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The Role of Microsomal Triglyceride Transfer Protein Inhibitors in the Treatment of Patients with Familial Hypercholesterolemia: Risks, Benefits, and Management

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Abstract Statins fail to adequately reduce low-density lipoprotein-cholesterol (LDL-C) in patients with homozygous familial hypercholesterolemia, requiring these patients to undergo weekly or bi-weekly sessions of LDL apheresis. Although efficacious, LDL apheresis is an invasive procedure with high cost and low availability, and additional options, such as inhibitors of microsomal transfer protein (MTP), may have benefit. Inhibition of MTP reduces levels of circulating cholesterol and triglycerides by preventing the formation of very-low-density lipoprotein and chylomicrons. LDL-C levels decrease by as much as 50 %. Unfortunately, adverse effects—the most common of which are gastrointestinal-related and hepatic lipid accumulation—limit broader use of the drug. Furthermore, the cardiovascular benefit of MTP inhibition remains unclear. However, MTP inhibition offers a viable additional lipid-lowering option for patients with homozygous familial hypercholesterolemia.

Keywords Familial hypercholesterolemia · Homozygous familial hypercholesterolemia · LDL apheresis · Lomitapide · MTP · LDL-C · LDL-Receptor · Abetalipoproteinemia

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Introduction

Patients with homozygous familial hypercholesterolemia (FH) respond inadequately or not-at-all to conventional lipid-lowering agents. Statins reduce cholesterol primarily through upregulation of hepatic low-density lipoprotein receptors (LDLR), and because homozygous FH has bi-allelic mutations in this receptor, statins have modest effects with substantial variability (0–25 % LDL-cholesterol (LDL-C) lowering) [1]. Combinations with other therapies such as bile acid sequestrants or ezetimibe can further lower LDL-C; yet, even these combinations fail to reduce LDL-C to acceptable values in individuals starting with such high levels [2].

Historically, such patients required surgical interventions such as partial ileal bypass or liver transplantation. Currently, the most effective treatment for homozygous FH (HoFH) patients is LDL apheresis, a well-established procedure that can appreciably lower LDL-C and possibly improve survival [3]. This treatment can be onerous as it occurs weekly or every other week and has several additional limitations. Given its invasive nature, vascular access problems occur and other adverse reactions can include hypotension, angina, hemolysis, and allergic or anaphylactic reactions. Perhaps the most prohibitive issues are high cost and low availability. Given the lack of adequate effect of currently available lipid-lowering drugs and barriers to apheresis, there is a need for additional effective orally available treatments for HoFH.

Microsomal Triglyceride Transfer Protein (MTP) and MTP Inhibitors

Microsomal triglyceride transfer protein (MTP) assists in the initial packaging of cholesterol esters and triglycerides into both chylomicrons and very-low-density lipoprotein (VLDL) in intestinal cells and hepatocytes, respectively, (Fig. 1) [4]. The implications of MTP inhibition are best characterized by patients with abetalipoproteinemia (OMIM # 200100), a rare autosomal recessive disorder due to mutations in the *MTP* gene. These patients have hypocholesterolemia and negligible levels of the apo-B containing lipoproteins due to improper packaging and secretion [5]. Total cholesterol levels are typically around 30 mg/dL, mostly from high-density lipoprotein (HDL), and triglyceride levels are typically around 60 mg/dL. Because of these extremely low lipid levels, MTP makes an attractive therapeutic target to lower both total cholesterol and triglyceride (TG).

Patients with abetalipoproteinemia manifest gastrointestinal symptoms due to intestinal fat malabsorption—similar to celiac syndrome—with accompanying fat-soluble vitamin deficiencies and have elevated hepatic fat content as neutral lipid cannot be trafficked out as VLDL. They suffer from progressive ataxic neuropathy and pigmentary degeneration of the retina as a result of vitamin E abnormalities [6], and they develop a characteristic malformation of red blood cells called acanthocytosis. Also of concern, it remains unclear the relationship of abetalipoproteinemia to atherosclerotic disease given the rarity of this entity.

