

cholesterol, can regress xanthomata and reduce CVD events in FH. Statins and ezetimibe can lower LDL cholesterol in patients with homozygous FH by potentially decreasing hepatic secretion of apoB, but these patients usually require apheresis [9]. If apheresis is not available, consideration should be given to the addition of lomitapide or mipomersen therapy to further lower LDL cholesterol. It is critical to ensure that all patients with FH follow the recommended treatment regimens. Patients should be counseled on all aspects of their care, including the warning signs of drug-related toxicity. [10] With the hope of providing additional approaches to lowering LDL-C levels, many agents which differ in actions are being investigated.

Microsomal transfer protein (MTP) inhibitors

Microsomal Triglyceride Transfer Protein (MTP), found in the endoplasmic reticulum of hepatocytes and enterocytes, has been identified as one of the promising targets for the treatment of hypercholesterolemia. MTP plays crucial role in the assembly of triglyceride rich chylomicrons in enterocytes, and VLDL in hepatocytes. Inhibition of MTP thereby leads to decrease of VLDL-C, LDL-C and TG levels. This is why MTP inhibitors could be helpful in treating FH. Lomitapide [AEGR-733, Juxtapid, Aegerion Pharmaceuticals, Cambridge, MA) is an oral microsomal triglyceride transfer protein inhibitor that decreases the hepatic production and secretion of VLDL. Lomitapide is licensed for the treatment of homozygous FH in the United States and Europe as an add-on therapy. The use of lomitapide may also result in significant reductions in other lipids and lipoproteins, including total cholesterol, apoB, triglyceride, and non-HDL cholesterol. Lomitapide may be hepatotoxic, can elevate plasma aminotransferases, and can increase intrahepatic fat content by approximately 6% after 26 and 78 weeks of therapy. It was also concluded that cytochrome P450 3A4 inhibitors increase the exposure to lomitapide [11]. Lomitapide may reduce the absorption of fat-soluble vitamins and essential fatty acids, so coadministration of appropriate supplements is recommended. Because of the risk of hepatotoxicity, in the United States, lomitapide must also be prescribed through an FDA approved Risk Evaluation Mitigation Strategy program. However, mipomersen and lomitapide are both FDA approved for the treatment of patients with homozygous FH. (Gerald F. Watts et al) Several other MTP inhibitors are in various stages of development. Such candidates are CP-346086 [12], JTT-130 [13], SLx-4090 [14], implitapide [15], dirlotapide [16] and its analogues.

Antisense oligonucleotides to Apo B

ApoB is required for the intracellular assembly and secretion of very low density lipoproteins (VLDL) and LDL by the liver. Thus, the number of apoB is positively correlated with the level of plasma LDL-C. Therefore, a possible approach has been taken to inhibit the formation of apoB during the process of translation from the gene into its protein product [17]. A potential approach to inhibit translation of mRNA is to block the process by using a single-strand antisense oligonucleotide (ASO) that is complementary to and will strongly hybridize to the mRNA. This will lead to the degradation of mRNA and eventually result in reduced

transcription of the encoded protein. ApoB ASO targeting apoB100 protein synthesis is an attractive ASO since apoB100 is highly distributed in the liver [18]. Current research mainly focuses on apoB100 ASO, with mipomersen monotherapy. [Mipomersen is an apolipoprotein B synthesis inhibitor for lowering of LDL-C in patients who are already receiving lipid-lowering drugs, including high-dose statins.] [19].

Mipomersen

Mipomersen (Kynamro; Genzyme, Cambridge, MA) is an antisense 20-mer oligonucleotide that binds to a complementary sequence messenger RNA encoding apoB, thereby inhibiting ribosomal translation. By inhibiting the biosynthesis of apoB, hepatic very-low-density lipoprotein (VLDL) production and secretion are significantly reduced. Mipomersen consists of a phosphorotioate backbone and 2'-O-(2-methoxyethyl)-modified ends, which provide biological stability. Subsequent to subcutaneous injection, mipomersen is concentrated in the liver, where it undergoes catabolism via the action of hepatic endonucleases and exonucleases [20]. Mipomersen is FDA approved for use in patients with homozygous FH. Mipomersen has been shown to reduce serum LDL cholesterol by approximately 25%, 28%, and 36% in patients with homozygous FH, heterozygous FH, and severe hypercholesterolemia with or without CHD, respectively. Mipomersen also induces substantial reductions in total cholesterol, apoB, triglycerides, non-HDL cholesterol, and Lp(a). In addition to frequent injection site reactions and short-lived fatigue and myalgia, mipomersen can induce hepatic steatosis in 16% of patients, as well as elevations in plasma aminotransferases in 8% of patients. These hepatic changes apparently resolve on discontinuing the drug [21, 22]. Mipomersen has orphan drug status and, because of the risk of hepatotoxicity, can only be prescribed in the United States through a Risk Evaluation Mitigation Strategy program [21, 22, 23].

