Review Article

Archives of Clinical and Medical Microbiology

Pharmacology and Therapeutic Potential of Pcsk9 Inhibitors

Jeetendra Kumar Gupta[1], Shivendra Kumar[2], Krishanveer Singh[3], Kuldeep Singh[4*], Km. Meenakshi[5]

Institute of Pharmaceutical Research, GLA University Mathura, Uttar Pradesh, INDIA

***Corresponding author**
Kuldeep Singh, Institute of Pharmaceutical Research, GLA University Mathura, Uttar Pradesh, INDIA

Submitted: 15 Oct 2022; **Accepted**: 26 Oct 2022; **Published**: 31 Oct 2022

Citation: *Jeetendra Kumar Gupta, Shivendra Kumar, Krishanveer Singh, Kuldeep Singh, Km. Meenakshi. (2022). Pharmacology and Therapeutic Potential of Pcsk9 Inhibitors. Archives Clin Med Microbiol, 1(1), 01-09.*

Abstract

Proprotein convertase subtilisin/Kexin type 9 (PCSK9) is a proteolytic enzyme that indirectly regulates serum LDL cholesterol by destroying LDL receptors. The main role of proprotein convertase subtilisin/Kexin type9 (PCSK9) inhibitor in cholesterol regulation was elucidated in clinical studies. It is produced in the liver but is also present in the kidney and intestine. It prevents HMGCo from synthesizing cholesterol. SREBP-2 is a reductase that is induced by statins. In a dose-dependent manner, increasing SREBP-2 levels enhanced LDL-R and PCSK9 gene expression. At the minimum, two procedures have been developed to overcome the plasma level of PCSK9 prohibit. This is the LDLR test, polyclonal antibodies, and sentience oligonucleotide. Lower dosage statin treatment with a proprotein convertase subtilisin/Kexin type9 inhibitor will be most efficient in lowering LDL and avoiding statin adverse effects. In multiple long-term trials, statins have been found to reduce cardiovascular mortality by 30% and stroke incidence by 20%. In this way, we conclude the role of PCSK9 in hypercholesterolemia.

Keywords: Cholesterol, Pcsk9 Inhibitors, Hmg-Coa, Ldl Receptor, Statins.

Introduction

Proprotein convertase subtilisin/Kexin type 9 is a proteolytic enzyme that binds to the LDL receptor in order to control serum LDL cholesterol level by inducing LDL receptor degradation [1]. A pair of the benefit of function mutations in the PCSK9 gene in a French family were shown to be responsible for autosomal dominant familial hypercholesterolemia (FH), a condition linked to premature cardiovascular disease (CVD) and death. It was the third part of an autosomal dominant mutation for familial hypercholesterolemia that increased mutations in the LDL-R (Receptor) and apolipoprotein B genes3 [2]. Clinical research has highlighted the main role of proprotein convertase subtilisin/Kexin type9 (PCSK9) inhibitor in cholesterol regulation [3]. PCSK9 (proprotein convertase subtilisin/Kexin type 9) is a serine protease of the subtilisin family that is excreted. It's made in the liver, but it's also found in the kidneys and intestine. In the pro-domain, c-terminal domain, catalytic domain, and signal sequence, PCSK9-pro, 692-AA (amino acid), and 75 KDa precursor of PCSK9 combine. It is produced in the endoplasmic reticulum (ER) and improved in the Golgi apparatus, where it is autocatalytically cleaved to enter the secretory pathway and then released into circulation [4]. SREBP-2 (sterol regulatory element bound protein -2) regulates hepatic LDL-R activity during transcription, while PCSK9 suppresses the LDL/LDL-R (Receptor) complex [5]. The maximal complex is internalized and attacked by the lysosome, resulting in a decrease in LDL-R and, as a result, a decrease in LDL-C (clearing), increasing LDL plasma levels. At the transcriptional level, both LDL-R and PCSK9 inhibitors are influenced by intracellular cholesterol levels via SREBP-2 (sterol regulatory element bound protein -2) [1]. It prevents HMGCo from synthesizing cholesterol. SREBP-2 is a reductase that is induced by statins. SREBP-2 elevated the expression of LDL-R and PCSK9 genes in a dose-dependent manner, with the former gene being more significantly regulated11. Increased PCSK-9 levels in fibrates via SREBP-2, as well as higher modulation of PCSK-9 levels by fibrates and statins, imply that PCSK-9 inhibition may improve the lipid-lowering efficacy of this similar medications [6].

