Lipid lowering with inclisiran: a single-center experience from Slovakia

Stefan Toth[1], Marianna Barbierik Vachalcova[2], Adriana Jarolimkova[1], Martin Sevcik[3], Tibor Poruban[2]
[1]Gerontology and Geriatrics Clinic and School of Medicine, Pavol Jozef Safarik University, Kosice, Slovakia
[2]East Slovak Institute of Cardiovascular Diseases and School of Medicine, Pavol Jozef Safarik University, Kosice, Slovakia
[3]Department of Infectious diseases, Faculty hospital of Jan Adam Rayman, Presov, Slovakia

Background: Inhibiting proprotein convertase subtilisin/kexin type 9 activity is an effective strategy to lower LDL cholesterol (LDL-C), a major cardiovascular risk factor. Inclisiran, the first small interfering RNA targeting PCSK9, has shown a 50% LDL-C reduction in clinical trials.
Aims: The aim of this study was to describe the effects of inclisiran in real-world clinical settings, along with the first clinical experiences of its use in Slovakia.
Methods: In this observational study, 36 patients were selected for inclisiran therapy as part of standard clinical assessments, procedures, and reimbursement from public health insurance. Each patient underwent a standard lipid profile assessment and high-sensitivity C-reactive protein (hsCRP) testing before submitting applications for therapy approval, and again one month after receiving two doses of inclisiran. The average change in lipid profile levels was calculated for each patient who completed the third dose of inclisiran.
Results: Inclisiran therapy was approved for 36 patients, including 27 with atherosclerotic coronary artery disease and 9 with prior strokes. The cohort included 1 statin-intolerant patient, 28 on maximum statin doses, and 7 on reduced doses. After 3 months, LDL-C dropped by 57.5 %, hsCRP to 1.2 mg/dL, and lipoprotein(a) by 14.3 ± 6.4 %. Safety outcomes mirrored clinical trials, with mild injection-site pain in 26 cases and flu-like symptoms in 3.
Conclusions: Inclisiran demonstrated an effective reduction in LDL-C and hsCRP levels, slightly exceeding clinical trial outcomes, but lipoprotein(a) reductions varied among patients. Safety was consistent with expectations, confirming inclisiran's potential for broader clinical use.

Key words: inclisiran, LDL-C, hsCRP, lipoprotein(a), target values.

Hypolipidemická liečba inklisiranom: skúsenosti jedného slovenského pracoviska

Úvod: Inhibícia aktivity proproteín konvertázy subtilizín/kexín typu 9 predstavuje účinnú stratégiu na zníženie LDL cholesterolu (LDL-C), ktorý je jedným z hlavných kardiovaskulárnych rizikových faktorov. Inklisiran, prvá malá interferujúca RNA cielená na PCSK9, preukázal v klinických štúdiách zníženie LDL-C o 50 %.
Ciele: Cieľom tejto štúdie bolo opísať účinky inklisiranu v reálnych klinických podmienkach spolu s prvými klinickými skúsenosťami s jeho používaním na Slovensku.
Metódy: V tejto observačnej štúdii bolo na liečbu inklisiranom vybraných 36 pacientov v rámci štandardných klinických vyšetrení, postupov a úhrady zo zdravotného poistenia. U každého pacienta sa pred podaním žiadosti o schválenie terapie vykonalo štandardné hodnotenie lipidového profilu a stanovenie vysokosenzitívneho C-reaktívneho proteínu (hsCRP), ktoré sa zopakovalo mesiac po podaní dvoch dávok

DECLARATIONS:

Ethics approval and consent to participate:
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Consent for publication:
Not applicable.

Availability of data and materials:
Not applicable

Competing interests:
The authors declare that they have no competing interests.

Funding:
Not applicable.

Contributions:
All authors contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

Clinical trial registration:
Not applicable.

Acknowledgements:
The authors would like to acknowledge the support staff for its timely effort, sincerity, and dedication towards work.