Proprotein Convertase Subtilisin Kexin type 9 inhibition

Proprotein convertase subtilisin/kexin type 9, also known as PCSK9, is an enzyme that in humans is encoded by the PCSK9 gene. This gene encodes a proprotein convertase belonging to the proteinase K subfamily of the secretory subtilase family. The encoded protein plays a major role in cholesterol homeostasis. Thus, drugs that block PCSK9 can lower circulating cholesterol. Although, the exact mechanism by which PCSK9 affects LDLR is yet to be determined, PCSK9 acts by targeting the LDLR to lysosomes in a process that involves a direct protein-protein interaction with the receptor and does not require its catalytic activity [24, 25]. Interestingly, statins and ezetimibe treatment were associated with increased levels of circulating PCSK9, which possibly attenuate the therapeutic effects of them. Thus, PCSK9 is considered by many to be a highly desirable therapeutic target for the generation of novel cholesterol-lowering drugs, or in combination with statins and ezetimibe to enhance the lipid-lowering efficacy [26].

PCSK9 inhibitors are not yet licensed for use in FH, but clinical trial data suggest that they may have broad

applications for patients with heterozygous FH who are not at LDL cholesterol targets on maximal statin therapy [27, 28] or who are intolerant to statins [29]. At least six different human mAbs and three gene-silencing approaches are under development. Among the mAb developed against PCSK9, clinical trial results are available for the three of them, alirocumab (SAR236553/REGN727), evolocumab (AMG145) and bococizumab (RN316/PF-04950615), while for RG7652, 1B20 and LGT209 no data were published yet. A large body of evidence is available so far for alirocumab and evolocumab. In addition, the association of alirocumab with fibrates slightly affected the efficacy of the antibody in decreasing LDL-C levels. An important consideration relates to the ability of anti-PCSK9 mAbs to decrease the Lp(a) plasma levels. Future studies are needed to characterize the mechanism underlying this effect. PCSK9 inhibitors might therefore represent an optimal therapeutic option to improve the lipid profile of subjects at high CVD risk characterized by elevated Lp(a) plasma levels. Phase I data with the siRNA ALN-PCS were recently released [30], and showed that the inhibition of PCSK9 synthesis by RNA interference (RNAi) provides a potentially safe mechanism to reduce LDL cholesterol concentration in healthy individuals with raised cholesterol. These results set the stage for further assessment of ALN-PCS in patients with hypercholesterolemia, including those treated with statins [31].

Thyromimetics

Thyroid hormone enhances the expression of the hepatic LDLR gene [32], thereby, increasing LDL clearance and decreasing plasma LDL-C levels [33]. Thyroid hormone (in particular 3,5,3'-triiodo-L-thyronine (T3) has, therefore, been tested for use as a cholesterol-lowering agent, but was associated with adverse effects on heart and bones [34]. It is known that T3 exerts its effects via four known isomorphs of the thyroid receptor (TR), TR- α -1, TR- α -2, TR- β -1 and TR- β -2. Further, TR- α plays a major role in the heart, while TR- β , highly expressed in the liver, controls cholesterolemia by mediating the activation of CYP7A in response to T3 [35, 36]. Subsequently, selectively targeting TR- β without the cardiac complications has been developed. Currently, one such agent eprotirome (KB2115), a selective agonist of TR- β , is undergoing clinical trial [37].

