ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 15, Issue 12, 2022

Online - 2455-3891
Print - 0974-2441

Review Article

INCLISIRAN (LEQVIO): A FIRST-IN-CLASS SMALL INTERFERING RNA THERAPEUTIC DRUG APPROVED BY FDA FOR TREATING PRIMARY HYPERCHOLESTEROLEMIA OR DYSLIPIDEMIA

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Received: 03 August 2022, Revised and Accepted: 13 September 2022

ABSTRACT

Elevated levels of low density lipoprotein (LCL) – cholesterols are an established risk factor for the development and progression of cardiovascular diseases, particularly atherosclerosis. Statins are the first-line treatment for dyslipidemia which helps in lowering lipid levels (bad cholesterol). Although statin therapy is a conventional and gold-standard method, some patients who have high cardiovascular risk are either intolerant to statins or have persistently elevated LDL levels despite receiving highest dose of statin. Therefore, for such patients, proprotein convertase subtilisin/kexin Type 9 (PCSK9) inhibitor drugs are recommended. This review highlights the importance of PCSK9 inhibitors, focusing mainly on the recently approved (Food and Drug Administration) first-in-class small interfering RNA therapeutic drug called inclisiran (Leqvio) developed by Novartis. The article also summarizes the safety and efficacy of inclisiran based on the ORION clinical trials, benefits, and cost-effectiveness over other previously approved PCSK9 inhibitor drugs.

Keywords: RNA interference therapeutics, Inclisiran, Lipoproteins, Statin intolerance, Cardiovascular diseases.

 DOI: http://dx.doi.org/10.22159/ajpcr.2022v15i12.46054. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

The WHO has recently reported cardiovascular disease (CVD) as one of the top 10 causes of death worldwide [1]. An estimated 17.9 million deaths are reported every year due to CVD [2]. Atherosclerotic CVD (ASCVD), the most predominant form of CVD, is restriction of arteries due to plaque formation caused by the accumulation of fat, calcium, and cholesterol, especially low-density lipoprotein-cholesterol (LDL-C), eventually resulting in organ damage. The major and well-known risk factor for CVD or ASCVD is elevated levels of cholesterol in the blood stream [3-5]. Maintaining optimum lipid profile by employing exercise, dietary/lifestyle modifications, and weight reduction, although beneficial, is not sufficient to reduce the risk of ASCVD. Therefore, drug therapy is often essential for patients at moderate or high risk of ASCVD [6]. LDL, often called as the "bad" cholesterol, in the bloodstream is generally transported to the liver for clearance. LDL particle is a major carrier of cholesterol and is predominantly composed of apolipoprotein B-100 [7]. On binding of LDL particles to the LDL receptors (LDL-R) present on the surface of the clathrin – coated hepatocytes, they are engulfed into endocytic vesicles, where the LDLR undergoes structural changes to release the LDL particles. These LDLRs are then recycled back to the surface to repeat the process, so as to collect more LDL particles from the bloodstream. In general, this recycling process of LDLR can occur about 100 times. The LDL particle is then broken down in the lysosome and cholesterol is released, which, in turn, lowers HMG-CoA reductase activity that plays a pivotal role in the biogenesis of cholesterol and LDLR expression [7,8].

The gold standard treatment for hypercholesterolemia is statins [3]. Apart from being a lipid-lowering drug, it also reduces the risk of CVD. Statins act by inhibiting the key player in cholesterol metabolism, HMG-CoA reductase, thereby blocking its conversion to mevalonic acid, a precursor of cholesterol. This results in the intracellular reduction of cholesterol [9]. While they are very efficient at reducing the plasma LDL-C levels and risk of ACVD, they possess that some critical limitations, for example, intolerance to statin, have been reported in some patients due to their adverse effects [10]. Moreover, statins are reported to lower the risk of ACVD but not completely prevent it. Lately, studies have reported a new player called proprotein convertase subtilisin/kexin Type 9 (PCSK9), which is involved in pathways similar to statins [11].