Cit. zkr: **Klin Farmakol Farm. 2025;39(1):14-21**
https://**doi**.org/**10.36290/far.2025.017**
Článek přijat redakcí: 31. 12. 2024
Článek přijat k tisku: 4. 2. 2025

MUDr. Tibor Poruban, Ph.D., MPH, MBA
tporuban@vusch.sk

inklisiranu. Priemerná zmena hladín lipidového profilu bola vypočítaná u každého pacienta, ktorý absolvoval tretiu dávku inklisiranu.

Výsledky: Liečba inklisiranom bola schválená pre 36 pacientov, z toho 27 s aterosklerotickým ochorením koronárnych artérií a 9 po prekonaní cievnej mozgovej príhody. Súbor zahŕňal 1 pacienta intolerantného na statíny, 28 pacientov na maximálnej dávke statínov a 7 na zníženej dávke. Po 3 mesiacoch sa hladina LDL-C znížila o 57,5 %, hsCRP na 1,2 mg/dl a lipoproteín(a) o 14,3 ± 6,4 %. Bezpečnostné výsledky boli v súlade s klinickými štúdiami – mierna bolesť v mieste vpichu sa vyskytla u 26 pacientov a chrípkové príznaky u 3 pacientov.

Záver: Inklisiran preukázal účinné zníženie hladín LDL-C a hsCRP, pričom výsledky mierne prevýšili klinické štúdie. Redukcia lipoproteínu(a) sa medzi pacientmi líšila. Bezpečnostný profil bol v súlade s očakávaniami, čo potvrdzuje potenciál inklisiranu pre širšie klinické využitie.

Kľúčové slová: inklisiran, LDL-C, hsCRP, lipoproteín(a), cieľové hodnoty.

Introduction

A significant advancement in both primary and secondary prevention of cardiovascular (CV) diseases, which remain the leading cause of mortality and morbidity. According to recent data, CV mortality in Europe accounts for 45 % of all deaths in women and 39 % in men, respectively (1). In Slovakia, CV diseases account for 45.3 % of all causes of death, while in the Czech Republic, they represent 38 %, reflecting the European trend (2, 3).

Hyperlipidemia is the most significant risk factor for the development and progression of atherosclerotic CV diseases (ASCVD). Lowering LDL cholesterol (LDL-C) levels is a fundamental pillar in the management of ASCVD. It has long been established that each 1 mmol/L reduction in LDL-C leads to a 22% decrease in the relative risk of CV events over a period of 5 years (4). In patients at very high CV risk, rapidly achieving target LDL-C levels, particularly in those following an acute coronary syndrome or revascularization, is crucial for stabilizing atherosclerotic plaques (5).

Inclisiran is a new long-acting parenteral lipid-lowering agent. This small interfering RNA (siRNA) inhibits hepatic production of proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 is a protease that, upon binding to the LDL receptor, induces its degradation in lysosomes. By inhibiting PCSK9 production, the degradation of LDL receptors is reduced, their recycling increases, and this results in a reduction in LDL-C (6).

The efficacy and safety of inclisiran are evaluated in the ORION clinical trial program. Phase II and III studies have shown that inclisiran reduces LDL-C by approximately 50 % with dosing once every six months and is effective in patients with ASCVD as well as those at high CV risk, including patients with heterozygous familial hypercholesterolemia (FH) (7,8). Currently, additional Phase III clinical trials are underway to provide evidence on the long-term safety and efficacy of inclisiran, as well as the ORION-4 study, which focuses on evaluating its impact on CV morbidity and mortality. Results are expected in 2026 (9).

Despite the absence of these data, inclisiran was approved by the European Medicines Agency at the end of 2020. It is indicated as an adjunct to dietary measures for individuals with heterozygous FH or non-familial hypercholesterolemia or mixed dyslipidemia at very high CV risk with manifest atherosclerotic disease, where existing high-intensity lipid-lowering therapy has proven insufficiently effective.

The aim of this study was to describe the effectiveness of inclisiran in a group of patients with very high CV risk according to current indication criteria in Slovakia, as well as to highlight specific aspects of managing these patients.

Methods

Between March 2023 and August 2024, 36 patients (25 men and 11 women, average age 60.2 ± 7.1 years) were included in this open cohort prospective registry. These patients had very high CV risk. Among them, 75 % had clinical atherosclerotic coronary artery disease (ASCAD).

