Internal Medicine and Medical Investigation Journal
E-ISSN: 2474-7750
Homepage: www.imminv.com

REVIEW ARTICLE

Pathophysiology of Dyslipidemia and Its Management by PCSK9 Inhibitors: A Literature Review

[1]Tooba Adnan, [2]Munazza Ahmad, [2]Wardah M. Chaudhri, [3]Ahsan Zil-E-Ali, [4]Muhammad Umar Masood Gondal, [4]Syed Muhammad Hammad Ali, [5]Maira Nusrat, [6]Saad Wasiq

[1]*Jinnah Postgraduate Medical Center, Karachi,*
[2]*Rashid Latif Medical College, Lahore,*
[3]*Fatima Memorial Hospital, Lahore,*
[4]*FMH College of Medicine, Lahore,*
[5]*CMH Lahore Medical College, Lahore,*
[6]*Wah Medical College, Wah Cantt*

Corresponding Author: Dr. Ahsan Zil-E-Ali, E-mail: ahsanzileali@gmail.com

ARTICLE INFO

Article history
Received: July 27, 2018
Accepted: Aug 20, 2018
Published: Sep 15, 2018
Volume: 3
Issue: 3

Conflicts of interest: None
Funding: None

Key words
Hyperlipidemia,
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors,
Dyslipidemia,
Hypercholesterolemia,
Statins

ABSTRACT

Dyslipidemia is a disease of abnormal lipid levels in the blood that contributes to the atherosclerotic process. This atherogenic process leads to the formation of plaque and also leads to thromboembolic events and other vascular accidents. It is known that high-density lipoprotein cholesterol serves as a protective effect on the vessel wall and causes the reduction in the progression of atherosclerosis. And multiple interventions are directed in maintaining a higher level of the aforementioned lipoprotein cholesterol. While the low-density lipoprotein stays controversial but lowering its levels through various therapeutic agents is the main goal in the management of dyslipidemia. A newer group of drugs, proprotein convertase subtilisin/kexin type 9 inhibitors lowers the levels of low-density lipoprotein through modulating proprotein convertase subtilisin/kexin type 9 gene involved in cholesterol metabolism and affects the levels of the lipoproteins by controlling the receptors. The inhibitors of this gene decrease proprotein convertase subtilisin/kexin type 9-induced low-density lipoprotein receptor degradation in the lysosomes of hepatocytes increasing its recfycling and expression on the cell surface, causing increased clearance of low-density lipoprotein from the circulation. These drugs Alicuromab, Evolocumab and along with other agents can be a novel approach in controlling dyslipidemic state. This review revisits the literature in understanding the pathophysiology of dyslipidemia along with its management by proprotein convertase subtilisin/kexin type 9 inhibitors, its mechanism of action, its pharmacokinetics, the results of the clinical trials and the limitations in its application.

INTRODUCTION

Atherosclerosis is a chronic inflammatory disease of the walls of large and medium-sized arteries. It is characterized by destruction of the normal arterial skeleton, involving collagen, elastin and smooth muscles, using enzymes and substituting this with disorderly laid collagen and elastin, along with cholesterol and foam cells [1]. Although a lot of information regarding atherosclerosis has been gained in the last five decades, it remains as one of the leading causes of mortality in both genders and the leading reason for poor quality of life [2]. This atherogenic cholesterol accumulation that damages the vascular anatomy is related to abnormal levels of lipid, often referred as dyslipidemia. Out of other causes of atherosclerosis, dyslipidemia stands prominently as a major contributor in the accumulation of fat in the lumen, narrowing the diameter of the vessels, reducing the per unit time blood supply and a major source of thromboembolic events. Dyslipidemia alone is related to stroke, transient ischemic attacks, ischemic heart disease, pulmonary and systemic embolism. Modulating the triggering elements of dyslipidemia or controlling this disease process can help control many other conditions, serve in comorbid processes and can help in a better quality of life. In past few decades, with sedentary lifestyles, high caloric food intake and commercialized less organic food products, the tendency to develop dyslipidemia have increased many folds and the need for more effective regimens are needed. Statins have been used as a gold standard treatment for three decades now, although with knowing multiple aspects of the disease process, newer and more effectual treatment is needed. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a pro-

Published by Mehrabani Publishing LLC.

http://dx.doi.org/10.24200/imminv.xxxxxx

tease and is expressed predominantly in the liver that plays a vital role in cholesterol metabolism by regulating the levels of low-density lipoprotein (LDL) receptors. PCSK9-inhibitors inhibit PCSK9 induced low-density lipoprotein receptor degradation, increasing its recycling and expression on the cell surface, causing increased clearance of low-density lipoprotein from the circulation and can therefore prove to be the wonder drug in management of hypercholesterolemia and help prevent atherosclerosis and development of congenital heart defect (CHD).

Atheroma Plaque Formation

When high-density lipoprotein (HDL) is not able to take up excess cholesterol from tissue turnover or maybe from dietary cholesterol that is accumulated as lipid layer along the blood vessels and serves in the formation of an atheroma plaque. It will be the role of inflammatory cells to digest the cholesterol not picked up by HDL and when inflammatory cells, particularly the macrophages, take up cholesterol, they cannot metabolize and become foam cells and start releasing cytokines that cause an inflammatory environment of the vascular endothelium. When the intima gets inflamed, the repair would require fibrosis and collagen fibrous plaque would be formed on top of the necrotic core of lipids and cholesterol cleft – this fibrous plaque is called atheroma plaque [3]. Plaque formation is pathognomonic of atherosclerosis. Deposition of cholesterol in lesions in the arterial walls leads to the formation of plaques. This reduces the diameter of the arterial lumen thereby decreasing the volume of blood per time that can pass through [2].