PCSK9 – A MAJOR THERAPEUTIC TARGET

PCSK9 is a 75 kDa precursor protein synthesized by liver, kidney, and intestine, which forms a heterodimer protein on autocatalytic cleavage in the endoplasmic reticulum. Ever since 2003, several studies have reported PCSK9 as a therapeutic target for hypercholesterolemia and in turn reducing the risk of CVD [12,13]. The primary function of PCSK9 enzyme is regulation of LDLR and therefore removal of LDL particles [14]. PCSK9 functions by binding to the hepatic LDLR and promoting its degradation, which, in turn, causes reduced LDL-C uptake, subsequently increasing its levels in circulation [13,15,16]. Elevated levels of PCSK9 have been reported in metabolic disorders, particularly obesity. Several studies have reported critical roles of PCSK9 in dyslipidemia which warranted the development of efficient and safe inhibitors for PCSK9 [14].

INHIBITION OF PCSK9

With the intent of controlling the affect from PCSK9 enzyme, inhibitors or drugs are the need of the hour. These inhibitors bind to the target PCSK9 protein, thereby arresting them from degrading the LDLR. Therefore, abundant LDLR will be recycled back to the surface of the liver cells for further binding of LDL particles, thus, resulting in the lowering LDL in circulation [17]. Two monoclonal antibodies have been approved by FDA and are in clinical use, namely, evolocumab (Repatha) and alirocumab (Praluent). Evidence indicate that both monoclonal antibodies have shown reduction in plasma LDL levels by >50% when used as monotherapy and 50–75% when combined with statin therapy. They are generally administered subcutaneously once every 2 or 4 weeks. The most preferred administration is combining with statin, since it will boost the benefit. On the other hand, PCSK9 inhibitors are predominantly prescribed for people with familial hypercholesterolemia, risk of CVD (such as stroke/heart attack) or those who have complications/side effects from using statins [8]. The high cost associated with alirocimab and evolocumab has prevented it from

making significant strides in the management of hypercholesterolemia. Small interfering RNA (siRNA) therapeutics are an upcoming area that is widely targeted in several diseases and using this technology to modulate PCSK9 seems to be an attractive option.

INCLISIRAN-SIRNA THERAPEUTICS

RNA interference (RNAi), also known as gene silencing, is a natural process which leads to the negative regulation or inhibition of target gene expression by non-coding RNA molecules such as microRNAs (miRNAs) and siRNAs, using sequence-specific complementarity leading to mRNA degradation. Due to their efficient and specific targeting potential, siRNAs are more preferred for gene knockdown when compared to miRNAs [18]. Inclisiran, generically known as Leqvio, was recently launched by Novartis (initially discovered by The Medicines Company) for the treatment of non-familial and heterozygous familial hypercholesterolemia or mixed dyslipidemia. This is the first and only siRNA drug approved for lowering LDL-C levels that are proven to be effective and provided sustained reduction of LDL [19]. The mechanism of action of inclisiran is different when compared to that of PCSK9 monoclonal antibodies, wherein, inclisiran inhibits PCSK9 by reducing its synthesis in the liver. Meanwhile, other monoclonal antibodies inhibit PCSK9 in the circulation [20]. Inclisiran is a commercially available, chemically modified siRNA, tagged with triantennary N-acetylgalactosamine (at the 3'end of the passenger strand), which makes it to selectively enter into the liver asialoglycoprotein receptor-mediated endocytosis. This siRNA duplex consists of 44 modified nucleotidesincluding one 2-deoxy, 11 2-fluoro, and 32 2-O-methyl modified nucleotides and the termini are modified with phosphorothioates, which renders the siRNA unable to elicit immunogenic reactions. The primary advantage of such modifications is that it provides the siRNA salient features such as organ-specificity (liver), molecular stability, and improved and efficient delivery to liver [20].

CLINICAL TRIALS

Inclisiran was first developed by Alnylam Pharmaceuticals (called as ALN-PCSSC) which later licensed the drug to The Medicines Company [21]. Among the 13 ORION clinical trials investigating inclisiran, nine trials are completed and the remaining four Phase III ORION trials are still ongoing. ORION-3 is an extension trial of inclisiran, where the participants (ASCVD or ASCVD-risk equivalents) were administered with 300 mg of inclisiran or 140 mg of evolocumab for the initial 336 days and then switched to 300 mg of inclisiran from day 360 up to 4 years. The ORION-5 trial comprised of two sequential parts, in that the first part was double-blind placebo-controlled (day 1–90) where the patients were randomized to receive either inclisiran or placebo. Meanwhile, the second part was an open-label follow-up period of inclisiran (18 months) where all the participants who received placebo were switched to inclisiran on day 180 and followed-up thereafter. Inclisiran was found to be effective in treating patients with ASCVD or ASCVD risk equivalents such as familial hypercholesterolemia and elevated LDL/dyslipidemia, according to the pooled *post hoc* analysis of Phase III ORION trials (ORION-9, 10 and 11) [22]. The completed and ongoing clinical trials for inclisiran are listed in Tables 1 and 2.

