**Review Article**

**LDL Cholesterol, Statins And PCSK 9 Inhibitors**

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**A R T I C L E  I N F O**

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**A B S T R A C T**

Reduction of low density lipoprotein cholesterol (LDLc) is of vital importance for the prevention of atherosclerotic cardiovascular disease (ASCVD). Statin is the most effective therapy today to lower LDLc by inhibiting HMG-CoA-reductase. However despite intensive statin therapy, there remains a residual risk of recurrent myocardial infarction in about 20–30% cases. Moreover a few patients develop statin intolerance.

For severe hypercholesterolemia, statins alone or in combination of ezetimibe, niacin and fenofibrate have been advocated. For homozygous familial hypercholesterolemia (HOFH), a microsomal triglyceride transfer protein MTP inhibitor (Lopitamide) and antisense oligonucleotide (ASO) (Mipomersen) have recently been approved by FDA, USA through ‘Risk evaluation and Mitigation Strategy (REMS)’. Possible future therapies include PCSK-9 inhibitors which have excellent lipid lowering properties. Three monoclonal antibodies (PCSK 9 Inhibitors) alirocumab, evolocumab and Bococizumab are under advanced clinical stage IV trials and awaiting approval by FDA and European Medicines Agency.

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**1. Introduction**

Adult treatment panel (ATP) guidelines of National Cholesterol Education Programme (NCEP) 2001 established the importance of lowering ‘low density lipoproteins’ (LDL) cholesterol as the mainstay of treatment of atherosclerotic cardiovascular disease (ASCVD). Statins and nonstatins were titrated to a LDLc goal of 60–80 mg/dl. The ideal principle ‘Treat to target’ was recommended and optimal LDLc level was considered 50–70 mg/dl (<70 mg/dl). Cholesterol Treatment Trialist Collaboration showed that benefit of statin therapy was tied to absolute ASCVD risk reduction and absolute lowering of LDLc levels. Statins are the most effective and validated therapy to lower LDLc by inhibiting cholesterol synthesis by inhibiting HMG-CoA reductase.

**2. Objective**

Recent literature was searched on ‘novel lipid lowering agents’ which could be used either as alternative monotherapy or in addition to statins in statin intolerant, high risk ASCVD, nonfamilial/familial hypercholesteremia cases and those who have failed to achieve ideal LDLc goals.

**3. Methods**

Beside recent journals, we searched Med Pub, Life Sciences Connect, Mediscape, Cardiosource, AHA/ESC Congress 2014 on treatment of severe hypercholesterolemia and on PCSK 9 inhibitors.
4. Results

Cholesterol treatment guidelines (CTG) to reduce atherosclerotic cardiovascular risk in adults have been recently revised by American College of Cardiology and American Heart Association (2013) in collaboration with National Heart Lung and Blood Institute (NHLBI). Four statins benefit group have been recognized. (i) Individual with clinical atherosclerotic cardiovascular disease (ASCVD) (ii) Individual with primary LDLc ≥ 190 mg/dl (iii) Individuals with Diabetes, age 40–75 yrs with LDLc 70–189 mg/dl but without ASCVD and (iv) Individual age 40–75yrs without diabetes and without ASCVD with LDLc 70–189 mg/dl and having an estimated CVD risk ≥ 7.5%. Calculation of CVD risk is based on ACC/AHA risk assessment equations. This group, however, requires clinician patient discussion.

UK, Europe and Canada have issued their own cholesterol treatment guidelines (CTG). ACC/AHA guidelines (2013) however, do not specify the lipid targets, CTG for individuals >75yrs are not clearly outlined. ASCVD risk is often over-estimated by equations advised by ACC/AHA. Discussing the implications of CTG 2013 (ACC/AHA), it was concluded that achieving concordance with the new guidelines would result in an uniform increase in the use of statins as well as significant reduction in non-statin therapies (like niacin, fibrates and bile acid sequestrants). In addition, risk factors like hypertension, diabetes, obesity, smoking etc must be carefully evaluated along with lifestyle management strategies.

