Inclisiran Lowers LDL-C and PCSK9 Irrespective of Diabetes Status: The ORION-1 Randomized Clinical Trial

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OBJECTIVE

To evaluate the efficacy and safety of inclisiran by diabetes status.

RESEARCH DESIGN AND METHODS

ORION-1 (ClinicalTrials.gov, NCT02597127) randomized 501 subjects with atherosclerotic cardiovascular disease (ASCVD) or ASCVD risk equivalents and high LDL cholesterol (LDL-C), despite maximally tolerated LDL-C–lowering therapies, to one or two doses of placebo or inclisiran. Levels of lipids and proprotein convertase subtilisin/kexin type 9 (PCSK9) at baseline and day 180 were compared.

RESULTS

Inclisiran was associated with marked declines in LDL-C (median −28% to −52%, $P < 0.0001$ and −28% to −55%, $P < 0.005$ for all doses in the without- and with-diabetes groups, respectively) and PCSK9. The inclisiran-treated groups also had lower apolipoprotein B, non-HDL cholesterol, and lipoprotein(a) but higher HDL cholesterol. Inclisiran had an adverse profile similar to that of placebo, and adverse events were proportionally balanced in the baseline with- and without-diabetes groups.

CONCLUSIONS

PCSK9-targeted siRNA-driven strategies may provide a novel therapeutic option for managing dyslipidemia in the presence and absence of diabetes.

Many individuals at high cardiovascular risk have LDL cholesterol (LDL-C) levels exceeding recommended targets (1,2). Diabetes is a risk factor for atherosclerotic cardiovascular disease (ASCVD), and guidelines underscore timely initiation of appropriately aggressive LDL-C–lowering pharmacotherapy in individuals who copresent with diabetes and dyslipidemia (3–5).

Although statins remain the cornerstone of LDL-C–lowering strategies, maximally tolerated doses of statins are not always sufficiently efficacious even when used with nonstatin lipid-lowering agents. The discovery that proprotein convertase subtilisin/kexin type 9 (PCSK9) modulates the degradation of LDL receptors (LDLRs) (6), and the linking of PCSK9 polymorphisms with serum LDL-C levels and cardiovascular outcomes (7) signaled a new era of lipid-lowering options. Novel approaches involving monoclonal antibodies that interfere with PCSK9-LDLR interaction or RNA interference preventing PCSK9 synthesis are associated with substantial LDL-C declines among individuals with suboptimal LDL-C levels despite being on optimal background statin therapy with or without other lipid-lowering agents (8–13). Furthermore,

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interventions targeting PCSK9 have demonstrated cardiovascular benefit in individuals with stable cardiovascular disease (9,10) and recent acute coronary syndromes (12,13) regardless of whether they have diabetes (10,12).

Inclisiran is a synthetic siRNA that drives PCSK9-specific mRNA degradation in the liver. The ORION-1 trial (ClinicalTrials.gov, NCT02597127) reported that people with ASCVD or ASCVD risk equivalents along with high LDL-C, despite management with maximally tolerated LDL-C–lowering therapies, had significantly lower LDL-C following inclisiran therapy (8,11). This post hoc analysis evaluated whether ORION-1 subjects with and without diabetes at baseline responded differently to inclisiran with respect to changes in lipid profiles, safety, and glycemic control.

RESEARCH DESIGN AND METHODS

Details for the ORION-1 trial have previously been published (8). Subjects were randomized to either one dose of placebo or inclisiran (200, 300, or 500 mg) on day 1 or two doses of placebo or inclisiran (100, 200, or 300 mg inclisiran on days 1 and 90). For this analysis, the subjects were divided into those with or without diabetes at baseline. The primary efficacy end point was the percent change from baseline LDL-C at day 180. Secondary efficacy end points included the percent change in lipid measures. Adverse events were documented up to day 210.

RESULTS

Of the 501 subjects randomized, 497 received their assigned study agent. A total of 67 had diabetes at baseline (n = 25 and 42 for the one-dose and two-dose substudies, respectively) and 415 did not (n = 218 and 197 for the one-dose and two-dose substudies). The baseline clinical characteristics were generally similar between the placebo- and inclisiran-treated groups, with minor exceptions. The placebo group tended to have higher BMI, and the inclisiran group with diabetes tended to be older. Median HbA_{1c} values in the groups without diabetes were ~5.6% (36 mmol/mol), while those in the groups with diabetes ranged between 7.6% (60 mmol/mol) and 8.5% (69 mmol/mol).

