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Update on Inclisiran for Treatment of Hypercholesterolemia

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ABSTRACT

Background: Inclisiran is a drug under development that inhibits the hepatic synthesis of proprotein convertase subtilistin/Kexin type 9 (PCSK9) leading to reduction in plasma levels of low-density lipoprotein-cholesterol (LDL-C).

Methods: Review of pertinent English literature by Pubmed search until June 12, 2020. Search terms are lipids, PCSK9, LDL-C, inclisiran, safety, efficacy. Studies included are randomized trials, meta-analyses, and review articles.

Results: Inclisiran is administered by subcutaneous (SC) injection at day 1, day 90, then every 6 months. In patients with atherosclerotic cardiovascular (CV) disease and those with heterozygous familial hypercholesterolemia receiving maximally tolerated statins, the placebo-adjusted percent reduction in LDL-C levels was 48% to 52% after 6 months. Inclisiran also lowers other atherogenic lipoproteins such non-high-density lipoprotein-cholesterol (non-HDL-C) by 43 to 47%, apoprotein B (apo B) 39% to 43%, lipoprotein(a) by 18-25% compared with placebo. Efficacy of inclisiran in lowering LDL-C levels was similar in patients with and without diabetes, and patients with normal renal function compared with those with severe renal impairment. Inclisiran is overall well-tolerated. Most common adverse effects are injection site reactions.

Conclusions: Inclisiran is an effective and long-acting drug for lowering LDL-C levels. Studies are underway to evaluate effects of inclisiran on CV events and mortality.

Keywords: Inclisiran, PCSK9, LDL-C, efficacy, safety, diabetes

Introduction

PCSK9 is a major determinant of LDL-C plasma levels. Synthesized in the endoplasmic reticulum of hepatocytes, PCSK9 promotes the degradation of LDL receptors by binding to the LDL receptor on the surface of hepatocytes. After such binding, the PCSK9-LDL-C receptor complex is internalized into the lysosomes inside the hepatocytes where it undergoes degradation [1]. Therefore, PCSK9 decreases the availability of LDL-C receptors leading to elevation of circulating levels of LDL-C [1]. Hence, inhibition of PCSK9 is expected to lower plasma levels of LDL-C by increasing number of LDL-C receptors. A recently discovered approach of inhibition of PCSK9 can take place by means of small interfering RNA (si RNA) molecules [2]. The receptor of inclisirian, called asialoglycoprotein receptor (AGPRS), is located and expressed exclusively on liver cells [3]. Inclisiran is conjugated to the triantennary N-acetylgalactosamine (GalNAc). Thus, inclisiran is delivered to the hepatocytes by interaction of GalNAc with the AGPRS [3]. The hepatic uptake of inclisiran is rapid. In fact, inclisiran is no longer detectable in plasma within 24-48 h after dosing [4]. After uptake by hepatic cells, si RNA inhibits synthesis of PCSK9 by cleaving the messenger RNA (mRNA) that specifically encodes PCSK9 in hepatocytes [1-3]. Inclisiran is currently under evaluation in clinical development program formed of a series of clinical trials called ORION-1 through ORION-12 [5].

Pharmacokinetics and Pharmacodynamics

Peak serum plasma levels occur approximately 4 hours after inclisiran CS administration [4]. Inclisiran half-life is 5-10 h, and the drug is excreted through the kidneys [4]. The large magnitude of effects of inclisiran on circulating lipoproteins is already apparent 14 days after administration of the 300 mg-dose and reach near maximal effect 90 days after dosing [6]. Duration of action of inclisiran is 6 months after 2 consecutive dosing of 300 mg at day 1 and day 90 [6]. The second dose at day 90 offers an additional reduction of in LDL-C levels of approximately 19% (from 36.6% versus 46.4%; P=0.002) [6].

Clinical Trials

Patients with Cardiovascular Disease

Inclisiran was evaluated in 2 phase 3 randomized, double-blind, placebo-controlled trials called ORION-10 (n=1561) and ORION-11 (n=1617) in patients with atherosclerotic CV disease who had elevated LDL-C levels despite receiving statin at maximum tolerated dose [7]. Patients' mean age was 66 years, 70% men, and 92% Whites. Mean baseline LDL-C concentrations were 105 mg/dl [7]. Subjects were randomized to either inclisiran 284 mg (equivalent to inclisiran sodium 300 mg) or placebo by

SC administration (1.5 ml) on day 1, day 90, then every 6 months over a period of 540 days (18 months) [7]. Results were overall similar in the 2 trials. Thus, in the ORION-10 trial, the percentage change in LDL-C levels at day 510 was 1.0% in the placebo group and -51.3% in the inclisiran group, resulting in a between-group difference of -52.3% (95% CI, -55.7 to -48.8; P <0.001) [7]. In the Orion-11 trial, corresponding between-group difference was -49.9%, 95% CI -53.1 to -46.6; P <0.001) [7].