Inclisiran was prescribed to patients with FH or mixed dyslipidemia who had a very high CV risk and clinical evidence of ASCAD, and whose LDL-C levels remained above 2.5 mmol/L despite receiving intensive lipid-lowering therapy. It was also recommended for individuals with heterozygous FH whose LDL-C levels exceeded 3.1 mmol/L despite high intensity therapy. Intensive lipid-lowering therapy was defined as the maximum tolerated dose of statins (atorvastatin or rosuvastatin) combined with ezetimibe, or in cases of statin intolerance, treatment with ezetimibe alone. Statin intolerance was identified if a patient could not tolerate at least two different statins, resulting in their discontinuation.

Prior to initiating treatment, each patient had a lipid profile done (including total cholesterol, LDL-C, HDL-C, triglycerides, and lipoprotein (Lp(a)), and liver parameters (alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyltransferase (GGT), as well as inflammatory markers (high-sensitivity C-reactive protein (hsCRP)) assessed, along with screening for other modifiable CV risk factors such as smoking, hypertension, diabetes, and obesity.

All patients met the Slovak criteria for insurance-covered PCSK9 inhibitor treatment with inclisiran (Figure 1). Inclisiran was initially administered as a 284 mg subcutaneous injection, followed by a second dose after three months, and then a third dose after six months. A lipid profile was measured before each injection. In addition, at each visit, clinical information was recorded, including any ASCVD events or side effects. The therapy was discontinued if patients were non-compliant or if the treatment was ineffective, defined as less than a 40% reduction in LDL-C by the sixth to ninth month, or failure to reach the LDL-C target.

All patients underwent standard cardiology examinations. From an ethical standpoint, this study adhered to standard treatment protocols and was conducted as an observational study based on anonymous processing of results from routine examinations after patients

were selected for inclisiran therapy by the cardiologist. All participating patients provided informed consent for the anonymous use of their clinical data for statistical analysis.

The data analyzed in this study were processed and evaluated using SPSS version 20.0 for Windows (IBM Corp, 2011. IBM SPSS, 20.0, Armonk, NY: IBM Corp.). Continuous data are presented as median [25th percentile; 75th percentile] and categorical data as counts (%). Lipid levels are reported in mmol/L, while Lp(a) values are given in mg/dL. The primary outcomes were efficacy, defined as the relative reduction in LDL-C, and safety, defined as any adverse effects identified during regular check-ups. Secondary outcomes included absolute reduction in LDL-C, achievement of target LDL-C levels according to ESC/EAS guidelines, specific side effects, and discontinuation of PCSK9 siRNA (inclisiran) therapy.

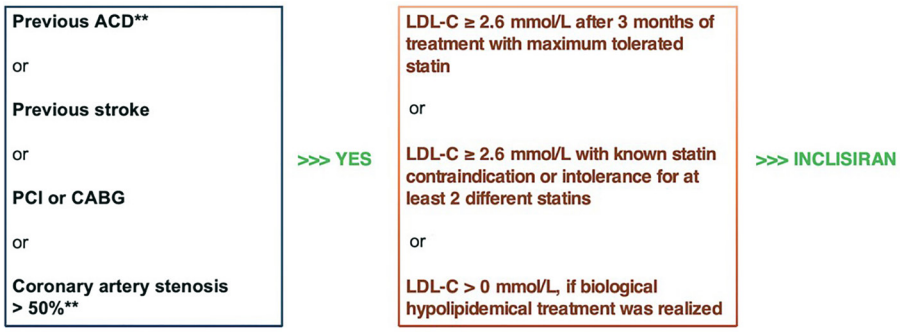
Results

Clinical characteristics of patients

During the observation period, a total of 36 patients in our clinic were approved for inclisiran therapy covered by health insurance. Of the 36 patients, 27 were diagnosed with ASCAD (75 %), including 15 patients with acute coronary syndrome (ACS) (41.67 %), 10 patients who underwent percutaneous coronary intervention (PCI) (27.77 %), and 2 patients who had coronary artery bypass graft surgery (CABG) (5.55 %) due to significant stenosis. Additionally, 9 patients had ischemic stroke (25 %). In terms of risk factors, 29 patients had arterial hypertension (80.6 %), 9 were obese (25 %), 4 had type 2 diabetes mellitus (11.1 %), and 16 patients were smokers (44.4 %), as shown in Table 1.