Inclisiran treatment was associated with robust reductions in mean LDL-C levels from day 14 until day 210 regardless of baseline diabetes status (Table 1). The LDL-C nadirs with the one-dose inclisiran regimens normally occurred at day 30; LDL-C remained significantly below baseline levels at day 180. The groups assigned to the two-dose inclisiran regimens demonstrated further LDL-C lowering after the second dose of inclisiran. The maximal changes in LDL-C between the baseline visits and those after the second inclisiran doses were greater than those noted for the one-dose regimens and displayed a slower return to baseline values for up to 210 days.

Inclisiran therapy was also associated with decreases in total cholesterol, atherogenic apolipoprotein B, non-HDL cholesterol, and lipoprotein(a), as well as a trend toward increases in HDL cholesterol, regardless of baseline diabetes status or whether they were assigned to the one-dose or two-dose regimen (Supplementary Table 1).

There were no clinically meaningful changes in HbA_{1c} 180 days after treatment initiation, and this persisted over the course of the study. The overall occurrences of adverse events were similar in subjects with and subjects without diabetes. There were no cases of myopathy and no persistent elevations of liver function tests considered to be related to inclisiran in subjects with or without diabetes.

CONCLUSIONS

We report that, regardless of diabetes status, silencing of the PCSK9 pathway via siRNA technology on a maximally tolerated statin background *1*) yields rapid, significant, and extended lowering of LDL-C levels with one to two injections; *2*) improves atherogenic lipid and lipoprotein profiles; and *3*) is safe and well tolerated, including neutral effects on glycemia and inflammatory markers.

The novel approach of using PCSK9-directed monoclonal antibodies provides an option for people who are at very high risk and who have been unable to achieve their LDL-C goals. Importantly,

Table 1—Similar lowering of LDL-C levels between the baseline and day 180 visits for the group without and group with diabetes

	Without diabetes (N = 415 [86% of cohort])				With diabetes (N = 67 [14% of cohort])			
	n (%)	Baseline LDL-C, mmol/L, median (IQR)	% LDL-C change, LS mean (95% CI)	P (vs. placebo)	n (%)	Baseline LDL-C, (mmol/L), Median, (IQR)	% LDL-C change, LS mean (95% CI)	P (vs. placebo)
One dose								
Placebo	57 (26)	3.1 (2.5, 3.8)	2.8 (−2.5, 8.2)	NA	6 (24)	2.3 (2.1, 2.9)	−4.3 (−20.9, 12.2)	NA
Inclisiran								
200 mg	53 (24)	3.1 (2.6, 3.5)	−28.0 (−33.6, −22.4)	<0.0001	7 (28)	2.9 (2.7, 3.0)	−27.6 (−42.9, −12.3)	0.0670
300 mg	54 (25)	2.8 (2.2, 3.8)	−36.9 (−42.4, −31.4)	<0.0001	6 (24)	2.7 (2.2, 3.4)	−52.0 (−68.5, −35.5)	0.0009
500 mg	54 (25)	3.5 (2.7, 4.4)	−41.4 (−47.0, −35.9)	<0.0001	6 (24)	3.6 (2.3, 4.3)	−45.8 (−62.3, −29.3)	0.0031
Two dose								
Placebo	52 (26)	2.8 (2.3, 3.8)	2.3 (−2.4, 7.1)	NA	9 (21)	3.3 (3.0, 3.6)	−1.2 (−12.7, 10.3)	NA
Inclisiran								
100 mg	49 (25)	3.1 (2.3, 3.8)	−35.1 (−40.0, −30.2)	<0.0001	10 (24)	3.3 (3.0, 3.6)	−37.2 (−48.1, −26.3)	0.0001
200 mg	44 (22)	3.1 (2.3, 4.4)	−43.6 (−48.8, −38.4)	<0.0001	16 (38)	3.0 (2.8, 3.8)	−48.3 (−57.0, −39.7)	<0.0001
300 mg	52 (26)	3.1 (2.5, 4.1)	−52.3 (−57.1, −47.5)	<0.0001	7 (17)	2.9 (2.5, 4.7)	−55.0 (−68.0, −42.0)	<0.0001

Data are presented for the modified intention-to-treat population. Subjects excluded because of missing data at day 180 were as follows: for the one-dose regimens, one in the placebo group (2%), two in the 300-mg inclisiran group (3%), and six in the 500-mg inclisiran group (9%); for the two-dose regimens, one in the placebo group (2%), three in the 100-mg inclisiran group (5%), three in the 200-mg inclisiran group (5%), and six in the 300-mg inclisiran group (10%). Least squares (LS) means from mixed model with treatment, visit, diabetes (yes/no), and their interactions and baseline value effects. P values, Dunnett one-sided adjusted pairwise comparison vs. placebo. IQR, interquartile range.

the available data indicate that the PCSK9 inhibitor strategy, when applied to a statin background, can lower LDL-C by as much as an additional 60% and is associated with clinically significant reductions of cardiovascular events (9,13–15). Enthusiasm for and uptake of PCSK9-directed monoclonal antibodies have, however, been dampened by cost, limited indications for coverage, and the need to self-inject every 2–4 weeks.