Lipoprotein apheresis and other invasive therapies

Lipoprotein apheresis (LA) is an extracorporeal treatment which removes apoB-containing lipoproteins from the circulation [38]. The removal of LDL by LA improves CHD outcomes, progression of atherosclerosis, aortic fibrosis, and endothelial function, in patients with FH [39]. LA is an FDA-approved therapy that is indicated for patients with homozygous or severe heterozygous FH with progressive CHD who are refractory to maximal pharmacotherapy [40]. By contrast to homozygous FH, the patient acceptability and cost-effectiveness of LA for treating refractory heterozygous FH remains unclear and needs further evaluation. Untreated patients with a homozygous phenotype typically have plasma LDL cholesterol 13 mmol/L and should be treated with maximally tolerated pharmacotherapy for at least 6 months before considering LA [39]. Untreated heterozygotes

typically have plasma LDL cholesterol from 5 to 13 mmol/L and may be truly nonresponders to or be intolerant of pharmacotherapy [39, 40]. LDL-cholesterol criteria for selecting the aforementioned patients for apheresis have been recommended elsewhere [41] but should be modified according to clinical context. Simple criteria are a reduction in 50 % LDL-cholesterol [39, 41]. Different thresholds for LDL cholesterol may be set according to the availability of resources for apheresis. Imaging should be carried out at baseline to assess aortic stenosis and aneurysms. Contraindications to apheresis methods that use heparin include hemorrhagic diatheses, resistance to adequate coagulation, and hypersensitivity to heparin. LA is efficacious, tolerable, and safe in the treatment of severe FH and may be commenced in children older than of 5 years of age,[42] or earlier in exceptional circumstances. Although lower body weight is a recognized risk factor for complications, successful outcomes have been reported with LA in very young children with homozygous FH [42, 43]. Women with severe FH may be successfully treated during pregnancy. There are several LA methods that are selective for LDL and Lp(a) levels by 50% to 70% after a single treatment [44]. The FDA-approved methods involve the extracorporeal precipitation of apoB-containing lipoprotein with dextran sulfate or heparin, whereas in other countries, alternative systems (immunoabsorption, double cascade filtration or hemoperfusion with direct absorption of lipoproteins, dextran sulfate or polyacrylate) are available [45]. Angiotensin-converting enzyme inhibitors are contraindicated with most systems, particularly the dextran sulfate LDL absorption and hemoperfusion methods because of bradykinin reactions. Patients who are intolerant of a particular method of LA should be tested on an alternative method, including plasma exchange if required. Long-term efficacy of treatment on carotid and aortic valve atherosclerosis should be assessed every 2 years in homozygotes using standard imaging methods [40]. Lomitapide should be considered as an adjunctive treatment to further lower LDL cholesterol in adults with homozygous FH on LA, [46] as well as in children and adolescents with homozygous FH on LA with rapidly progressive atherosclerosis. In those who cannot tolerate lomitapide, mipomersen should be accordingly considered. Novel LDL cholesterol-lowering therapies may reduce the need for or the frequency of LA in severe FH,[47-49] but this needs to be demonstrated. Orthotopic liver transplantation should also be considered in younger homozygous patients when LA is not available, or cannot be tolerated, and LDL cholesterol cannot be adequately controlled with intensive pharmacotherapy [50]. Coronary artery bypass surgery, aortic valve replacement, or a combined heart transplantation should be considered according to clinical context before liver transplantation. Partial ileal bypass should be considered in heterozygous patients who are drug-intolerant [51-53]. There may be a future role for gene therapy in treating severe FH [54, 55].

2. Conclusion

It is clear that more than 70% of the body's cholesterol is derived from the de novo cholesterol biosynthesis. Thereby, the inhibition of de novo cholesterol biosynthesis by statins is currently the most effective therapeutic approach to

reduce plasma LDL-C. Statins. However, such recommendations are questionable because muscular side effects and drug interactions of statins are now better understood. In spite of several adverse effects, statins have blockbuster fame, and the novel hypolipidemic drugs have a task difficult to achieve because their hypolipidemic effect should be better or at least comparable to statins and in addition, toxicity, drug interactions and side effects should be minimal. Thus, In addition to existing treatments, some other aforementioned approaches for the development of novel familial hypercholesterolemic treatments are discussed herein. But none of these approaches are currently approved for use in humans. Several ongoing agents are in their different stages of clinical trials, in expectation of promising antihyperlipidemic drugs.

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