Due to the therapeutic potential of MTP inhibition supported by abetalipoproteinemia, several pharmaceutical companies pursued the development of MTP inhibitors. However, most abandoned the production of it in the early 2000s due to poor gastrointestinal tolerability, elevations in hepatic transaminases, and a high rate of hepatic steatosis [7]. One compound, BMS-201038 (now called AEGR-733 or lomitapide), eventually found its way to individual academic investigators. Rader et al. administered the drug to six HoFH patients in a proof-of-concept phase 2 open-label study [8]. After 4 weeks of therapy at each of four escalating doses (16 weeks total), LDL-C decreased by 51 % at the highest dose (1 mg/kg/day, mean 67 mg/day). However, serum alanine aminotransferase and intrahepatic triglyceride (IHTG, as measured by proton magnetic resonance spectroscopy) content rose in four out of six patients. As expected, most patients had gastrointestinal side effects including increased stool frequency of mild to moderate intensity. No subjects discontinued the study due to these symptoms, but they generally followed a low-fat diet (17 % of calories) which likely modified this effect.

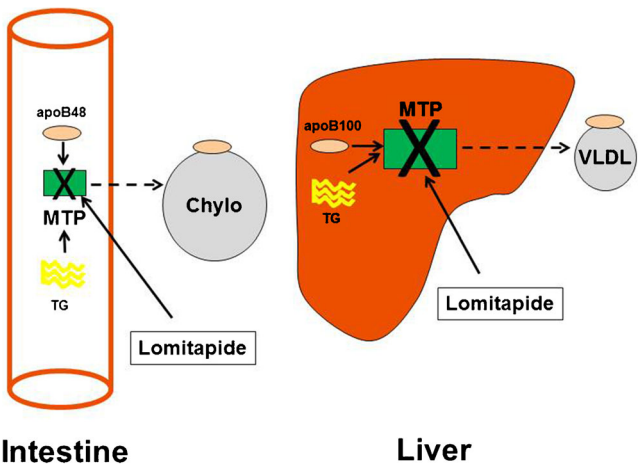

Fig. 1 Mechanism of action of lomitapide. Lomitapide inhibits microsomal triglyceride transfer protein (MTP) in both the liver and intestine. MTP inhibition in the liver blocks the assembly of very-low-density lipoprotein from apolipoprotein B100 (apo-B100) and triglycerides, and in the intestine, blocks the assembly of chylomicrons from apo-B48 and triglycerides

Lomitapide (Juxtapid™, Aegerion Pharmaceuticals) obtained FDA approval for use in HoFH patients in December 2012 and European Commission approval in July 2013. It is orally administered once daily in doses ranging from 5 to 60 mg, with high first-pass metabolism such that only 7 % is bioavailable [9]. It has a half-life of 39.7 h and reaches plateau LDL-C lowering after 14 days [10••]. Lomitapide is extensively metabolized by the cytochrome P450 (CYP) 3A4 system. Drug levels are increased in patients with hepatic impairment but are not meaningfully affected by mild to moderate renal insufficiency.

Benefits of Lomitapide Therapy

Pivotal Phase III Trial

The most informative data regarding the effects of lomitapide in HoFH derive from a 78-week phase III study that was the basis for FDA approval [11••]. This open-label, single-arm, forced titration study evaluated the safety and effectiveness of lomitapide to reduce LDL-C levels in 29 adult patients with HoFH. The primary endpoint was mean percent change in LDL-C from baseline to 26 weeks on top of background therapy, with further safety and efficacy follow-up for an additional 52 weeks. Background lipid-lowering therapy included statins in 27 patients, ezetimibe in 22, and apheresis in 18, with the mean baseline LDL-C of 336 mg/dL despite these treatments. Lomitapide was initiated at 5 mg daily and titrated to a maximum of 60 mg, with a median dose of 40 mg at the end of the 26-week efficacy period. Six patients discontinued therapy during the efficacy phase, including 4 for adverse reactions, leaving 23 patients who completed both the initial phase and the total 78-week protocol.

At the end of 26 weeks, lomitapide added to standard treatments further reduced LDL-C by 40 % (mean follow-up LDL-C 190 mg/dL) in the 29 patients in the intention-to-treat

cohort and by 50 % in the 23 subjects who remained on therapy [9, 11••]. In the subsequent 52-week safety phase where background treatment adjustments were permitted, 6 subjects either stopped or increased the interval between LDL apheresis treatments and mean LDL-C remained 38 % lower compared with that of baseline. Over the course of the study, 16 subjects achieved an LDL-C <100 mg/dL at some point. Of note, HDL-C declined during the initial 26-week period which may be due to fat malabsorption but returned to baseline at the end of 78 weeks.

