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Novel lipid-lowering strategies for prevention of Atherosclerotic events among Hypercholesteremic patients

Dr. Ayman Joarder [1], Dr. Kaisar Nasrullah Khan [2], Dr. Tanveer Ahmad [3], Dr. Mahmood Hasan Khan [4]

Corresponding Author: Dr. Mahmood Hasan Khan,

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Abstract

Over the last decade, a substantial increase in the prevalence of Hypercholesterolaemia induced Atherosclerotic cardiovascular events have been reported globally. This suggests that prevention and treatment of Hypercholesterolaemia should be considered as an integral part of cardiovascular disease (CVD) prevention, particularly among high-risk patients. Lowering serum low-density lipoprotein cholesterol (LDL-C) is one of the key treatment strategies for the prevention of CVD. Until the last decade, Statins, Ezetimibe, Fibrates, Niacin, Bile acid sequestrants and Nicotinic acids were considered as the first-line lipid-lowering options. However, due to the increase in resistance, tolerance and non- adherence to these conventional lipid-lowering options, high-risk patients can no longer achieve and maintain the optimum LDL-C level. Thus, exposing themselves at constant risk of developing cardiovascular diseases. This resulted in a need for newer and more effective lipid-lowering strategies to achieve better treatment outcome and reduce the overall risk of developing cardiovascular events. Several newer lipid-lowering strategies have emerged as a solution for better lipid management. Such newer strategies include the inhibition of proprotein convertase subtilisin/kexin type 9(PCSK9); inhibition of Apolipoprotein (apo-B), ApoC-III synthesis and inhibition of microsomal triglyceride transfer protein (MTP). However, these newer strategies have their own distinct shortcomings. The aim of this literature review is to focus on the evaluation and analysis of the therapeutic efficacy and safety profile of these newer strategies in the treatment of Hypercholesterolaemia among high-risk patients who were previously treated with conventional lipid-lowering agents based on the evidence available in current literature.

Keywords: *Proprotein convertase subtilisin/kexin type 9, Microsomal triglyceride transfer protein, Alirocumab, Lomitapide, Mipomersen, Evolocumab*

Introduction

Atherosclerotic cardiovascular events account for nearly 17 million deaths in the world every year[1], and it is believed that it will turn out to be one of the main cause of death and disability worldwide by the year 2021[1, 2]. Based on research, it is believed that the rapid increase in the prevalence of Hypercholesterolemia is one of the main alarming risk factors for developing Atherosclerotic cardiovascular events [3]and lately it has become a global health concern[4]. Lipids are macronutrients mandatory for the proper functioning of the body[5], and it is transported through the blood via lipoproteins[6]. Among the various types of lipoproteins, low-density lipoproteins (LDL) are often referred to as "bad cholesterol" [7]as it is responsible for causing atherosclerotic cardiovascular events when they are present in excessive amounts[7]. Hypercholesterolemia is characterised by highly elevated LDL-C levels which increases the risk of premature Atherosclerotic cardiovascular events among high-risk patients[8]. Traditional lipid-lowering therapies used in the treatment of Hypercholesterolemia have significant limitations which cannot be overlooked due to the increased incidence of Hypercholesterolemia despite the increased consumption of lipid- lowering agents worldwide[1]. Therefore, there is a substantial need for newer lipid- lowering therapies for the treatment of Hypercholesterolemia among individuals who remain at a high risk of developing Atherosclerotic cardiovascular events despite being on regular treatment with traditional lipid lowing strategies. The aim of this literature review is to focus on the evaluation and analysis of the therapeutic efficacy and safety profile of newer lipid- lowering strategies in the treatment of Hypercholesterolaemia among patients who were previously treated with conventional lipid-modifying agents based on the evidence available in current literature.

Traditional LDL-Lowering Drugs

Traditional LDL-Lowering drugs include Statins, Ezetimibe and Bile Acid Sequestrants [9-12]. Each one has its own distinct major limitations which affect their therapeutic efficacy and markedly decline their safety profile, particularly in long-term usage. Thus, creating room for further research into the development of newer generation lipid-lowing drugs. Among the conventional ones, Statins are the most widely prescribed one, which reduces elevated LDL-C in Hypercholesterolaemia patients [13]. However, many patients are intolerant to statins and become nonadherent to the therapy because of side effects like the statin-associated musculoskeletal system disorders like myopathy [14]. Any condition that increases serum statin levels also increases the risks of statin intolerance which is multifactorial, and dose related [15]. This suggests that although statins have been the most frequently

prescribed lipid- lowering agent, it is gradually losing its therapeutic potentials as more and more high-risk patients are either becoming resistant or intolerant to statins in the course of treatment. This indicates that statin- intolerant or statin-resistant high-risk patients are in need of safer and effective therapeutic alternatives for better lipid management.

Fibrates, on the other hand, is another major LDL-lowering agent and is also known to be associated with severe side effects related to the musculoskeletal system such as fibrate induced skeletal muscle toxicity [16] and loss of vascular smooth muscle contractility [16]. It is also known to cause hepatotoxicity as it gets metabolised through the Liver [17]. These sides effects following treatment with fibrates can no longer be overlooked because of the recent increase in the incidence of Hypercholesterolemia and increased consumption of Fibrates worldwide, similar to statins. Ezetimibe is another traditional lipid lowering strategy which is comparatively a safer alternative medication for high-risk patients, intolerant or resistant to other traditional lipid-lowering agents like Statins and Fibrates[18].

However, similar to Statins and Fibrates, Ezetimibe also causes adverse effects related to the musculoskeletal system like muscle tenderness, wasting or weakness [18]. As for Bile Acid Sequestrants which is also a traditional lipid-lowering strategy is comparatively a less common choice among physicians for lipid management as its long term intake is associated with chronic complication like, gall-stone formation which requires surgical intervention to be cured [19]. Thus, considering the therapeutic efficacy and safety-related shortcomings of these traditional LDL-lowering strategies and its adverse impact on health, there is a strong need for newer LDL-lowering agents, and this literature review focuses on a few on such newer strategies.

