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REVIEW

Inclisiran for the Treatment of Cardiovascular Disease: A Short Review on the Emerging Data and Therapeutic Potential

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Constantine E Kosmas[1]
Alba Muñoz Estrella[2]
Andreas Skavdis[3]
Edilberto Peña Genao[4]
Ian Martinez[5]
Eliscer Guzman[1]

[1]Department of Medicine, Division of Cardiology, Montefiore Medical Center, Bronx, NY, USA; [2]Department of Medicine, Mount Sinai St. Luke's-West Hospital, New York, NY, USA; [3]School of Medicine, University of Athens, Athens, Greece; [4]Cardiology Clinic, Cardiology Unlimited, PC, New York, NY, USA; [5]Department of Medicine, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL, USA

Abstract: Proprotein convertase subtilisin kexin 9 (PCSK-9)-targeting therapy has arisen as a new line for the treatment of hyperlipidemia. Inclisiran is a double-stranded small RNA molecule that works by blocking the transcription of PCSK-9, leading to a reduction of PCSK9 levels in the hepatocytes, resulting in an increased expression of low-density lipoprotein (LDL) receptors in the hepatocyte membrane and, as a consequence, it reduces the circulating levels of LDL cholesterol (LDL-C). Compared to the other LDL-C-lowering medications, such as statins, ezetimibe and PCSK-9 inhibitors, inclisiran proposes an infrequent dosing of twice a year, while simultaneously providing a significant reduction of LDL-C. Its prolonged effect offers an advantage against medication non-compliance, which is one of the main causes for not achieving LDL-C goals with standard therapy. Inclisiran has also proven to have a relatively safe profile with adverse effects occurring in similar frequency as with placebo. This review aims to present and discuss the current clinical and scientific data pertaining to the role of inclisiran in the management of hypercholesterolemia and treatment of cardiovascular disease (CVD).

Keywords: proprotein convertase subtilisin kexin 9, PCSK-9, inclisiran, hypercholesterolemia, cardiovascular disease, CVD

Introduction

Cardiovascular disease (CVD) represents the leading cause of death worldwide.[1] Lipid-lowering therapy is one of the mainstay therapies for cardiovascular risk reduction. Clinical studies have shown a proportional relationship between reduction of low-density lipoprotein cholesterol (LDL-C) and reduction of cardiovascular risk.[2] Per guidelines,[3,4] statins represent the first line of treatment for LDL-C lowering, with second-line medications including ezetimibe and PCSK9 inhibitors. Failure to achieve optimal levels of LDL-C may be of multifactorial etiology; however, in the majority of the cases, it has been related to low adherence.[5–7] Factors leading to low adherence may include dosing frequency, number and cost of the medications and intolerability to adverse effects.[5,6] Statins and ezetimibe require daily dosing, while PCSK9 inhibitors are administered every 2 or 4 weeks. Here, it has to be stressed that poor adherence to statins is associated with significant increases in total mortality, as well as cardiovascular morbidity and mortality.[8–11]

In February 2003, the discovery of PCSK9, a serine protease that binds to and targets the LDL receptors for lysosomal degradation, opened new research avenues

Correspondence: Constantine E Kosmas
Tel +1-646-734-7969
Email cekosmas1@gmail.com

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into novel therapeutic options to decrease blood levels of LDL-C.[12] Monoclonal antibodies against PCSK9 have been already approved by the FDA for the treatment of persistent hypercholesterolemia despite maximal therapy with statins. In addition, other lipid-modifying molecules targeting PCSK9, such as small interfering RNA (siRNA) molecules, small molecule inhibitors that disrupt the processing of PCSK9, as well as adnectins, which block the binding of PCSK9 to the LDL receptor, are currently under ongoing investigations.[13] Inclisiran, a long-acting double-stranded small RNA that halts the transcription of PCSK9, works intracellularly by decreasing the generation of PCSK9 in the hepatocytes, thus leading to an increased number of LDL receptors in the hepatocyte membranes, which results in decreased levels of LDL-C in the blood.[14]

This review aims to present and discuss the current clinical and scientific data pertaining to the role of inclisiran in the treatment of CVD.

