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CURRENT SCENARIO AND FUTURE ORCHESTRATIONS IN THE BATTLE AGAINST DYSLIPIDEMIA: REVIEW ON NOVEL HYPOLIPIDEMIC DRUGS

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Cholesterol is an essential constituent of the cell membrane. It coordinates carbohydrate, major ions, and bone homeostasis respectively. [1] Cholesterol is the progenitor for all glucocorticoids, mineralocorticoids, sex hormones, steroids, and cholecalciferol. Cholesterol is transported into the blood via spherical macromolecules like chylomicrons, HDL, LDL, and VLDL. [2] These properties make it an essential biomolecule for most physiological mechanisms. Triglycerides performing a key role in providing energy to cells. [3] In excess amounts, these biomolecules are not good for health and produce hyperlipidemia. [4] Hyperlipidemia is responsible for many long-term side effects in the body. Hyperlipidemia increases the risk of formation of plaques, which promotes the risk of heart attack and stroke in persons with atherosclerosis and coronary heart diseases. [5] Statins are the evidence-based treatment option for hyperlipidemia according to published guidelines. [6] Statins are the lipid-lowering agents that mainly inhibit HMG-Co-AR (3-hydroxy-methyl-glutaryl-CoA reductase). [7] Established therapeutic options with or without statins are omega 3 fatty acids, fibrates, bile acids, and ezetimibe. [8] Recently many clinical trials discover novel therapeutic agents for dyslipidemia. Recent studies highlighted the different approaches by which we can target hypercholesterolemia. New drugs which mainly acts on (i) triglyceride levels; (ii) LDC-c molecule and (iii) Lipoprotein (a) molecule. [9] The emergence of new hypolipidemic drugs may fulfill the gap. Some novel compounds have a mechanism of

action already explored while others still under trials with unknown mechanisms. [10] The present review is done to find out the current status and comparative discussion between statins and novel pharmacological drugs.

Drugs mainly act on LDL

Low-density lipoproteins (LDL-C) are the main mutable factor in reducing cardiac and vascular events. [11] Different types of genetic and clinical studies revealed that low-density lipoprotein has a direct job in causing atherosclerotic cardiovascular disease (ASCVD). [12]

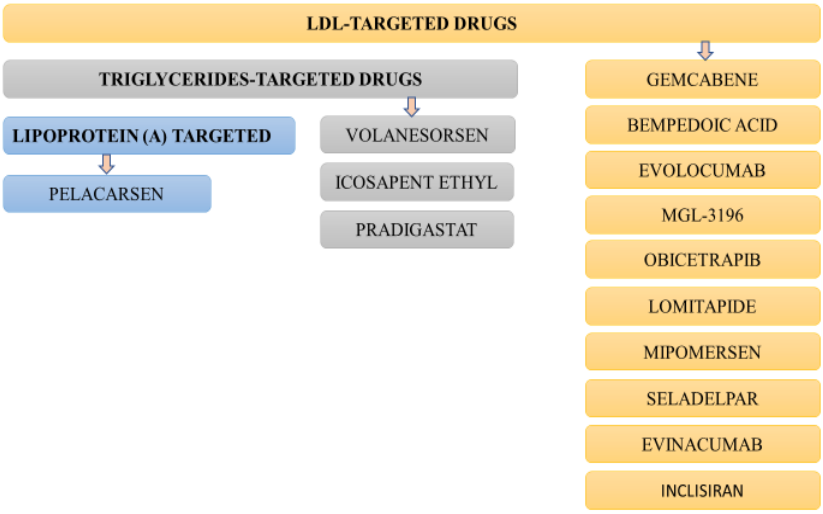

Figure 1: Novel hypolipidemic compounds acting on targeted molecules.

Gemcabene

Gemcabene is a small molecule of dialkyl ether dicarboxylic acid that is a monocalcium salt. It shows hypolipidemic properties. [13] Gemcabene is a new drug that acts mainly by lowering LDL-C (low-density lipoprotein cholesterol) and decreasing triglycerides. [14] It also involves the removal of very low-density lipoproteins (VLDL) through suppression of liver apolipoprotein C-III (Apo C-III) mRNA. [15] Gemcabene inhibits carboxylase Ac-CoA and leads to the depletion of hepatic triglycerides and LDL levels, however, the mechanism of action is not yet fully discovered. [16]

A phase III trial (COBALT-1) was conducted by Gemphire (Livonia, MI) at 9 hospital setups in Canada, US, and Israel. Randomization of 8 patients was done between June 16, 2016, to July 13, 2017. Eight with HoFH already on PCSK9 inhibitors statins and ezetimibe were managed to provide gemcabene for 12 weeks. All Patient gets gemcabene 300 mg during the initial 4 weeks, 600 mg during the subsequent 4 weeks, and provided last 4 weeks 900mg. After completion of 12 weeks of trial, the mean percentage difference from the control line in LDL-C with 300 mg was 26% in the 4th week, 600 mg was 30% at week 8, and 900 mg was 29% at week 12. Finally,

it was found that gemcabene has significant capability to diminish LDL-C as a supporting therapy in the cure of FH (familial hypercholesterolemia) patients. An insignificant increase in the baseline level of serum creatinine was associated with all doses of gemcabene respectively. [17]

