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ORIGINAL ARTICLE

Experience with the New Generation of Lipid-lowering siRNA-based PCSK9 Inhibitor (Inclisiran) in Patients Undergoing LMCA Intervention

Uzeyir Rahimov[1], Khatira Abdulalimova[1], Emin Karimli[1], Shafag Mustafayeva[1], Leyla Suleymanli[2], Jamala Temishova[1], Jamil Babayev[1], Ziya Salimov[2], Elkhan Hajiyev[3], Aysel Islamlı[3], Kamal Jumshudov[3], Kamran Musayev[4], Huriya Shahbazova[4], Vugar Zamanov[5], Galib Imanov[6], Rahima Gabulova[6], Tofiq Cahangirov[7]

[1]Department of Cardiology, Universal Hospital, Baku, Azerbaijan

[2]Baku Medical Plaza, Baku, Azerbaijan

[3]Department of Cardiology, Baku Health Center, Baku, Azerbaijan

[4]Central Clinic Hospital, Baku, Azerbaijan

[5]Mediland Hospital, Baku, Azerbaijan

[6]Azerbaijan Medical University, Baku, Azerbaijan

[7]Azerbaijan State Advanced Training Institute for Doctors named after A.Aliyev, Baku, Azerbaijan

ABSTRACT

Background: Coronary artery diseases are one of the leading risk factors for global death. Reducing the levels of low-density lipoprotein (LDL) cholesterol to the normal value is crucial for its treatment. Although medications such as statins and ezetimibe remain the primary therapeutic options in such cases, more effective treatment choices are warranted for high-risk patients, particularly those with a history of cardiovascular events. The new-generation lipid-lowering siRNA drug PCSK9 inhibitor may offer an advantage in controlling LDL levels in such a patient group, especially when used in combination with other hypolipidemic drugs.

Aim: To investigate the effect of PCSK9i in patients with prior left main coronary artery intervention.

Study Design: Retrospective cohort study.

Methods: This study was conducted in Azerbaijan during 2022-2023 with 279 patients who underwent left main coronary artery (LMCA; angioplasty and bypass) intervention. All patients were initiated on statin-based antilipidemic therapy after the intervention. Over one year, the statin dose was titrated to the maximum levels, and ezetimibe was added to the treatment when needed. At the end of the year, patients who had not yet reached the target LDL levels inclisiran were added to the treatment for those who accepted it. Under inclisiran therapy, the patients were monitored for the next 12 months. After the first dose of inclisiran, the second and third doses were administered at the 3rd and 9th months, respectively, and LDL levels were measured at the 6th and 12th months. During the treatment period, LDL levels, liver enzymes, and other potential side effects were monitored.

Results: In patients who received inclisiran therapy (15), the average LDL level directly before inclisiran treatment was 134.9 mg/dL, and six months after treatment with inclisiran, this value dropped to 64.6 mg/dL. In other words, 6 months after starting inclisiran therapy, an average reduction of 52% in LDL levels was observed compared with the previous value. In patients who continued inclisiran treatment, the LDL level at the 12th month decreased to even lower values (an average of 43.1 mg/dL) compared with the previous measurement. Additionally, only a few patients reported side effects, which were temporary and not clinically significant.

Conclusion: Inclisiran significantly reduces LDL levels in patients with LMCA intervention and helps optimize the treatment strategies for achieving target LDL values. However, the high cost and the lack of patient awareness were the key barriers to its widespread use. Reforms in the healthcare system and expanded treatment coverage are expected to improve the effectiveness of Inclisiran and help prevent future cardiovascular diseases.