As expected, lomitapide use resulted in accumulation of IHTG. Ten of the 29 patients in the phase III study had at least one elevation in liver enzymes greater than or equal to three times the upper limit of normal [11••]. In four of those patients, liver enzyme elevation exceeded or was equal to five times the upper limit of normal. IHTG increased from a baseline of 1 % to a median absolute increase of 6 % at 78 weeks. Eighteen (78 %) of 23 subjects demonstrated a maximum absolute increase in hepatic fat >5 %, and three (13 %) had an absolute increase >20 %. In addition, mild to moderate gastrointestinal side effects were experienced by 93 % of subjects during the efficacy period and 74 % in the safety period, which were the most common reasons inhibiting further titrations of lomitapide. Data presented but not yet published for an additional ~2.5 years of follow-up period in 19 of these subjects suggest a consistent side effect profile with median IHTG content of 7.7 % at the end of this period and GI symptoms experience in 63 % of subjects [12].

A recent analysis of this study suggested variability in response to lomitapide when patients were stratified by the type of *LDLR* mutation [13]. Interestingly, subjects with mutations resulting in deficient LDL receptors (class 1 and 2A mutations) had greater total LDL-C lowering and LDL-C lowering per milligram of lomitapide than those with mutations resulting in defective mutations (classes 2B, 3, 4, and 5). These findings may relate to the enhanced apo-B and VLDL production rate in HoFH with null receptors [14]. In contrast, a recent study examining PCSK9 inhibitors in HoFH patients observed the opposite findings: no LDL-C lowering effect in those with the *LDLR* null mutations but modest lowering in those with *LDLR* defective mutations [15].

Beyond LDL-C Lowering

It is important to note that although lomitapide has been shown to effectively lower LDL-C in patients with HoFH, its effects on atherosclerotic events have not been established. In this regard, whether it is superior to placebo or even to LDL apheresis for cardiovascular outcomes is unknown.

Animal models of MTP inhibition have demonstrated an antiatherosclerotic effect. Inactivation of MTP in a conditional knockout mouse model not only markedly reduced cholesterol levels but also prevented the development of aortic atherosclerosis [16]. In addition, the MTP inhibitor implitapide has been shown to markedly reduce atherosclerotic lesion area in apo-E knockout mice [17]. Lomitapide has also been tested in a Zucker rat model where it improved insulin sensitivity, lowered triglycerides and LDL, and reduced atherogenesis [18]. Nevertheless, other lipid-modifying therapies have shown favorable effects on lipid biomarkers and atherogenesis in animal models with actual increase in cardiovascular events in humans [19, 20].

Given the central role of LDL-C in the pathogenesis of HoFH and the inadequate therapeutic options in patients affected by this disorder, lomitapide remains a reasonable treatment option despite the lack of clinical outcomes data. However, it is currently not approved for other forms of dyslipidemia, including heterozygous FH, particularly in light of its adverse risk factor profile.

Common Side Effects and Management Strategies

Several of the side effects of lomitapide can be anticipated given its mechanism of action and pharmacology. Careful attention to these side effects and implementation of strategies to modify their impact can significantly improve the tolerability of this agent (Tables 1 and 2).

Gastrointestinal Effects

Among all patients exposed to lomitapide, 93 % experienced at least one gastrointestinal-related adverse event with the most common being diarrhea, nausea, vomiting, dyspepsia, and abdominal pain [9, 11••]. These occur due to MTP inhibition in intestinal cells that result in sloughing of lipid-filled enterocytes. In order to minimize the gastrointestinal-related adverse events, patients must modify their diet to include <20 % energy from fat. In the long-term phase III study, 3 subjects dropped out early due to GI side effects, but the remaining subjects were able to remain in the trial up to 78 weeks suggesting the ability to accommodate to this side effect.

Hepatic Steatosis

Lomitapide use results in accumulation of IHTG leading to drug-induced non-alcoholic fatty liver disease (NAFLD). In the HoFH phase III study, IHTG increased from a baseline of 1 % to a median of 6 % at 78 weeks. Eighteen (78 %) of 23 subjects demonstrated a maximum absolute increase in hepatic fat >5 %, and 3 (13 %) had an absolute increase >20 %.