A randomized, phase 2 study was conducted for 8-week. Randomization of 66 patients in 1:1:1 with gemcabene subsequently with 300 mg, 900 mg, and placebo QD. The study included women ≥ 18 and ≤ 65 years mainly postmenopausal and men with LDL-C ≥ 130 mg/dL. Results show gemcabene subsequently at 300 and 900 mg generate a average percentage difference in LDL-C of 23.4% and 27.7 % subsequently, vs 6.2 % for the counter-agent group. It was concluded that gemcabene can provide effective add-on therapy on the background of statins.[18]

Bempedoic acid

Bempedoic acid impacts on biosynthesis pathway of cholesterol in the liver. [19] An oral pro-drug that is transmuted to its operated form by Acyl-CoA synthetase-I (ACSVL1). [20] Bempedoic acts by inhibiting ATP-citrate-(pro-S)-lyase (ACL). [21]It was made by Esperion Therapeutics Inc. and gets approval on February 21, 2020, by FDA. Bempedoic acid is chiefly present throughout the liver and absents mostly in peripheral tissues. Those properties differentiate bempedoic acid from statins in their liver-specific actions. [22] FDA recommended daily dose of bempedoic acid is 180mg once with the food or without. [23]

A CLEAR Serenity Phase 3 study was done on a total of 345 patients who suffered from hypercholesterolemia. Signs of intolerance to at least two statins. Treatment is given 180 gm of bempedoic acid and placebo for 24 weeks daily one time. The first final point targeted was the average percentage difference from the control line in LDL-C on the 12th week. Bempedoic acid remarkably decreases LDL-C from baseline on the 12th week. Significant depletion occurs with BA in comparison to placebo was also spotted in non–HDL-C, C-reactive protein, and Apo-B. Bampedoic acid was found a secure and beneficial oral medicinal option for lipid lowering in candidates, who are not able to bear statins. However, muscle-related adverse side effects like myalgia were detected. [24]

A Phase3, double-blind, randomized, clinical trial was piloted at 91 hospitals in Europe and North America between 2016 (November) to 2018 (September). Overall, 779 subjects were selected with ASCVD and HoFH. Subjects were haphazardly divided into 2:1 and provided bempedoic acid (180mg) (n=522) and placebo (n=257) for 52weeks once a day. Among 779 patients 740 completed the trial. Inclusion of bempedoic acid turns in a remarkable depletion of LDL-C concentration during 12 weeks during comparison with placebo. Adverse reactions found were urinary tract infections, hyperuricemia, and nasopharyngitis. Elevations in levels of aminotransferase enzyme more than three times the top concentration were 1.1% detected with bempedoic acid batch and 0.8% found in the placebo group. [25]

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Evolocumab and Alirocumab

Evolocumab and Alirocumab both are novel drugs, FDA sanctioned. [26] Both are engaged in the depletion of (LDL and are anti-PCSK9 (Proprotein convertase subtilisin/Kexin type 9) antibodies. PCSK9 was discovered in 2009 and denoted as the ninth partner of the proprotein convertase family by Seidah et al. [27] PCSK9 is a structured protein mainly found in the hepatic cells, kidney, and bowel. [28] It was noticed that PCSK9 boosts the degeneration of LDL receptors by the complex formation in the liver. [29]

PCSK9 directly links with the LDLR complex both inside and outward of the plasma membrane. According to a few studies secreted PCSK9 primarily acts on the LDLR and helps in the depletion of LDLR protein mass in the liver mainly. This PCSK9-LDLR complex disrupts the typical processing of LDLR on the plasma membrane and promotes the lysosomal degeneration of LDLR. [27] At the transcription level, there is a linkage between LDLRs and PCSK9. Demonstration of LDLR and PCSK9 takes place via sterol regulatory element-binding protein-2 (SREBP-2), causing the increased formation of LDLRs and PCSK9. [30] Evolocumab was first introduced in the market EU in July 2015. Indicated in patients with mixed dyslipidemias and familial/nonfamilial hypercholesterolemia. Those who are unable to reach the therapeutic goal with other hypolipidemic drugs. [31]

Alirocumab is a monoclonal antibody sanctioned for the cure of primary HoF and nonfamilial hypercholesterolemia or mixed dyslipidemia. [32]

A randomized Fourier trial was done and the result was assembled from 2013 (February) to 2016 (November) and analyzed from March 2018 to 2020 later. Overall, 27342 patients included in the study. 20623 men with baseline syndrome X were at top risk of cardiac events when analyzed with patients who don't have metabolic syndrome. It was found that evolocumab decreases LDL-C uniformly in patients with syndrome-X and without metabolic syndrome. Subsequently, it was found that evolocumab doesn't escalate the possibilities of new-onset diabetes as compared to placebo with syndrome-X patients.

