–16 years showed a significant decrease in TG levels by − 39.1% in the treatment group ($n = 65$) compared to − 14.6% in the placebo group ($n = 65$) [77].

Inclisiran

Inclisiran is a small interfering RNA targeting hepatic PCSK9 synthesis, which has been studied in clinical trials and has very recently received FDA approval for use in the U.S. Orion-9 was a phase 3 double-blind randomized placebo-controlled trial on use of inclisiran in adults with HeFH already receiving statin therapy [78]. Results showed that the subjects treated with inclisiran 300 mg injection 4 times (days 1, 90, 270, 450) over 15 months demonstrated a reduction in LDL-C of − 39.7% (− 59 mg/dL) from baseline, compared to placebo-treated subjects who showed a + 8.2% LDL-C increase (+ 9.9 mg/dL). Findings included a reduction of Lp(a) by − 17.2% from baseline.

At the present time, a phase 3 double-blind, placebo-controlled clinical trial to study the safety and efficacy of inclisiran in adolescents is in progress, to be followed by an open label extension (OLE) study (ORION-16) [79].

Medications Studied in Clinical Trials, but Not FDA-Approved (Table 3)

Mipomersen

Mipomersen is an apoB inhibitor, approved by the FDA in 2013 for use in adults with HoFH, but withdrawn from the market in 2019. Delivered by weekly subcutaneous injection, this antisense oligonucleotide bound to the mRNA of apoB-100, a protein essential for assembly and packaging of VLDL, the precursor to LDL-C. A 6-month phase 3 RCT of 51 study subjects (including 7 pediatric patients 12–18 years) [80] determined that mipomersen overall reduced LDL-C by − 24.7%, with reductions in apoB (− 26.8%) and lipoprotein(a) (− 31.1%). A later subanalysis of the pediatric data ($n = 7$) [81] indicated that 3 treated children ($n = 3$) in the RCT exhibited − 43%% LDL-C and − 46% apoB reduction. Of the youth enrolled in an open-label extension study, 3 previously placebo-treated youth responded to 1–2 years of mipomersen treatment, with − 26.5 to − 42.1% LDL-C reduction, and 1 subject observed an LDL-C increase. A post hoc analysis of 3 RCTs and the OLE study including adults and youth reported that

Table 3 Lipid-lowering medications with no current approved indication — studies including children and adolescents

Class of medication and drug name	Age range of children studied	Indication studied in children	Duration of treatment	Reported lipid outcome measures (% change from baseline)				Reference
				LDL-C	Apo B	TG	Lp(a)	
ApoB inhibitor								
Mipomersen	12 years and older	HoFH, RCT, $n = 51$ (children $n = 7$)	6 months	− 24.7%	− 26.8%	− 17.4%	− 31.1%	Raal et al. [80]

This table lists non-statin medications that are currently not FDA-approved for any indication, but may have been studied in children and adolescents. Included are lipid outcome measures from studies that included subjects age 17 years or younger

HeFH heterozygous familial hypercholesterolemia, *HoFH* homozygous familial hypercholesterolemia, *NR* not reported, *RCT* randomized controlled trial, *LDL-C* low-density lipoprotein cholesterol, *Apo B* apolipoprotein B, *TG* triglyceride, *Lp(a)* lipoprotein(a), *RNA* ribonucleic acid, *PCSK9* proprotein convertase subtilisin/kexin type 9 serine protease, *Apo B* apolipoprotein B

major adverse cardiac events occurred less frequently during the 24 months after treatment with mipomersen [82]. Adverse effects included injection site reactions, flu-like symptoms, and risk of hepatic steatosis and hepatotoxicity. During the last time, mipomersen was commercially available; prescribers underwent REMS training for liver enzyme monitoring and dose titration.

Insurance Coverage for Advanced Lipid-Lowering Agents

The Affordable Care Act (ACA) expanded health care coverage across the nation, which increased opportunities for coverage through payors including state-sponsored health plans, such as Medicaid. In line with the US Preventive Task Force (USPTF) recommendations, health plans under the ACA are required to cover statins for primary prevention of CVD [83]. However, insurance coverage of PCSK9 inhibitors and lomitapide are likely subject to step-therapy requirements in a tier-based formulary and require prior authorization. Therefore, careful documentation of a patient's medication history in clinic notes (including those attempted and failed or not tolerated in the past) is essential for patient advocacy.

For step-therapy, a health plan may require that specific criteria be met before authorizing coverage of advanced lipid-lowering agents. Examples of such criteria include history of treatment with at least two statin medications and at least three non-statin medications, and evidence of subclinical atherosclerotic disease. The health plan will require lipid test results, cardiovascular imaging reports, and may request apoB test results.

If a prior authorization request is unsuccessful, the lipid specialist may request to speak with a pharmacy reviewer. Clarifications may result in reversal of a denial. The clinician may also file an appeal and submit additional documentation or supporting evidence from the literature.

Pharmaceutical companies may contract with third party groups to work with physician offices to facilitate the prior authorization process. With parent/guardian consent, these services may be a helpful resource for the lipid specialist and the patient/family. If prior authorization is ultimately denied, these companies may be knowledgeable about the availability of patient assistance programs to cover the medications.

Conclusion

The range of FDA-approved pharmacologic options for lipid-lowering therapy for children with HeFH and HoFH is narrower than that for adults. However, approval of medications in the PCSK9 inhibitor and ANGPTL3 inhibitor classes for adolescents expands the opportunities to lower LDL-C in children and adolescents with hypercholesterolemia. Ezetimibe, colesevelam, evolocumab, and now evinacumab are approved for pediatric use. Continued efforts are needed to include youth less than 18 years of age in clinical trials for drug development.

Declarations

Conflict of Interest Waleed Z. Butt has nothing to disclose.
Jennifer K. Yee reports Member, Lipid Special Interest Group, Pediatric Endocrine Society.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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