Management of Patients With Homozygous Familial Hypercholesterolemia

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Introduction

Homozygous familial hypercholesterolemia (HoFH) is an ultra rare genetic lipid disorder that if untreated results in extremely elevated levels of low-density lipoprotein cholesterol (LDL-C) in the blood. Historical figures have indicated that HoFH affects approximately 1 in 1 million individuals worldwide and the more common heterozygous form occurs in approximately 1 in 500 people.[1-5] However, recent data suggest these estimates are likely low due to the underdiagnoses of these conditions. According to a recent consensus statement from the European Atherosclerosis Society, the prevalence of the heterozygous form of familial hypercholesterolemia (FH) is between 1 in 200 and 1 in 500, or 14 to 34 million people worldwide. Similar underestimations are also likely for the rarer HoFH.[4]

FH is characterized by severe hypercholesterolemia, typically inherited as an autosomal dominant trait. Patients with the heterozygous form have inherited a mutated gene from 1 parent, whereas those with HoFH have inherited 2 mutated genes, 1 from each parent. The most common cause of FH is a mutation in the low-density lipoprotein receptor (LDLR) gene. Rare forms involving other mutations, such as in the apolipoprotein B (ApoB) gene, the proprotein convertase subtilisin/kexin 9 (PCSK-9) gene, and the very rare autosomal recessive hypercholesterolemia adaptor protein (ARH), have also been described.[2,3,5,6] Also, there may be genes associated with FH that have yet to be identified, and thus individuals with FH who have no detectable mutation may have polygenic causal mutations as the basis for their elevated LDL-C levels.[4,7]

Patients with HoFH typically have untreated LDL-C levels greater than 500 mg/dL, although levels have been reported to range from approximately 350 mg/dL to more than 1000 mg/dL.[1,8] However, most patients with HoFH are treated with lipid-lowering therapies, but do not typically reach established treatment goals. Treatment with conventional lipid-lowering agents has shown varying levels of effectiveness, lowering LDL-C concentrations by 0% to 48%.[1,6] Thus, in a population of treated patients, it is not uncommon to see a wide variation in LDL-C levels, with some patients at the lower end of the spectrum presenting with LDL-C levels around 200 mg/dL.[2,5,9-11]

Abstract

Familial hypercholesterolemia (FH) is a genetic disorder that results in severe elevations of cholesterol in the blood. If untreated or undertreated, FH can result in premature development of severe atherosclerosis, cardiovascular disease, and possibly death. Heterozygous FH is the most common form of the disease, with an estimated prevalence ranging from 1 in 200 to 500 in the general patient population. Homozygous FH (HoFH) is much more rare. Historical estimates suggest a prevalence of 1 in 1 million people for HoFH worldwide; however, more recent data suggest this historical estimate is likely conservative due to the underdiagnosis of FH.

Patients with HoFH often require aggressive lipid lowering of 80% or more, as cholesterol levels among patients with HoFH are typically higher than the levels found in patients with the heterozygous form of the disease. Clinical trials have shown limited success with conventional lipid-lowering drugs, including combinations of statins and ezetimibe (a cholesterol absorption inhibitor). However, more often than not cholesterol levels among patients with HoFH remain well above established treatment targets. Therefore, additional lipid-lowering treatments are generally required to help reduce the morbidity and mortality in this high-risk population. Apheresis, an invasive procedure involving the removal of low-density lipoprotein (LDL) and apolipoprotein particles from the blood, is an option for some patients. However, apheresis is expensive and must be performed weekly or biweekly to keep cholesterol levels from rising. Despite available treatments, HoFH remains both underdiagnosed and undertreated. Recently, the US Food and Drug Administration approved 2 orphan drugs—lomitapide and mipomersen—as adjunctive treatment to lower LDL cholesterol specifically for patients with HoFH. Detailed analyses of these 2 drugs are provided in this review article.

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For author information and disclosures, see end of text.