Finally, it was concluded that evolocumab remarkably reduces the LDL and possibilities of cardiac and vascular diseases in metabolic syndrome patients. [33]

GLAGOV clinical trial was conducted from May 2013 to January 2015. Included 968 patients at 197 hospitals from six different continents, enrolled for coronary angiography. 846 patients underwent imaging at follow-up. During comparison with the placebo, it was found that the evolocumab group attained lesser mean, LDL-C levels. The percentage rate of plague regression was more in the evolocumab receiving group than placebo. The inclusion of evolocumab in patients with statin treatment results in decreases in PAV (percent atheroma volume) following 76 weeks of therapy when compared with placebo. This study doesn't show any change in HbA1c levels. Rare adverse outcomes like cardiovascular, nonfatal myocardial infarctions, injection site reactions, myalgia, and neurocognitive events were cited.[34]

MGL-3196

MGL-3196 is a beta-receptor agonist. [35] MGL-3196 has shown favorable outcomes on metabolic disbalance, encircling non-alcoholic fatty liver disease (NAFLD) by triggering thyroid

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hormone receptor β (THRβ). [36] Few research has found that the stimulation of THR-β has beneficial results on triglycerides and cholesterol levels and a protective role in hepatic steatosis. [37] It was observed that it also has a protective role in the cardiometabolic profile. [38] In preclinical studies, MGL-3196 has shown beneficial effects in diabetes and obesity models. [39] Among TRα and TRβ, TRβ is predominantly found in the liver and helps in reducing cholesterol levels while TRα adversely affects bone and heart. [40]

A 36-week phase 2 testing was done at 25 centers in the USA. Randomization of patients allocated 2:1 by a computerized system. Patients were provided resmetirom 80 mg and a placebo, a single dose during a day. Measurements of sequential liver fat were calculated during the 12th and 36th weeks of medication, followed by a subsequent liver biopsy prevailed at week 36. Overall, 348 patients were recruited and randomized of 84 subjects to resmetirom and 41 subjects to placebo at different 18 locations in the USA. Treatment with resmetirom showed a remarkable depletion in liver fat following therapy, on the 12th and 36th week in NASH. Episodes of nausea and transient mild diarrhea were noted with resmetirom.[41]

Obicetrapib

Obicetrapib, a CETPi (cholesteryl ester transfer protein inhibitor) can decrease the level of LDL-C. [42] CETP linked to HDL permits the relocation of cholesterol esters from HDL to apoB particles. According to a few studies deficiency of CETP leads to an increased level of HDL-C, while depletion of LDL-C at some level. [43] CTEP promotes the relocation of cholesteryl esters by two directional processes. The first one is the shuttle mode: CTEP linked to a lipoprotein of HDL molecule, interchanging triglycerides and cholesteryl esters, then detachment occurs and it will bind to another molecule for the same process. Second is tunnel mechanism: formation of CETP-HDL complex by attachment of N-terminal to an HDL molecule, further this compound bound to LDL or VLDL along the C-terminal, tertiary complex is formed. [44]

ROSE trial was done, randomization of 120 patients provided therapy with obicetrapib 5 and 10 mg subsequently with placebo. Subjects have been provided atorvastatin 80 mg add-on with rosuvastatin 20 mg throughout 8 weeks before starting obicetrapib therapy. After completion, 8 weeks, obicetrapib 5 and 10 mg depleted LDL-C by 42% and 51% from the control line significantly. Subjects achieved an LDL-cholesterol aim of less than 70 mg/dL in patients treated with the 10-mg dose. No life-threatening effects were found in the whole trial period.

Lomitapide

Lomitapide, refer to as a microsomal triglyceride transfer protein inhibitor. [45] Lomitapide promotes a decreased production of apolipoprotein B through inhibiting MTP (microsomal triglyceride transfer protein). [46] subsequently, this depletes the LDL-C level that is unconstrained with LDL-R. [47] Approval of lomitapide done by the US-FDA is mainly used during the medication of HoFH. [48] Recent studies denote the inclusion of lomitapide in the ongoing therapies helping cessation of LA (Lipoprotein apheresis) in many patients. [49]

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Lomitapide is metabolized via CYP3A4 in the liver and converted into M1 and M3 metabolites. Metabolism is hampered in patients with hepatic and renal impairment. [48]
A multicenter retrospective, test on 75 patients with HoFH medicated with lomitapide. An observational study in a hospital setting in 9 European countries. LDL-C decreased by 60% after a median of 19months of cure following a mean prescribed dose of 20mg of lomitapide. On the final appointment, 32.0% of subjects reached at LDL-C <100mg/dL and 18.7% <70mg/dL. Initially, 38 subjects with HoFH were taking LDL Apheresis (LA), but following add-on lomitapide, 36.8% of sufferers stops LA. It was concluded that lomitapide has an effective role in decreasing LDL-C in HoFH. Adverse events like nausea and diarrhea were found in the first 3 months of therapy. 10% to 13% of patients found an elevation of LFTs.[50]

A phase 3, single-arm, test was organized in Japan and included adult patients with HoFH. Nine patients were included, out of nine, eight finished 56 weeks. LDL-C mean was decreased at 26 weeks significantly. Reduction of 50% in LDL-C ＜100 mg/dL was accomplished by five out of nine subjects at 26 weeks. 38% depletion in LDL-C level was found at the completion of 56 weeks. The conclusion was made that lomitapide has a significant role in depleting LDL-C in adult Japanese subjects with HoFH. Elevations in AST and ALT levels up to ≥ 3×ULN (upper limit normal) were found in three of the total patients.[51]