Patients with Heterozygous Familial Hypercholesterolemia

In a phase 3, double-blind trial, 482 adults (mean age 56, 47% men) with heterozygous familial hypercholesterolemia were randomized to subcutaneous inclisiran 284 mg or matching placebo on days 1, 90, 270, and 450 [8]. Ninety per cent of patients were on statin and 53% on ezetimibe [8]. Mean baseline LDL-C plasma levels were 153 mg/dl. At day 510, the percent change in plasma LDL-C concentrations 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% (95% CI, -53.5% to -42.3%; P<0.001) [8].

Patients with Homozygous Familial Hypercholesterolemia

In a pilot trial (ORION-2), inclisiran sodium 300 mg given on day 1 and 90 was evaluated in 4 patients with homozygous familial hypercholesterolemia with baseline LDL-C levels ranging from 189 to 614 mg/dl [9]. Three of the 4 patients had moderate reduction of LDL-C levels ranging from -17.5% to -37.0 % at day 180 [9]. The remaining patient did not have any reduction in LDL-C levels although his/her plasma PCSK9 were significantly reduced by inclisiran [9]. These results suggest that efficacy of inclisiran may be diminished in patients with homozygous familial hypercholesterolemia.

Effects of Inclisiran on other Lipoproteins

Inclisiran lowers plasma levels of other atherogenic lipoproteins such as non-HDL-C, apo B, and triglycerides (table 1). It also significantly lower levels of very low lipoprotein density-cholesterol (VLDL-C) by 16% versus placebo [10]. Inclisiran modestly raises serum levels of HDL-C by 5-6% versus placebo (table 1) [7]. The response of inclisiran is generally homogenous with little variation among patients. However, there was larger inter-individual variation with respect to reductions of levels of VLDL-C, triglycerides and lipoprotein (a) [10].

Effects of Inclisiran in Patients with Diabetes

In the ORION-10 and ORION-11 trials, 40% of patients had diabetes at baseline [7]. The LDL-C lowering effect of inclisiran did not differ between patients with or without diabetes [7]. Moreover, available data suggest that there was no increase in risk in development of new onset diabetes [7, 13].

Use of Inclisiran in Patients with Renal Impairment

Single dose of 300-mg inclisiran sodium was evaluated in a limited number of subjects (n=31) with varying degrees of renal impairment ranging from normal renal function to severe renal impairment (creatinine clearance 15-30 ml/min) [4]. Patients with end-stage renal disease on hemodialysis were excluded [4]. Inclisiran exposure as reflected by maximum plasma concentrations (Cmax), and area under the curve (AUC from 0 to infinity) significantly increases as renal function worsens [4]. In addition, renal clearance was reduced with greater degree of renal impairment [4]. However, inclisiran was not detected in plasma 48 h after administration in all patients irrespective of renal function, and no change in drug half-life was noted [4]. No adverse effects were recorded. The authors concluded that inclisiran can be safely used without need of dose change in patients with mild to severe renal impairment [4]. However, before concluding that inclisiran use in kidney disease, more data are needed using multiple drug doses and greater number of patients.

In the ORION-10 and ORION-11 trials, 40% (1270 of 3178) of patients had moderate degree of renal impairment at baseline defined as estimated glomerular filtration rate (eGFR) 30 to 59 ml/min/1,73 m^2 [7]. Reduction of LDL-C levels by inclisiran was similar irrespective of renal function [7].

Safety of Inclisiran

Available data from the largest 3 clinical trials lasting up to suggest that inclisiran is well tolerated among 1833 patients exposed to the drug [7, 8]. Proportions of patients who discontinued inclisiran due to adverse effects were marginally higher than placebo, 2.4% and 2.2% in ORION-10, and 2.8% and 2.2% in ORION-11, respectively [7]. The most common adverse effect of inclisiran is transient injection site reaction. These reactions were described as mild to moderate and occurred in 2.6% to 4.7% with inclisiran use compared with 0.5% to 0.9% with placebo [7]. Safety concerns when using RNA-targeted therapy, such as inclisiran, were also addressed, specifically thrombocytopenia, activation of the inflammatory and immune systems [14]. In one safety analysis of patients receiving different doses of inclisiran over 180 days, no adverse effects were shown related to blood components, particularly thrombocytopenia [14]. In addition, no effects were observed on the inflammatory markers: tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) [14]. Regarding immunogenicity, no relevant antibodies to inclisiram were induced [14].