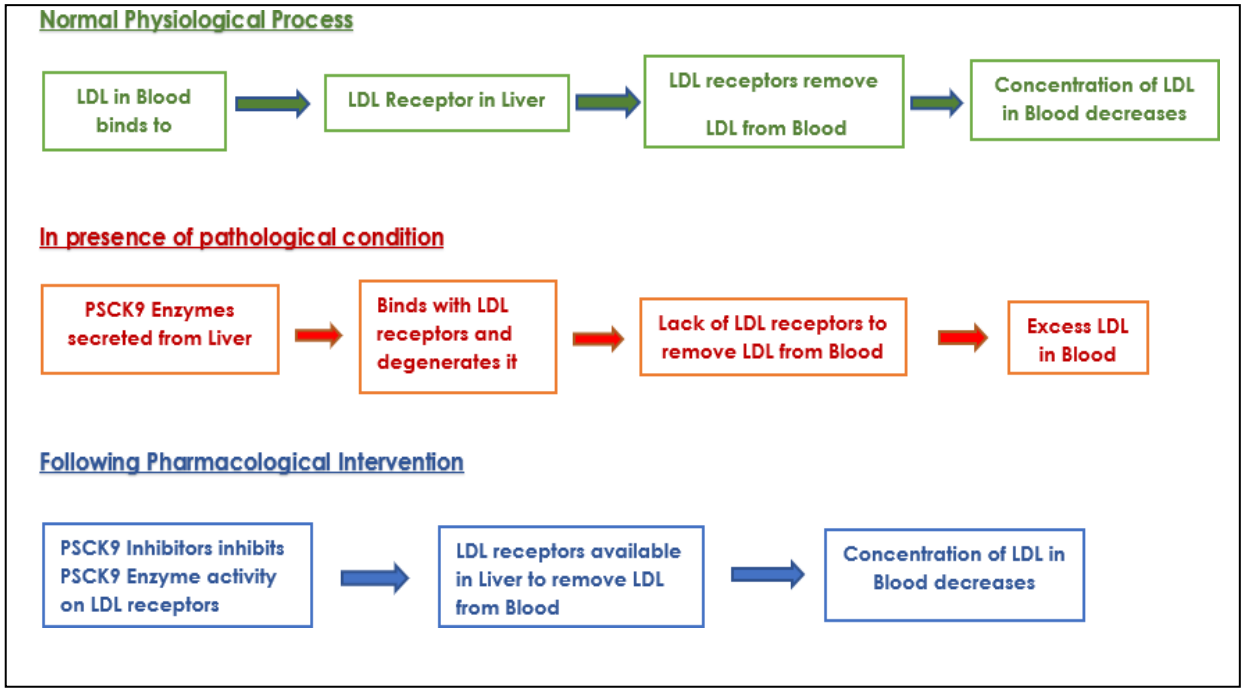
Newer LDL-lowering strategies: PCSK9 Inhibition for management of Hypercholesterolemia

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a protein-based enzyme encrypted by the PCSK9 gene in human chromosome [20]. The evidence available in relevant literature [20] regarding the mechanism of PCSK9 enzyme states that this enzyme is produced in the Liver and binds to low-density lipoprotein receptors (LDLR) present on the surface of hepatocytes and promote degradation of these LDLR within the Liver [20, 21]. Since LDL-R is the main receptor that eliminates circulating LDL-C from blood, degradation of the LDLR by the enzyme PCSK9, results in higher levels of circulating LDL-C in blood [22]. High level of circulating LDL-C in the blood increases the risks of atherosclerotic cardiovascular events [23]. Therefore, inhibition of the activity of the PCSK9 enzyme, as shown in Figure 1, could be a new therapeutic strategy for the management of

Hypercholesterolaemia among high-risk patients. Based on theory of PCSK9 enzyme inhibition for lipid management, a newer group of LDL- lowering drugs known as PCSK9 inhibitors were developed over the recent years. Alirocumab and Evolocumab are the drugs of this new group which have received FDA approval [23]. Alirocumab and Evolocumab are produced by recombinant DNA technology and lowers LDL-C by Inhibition of the PCSK9 enzymes and halts the degradation of the LDL receptors (LDL-R) within the Liver [24, 25]. Thereby increasing the number of LDL receptors available to eliminate the circulating LDL-C from blood and reduce the risks of stroke and other Atherosclerotic cardiovascular events like Myocardial infarction.

Comparison of therapeutic efficacy and safety profile of PCSK9 Inhibitors against traditional LDL-Lowering strategies

Unlike Statins which only lowers LDL-C, PCSK9 Inhibitors also improves the lipid profile by other means [23, 26]. This is because due to the inhibition of degradation of LDL receptors by PCSK9 inhibitor, LDL receptors are now available insufficient amount in the Liver to bind with other residues of Low-Density Lipoproteins which are rich in triglycerides (VLDL) and intermediate-density lipoproteins (IDL) and eliminates them from blood circulation [26]. Therefore, treatment with PSCK9 inhibitors not only lowers LDL-C but also reduces VLDL, ILD and triglycerides. This indicates a better therapeutic efficacy of PSCK9 inhibitors compared to traditional Statins. In lights of such improved therapeutic efficacy of PSCK9 inhibitors compared to Statins, it can be a potential lipid management option for Hypercholesterolemia [22] among patients who are unable to reach the



optimum LDL- C targets even with the maximum tolerated dose of statins[23]. It can also be a potential alternative lipid management strategy for statin-intolerant, statin resistant, and Statin contraindicated high-risk patients of Hypercholesterolemia [23].