Only 11 of the 29 patients in the HoFH study had at least one elevation in liver enzymes greater than or equal to three times the upper limit of normal. Transaminases remained

Table 1 Adverse effects of lomitapide and management strategies[a]

Adverse effect	Management strategies
Gastrointestinal adverse reactions: most commonly diarrhea, nausea, vomiting, dyspepsia, and abdominal pain	• Adhere to low-fat diet supplying <20 % of energy from fat
Hepatotoxicity	• Measure AST, ALT, alkaline phosphatase, and total bilirubin before initiating therapy and then AST and ALT regularly • Reduce dose if either ALT or AST is ≥3 times ULN • Discontinue for AST or ALT ≥5× ULN
Hepatic steatosis (note that ALT and AST may or may not increase)	• Avoid in patients with moderate or severe hepatic impairment (Child-Pugh category B or C) or active liver disease including unexplained persistent abnormal liver function tests • Caution with other meds known to have hepatotoxicity (isotretinoin, amiodarone, methotrexate, tetracyclines, tamoxifen, etc.)
Fat-soluble vitamin deficiencies	Take the following vitamin supplements: • 400 international units vitamin E • 200 mg linoleic acid • 210 mg ALA • 110 mg EPA • 80 mg DHA
HDL-C reduction (12 %)	• Transient, no intervention needed

[a] Adapted from lomitapide package insert

within normal limits in many of the participants with increased IHTG—a phenomenon of unclear significance—making transaminase measurements an insensitive method to screen for hepatic fat accumulation [7].

It remains unclear as to whether lomitapide-induced NAFLD resembles the typical obesity-related non-drug-induced NAFLD with regard to long-term complications. Drug-induced NAFLD is not well studied with regard to long-term consequences; it is well known that non-drug-induced NAFLD can progress to cirrhosis and is associated with insulin resistance and increased cardiovascular risk [21]. Of note, in the phase II study of lomitapide, IHTG assessment was also performed after study end and revealed resolution of elevated IHTG after cessation of therapy [8].

Only one patient has received long-term treatment with lomitapide. Hegele et al. [22•] reported a patient who received lomitapide for 15 years to treat severe hypertriglyceridemia due to homozygous mutations in lipoprotein lipase (*LPL*). This patient suffered from recurrent bouts of pancreatitis since age 15, and at age 44, she started lomitapide therapy with institutional review board approval for emergency investigational new drug use. Once on the 40-mg-per-day dosage, triglycerides reduced by roughly 80 % compared with pre-lomitapide levels. Bouts of pancreatitis ceased. However, liver enzymes, which were normal prior to lomitapide treatment, rose after starting treatment and slowly increased to greater than three times the upper limit by 12 years. Serial liver biopsies showed steatosis progressing to steatohepatitis and

Table 2 Warnings and precautions with lomitapide therapy[a]

Drug interactions	
Embryo-fetal toxicity	• Contraindicated in pregnancy • Prior to initiating, check urine pregnancy test in females of reproductive potential and use contraception during treatment
Interaction with CYP3A4 inhibitors	• Maximum dosage of lomitapide is 30 mg • Daily with concomitant use of weak CYP3A4 inhibitors such as alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, lapatinib, nilotinib, oral contraceptives, pazopanib, ranitidine, ranolazine, ticagrelor, zileuton • Avoid grapefruit juice
Increased risk of myopathy with concomitant use of simvastatin or lovastatin	• Reduce simvastatin and lovastatin by 50 % • Limit simvastatin maximum dose to 20 mg daily
Risk of supratherapeutic or subtherapeutic anticoagulation with warfarin	• Monitor INR closely

[a] Adapted from lomitapide package insert

eventually fibrosis after 12 years of therapy. Since LPL deficiency is known to also cause liver disease, it remains unclear whether lomitapide, LPL deficiency, or the combination of the two caused the progression of her liver disease.

Fat-Soluble Vitamins

Lomitapide leads to deficiencies in fat-soluble nutrients by inducing intestinal fat malabsorption [7]. In the phase two study by Rader et al. [8], serum levels of several fatty acids declined including alpha-linolenic acid, gamma-linolenic acid, linoleic acid, arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid. In the larger phase 3 trial, subjects consumed dietary supplements containing vitamin E, linoleic acid, alpha-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid. Levels of vitamins A and D increased while vitamin K was unchanged. Total vitamin E decreased by a median of −43.3 % at week 26 and −40.7 % at week 78—an expected finding since apo-B-containing lipoproteins are required for vitamin E absorption and transport. The ratio of serum vitamin E:lipid remained stable, suggesting that decreases in vitamin E occur due to lomitapide's effect on serum lipoproteins [7]. For clinical practice, patients taking lomitapide require dietary supplements that provide approximately 400 IU vitamin E, 200 mg linoleic acid, 110 mg eicosapentaenoic acid, 220 mg alpha-linolenic acid, and 80 mg docosahexaenoic acid per day.