Mipomersen

Mipomersen mainly acts on apolipoprotein B-100 mRNA, an antisense oligonucleotide inhibitor. [52] Effective role in the degradation of the apoB-100 by binding apoB to mRNA leading to inhibition of protein translation. [53] Finally, it will cause substantial depletion in LDL-C and different lipoproteins levels. [54] Mipomersen is now indicated in the treatment of HoFH. [55] Mipomersen is sanctioned as an adjunct therapy to reduce LDL cholesterol. It is not suggested in patients with LDL apheresis therapy. [56]
In a multicenter, a placebo-controlled, the test was done by **Mc Gowan et al.** total of 58 patients ≥18 years with LDL-C ≥7.8 mmol/L and LDL-C ≥5.1 mmol/L with coronary heart problems, on maximum permitted lipid-decreasing dose were included. Mipomersen 200 mg add-on weekly to lipid-depleting therapy for 26 weeks subcutaneously in injection form. Percentage depletion was observed in LDL-C in comparison to two weeks followed by final dose of medication. Mipomersen decreases LDL-C up to 36%, from a control line of 7.2 mmol/L, for an average depletion of 2.6 mmol/L. Mipomersen produced significant depletions in Apo-B and lipoprotein(a), with nil difference in HDL-C. Few incidents of increased serum creatinine and cardiac adverse event were found.[57]

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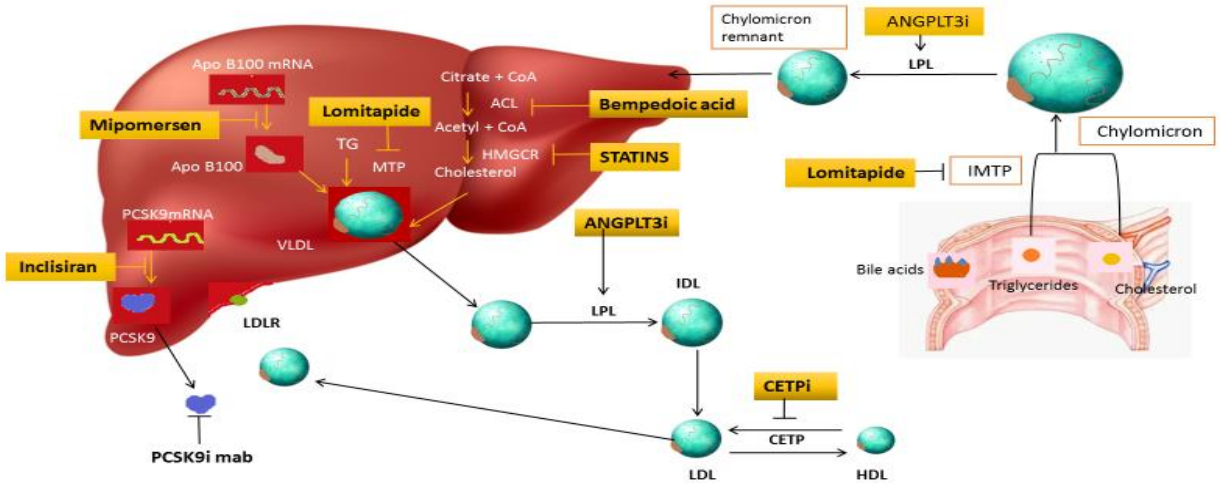

Figure 1: Mode of action of some mentioned therapies: Inclisiran stops translation of proprotein convertase subtilisin–kexin type 9 mRNA. Lomitapide intervene with very low-density lipoprotein (VLDL) and chylomicron through microsomal triglyceride transfer protein (MTP) inhibition. Bempedoic acid arrests cholesterol formation by suppression of ATP citrate lyase (ACL). Statins inhibits 3-hydroxy-3-methylglutaryl coenzyme reductase (HMGCR). Angiopoietin-like 3 protein inhibitors (ANGPTL3i) amplify lipoprotein lipase (LPL) function. Mipomersen targets hepatic apolipoprotein B100 (apoB100) mRNA. PCSK9 suppression of monoclonal antibodies (PCSK9i) inhibits PCSK9 binding to low-density lipoprotein receptor (LDLR). Cholesteryl ester transfer protein inhibitors (CETPi) inhibits transportation of cholesterol esters from high-density lipoprotein to apoB particles, predominantly low-density lipoprotein (LDL) particles.

Table: 1 Modern hypolipidemic drugs, mechanism of action, and their possible indications.

DRUGS	MECHANISM OF ACTIONS	INDICATION
GEMCABENE	acts mainly by depleting LDL-C, decreasing triglycerides, and increasing HDL-C	HoFH (Homozygous Familial Hypercholesterolemia)
BEMPEDOIC ACID	acts by inhibiting ATP-citrate (pro-S)-lyase (ACL)	Atherosclerotic cardiovascular disease, HoFH
EVOLOCUMAB/ ALIROCUMAB	anti-PCSK9 antibodies, mainly act by a reduction in LDL-C	Primary HoF and nonfamilial hypercholesterolemia or combined dyslipidemia
MGL-3196	Acts by activating thyroid hormone receptor β (THRβ)	Metabolic disbalance, including Non-alcoholic fatty liver disease (NAFLD)