Inhibitors of Pcsk9

Inhibitors of PCSK9 leads to a new class of drugs category that lowers LDL level or bad-cholesterol. At present, very few drugs have been approved by the United States Food and Drug Administration (US-FDA), such as alirocumab and evolocumab. These are having characteristics-

a) Atherosclerotic cardiovascular disease (CVD) where a sufficient LDL level with existing therapy (statins) is not obtainable
b) Adult patients having familial hypercholesterolemia
c) In the patient with having intolerance

Alirocumab

The human monoclonal antibody i.e., alirocumab. That is work with the help of liver reduced the level of 'Bad' cholesterol LDL-

(low-density lipoprotein) circulating in our blood [7]. It is used in individuals having heart disease to reduce the risk of heart attack, a certain type of chest pain (unstable/ angina) and stork condition require hospitalization [8]. It is used together with a freely low diet, alone or together with other cholesterol with lowing medicines in the adult with high blood cholesterol level also called primary hyperlipidemia (includes high cholesterol called heterozygous) FH (Familial hypercholesterolemia)/ inherited types of high cholesterol [9, 10]. This situation can cause higher blood levels of LDL cholesterol & also can cause plaque inside our arteries [11]. Praluent is mainly used along with other LDL- lowing treatments in the adult with high cholesterol called homozygous familial hypercholesterolemia to need additional lowing of LDL-C (low-density lipoprotein-c) [12].

Mechanism of Action

Alirocumab inhibits the PCSK9 protein, which binds to the LDL-R (low-density lipoprotein receptor), causing cholesterol to be removed from circulation and the receptor to be destroyed, decreasing LDL cholesterol that is removed from circulation [13].

Dosing Information

Adult dose for hyperlipidemia patients

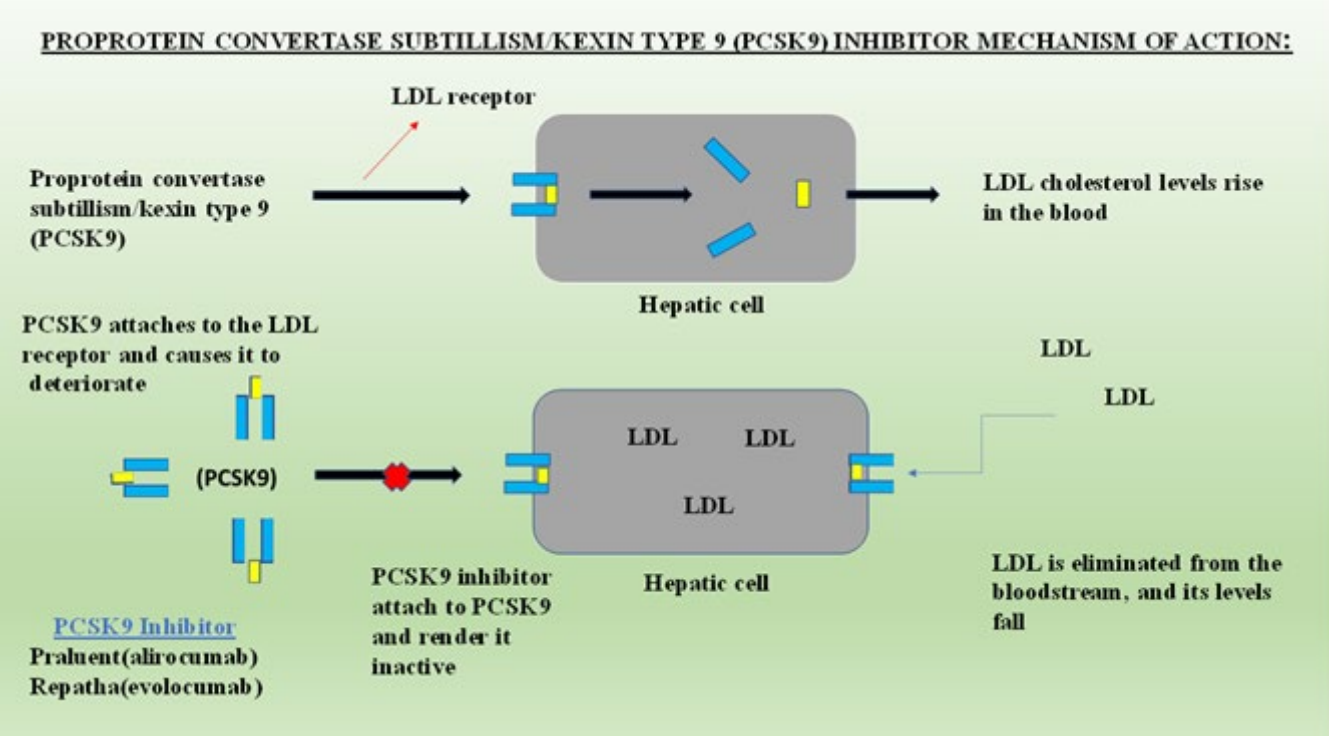
The usual dose of alirocumab is 75mg subcutaneously every 2 weeks or 300 mg subcutaneously once every 4 weeks [1]. For inadequate LDL-(low-density lipoprotein) response may adjust close to 150 mg subcutaneously every 2 weeks [12].Patient with heterozygous familial hypercholesterolemia (HFH) undergoing LDL aphaeresis- 150mg subcutaneously once every 2 weeks [14].