Monitoring of lipid profile during statin therapy

2013 ACC/AHA guidelines on cholesterol management have not recommended specific LDL (c) and non-HDL (c) targets when the patients has been put on high intensive statin therapy (e.g. atorvastatin 80 mg/day or rosuvastatin 40 mg/day). This shift in the management has become a subject of major controversy. Many advanced countries follow their own guidelines. Even in our country, recent consensus on management of dyslipidemia in Indian subjects have raised observations regarding ACC/AHA guidelines and their relevance in Indian population. High intensity statin therapy is intended to reduced CV risk by >50% which is related to lowering of LDL(c) levels. This is consistent with the recent standards of medical care in diabetes. Hence it may be justified to monitor LDL (c) in order to judge CV Risk reduction. In addition, individual response and tolerability to high intensity statin therapy may vary considerably. South Asians including Indians respond differently compared to their Western counterparts. Although statins are pretty safe drugs but instance of muscle toxicity has been reported in 10–20% cases. Severe myositis with raised serum creatine phosphokinase (CPK) and even rhabdomyolysis with myoglobinuria and raised serum creatinine have been described. Under such circumstance of statin intolerance, alternative lipids lowering drugs are required.

PROVE IT TIMI-22 Trial has provided uncontroversial data to prove the beneficial effects of intensive lipid lowering in acute coronary syndrome and diabetes. However about 20% patients on maximally tolerated statins therapy continue to exhibit residual cardiovascular risk. The CV risk is reduced considerably but not to zero. Further, optimal LDLc target of <70 mg/dl may not be achieved. Another 15–20% patient develop statin intolerance in the form of mild to severe muscular pain, tenderness, cramps, stiffness, fatigue etc with or without raised creatine phosphokinase (CPK) levels. If symptoms improve on stoppage of statin and reappear on its resumption, statin intolerance is clinically considered. Many comorbidities predispose individuals to adverse effects of statins. A few of them include renal/hepatic insufficiency, raised transaminases, past history of hemorrhagic stroke and statin intolerance. Under these conditions alternative treatment may be required with or without statins.

AIM HIGH INVESTIGATORS (2011) administered Niacin in addition to statins to raise HDLC and lower LDLc to prevent adverse CV events. Additional benefits with niacin could not be established. Relationship between Niacin, lipoproteins and cardiovascular outcome has been studied in 3196 patients with established atherosclerotic cardiovascular disease. 1440 were given extended release niacin (ER NIACIN) 1500–2000 mg in addition to statins with or without ezetimibe. The patients were followed for three years with treatment. Niacin could not achieve additional clinical benefit over statin group despite a 15% higher High Density Lipoprotein (HDL) cholesterol level in group receiving Niacin.

IMPROVED REDUCTION OF OUTCOME VYTORIN EFFICACY INTERNATIONAL TRIAL (IMPROVE IT) studied the efficacy of ‘ezetimibe’ when added to simvastatin. A total of 18444 patients were randomized at 1158 centers in 39 countries; 9067 were given ezetimibe (10 mg) plus simvastatin (40 mg) while 9077 received simvastatin (40 mg) orally. Baseline clinical and biochemical data were almost identical in the two groups and their mean basal LDLc was 95 mg/dl. After one year of therapy, mean LDLc levels in the two groups were 53.7 mg/dl and 69.7 mg/dl respectively. However the primary end point of CV death, myocardial infarction (MI) or unstable angina (UA) or stroke was significantly lower in ezetimibe PLUS simvastatin group (20.4%) compared with simvastatin alone group (22.2%). IMPROVE IT trial concluded that addition of ezetimibe produced lower LDLc and better CV end results than simvastatin alone. Trial also confirmed the earlier notion about LDLc “the lower the better”.