Inclisiran: Structure and Function

Inclisiran is an siRNA molecule, which targets the hepatic production of PCSK9.[14] siRNAs interfere with the expression of specific genes with complementary nucleotide sequences by selectively and catalytically silencing the translation of their complementary target messenger RNAs (mRNAs) in a sequence-specific manner via intracellular binding to effector RNA-induced silencing complexes.[14,15]

Thus, as it was mentioned earlier, inclisiran, by halting the transcription of PCSK9, increases the numbers of LDL receptors in the hepatocyte membranes, thus resulting in decreased levels of LDL-C in the blood.

This was initially tested in a Phase 1 trial in healthy volunteers with an LDL-C level ≥100 mg/dl. In this study, inclisiran was administered subcutaneously in single-dose or multiple-dose regimens. It was shown that doses of 300 mg or more (in single or multiple doses) significantly reduced LDL-C and PCSK9 levels for at least 6 months. In addition, all multiple-dose regimens of inclisiran reduced LDL-C and PCSK9 levels by up to a least-squares mean reduction of 59.7% and 83.8%, respectively, from baseline to day 84. There were no serious adverse events observed with inclisiran in this phase 1 trial, the most common adverse events being cough, musculoskeletal pain, nasopharyngitis, headache, back pain, and diarrhea.[16]

Inclisiran in Cardiovascular Disease

Based on the above, the ORION program was initiated, which is a composite of different worldwide trials, with the purpose of evaluating the efficacy of inclisiran in a variety of subjects, including individuals with high risk for atherosclerotic cardiovascular disease (ASCVD), established ASCVD, as well as patients with familial hypercholesterolemia (FH). The ORION program also focuses on the safety profile of the drug in the short- and long-term period, as well as on its effect on cardiovascular risk.

The ORION-1 Phase 2, multicenter, double-blind, placebo-controlled trial included 501 individuals at high risk for CVD who had elevated LDL-C levels. The mean age of the participants was 63 years, 65% were men, 69% had established ASCVD, and 6% had FH. Overall, 73% of the participants were receiving statin therapy. The participants were randomized to receive a single dose of placebo or 200, 300, or 500 mg of inclisiran or two doses (at days 1 and 90) of placebo or 100, 200, or 300 mg of inclisiran. The study assessed the percentage change of LDL-C with different doses of inclisiran at 180 days. At day 180, the least-squares mean reductions in LDL-C levels, as compared with placebo, were 27.9% to 41.9% after a single dose of inclisiran and 35.5% to 52.6% after two doses ($p < 0.001$ for all comparisons vs placebo). The greatest reduction was observed with the two-dose regimen of 300 mg of inclisiran, which decreased LDL-C, PCSK9, and high sensitivity C-reactive protein (hsCRP) by 52.6% ($p <0.001$), 69.1% ($p < 0.001$), and 16.7% ($p < 0.05$), respectively.[14] Serious adverse events occurred in 11% of the patients who received inclisiran and in 8% of the patients who received placebo. Injection-site reactions occurred in 4% of patients who received one dose and in 7% of patients who received two doses of inclisiran.[14,15] The most common adverse events (occurring in >2% of patients) were myalgia, headache, fatigue, nasopharyngitis, back pain, hypertension, diarrhea, and dizziness. The incidences of these adverse events were not significantly different between groups receiving inclisiran and those receiving placebo.[15] Furthermore, in a study which evaluated the efficacy and safety of inclisiran in the ORION-1 trial by diabetes status, it was shown that inclisiran treatment was associated with marked reductions in mean LDL-C levels from day 14 until day 210 regardless of baseline diabetes status, which indicates that inclisiran may be a viable therapeutic option for lowering LDL-C in the presence and absence of diabetes. Importantly, there were no clinically meaningful changes in glycated hemoglobin (HbA1c) 180 days after treatment initiation, and this persisted over the course of the study.[17] In conclusion,

in ORION-1 trial, inclisiran produced significant reductions in LDL-C and PCSK9 levels with a safe side effect profile.