Evolocumab

Evolocumab (Repatha) has a human monoclonal antibody [15]. That is works with the helping liver reduce the level of 'Bad' cholesterol (LDL) circulating in our blood11. It is used in combination with a low-fat diet and other cholesterol lowing medication in people with homozygous or heterozygous familial hypercholesterolemia (FH) [16]. It is mainly used to help reduce the risk of stroke, heart attack, or other heart problems in people who have or have had vessel problems caused by plague in the arteries [17].

Mechanism of Action

Proprotein convertase subtilisin/Kexin type 9 is studied using a monoclonal antibody (PCSK9). the LDL-R pathway is particularly important in clearing LDL-C from circulation. PCSK9 is a serine protease that breaks down LDL-R in the liver, lowering LDL-C clearance and increasing plasma LDL-C. PCSK9 inhibitor reduces LDL-R degradation by PCSK9, which improves LDL-C clearance and lowers plasma LDL-C levels [18].



Absorption

Evolocumab is a drug that is used to treat a variety of conditions The peak plasma concentration is 18.6mcg/ml and lasts 3-4 days. As a result, it has a 72 percent bioavailability in humans. evolocumab has an AUC (least) of 188 days mcq/ml (140 mg) and a Vd of 3.3L. (420mg).

Metabolism

Lower concentration: saturable bound to PCSK9 target is the primary mode of elimination.

Higher concentration: evolocumab is mostly eliminated by a non-saturable proteolytic route [1].

The half-life of evolocumab is (11-17 days) [19].

Dosing Information

In the intervention arm, high cardiovascular risk hemodialyzed statin intolerant patients with hypercholesterolemia will receive evolocumab 140 mg subcutaneous every 2 weeks for 24 weeks.

PCSK9 is standing for proprotein appropriate subtilisin / Kexin 9 inhibitor. (PSCK) a polar regular of poor Solidity lipoprotein receptor of (LDL), and hence Level of LDL cholesterol1.PCSK9 inhibitor is principally symphonized through the Hepatocytes [1]. It suffers from a mechanical cleft in the (ER) endoplasmic reticulum at the Golgi apparatus. PCSK9 is one of 33 genes organized through the sterol regulatory elements (SRE) protein binding (SREBP) family of copied factors. PCSK9 promoter rapidity increases when there is inhibition in cell cholesterol transcription or cell synthesis [20]. Leading to an enhanced transcription. The PCSK9 inhibitor of nuclear 1 (HNF1) is the second factor of transcription implicated in the arrangement within the hepatocyte factor [21]. Already secreted, PCSK9 cleaves epidermal growth factor identical homology domain A (EGFA) by that catalytic domain to the receptor of (LDLR). This promotes the objection of LDLR to the lysosome, intended to accept it to recycle within the surface cell22. Their degeneration response suppresses LDLR number on hepatocytes but by the liver uptake of circulating LDL Particle [22]. To the purpose, gain-of-function of PCSK9 genetic (GOF) variations is equivalent to HYPERCHOLESTEROLEMIAconsideration24. Although its Prohibition of pharmacological has been adjudging like an intervention of new line to inhibiting cardiovascular disease [23]. At the minimum smallest two procedures have been developed to overcome the plasma level of PCSK9 to prohibit. This is the LDLR trying, polyclonal antibodies, and sentience Oligonucleotide [24]. Though, a pharmacological strategy to prohibit PCSK9 can do immersed.