Keywords: Inclisiran, left main coronary artery, LMCA bypass, LMCA stent implantation, LDL, hypercholesterolemia, ischemic heart disease

INTRODUCTION

According to the World Health Organization, ischemic heart diseases are one of the major causes of death, accounting for nearly 10 million deaths annually.[1] Coronary artery diseases, especially left main coronary artery (LMCA) stenosis, are significant risk factors for the occurrence of myocardial infarction and cardiovascular complications. Therefore, the management and prevention of ischemic heart diseaseremain critical in modern medicine. According to the current recommendations, revascularization is recommended for all patients with ≥50% stenosis

Address for Correspondence: Khatira Abdulalimova, FESC, MD, Department of Cardiology, Universal Hospital, Baku, Azerbaijan
E-mail: khatira.abdulalimova@gmail.com **ORCID ID:** orcid.org/0000-0002-8101-3406

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of the LMCA, irrespective of their symptoms or ischemic burden.[2] Reducing morbidity and mortality is closely linked not only to interventions performed but also to a careful follow-up of these patients. We, therefore,aimed not only to focus on revascularization but also to modify risk factors such as hypercholesterolemia as well as emphasize the role of modern treatment methods in achieving the target lipid values.

Aggressive lipid-lowering therapy plays a crucial role in the prevention of atherosclerosis for primary and secondary prevention in patients with high ischemic risk.[3] Statin and ezetimibe therapy, either alone or in combination, are among the primary treatment strategies for lowering the low-density lipoprotein (LDL) levels.[4] The use of new-generation lipid-lowering siRNA-based PCSK9 inhibitors is particularly important for patients intolerant to statins or failing to achieve the target LDL levels.[5]

The present study, which was conducted in Azerbaijan, is a multicenter, retrospective study that aimed to demonstrate the benefit of adding PCSK9 inhibitors to the treatment of patients who had undergone LMCA intervention and were receiving a statin + ezetimibe combination but could not achieve the targeted LDL values. Moreover, the safety of PCSK9 inhibitors in the studied population was evaluated.

METHODS

This was a multicenter, retrospective study. The subject inclusion criteria were a recent LMCA intervention and no prior antilipidemic therapy. As such, 279 patients were included from across 4 different centers. The patients had received at least 1 year of antilipidemic treatment (with statin or statin + ezetimibe combination) after the intervention. Only patients followed by a cardiologist within 1 year after coronary revascularization were included in the study. The remaining patients were excluded from the study due to the lack of 1-year follow-up data. The target LDL level in the present study was set at <55 mg/dL based on the latest recommendations.[6]

All patients were followed by a cardiologist during the 1 year after the intervention and received statin or statin + ezetimibe combination at the maximum tolerable doses. The maximum dose of statins used in the study was 40 mg for atorvastatin and rosuvastatin. The LDL levels were measured in all patients after 1, 6, and 12 months. In patients who did not achieve the target LDL values by the 6th month, the statin + ezetimibe combination was then initiated. A total of 77 patients continued the study with the regular cardiologist follow-up for over 1 year. During the 1-year observation period, among the 77 patients, 63 of those who did not achieve the target LDL levels despite having received the maximum tolerable dose of the statin + ezetimibe combination were recommended to add the PCSK9 inhibitor to their treatment regimen. Because only inclisiran was available in Azerbaijan, it was used as a PCSK9 inhibitor. Only 15 patients accepted inclisiran therapy. The treatment was initiated with inclisiran at a dose of 1.5 mL/300 mg. The LDL levels were rechecked at the end of the 6th and 12th months after the inclisiran therapy. Patients received the second and third doses of inclisiran at the 3rd and 9th months, respectively.

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and gamma-glutamyl transferase (GGT) levels were assessed before and after inclisiran treatment, and any adverse effects were monitored.

Our study was conducted with the approval of Research Ethic Committee of the National Cardiac Society of Azerbaijan (decision no: 01/2025, date: 05.01.2025).

Statistical Analysis

Descriptive statistics were employed to summarize the patient characteristics and LDL levels at different time points. Statistical assumptions were examined before conducting the tests. Normality was assessed using the Shapiro-Wilk test and histograms. Continuous variables are presented as the means and standard deviations (SD) for normally distributed data. Categorical variables were reported as frequencies and percentages.