5. Recently approved therapies for homozygous familial hypercholesterolemia (HOFH)

Microsomal triglyceride transfer protein (MTTP) inhibitor ‘LOMITAPIDE’ (Aegerion Pharmaceuticals, USA) and Apoprotein B (Apo B) antisense oligonucleotide (ASO) ‘Mipomersen’ (Kynamro Genzyme Corporation, USA) have been recently approved by FDA, for restricted use in HOFM through Risk Evaluation and Mitigation Strategy (REMS) since their safety has not been fully evaluated. Lomitapide but not Mipomersen has been approved by European Medicines Agency for HOFH only. Both drugs are prohibitively costly. Microsomal triglyceride transfer protein (MTTP) inhibitor ‘Lomitapide’ inhibits the production of Apo-B resulting in diminished secretion of chylomicrons, VLDL and LDL. The
efficacy and safety of Lomitapide has been studied in 29 HOFH patients.20 The drug was given in the increasing doses from 5 to 60 mg/day for 26 weeks and followed till 78 weeks for safety assessment. 23 patients completed 78 weeks of study with a median dose of 40 mg/day along with statin and nonstatin drugs. Mean LDLc diminished from baseline of 336 mg/dl to 166 mg/dl at 26 weeks but increased to 208 mg/dl at 78 weeks. The side effects were nausea, diarrhea and raised transaminases.

Antisense oligonucleotide (ASO) ‘mipomersen’ binds with RNA of Apo-B in the liver and reduces the synthesis of all lipoproteins including LDLc. Mipomersen was studied in 158 hypercholesterolemic patients with baseline LDLc >100 mg/dl, who were receiving maximally tolerated lipid lowering therapy.21 Patients received weekly subcutaneous mipomersen 200 mg (n = 105) or placebo (n = 52) for 26 weeks with a 24 weeks follow up; 60 on mipomersen and 44 on placebo completed 50 weeks. Mean baseline LDLc levels were 122.6 mg/dl in the mipomersen and placebo groups respectively. Mipomersen reduced LDLc by 36.9% compared with 4.5% in placebo group. Side effects with mipomersen were skin reaction at injection site (78%), flu like symptoms (34%) and raised transaminases (10%). Of 54 patients who discontinued, 45 were in the mipomersen group and 9 in placebo group. Hence, mipomersen appears toxic for routine use.

Both above drugs not recommended for nonfamilial hypercholesterolemia.

6. Future therapy – PCSK 9 inhibitors

Proprotein convertase subtilisin/Kexin 9 (PCSK-9) is an enzyme discovered in 2003. It is encoded by PCSK-9 gene. It is chiefly expressed in the liver and intestines. PCSK-9 is an inhibitor of LDL receptors (LDL R) which is a preferential pathway through which LDLc is normally cleared from the blood. LDLc gets bound to LDL (R) on the surface of liver cells and then internalized into the liver cells where LDL is further metabolized while LDL(R) returns back to the surface of liver cells for further interaction the LDLc. This process continues for several cycles. PCSK 9 binds with LDL(R) on the surface of liver cells and promotes degradation of LDL(R) in the liver cells by the lysozyme pathway and prevents its recycling back to the liver cell surface.

PCSK 9 inhibitors inhibit the binding of PCSK 9 with LDL(R) and prevent the degradation of LDL(R) which is thus available to mop more LDLc for metabolism. It was observed that a rare ‘gain of function’ by gene mutation of PCSK 9 leads to severe elevation of LDLc and premature ASCVD whereas rare ‘loss of function’ by gene mutation of PCSK 9 reduces LDLc and decreases the incidence of ASCVD.22 This research provided impetus and rational to develop PCSK 9 inhibitors to lower LDLc. Elevated serum levels of PCSK 9 have been reported during statin therapy and in familial hypercholesterolemia. Elevated plasma PCSK 9 levels is equally detrimental for patients with nonfamilial hypercholesterolemia and heterozygous familial hypercholesterolemia, irrespective of LD(R) defects.23 PCSK 9 inhibitors restore the activity of LDL(R) and reduce LDLc. Three monoclonal antibodies have emerged as prominent PCSK 9 inhibitors.24–26 These are alirocumab (Aventis/Regeneron), Evolocumab (Amgen) and bococizumab (Pfizer). The first two have undergone considerable clinical research and are in advanced stage for approval by FDA. These monoclonal antibodies are administered subcutaneously once in two weeks or monthly which reduces LDLc by over 50% in most patients. LDLc may get markedly reduced down to 25–40 mg/dl in few cases. A doubt of neurological adverse effects has been raised in such cases, especially of hemorrhagic stroke when LDLc <25–30 mg/dl.