Alirocumab has nearly 90% bioavailability and a long half-life of around 17–20 days which is 50% higher compared to Statins and other traditional lipid- lowering agents. [22, 27]. This suggests that nearly twice the amount of PSCK9 inhibitors is absorbed in the intestines and are eventually available for producing its therapeutic effects in the liver cells, blood circulation and tissues in the body. This once again translates to a better therapeutic efficacy over the conventional strategies. The recommended dose of PSCK9 inhibitors is 75 mg which is to be administered subcutaneously once every two weeks [27] unlike Statins and other traditional lipid-lowering agents which must be taken once daily. Such convenient and infrequent dosing are more likely to result in better treatment compliance among patients and help to avoid drug tolerance and resistance resulting from missed dosages. Although the subcutaneous route of administration of PSCK9 inhibitors [28] over the oral route for traditional lipid- lowering agents might be a potential negative factor against better treatment compliance among a certain category of patients who prefer oral medication over a needle prick. Besides the recommended dose, an initial dose of 150 mg, can be safely given once every two weeks to patients requiring a major 60% reduction in LDL-C [27, 28]. This suggests that the dose of PSCK9 inhibitors can be tailored according to the patient's needs and their baseline LDL-C levels, without resulting in any drug- related adverse reactions. This also indicates a significantly improved safety profile over the traditional lipid-lowering strategies even at a double concentration of the recommended dosage.

According to evidence in the relevant literature [29], statins, and other traditional lipid-lowering agent like Ezetimibe may inhibit the production of PCSK9 enzyme in the human body as well[29]. This suggests that if PSCK9 inhibitors are used in combination with other traditional Lipid- lowering agents, then there is a higher likelihood to achieve an improved therapeutic effect due to the synergism of the combination therapy. This synergistic effect is more likely to produce a more targeted effect on PCSK9 enzyme inhibition rather than an overall systemic effect observed in treatment with traditional lipid-lowering agents[29]. With the replacement of the overall systemic exposure with a more targeted lipid-lowering approach, the likelihood of PSCK9 inhibitor-associated systematic adverse effects like the development of Type 2 Diabetes Mellitus is also likely to be minimised [30]. Thus, this indicates that PSCK9 inhibitors offers a significantly better safety profile when used in combination with traditional agents rather than as a monotherapy. Further evaluation of the safety profile of PSCK9 inhibitors is shown in Figure 2. Recently, conducted studies[30, 31] evaluating the pharmacokinetic interactions

between Statins and PSCK9 inhibitors[30, 31] reported 20% increase in the clearance of PSCK9 enzymes after addition of PSCK9 inhibitors among patients who were on a statin - based lipid management. This once again proves a better therapeutic response due to the effect of synergism.

Evidence of safety profile and therapeutic efficacy of PSCK9 inhibitors from clinical trials

Based on findings of recent clinical trials[25, 32, 33] as shown in Table 1, both Alirocumab and Evolocumab in doses ranging between 140 - 420mg produced a significant 30-75% reduction in LDL-C levels among patients with baseline LDL-C >100 mg/dL as shown in Table 1. According to the report of the study conducted by Raal et al.,2015[25] Evolocumab, showed a similar rate of reduction in LDL-C level irrespective of whether the patients were suffering from Familial or non-familial Hypercholesterolaemia and whether the patients were on statin therapy or on diet modification alone[25]. RCT by Kiyosue et al.,2016 [32] was conducted with patients of Primary Hypercholesterolemia with statin-intolerance. Evolocumab in combination with Atorvastatin used as an intervention strategy, reduced LDL-C by 75% more compared to the control group which received Atorvastatin only. This is significant evidence of the improved therapeutic response produced by the synergistic effect of the combination therapy. According to the report of the study conducted by Cannon et al.,2015 [33] Alirocumab in combination with Atorvastatin also induced a greater LDL-C reduction of over 29.8 % than the group of patients that received a combination of two traditional lipid-lowering agents like Ezetimibe and Atorvastatin. This once again suggests that PSCK9 inhibitors, when used in combination with any traditional lipid lowering strategy, results in a significantly higher reduction in LDL-C compared to the combination of any two traditional lipid-lowering strategies.

Thus, based on the reports of the clinical trials[25, 32, 33], it can be stated that PSCK9 inhibitor is a new category of lipid-lowering drugs that is expected to be a potential treatment option in reducing the incidence of stroke and other Atherosclerotic cardiovascular events like Myocardial infarction among patients suffering from Hypercholesterolaemia. Nevertheless, there are gaps in existing evidence regarding the therapeutic potentials of PSCK9 Inhibitors as a monotherapy in the treatment of Hypercholesterolaemia which needs to be addressed in the future clinical trials.