The development and identification through orally absorbed tinny molecule within the activity of PCSK9 [20]. Pharmacological history has granted enthralling evidence of the significance of recognized naturally arising chemical moieties to capable therapeutic effects. Because, with this reason in the current review, our selves epitomized the Attending knowledge within essential combination obtained that have seen important activity of PCSK9 inhibitory [25].Naturally occurring inhibitors of PCSK9 are quite common in phytomedicines.

Berberine

Berberine is a moiety of chemicals rescued in different plants along with European barberry [26], goldenseal, Oregon grape, Goldthread, greater celandine, philodendron, and tree turmeric [27]. This is mostly coarse taken for diabetes, strong levels of cholesterol or other fats lipids in the bloodstream (hyperlipidemia), and high blood pressure [28]. Its berberine has specified that it cure & treatment many metabolisms health condition [29].

- o polygenic disorder
- o stoutness
- o cardiac problems

Benefits

Bacterial Infection

It inhibits the growth /Prevent the Staphylococcus Aureus and cure & fight many problems sepsis, pneumonia, meningitis. It also helps in the skin conditions and problems [30].

Diabetes

Its benefit found on studied bases positive effect on blood sugar, insulin, and triglyceride [31].

High Blood Pressure

It's a new drug leading blood pressure cures of heart disease in berberine present a Meta-analysis bind with BP reduced drug was much Efficacious other than single. Berberine could detain the just that time high blood pressure and then developed, that moment Berberine help reduced its Severity [32].

Obesity

It is a common problem. It's can gain the probability of Type-2 Diabetes, Cardiac problems, increase BP, and also risk with cholesterol [33].

Dose

Dose in case of obesity people took 750 mg of Berberine twice a day for 90 Days [34].

High Cholesterol

High level of poor solidity lipoprotein(LDL) triglycerides and cholesterol1.It's maybe higher the risk of Heart stokes and problems [35].People took 750mg of barberry two times a day for 90 days. Decrease loss in body weight [36].Take 200mg berberine three times a day experimented with people's decrease in Body Mass index reading [29].

Polycystic Ovary Syndrome

PCO5 Syndrome is feminine has a high level of certain masculine hormones [37].

These concerns are as follows

- Increase insulin
- High level of cholesterol
- Heavy body weight
- Increase Blood pressure

Cancer

Berberine can cause much differentiation by the molecule of cell / tissue [38].It also benefits another potential fighting within cancer [39].

The following points on cancer are also mentioned as inhibitory effects.

- Colorectal cancer
- Cancer of lungs
- Cervical cancer
- Cancer of Prostate
- Cancer of ovary

Dose

Barbering capsules formulations dose took some people, but there is no fixed quantity dosage mostly use 1000 to 1500mg per Day [40].

Vegetable Proteins and Sterol /Stanols

There is an obtainable dietary supplement substituent within cholesterol decrease, plant sterol/stanols obtain one of broad put to use. There are no clear data on these given substances, requiring this inhibitor to show no activity on the PCSK9 level and findings in any case [41]. Two groups have analyzed the PCSK9 layer under the influence of plant stanol inlet in LDL-C poor condition [42]. Simenon it all in a randomly imperturbable double-blind trial in rational and Hypercholesteremic subject, evacuate the effect of six months depletion of oil of vegetables spread (20g/day) [43]. Improve control group or not plant stanol group through stanol 3g in a day like an ester. The long time/ duration take consumption of plant stanol ester decreased LDL - C through 7-10% in the absence of influencing either PCSK9 plasma congregation or the liver disease levels of LDLR, Plant stanol esters without those interesting within PCSK9 metabolism may impair LDL-C by inhibition of cholesterol absorption [43]. The case is the blotted soy and lupine peptide mixture that achieved a reduced activity of HMG-CoA at the 0.5 mg/mL level, which is 50% lower than the nanomolar IC of known statins, with poor initiation activity invariably. Decreases [44].