The blood analysis carried out during routine cholesterol level assessment is known as the lipid profile. This lipid profile constitutes the following

- Low-density lipoprotein cholesterol (LDL-C)
- High-density lipoprotein cholesterol (HDL-C)
- Triglycerides (TGs) (blood fats)

Customarily, during evaluation of LDL-C and triglycerides, values towards the lower end of the normal range are desired. This is due to the fact that these lipids are the main driving force behind the development and advancement of atherosclerosis. Conversely, a higher value of HDL-C, in most cases, is preferred as it offers a protective effect on the vessel walls and opposes the occurrence and progression of atherosclerosis [1, 4]. Studies carried on both men and women, suggests an inverse relationship between HDL-C and the risk of developing atherosclerosis, that is, a higher value of HDL-C means a lower risk for atherosclerosis while a lower value of HDL-C (1 milligram HDL-C per 1 deciliter of blood) indicates a greater risk for atherosclerosis [5]. Measurement of the cholesterol content of HDL-C was made possible due to advances in precipitation of apolipoprotein B (ApoB) containing lipoproteins. These measurements were done in a large number of subjects and this enabled grand scale epidemiological studies to determine the relationship between HDL-C and coronary heart disease. The reports that initially compelled the strong inverse association between HDL-C and coronary heart disease lead to Framingham Heart Study [6]. Data interpreted from this study formed the basis for the widely endorsed concept of HDL as the good cholesterol. This led to a conclusion that HDL may possess properties that are protective against coronary heart disease, in turn leading to the conclusion that raising the level of HDL-C through medical intervention would lessen the risk of coronary heart disease (the HDL hypothesis).

Controversy of HDL-C

Even though HDL-C has been shown to possess qualities that are protective against atherosclerosis, the association between HDL-C and atherosclerosis has not been clearly defined. Cynicism regarding the HDL hypothesis has arisen due to certain unsuccessful clinical trials and human genetic studies [7]. Despite the fact that there are questions regarding the HDL hypothesis, the ability of HDL to predict cardiovascular events remains incontrovertible. Affirmation about HDL-C being a strong, consistent and independent predictor of cardiovascular incidences (myocardial infarction, ischemic stroke) has been displayed in multiple studies including various races and ethnicities all over the world [8,9]. Compelling information has also been gathered regarding the role of HDL-C in predicting the risk of cardiovascular events for patients with known history of cardiac diseases, for the purpose of secondary prevention. The predictive property of HDL-C for cardiovascular events in patients undergoing treatment was accurate in a few clinical trials while in some others it was inaccurate [10, 11]. Also, the randomized controlled trials and human genetic studies have provided much of the information that disputes the HDL hypothesis. Research about Mendelian disorders has contributed much to this matter. The three Mendelian disorders causing primary extreme low HDL-C include mutations in apoA1, ABCA1, and LCAT [12]. Although HDL-C levels are lower than the 5th percentile in all of these disorders, none of them are explicitly related to the development of premature coronary heart disease [12].

Furthermore, it has been proved that along with the part that LDL-C plays in raising the rate of cardiovascular events and, the supplementation of diet with statin therapy, exercise, and stoppage of smoking are extremely efficacious in lowering the incidence and prevalence of hyperlipidemia. Although there is a presence of dependable genetic, biological and epidemiological data as well as information from randomized trials, LDL-C remains a topic of controversy between national guidelines and clinical practice. Points of contention include measurement of LDL levels, benefits of population population-based screening, the net benefit to risk ratio for different drugs that decrease LDL, the usefulness of treatment targets and the safeness of vigorously lowering LDL [13].

Nonetheless, to this day, there have been various different drugs that are used for the treatment of dyslipidemia that acts by lowering LDL-C and triglycerides.

Novel Treatment of Dyslipidemia

The safety and efficacy of statins have been proven in a large number of randomized clinical trials, therefore becom-

ing the drug of choice in treating atherogenic dyslipidemia. Nevertheless, even in the presence of optimum treatment with statins, there still remains a 60% to 80% risk of a cardiovascular event [14]. In recent times, there has been a development of a new class of lipid lipid-lowering drugs with some of them being made ready for use in clinical practice. The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor acts by increasing the production of low-density lipoprotein (LDL) receptors in hepatocytes. It achieves this by augmenting LDL receptor recycling [15]. The microsomal triglyceride transport protein (MTP) inhibitor and antisense oligonucleotide against apolipoprotein B (Apo-B) act by decreasing the Apo-B containing lipoprotein. This is accomplished by obstructing the hepatic very low low-density lipoprotein synthesis pathway [16,17]. The apolipoprotein A1 (ApoA1) mimetics act by mimicking the effect of apolipoprotein A1. Their effects are similar to the protective effect of HDL-C and can even overturn the progress of atherosclerosis [18]. However, some of the data gathered from clinical trials with Apo-A1 mimetics is contentious and further testing is required for their acceptability in humans [13]. Encouraging results were shown by the PCSK9 inhibitors in recent studies, including a critical decrease in LDL-C in familial hypercholesterolemia patients from the long long-term phase III trials.