DOSING

Based on the trial results, Novartis has reported that inclisiran would provide long-term adherence and will be administered as 300 mg dose of injections (subcutaneously), two doses per year, with the second dose administered 3 months after the initial dose. This makes it very convenient for patients due to the lesser number of doses required unlike other PCSK9 drugs that require frequent dosing every 2–4 weeks. It can be administered either as a monotherapy or as a combination therapy along with statins or other lipid-lowering therapies in patients unresponsive even with the maximally tolerated dose of a statin or for those who are statin-intolerant, or for whom a statin is contraindicated [19].

EFFICACY

The approval for Inclisiran was provided based on the ORION Phase III and clinical trials, namely – ORION-9, ORION-10, and ORION-11. The ORION-9 placebo-controlled, double-blind, and randomized study estimated the efficacy, safety, and tolerability of inclisiran sodium salt 300 mg, injected subcutaneously, followed by a subsequent dose after 3 months and thereafter once every 6 months. This trial was conducted at 46 sites in eight different countries and enrolled 482 participants with heterozygous familial hypercholesterolemia and elevated LDL-C. These participants were unresponsive even after administering maximum tolerated dose of other LDL-C-lowering therapies such as statin or ezetimibe. The primary endpoints of the trial are as follows: LDL-C was found to be significantly reduced by 48% at 17 months and 44% from 3 to 18 months after adjusting for placebo and time, respectively The ORION-10 trial was conducted at 145 sites in the U.S, comprising 1561 participants with ASCVD and elevated LDL-C, for whom statin and/or ezetimibe treatment was ineffective. The participants were given 300 mg of inclisiran subcutaneously, followed by a booster dose at 3 months and then once every 6 months. The study revealed a mean placebo-adjusted 52% reduction in LDL-C at 17 months and a time-adjusted reduction by 54% from 3 to 18 months. Similar endpoints were observed in the ORION-11 Phase III trial which consisted of 1617 patients with ASCVD or ASCVD-risk equivalents, elevated LDL-C, and unresponsive to statin and/or ezetimibe treatment. The study which was conducted at 70 sites in seven different countries revealed LDL-C reductions by 50% at 17 months and 49% from 3 to 18 months [23].

SAFETY

For ORION-9, no adverse events were observed. Injection-site reactions were evaluated using pre-specified terms. Vital signs and ECG were recorded on the first and the end of trial visit [23]. The safety population for ORION-10 consisted of 781 patients in the inclisiran group and 778 patients in the placebo group. Meanwhile, for ORION-11, it consisted of 811 patients in inclisiran group and 804 patients in the placebo group. In both trials, two patients in placebo group did not receive placebo and one patient in the placebo group in ORION-11 was mistakenly administered inclisiran. The adverse events in ORION-10 were reported in 574/781 patients (73.5%) among inclisiran group and 582/778 (74.8%) among placebo group. For ORION-11 trial, 671/811 patients (82.7%) in inclisiran group and 655/804 (81.5%) in placebo group reported adverse events. All events reported in both trials were found to be mild-to-moderate and did not differ significantly among the inclisiran and placebo groups. Laboratory investigations including creatine kinase, high-sensitivity C-reactive protein, and platelet count did not falter among the groups. Mild events such as injection-site reactions were found to be higher in patients who received inclisiran when compared to the placebo group. The presence of antidrug antibodies was quite limited in the inclisiran treated patients, with about 2% in ORION-10 and 2.5% in ORION-11 trial and these antibodies were observed predominantly only in the pre-treatment samples. The post-treatment samples exhibited very low titer of antidrug antibodies and were also not as a result of any pharmacological or clinical variables or treatment augmented. The incidence of most of adverse events was similar among inclisiran and placebo groups and the most common adverse events related to the treatment include injection site reactions which were observed in 5.4% and 0.8% of patients receiving inclisiran and placebo, respectively. Some of the serious adverse events including all-cause mortality, cancer-related deaths, new, worsening or recurrent cancers, and cardiovascular events (fatal/non-fatal) accounted to about 20% and 23% of patients in the inclisiran and placebo groups, respectively. This indicated that the incidence of such serious adverse events was low and similar among the two groups [24,25].