Regarding lipid-lowering therapy, 1 patient was included due to statin intolerance (2.8 %), 28 patients were on the maximum statin dose (77.8 %, atorvastatin 80 mg), and 7 patients were on a reduced dose (19.4 %): 3 patients on atorvastatin 40 mg (8.3 %), 2 patients on atorvastatin 20 mg (5.6 %), and 1 patient on lovastatin 20 mg (2.8 %). Six patients were also taking ezetimibe as a co-medication (16.7 %). The low percentage is due to the fact that ezetimibe use is not a criterion for inclisiran approval in Slovakia, and for most patients, LDL-C reduction with ezetimibe alone would not be sufficient to reach target LDL-C levels, but its use could disqualify patients from inclisiran therapy for failing to reach LDL-C levels > 2.6 mmol/L. There was no significant variation in the sample characteristics between genders.

Fig. 1. *Indication criteria of inclisiran in Slovakia*



ACD – acute coronary disease, CABG – coronary artery bypass graft surgery, LDL-C – low density lipoprotein, PCI – percutaneous coronary intervention

The baseline characteristics of the patients and their initial lipid profile levels, along with hsCRP values, are shown in Table 1.

Therapy effectiveness

During inclisiran administration, we observed a variable response in terms of changes in selected lipid parameters and hsCRP, as shown in Table 2. The reduction in LDL-C levels ranged from 41.88 % to 86.25 %, with a median of 57.5 ± 7.5 % (Figure 2). Patients who were on the maximum dose of high-intensity statins as concurrent therapy and had undergone a third blood draw (n = 28) experienced a greater median reduction in LDL-C compared to those on a reduced statin dose (n = 7): 61.5 ± 12.3 % vs. 53.2 ± 5.9 %. The absolute reduction in LDL-C levels was 2.1 ± 0.5 mmol/L. The reduction in Lp(a) levels was highly individual, ranging from 0 % to 58.33 %, with

Tab. 1. *Summarized characteristics of participants*

Determinant	
Patients (*n*)	36
Age (years)	60.2 ± 7.1
Male (*n*)	25 (69.4 %)
Female (*n*)	11 (30.6 %)
BMI (kg/m^2)	27.3 ± 3.6
ASCAD (*n*)	27 (75 %)
ACS (*n*)	15 (41.7 %)
PCI (*n*)	10 (27.8 %)
CABG (*n*)	2 (5.5 %)
Stroke (*n*)	9 (25 %)
Arterial hypertension (*n*)	29 (80.6 %)
Type 2 diabetes (*n*)	4 (11.1 %)
Obesity (*n*)	9 (25 %)
Smoking (*n*)	16 (44.4 %)
Statin – the highest tolerated dose (*n*)	28 (77.8 %)
Statin – reduced dose (*n*)	7 (19.4 %)
Statin intolerance (*n*)	1 (2.8 %)
Ezetimibe (*n*)	6 (16.7 %)
LDL cholesterol (mmol/L)	3.56 ± 0.53
HDL cholesterol (mmol/L)	1.32 ± 0.39
Total cholesterol (mmol/L)	5.36 ± 0.58
Triacylglyeroles (mmol/L)	1.6 ± 0.32
Lp(a) (mg/dL)	142.8 ± 45.62
hsCRP (mg/L)	0.35 ± 0.09

ACS – acute coronary syndrome, ASCAD – atherosclerotic coronary artery disease, BMI – body mass index, CABG – coronary artery bypass graft, HDL – high density lipoprotein, hsCRP – high sensitive C-reactive protein, LDL – low density lipoprotein, Lp(a) – lipoprotein a, PCI – percutaneous coronary intervention

a median of 14.3 ± 6.4 % (Figure 3). Regarding inflammatory markers, we observed a percentage decrease in hsCRP levels of 14.8 ± 8.7 %. There was no significant difference in the characteristics of the sample between genders. Additionally, significant LDL-C and Lp(a) levels reduction was observed also in patient with statin intolerance and ezetimibe monotherapy only.