Treatment for HoFH includes dietary modification, multiple lipid-lowering agents (eg, statins, ezetimibe, bile acid sequestrants), and/or low-density lipoprotein (LDL) apheresis, a method that removes LDL and apolipoprotein particles from the blood.[2] As will be discussed in the treatment section of this article, these treatments are often ineffective in reducing LDL-C to recommended levels in patients with HoFH (ie, LDL-C <100 mg/dL).[2,4] This is largely due to the pathophysiology of HoFH. Statins, for example, reduce LDL-C levels by up-regulating hepatic LDLRs. This mechanism of action is less effective in patients with HoFH, which is characterized by either a reduction in or complete absence of LDLR activity. The average reduction in LDL-C in patients genetically lacking LDLRs is approximately 15% with statin therapy, and about 26% in patients with mutated, less functional LDLRs.[1] It is important to note that undertreated patients have elevated cholesterol levels that may increase their risk for the development of severe premature atherosclerosis and cardiovascular disease (CVD).[3] Even patients undergoing LDL apheresis are at risk for CVD. Thompson et al (2010) noted that 20% to 35% of children with HoFH who received regular LDL apheresis developed CVD while undergoing treatment.[12]

The rarity of the disease and the lack of a standardized definition may lead many medical professionals to underdiagnose HoFH.[4] Thus, patients may not receive appropriate therapy that could further lower their LDL-C levels to goal. It is also important that managed care professionals be familiar with recently US Food and Drug Administration (FDA)-approved treatment options for patients with HoFH.

Two new FDA-approved orphan drugs indicated specifically for patients with HoFH offer new treatment options for this undertreated patient population.[10,13]

Pathophysiology

HoFH is an inherited disorder usually caused by mutations in genes that affect the functionality of the LDLR. To date, more than 1600 causal mutations of the LDLR gene have been identified.[3] Due to the rarity of HoFH, scientists may not have identified all the genes and/or mutations leading to the condition. As a result, HoFH is only partially understood. In most cases of HoFH, it is believed that the mutations are on the LDLR gene. However, mutations in at least 2 other genes (for ApoB-100 and PCSK9) may also result in HoFH. Patients with HoFH and mutations in the LDLR gene may be true homozygotes (having the same mutation in both LDLR alleles) or compound heterozygotes (having different mutations on each LDLR allele).[1] It is also possible that a person will have 1 mutation in the LDLR gene and 1 mutation in the ARH adaptor gene, resulting in a phenotype that is an intermediate between the heterozygous and homozygous phenotypes (double heterozygous).[4]

Impaired LDLR function leads to extremely high cholesterol levels, resulting in premature aortic stenosis and progressive atherosclerosis in childhood or adolescence. Compared with the heterozygous form, those with HoFH tend to have higher LDL-C levels and earlier CVD onset.[3] Left undertreated, most patients with HoFH will develop severe CVD in early adulthood; however, some patients with HoFH die of complications due to CVD in childhood.[3,14]

Diagnosis

Clinical diagnosis of HoFH is typically based on the presence of a positive family history of hypercholesterolemia and/or premature heart disease in both parents. The presence of xanthomas (deposits of cholesterol in extensor tendons) is also common, but may in some instances be overlooked by clinicians. Another manifestation of HoFH may be corneal arcus at an early age.[1] The most robust symptom of HoFH is the extremely elevated LDL-C concentrations. A recent review of the literature by Raal et al (2012) found typical HoFH diagnostic criteria to include an untreated LDL-C concentration greater than 500 mg/dL, a treated LDL-C concentration greater than or equal to 300 mg/dL, or a non-high-density lipoprotein cholesterol (non-HDL-C) greater than or equal to 330 mg/dL.[1] However, several recent clinical trials in patients with confirmed HoFH illustrate that treated baseline levels of LDL-C concentrations in this population are variable (from approximately 200 mg/dL to approximately 700 mg/dL).[9-11] Given that it is atypical for physicians to measure cholesterol levels in children, diagnosis in childhood is often the result of a family member or a dermatologist suspecting HoFH.[15]