History and Discovery of PCSK9

In the beginning, PCSK9 was classified as a new addition to the proprotein convertase family and was thought to be involved in some way in the differentiation of cortical neurons and in the process of hepatic regeneration [19]. The PCSK9 (proprotein convertase subtilisin/kexin type 9 [MIM 607786]) gene is responsible for encoding a cholesterol-regulated proprotein convertase. Selected missense mutations in PCSK9 were described in 2003, which gave rise to a new type of autosomal dominant hypercholesterolemia (MIM 603776) [20]. This revelation brought to light a hitherto unknown process that has a major impact on the circulating level of low-density lipoprotein cholesterol (LDL-C). The role of cholesterol in the regulation of PCSK9 was also noted [20].

What is PCSK9 gene? Function and Physiology

PSCK9 became the 9th substance to be classified as a part of the subtilisin family of kexin-like proconvertases [21]. The signal sequence (amino acids 1-30) in PCSK9, in a similar fashion to the other members of the group, precedes the prodomain (amino acid 31-152) and the catalytic domain [19]. PCSK9 is classified as a 72-kd kD protease and is expressed predominantly in the liver. Structural properties of PCSK9 include three recognizable domains, a catalytic domain, an N-terminal prodomain and a carboxyl-terminal domain whose function is as yet unknown. Similarities between the carboxyl-terminal domain and resistin, which is an inflammatory cytokine that is correlated with insulin resistance, were discovered on performing crystallographic studies [22]. PCSK9 plays a crucial part in cholesterol metabolism, which has led scientists in both academic and industrial circles to be highly optimistic regarding its role in the treatment of hypercholesterolemia. It›s Its mechanism of action includes regulation of LDL receptor levels [23]. These receptors are plasma membrane glycoproteins that cause the removal of cholesterol-rich LDL particles from the plasma [24,25]. Reduction in the level of LDL receptors occurs due to gain-of-function mutations, leading to increased levels of LDL-C in plasma and increased risk of development of cardiovascular disease. Conversely, loss-of-function mutations cause an increase in the number of LDL receptors, therefore decreasing the level of LDL-C and providing a protective effect against coronary heart disease [26,27].

Role of PCSK9 in Controlling Cholesterol

The process by which LDL receptor levels are decreased by PCSK9 has perplexed scientists for a long time, but progress in understanding its mechanism of action has been made due to studies conducted in recent years. PCSK9 adheres to the LDL receptors which are present on the surface of cells. The elimination of LDL receptors involves internalization of this LDL receptor-PCSK9 complex. Within the cell, when this complex enters the endosome, the acidic environment causes an increase of about 150-fold in the affinity of PSCK9 for the LDL receptor [28,29]. The region which PCSK9 binds to on the LDL receptor is the epidermal growth factor (EGF)-like repeat A [28]. This region has been established to play a pivotal role in the recycling of the LDL receptor to the cell surface from the endosomes [30]. The binding site of PCSK9 on the LDL receptor is some distance away from its catalytic site, as disclosed by studies involving a crystal structure of PCSK9 bound to the EGF-like repeat A [31]. Consequently, this binding of PCSK9 to the LDL receptor leads to a shift in the location of the LDL receptors from the cell surface to lysosomes [32]. In this manner, PCSK9 seems to divert the route of internalized LDL receptors, leading them to the lysosomes for destruction instead of the usual pathway of recycling to the cell surface [28,29,32]. (Figure 1)

PCSK9 Inhibitors: A new Regulator of Cholesterol Trafficking

Praluent (Alirocumab) injection is a new kind of drug that was approved for use by the U.S. Food and Drug Administration on 24th July 2015. This drug became the first of its kind to be approved for the treatment of hyperlipidemia and belongs to a family of drugs known as proprotein convertase subtilisin/kexin type 9 inhibitors [33].

Mechanism of Action

PCSK9 is classified as a serine protease and performs a critical part in the regulation of cholesterol metabolism in the liver. It achieves this by causing an increase in the destruction of LDL receptors. Surface expression of LDL receptors can be raised by inhibiting the process by using PCSK9 inhibitors which in turn decreases the degradation

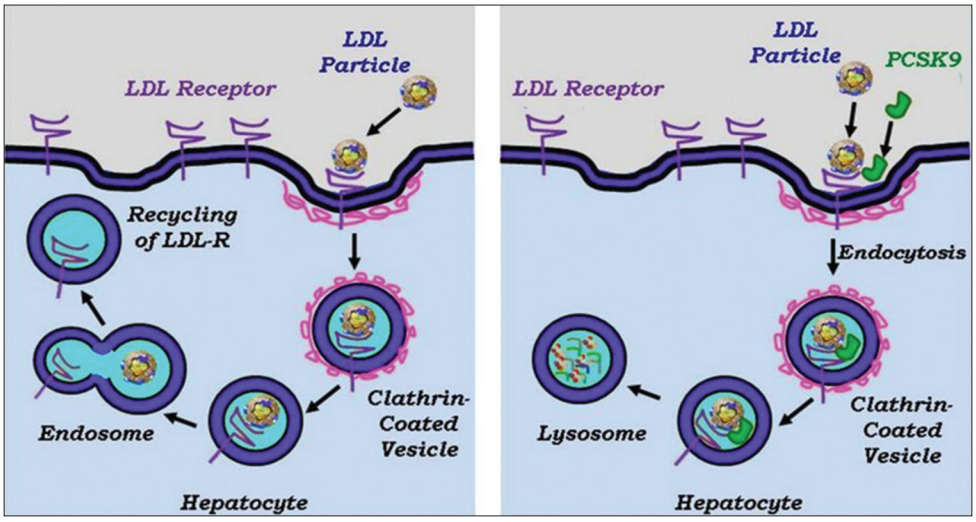

Figure 1. Recycling of LDLR during the metabolism of LDL-C, in the absence (left) and in the presence (right) of PCSK9. Right side shows LDL-C particle attachment to the LDLR and subsequent endocytosis via clathrin-coated vesicle. LDL-C is then degraded in the endosome while LDLR is recycled back on to the surface of hepatocyte. Left side shows binding of PCSK9 to the LDL-C-LDLR complex with subsequent internalization, however the presence of PCSK9 on LDLR directs this vesicle to the lysosomes where the LDLRs are degraded in an acidic environment. (LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9.)