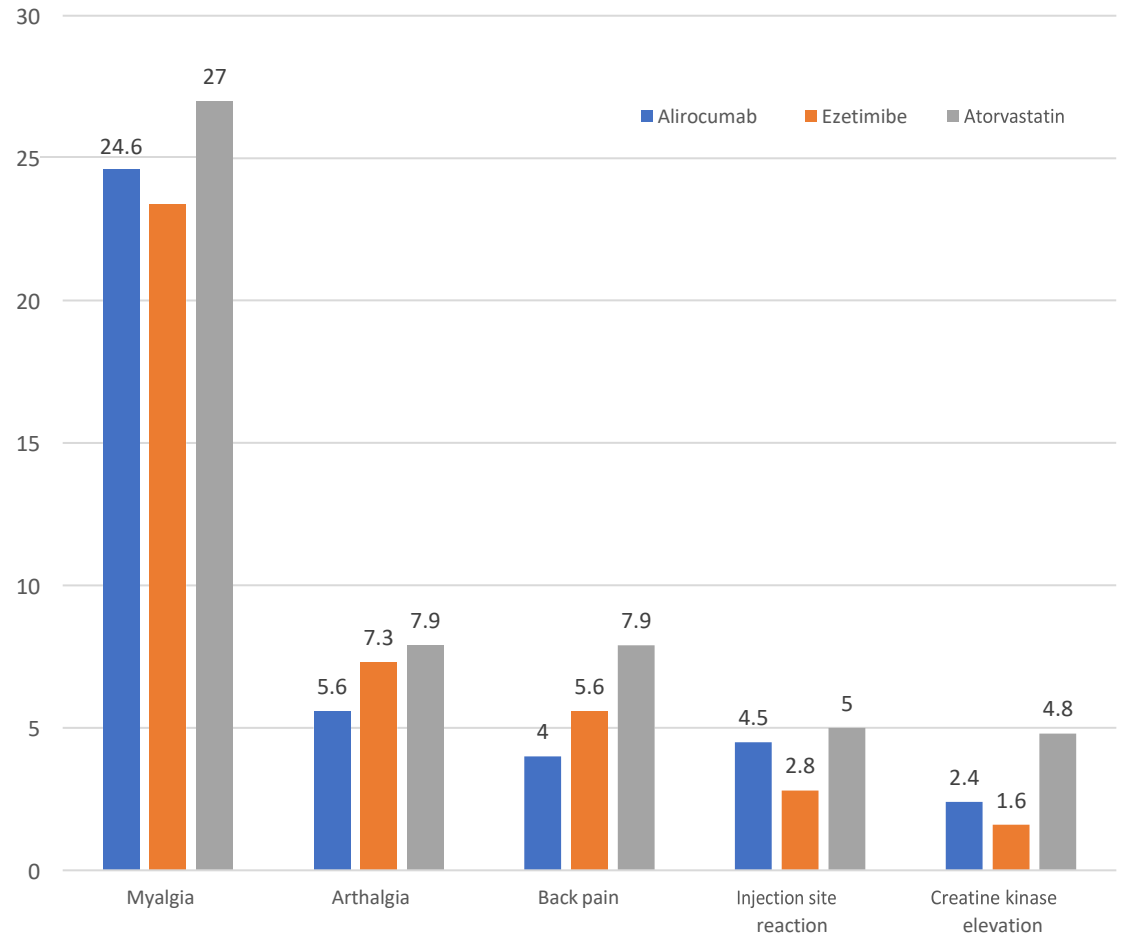


Fig 2. Comparing the percentage of patients who experienced each type of adverse effects following treatment of Hypercholesterlaemia with Alirocumabagainst treatment with traditional lipid lowering agents .Adapted from [30].

Table 1 Details of the studies that compared the therapeutic efficacy of PSCK9 inhibitors in reducing LDL-C when used in combination with traditional lipid lowering agents for treatment of Hypercholesterolemia

Studies	Study design	No of patients in Intervention Group	No of patients in Control Group:	Intervention Group Treatment	Control Group Treatment	Disease of the Patients	Treatment duration	Outcome: Therapeutic Efficacy	Conclusion
								Percentage of LDL-C reduction	
Raal et al., 2015 [25]	Randomized double blind controlled study	218	107	Evolocumab 140 mg/ 420 mg	Placebo	Hypercholesterolemia	12 weeks	60% at 140 mg 56% at 420 mg	60% reduction at 140mg and 56% reduction at 420 mg of Evolocumab was observed which was significantly higher compared to the group receiving placebo were no reduction of LDL-C was reported
Kiyosue et al., 2016 [32]	Randomized double blind controlled study	100	99	Atorvastatin 20 mg + Evolocumab 140 mg	Atorvastatin 20 mg + placebo	Hypercholesterolemia	12 weeks	75% at 140 mg 70% at 420 mg	70% reduction at 140mg and 75% reduction at 420 mg of Evolocumab in combination with Atorvastatin 20 mg was observed which was significantly higher compared to the group receiving Atorvastatin 20 mg only were minor reduction was observed.
Cannon et al., 2015 [33]	Randomized control trial	360	360	Alirocumab 75 mg + Atorvastatin 20 mg	Ezetimibe 10 mg + Atorvastatin 20 mg	Hypercholesterolemia. LDL-C ≥70 -100 mg/dL	24 weeks	29.8%	29.8% higher reduction of LDL-C in the intervention group compared to the control group was observed.

LDL-C: Low density lipoprotein cholesterol

Table 2 Details of the studies that compared the efficacy of MTP inhibitor- Lomitapide in reducing LDL-C and Apo B-100 when used in combination with traditional lipid lowering agents for treatment of Hypercholesterolemia

Studies	Study design	No of patients in Intervention Group	Intervention Group Treatment	Disease of the Patient	Ongoing Medication	Treatment duration	Outcome Therapeutic Efficacy		Conclusion
							Percentage of LDL-C reduction	Percentage of Apo B-100 reduction	
Samaha et al., 2008 [47]	RCT	28	Lomitapide 10 mg	Hypercholesterolemia	Conventional lipid lowering drugs	12 weeks	30% at 10 mg	24%	30 % reduction of LDL-C and 24 % reduction of Apo B-100 following 10mg Lomitapide addition was observed in Hypercholesteraemic patients on traditional lipid lowering medication
Yahya et al., 2016 [48]	Retrospective Observational study	4	Lomitapide 5 to 30 mg	Hypercholesterolemia	Conventional lipid lowering drugs	9-36 weeks	34 - 89 % at 5 to 30 mg	42 - 89 % at 5 to 30 mg	34 - 89 % reduction of LDL-C and 42 to 89 % reduction of Apo B-100 following intervention with 5 to 30 mg of Lomitapide was observed among Hypercholesteraemic patients on traditional lipid lowering medication
Cuchel et al., 2013 [46]	Retrospective Observational study	29	Lomitapide 40 mg	Hypercholesterolemia	Conventional lipid lowering drugs	26-78 weeks	50% at 40 mg	49 % at 40 mg	50 % reduction of LDL-C and 49 % reduction of Apo B-100 levels following intervention with 40mg of Lomitapide was observed among Hypercholesteraemic patients on traditional lipid lowering medication.