Genetic testing may be helpful for confirmation of HoFH. However, it is usually unnecessary to perform genetic testing to obtain an accurate diagnosis.[1,15] More recent advancements in understanding the genetic causes of the disease suggest that many patients who have a clinical diagnosis of FH may not have a detectable causal mutation. In fact, recent reviews estimate that anywhere from 10% to 40% of FH patients will have an undetectable mutation.[1,2,4] Thus, a negative result from a genetic test does not necessarily indicate the absence of HoFH.[1,3,4]

Treatment

Current FH guidelines recommend drug therapy to achieve an LDL-C reduction of 50% or more. However, higher-risk patients such as those already having had a CVD event may

Table. Lipid and Lipoprotein Concentrations at Baseline and Week 26 for Lomitapide[22]

Parameter	Baseline Mean (SD)	Week 26 (N = 23)	
		Mean (SD)	Mean % Change
LDL-C, direct (mg/dL)	336 (114)	166 (97)	–50[a]
TC (mg/dL)	430 (135)	235 (111)	–46[a]
apo B (mg/dL)	259 (80)	130 (70)	–49[a]
Non-HDL-C (mg/dL)	386 (132)	197 (101)	–50[a]

[a]Statistically significant compared with baseline (P <.0001). Significance of the percent changes in LDL-C from baseline to 26 weeks was assessed with a mixed linear model.
ApoB indicates apolipoprotein B; HDL, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; TC, total cholesterol.

need intensification of drug treatment to achieve more aggressive goals of LDL-C less than 100 mg/dL (or an optional <70 mg/dL for those at the highest risk level) and a non-HDL-C level of less than 130 mg/dL.[2,16] For many patients with HoFH, achieving that target is difficult.

A patient with HoFH should be managed by a lipid specialist with the main treatment goal being to lower LDL-C levels in an effort to possibly attenuate the progression toward premature cardiovascular complications. The use of standard treatments for hypercholesterolemia may or may not be effective in patients with FH. Dietary management alone is generally ineffective.[15] Numerous clinical trials have shown some success with statins and ezetimibe in patients with HoFH; however, these agents generally do not lower the LDL-C levels enough to achieve targets recommended for patients at very high risk for CVD (ie, LDL-C <100 mg/dL or <70 mg/dL), and may not be well tolerated by some patients.[2,16,17] Recent clinical trials enrolling patients with HoFH who were being treated with standard lipid-lowering therapy had mean baseline LDL-C levels of 336 mg/dL (range, 152-564 mg/dL), 439 mg/dL (range, 190-704 mg/dL), and 442 mg/dL (range, 218-563 mg/dL).[9-11]

LDL apheresis is indicated and used in some patients who do not have an adequate response to maximum tolerated drug therapy. The procedure is generally effective in lowering LDL-C levels by more than 50%.[4,12,17] Although effective in lowering LDL-C transiently, the procedure is invasive and may be burdensome to patients. Due to the rapid rebound of LDL-C levels the procedure must be performed at weekly or biweekly intervals (in 3-hour sessions). In addition, many patients still do not achieve sustainable target LDL-C levels. The cost and limited number of LDL apheresis centers can reduce patient access to this treatment option.[18,19]

Recently, 2 orphan drugs with novel mechanisms of action independent of the LDLR were approved by the FDA for the treatment of patients with HoFH, providing additional options for this undertreated, high-risk population.[20,21]