In the one-year follow-up of the ORION-1 trial, it was shown that one dose of inclisiran on day 1 and two doses of inclisiran on days 1 and 90 lowered time-averaged LDL-C levels over 1 year by 29.5% to 38.7% and by 29.9% to 46.4%, respectively, in a dose-dependent manner. A 50% LDL-C reduction was maintained for at least 6 months after 2 doses of 300 mg of inclisiran on days 1 and 90. In addition, this 2-dose 300-mg regimen of inclisiran produced the greatest mean reduction in LDL-C over 1 year. Incidence of adverse events was similar through to 1 year. Thus, inclisiran emerged as a novel promising therapeutic option for the management of hypercholesterolemia with the convenience of a twice-a-year dosing regimen.[18]

The ORION-3 trial, a phase 2 open-label extension study of the ORION-1 trial, achieved its primary completion in August 2018. At day 210 of ORION-3 trial, LDL-C was reduced by a mean of 51% and PCSK9 levels were decreased by a mean of 77%. A consistent long-term effect of the 300 mg dose of inclisiran on LDL-C lowering was observed in ORION-3 over approximately 22 months and the time-averaged lowering of LDL-C was approximately 60 mg/dL. During at least 3 years of follow-up, there were no changes in the overall safety profile and no laboratory test abnormalities associated with the treatment, including liver and kidney function tests.[19] The ORION-3 trial is expected to be completed in 2022.

The ORION-10 and the ORION-11 were two randomized, double-blind, placebo-controlled, parallel-group, Phase 3 trials. The objectives of the ORION-10 and ORION-11 trials were to assess the efficacy, safety, and adverse-event profile of inclisiran over a period of 18 months. The ORION-10 trial was conducted in the United States and included adults with ASCVD with an LDL-C level ≥70 mg/dl. The ORION-11 trial was conducted in Europe and South Africa and included adults with ASCVD with an LDL-C level ≥70 mg/dl or an ASCVD risk equivalent (type 2 diabetes, familial hypercholesterolemia, or a 10-year risk of a cardiovascular event of ≥20% as assessed by the Framingham Risk Score for CVD or equivalent) with an LDL-C level ≥100 mg/dl. A total of 1561 and 1617 patients underwent randomization in the ORION-10 and ORION-11 trials, respectively. The use of stable doses of statin therapy was 89.2% in the ORION-10 trial and 94.7% in the ORION-11 trial. Patients were randomly assigned to receive either inclisiran (284 mg) or placebo, administered by subcutaneous injection on day 1, day 90, and every 6 months thereafter over a period of 540 days. The mean LDL-C levels at baseline in ORION-10 and ORION-11 were 104.7 mg/dl and 105.5 mg/dl, respectively. At day 510, inclisiran reduced LDL-C levels by 52.3% in the ORION-10 trial and by 49.9% in the ORION-11 trial with corresponding time-adjusted reductions of 53.8% and 49.2%, respectively ($p < 0.001$ for all comparisons vs placebo). Furthermore, at day 510, inclisiran reduced the levels of PCSK9 by 69.8% in the ORION-10 trial and by 63.6% in the ORION-11 trial with corresponding between-group differences (vs placebo) of 83.3% and 79.3%, respectively ($p < 0.001$ for all comparisons vs placebo). In addition, in the ORION-10 trial, inclisiran decreased total cholesterol (TC), apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), triglycerides (TG), and lipoprotein (a) [Lp(a)] by 33.1%, 43.1%, 47.4%, 12.6%, and 25.6%, respectively, as compared with placebo, and increased high-density lipoprotein cholesterol (HDL-C) by 5.1%, as compared with placebo. Similarly, in the ORION-11 trial, inclisiran decreased TC, ApoB, non-HDL-C, TG, and Lp(a) by 29.8%, 38.9%, 43.3%, 7.0%, and 18.6%, respectively, as compared with placebo, and increased HDL-C by 6.1%, as compared with placebo. Adverse events were in general similar in the inclisiran and placebo groups in each trial, although injection-site reactions were more frequent with inclisiran than with placebo (2.6% vs 0.9% in the ORION-10 trial and 4.7% vs 0.5% in the ORION-11 trial). These reactions were in general mild and not persistent. Importantly, there were no significant changes in the incidence of diabetes mellitus between inclisiran and placebo groups in both trials.[20]

