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Inclisiran, a Potent Lipid Lowering Treatment for Reaching LDL Goals on Top of Statins and Ezetimibe: A Single User Experiences

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Abstract

BACKGROUND: Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of morbidity and mortality, and reducing LDL cholesterol is a key strategy in lowering cardiovascular risk. Inclisiran, a small interfering RNA that targets PCSK9, is an effective lipid-lowering treatment.
AIM: This study evaluates the long-term efficacy of inclisiran in patients with high cardiovascular risk who fail to reach LDL goals despite statin and ezetimibe therapy.
METHODS: A total of 33 patients with high-risk atherosclerotic disease and elevated LDL cholesterol levels, despite maximal statin/ezetimibe therapy or patients who couldn't tolerate statins, were administered inclisiran at baseline with 21 patients receiving a second dose at 3 months. Lipid profiles were measured at baseline, 3 months after first dose, and 3 months after second dose. The primary outcome was the change in LDL-C levels from baseline to post-treatment.
RESULTS: Inclisiran significantly reduced LDL-C levels from a baseline mean of 2.66 mmol/L to 1.49 mmol/L after the first dose ($p < 0.001$). A total of 73.0% of patients achieved LDL-C levels below 1.8 mmol/L, 57.7% below 1.4 mmol/L, and 34.6% below 1.0 mmol/L, with 42.3% experiencing a reduction of more than 50% after the first dose. These reductions were maintained after the second dose, with LDL-C levels remaining significantly lower than baseline.
CONCLUSION: Inclisiran provides significant and sustained LDL-C reductions in patients with high cardiovascular risk and represents an effective long-term treatment option for reducing cardiovascular risk.

Introduction

Ischaemic heart disease is the leading cause of death worldwide [1]. Multiple lines of evidence have established that cholesterol-rich LDL is directly implicated in the development of atherosclerotic cardiovascular disease (ASCVD) [2]. Conversely, therapies that lower LDL-C levels slow the progression of atherosclerosis and reduce CV events and death [3].

Among lipid-lowering drugs, statins and ezetimibe are the cornerstone of therapy, in addition to healthy lifestyle interventions [4], [5]. Despite this, up to 80% of patients with established ASCVD treated with statins fail to achieve the guideline-recommended target LDL-C levels. Therefore, remaining at an elevated risk of major adverse cardiovascular events [3], [5], [6], [7]. When ezetimibe is added, this failure rate decreases to around 70%, meaning a significant proportion of patients remain at elevated risk for major adverse cardiovascular events [8]. Low adherence to treatment and underutilization of more effective lipid-lowering therapies are primary factors contributing to the failure in achieving LDL-C targets [3].

Monoclonal antibody (Evolocumab) that inhibits proprotein convertase subtilisin–kexin type 9 (PCSK9) lower low-density lipoprotein (LDL) cholesterol levels by approximately 60%, but they require subcutaneous injection every 2 to 4 weeks [9].

Current clinical problems in treating patients with ASCVD are the tolerability of current treatments, compliance, ability to treat to target lipid levels and accessibility [4].

Inclisiran is a first-in-class small interfering RNA that inhibits hepatic PCSK9 production, increasing hepatic expression of the LDL receptor and LDL clearance [10], [11], [12].

Placebo-controlled, double-blind, randomized studies have shown reductions in LDL cholesterol levels of approximately 50% with inclisiran, administered subcutaneously on day 1, day 90, and every 6 months onward for 540 days [3]. Because of therapy costs the target population should be particularly patients at very high risk of ASCVD, including those with familial hypercholesterolemia (FH) and who have already experienced an acute coronary syndrome (ACS) [13], [14].

Methods

A total of 39 patients were included in this analysis. 6 patients were unable to tolerate inclisiran and discontinued treatment after the first administration and were excluded from the study. All of them also exhibited intolerance to statins. We included patients with high-risk atherosclerotic disease and high LDL levels despite maximal statin treatment or patients who couldn't tolerate statins [6], [7]. Some patients were concurrently on statins and/or ezetimibe as part of their lipid-lowering therapy. A single cardiologist, a member of the ILEP recommendations, selected the treatment regimen for each patient based on the efficacy of peroral therapy, individual cardiovascular risk, and treatment goals [4]. Each patient received 284 mg of inclisiran administered subcutaneously, with the second dose administered six months after the first. All patients received the first dose of inclisiran at baseline, with 21 of these patients receiving a second dose 3 months later. We measured the patients' lipid profiles using fasting blood samples collected at baseline, three months after the first dose, and three months after the second dose of inclisiran. The primary outcome was the change in LDL-C levels from baseline to post-treatment. Secondary outcomes included changes in total cholesterol, HDL-C, and triglycerides.