Recently Approved Orphan Drugs

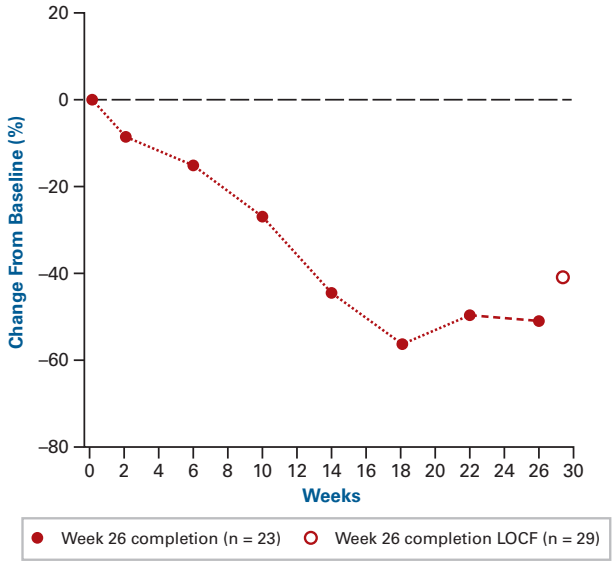
Lomitapide

Lomitapide is an inhibitor of the microsomal triglyceride transport protein, a protein required for the synthesis and secretion of ApoB-containing lipoproteins in the liver and intestine.[22] The reduced synthesis of these lipoproteins leads to reduced levels of plasma LDL-C.[13]

Lomitapide is indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce LDL-C, total cholesterol, ApoB, and non-HDL-C in patients with HoFH. Lomitapide is an oral medication available in 5-mg, 10-mg, and 20-mg capsules to be taken daily. The recommended starting dosage of lomitapide is 5 mg once daily, and the dose should be escalated gradually based on acceptable safety and tolerability.[13] In addition, vitamin E and fatty acid supplementation are recommended.[13] Lomitapide can cause elevations in transaminases, and transaminases should be measured prior to any increase in dose. Lomitapide has also been shown to increase hepatic fat with or without concomitant increases in transaminases. The maintenance dosage of lomitapide should be individualized, taking into account patient characteristics such as goal of therapy and response to treatment, to a maximum of 60 mg daily. Dosing modifications may be necessary for patients taking concomitant CYP3A4 inhibitors or with renal impairment or baseline hepatic impairment. Dose adjustments may also be necessary for patients who develop elevated transaminase values.[13]

FDA and EU approvals of lomitapide were based on a single-arm, open-label, phase 3 study in which 29 adults with HoFH from 11 centers in 4 countries (United States, Canada, South Africa, and Italy) completed both the efficacy phase (26 weeks) and the full study (78 weeks).[13,22]

Figure 1. Lomitapide 26-Week Trial Results: Mean Percent Changes in LDL-C From Baseline to Week 26[13,a]



[a]Based on intent-to-treat population with LOCF.
LDL-C indicates low-density lipoprotein cholesterol; LOCF, last observation carried forward.

The study included patients with HoFH diagnosed based either on 1) clinical criteria: history of untreated total cholesterol (>500 mg/dL) and triglycerides (<300 mg/dL); 2) both parents with history of untreated total cholesterol (>250 mg/dL); or 3) documented mutation(s) in both alleles of the LDLR or of other genes known to affect LDLR function.[13,22] Baseline use of lipid-lowering treatments included statins (93%), ezetimibe (76%), nicotinic acid (10%), bile acid sequestrant (3%), and fibrate (3%). Also, 62% of the patients were receiving apheresis.[13] The primary efficacy end point was percent change in LDL-C from baseline to week 26. The mean LDL-C level was 336 mg/dL (standard deviation [SD], ± 114 mg/dL), and mean total cholesterol was 430 mg/dL (SD, ± 135 mg/dL) at baseline.[22] At the end of the 26-week efficacy phase, LDL-C was significantly reduced by 50% (166 mg/dL; SD, ± 97 mg/dL; P <.0001) and total cholesterol significantly reduced by 46% (235 mg/dL; SD, ± 112 mg/dL; P <.0001; **Table**).[22] Concentrations of LDL-C remained reduced by 44% at week 56 (197 mg/dL; SD, ± 124 mg/dL; P <.0001) and 38% at week 78 (208 mg/dL; SD, ± 131 mg/dL; P <.0001).[22] The US prescribing information describes the results of the protocol-specified intent-to-treat analysis (n = 29) with last observation carried forward for patients who discontinued treatment prematurely. Based on this analysis, the mean and median percentage decreases from baseline in LDL-C levels at 26 weeks were 40% (P <.001) and 50%, respectively (**Figure 1**). Eight patients had LDL-C levels lower than 100 mg/dL at week 26, and 1 patient reached LDL-C less than 70 mg/dL. Three patients taking lomitapide discontinued LDL apheresis, and 3 additional patients decreased their frequency of apheresis treatments during weeks 26 to 78.[22]