Evolocumab is a fully human monoclonal antibody. Phase I and II trials27–29 showed that evolocumab is able to reduce LDLc from 40 to 80%, apolipoprotein B from 30 to 59% and lipoprotein A from 18 to 36%. The reduction of LDLc is on monotherapy as well as when given with statins and the reduction is dose dependent. There were few side effects limited to nasopharyngitis, local skin reaction at injection site and arthralgia. MANDEL-230 Phase III clinical trial was anti-PCSK-9 monotherapy for hypercholesterolemia in 614 patients who were randomly assigned to Evolocumab (n = 306), placebo (n = 155) and ezetimibe (n = 154). Evolocumab was given 140 mg once in two weeks (n = 153) or 420 mg once a month (n = 163). LDLc decreased from baseline on average by 56% in comparison with 17.8% with ezetimibe and <1% on placebo. Serious side effects encountered with evolocumab were acute pancreatitis (one patient) and raised transaminases (one patient).

GAUSS2 randomized placebo controlled trial31 studied the role of Evolocumab in 307 statin intolerant patients with severe muscle related side effects. Evolocumab was given 140 mg once in two weeks or 420 mg once a month to 205 patients while ezetimibe was given to 102 patients (control). Baseline LDLc was 193 ± 59 mg/dl. Evolocumab achieved significant 56.1% reduction of LDLc in comparison to 36.9% with ezetimibe. 282 subjects were studied32 in LAPLACE-TIMI 57 (LDLc Assessment with PCSK-9 monoclonal antibody (AMG145) Inhibition combined with statin therapy Thrombolysis in Myocardial Infarction) at high CV risk according to NCEP-ATP III criteria. Over 90% patients achieved NCEP-ATP III goal of LDLc <70 mg/dl, non HDLc <100 mg/dl and Apo B <80 mg/dl. The efficacy and safety of long term evolocumab in hypercholesterolemia patients has been recently analyzed in Open Label Study of Long Term Evaluation of Evolocumab against LDLc (OSLER) randomized trial.33 Further studies on Evolocumab are in progress under PROFICID (Programme to reduce LDLc and cardiovascular outcomes following Inhibition of PCSK 9 in different populations) at 22 centers.34 RUTHERFORD-2 deals with Heterozygous Familial Hypercholesterolemia (49 patients) and FOURIER (Further cardiovascular Outcome Research with PCSK-9 inhibitors) to analyze the long term safety and efficacy in about 27000 patients in many countries of the world. Telsa Study35 deals with 8 patients of HOFH treated with Evolocumab (AMG 145).

Alirocumab (REGN 727) is another monoclonal antibody discovered by the scientific team of Aventis/Regeneron, USA. It is a PCSK 9 inhibitor and protects LDL(R) from degradation in the liver. It has been used as monotherapy as well as in combination with statins and ezetimibe and has shown remarkable reduction in LDLc in nonfamilial and familial hypercholesterolemia.36–38 Table 1 summarizes the results of a few published trials on PCSK 9 inhibitors. Recent trials with
alirocumab include Odyssey FH1 and FH2, Odyssey Combo and Odyssey Long Term Trial. These are Phase 3 and Phase 4 trials.

7. Odyssey FH1 and FH2

Familial hypercholesterolemia is due to genetic mutation of gene resulting in either absence or defective LDL(R). There is excessive cumulative load of LDLc leading to premature ASCVD.

In homozygous familial hypercholesterolemia (HOFH), LDL(R) is either totally absent or grossly defective due to two identical mutations while in heterozygous familial hypercholesterolemia (HeFH), LDL(R) is defective but not totally absent due to single mutation. In HOFH, LDLc is usually markedly raised (>500 mg/dl), while in HeFH >190–400 mg/dl. The ASCVD outcome is seriously affected due to raised LDLc. Alirocumab inhibits PCSK 9 and preserves LDL(R) and reduces LDLc in HeFH. In HOFH, alirocumab may be helpful if LDL(R) is only defective but not absent. Odyssey FH1 and FH2 are being conducted simultaneously in N America, Europe and S Africa and includes 735 HeFH patients. Alirocumab is given in dose of 75 mg once in two week. 40% required upgradation of dose to alirocumab to 150 mg once in two weeks. LDLc reduction with alirocumab has been significant (49%) and sustained.