Adherence to Therapy and Prevalence of Adverse Effects

A total of 97 doses of inclisiran were administered, including the first dose (n = 36), second dose (n = 32), third dose (n = 28), and fourth dose (n = 5). For 26 administrations (26.8 %), patients reported a burning sensation during the injection, which did not last more than 30 minutes after administration. In 4 cases (11.1 %), flu-like symptoms were reported the following day, but these did not persist for more than 24 hours. Adherence to therapy was nearly complete, with two patients refusing the second dose (5.55 %).

Discussion

This prospective study aimed to track the specifics of administering inclisiran in Slovakia, patient management, the efficacy of inclisiran administration compared to the documented results of clinical studies on reducing LDL-C and Lp(a) levels, as well as adherence and possible adverse effects, based on experiences from a single center.

As part of the management, patients were enrolled based on the indication restrictions for treatment covered by public health insurance (scheme). This included patients with a history of ACS, PCI, or CABG on arteries, or patients with confirmed stenosis in arteries > 50 %. These patients, who did not reach LDL-C levels ≥ 2.6 mmol/L after 3 months of treatment with the maximum tolerated statin (with or without ezetimibe), had documented statin intolerance as defined, or were already receiving approved biological hypolipidemic therapy, were indicated for therapy with inclisiran.

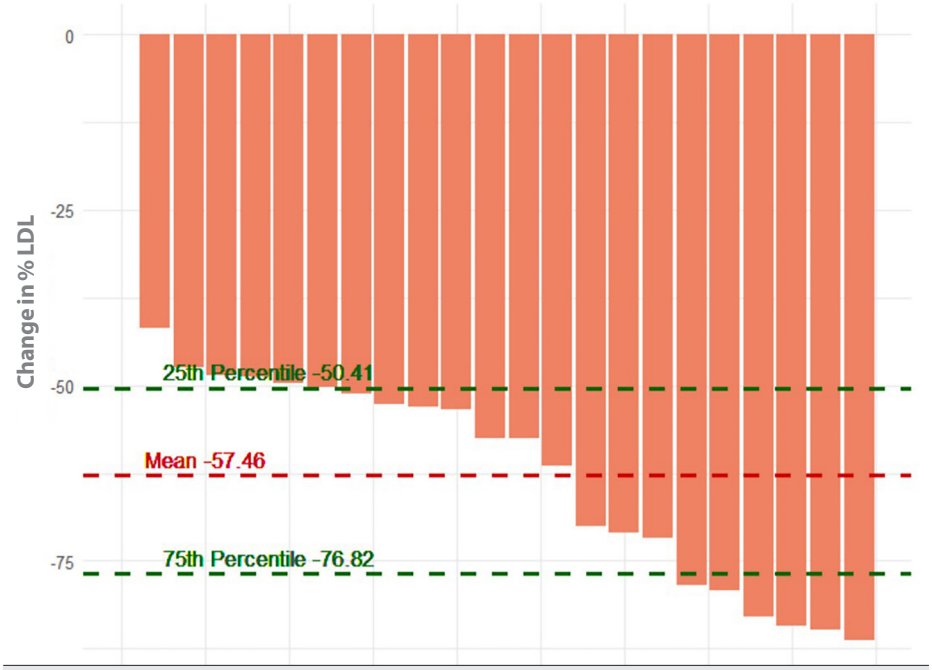
After meeting the criteria for covered therapy, a pre-prepared Excel file was used for the simple entry of patients, generating a request for approval of therapy by the insurance company, and calculating the intervals for the first,

Tab. 2. *The effect of administering 3 doses of inclisiran on selected biochemical parameters compared to baseline values*

Determinant	Value	P-value
LDL cholesterol (% change, mmol/L)	57.5 ± 7.5	< 0.001
LDL-C – highest toleranted statin (% change, mmol/L)	61.5 ± 12.3	< 0.01
LDL-C – reduced statin (% change, mmol/L)	53.2 ± 5.9	< 0.01
Lp(a) (% change, g/L)	14.3 ± .6.4	< 0.05
hsCRP (mg/L)	14.8 ± 8.7	< 0.05