OBICETRAPIB	CETP (cholesteryl ester transfer protein) inhibitor can decrease the level of LDL-C	Hypercholesterolemia
LOMITAPIDE	A microsomal triglyceride transfer protein inhibitor	HoFH
MIPOMERSEN	An antisense oligonucleotide inhibitor	HoFH (Homozygous Familial Hypercholesterolemia)
SELADELPAR	Selective novel PPAR δ agonist	diabetes, atherogenic dyslipidemia, and nonalcoholic steatohepatitis
EVINACUMAB	acts by inhibition of angiopoietin-like protein-3	HoFH
INCLISIRAN	A synthetic long-action anti-PCSK9	Hypercholesterolemia
VOLANESORSEN	An inhibitor of apoC3 which helps in reducing the level of triglycerides	Hypertriglyceridemia and pancreatitis
ICOSAPENT ETHYL	decrease level of triglycerides in the blood	Hypertriglyceridemia
PRADIGASTAT	highly potent diacylglycerol acyltransferase 1 (DGAT1) inhibitor	familial chylomicronemia syndrome (FCS)
PELACARSEN	hepatocyte-directed antisense oligonucleotide mainly acts via Lipoprotein-A gene mRNA	decreases in Lp(a) levels in Hypercholesterolemia

MBX-8025

MBX-8025 (Seladelpar) is an emerging PPAR-δ agonist. [58] ubiquitous expression in tissues makes it an essential therapeutic target in many diseases like diabetes, atherogenic dyslipidemia, and nonalcoholic steatohepatitis. [59] During trials, it was found that MBX-8025 has a significant role in correcting abnormal cholesterol profiles in obese and persons with metabolic disorders. It was found that MBX-8025 decreases LDL, increases HDL, and also sensitizes insulin. [60] Recent studies show MBX-8025 effectiveness in NAFLD. [61]

A placebo-controlled, research was organized at 30 U.S. research locations. Overweight men and women total of 181 with combined hyperlipidemia were included in the trial. MBX-8025 at doses of 50 or 100 mg single or in combination with 20 mg atorvastatin and placebo were given for 8 weeks. In comparison to the placebo, MBX-8025 solo and in mix up to atorvastatin remarkably decreases Apo-B-100, 20–38%; LDL 18–43%, triglycerides concentration 26–30%. MBX-8025 has an effective role in several metabolic parameters with or without atorvastatin. Adverse events like upper respiratory tract infection, nasopharyngitis, and muscle weakness were found during the study.[62]

In a randomized parallel arm, placebo-controlled research was done for 8 weeks. A total of 166 obese patients were cured with Seladelpar (50 and 100 mg/d) with atorvastatin 20 mg/day or

without. At 50 and 100 mg doses, MBX-8025 shows depletions of small and very small LDL molecules and improves the concentration of High LDL. It was found that PPAR-δ with statins has additional outcomes in increasing lipoprotein subfractions linked to atherogenic dyslipidemia. [63]

Evinacumab

Evinacumab mainly acts by inhibiting angiopoietin-like protein 3 results in enhancing the breakdown of fats in the body. [64] Evinacumab decreases LDL-C chiefly by enhancing apo-B lipoprotein removal from the blood circulation. [65] Three types of angiopoietin-like protein, ANGPTL3, ANGPTL4, and ANGPTL8 have a crucial role in cholesterol metabolism. The liver is the main source of ANGPTL3. [66] Evinacumab was sanctioned recently by the FDA on February 6th for LDL-C-depleting therapies in adult and adolescent patients (12 years of age or more). [67] ANGPTL3 inhibition cause induction of local pro-inflammatory effects in the vascular wall by enhancing endothelial lipase. [68]

ELIPSE phase 3, the trial was done. 65 subjects were randomly selected with a ratio of 2:1 with HoFH, providing an intravenous infusion of evinacumab 15 mg/kg for up to 4 weeks or a placebo. The average control line of LDL cholesterol concentration in both groups was 255.1 mg per deciliter, already on the highest doses of lipid-depleting therapy. In the 24th week, evinacumab group shows a depletion from the control line in the LDL cholesterol amount of 47.1%, in the comparison along with the placebo group (1.9% increment). The LDL-C concentration was decreased to belong to evinacumab group in comparison to the placebo. Finally, it was concluded that evinacumab has a lipid-lowering property by reducing LDL amount in patients with HoFH.[69]

Inclisiran

Inclisiran is a long-action anti-PCSK9, which is conjugated to N-acetyl-galactosamine (GalNAc) carbohydrates. A recently discovered molecule siRNA promoted inhibition of PCSK9 levels. [70]
The mode of action of Inclisiran is rest on RNA interference, which is a biological procedure in which double-stranded RNA silences the particular gene by activating mRNA degradation. [71]
Inclisiran plunge into the hepatocyte, Guided strands link to the RNA-induced silencing complex (RISC) via a connection between GalNAc and ASGPR (Asialoglycoprotein receptor). [72]
Overall, 1561 patients with ASCVD and 1617 with an ASCVD receiving statin medication at the extreme tolerated dose for elevated LDL level were randomized under ORION-10 and ORION 11 subsequently. Randomization was done in a 1:1 fraction, patient acquiring either inclisiran 284 mg or placebo, in the form of injections given subcutaneously on first day, day 90, and every six months over 540 days. Inclisiran depleted LDL-C levels by 52.3% in the ORION-10 test and by 49.9% in the ORION-11 on day 510 of trial.

The conclusion was made that the 6 monthly subcutaneous injections of inclisiran can reduce approximately 50 % of LDL cholesterol. Reactions were recorded with inclisiran at the injection site. [73]

Triglycerides level inhibitors

Increased triglycerides level is a usual finding in medical practice. [74] To date, three different classes are used in the cure of high triglyceride levels: fibrates, omega-3 fatty acids, and Vitamin B3. [75] Hypertriglyceridemia is the risk factor for many metabolic disorders. [76] Nowadays there is the emergence of novel therapeutic options with a different mechanism of action for balancing the triglyceride level.