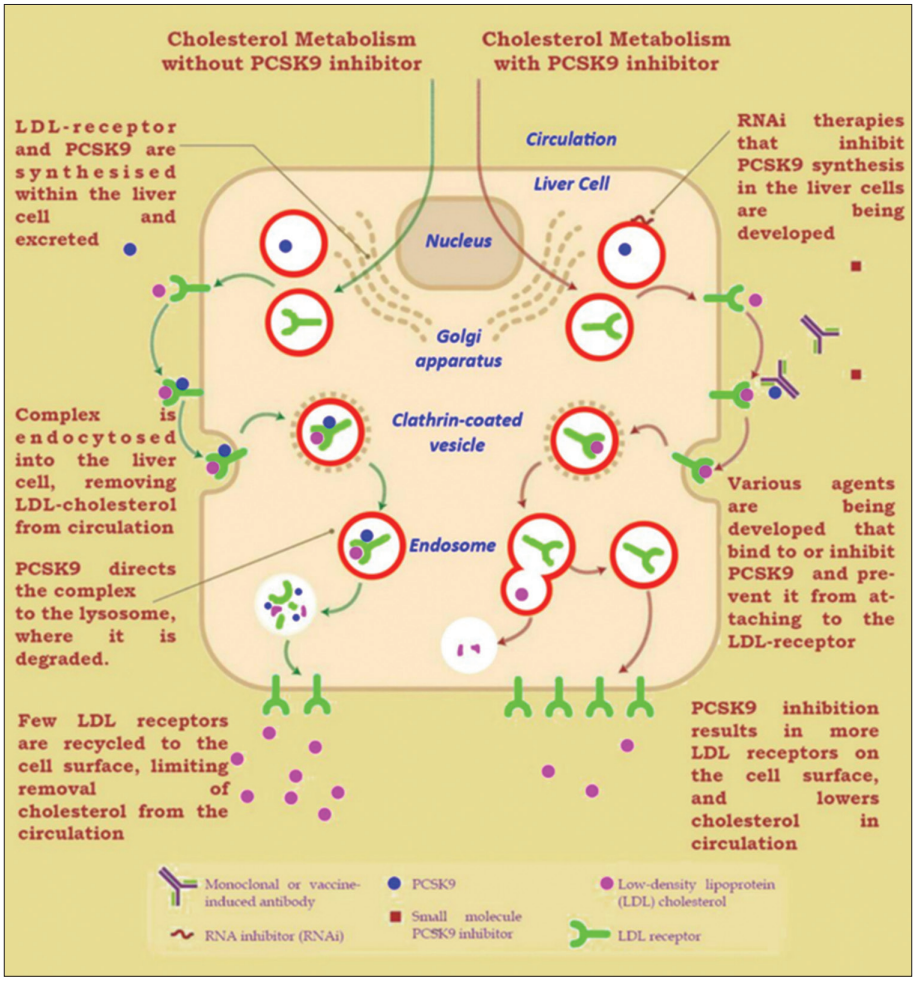

Figure 2. Effect of PCSK9 inhibitors on LDL-C metabolism. Under physiologic conditions, LDLRs and PCSK9 are synthesized in hepatocytes and are secreted into the circulation. Here LDLRs binds LDL-C and is also attached by PCSK9. This complex is endocytosed and directed to lysosome by PCSK9 for destruction. Fewer LDLRs are recycled to the surface of hepatocytes to remove LDL-C. PCSK9 inhibitors, however, prevents this destruction of LDLRs in lysosome and more LDLRs are recycled back to remove LDL-C from the circulation. (LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9)

of LDL receptors (LDLRs). This leads to an increase in the recycling of LDLRs which subsequently causes a reduction in the levels of LDL-C (Figure 2). Various methods have been suggested for the inhibition of PCSK9 so far. Some of these include small interfering RNA, monoclonal antibodies, mimetic peptides and antisense oligonucleotides. Out of all of these, the most promising data on humans has indubitably been displayed by the fully humanized monoclonal antibody against PCSK9 [34].

Kinetics of PCSK9 Inhibitors

Alirocumab

Maximum serum concentration is achieved in 3-7 days and the serum concentration-time profiles for different injection sites, including the abdomen, upper arm and thigh are almost alike. On average, about 3-4 doses are required to achieve steady steady-state concentration. When administered intravenously, the volume of distribution is 0.04 to 0.05 L/Kg. When given at a dose of 75mg to 150mg every fortnight, the median half-life (t1/2) was revealed to be between 17 to 20 days. Removal of Alirocumab occurs in two phases, based on its concentration in plasma. When the concentration in plasma is low, the main route by which Alirocumab is eliminated is by saturation of the targets (PCSK9) bound to the antibodies. On the other hand, when plasma concentration is high, the proteolytic pathways are the predominant mode of elimination [35].