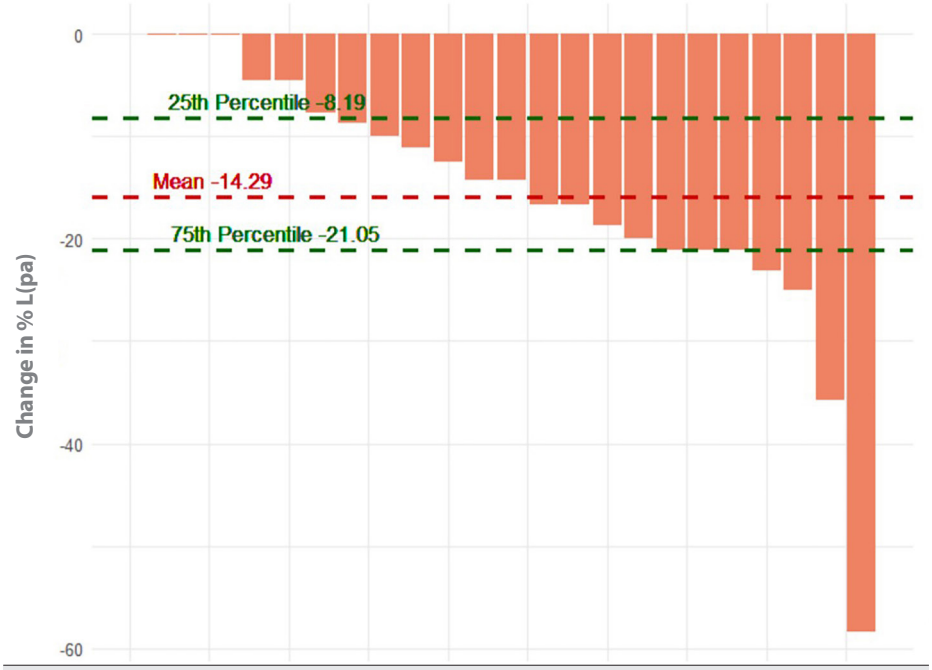
hsCRP – high sensitive C-reactive protein, LDL – low density lipoprotein, Lp(a) – lipoprotein a

Fig. 2. *Percentage change in LDL-C levels in individual patients after two doses of inclisiran compared to baseline values*



LDL – low density lipoprotein

Fig. 3. *Percentage change in Lp(a) levels in individual patients after two doses of inclisiran compared to baseline values*



Lp(a) – lipoprotein a

second, and subsequent doses, as well as for sampling before further approvals. The prepared application was then sent by mail or electronically, and the response was mostly recorded within a week. After approval of therapy for 2 doses and scheduling the patient for the administration date, the current dose of inclisiran was ordered based on the approval code from any pharmacy directly by our office, as it is a category A drug. The invoice due date for the pharmacy is usually 60–75 days, so the office incurs no costs before the payment of health therapy by the insurance company, which is guaranteed by the issued approval. During the administration of inclisiran, we encountered no problems. While submitting the application for therapy approval, 5 requests were rejected, due to the non-utilization of prescribed statin therapy by the pharmacy (for 2 patients), due to concurrent titration of the maximum tolerated dose of statin by the general practitioner (1 patient), and due to a one-week pause in the prescription of the maximum tolerated dose of statin (2 patients).

In terms of therapy efficacy, we observed similar results in our cohort of patients indicated for the therapy with inclisiran as in large clinical studies (10–13). We recorded a similar therapeutic effect on LDL-C levels, overall efficacy, and safety of therapy. However, we observed interindividual differences in the reduction of LDL-C, as well as in other monitored parameters. In this study, we found a median LDL-C reduction of 57.5 ± 7.5 %, which is higher than the reduction reported in other studies, where it ranged from 41 % to 46 % (or 49 % to 52 % when adjusted to placebo). Overall, the reduction of LDL-C in our study ranged from 41.88 % to 86.25 %.