Volanesorsen

Volanesorsen (ISIS 304801) is a next-generation 2'Omethoxyethyl chimeric ASO (antisense oligonucleotide). [77] Volanesorsen is an inhibitor of apoC3 which helps in reducing the level of triglycerides, and further reduces the incidence of pancreatitis. [78] Effectivity and safety of volanesorsen have been observed in several studies with FCS (Familial chylomicronemia syndrome). [79] However, safety issues are a matter of discussion due to platelet imbalance.

A double-blind, phase 3 randomized 52-week trial was done by Ionis Pharmaceuticals. 66 patients were included with FCS. Subjects were haphazardly allocated, in a 1:1 proportion, who gets 300mg of volanesorsen per week or a placebo. Patients on volanesorsen resulted in a 77% depletion in average triglyceride level, while patients on placebo indicated an 18% increment in the average triglyceride concentrations. After three months, 77% of the subjects of the volanesorsen group, as compared with 10% of the placebo group, showed triglyceride levels lower than 8.5 mmol per liter. Injection site adverse effects and thrombocytopenia were recorded in patients on volanesorsen. It was concluded that volanesorsen has an effective capability to reduce triglyceride levels.[80]

Icosapent Ethyl

Icosapent ethyl compound shows favorable impacts on dealing with high triglycerides levels. [81] icosapent ethyl (Vascepa) is sanctioned by the FDA as adjunctive therapy to inhibit triglyceride (TG) concentrations. [82] The mechanism of action is less understood given that Icosapent ethyl reduces triglyceride levels. Two other mechanisms suggest are anti-platelet and anti-inflammatory. [83]

An ANCHOR study was done. 702 subjects on statins with high cardiac and vascular risk with triglycerides 200–499 mg/dl and LDL-C 40–99 mg/dl were included. Icosapent ethyl (4g/day) vs. placebo effects on fatty acid levels in RBCs and plasma under a gas chromatograph assay procedure with a flame ionization observer were detected. Medication with icosapent ethyl shows a remarkable increment versus placebo in the mean level of EPA (eicosapentaenoic acid) in plasma. Finally, the conclusion was made that icosapent ethyl remarkably improves EPA

(eicosapentaenoic acid) in plasma which causes a decreased level of triglycerides in the blood. [84]

Lipoprotein (a) Targeting

Pelacarsen (AKCEA-Apo (a) LRx)

APO(a)-LRx, an antisense oligonucleotide (ASO), has provided good results in clinical trials and will include in clinical practice shortly. [85] APO(a)-LRx, is also classified under the RNA-based therapies and can decrease Lp(a). [86] A hepatocyte-directed antisense oligonucleotide, pelacarsen mainly acts via LPA gene mRNA. During the various trials, Pelacarsen receives many names like TQJ230, IONIS APO(a)-LRx, AKCEA-APO(a)-LRx, and ISIS 681257. Administered subcutaneously weekly or monthly. [87] The potency of pelacarsen increases when it will combine with GalNAc3 (N-Acetylgalactosamine). [88]

A Phase 2b, double-blind study was run on 286 subjects. Randomization was done with different doses of 60 mg every 4 weeks, 20 mg for every 2 weeks subsequently, and 20 mg every week, or placebo in the subcutaneous injection form for 6 to 12 months. Several subjects were <65 years of age, and roughly 50% had early coronary artery disease and before myocardial infarction. LDL-C levels were cured with 90% of subjects on statins, 50% on ezetimibe, and 20% on PCSK9 inhibitors. Pelacarsen brought depletion in dose-dependent Lp(a) levels, with a average percent reduction of 35% to 80%, as compared to the placebo group (6% reduction). [89]

DGAT inhibitor

Diacylglycerol acyltransferases (DGATs) are found in two isotypes, DGAT-1 and DGAT-2. It mainly catalyzes the end step of triglyceride synthesis. [90] DGAT-1 is mainly found in the hepatic cells, small intestine, and adipocerous cells. [91] DGAT-1 has a key performance in lipid absorption. According to recent studies going on it was found that DGAT-1 has a main therapeutic role in obesity and hypertriglyceridemia. [92] Pradigastat is a specific highly potent diacylglycerol acyltransferase 1 (DGAT1) depilator that inhibits chylomicron triglyceride formation. Pradigastat is an effective therapeutic agent involved in maintaining triglycerides levels in humans. [93]

An open-label clinical study was done on six patients with known familial chylomicronemia syndrome (FCS). Treatment was provided with pradigastat at three various doses of 20, 40 & 10 mg, subsequently for 21 days. Medication duration span separated by washout periods of ≥4 weeks. In the result, it was found that pradigastat is responsible for 41% (20 mg) and 70% (40 mg) depletion in fasting triglyceride during 21 days of treatment. Pradigastat therapy also provokes substantial reductions in postprandial TG as well as apo48. Just mild, gastrointestinal adverse reactions were found. The conclusion was made that the pradigastat (DGAT1 inhibitor) potentially reduces plasma TG levels and is a promising agent in FCS patients.[94]

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Table: 2 Results of completed Randomized Clinical Trials on hypolipidemic agents