Five (17%) of the 29 patients withdrew from the phase 3 study due to a treatment-emergent adverse reaction. Gastrointestinal symptoms were the most common adverse event (AE) reported in the trial and 3 patients discontinued the study due to gastrointestinal symptoms by week 12 of the efficacy phase.[22] One additional patient is described in the US prescribing information as discontinuing due to a gastrointestinal AE (4 patients total).[13] The fifth patient withdrew due to difficulty in controlling INR on warfarin.[13,22]

Three patients in the intent-to-treat group (n = 29) had serious AEs; however, it was determined that none of the events were related to the study drug.[22] Ten patients experienced elevated levels of ALT and/or AST of more than 3 times the upper limit of normal (ULN) at least once during the study. Four of these patients had ALT increases more than 5 times the ULN and 1 patient had a similar elevation in AST. No patient discontinued treatment permanently due to liver enzyme elevations, and all elevations were managed either by dose reduction or temporary interruption of lomitapide. No patient met Hy's law criteria.[22]

Although the efficacy of lomitapide in patients with HoFH has been established, there are still concerns regarding the drug's long-term safety. A long-term follow-on study assessing the efficacy and safety is currently ongoing.[23]

The FDA has requested 3 postmarketing studies of lomitapide[5,20]:

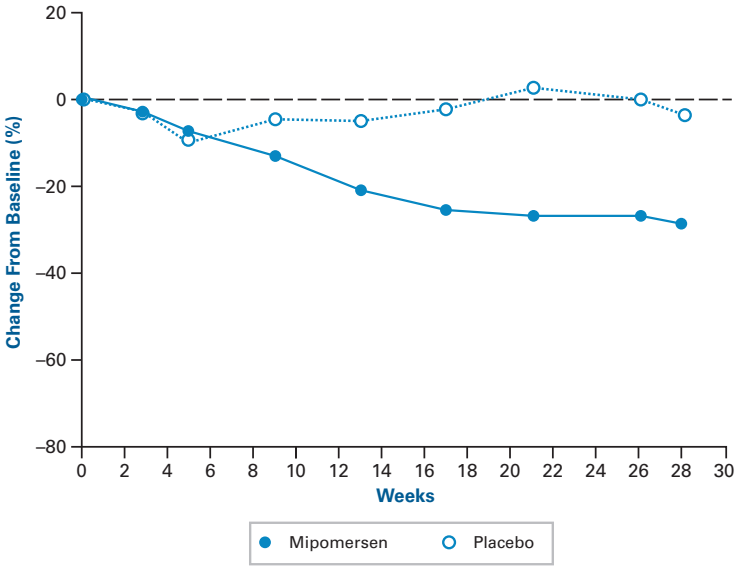
- An animal study to evaluate the potential for toxicity in children and teens
- A long-term registry of patients with HoFH treated with lomitapide to determine long-term safety
- An enhanced pharmacovigilance program to monitor reports of malignancy, teratogenicity, and hepatic abnormalities

Mipomersen

Mipomersen is a second-generation antisense oligonucleotide that binds a selected nucleotide sequence in ApoB mRNA resulting in decreased synthesis of apolipoprotein of LDL-C and very low density lipoprotein.[6,10]