Evolocumab

Evolocumab exhibits non-linear pharmacokinetic properties in absorption when the dosage is less than 140mg. Conversely, when the dosage is between 140mg to 420mg, it is noted that the pharmacokinetics become linear. Following administration of one dose, 3-4 days are required to achieve maximum concentration. Administration of a solitary dose of 420mg results in approximately 3.3 L ± 0.5 L of the volume of distribution. Dosing for nearly 12 weeks is needed to obtain a steady steady-state in serum. Evolocumab has a half half-life (t1/2) somewhere between 11 days to 17 days. A Dosage dosage of 140mg once a fortnight and dosage of 420mg once monthly produced nearly identical results in maximal lowering LDL cholesterol levels and took about 14 days to take effect. Mild and moderate dysfunction of liver or kidneys does not produce any variation in the pharmacokinetics of Evolocumab according to data collected during clinical studies. On the other hand, no data is available regarding the effect on pharmacokinetics in individuals with severe hepatic and renal impairment [36].

Clinical Trials

In contrast to treatment with statins alone, the addition of monoclonal antibodies that inhibit PSCK9 along with statin therapy brings a 50%-60% further lowering of LDL-C, as shown by phase I, II, and III trials. Data collected from short-term trials show that PCSK9 inhibitors had a very low occurrence of harmful effects and were tolerated reasonably well. Data is being gathered by progressive phase III trials which will tell whether the drug is safe to use over a long period of time and its effectiveness in averting cardiovascular disease [37].

In comparison to a placebo, Alirocumab, and Evolocumab, which are both administered by injection, cause a massive decrease in the level of LDL-C (39 to 62% decrease for Alirocumab and 47 to 56% for Evolocumab). Level of LDL-C decreased to less than 25mg per deciliter on two successive readings in about 37% of subjects being treated with Evolocumab and about 24% of subjects being treated with Alirocumab during programs for developing the drugs [38]. During studies conducted on animals, it was found that inhibition of PCSK9 in zebrafish embryos leads to disorganized neuronal growth and can be fatal [39]. However, lackof PCSK9 in mice does not cause any neurological problems and their growth occurs normally [40]. In humans, individuals who are heterozygous for loss-of-function mutations in PCSK9 appear to have no health issues and have similar life spans as individuals with no mutations [26,41]. A study was conducted on PCSK9 involving 18 subjects, 10 females and 8 males, and was divided into two time periods along with being placebo-controlled. The subjects were given two doses of placebo at a gap of two weeks after which they were administered 5 doses of 150mg of Alirocumab at a gap of two weeks each. Effect of Alirocumab was to decrease LDL-C, separated by ultracentrifugation, by 55.1%. LDL-ApoB was decreased by 56.3% and reduction in plasma Lp lipoprotein (a) was 18.7%. An 80.4% rise in LDL-ApoB FCR (Fractional catabolic rate) along with a 23.9% decrease in LDL-ApoB PR (Production rate) appears to be the main cause of the reduction of LDL-ApoB. The LDL-ApoB is related to a 46.1% rise in IDL-ApoB FCR linked with a 27.2% reduction in the formation of LDL from IDL. There was no variation in apo(a) PR ApoA1 PR while the FCR of apo(a) ApoA1 was prone to increase. No effect of Alirocumab was observed on FCRs or PRs of VLDL-ApoB and VLDL-TG (Triglyceride) as well as on plasma TG after meals or ApoB48 levels [42].

A trial conducted to investigate the effectiveness of PCSK9 inhibitors, known as the Therapy for Easing Lipid Levels (MENDEL) trial, included 406 subjects with hypercholesterolemia and intolerance to statin therapy. The subjects were randomly divided into groups and each group was allocated a treatment regimen. These included a fortnightly dose of 70mg, 105mg and 140 mg of Evolocumab; a monthly dose of 280mg, 350mg, and 420mg of Evolocumab; fortnightly or monthly dose of placebo or a single daily dose of Ezetimibe. LDL-C levels were decreased in all groups with Evolocumab and the maximum effect was shown by the dosage of 140mg every fortnight (~51 %) without any harmful side effects being observed [43]. Massive improvement in LDL-C level by Alirocumab and Evolocumab were reported in one review. The results were more powerful for Alirocumab, as compared to Evolocumab, in subjects at high risk of a cardiovascular event who had poor LDL-C levels. Conversely, in subjects with heterogeneous familial hypercholesterolemia and subjects with varied risk of a cardiovascular event with deranged LDL-C values, Evolocum-

ab showed a greater result. Data collected from a previous analysis on adjudicated cardiovascular outcomes showed no significant advantage for Alirocumab and was inconclusive for Evolocumab. But for longer duration use, vital answers are still required regarding the effects of both Evolocumab and Alirocumab on health and fitness [44]. An additional clinical trial was conducted with 968 subjects who all had a history of cardiovascular disease. They were also divided into two groups at random and one was given the PCSK9 inhibitor Evolocumab while the other group was assigned a placebo. The drugs were taken once a month for 19 months and intravascular ultrasounds were done sequentially to ascertain the volume of coronary atheroma. In the Evolocumab group, the LDL-C levels were noted to be lower (36.6 vs 93.0 mg/dL) and the number of subjects showing plaque reversal was observed to be higher (64.3% vs 47.3%). The Evolocumab group also showed a decrease in the percent atheroma volume (−0.95%). No such effect was noted for the placebo group [45].