Recently, several observational studies have been published with real clinical data regarding the efficacy and safety of inclisiran administration. Some of them pointed to similar LDL-C reductions as in the ORION-9–10–11 studies, while others indicated a lower decrease (14, 15). The authors reported a lower reduction in LDL-C levels than in clinical studies, with a median of 38 % in patients without statin co-medication and 45 % in patients with statin co-medication. Another study from the UK described an average decrease of 49 %, with the group receiving statin co-medication achieving up to 56% decrease, which represents similar results as in our cohort and in clinical studies (16). A lower efficacy was also demonstrated in a German cohort of 153 patients, which showed a reduction of 32 % in non-statin users and 42 % in patients with statin co-medication after a 3-month follow-up. After 9-month follow-up, reduction in LDL-C levels was observed compared to the 3-month follow-up (17). Since we did not have data from patients without statin medication after 2 doses of statins, we compared LDL-C reduction based on titrated statin therapy. We found that patients who had a maximum statin dose experienced a higher reduction in LDL-C (61.5 ± 12.3 %) compared to patients with a reduced statin dose (53.2 ± 5.9 %).

Differential efficacy in clinical studies and real-world data can be explained by several factors. First, some studies had follow-ups lasting 2 months instead of 3, while in our study, we compared LDL-C values one month after the third dose, which represents the standard procedure for approving the continuation of inclisiran therapy in Slovakia. The ORION-1 study indicated that the average LDL-C reduction was approximately 50 % after 2 months and 45 % after 3 months of inclisiran administration. Given the pharmacokinetics and effect of inclisiran, it is assumed that the most relevant data point is the LDL-C value after the third administration of therapy, as observed in the ORION studies. Additionally, the aforementioned British study had a higher percentage of patients with statin co-medication compared to the study by Mulder et al. (18) (53 % vs. 37 %), which may also have played a role, as demonstrated in other studies with PCSK9-mAbs (mAb – monoclonal antibodies), and which we also demonstrated in our study in the group with maximum doses of high intensity statins (18).

The cohort of most real-world studies is highly heterogeneous regarding accompanying lipid-lowering therapy. In our study, we found that patients treated with statins, especially at maximum doses, had significantly greater LDL-C reduction than patients not using statins. This finding is consistent with previous publications evaluating inclisiran in a real-world clinical practice cohort.

It is well known that statins induce the expression of the sterol regulatory element – binding protein 2 (SREBP-2), a process leading to increased transcription of LDL-R mRNA, as well as PCSK9, and thus to increased concentrations of PCSK9 in plasma (19). Previous studies have also shown that a greater reduction in LDL-C in response to statins is positively associated with plasma levels of PCSK9 (20). Moreover, the relationship between statin treatment and plasma concentrations of PCSK9 may explain variations in LDL-C response to statin therapy and subsequently to inclisiran response (21, 22).

Interindividual differences were also observed in the HEYMANS registry focusing on the real analysis of evolocumab PCSK9-mAb, which demonstrated substantial interindividual variability in LDL-C reduction (23). In addition to biochemical and molecular characteristics, there are also other possible factors explaining these differences. In controlled clinical studies, patients exhibit greater adherence to prescribed medications compared to observational studies due to more thorough supervision, regular monitoring, and a higher level of engagement. Furthermore, patients admitted to special lipid clinics are characterized by multiple drug intolerances. Thus, the cohort of observational studies with real clinical data may differ from clinical studies (24).

Some studies also described a slight increase in LDL-C levels after switching from PCSK9-mAb administration to inclisiran (25). In our cohort, we did not monitor the effect of this transition; however, it is known that the inhibition of PCSK9-mAb increases plasma concentrations of PCSK9 during the first 3 months after the injection of PCSK9-mAb due to delayed plasma clearance of PCSK9 induced by the PCSK9-mAb complex. This could be a potential reason why pre-treatment with PCSK9-mAb was associated with a less pronounced reduction in LDL-C. To what extent this may influence the magnitude of LDL-C reduction in response to inclisiran and what other pathways may contribute to the relationship between PCSK9 protein and LDL-C reduction is not fully known; however, it is assumed that after switching to inclisiran and stabilizing levels, any increase in LDL-C should not be significant.