Other Considerations

Two additional practical issues are relevant for lomitapide use: slow titration and drug interactions. Titration to full dose takes 4–5 months with frequent clinic visits and careful monitoring for gastrointestinal-related adverse events and liver enzyme elevation. Only 40 % of patients in the phase III tolerated the full dose of 60 mg [7]. Lomitapide is a CYP3A4 substrate, and it increases simvastatin exposure [7]—perhaps raising the risk of myopathy. With atorvastatin, lomitapide dose should not exceed 30 mg daily; the same is true for oral contraceptives—a potential issue since women of childbearing age must use contraception with lomitapide. Concomitant use with other moderate or strong CYP3A4 inhibitors has not been evaluated in a randomized, placebo-controlled trial.

Data are lacking regarding lomitapide's long-term safety and cardiovascular benefit. Pooling data from all phase 2 and 3 lomitapide trials, 3 (1.2 %) of 255 subjects treated with lomitapide monotherapy had at least one cardiovascular event recorded compared with none of the 191 subjects treated with lomitapide combination therapy (e.g., lomitapide + lipid-lowering therapy), none of the 98 treated with placebo, and none of the 78 subjects treated with an active control [7]. Also of concern, lomitapide transiently reduces HDL-C by 12 % [23]. Given the paucity of events in the lomitapide development program, none of which were adjudicated, it is premature to make conclusions regarding the effect of lomitapide on cardiovascular events [7].

Due to the careful balance of risk and benefits of prescribing lomitapide, specifically due to the risk of hepatotoxicity, the US Food and Drug Administration require a risk evaluation and mitigation (REMS) strategy for this agent. The REMS program involves educating practitioners about the risk of hepatotoxicity, restricting access to only patients with the diagnosis of HoFH, and requiring prescribers to undergo training and certification in its use [24].

Other MTP Inhibitors

In contrast to systemically inhibiting MTP, an alternative approach involves designing an inhibitor only for MTP localized to intestinal cells. An intestinal-specific MTP inhibitor would reduce chylomicron formation—offering a therapy for patients with familial chylomicronemia syndrome—and provide a key advantage over systemic MTP inhibitors: a better safety profile with regard to accumulation of IHTG. Two such drugs are under development. Surface Logix developed SLx-4090 [25], and Japanese Tobacco Inc. developed JTT-130 [26]. In early trials, SLx-4090 decreased postprandial triglycerides up to 50 % in healthy subjects while transaminases remained normal. The only side effects noted were headache, flatulence, and diarrhea. Such a drug may provide a novel mechanism for triglyceride lowering that targets chylomicron formation although it will not be an effective agent for Ho FH.

Conclusion

Lomitapide is a novel oral agent than can effectively lower LDL-C by approximately 40 % in patients with HoFH. This therapy on top of other standard LDL-C lowering treatments can lower LDL-C to acceptable levels in some and may reduce the frequency or need for LDL apheresis in others. There are several adverse effects that must be addressed including gastrointestinal effects, fat-soluble vitamin deficiencies, and most notably hepatotoxicities in the form of increased hepatic fat content and elevated liver function tests. Careful monitoring for these side effects and employing strategies to minimize their impact can significantly improve the tolerability of this drug such that most are able to maintain treatment for long term. The long-term effects of lomitapide therapy on cardiovascular outcomes as well as the sequelae of lomitapide induce NAFLD are unknown. However, given the significant premature cardiovascular morbidity and mortality suffered by patients with HoFH due to their marked LDL-C elevations,

the risk:benefit ratio favors lomitapide use for these individuals.

Compliance with Ethics Guidelines

Conflict of Interest Zahid Ahmad has moderated educational talks for Sanofi-Aventis and Genzyme and participated in an advisory board for Aegerion Pharmaceuticals.

Amit Khera declares no conflict of interest.