RCT: Randomised control Trials, LDL-C: Low density lipoprotein cholesterol, ApoB -100 : Apo B-100 apolipoprotein, Conventional lipid lowering drugs : Statins/ Ezetimibe

Table 3 Details of the studies that compared the efficacy of MTP inhibitor- Mipomersen in reducing LDL-C level when used in combination with traditional lipid lowering agents for treatment of Hypercholesterolemia

Studies	Study design	No of patients in Intervention Group	No of patients in Control Group:	Intervention Group Treatment	Control Group Treatment	Disease of the patient and their baseline LDL-C level	Ongoing Medication	Treatment duration	Outcome Therapeutic Efficacy Percentage of LDL C reduction	Conclusion
Raal et al. 2010 [64]	Randomized double-blind Placebo-controlled trial	34	17	Mipomersen 200 mg once weekly	Placebo	Hypercholesterolaemia Baseline LDL-C ≥131.5 mg/dL	Maximum tolerated dose of Statin	26 weeks	24·7% at 200 mg	24.7 % reduction in LDL-C level following addition of Mipomersen 200 mg in Hypercholesteraemic patients on high-dose statins.
Stein et al. 2012 [65]	Randomized double-blind, placebo-controlled, phase III clinical study	83	41	Mipomersen 200 mg once weekly	Placebo	Hypercholesterolaemia Baseline LDL-C >190 mg/dL	Maximum tolerated dose of Statin	26 weeks	28.0% at 200 mg	28 % reduction in LDL-C level following addition of Mipomersen 200 mg in Hypercholesteraemic patients on high-dose statins.
Thomas et al. 2013 [62]	Randomized double-blind, placebo-controlled, parallel group clinical study	105	52	Mipomersen 200 mg once weekly	Placebo	Hypercholesterolemia Baseline LDL-C ≥100 mg/dL	Maximum tolerated dose of Statin	26 weeks	36.9% at 200 mg	39 % reduction in LDL-C level following addition of Mipomersen 200 mg in Hypercholesteraemic patients on high-dose statins

LDL-C: Low density lipoprotein cholesterol, CVD: cardiovascular diseases

Microsomal transport protein (MTP) Inhibitor – Lomitapide for management of Hypercholesteremia

Lomitapide

Apolipoprotein B-100 (apo B-100) is the main apolipoprotein necessary for the assembly and secretion of LDL and VLDL[34], and it carries LDL and VLDL around the body to all cells and tissues[34, 35]. Microsomal Triglyceride Transfer Protein (MTP) is an important intracellular protein found in the liver and intestine cells which are necessary for the production of the Apolipoprotein B -100 (apoB)[34]. Lomitapide is a drug that belongs to a new generation of lipid-lowering agents which selectively inhibits these microsomal transport protein (MTP)[36]. Therefore, by inhibiting MTP, Lomitapide blocks the production of apo B[36] as shown in Figure

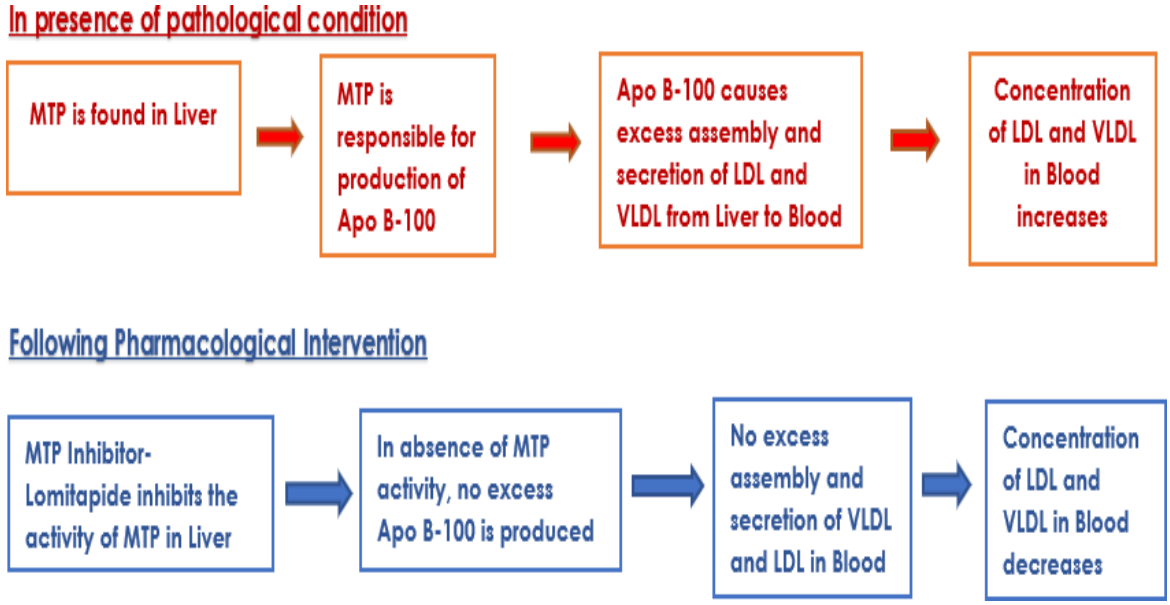


Fig 3. Mechanism of action of MTP Inhibitor- Lomitapide. Adapted from [34-37]

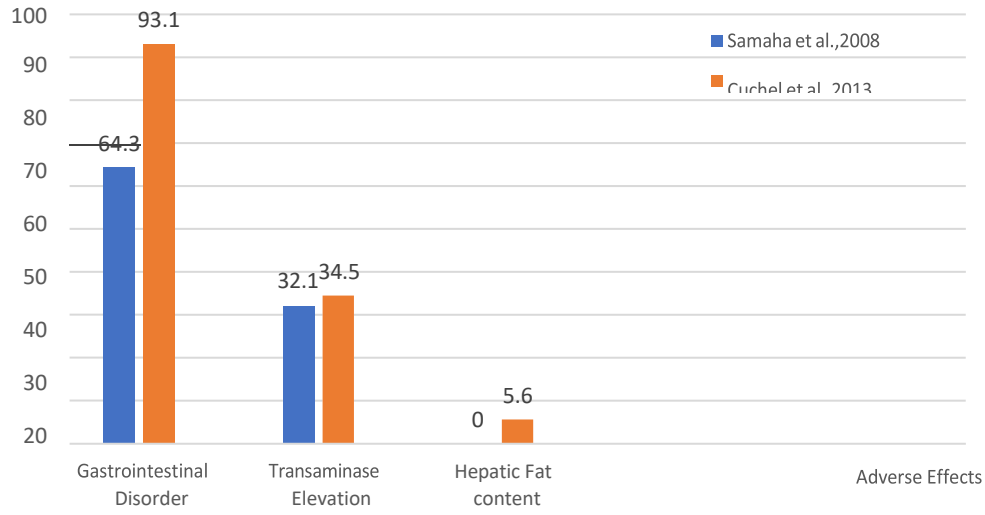


Fig 4. Comparing the percentage of patients who experienced each type of adverse effect following treatment of Hypercholesterolaemia with Lomtaptide.Adapted from [46-47].