REGULATORY STATUS

The new and innovative therapeutics launched by Novartis in partnership with European healthcare systems will help patients with ASCVD and elevated LDL-C to reach their goals. On December

Table 1: List of clinical trials for inclisiran that are completed till date

S. No.	Trial Name	Identifier	Condition/disease	Inclisiran dose	Placebo/ comparative drug	Sponsor	Status
1	ALN-PCS02	NCT01437059	Elevated LDL	Dose levels between 15 µg/kg and 400 µg/kg (intravenous infusion)	Placebo	Alnylam Pharmaceuticals	Phase I
2	ALN-PCSSC	NCT02314442	Hypercholestrolemia		Placebo	Alnylam Pharmaceuticals and The Medicines Company	Phase I
3	ORION-1	NCT02597127	ASCVD; familial hypercholestrolemia	200 mg (ALN-PCSSC)	Placebo	The Medicines Company	Phase II
4	ORION-2	NCT02963311	Homozygous familial hypercholestrolemia	300 mg (ALN-PCSSC)	Standard of care (statin therapy/ other LDL lowering therapies)	The Medicines Company	Phase II
5	ORION-3	NCT03060577	ASCVD; symptomatic atherosclerosis; type-2 diabetes	300	Evolocumab (140 mg)	Novartis	Phase II
6	ORION-5	NCT03851705	Homozygous familial hypercholestrolemia	300 mg	Placebo	Novartis	Phase III
7	ORION-7	NCT03159416	Renal impairment	300 mg	-	The Medicines Company	Phase I
8	ORION-9	NCT03397121	Heterozygous familial hypercholesterolemia; elevated LDL	300 mg	Placebo	The Medicines Company to Novartis	Phase III
9	ORION-10	NCT03399370	ASCVD; elevated LDL	300 mg	Placebo	The Medicines Company	Phase III
10	ORION-11	NCT03400800	ACVD; CVD risk; elevated LDL	300 mg	Placebo	The Medicines Company	Phase III
11	ORION-14	NCT04774003	Elevated LDL	100 mg and 300 mg	Placebo	Novartis	Phase I

LDL: Low density lipoprotein, ASCVD: Atherosclerotic cardiovascular disease

Table 2: List of active and ongoing clinical trials for inclisiran

S. No.	Trial name	Identifier	Condition/disease	Inclisiran dose	Placebo/ comparative drug	Sponsor	Status
1	ORION-4	NCT03705234	ASCVD	300 mg	Placebo	University of Oxford	Phase III
2	ORION-8	NCT03814187	ASCVD; elevated LDL; heterozygous and homozygous familial hypercholestrolemia	300 mg	-	Novartis	Phase III
3	ORION-13	NCT04659863	Homozygous familial hypercholestrolemia	300 mg	Placebo	Novartis	Phase III
4	ORION-16	NCT04652726	Heterozygous familial hypercholestrolemia	300 mg	Placebo	Novartis	Phase III
5	Spirit	NCT04807400	ASCVD; elevated LDL	300 mg	Behavioral support	Novartis	Phase III
6	V-Inception	NCT04873934	ACS	300 mg	-	Novartis	Phase III
7	V-Initiate	NCT04929249	ASCVD	300 mg	-	Novartis	Phase III
8	V-Difference	NCT05192941	Hypercholesterolemia	300 mg inclisiran+ rosuvastatin	Placebo+rosuvastatin	Novartis	Phase IV
9	V-Plaque	NCT05360446	CAD (non-obstructive)	300 mg	Placebo	Novartis	Phase III
10	Victorion-2P	NCT05030428	ASCVD	300 mg	Placebo	Novartis	Phase III
11	Inclisiran	NCT04666298	Hypercholesterolemia; Heterozygous familial hypercholestrolemia	300 mg	Placebo	Novartis	Phase II
12	Inclisiran	NCT04765657	ASCVD; hypercholestrolemia	300 mg	Placebo	Novartis	Phase III

LDL: Low density lipoprotein, ASCVD: Atherosclerotic cardiovascular disease

9, 2020, the European Commission approved inclisiran (Leqvio) for the treatment of adults with primary hypercholesterolemia or mixed dyslipidemia, based on the analysis of the ORION clinical development program [19,26]. The authorization is valid in the 27 EU countries. Meanwhile, in Norway, Iceland, and Liechtenstein, the decisions will be depending on the European Commission's recommendation. In December 2020, the US FDA had declined approval for inclisiran citing unresolved facility inspection-related issues at their third-party facility in Europe which was later addressed by Novartis in early 2021. On December 22, 2021, Novartis announced that inclisiran (Leqvio) was approved by US FDA for lowering LDL levels in patients with ASCVD or ASCVD-risk equivalents.