Lupin Protein

The probed lupine peptides is derived from a protein rich grain legumei.e., Lupinus albus (white lupin), L. luteus (yellow lupin), L. mutabilis (pearl lupin) and L. angustifolius (sweet leaf lupin; Fabaceae). Lupin proteins have been investigated for several years, primarily for their ability to lower plasma cholesterol levels, which is due in part to an LDLR-activating mechanism. Lupin proteins have been shown to have hypolipidemic and antiatherosclerotic properties in animal models [45]. The % of sequence homology present within the display template allows obtaining models within the reasonable quality that is supported by MD simulation. The last stage of stimulation. The short peptide has a small amount of energy in the form of a minimum level of structure [46]. T1, T2, and T16 showed the helix to be correct. T3, T4, T5, T6, and T9 folded into a permanent sequence such as the confounding coils P1, P3, P5, P7, P10, and P6, the peptide is predominantly PCSK9/ LDLR PPI. were responsible for the prohibition [47].

Soy Proteins

Soy protein has been demonstrated to have decreasing properties in different populations from children (Laurie et al. 1991) to renal patients (D' Amico 1992). The ultimate mechanism was dependable for the plasma cholesterol decease. Direct execution of the major isoflavones in soybeans. Alternatively, the protein constituent mainly 7s globulin from soybean and their fragments [48].It's recently approved by the health claim role of soya protein in decreasing the risk factor of coronary heart disease (FDA 1999) [49].

Dose

Research by some people took those 25 grams of soy protein in a day. It's mostly given cholesterol decreasing effect [50].

Polyphenols

Polyphones is derived from the plant secondary metabolites present in fruit, nut, seed, vegetable, stem, herbs, and flower. It's also found in tea and red urine [51].This class undergoes the counting of different substances as flavonoids, lignans, stilbenes, and condensed (flavan-3-ol polymers known as proanthocyanin's) Or hydrolysable, phenolic polymer many epidemiological studied like as clinical trial, the reported different cardiovascular benefits of polyphones.

There are several mechanism actions including plasma LDL poor (decrease) activity of cholesterol. Most substances (molecules) act through up-regulation of LDLR on the located Hepatic surface [52]. This proof led researchers to analyze the potential influence of polyphenols on PCSK9. It also helps in reducing the chances probability of inflammation in the body cells. Polyphenols may have a role in anti-inflammatory effects, especially modulation of the activity of enzymes found in arachidonic acid metabolism (phospholipase A2, COX) by radical scavenging activity and this includes arginine metabolism (NOS) [53].

Quercetin

It is the plant of flavonoid onward the flavonoid cluster of polyphenols. It is present in different fruits, leaves, seeds, vegetables, and grains [54]. It's also found red onion and kale are coarse food containing an appreciable amount of Quercetin. In vitro study exposed that Quercetin within its Glycosylated form incubated to HepG -2 cells [55]. The concentration of range 1 to micron deceased PCSK9 mRNA point through 20 - 30 %. It seems

to be authorized that the intracellular PCSK9 point in the culture medium is increased by 20 - 90% and PCSK9 secretion by 30 - 35%. The role of Quercetin is as an antioxidant and anti-inflammatory effect it mostly helps in reducing inflammation, killing cancer cells, and regulating blood sugar it also prevents heart disease [1].

Dose

This takes as a supplement daily routine common dose is 500mg per day.

Eugenol

It is the grated component of (4-allyl-2-methoxyphenyl) essential oil (Syzygium aromatic L). cloves. It is a phenolic nutraceutical with recognized hypocholesterolemia activities. It has a large human body-friendly daily intake of 25 mg/kg as a safe nutrient. Eugenol appears to reduce blood cholesterol levels and prevent lipogenesis in the liver in the animals investigated, implying a protective action against atherosclerosis and fatty liver disease. Molecule docking determines whether hydrophobic interactions are detected within the ligand's eugenol and PCSK9 [56]. The ligands eugenol and PCSK9 are in the mixture. Eugenol was present to kill the PCSK9 aspect in Jurkat cells [57].