To evaluate the effect of inclisiran treatment on the LDL levels over time, a paired t-test was conducted to compare the LDL levels before treatment with those at 6 months and 1-year post-treatment. The mean differences, SD, standard errors of the mean (SE), 95% confidence interval (CI), t-statistics, and p values were reported. $P<0.05$ was considered to indicate statistical significance. All statistical analyses were conducted using Statistical Package for the Social Sciences.

RESULTS

Out of 77 patients, 35 underwent percutaneous coronary intervention (PCI) and 42 underwent coronary artery bypass grafting (CABG). At the 6th month after revascularization, only 2 patients (1 who underwent PCI and 1 who underwent CABG) who received the maximum dose of statin alone showed an LDL value of <55 mg/dL. In the remaining 75 patients, statin + ezetimibe combination therapy was initiated. At the end of the 1-year follow-up, only 12 patients (5 who underwent CABG and 7 who underwent PCI) achieved an LDL value of <55 mg/dL while receiving the statin + ezetimibe combination. The average age of the 77 patients who were followed up was 67 years (age range: 43-85 years, SD ±9).

At the end of the 1st year, 15 out of 63 patients who did not achieve the target LDL values were started on inclisiran therapy. The average age of the 15 patients who received inclisiran therapy was 55 years (SD ±10.5). Of the 15 patients, 12 had diabetes, while 13 had hypertension. The average LDL value before starting the inclisiran therapy for these 15 patients was 134.9 mg/dL (range: 75-247, SD ±49 mg/dL) (Table 1).

After administering 2 doses of inclisiran, the LDL levels were measured at the 6th month of follow-up. A significant reduction was then observed in the LDL values at the first follow-up. Specifically, the average LDL cholesterol level decreased to 64.6 mg/dL (range: 22-129, SD ±32.2 mg/dL) after the two doses of inclisiran. Among the 15 patients, 7 (46.7%) achieved the target values after the second dose. The mean decrease in LDL at 6 months was 70.27 mg/dL (SD=51.28, SE=13.24), with a 95% CI ranging from 41.87 to 98.67 mg/dL. The t-statistic was 5.307 with

14 degrees of freedom (df), and the p-value was <0.001, indicating a highly significant reduction in the LDL level. After the third dose, only 6 patients attended the LDL control in the 12th month. The average LDL value of these 6 patients at the 6th month was 63 mg/dL (SD ±24 mg/dL), at the 12th month was 43.1 mg/dL (SD ± 24.4 mg/dL), and at 1 year was 82.5 mg/dL (SD=28.85, SE=11.78), with a 95% CI of 52.22-112.78 mg/dL and a t-statistic of 7.005 (df=5, p=0.001). These findings confirm that inclisiran treatment leads to a sustained and significant decrease in LDL levels over time, with the reduction being more pronounced in the first year compared to that at 6 months. These findings suggest that inclisiran treatment causes a substantial and sustained reduction in LDL levels over time (Tables 2, 3).

Table 1. Demographic characterization and risk factors

	Sex	Age	Bilirubine mg/dL	Hypertension	Diabetes mellitus
1	M	60	0.4	+	+
2	M	62	0.04	+	+
3	M	51	0.1	-	-
4	F	62	0.5	+	+
5	M	40	0.9	-	+
6	F	47	0.1	+	+
7	M	41	0.05	+	+
8	M	62	0.02	+	+
9	F	74	0.5	+	+
10	F	52	0.6	+	+
11	M	44	0.03	+	-
12	M	69	0.5	+	+
13	M	57	0.8	+	+
14	F	60	0.02	+	-
15	M	42	0.4	+	+

M: Male, F: Female

In the 3rd month of treatment with inclisiran, one patient exhibited a twofold increase in the ALT levels (81 U/L; normal range: 10-40 U/L) and an increase in the AST levels to the upper limit of the normal range (35 U/L; normal range: 9-35 U/L). In addition, one patient experienced a fourfold rise in the GGT levels (246 U/L; normal range: 8-61 U/L) in the 6th month of treatment. Changes in the liver enzymes were transient and spontaneously resolved. Subsequent follow-ups revealed that these values had restored; therefore, the inclisiran therapy was continued.