REAL WORLD EFFECTIVENESS OF THE DRUG

As inclisiran was only recently approved by FDA, there are two ongoing trials investigating the real-world effectiveness of the drug in China (NCT05118230) and Germany (NCT05362903). These trials are multi-centric and will be recruiting patients with primary hypercholesterolemia and mixed dyslipidemia. At present, there are no findings from both trials as they were initiated only by the end of 2021 and early 2022. Individuals with elevated levels of LDL-C with the presence of a previous cardiovascular event (heart attack, unstable angina, or stroke) are intolerant to statins or their LDL levels remain persistently high even after maximal dose of statins are ideal candidates to receive inclisiran.

INCLISIRAN VERSUS OTHER PCSK9 INHIBITOR DRUGS

Evolocumab (Repatha) and alirocumab (Praluent) were the first two PCSK9 inhibitor drugs that were approved by the US FDA for lowering LDL levels and treating ASCVD patients. Both the drugs were approved in 2015 as an adjunct therapy to diet, statins, and other LDL lowering drugs [17,27]. These monoclonal antibodies possess an external approach where they target plasma PCSK9. Meanwhile inclisiran is an siRNA molecule which acts internally by preventing the translation of PCSK9 mRNA to protein through RNAi technology. Hence, instead of inhibiting PCSK9 activity, inclisiran inhibits the production of PCSK9. It is the first siRNA therapeutic drug to obtain US FDA approval for treating elevated LDL levels. The siRNA molecule and the monoclonal antibodies have proven to reduce LDL levels by 50%. The major difference between inclisiran and the other two drugs is dosing regimen. Evolocumab and alirocumab are administered every 2–4 weeks, whereas inclisiran only requires two doses biannually [17,25].

COST-EFFECTIVENESS OF INCLISIRAN

Statins are the conventional method of treatment for lowering the LDL-C levels, preventing the risk of cardiovascular events, and are priced at approximately AU$223/person. However, in patients with persistent elevated LDL levels in spite of maximal dose of statins administration, PCSK9 inhibitors like evolocumab (Repatha) are prescribed. The annual cost of this PCSK9 inhibitor was AU$6334 (according to the 2020 data) and the cost of inclisiran is expected to be equivalent to evolocumab [28]. According to a recent report by Institute for Clinical and Economic Review (ICER), the annual cost of inclisiran is estimated at $5644 with the health benefit price benchmark ranging from $3000 to $6000 per year and approximately $3250 per dose, making the drug cost-effective due to its higher health benefits [25,29].

Limitations

Apart from the several advantages of inclisiran with respect to safety and efficacy, there are certain limitations. Inclisiran has been reported to lower LDL levels better than statins suggesting that the drug will be beneficial for patients who are intolerant to statin therapy. However, trials involving patients with statin intolerance are limited and still ongoing. In addition, the safety, tolerability, and effectiveness of inclisiran have not been explored across different racial and ethnic populations.

CONCLUSION

This review highlights the emergence of a molecule that uses siRNA technology, an advanced form of treatment that is still in the development stage for many diseases. The analysis of the ORION trial reports revealed that inclisiran is a promising siRNA therapeutic drug which will help in the sustained reduction of LDL-C levels in patients with hypercholesterolemia and lower the risk of ASCVD. Furthermore, inclisiran can be used as a combination therapy along with statins or other lipid-lowering drugs for robust reduction of LDL-C levels in patients who are unresponsive to conventional therapies.

AUTHOR CONTRIBUTION

All authors contributed significantly to the article. Data collection, literature review, and the first draft of the manuscript were written by Priyanka Venugopal. The manuscript was reviewed by Karthikeyan Balakrishnan, Melvin George, and Damal Kandadai Sriram. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors did not have any conflict/competing interests.

FUNDING

No funding was received for this article.

ETHICS APPROVAL

Not applicable.

CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable availability of data and material: Not applicable Code availability: Not applicable.

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