Nutrients

The hepatic nuclear transcription representative, active hepatocyte nuclear proxy 1 (HNF1), which is known to ultimately involve pancreatic insulin secretion in the fasted state, decreased the hepatic HNF1 protein aspect, interestingly, the PCSK9 gene had HNF1. Sterol homology element site of the PCSK9 promoter, and reduced amounts of dead PCSK9 protein in the HNF1 protein [58]. It may also bind to cell signaling pathways that use serine-threonine kinase to hinder its mechanistic targeting of rapamycin (mTOR) [59]. Research in mice with dysregulated mTOR difficult 1 activity through the exit from the upstream inhibitory tuberous sclerosis complex resulted in concurrent upregulation of HNF1 and PCSK9 expression in hepatic LDLR protein concentration, a decrease in rapamycin (mTOR complex 1 dysregulated PCSK9 mRNA expression) [60]. The aggression response to decreased PCSK9 expression may therefore be involved in FA catabolism of fenofibrate (a PPAR agonist), which appears to reduce PCSK9 mRNA expression through repressed PCSK9 promoter activity in human hepatocyte [61]. The aggression response to decreased PCSK9 expression may therefore be involved in FA catabolism of fenofibrate (a PPAR agonist), which appears to reduce PCSK9 mRNA expression through repressed PCSK9 promoter activity in human hepatocyte [61]. Hepatic PPAR agonist mRNA expression is spent in the chronic stage (48 h) hamsters: PPAR mRNA agonist treatment does not reduce the PCSK9 protein or mRNA aspect upon engraftment of primary hepatocytes. Collectively, it seems that SREBP2 is an ascending nuclear transcription factor that involves the coordination of PCSK9 in the feed-derived state. However, SREBP1C and HNF1 also induce the PCSK9 aspect to be cleaved in the feed-deprived state [62].

Curcumin

Curcumin and its depreciation. The active constituents responsible for the major medicinal properties of turmeric are curcuminoids. Turmeric is obtained from the rhizome of the long curcuma [63]. Ant It has also been used as a food ingredient in Asian cooking and the practice of Chinese medicine. Similar antioxidant and anti-inflammatory, anti-thrombotic activities for the prevention or treatment of inflammatory processes [64]. It also cures and helps with neurodegenerative disorders and heart disease problems. It has been reported that curcumin restricted lipid accumulation in peritoneal macrophages isolated from LDLRs from rats fed within a high-fat diet [65]. Its curcumin attenuates oxLDL-induced CD36 and scavenger receptor-A (SR-A) aspects. This results in increased oxLDL uptake in PMA-differentiated THP-1 macrophages [66].

Lycopene

Lycopene is the most powerful efficient antioxidant equivalent to the major carotenoid, which has been linked to an increased risk of cardiovascular disease (CVD). Endothelin-1 (ET-1) is an omnipotent vasopressor synthesized through the endothelial cell and displays an important character in the pathophysiology of CVD [67]. The effect of lycopene on Vascular endothelial cells has not been adequately described. This study investigated the execution of lycopene on the ET-1 aspect induced by cyclic stress in human umbilical cord endothelial cells (HUVECs) and identified the pathways involved in this process [68]. Cultured HUVECs were susceptible to cycle stress and stress-induced manipulation of the ET-1 aspect in the lycopene aspect or defect [69]. Oxidative stress, external person. Ordinated kinase (ERK) phosphorylation and therefore oxygenase-1 (HO-1) induced was determined [70]. Lycopene inhibited cyclic stress-induced ET-1 factor and ERK phosphorylation. Furthermore, lycopene reduced cyclic stress-induced p22Fox mRNA levels through the NAD(P)H oxidase response and reactive oxygen splice production [71]. Production, lycopene treatment improves HO-1 factor; Furthermore, HO-1 silencing almost abolished the repressive execution of lycopene on the stress-induced ET-1 aspect [72]. This study reports for an earlier time that lycopene prevents cyclic stress-induced ET-1 secretion by suppression of p22 and induction of HO-1 in HUVECs. These, this study provides effective new insights into the molecular pathways that may improve the proposed beneficial performance of lycopene on the cardiovascular system [69].