3. In the absence of apo B, the assembly and secretion of LDL and VLDL in blood circulation are halted[37]. Thereby reducing LDL and VLDL concentration in blood. Lomitapide is administered as an oral medication and can be used as a monotherapy [36]or even in combination therapy as an adjunct to other traditional lipid-lowering therapies like Statin for treatment of Hypercholesterolaemia[37, 38] among patients who, despite being on traditional lipid-lowering therapies like Statins, do not reach the optimum target level of LDL and remains at constant risk of developing cardiovascular disease[37, 39].

Pharmacokinetic and pharmacodynamic properties of Lomitapide affecting its therapeutic efficacy and safety profile

Lomitapide has several limitations surrounding its pharmacokinetic and pharmacodynamic properties[40]. It has a very low oral bioavailability of only 7% due to an extensive first-pass effect[40, 41]. An extensive first-pass effect suggests that a high concentration of Lomitapide gets metabolised before reaching the systemic circulation and exerting its therapeutic effects. According to the basic rules of pharmacology[42], this extensive first-pass effect is supposed to reduce its efficacy.

According to the guideline[41], Lomitapide has to be taken in an empty stomach, specifically two hours after the meal[41, 43]. This suggests that the presence of food adversely affects the gastrointestinal tolerability of Lomitapide. This strict and specific time limitation regarding its administration often affects its potency and efficacy, as research[43] has shown that patients often tend to be ignorant about maintaining such timely intake of medications. As per guideline, the starting dose of Lomitapide is 5 mg/day[40], which must be increased gradually up to the maximum dose of 60 mg after several weeks in the course of treatment to achieve the optimum therapeutic effect[40, 44]. However, this regulation of dosage via consultation with a physician often becomes a potential reason for patient non-compliance. According to research[45], a vast majority of patients often finds it cumbersome to check their lipid profile weekly and consult their physician for dose regulation throughout the course of treatment with Lomitaptide. This results in treatment failure and the development of tolerance. However, there is a noticeable gap in research concerning the drug interaction of Lomitapide. Little is mentioned about its interactions with Warfarin[41, 46] in relevant literature which states that Lomitapide increases the plasma concentration of Warfarin[40, 41]. This suggests that if a patient who is currently on Warfarin therapy has the risk of suffering from adverse effects like over coagulation if prescribed with Lomitapide. To avoid this, patients taking Warfarin along with Lomitapide should always have their INR monitored regularly [43].

Evidence of therapeutic efficacy and safety profile of Lomitapide from Clinical trials

The therapeutic efficacy of Lomitapide was evaluated in this review based on findings from a randomised controlled trial and two retrospective observational studies [46-48] comprising a total of 61 patients suffering from hypercholesterolemia as shown in Table 2. These patients were on ongoing treatment with traditional lipid-lowering agents like statins or ezetimibe. Following the addition of Lomitapide in combination with either statins or ezetimibe, a marked dose- dependent

increase in reduction of LDL and Apo B-100 levels were observed as shown in Table 2. At 10 mg [47], 30 mg[48] and 40 mg[46] of Lomitapide, a reduction of 30%[47], 34%[48] and 50%[46] LDL-C and

24%[47], 42%[48] and 49%[49] reduction of Apo B-100 level respectively were reported. This suggests that with an increase in dose, the therapeutic efficacy of Lomitapide increases. A similar trend was observed between the duration of treatment and therapeutic efficacy of Lomitapide as the reduction in the percentage of LDL and Apo B-100 increased with increase in the duration of treatment as shown in Table 2. These studies[46-48] also reported minor improvement in HDL-C levels following Lomitapide intervention. The overall findings of the studies [47-49] reviewed suggest that Lomitaptide when used in combination with other traditional lipid- lowering drugs like Statins or Ezetimide, reduces LDL and Apo B-100 significantly.

Unlike most traditional lipid-lowering strategies, Lomitapide has a comparatively better safety profile, as shown in Figure 4. Based on findings of the studies [46, 47] the most commonly reported adverse-effects of Lomitapide are minor gastrointestinal disorder observed among 93.1%[46] and 64.3% [47] patients as shown in Figure 4. However, there are fewer reports of serious ones like abnormal increase in liver transaminases leading to transaminitis among 34.5%[46]and 32.1% [47] patients following the addition of Lomitapide. Increased hepatic triglyceride levels leading to hepatic steatosis was the least common adverse effects experienced by only 5.6% of patients [46]from long term usage, as shown in Figure 4. Therefore, based on the findings of the studies reviewed, it can be suggested that unlike other traditional lipid-lowering agents, Lomitapide is the least hepatotoxic and contributes least to the development of hepatic steatosis. However, there is an ongoing debate regarding the balance between benefits and risks of adding Lomitapide as an additional lipid-lowering medication with ongoing traditional agents due to the ever-increasing concerns of hepatic complications among clinicians and patients [44].