To assess the clinical efficacy of inclisiran, patients were divided into groups based on whether their LDL cholesterol levels reached specific thresholds. These thresholds were chosen in accordance with current international guidelines on lipid management and cardiovascular risk reduction [5-7]. Specifically, patients were grouped based on whether they achieved LDL-C levels of <1.8 mmol/L, <1.4 mmol/L, <1.0 mmol/L, and a >50% reduction from baseline.

Descriptive statistics were used to summarize baseline characteristics and lipid levels. Paired t-tests were conducted to compare lipid levels before and after treatment. The percentage of patients achieving specific LDL-C thresholds was calculated. All analyses were performed using the SPSS program, with a p-value of <0.05 considered statistically significant.

Results

The study included 39 patients (25 males, 14 females), of which 6 patients were excluded due to intolerance for inclisiran. The 33 patients who completed the study had a mean age of 65.6 years, ranging from 46 to 71 years. The majority were male (76%), and the average BMI was 28.44 kg/m². In terms of lipid-lowering therapy, 18.18% were not on any therapy, 33.33% were on statin monotherapy, and 48.48% were receiving a combination of statins and ezetimibe. Their baseline lipid profiles had a mean total lipid level of 4.40 mmol/L (SD = 1.20), mean LDL cholesterol of 2.66 mmol/L (SD = 1.14), mean HDL cholesterol of 1.20 mmol/L (SD = 0.33), and mean triglycerides of 1.67 mmol/L (SD = 0.97).

Table 1: Baseline Characteristics of the Study Cohort

Basic characteristics; Mean (SD) or N(%)	
Total No.	33 (100%)
Age (years)	65.6 (11.42)
Sex (Male/Female)	25 (76%) / 8 (24%)
BMI (kg/m²)	28.44 (3.53)
Therapy; N(%)	
No Therapy	6 (18.18%)
Statin	11 (33.33%)
Statin+Ezetimibe	16 (48.48%)
Blood biomarkers; Mean (SD)	
Total Lipids (mmol/L)	4.40 (1.20)
LDL (mmol/L)	2.66 (1.14)
HDL (mmol/L)	1.20 (0.33)
TAG (mmol/L)	1.67 (0.97)

After the first dose of inclisiran we observed a significant reduction in LDL cholesterol from a baseline mean of 2.66 mmol/L to 1.49 mmol/L (SD = 0.92), which was a statistically significant change ($p < 0.001$). We also observed a statistically significant decrease in total cholesterol levels, from 4.40 mmol/L to 3.13 mmol/L (SD = 1.04, $p < 0.001$), triglycerides decreased slightly (1.67 mmol/L to 1.38 mmol/L, $p = 0.016$). In contrast, there was no significant change in level of HDL cholesterol (1.20 mmol/L to 1.15 mmol/L, $p = 0.140$).

Table 2: Changes in Lipid Parameters Before and After Inclisiran Treatment

Parameter	Mean Before (SD)	Mean After First Dose (SD)	Mean After Second Dose (SD)
Total Lipids (mmol/L)	4.40 (1.20)	3.13 (1.04)	3.64 (1.35)
LDL (mmol/L)	2.66 (1.14)	1.49 (0.92)	1.83 (1.23)
HDL (mmol/L)	1.20 (0.33)	1.15 (0.29)	1.21 (0.30)
TAG (mmol/L)	1.67 (0.97)	1.38 (0.71)	1.56 (1.03)

Before the end of the study 21 of our patients had also received a second dose of inclisiran, 3 months after the first. Among these patients, LDL cholesterol levels remained at a significantly lower level than baseline, with a mean value of 1.83 mmol/L (SD = 1.23). This represented a slight increase from the post-first dose levels (1.49 mmol/L), but the difference was not statistically significant ($p = 0.063$). However, the reduction from baseline to the post-second dose remained highly significant ($p = 0.002$). Similarly, total lipid levels remained significantly lower than baseline values (mean = 3.64 mmol/L, $p = 0.007$), and the difference compared to post-first dose levels was not significant ($p = 0.054$).

After the first dose, 73.0% of patients achieved LDL-C levels below 1.8 mmol/L, 57.7% achieved levels below 1.4 mmol/L, and 34.6% reached levels below 1.0 mmol/L, while 42.3% of patients had a reduction in LDL-C cholesterol of more than 50% from baseline.