Odyssey Combo Trial includes 720 hypercholesterolemia patients with high CV risk and inadequately controlled by maximally tolerated statins plus ezetimibe. 479 of them were given alirocumab (either 75 or 150 mg once in two weeks), while the remaining 241 continued on statin plus ezetimibe. Results are awaited.

Odyssey Long Term Trial has included 2341 patients, mean age 64yrs, 37% women, 35% diabetics and mean BMI 30 kg/m². 18% patients were HeFH. All patients had elevated LDLc and high CV risk. Mean basal LDLc on maximally tolerated statin was 122 mg/dl. Out of 2341 cases, 1553 received alirocumab 150 mg once in two weeks while 788 served as control. After 65 weeks, 81% patients on alirocumab achieved mean LDLc of <70 mg/dl. There was 54% reduction in major adverse CV events (MACE) defined as CV death, MI, stroke or UA requiring hospitalization. Discontinuation of therapy was 6.2% with alirocumab versus 5.5% in controls.39

Choice I and Choice II are ongoing trials to analyze frequency of doses of alirocumab either once in two weeks or once in a month.

Bococizumab is a PCSK 9 inhibitor sponsored by Pfizer. The drug is under research in Phase 2/3 under SPIRE 1 and SPIRE 2. Bococizumab (RN316) is reported to significantly reduce LDLc in statin treated patients with high cholesterol in Phase 2(b) study presented at ACC in March 2014. The drug was given subcutaneously in doses of 150 mg once in two weeks or 300 mg once a month. The mean decrease in LDLc from the baseline at 12 weeks was 53.4 mg/dl with 150 mg dose and 44.9 mg/dl with 300 mg dose of bococizumab. Phase III clinical trial of bococizumab is likely to involve many more patients and is divided into SPIRE (HF) with HeFH cases, SPIRE (HR) with very high CV Risk and SPIRE-LDL. The results are likely to be available in 2016–2018.
8. Conclusion

Today statins are the most validated and effective therapy in lowering LDLc in clinical practice with a view to reduce ASCVD and adverse CV events. However in about 20% patients, statins fail to achieve the desired LDLc target of <70 mg/dl; and a few patients are unable to tolerate statins. Further CV events do recur inspite of effective statin therapy. Under these circumstances, additional therapy with ezetimibe may be beneficial. PCSK 9 inhibitors have excellent lipid lowering properties and beneficial effect on CV outcome. Evolocumab and Alirocumab have entered Phase IV clinical trials on their long term safety. If found cost effective and safe on long term basis, PCSK 9 inhibitors may prove invaluable in treating hypercholesterolemia of varying aetiologies. PCSK 9 inhibitors still await approval by FDA, European Medicines Agency and other medicine controlling authorities in various countries.

PCSK9 inhibitors are not intended for primary prevention in general public. The possible indications could be as follows:

1. Patients suffering from homozygous familial hypercholesterolemia (HOF H) and heterozygous familial hypercholesterolemia (HeFH)
2. Non familial hypercholesterolemia patients who are severely statin intolerant (secondary prevention).
3. As a research tool.

PCSK 9 inhibition is a new concept in the management of cholesterol. Till now, the emphasis was either reduced cholesterol intake or reduced cholesterol synthesis. PCSK 9 inhibitors inhibit the binding of PCSK 9 enzyme with LDL receptors and prevent degradation of LDL receptor. Thus LDL receptor is available to bind with LDL(c) and its disposal by hepatocytes.

Administration of PCSK 9 inhibitors by subcutaneous route may cause skin discomfort and local reaction. Trials undertaken so far have not reported any major side effects during the study periods varying 6-18months. Further ongoing research on the development and refinement of PCSK 9 inhibitors may culminate in the synthesis of safer and more acceptable analogs. Since the drugs are yet not marketed, their cost is not known. Long term safety and cost effectiveness are important factors to decide the future of this innovative treatment. The research for new acceptable analogs must continue if we desire purposeful results.

Conflicts of interest

The author has none to declare.

References