Mipomersen is indicated as an adjunct to lipid-lowering medications and diet to reduce LDL-C, ApoB, total cholesterol, and non-HDL-C in patients with HoFH. Mipomersen is injected subcutaneously on a weekly basis at a recommended dose of 200 mg. Injections can be performed by a patient or caregiver following appropriate education by a qualified healthcare professional. Elevated transaminase levels may occur following treatment with mipomersen. If elevated levels are accompanied by clinical symptoms of liver injury, treatment should be discontinued. Mipomersen has also been shown to increase hepatic fat with or without concomitant increases in transaminases. It is advised that after initiating mipomersen therapy lipid levels be monitored at least every 3 months for the first year. Clinicians are advised to assess the patient's LDL-C level after 6 months to determine if the reduction is sufficiently robust to warrant the potential risk of liver toxicity.[10]

Figure 2. Mipomersen 28-Week Trial Results: Mean Percent LDL-C Change From Baseline to End of Treatment[10,a]



[a]Based on intent-to-treat population with LOCF.
LDL-C indicates low-density lipoprotein cholesterol; LOCF, last observation carried forward.

FDA approval was based on the results of a randomized, double-blind, placebo-controlled phase 3 study undertaken in 9 lipid clinics in 7 countries.[18] Adult patients (mean age, 32 years) were randomly assigned to mipomersen (200 mg subcutaneously every week; n = 34) or placebo (n = 17) for 26 weeks. A diagnosis of HoFH was defined by the presence of one of the following criteria: (1) history of genetic testing confirming 2 mutated alleles at the LDLR gene locus, or (2) documented history of untreated LDL-C greater than 500 mg/dL, or at least 1 of the following criteria: (a) tendinous and/or cutaneous xanthoma prior to age 10 years, or (b) documentation of LDL-C greater than 190 mg/dL prior to lipid-lowering therapy consistent with heterozygous FH in both parents. Most patients (98%) at the start of the study were taking statins to lower their lipid levels and 74% were also taking ezetimibe.[18] None of the patients were treated with LDL apheresis.[18]

The primary efficacy end point was percent change in LDL-C from baseline to week 28 (26-week treatment period). As shown in **Figure 2**,[10] at 28 weeks, the mean percentage change in LDL-C concentration was significantly greater with mipomersen (–24.7%; 95% confidence interval [CI] –31.6 to –17.7) than with placebo (–3.3%; 95% CI –12.1 to 5.5; P = .0003). Total cholesterol also improved with mipomersen (–21.2%, 95% CI –27.4 to –15.0) compared with placebo (–2.0%, 95% CI 9.6-5.6; P = .0002).[10,18] Improvements in other secondary end points compared with placebo included ApoB (–27% vs –3 %; P <.0001) and non-HDL-C (–25% vs –3%; P = .0002).[10,18]

The most common AEs were injection site reactions and the development of flu-like symptoms. In the group receiving mipomersen, 6 withdrew before completing the 28-week study. Reasons for withdrawal were: injection site reactions (n = 2); rash (n = 1); increased alanine aminotransferase levels (n = 1); noncompliance (n = 1); and consent withdrawn (n = 1).[18] Increases of greater than or equal to 3 times the ULN occurred in 4 (12%) patients who received mipomersen versus none in the placebo group. The fourth patient had an increased ALT (>5 times the ULN) before dosing at week 17. This ALT value met the protocol-defined stopping rule. No cases of ALT more than 8 times the ULN were noted, and no patient met Hy's law criteria. Of the 45 patients who completed the 28-week study, 38 patients joined the open-label extension study, more than half of whom ultimately discontinued therapy. Nearly half of these patients (47.4%) discontinued due to an adverse event.[24] Although the efficacy of mipomersen in patients with HoFH has been established, there are still concerns regarding the drug's long-term safety. An open-label extension study to assess the long-term safety and efficacy of mipomersen is currently ongoing.[25]