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.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Marais AD et al. A dose-titration and comparative study of rosuvastatin and atorvastatin in patients with homozygous familial hypercholesterolaemia. Atherosclerosis. 2008;197(1):400–6.
2. Gagne C et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol. 2002;90(10):1084–91.
3. Thompson GR, Miller JP, Breslow JL. Improved survival of patients with homozygous familial hypercholesterolaemia treated with plasma exchange. Br Med J (Clin Res Ed). 1985;291(6510):1671–3.
4. Hussain MM et al. Multiple functions of microsomal triglyceride transfer protein. Nutr Metab (Lond). 2012;9:14.
5. Wetterau JR et al. Absence of microsomal triglyceride transfer protein in individuals with abetalipoproteinemia. Science. 1992;258(5084):999–1001.
6. Kane J, Havel R. Disorders of the biogenesis and secretion of lipoproteins containing the B apolipoproteins. In: Beaudet A, Scriver CR, Sly WS, Valle D, editors. The metabolic and molecular basis of inherited disease. New York: McGraw-Hill; 2001. p. 2717–52.
7. FDA Briefing Document: NDA 203858, Lomitapide mesylate capsules 5 mg, 10 mg, 20 mg. 2012; Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM323841.pdf.
8. Cuchel M et al. Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. N Engl J Med. 2007;356(2):148–56.
9. Aegerion Pharmaceuticals, Juxtapid package insert 2012: Cambridge, MA.
10. •• Rader DJ, Kastelein JJ. Lomitapide and mipomersen: two first-in-class drugs for reducing low-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia. Circulation. 2014;129(9):1022–32. *This article provides a contemporary, state-of-the-art review of the biology, clinical considerations, and comparative data on two novel agents for the treatment of homozygous familial hypercholesterolemia.*
11. •• Cuchel M et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet. 2013;381(9860):40–6. *This is the pivotal phase III study of lomitapide leading to its approval. The trial provides insight into the efficacy and side effects observed with this agent.*
12. Cuchel M et al. Sustained LDL-C lowering and stable hepatic fat levels in patients with homozygous familial hypercholesterolemia treated with microsomal triglyceride transfer protein inhibitor, lomitapide. Circulation. 2013;128A, A16516.
13. Sirtori CR, Pavanello C, Bertolini S. Microsomal transfer protein (MTP) inhibition-a novel approach to the treatment of homozygous hypercholesterolemia. Ann Med. 2014;2:1–11.
14. Millar JS et al. Complete deficiency of the low-density lipoprotein receptor is associated with increased apolipoprotein B-100 production. Arterioscler Thromb Vasc Biol. 2005;25(3):560–5.
15. Stein EA et al. Effect of the proprotein convertase subtilisin/kexin 9 monoclonal antibody, AMG 145, in homozygous familial hypercholesterolemia. Circulation. 2013;128(19):2113–20.
16. Lieu HD et al. Eliminating atherogenesis in mice by switching off hepatic lipoprotein secretion. Circulation. 2003;107(9):1315–21.
17. Ueshima K et al. Implitapide, a microsomal triglyceride transfer protein inhibitor, reduces progression of atherosclerosis in apolipoprotein E knockout mice fed a Western-type diet: involvement of the inhibition of postprandial triglyceride elevation. Biol Pharm Bull. 2005;28(2):247–52.
18. Dhote V et al. Inhibition of microsomal triglyceride transfer protein improves insulin sensitivity and reduces atherogenic risk in Zucker fatty rats. Clin Exp Pharmacol Physiol. 2011;38(5):338–44.
19. Morehouse LA et al. Inhibition of CETP activity by torcetrapib reduces susceptibility to diet-induced atherosclerosis in New Zealand White rabbits. J Lipid Res. 2007;48(6):1263–72.
20. Barter PJ et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med. 2007;357(21):2109–22.
21. Stepanova M, Younossi ZM. Independent association between nonalcoholic fatty liver disease and cardiovascular disease in the US population. Clin Gastroenterol Hepatol. 2012;10(6):646–50.
22. • Sacks FM, Stanesa M, Hegele RA. Severe hypertriglyceridemia with pancreatitis: thirteen years' treatment with lomitapide. JAMA Int Med. 2014;174(3):443–7. *This article presents long-term follow-up observations of 13 years of experience with lomitapide in a single patient with extreme hypertriglyceridemia.*
23. Raal FJ. Lomitapide for homozygous familial hypercholesterolaemia. Lancet 2012.
24. Aegerion Pharmaceuticals. Juxtapid REMS program. 2012 [August 11, 2014]; Available from: http://www.juxtapidremsprogram.com/.
25. Kim E et al. A small-molecule inhibitor of enterocytic microsomal triglyceride transfer protein, SLx-4090: biochemical, pharmacodynamic, pharmacokinetic, and safety profile. J Pharmacol Exp Ther. 2011;337(3):775–85.
26. Mera Y et al. Pharmacological characterization of diethyl-2-({3-dimethylcarbamoyl-4-[(4'-trifluoromethylbiphenyl-2-carbonyl)amino]phenyl}acetyloxymethyl)-2-phenylmalonate (JTT-130), an intestine-specific inhibitor of microsomal triglyceride transfer protein. J Pharmacol Exp Ther. 2011;336(2):321–7.