Effects of Inclisiran on Cardiovascular Events

In ORION-10, nonadjudicated prespecified exploratory analysis of CV end points showed that CV events occurred 58 patients (7.4%) in the inclisiran group and 79 (10.2%) in the placebo group had CV event (risk ratio RR 0.7, 95% CI 0.5-1) [7]. Likewise, in ORION-11, 63 patients (7.8%) in the inclisran group versus 83 patients (10.3%) in the placebo group had CV event (RR = 0.8, 95% CI 0.6-1.0) [7]. P values were not reported in previous 2 comparisons [7]. Meanwhile, a meta-analysis of 4 randomized controlled trials (including ORION-10 and ORION-11) did not show any significant difference in proportions of patients randomized to inclisiran compared with placebo in CV mortality, 0.9% and 0.8%, respectively, RR 1.11 (95% CI, 0.56-2.21, P=0.77) [15]. Likewise, meta-analysis from 3 randomized trials showed no significant effect of inclisiran on myocardial infarction, 1.8% vs 2.3% with placebo, RR= 0.85, 95% CI, 0.37-1.95, P= 0.7), and fatal plus non-fatal stroke, 0.7% vs 0.8% with placebo, RR=0.69, 95% CI 0.11-4.21, P=0.69 [15].

However, CV events were not the primary outcome of these trials and were not adjudicated [7]. Moreover, number of events was too small to draw a valid conclusion, ranging from 13 to 41 events among the groups [7, 15]. In addition, duration of follow-up was short ranging from 210 to 540 days (mean 458 days) [15].

Inclisiran Versus PCSK9 Monoclonal Antibodies

Evolocumab and alirocumab are already approved 2 monoclonal antibodies that bind and inactivate PCSK9 [11, 12]. Although they have the same target as inclisiran, i.e PCSK9, there are many differences between inclisiran and these 2 drugs summarized in table 1.

Table 1: Inclisiran Versus PCSK9 Monoclonal Antibodies

	Inclisiran [7]	PCSK9 monoclonal antibodies [11,12]
Mechanism of action	Inhibition of synthesis of PCSK9 by silencing PCSK9 mRNA	Direct binding and inhibition of PCSK9
Members	Inclisiran (under development)	Evolocumab (Repatha), alirocumab (Praluent) both drugs are already approved.
Frequency of subcutaneous administration	2 initial injections at day 1 and 90 followed by an injection every 6 months	Every 2 weeks or 1 month
*Effects on LDL-C	-48% to -52%	-55%
* Effects on non-HDL-C	-43.3% to -47%	-50% (both)
*Effects on HDL-C	to +5.1% to + 6.1%	+ 6% to +12%
*Effects on triglycerides	-7.0% to -12.6	-6% to -17%
*Effects on apoprotein B	-38.9% to -43.1%	-40% to -50%
*Effects on lipoprotein a	-18.6% to -25.6%	-25% to -27%
Effects on cardiovascular events	Not available as primary outcome	Significant decrease by ~ 15%
Frequency of injection site reactions	Every 6 months	Every 2 or 4 weeks

*Placebo-adjusted difference

Conclusion and Future Needs

No doubt, inclisisran represents a promising addition to lipid-lowering agents. It can be added to statins and ezetimibe in patients who do not reach target LDL-C levels. Its main advantages are its high efficacy comparable to that of PCSK9 monoclonal antibodies, but with less frequent subcutaneous administration at 6 monthly intervals. The latter property may simplify long-term adherence to inclisiran therapy. The drug is overall well-tolerated up to 18 months with no evidence of adverse effects observed with other nucleotide therapies such as stimulation of inflammatory and immune systems and thrombocytopenia. However, before approval of inclisiran to treat hyperlidipidimia, its safety and efficacy should be established in large trials with longer duration of follow-up. These trials should include patients with wide range of age and ethnicity, more women than previous studies, subjects with and without diabetes, and with various degrees of renal function. Furthermore, the effects of inclisiran on hard CV outcomes and mortality should be evaluated in trials specifically designed and powered to examine CV events as primary outcome. Example of such trials is the ORION-4 trial including 15,000 patients and its results are expected in 2024 [4].

Conflict of Interest

The author has no conflict of interest to declare.

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