The FDA is requiring 4 postmarketing studies for mipomersen[21]:

- Development of a sensitive assay that binds double-stranded (ds) DNA
- A study to assess for the presence of antibodies in ds-DNA in patients treated with mipomersen
- A long-term registry of patients with HoFH to determine the long-term safety of mipomersen
- An enhanced pharmacovigilance program to monitor reports of malignancy, immune-mediated reactions, and hepatic abnormalities in patients treated with mipomersen

Other Considerations of Use

Both lomitapide and mipomersen carry boxed warnings for risk of hepatotoxicity. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin need to be measured prior to initiating treatment; then ALT and AST levels should be monitored regularly. With lomitapide, if ALT or AST levels reach 3 times the ULN, the dose is to be adjusted; with mipomersen, the dose should be withheld if ALT or AST levels reach 3 times the ULN. The labeling for both drugs also carries a warning that they should not be used with other drugs that can increase hepatic fat. Due to the risk of hepatotoxicity, these drugs are only available through a restricted program (Risk Evaluation and Mitigation Strategies [REMS] program). Nursing mothers should discontinue use of the drug, or discontinue nursing. Safety and effectiveness have not been established in pediatric patients. Safety and effectiveness have not been established in patients with hypercholesterolemia who do not have HoFH. Additionally, it is important to note that although these drugs have been shown to lower LDL-C, the long-term effects on cardiovascular morbidity and mortality are not known.[10,13] The use of mipomersen as an adjunct to LDL apheresis is not recommended.[10]

Orphan Drugs and Managed Care

HoFH is an ultra rare disease with approved orphan drugs that meet the FDA's orphan drug standards for a safe and effective treatment. When evaluating a new drug, the FDA examines the risks and benefits associated with the drug based on data from clinical trials; ideally, these trials include large numbers of participants. Because HoFH is so rare, the FDA recognizes that it is difficult to enroll large numbers of participants for clinical trials. Therefore, the FDA uses less traditional methods to evaluate the risks and benefits for orphan drugs. To help ensure the drugs' safety, implementation of REMS is required. The REMS includes certification of prescribing healthcare providers and dispensing pharmacies to assure knowledge of potential safety risks and efforts to limit prescriptions for the drugs to patients with clinical or laboratory diagnoses of HoFH. Postmarketing studies are also under way for both drugs, and the results of these studies will be reviewed by the FDA.[26]

Lomitapide is approved for individualized dosing from 5 mg to 60 mg daily to be taken orally. According to the Red Book, in October 2013, the average wholesale price (AWP) for a year of treatment with lomitapide was $353,997 for daily dosing of 5 mg, 10 mg, or 20 mg.[27]

Mipomersen is approved at a weekly subcutaneous injection of 200 mg in a 1-mL solution. The AWP for mipomersen at the recommended 200-mg weekly dose is $252,744 for a year of treatment.[27]

The pricing of these medications will be a consideration for managed care, but the rarity of the disease makes the total cost to the healthcare system less substantial, especially when complications due to HoFH are considered. If health insurance companies deny coverage for a newly approved orphan drug, the patient and clinician may appeal as long as the indication for which the orphan drug is being prescribed is approved by the FDA. Rules for appeal vary among insurance plans and states.

Conclusions

HoFH is an ultra rare form of FH that is underdiagnosed and undertreated. In both HoFH and the heterozygous form of FH, patients have genetic mutations that result in elevated LDL-C. Having mutations on both alleles of the LDLR gene (or other genes associated with HoFH) makes it very difficult for patients to reach target goals (ie, LDL-C <100 mg/dL). The recent approval of 2 orphan drugs as adjunctive therapy specifically for patients with HoFH provides a new and possibly more effective means to reduce LDL-C in these hard-to-treat patients. Managed care companies need to be aware of the advantages and disadvantages of both of these therapies in order to assess the best treatment approach for their HoFH population.

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Notes