The debate about the efficacy and possible negative consequences of these unfamiliar drugs is ongoing and has involved a multitude of experts.

Clinical uses of PCSK9 Inhibitors

One of the chief advantages of PCSK9 inhibitors is its usage in therapy for familial hypercholesterolemia in people overly sensitive to statins and also in people whose low-density lipoprotein-cholesterol LDL-C levels remain high even after they have been put on the maximum dose of statins that can be safely prescribed. Interestingly, combination therapy of low dose statins with PCSK9 inhibitors is more efficacious for decreasing LDL-C levels and preventing adverse effects of statins. This is due to the fact that combination of PCSK9 inhibitors with both low dose and high dose statins have shown effects nearly identical to each other [46].

Potential Barriers

Large-scale use of PCSK9 inhibitors may be prevented by the presence of various probable hurdles. First of all, the efficacy of statins in treating hypercholesterolemia has been confirmed by the results of several long long-term studies, this makes statins a better option over the PCSK9 inhibitors, which is still to evaluated in terms of outcomes, efficacy and side-effects. [47,48]. This lack of extensive post-market trials and primitive phases of surveillance makes it a potential barrier in physician's first choice over statins. Additionally, a further hurdle faced by the PCSK9 inhibitors may be their retail price. According to The Institute for Clinical and Economic Review (ICER), the amount required for treatment for 5 years to prevent a single major cardiovascular incident (NNT5) happens to be 28. But the cost-effectiveness ratio calculated by the manufacturer's suggested retail price is much higher than the established threshold of $100000/quality-affected life-years. A drop of 60% to 65% in the presently suggested price would be needed to attain cost-effectiveness at this threshold [49].

Adverse effects and Contraindications of Alirocumab and Evolocumab

Data collected from more than 7000 patients who were being given PCSK9 inhibitors has been observed and the side effects recorded tillnow state the findings as mentioned below. Treatment with Alirocumab is not advisable in people who are sensitive to it and may in the past have displayed severe hypersensitivity reactions like hypersensitivity vasculitis or needed a hospital stay due to a severe allergic reaction after its consumption. The most frequently reported side effects of Alirocumab are: nasopharyngitis, injection site reactions (erythema, itchiness, swelling, pain or tenderness), influenza, urinary tract infection, diarrhea, bronchitis, myalgia, muscle spasms, sinusitis, cough, contusion and musculoskeletal pain. The most frequent reasons for stoppage of drug use include allergic reactions and elevated liver enzymes [46].

Reasons for the avoidance of Evolocumab are mostly the same as those for Alirocumab. In comparison to a placebo, the occurrence of negative effects for a single dose of 140mg Evolocumab once a fortnight was 43.6% (Evolocumab) vs 41% (placebo). The most frequent side effects reported were nasopharyngitis, upper respiratory tract infection, back pain and nausea. The most frequent reasons for halting drug use were dizziness, myalgia, and nausea. Some of the more severe side effects include cardiovascular disorders, seen in 2.4% of the patients, like palpitations, angina pectoris, and ventricular extrasystoles [46]. Furthermore, information collected from various clinical trials which assessed Evolocumab and Alirocumab has displayed that individuals on PCSK9 inhibitor therapy have exhibited a greater amount of side effects involving cognitive ability [36, 50].

CONCLUSION

An essential aspect of assessing pharmaceutical drugs belonging to a new class is to demonstrate proof of their intended effect on the subject, which in this case is a decreased risk of cardiovascular incidents. Even though with Alirocumab and Evolocumab the decrease in LDL-C is considerable, conclusive proof that the rate of occurrence of cardiovascular incidents has lowered is indispensable. A few clinical trials are specifically being conducted to gather data that can be used to illuminate the clinical advantages of these drugs as well as potential adverse effects. The possible advantages from the remarkable decrease in LDL-C levels achieved by these medications should be cautiously evaluated in contrast to their long long-term safety profile which is as yet inconclusive.

ACNOWLEDGMENTS

Authors are thankful to Zubair Ahmed, Medical Student from FMH College of Medicine for his contribution in the preparation of images.

AUTHOR CONTRIBUTIONS

Article Concept, Literature Review, Critique and Image Concept: T Adnan, M Ahmad, WM Chaudhri, A Zil-E-Ali.

Article Revision and Editing: MUM Gondal and SMH Ali.

Proof Reading: M Nusrat and S Wasiq.

CONFLICT OF INTERESTS

None.