ORION-9 was a double-blind, randomized, placebo-controlled, phase 3 trial, which was conducted to assess the use of inclisiran in a large cohort of adult patients with heterozygous familial hypercholesterolemia (HeFH) who had been treated with a maximally tolerated dose of statin therapy. A total of 482 adults with HeFH were randomized to receive subcutaneous injections of 300 mg of inclisiran sodium (equivalent to 284 mg of inclisiran) or matching placebo on days 1, 90, 270, and 450. The mean LDL-C level at baseline was 153 mg/dl. At day 510, the mean percent change in the LDL-C level was a reduction of 39.7% in the inclisiran group versus an increase of 8.2% in the placebo group, for a between-group difference of −47.9 percentage points ($p < 0.001$). In addition, at day 510, the percent

Table 1 Summary of Inclisiran Clinical Trials

Trial	Design	Participants	Intervention	Results
Fitzgerald K et al[16]	Phase 1, randomized, single-blind, placebo-controlled study.	Men and women (18 to 60 years of age in the single-dose phase and 18 to 75 years of age in the multiple-dose phase) who had a serum LDL-C level of at least 100 mg/dl and a fasting triglyceride level of less than 400 mg/dl (4.5 mmol/L).	Single-ascending-dose phase of inclisiran or placebo: at a dose of 25, 100, 300, 500, or 800 mg. Multiple-ascending-dose phase of inclisiran or placebo: 125 mg weekly for four doses, 250 mg every other week for two doses, or 300 or 500 mg monthly for two doses, with or without concurrent statin therapy.	Single-dose phase: showed reduction of LDL-C up to 50.6% from baseline with inclisiran dose of 100 mg or more. Also, reduction in PCSK9 level up to 74.5% from baseline with inclisiran dose of 300 mg or more. The reductions were maintained at day 180 for doses 300 mg or more. Multiple-dose phase: showed reduction of LDL-C up to 59.7% from baseline to day 84. Also, reduction in PCSK9 level up to 83.8% from baseline. No serious adverse events observed with inclisiran.
ORION-1[15]	Phase 2, multicenter, double-blind, placebo-controlled study.	501 men and women, 18 years of age or older with LDL level at screening higher than 70 mg/dl (for patients with a history of atherosclerotic cardiovascular disease) or higher than 100 mg/dl (for patients without a history of atherosclerotic cardiovascular disease).	One dose (200, 300, or 500 mg on day 1) or 2 doses (100, 200, or 300 mg on days 1 and 90) of inclisiran sodium or placebo.	At day 180, the mean reductions in LDL-C levels were 27.9% to 41.9% after a single dose of inclisiran and 35.5% to 52.6% after two doses ($P<0.001$ for all comparisons vs placebo). The two-dose 300-mg inclisiran regimen produced the greatest reduction in LDL-C levels: 48% of the patients who received the regimen had an LDL-C level below 50 mg/dl (1.3 mmol/L) at day 180. At day 240, PCSK9 and LDL-C levels remained significantly lower than at baseline in association with all inclisiran regimens. Serious adverse events occurred in 11% of the patients who received inclisiran and in 8% of the patients who received placebo.
ORION-1 1-year follow-up[18]	Phase 2, multicenter, double-blind, placebo-controlled study.	501 men and women, 18 years of age or older with LDL-C level at screening higher than 70 mg/dl (for patients with a history of atherosclerotic cardiovascular disease) or higher than 100 mg/dl (for patients without a history of atherosclerotic cardiovascular disease).	One dose (200, 300, or 500 mg on day 1) or 2 doses (100, 200, or 300 mg on days 1 and 90) of inclisiran sodium or placebo.	One dose of inclisiran on day 1 and two doses of inclisiran on days 1 and 90 lowered time-averaged LDL-C levels over 1 year by 29.5% to 38.7% and by 29.9% to 46.4%, respectively, in a dose-dependent manner. A 50% LDL-C reduction was maintained for at least 6 months after 2 doses of 300 mg of inclisiran on days 1 and 90, producing the greatest mean reduction in LDL-C over 1 year. Incidence of adverse events was similar through to 1 year.
ORION-3[19]	Phase 2, open-label, long-term extension study of the ORION-1 study.	490 participants who completed the ORION-1 study and were previously treated with any dose of inclisiran.	Patients were treated with 300 mg inclisiran sodium twice per year (n = 290) or 140 mg evolocumab (Repatha, Amgen) every 2 weeks for 1 year followed by 300 mg inclisiran sodium on day 360, day 450 and every 6 months after that (n = 92)	At day 210 of ORION-3 trial, LDL-C was reduced by a mean of 51% and PCSK9 levels were decreased by a mean of 77%. A consistent long-term effect of the 300 mg dose of inclisiran on LDL-C lowering was observed in ORION-3 over ~22 months and the time-averaged lowering of LDL-C was ~60 mg/dL. During at least 3 years of follow-up, there were no changes in the overall safety profile and no laboratory test abnormalities associated with the treatment.