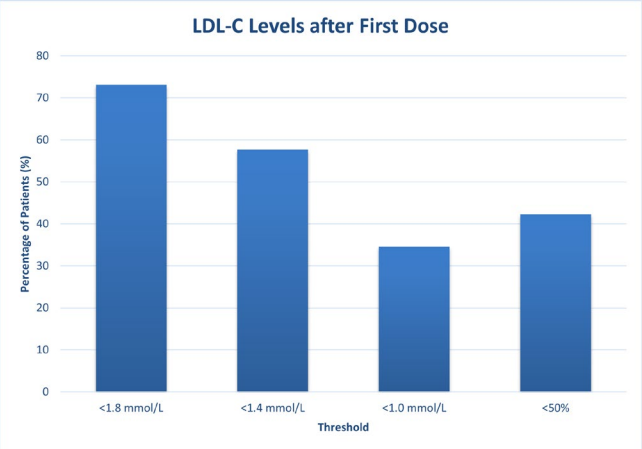


Figure 1: Percentage of Patients Achieving LDL-C Thresholds After First Dose of Inclisiran

After the second dose, the percentage of patients achieving LDL-C levels below 1.8, 1.4, and 1.0 mmol/L was 64.7%, 58.8%, and 17.6%, respectively, with 29.4% of patients experiencing a reduction of more than 50% in LDL-C levels.

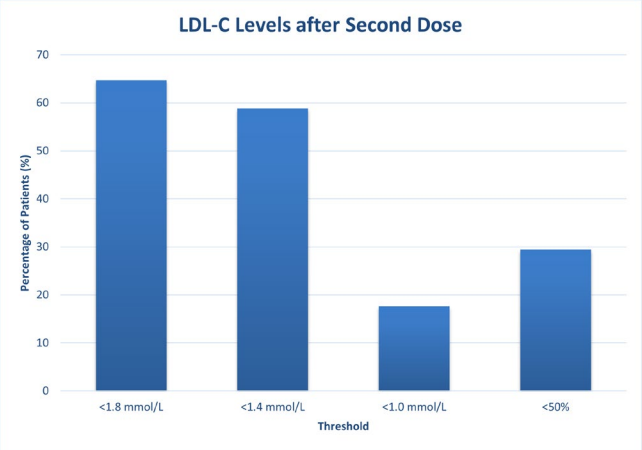


Figure 2: Percentage of Patients Achieving LDL-C Thresholds After Second Dose of Inclisiran

Discussion

This study supports the growing body of evidence demonstrating the efficacy of inclisiran in significantly lowering LDL cholesterol levels in patients with elevated cardiovascular risk. After the first dose, inclisiran resulted in a significant reduction in LDL cholesterol levels, with 73.0% of patients achieving LDL levels below 1.8 mmol/L, and 42.3% experiencing a reduction of more than 50% from baseline. These results are consistent with previous clinical trials, where inclisiran has been shown to reduce LDL levels by approximately 50% across various patient populations, including those with heterozygous familial hypercholesterolemia and atherosclerotic cardiovascular disease [3], [11], [12]. The LDL reduction observed after the first dose of inclisiran was substantial and statistically significant.

While significant LDL reductions were observed, inclisiran's effect on HDL cholesterol and triglycerides was minimal. This aligns with the drug's mechanism of action, which is aimed at lowering LDL cholesterol by targeting PCSK9 synthesis in the liver [10].

By achieving target LDL levels in a significant proportion of patients, inclisiran addresses a major gap in lipid management. Many high-risk patients, particularly those on statin therapy, fail to reach LDL targets, leaving them at continued risk for adverse cardiovascular events [11]. In this study, inclisiran enabled a large proportion of patients to meet LDL thresholds recommended for high- and very high-risk populations [5], [6], [7].

The lipid levels observed after the second dose were comparable to those measured after the first dose. While there was a slight increase in LDL-C between the first and second doses, this difference was not statistically significant, suggesting that the initial dose of inclisiran provides the majority of the lipid-lowering effect. This implies that one dose of inclisiran may be sufficient to achieve the desired therapeutic impact, and that subsequent doses serve primarily to maintain LDL-C at target levels over time. This slight increase could also, in part, be attributed to potential changes in adherence to previous statin therapy once inclisiran treatment begins.

Conclusion

Inclisiran represents a safe and effective option for patients requiring additional LDL-C lowering beyond what can be achieved with statins and other oral therapies. The sustained LDL-C reductions observed in this study support their use as a long-term treatment option, particularly in patients with high cardiovascular risk. The effect of LDL reduction with inclisiran on cardiovascular outcome is still to be evaluated.

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