Clinical trials and compounds	Study design	Population	Interventions	Outcomes
Gemcabene (COBALT-1) Clinical Trials. gov. Identifier:	Randomized control trial phase 3 for 12 weeks	8 patients with HoFH (Homozygous Familial Hypercholesterolemia)	Patients provided 300 mg gemcabene for the initial 4 weeks, subsequently 600 mg for the next 4 weeks, and 900 mg for the last 4 weeks	significant capability to reduce LDL-C as additional therapy in treatment for FH (familial hypercholesterolemia) [17]
Phase 2 trial Clinical Trials. gov. Identifier:	Placebo-controlled, Double-blind, randomized trial	66 subjects were randomized 1:1:1 to gemcabene or placebo QD	gemcabene 300 mg, 900 mg, or placebo QD for 8 weeks	gemcabene can provide effective add-on therapy on the background of statins [18]
Bempedoic acid CLEAR Serenity Clinical Trials. gov. Identifier: NCT02988115	double-blind phase 3, placebo-controlled	345 subjects with hypercholesterolemia and a recorded non-tolerance to at least 2 statins, including	bempedoic acid 180 mg or placebo for 24 weeks, once daily	Effective oral treatment for hyperlipidemia in statin in tolerated people. [24]
Phase 3 trial Clinical Trials. gov. Identifier: NCT02991118	Randomized, placebo-controlled clinical test	779 subjects with ASCVD, HoFH	180 mg of bempedoic acid or placebo for 52 weeks daily once.	LDL-C levels reduce remarkable higher than placebo at the 12^{th} week by bempedoic acid [25]
Evolocumab Fourier trial Clinical Trials. gov. Identifier: NCT01764633	Randomized, controlled phase 3 clinical trial	27342 patients randomly were included in the trial	Evolocumab 140mg subcutaneously every 2 weeks and 420 mg for the next 2 weeks monthly, or matching placebo	significantly reduce the LDL and risk of cardiovascular diseases in persons with metabolic syndrome [33]

GLAGOV clinical trial Clinical Trials. gov. Identifier: NCT01813422	double-blind multicenter, placebo-controlled randomized	968 patients at 197 hospitals in South Africa, North America, Europe, South America, Asia, and Australia enrolled for coronary angiography	Evolocumab 420 mg or placebo provided every month through subcutaneous injection for 76 weeks	The percentage rate of plague regression was more in an evolocumab receiving group than placebo [34]
MGL-3196 Phase 2 trial Clinical Trials. gov. Identifier: NCT02912260	Double-blind, controlled test completed at 25 centers in the USA	348 subjects were selected and 84 were assigned haphazardly to resmetirom and subsequently 41 to placebo at 18 different sites in the USA	Subjects were allocated randomly 2:1 receive resmetirom (MGL-3196) 80 mg or matching placebo, daily per mouth	Remarkable depletion in liver fat following 12 weeks and 36 weeks of medication in subjects with NASH [41]
Obicetrapib ROSE trial Clinical Trials. gov. Identifier: NCT04753606	Phase 2 Randomized control trial	Overall, 120 patients were recruited; patients were provided atorvastatin 80 mg or rosuvastatin 40 mg for at least 8 weeks prior randomization	Received medication 5 and 10 mg obicetrapib or placebo throughout eight weeks	obicetrapib 5 and 10 mg decreases LDL cholesterol by 42% and 51% from the control line significantly
Lomitapide	multicenter retrospective, an observational study done in a clinical setting from 9 European countries	The trial included 75 HoFH patients	20mg of lomitapide for 19 months	Effective role in decreasing LDL-C in HoFH [50]
Phase 3 trial	A single-arm, open-label research was conducted in Japan	the study included 9 HoFH patients	Started with 5 mg/day and accelerate to the highest tolerated dose (60 mg/day)	lomitapide has a remarkable role in reducing LDL-C and other atherogenic Apo B-containing

			over 14 weeks for a total of 56 weeks	lipoproteins. [51]
Mipomersen Mc Gowan et al. Clinical Trials. gov. Identifier: NCT00794664	Placebo-controlled, trial with randomization	Overall, 58 patients up to 18 years or more with LDL-C (7.8 mmol/L or more) or LDL-C (5.1 mmol/L or more) with CHD disease, on highest tolerated hypolipidemic medication were included	Mipomersen 200 mg subcutaneously or placebo were provided weekly for lipid-depleting therapy for 26 weeks	significant depletion in Apo B and Lp (a), with null change in HDL-C [57]
Seladelpar	A double-blind, placebo-controlled, trial conducted at 30 U.S. research sites	181 overweight men and women with mixed dyslipidemia were included in the trial	MBX-8025 at 50 or 100 mg solo or in addition with 20 mg atorvastatin and placebo were given for 8 weeks	MBX-8025 alone and in addition with atorvastatin remarkably decreases Apo B-100, LDL, triglycerides, and non-HDL-C [62]
Trial	A randomized parallel arm, double-blind trial	Overall, 166 overweight or obese patient were included	Seladelpar (50 and 100 mg/d) add-on therapy on atorvastatin 20 mg/day	PPAR-δ and statin have additional roles in enhancing lipoprotein subfractions related to atherogenic dyslipidemia [63]
Evinacumab ELIPSE trial Clinical Trials. gov. Identifier: NCT03399786	phase 3, a double-blind, placebo-controlled study was done	65 patients were randomly selected divided by a ratio of 2:1 with homozygous familial hypercholesterolemia	Evinacumab 15 mg/kg of body weight given subcutaneously every 4 weeks or placebo	evinacumab has a lipid-depleting property by reducing LDL-C concentrations in patients with HoFH [69]
Inclisiran ORION-10 and 11 Clinical	Double-blind placebo-controlled randomization	Overall, 1561 and 1617 patients with ASCVD and an ASCVD provided	Patients were allocated haphazardly in a 1:1 ratio to get either	6 monthly subcutaneous injections of inclisiran can reduce