(*Continued*)

Table 1 (Continued).

Trial	Design	Participants	Intervention	Results
ORION-10[20]	Phase 3, randomized, double-blind, placebo-controlled, parallel group study.	1561 adults in the United States with atherosclerotic cardiovascular disease and LDL-C levels at screening 70 mg/dL or higher.	Patients were randomly assigned in a 1:1 ratio to receive either inclisiran (284 mg) or placebo, administered by subcutaneous injection on day 1, day 90, and every 6 months thereafter over a period of 540 days.	At day 510, inclisiran reduced LDL-C levels by 52.3% with corresponding time-adjusted reductions of 53.8% (P<0.001 for all comparisons vs placebo). Adverse events were generally similar in the inclisiran and placebo groups, although injection-site adverse events were more frequent with inclisiran than with placebo (2.6% vs 0.9%).
ORION-11[20]	Phase 3, randomized, double-blind, placebo-controlled, parallel group study.	1617 adults in Europe and South Africa with atherosclerotic cardiovascular disease or an atherosclerotic cardiovascular disease risk equivalent and LDL-C levels at screening 70mg/dl and 100 mg/dL or higher, respectively.	Patients were randomly assigned in a 1:1 ratio to receive either inclisiran (284 mg) or placebo, administered by subcutaneous injection on day 1, day 90, and every 6 months thereafter over a period of 540 days.	At day 510, inclisiran reduced LDL cholesterol levels by 49.9% with corresponding time-adjusted reductions of 49.2% (P<0.001 for all comparisons vs placebo). Adverse events were generally similar in the inclisiran and placebo groups, although injection-site adverse events were more frequent with inclisiran than with placebo (4.7% vs 0.5%).
ORION-9[21]	Phase 3, double-blind, randomized, placebo-controlled study.	482 adults with diagnosis of heterozygous familial hypercholesterolemia with LDL of at least 100 mg/dL, despite receiving a maximally accepted dose of statin therapy with or without ezetimibe.	The patients were assigned in a 1:1 ratio to receive inclisiran sodium (at a dose of 300 mg) or matching placebo, which were both administered as a 1.5-mL subcutaneous injection on days 1, 90, 270, and 450.	At day 510, the percent change in the LDL-C level was a reduction of 39.7% in the inclisiran group and an increase of 8.2% in the placebo group, for a between-group difference of −47.9 percentage points. Adverse events and serious adverse events were similar in the two groups.
ORION-5[22] (Ongoing)	Phase 3, double-blind, placebo-controlled, open-label, multicenter study.	45 adults with diagnosis of homozygous familial hypercholesterolemia with LDL of at least 100 mg/dL, despite receiving a maximally accepted dose of statin therapy with or without ezetimibe.	Part one: patients will receive two 300-mg doses of inclisiran sodium or placebo at day one and day 90 (three months). Part two: patients will receive a 300-mg dose of inclisiran sodium on day 270 (nine months), day 450 (15 months) and day 630 (21 months).	Estimated study completion date: September 2021.
ORION-4[24] (Ongoing)	Phase 3, double-blind, randomized, placebo-controlled study.	15,000 participants aged 55 years or older with pre-existing ASCVD.	Patients will receive inclisiran 300 mg or placebo on the day of randomization, at 3 months and then every 6 months.	Estimated primary completion date: December 2024. Estimated study completion date: December 2049.