Another patient experienced side effects such as muscle and joint pain.

After the use of inclisiran, the bilirubin levels were also checked, and no abnormalities were detected in any of the patients.

Among the 15 patients who received inclisiran therapy, the lowest recorded LDL level was 9 mg/dL. No adverse effects related to the low LDL level were observed in this patient.

More than 50% of the patients who received inclisiran therapy had an LDL level of >120 mg/dL, with an average age of 54 (SD ±10.5). In addition, these patients had risk factors such as diabetes and hypertension.

DISCUSSION

The present findings demonstrated that the PCSK9 inhibitor, inclisiran, could reduce the LDL cholesterol levels by an average of 52% after two doses in patients who underwent LMCA intervention and received the ezetimibe + statin combination. After the third dose, the patients who continued with the inclisiran therapy exhibited further reductions in their LDL levels, demonstrating its effectiveness in achieving even lower values. No significant side effects were identified during the use of the drug.

Although the risk of restenosis and thrombosis has decreased with the use of intravascular imaging, new-generation stents, and advanced technical methods in stent implantation, failure to achieve the target LDL levels post-procedure remains associated with poor long-term outcomes.

Table 2. Changes in the LDL levels before and after inclisiran treatment

Comparison	Mean difference (mg/dL)	Standard deviation	Standard error	95% confidence interval (lower)	95% confidence interval (upper)	t-value	df	p value
LDL before vs. 6 months after inclisiran	70.27	51.28	13.24	41.87	98.67	5.307	14	<0.001
LDL before vs. 1 year after inclisiran	82.50	28.85	11.78	52.22	112.78	7.005	5	0.001

p<0.05; p<0.01 indicate statistically significant differences.
LDL: Low-density lipoprotein

Table 3. Descriptive statistics for the LDL levels before and after inclisiran treatment

Timepoint	N	Minimum (mg/dL)	Maximum (mg/dL)	Mean (mg/dL)	Standard deviation
Overall LD levels	77	42	331	104	59
Before inclisiran	15	75	247	135	49
6 months after	15	22	129	65	32
1 year after	6	9	75	43	24

LD: Lactate dehydrogenase, LDL: Low-density lipoprotein

As in all of the ischemic patient groups, statins play a crucial role in LDL control among patients who have undergone LMCA intervention. However, in the majority of patients, the target LDL levels are not achieved. Despite receiving maximal doses of statin + ezetimibe therapy, patients with residual high LDL levels, as well as those with statin intolerance, required additional treatment options. This finding indicated that increasing the use of PCSK9 inhibitors may help reduce future cardiovascular events.

Based on our observations, we suggest that, in complex coronary interventions, particularly in cases of multivessel disease, high thrombotic events, and atherosclerotic vascular diseases with active inflammation, aggressive lipid-lowering therapy and the early addition of PCSK9 inhibitors to the treatment should be considered.

Based on the study results, it can be concluded that, out of the total 279 patients included in the study, only 77 attended regular follow-up visits during one year. This finding shows that educational efforts are important to improve patient adherence to treatment. Our observations suggested that patients' awareness of their condition is not sufficiently high. Several patients have limited information about dyslipidaemia, cardiovascular diseases, and their complications, which leads to irregular medication adherence and inconsistent doctor follow-ups. The results of the SURF CHD II study, which also included patient data from Azerbaijan, highlight the negative factors such as the lack of patient knowledge, irregular drug intake, and patients not attending follow-up appointments for the management of chronic heart diseases.[7]

Under inclisiran treatment, only 2 out of 77 patients who attended the follow-up after 1 year did not reach the target LDL levels. However, a significant reduction in the LDL levels was observed in both of these patients when compared with their baseline levels.