Trials. gov. Identifier: NCT03399370 and NCT03400800	test	statin medication at the highest tolerated dose for an elevated LDL level	inclisiran 284 mg subcutaneously or placebo, on day 1, followed by day 90, and every 6 months over 540 days	approximately 50 % of LDL-C [73]
Volanesorsen Trial by Ionis Pharmaceuticals and Akcea Clinical Trials. gov. Identifier: NCT02211209	A double-blind, phase 3 randomized trial	66 subjects with familial chylomicronemia syndrome	Patients were haphazardly assigned, in a 1:1 ratio, who receive volanesorsen 300 mg per week or a placebo	volanesorsen having the effective capability to reduce triglyceride levels [80]
Icosapent ethyl ANCHOR study Clinical Trials. gov. Identifier: NCT01047501	A double-blind, phase 3 randomized trial	Overall, 702 statin-medicated subjects at increased cardiovascular risk with triglycerides 200–499 mg/dl were included	Patients received icosapent ethyl approximately 4 g/day, 2 g/day, or placebo up to 12 weeks	Significant decrease in triglycerides levels in blood [84]
PRADIGASTAT Clinical Trials. gov. Identifier:	open-label clinical trial	six patients with known familial chylomicronemia syndrome (FCS)	21-day of medication with pradigastat at 20, 40 & 10 mg, respectively given to patients	pradigastat (DGAT1 inhibitor) potentially reduces plasma TG levels [89]
PELACARSEN Clinical Trials. gov. Identifier: NCT01146522	Double-blind, placebo-controlled trial on phase 2b with randomization	Overall, 286 subjects were included	The patient received doses of 20, 40, or 60 mg every four weeks, then 20 mg every two weeks, and 20 mg every week, or placebo subcutaneously for 6	dose-dependent depletion in Lp(a) levels [94]

			to 12 months	

Statins

Statins are the main therapy to date in dyslipidemias and use in the prevention of Atherosclerotic cardiovascular disease (ASCVD). [95] Stains play an inhibitory role in the mevalonate (MVA) pathway by completely inhibiting the 3-βhydroxy 3β-methylglutaryl Coenzyme A reductase. [96] It was found in few studies that statins help decrease morbidity and mortality in persons with occlusive vascular disorders by inhibiting the formation of cholesterol from the liver. On the other hand, HMG, a Co-A reductase enzyme also has some beneficial effects on hemoglobin, vitamin D, a steroid hormone, and other molecules. [97] In addition to lipid-lowering effects, statins are known for their pleiotropic effects including the anti-inflammatory action and decreasing oxidative stress. [98] After 3 decades of introduction, it was found that statins also have an effective role in the precaution of cardiovascular disorders, diabetes, and premature mortality apart from lipidemic disorders. [99] Several statins are discovered to date and have some differences in pharmacokinetics, pharmacodynamics, clinical efficacy, and side effects over each other. [100] It is observed in many studies that high doses of statins are responsible for myopathies and weakness. [101] Apart from these side effects, stains are known for their pleiotropic effects, like reduction of oxidative stress, inhibition of inflammatory responses, decrease cardiovascular risks and improve quality of life ultimately. [102] several studies revealed that statins users have a low incidence of depression and anxiety-like disorders than non-statin users. [103]

Conclusion

In the current scenario, medical science is being changed by running discoveries. New discoveries impressively advance the way of diagnosis and treatment of diseases that are present in our society. Statins are the choice of drugs, used for decades in the medication of hyperlipidemia. Statins are known for their pleiotropic effects, having an effective role in the prevention of cardiovascular disorders. Evaluation of statins effectivity in neuro-psycho disorders showing positive results in hyperlipidemic patients. Apart from the pleiotropic effect statins are responsible for serious disorders like arthralgia, muscular pain, nasopharyngitis, and diarrhea. In the last couple of decades emerging of some novel, drugs proved the hope of decreasing the use of statins. Their mode of action is different from the existing statins. Novel lipid-lowering drugs have direct or indirect triglyceride, LDL, and Lipoprotein-a targeting actions. Novel drugs like lomitapide, mipomersen, evinacumab, gemcabene, and bempedoic acid have an effective role in HoFH (Homozygous Familial Hypercholesterolemia). Volanesorsen, icosapent ethyl and pradigastat are indicated in hypertriglyceridemia. The main difference between statins and described novel compounds is that they have more target actions so the adverse effects are also targeted. Data about the pleiotropic effects of novel compounds are not available to date. How they can impact patients' neuro-psychology is also a matter of discussion. But there is a hope that with continuous research on discussed medicines we can find out

effective results. Statins are also undergone a research process, giving emerging stains of a new era with fewer side effects. We can't say exactly who will win the race, after-all with every novel discovery patient is always a winner.

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