change in the PCSK9 level was a reduction of 60.7% in the inclisiran group versus an increase of 17.7% in the placebo group, for a between-group difference of −78.4 percentage points ($p < 0.001$). The time-averaged percent change in the LDL-C level between day 90 and day 540 was a reduction of 38.1% in the inclisiran group versus an increase of 6.2% in the placebo group, for a between-group difference of −44.3 percentage points ($p < 0.001$). There were marked reductions in LDL-C levels in all genotypes of FH. The incidence of adverse events and serious adverse events was similar between the two groups.[21]

On the other hand, ORION-5 is an ongoing phase 3, double-blind, placebo-controlled, open-label, multicenter study [ClinicalTrials.gov Identifier: NCT03851705], which

will evaluate the safety, tolerability, and efficacy of inclisiran in subjects with homozygous familial hypercholesterolemia (HoFH).[22]

In a meta-analysis, which assessed data from 3 randomized clinical trials comprising 3,660 patients, it was shown that inclisiran, as compared with placebo, decreased LDL-C levels by 51% ($p < 0.001$). It also significantly decreased TC by 37%, ApoB by 41%, and non-HDL-C by 45% (all $p < 0.001$). Most importantly, in this meta-analysis, inclisiran was also associated with a 24% lower major adverse cardiovascular events rate. No differences were found in adverse events, abnormalities in liver function tests, or creatine kinase levels between the inclisiran and placebo groups. However, mild injection site reactions occurred more frequently in the inclisiran group.[23]

Based on the current available data, as described above, inclisiran appears to have a consistent long-term effect on LDL-C lowering and a favorable side effect profile. However, further long-term outcome trials are required to definitely establish the beneficial role of inclisiran in the reduction of cardiovascular risk.

To that effect, ORION-4 is an ongoing double-blind, randomized, placebo-controlled, phase 3 trial [ClinicalTrials.gov Identifier: NCT03705234], which will assess the effects of inclisiran on clinical outcomes among patients with ASCVD. The study started in October 2018 and its primary completion date is estimated to be in December 2024. The study is intended to be conducted at approximately 180 clinical sites in the UK and the USA. Approximately 15,000 participants aged 55 years or older with pre-existing ASCVD will be randomized between inclisiran sodium 300 mg and matching placebo (given by subcutaneous injection on the day of randomization, at 3 months and then every 6 months) in a 1:1 ratio for a planned median follow-up duration of about 5 years. The primary outcome of ORION-4 is defined as time to first occurrence of coronary heart disease (CHD) death, myocardial infarction (MI), fatal or non-fatal ischemic stroke, or urgent coronary revascularization procedure. The secondary outcomes include the number of participants with a composite of CHD death or MI and the number of participants with cardiovascular death.[24] The results of the ORION-4 trial will provide valuable information regarding the benefit of inclisiran in reducing major adverse cardiovascular events and improving outcomes in patients with ASCVD.

A summary of the above-mentioned clinical trials with inclisiran is shown in Table 1.

Conclusions and Future Directions

In conclusion, inclisiran has thus far demonstrated to provide significant long-term reductions in the levels of LDL-C in blood associated with notable decreases in PCSK9 levels. Furthermore, inclisiran appears to have a generally favorable side effect profile. The convenience of a twice-a-year dosing regimen offers an advantage against medication non-compliance, which is one of the main causes for not achieving LDL-C goals with standard therapy. Thus, inclisiran has emerged as a novel promising therapeutic option for the management of hypercholesterolemia. As it was mentioned above, the results of the ORION-4 trial are expected to shed more light regarding the effect of inclisiran in the reduction of major adverse cardiovascular events and the improvement of outcomes in patients with ASCVD.

Disclosure

Dr. Kosmas and Dr. Guzman have served on the Dyslipidemia Speaker Bureau of Amgen, Inc. Constantine E Kosmas and Eliscer Guzman report personal fees from Amgen, outside the submitted work. The authors report no other conflicts of interest in this work.

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