In addition to medical treatment, detailed discussions were held with these patients regarding modifiable risk factors. In a study published during 2019-2021, which included data collected from Azerbaijan, the management of comorbidities and the modification of risk factors in patients with high ischemic risk were emphasized as crucial factors for improving patient outcomes. The study also highlights the gaps in our healthcare system regarding these areas.[8]

Although all patients received statin or statin + ezetimibe combination therapy after the LMCA intervention, the target LDL levels were achieved in only a small number of patients (14 of 77) over the course of 1 year. However, by the end of the 6th month, of the 15 patients who received inclisiran, 7 patients had already achieved their target LDL level. One nuance we would like to emphasize is that, no matter how aggressive the lipid-lowering therapy may be, the influence of concomitant risk factors such as familial hyperlipidaemia and diabetes on the LDL levels is undeniable.

During the study, in patients who received statin + ezetimibe combination therapy but did not reach the target LDL level, only 15 out of the 63 patients accepted treatment with inclisiran. An adequate organization of drug provision by the insurance system for regular adherence to lipid-lowering therapy is one of the key factors that can enhance patient compliance. The high cost of inclisiran was observed as one of the main factors that could prevent reaching the target LDL levels. Resolving these problems, along with improving the quality of treatment in the healthcare system, can significantly contribute toward enhancing patients' health and reducing mortality from cardiovascular diseases. Future clinical trials and reforms in healthcare policy are expected to play a crucial role in this direction. Unfortunately, due to the widespread prevalence of cardiovascular diseases, delays in early diagnosis, and the limited accessibility to healthcare in Azerbaijan, life expectancy here is significantly lower when compared to that in other European countries, only surpassing one country.[9]

Our observations lead us to believe that if siRNA therapy is covered by insurance, there will be a considerable decrease in the number of cardiovascular diseases and their complications, and the outcomes of medical interventions will improve.

Study Limitations

One of the main limitations of the study was the lack of randomization and the small number of patients enrolled. Moreover, only a limited number of patients who underwent LMCA intervention attended follow-up. In addition, owing to the lack of basal LDL levels of patients, we could not compare the LDL levels at the end of the 2nd year after statin, statin + ezetimibe, and inclisiran therapies. Furthermore, the majority of the patients recommended for inclisiran therapy did not accept it. After 6 months of the initiation of inclisiran, only 6 patients had their LDL levels reassessed at the 12-month follow-up, and the results of the remaining 9 patients' results were not included in the study. Another limitation of the study is that there was no control group for comparison. Risk factors such as smoking and family history were also not fully assessed in the included patients, and concomitant medications (other than anti-lipid treatment) were not included in the study. In the future, the progression of cardiovascular events should be compared between patients who received or did not receive inclisiran therapy.

CONCLUSION

The results of this multicenter, retrospective study demonstrated that inclisiran significantly reduced the LDL levels in patients undergoing LMCA intervention. In the first follow-up after inclisiran treatment, a 52% reduction was achieved in the LDL levels when compared with that with the statin + ezetimibe combination therapy. After the second and third doses, this value was reduced even further. This finding suggests that inclisiran is a valuable additional treatment for high-risk patients, particularly for those who are intolerant to statins or are unable to reach the target LDL levels. Despite its effectiveness, the high cost and patients' lack of awareness were identified as the major barriers to its widespread use. Addressing these challenges through healthcare system reforms and expanded treatment coverage is expected to increase the effectiveness of inclisiran, thereby helping prevent cardiovascular diseases in the future.

Ethics Committee Approval: Our study was conducted with the approval of Research Ethic Committee of the National Cardiac Society of Azerbaijan (decision no: 01/2025, date: 05.01.2025).

Informed Consent: Because it is a retrospective study, informed consent is not required.

Authorship Contributions: Concept: U.R., E.K., Design: U.R., E.K., Data Collection or Processing: U.R., S.M., L.S., J.T., J.B., Z.S., A.I., K.J., K.M., H.S., V.Z., G.I., Analysis or Interpretation: U.R., K.A., E.K., S.M., Literature Search: U.R., K.A., Z.S., R.G., T.C., Writing: U.R., K.A., E.K., S.M., E.H., R.G., T.C.

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