As a concluding thought regarding Lomitapide based on evidence from studies reviewed, it can be suggested that Lomitapide, in combination with other lipid- lowering agents, have a significant role in the management of Hypercholesterolaemia. Its therapeutic potentials far outweighed the risks of Lomitaptide induced adverse events. Although its effect on different clinical subtypes of Hypercholesterolaemia was not analysed in this review. Furthermore, there are potential gaps in research regarding the serious adverse effects of Lomitaptide like hepatic steatosis, transaminitis and elevation of hepatic enzymes and its effect on mortality and morbidity of patients.

Microsomal transport protein (MTP) Inhibitor –Mipomersen for management of Hypercholesterolaemia

Mipomersen

Similar to Lomitaptide, Mipomersen is also a Microsomal transport protein (MTP) Inhibitor [50, 51]but it exerts its therapeutic actions in the management of Hypercholesterolaemia via a slightly different mechanism[52]as shown in Figure

5. As discussed earlier, Apolipoprotein B-100 (apo B-100), is the main protein constituent of VLDL and LDL, and it is necessary for the assembly and secretion of LDL and VLDL[52]. Apo B-100 carries LDL and VLDL around the body to various cells and tissues[52]. Similar to Apo B-100, Apo-C III is another Apolipoprotein also secreted by the Liver and the small intestine[53, 54]. Like Apo B-100, Apo-C III also forms a major structural component of VLDL and LDL and promotes its hepatic assembly and secretion[52]. Apo C-III is also responsible for the Inhibition of the hepatic uptake of circulating LDL and VLDL in blood[53]. High plasma concentrations of Apo C-III in the body is associated with high plasma triglyceride concentrations[55].

Mipomersen is an MTP inhibitor which by nature is an antisense oligonucleotide. It acts on Liver and inhibits the production of both ApoB-100 and Apo-C III by inhibiting the process of translation of the mRNA responsible for the synthesis of ApoB-100 and Apo-C III[56, 57]. Thus, by Inhibition the synthesis of Apo B-100 and Apo C III, Mipomersen reduces the assembly and secretion of LDL and VLDL in blood circulation, as shown in Figure 5.

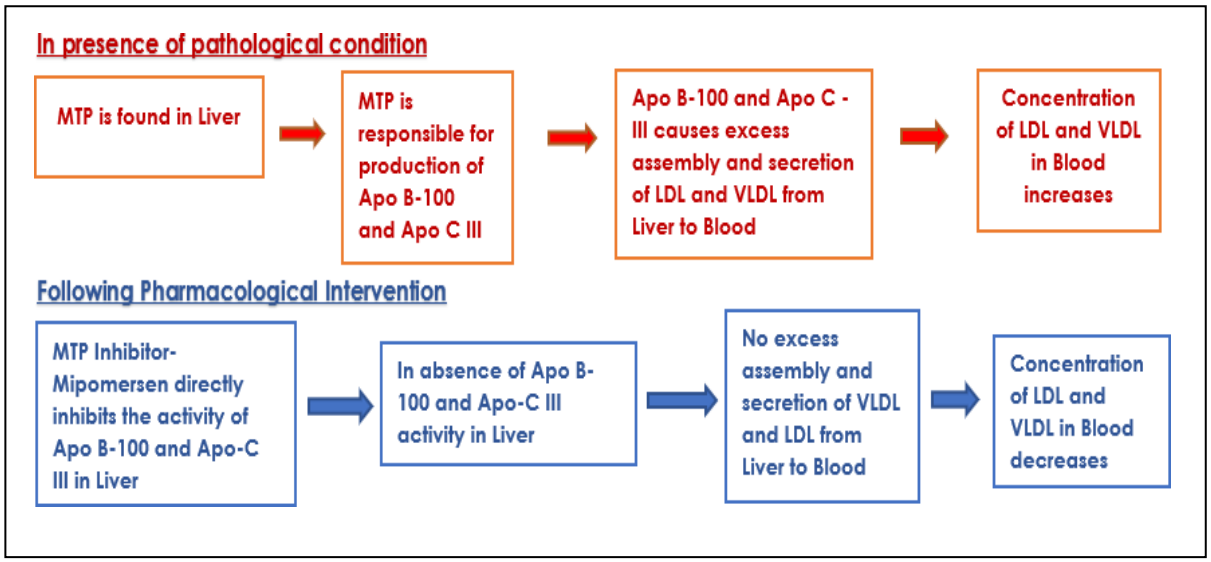


Fig 5. Mechanism of action of MTP Inhibitor -Mipomersen. Adapted from [52-55].

Based on evidence from current literature[58], Mipomersen, when it is used in combination with other traditional lipid- lowering agents like Statins has proven to be an efficacious lipid-lowering agent for reducing up to 20 % of LDL level from baseline in patients suffering from uncontrolled Hypercholesterolaemia [58,

59] with LDL levels above 500 mg/dL [60]. This category of Hypercholesteraemic patients suffers from the severe cardiac consequences resulting from such elevated levels of LDL in blood circulation despite being on regular lipid-lowering management with traditional drugs like Statins. This is because this category of patients has developed tolerance and resistance against Statins[61, 62]. Thus, even a reduction of 20 % in LDL levels following treatment with Mipomersen can prove to be a lifesaving therapeutic option for such high-risk patients.

Pharmacokinetic and pharmacodynamic properties of Mipomersen affecting its therapeutic efficacy and safety profile

Mipomersen reduces LDL in a dose- dependent manner[57]. The dose- dependent relationship suggests that the effects of the drug changes with alteration in dosage. This indicates that the dose of the drug varies between patients depending on the extent of abnormalities in their lipid status and needs to be tailored as per advice of the clinician to achieve the optimum therapeutic effect. Thus, the absence of a fixed recommended dose, unlike other traditional lipid-lowering agents, often makes the therapeutic outcome of the treatment using Mipomersen heavily dependent on the expertise of the doctor in regulating the dose appropriately. This suggests the possibilities of an inadequate therapeutic response of Mipomersen among patients in case of incorrect dose regulation.