REFERENCES

1. Ross R, Harker L.: Hyperlipidemia and atherosclerosis. Science. 1976, 4258:1094-100. 10.1126/science.822515
2. Toth PP: The "good cholesterol". Circulation. 2005, 5:89-91. 10.1161/01.CIR.0000154555.07002.CA.
3. Cilla M, Pena E, Martinez MA: Mathematical modelling of atheroma plaque formation and development in coronary arteries. Journal of the Royal Society, Interface. 2014, 90:20130866. 10.1098/rsif.2013.0866
4. Al-Rasadi K, Al-Waili K, Al-Sabti HA, et al: Criteria for diagnosis of familial hypercholesterolemia: A comprehensive analysis of the different guidelines, appraising their suitability in the Omani Arab population. Oman medical journal. 2014, 2:85.
5. Stefanick ML, Mackey S, Sheehan M, et al: Effects of diet and exercise in men and postmenopausal women with low levels of HDL cholesterol and high levels of LDL cholesterol. N Engl J Med. 1998, 339:12-20. 10.1056/NEJM199807023390103
6. Kannel WB, Dawber TR, Friedman GD, et al: Risk factors in coronary heart disease: an evaluation of several serum lipids as predictors of coronary heart disease: The Framingham Study. Annals of internal medicine. 1964, 5:888-99. 10.7326/0003-4819-61-5-888
7. Rader DJ, Hovingh GK.: HDL and cardiovascular disease. The Lancet. 2014, 9943:618-25. 10.1016/S0140-6736(14)61217-4
8. Toth PP, Barter PJ, Rosenson RS, et al: High-density lipoproteins: a consensus statement from the National Lipid Association. Journal of clinical lipidology. 2013, 5:484-525. 10.1016/j.jacl.2013.08.001
9. Goff DC, Lloyd-Jones DM, Bennett G, et al: 2013 ACC/AHA guideline on the assessment of cardiovascular risk. Circulation. 2014, 25:49-73. 10.1161/01.cir.0000437741.48606.98
10. Olsson AG, Schwartz GG, Szarek M, et al: High-density lipoprotein, but not low-density lipoprotein cholesterol levels influence short-term prognosis after acute coronary syndrome: results from the MIRACL trial. European heart journal. 2005, 9:890-6. 10.1093/eurheartj/ehi186
11. Ray KK, Cannon CP, Cairns R, et al: Prognostic utility of ApoB/AI, total cholesterol/HDL, non-HDL cholesterol, or hs-CRP as predictors of clinical risk in patients receiving statin therapy after acute coronary syndromesArterioscler., Thromb., Vasc. Arteriosclerosis, Thrombosis, and Vascular Biology. 2009, 3:424-30. 10.1161/ATVBAHA.108.181735
12. Rader DJ, deGoma EM.: Approach to the patient with extremely low HDL-cholesterol. J. Clin. Endocrinol. Metab. 2012, 10:3399-407. 10.1210/jc.2012-2185
13. Ridker PM.: LDL cholesterol controversies and future therapeutic directions. The Lancet. 2014, 9943:607-17. 10.1016/S0140-6736(14)61009-6
14. Ahn CH, Choi SH: New drugs for treating dyslipidemia: beyond statins. Diabetes Metab. 2015, 2:87-94. 10.4093/dmj.2015.39.2.87
15. Horton JD, Cohen JC, Hobbs HH: Molecular biology of PCSK9: its role in LDL metabolism. Trends Biochem Sci. 2007, 2:71-7. 10.1016/j.tibs.2006.12.008
16. Choi SH, Ginsberg HN: Increased very low density lipoprotein (VLDL) secretion, hepatic steatosis, and insulin resistance. Trends Endocrinol. Metab. 2011, 9:353-63. 10.1016/j.tem.2011.04.007
17. Cuchel M, Bloedon LT, Szapary PO, et al: Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. N. Engl. J. Med. 2007, 2:148-56. 10.1056/NEJMoa061189
18. Sahebkar A, Watts GF: New therapies targeting apoB metabolism for high-risk patients with inherited dyslipidaemias: what can the clinician expect?. Cardiovasc Drug Ther. 2013, 27:559-567.
19. Seidah NG, Benjannet S, Wickham L, et al: The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC- 1): liver regeneration and neuronal differentiation. Proc.Natl. Acad.Sci U S A. 2003, 3:928-933. 10.1073/pnas.0335507100
20. Maxwell KN, Soccio RE, Duncan EM, et al: Novel putative SREBP and LXR target genes identified by microarray analysis in liver of cholesterol-fed mice. J. Lipid Res. 2003, 11:2109-19. 10.1194/jlr.M300203-JLR200
21. Basak A: Inhibitors of proprotein convertases. J. Mol. Med. 2005, 83:844-55. 10.1007/s00109-005-0710-0
22. Hampton EN, Knuth MW, Li J, Harris JL, Lesley SA: Spraggon G. The self-inhibited structure of full-length PCSK9 at 1.9 Å reveals structural homology with resistin within the C-terminal domain. Proc. Natl. Acad. Sci U S A. 2007, 104:14604-9. 10.1073/pnas.0703402104
23. Benjannet S, Rhainds D, Essalmani R, et al: NARC-1/PCSK9 and its natural mutants zymogen cleavage and effects on the low density lipoprotein (LDL) receptor and LDL cholesterol. J. Biol. Chem. 2004, 279:48865-75. 10.1074/jbc.M409699200
24. Brown M, Goldstein J.: Lipoprotein receptors in the liver. Control signals for plasma cholesterol traffic. J Clin Invest. 1983, 72:743. 10.1172/JCI111044
25. Goldstein L, Brown S: The low-density lipoprotein pathway and its relation to atherosclerosis. Annu Rev Biochem. 1977, 46:897930. 10.1146/annurev.bi.46.070177.004341
26. Cohen JC, Boerwinkle E, Mosley Jr TH, et al: Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med. 2006, 354:1264-72. 10.1056/NEJMoa054013
27. Zhao Z, Tuakli-Wosornu Y, Lagace TA, et al: Molecular characterization of loss-of-function mutations in PCSK9 and identification of a compound heterozygote. Am J Hum Genet. 2006, 79:514-23. 10.1086/507488