Clinically Available Pcsk9 Inhibitors

In 2013, at the American College of Cardiology/American Heart Association cholesterol management center, the first patient with a decreased risk of CVD event was identified [73]. Treating the risk, those who take medication (statin) have been shown to have fewer CVD incidents in the future [74]. Patients with FH (familial hypercholesterolemia) who are statin resistant or have increased LDL-C levels despite being on maximum tolerated statin medication benefit from PCSK9 inhibitors [75]. PCSK9 inhibitors combined with low-dose statin therapy will be most successful in lowering LDL while avoiding statin side effects [75].

In multiple long-term studies1, statins have been proven to reduce cardiovascular mortality by 30% and stroke incidence by 20%. If the LDL-C is less than 70 mg/dl, the patient will be given 75 mg of alirocumab every two weeks, and subsequently 150 mg every two weeks [76]. In addition to statin therapy or in patients who were statin intolerant, the maximum dose of alirocumab in these trials was 150mg every 2 weeks, which decreased plasma LDL-C level by approximately 60%, similar to what was seen in the evolocumab regimen of 300mg every 4 weeks, which decreased plasma LDL-C level by 55-60 percent [75].

Pcsk9 Inhibitors and Adverse Effects

o Nasopharyngitis
o No increased signal for hepatotoxicity
o Injection site reactions are generally mild
o Muscle-related symptoms did not rise, nor did muscle enzymes.
o No increased risk of cognitive impairment
o Muscles toxicity
o Neurocognitive toxicity
o No clinically significant drug-drug interaction

Side Effects

- o Cold and flu-like symptoms
- o Pain or swelling at the injection site
- o Allergic skin reaction
- o Muscle pain
- o Diarrhea
- o Back pain
- o Redness
- o Cough

Conclusion

PCSK9 (Proprotein convertase subtilisin/Kexin type 9) is a proteolytic enzyme that destroys LDL receptors and hence indirectly modulates serum LDL cholesterol. Clinical investigations have revealed the primary involvement of the proprotein convertase subtilisin/Kexin type9 (PCSK9) inhibitor in cholesterol control. The liver produces it, although it's also found in the kidneys and gut. Because of this inhibitor, HMGCo is unable to synthesize cholesterol. Statins activate SREBP-2, a reductase enzyme. In a dose-dependent manner, increasing SREBP-2 levels enhanced LDL-R and PCSK9 gene expression. PCSK9's relevance as a novel molecular target for treating hypercholesterolemia and related cardiovascular illnesses has been demonstrated by the clinical success of two FDA/EMA-approved monoclonal antibodies, alirocumab and evolocumab. However, these monoclonal antibodies, which are the only anti-PCSK9 therapy now available, have a number of disadvantages: exorbitant costs, subcutaneous administration (low compliance and convenience), and long-term immunogenicity. Inclisiran is a short interfering RNA (siRNA) developed to target hepatic PCSK9 mRNA and is a more modern alternative to anti-PCSK9 antibodies. However, there are several disadvantages to this technique, such as a protracted pharmacokinetic profile, parenteral delivery, and an uncertain safety profile. As a result, small-molecule medications that are less expensive and may be used orally are desperately needed. The discovery of natural substances with lipid-lowering activity linked to an anti-PCSK9 inhibitory effect might be a solution to this problem. Many substances with efficient anti-PCSK9 inhibitory activity were discovered in this study, mostly through acting at the transcriptional level, with just a few examples of the autocatalytic secretion phase or PCSK9 interaction with the LDL receptor. Finally, proof must be founded on in vitro mechanisms of action of active ingredients, preclinical investigations in experimental animals, and finally, human safety and efficacy. All of these properties were not always available for the natural compounds mentioned in this review. As a result, the compounds chosen can only be considered a starting point for future oral PCSK9 inhibitor development. Finally, proof must be founded on in vitro mechanisms of action of active ingredients, preclinical investigations in experimental animals, and finally, human safety and efficacy. All of these properties were not always available for the natural compounds mentioned in this review. As a result, the compounds chosen can only be considered a starting point for future oral PCSK9 inhibitor development.

Conflict of Interest

None

Reference

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