Rather than targeting the downstream PCSK9 protein like monoclonal antibodies do, inclisiran acts upstream to inhibit PCSK9 synthesis. Inclisiran was associated with sustained declines in LDL-C (8) and atherogenic lipoproteins (11) that were comparable with those observed with the PCSK9-directed monoclonal antibody evolocumab (9). The current analysis extends the primary ORION-1 findings by demonstrating that inclisiran therapy, especially the two-dose regimens, was associated with substantial and sustained LDL-C reductions in the subjects with diabetes. Our findings that targeting PCSK9 signaling positively alters the lipid profiles of individuals without and with diabetes align with the diabetes analysis from the Further cardiovascular Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk (FOURIER) (10) and Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY Outcomes) trials (12). Subjects in the FOURIER and ODYSSEY Outcomes trials who were randomized to evolocumab and alirocumab, respectively, exhibited considerable cardiovascular risk reduction regardless of whether they had diabetes at baseline (10,12). Whether the ORION-1 subjects assigned to inclisiran would also experience diminished cardiovascular risk and whether this phenomenon would be present in individuals with and individuals without diabetes to the same magnitude as that observed among the FOURIER subjects remain to be determined.

The main limitation of this analysis is the small numbers of subjects with diabetes in each subgroup, which limited the power to make specific conclusions. That said, the sustained reduction in clinically meaningful LDL-C is notable. Given the greater and sustained LDL-C–lowering outcome observed with the two-dose regimens and the fact that the two-dose 300-mg regimen was at least as effective as the one-dose 500-mg regimen, the inclisiran dosing regimen in all studies moving forward will be a 300-mg dose administered on day 1 and day 90 and then every 180 days. The use of a twice-a-year therapy for LDL lowering on top of a daily statin has the potential for improved adherence and more complete LDL-C goal attainment.

In conclusion, this analysis suggests that inclisiran may be a viable lipid-lowering alternative in people with and people without diabetes.

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References

1. Reiner Ž, De Backer G, Fras Z, et al.; EURO-ASPIRE Investigators. Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries–findings from the EURO-ASPIRE IV survey. Atherosclerosis 2016;246:243–250

2. Leiter LA, Lundman P, da Silva PM, Drexel H, Jünger C, Gitt AK; DYSIS Investigators. Persistent lipid abnormalities in statin-treated patients with diabetes mellitus in Europe and Canada: results of the Dyslipidaemia International Study. Diabet Med 2011;28:1343–1351

3. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. Endocr Pract 2017;23(Suppl. 2):1–87

4. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 focused update of the 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol 2017;70:1785–1822

5. Landmesser U, Chapman MJ, Stock JK, et al. 2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia. Eur Heart J 2018;39:1131–1143

6. 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;100:928–933

7. Cohen JC, Boerwinkle E, Mosley TH Jr., Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med 2006;354:1264–1272

8. Ray KK, Landmesser U, Leiter LA, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. N Engl J Med 2017;376:1430–1440

9. Sabatine MS, Giugliano RP, Keech AC, et al.; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713–1722

10. Sabatine MS, Leiter LA, Wiviott SD, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. Lancet Diabetes Endocrinol 2017;5:941–950

11. Ray KK, Stoekenbroek RM, Kallend D, et al. Effect of an siRNA therapeutic targeting PCSK9 on atherogenic lipoproteins. Circulation 2018;138:1304–1316

12. Ray KK, Colhoun HM, Szarek M, et al; ODYSSEY Outcomes Investigators. Alirocumab and cardiovascular outcomes in patients with acute coronary syndrome (ACS) and diabetes—prespecified analyses of ODYSSEY OUTCOMES (Abstract). Diabetes 2018;67(Suppl. 1):6-LB
13. Schwartz GG, Szarek M, Bhatt DL, et al. The ODYSSEY OUTCOMES trial: topline results alirocumab in patients after acute coronary syndrome. Presented at the 67th Scientific Sessions of the American College of Cardiology, 10–12 March 2018, at the Orange County Convention Center, Orlando, FL
14. Robinson JG, Farnier M, Krempf M, et al.; ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015; 372:1489–1499
15. Sabatine MS, Giugliano RP, Wiviott SD, et al.; Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372:1500–1509