28. Zhang D-W, Lagace TA, Garuti R et al: Binding of proprotein convertase subtilisin/kexin type 9 to epidermal growth factor-like repeat A of low density lipoprotein receptor decreases receptor recycling and increases degradation. J Biol Chem. 2007, 282:18602-12. 10.1074/jbc.M702027200
29. Fisher TS, Surdo PL, Pandit S, et al: Effects of pH and low density lipoprotein (LDL) on PCSK9-dependent LDL receptor regulation. J Biol Chem. 2007, 282:20502-12. 10.1074/jbc.M701634200
30. Rudenko G, Henry L, Henderson K, et al.: Structure of the LDL receptor extracellular domain at endosomal pH. Science. 2002, 298:2353-2358. 10.1126/science.1078124
31. Kwon HJ, Lagace TA, Mcnutt MC, Horton JD, Deisenhofer J: Molecular basis for LDL receptor recognition by PCSK9. Proc Natl Acad Sci USA. 2008, 105:1820-1825. 10.1073/pnas.0712064105
32. Maxwell KN, Fisher EA, Breslow JL: Overexpression of PCSK9 accelerates the degradation of the LDLR in a post-endoplasmic reticulum compartment. Proc Natl Acad Sci USA. 2005, 102:2069-2074. 10.1073/pnas.0409736102
33. FDA approves Praluent (alirocumab) Injection for treatment of patients with high LDL cholesterol. (2015). Accessed: May 21, 2018: https://www.news-medical.net/news/20150725/FDA-approves-Praluent-(alirocumab)-Injection-for-treatment-of-patients-with-high-LDL-cholesterol.aspx.
34. Noto D, Cefalù AB, Averna MR: Beyond statins: new lipid lowering strategies to reduce cardiovascular risk. Curr Atheroscler Rep. 2014, 16:414. 10.1007/s11883-014-0414-4
35. Raal FJ, Stein EA, Dufour R, Turner T, et al.: PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD- 2): a randomised, double-blind, placebo-controlled trial. The Lancet. 2015, 385:331-340. 10.1016/S0140-6736(14)61399-4
36. Koren MJ, Giugliano RP, Raal FJ, et al.: Efficacy and safety of longer-term administration of evolocumab (AMG 145) in patients with hypercholesterolemia: 52-week results from the Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER) randomized trial. Circulation. 2014, 129:234-243. 10.1161/CIRCULATIONAHA.113.007012
37. Dadu RT, Ballantyne CM: Lipid lowering with PCSK9 inhibitors. Nat Rev Cardiol. 2014, 11:563-575. 10.1038/nrcardio.2014.84
38. Everett BM, Smith RJ, Hiatt WR: Reducing LDL with PCSK9 Inhibitors — The Clinical Benefit of Lipid Drugs. N Engl J Med. 2015, 373:1588-1591. 10.1056/NEJMp1508120
39. Poirier S, Prat A, Marcinkiewicz E, et al.: Implication of the proprotein convertase NARC-1/PCSK9 in the development of the nervous system. J Neurochem. 2006, 98:838-850. 10.1111/j.1471-4159.2006.03928.x
40. Rashid S, Curtis DE, Garuti R, et al.: Decreased plasma cholesterol and hypersensitivity to statins in mice lacking Pcsk9. Proc Natl Acad Sci USA. 2005, 102:5374-5379. 10.1073/pnas.0501652102
41. Cohen J, Pertsemlidis A, Kotowski IK, et al.: Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. Nature genetics. 2005, 37:161-165. 10.1038/ng1509
42. Reyes-soffer G, Pavlyha M, Ngai C, et al.: Effects of PCSK9 Inhibition With Alirocumab on Lipoprotein Metabolism in Healthy Humans. Circulation. 2017, 135:352-362. 10.1161/CIRCULATIONAHA.116.025253
43. Latimer J, Batty JA, Neely RDG, et al.: PCSK9 inhibitors in the prevention of cardiovascular disease. J Throm Thrombolysis. 2016, 42:405-419. 10.1007/s11239-016-1364-1
44. McDonagh M, Peterson K, Holzhammer B, et al.: A Systematic Review of PCSK9 Inhibitors Alirocumab and Evolocumab. J Manag Care Spec Pharm. 2016, 22:641-653. 10.18553/jmcp.2016.22.6.641
45. Nicholls SJ, Puri R, Anderson T, et al.: Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. JAMA. 2016, 316:2373-2384. 10.1001/jama.2016.16951
46. Chaudhary R, Garg J, Shah N, Sumner A: PCSK9 inhibitors: A new era of lipid lowering therapy. World J Cardiol. 2017, 9:76-91. 10.4330/wjc.v9.i2.76
47. Minder CM, Blumenthal RS, Blaha MJ: Statins for primary prevention of cardiovascular disease: the benefits outweigh the risks. Curr Opin Cardiol. 2013, 28:554-560. 10.1097/HCO.0b013e32836429e6
48. Group HPSC: MRC/BHF heart protection study: randomised placebo-controlled trial of cholesterol-lowering with simvastatin in 20,536 high-risk individuals. Lancet. 2002, 360:7-22. 10.1016/S0140-6736(02)09327-3
49. Anderson JL, Heidenreich PA, Barnett PG, et al.: ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures. Circulation. 2014, 129:2329-45. 10.1016/j.jacc.2014.03.016
50. Dias CS, Shaywitz AJ, Wasserman SM, et al.: Effects of AMG 145 on low-density lipoprotein cholesterol levels: results from 2 randomized, double-blind, placebo-controlled, ascending-dose phase 1 studies in healthy volunteers and hypercholesterolemic subjects on statins. J Am Coll Cardiol. 2012, 60:1888-98. 10.1016/j.jacc.2012.08.986