Mipomersen by nature is a protein- bound drug and has an elimination half-life ranging between one to two months[57, 63]. This suggests that the drug remains in blood circulation for months after discontinuing the treatment. Such prolonged therapeutic effect of a lipid- lowering drug in the human body has both a positive and negative impact on patient's health. From a positive aspect, a longer elimination half-life ensures that the drug provides a long-term therapeutic coverage of lipid management. This shortens the overall duration and cost of treatment, enhancing patient compliance. This prolongs therapeutic effect also ensures long-term protection against sudden death due to cardiac cause. From the negative aspect, a long-lasting therapeutic effect indicates the possibilities of long-term Mipomersen induced side effects [55] even after discontinuing the treatment.

Based on the evidence available in the current literature[62, 64, 65], Mipomersen seems to be well-tolerated among the majority of patients. However, studies[62, 64, 65] reported several minor adverse

effects like injection site reaction in the form of an erythema, haematoma or inflamed nodules causing pain, swelling discolouration and itching at the site of injection[55]. Other minor side effects include fatigue, dizziness, diarrhoea, constipation, headache, low back pain, muscle stiffness, cough and flu-like symptoms [55] Major adverse effects include Urinary Tract infection, Fatty Liver, elevation of liver enzymes, serum creatinine and C-reactive protein [55]. However, the severity of these adverse effects was never intense enough to discontinue the treatment as the studies [62, 64, 65] did not report any significant drop out of participants as a result of any Mipomersen induced adverse effects. Moreover, the elevated liver enzymes, serum creatinine and C-reactive protein levels soon returned to normal baseline values following a period of treatment discontinuation [55]. Nevertheless, the effect of Mipomersen induced side effects on health from long- term usage is yet unknown.

Evidence of the therapeutic efficacy and safety profile of Mipomersen from clinical trials

The lipid-lowering effects of Mipomersen have been evaluated in this review based on findings from three randomised, double- blind placebo-controlled clinical trials[62, 64, 65] involving a total of 222 patients suffering from Hypercholesterolaemia with LDL-C levels above 100 mg/dL despite taking the maximum tolerated dose of statins as shown in Table 3 below. Mipomersen was added as add-on therapy with the ongoing lipid-lowering medication. Twenty-six weeks after the addition of Mipomersen as add-on therapy with the maximum tolerated dose of Statin, a reduction of 37%[62], 28%[65], and 24.7%[64] in levels of LDL was observed as shown in Table 3. More than half of the Mipomersen-treated patients were able to reach the optimum target level of LDL after completion of the treatment. Considering the effectiveness of Mipomersen as an add-on therapy, it was approved in the United States by the FDA for treatment of Hypercholesterolaemia[66] among high- risk statin-resistant patients with uncontrolled lipid status.

However, few major side-effects following intervention with Mipomersen have been reported among participants of the study conducted by Akdim et al., 2010 [55] as shown in Figure 6. Such adverse effects include the elevation of liver enzymes like the plasma alanine aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline phosphatase and total bilirubin level. Hepatic fat accumulation leading to hepatic steatosis was observed among 17% of patients, as shown in Figure 6. Thus, making it contraindicated for patients with existing hepatic dysfunction. These side- effects were also associated with treatment with Lompatide, as discussed earlier in the review. However, these side-effects were related to the drug's core mode of action[67] as shown in Figure 3.

Minor adverse effect like injection site reactions was the only adverse effect which was most predominantly experienced by patients on Mipomersen therapy[55].This indicates a satisfactory safety profile of the drug for large-scale usage among a wider population of Hypercholesteraemic patients. However, similar to Lomitapide, little is known about the long-term prognosis of Mipomersen-induced transaminase elevations and hepatic steatosis from the evidence available in current literature. Thus, there is a significant gap in knowledge regarding the liver-related adverse effects induced by Mipomersen which needs to be addressed through large clinical trials in future.

Conclusion

Based on the evaluation of evidence available in the current literature, it can be concluded that PSCK9 inhibitor is a novel category of lipid-lowering agents with a satisfactory safety profile that is expected to be a potential treatment option for maintaining an optimum lipid status and reducing the risks of cardiovascular events among high-risk patients of hypercholesterolaemia. Among the two MTP inhibitors - Lomitapide and Mipomersen evaluated and analysed in this review, Mipomersen can be used cautiously to treat Statin-resistant patients of Hypercholesterolaemia under regular monitoring of Hepatic enzyme status. Lomitapide, on the other hand, portrayed a satisfactory therapeutic efficacy when used in combination with traditional lipid lowering agents like Statins or Ezetimibe. Lomitapide had the potentials for reducing LDL levels among high-risk statin-intolerant Hypercholesteraemic patients with uncontrolled lipid status despite being on regular treatment with traditional lipid lowering agents. However, there is a significant gap in knowledge from the evidence available in current literature regarding the exact mechanism of the action responsible for the synergistic effects which occur when these novel lipid- lowering therapies - PSCK9 and MTP inhibitors are used in combination with traditional lipid-lowering agents like Statins Ezetimibe or Fenofibrate. The exact mechanism of synergism needs to be addressed in future research carried out in this area. In addition, to consider Lomitapide as a potential therapeutic agent for the treatment of Hypercholesterolaemia, a systematic review needs to be carried out in future based on recently published randomised control trials and observational studies for further evaluation and analysis of its therapeutic potentials in treatment of different subtypes of Hypercholesterolaemia such as Homozygous and Heterozygous Familial Hypercholesterolaemia. Specifically, in Homozygous Familial Hypercholesterolaemia (HoFH). Since still today, patients of HoFH worldwide are still constantly facing an enhanced risk of sudden cardiac death resulting from severely elevated and yet uncontrolled lipid profile parameters. Future systematic reviews should also focus on a detailed analysis of Lomitapide induced adverse effects in different age group, gender and ethnicity to settle the existing controversies surrounding the liver damaging adverse

effects associated with treatment using Lomitapide. Perhaps future research will fill in the existing gap in knowledge regarding these novel lipid lowering strategies and create hope for a better tomorrow for patients suffering from Hypercholesterolaemia.

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