Large clinical studies have demonstrated a reduction in Lp(a) levels of up to 30 % of

baseline values. The ORION-1 study showed a 15–19% reduction after 1 dose of inclisiran and a 19–25% reduction after 2 administrations over 150 days, but none of the reductions reached statistical significance. In the ORION-3 study, in the open-label continuation of ORION-1, the decrease was only by 6.3 % and 14.3 % in the group transitioning from PCSK9-mAbs (11). In the ORION-9 study monitoring patients with HeFH, the reduction was 17.2 % compared to placebo, but again, it was not significant (12). In contrast, the reduction in the ORION-10 studies was 25.6 % compared to placebo, while in the ORION-11 study, it was 18.6 %. All results were consistent with findings from studies involving PCSK9 antibodies, which also observed a similar decrease (13).

Monoclonal antibodies (mAbs) against PCSK9 reduce Lp(a) levels by approximately 20–30 % (16). In large clinical studies such as FOURIER with evolocumab and ODYSSEY OUTCOMES with alirocumab, a reduction of about 25 % in major adverse CV events (MACE) was noted (26, 27). In the ODYSSEY OUTCOMES study, patients with recent acute coronary syndrome had LDL-C levels close to 1.8 mmol/L and Lp(a) levels ≥ 13.7 mg/dL, which were associated with a significant clinical benefit from alirocumab therapy. In contrast, patients with LDL-C around 1.8 mmol/L but Lp(a) < 13.7 mg/dL showed no reduction in MACE with alirocumab, whereas patients with higher LDL-C levels consistently benefited from alirocumab treatment, regardless of Lp(a) levels (28).

In our study, we found a significant interindividual variation in Lp(a) reduction, ranging from 0 % to 58.33 %. In patients with elevated Lp(a) levels > 50 mg/dL (n = 5), the reduction in levels after adding inclisiran was more pronounced compared to patients with normal Lp(a) levels: 16.66 ± 5.7 % vs. 15.47 ± 5.4 %, which may explain and align with the findings from the aforementioned ODYSSEY OUTCOMES study. The exact mechanism by which PCSK9 inhibitors reduce Lp(a) levels remains unclear. Current hypotheses include increased clearance of Lp(a) particles through LDL receptors (LDL-R), increased clearance of Lp(a) via other receptors (LDL-R-related protein 1, cluster differentiation receptor 36, Toll-like receptor 2, scavenger receptor B1, and plasminogen receptors), as well as reduced production, secretion, or assembly of apo(a) (29).

hsCRP has been shown to be a reliable marker of underlying systemic inflammation, a strong and independent predictor of future CV events in individuals with and without established CV disease. Measurement of hsCRP can aid physicians in assessing CV risk and monitoring therapeutic interventions (30). Although PCSK9 inhibition does not reduce CRP levels in clinical studies, including ORION-1, -2, and -7, preclinical studies have provided substantial evidence for a relationship between PCSK9 and inflammation, as well as the impact of PCSK9 inhibition on the overall inflammatory process (31). In our study, we observed an average hsCRP reduction of 14.8 ± 8.7 %, but significant interindividual differences were present. Based on the sample size, it is difficult to predict the effect of inclisiran on hsCRP levels; we rather assume that it was influenced by the titrated statin levels or the interaction of the PCSK9 inhibition pathways themselves, but further studies are needed to demonstrate this effect.

In terms of side effects, our study showed slightly higher rates of local reactions compared to the clinical studies ORION-3, -9, -10, and -11 (14). When assessing adverse effects, we found that mild burning occurred in 38.23 % of total administrations during therapy. In studies ORION-3, -9, -10, and -11, the prevalence of injection site reactions was 3–17 % (15). The aforementioned UK real-world registry reported only 1 patient (1.3 %) with a moderate injection site reaction, while the German study reported 5 patients (3 %) (16,17). In our study, we did not observe any moderate or severe reactions. In studies ORION-9, -10, and -11, other types of reported side effects occurred with similar frequency in both groups (14). In real-world studies, fewer side effects (4–6 %) were reported, which were of a similar nature: myalgia, dizziness, headache, and fatigue, in addition to the previously mentioned mild injection site reaction (15). In our study, we monitored the above symptoms in 5.9 % of administrations, with a maximum duration of up to 24 hours. In the German study with PCSK9 mAbs, most side effects (74 %) were also reported in patients without concurrent lipid-lowering therapy. Although the etiology is not always known, for example, in the case of myalgia symptoms, it is important to listen to patients to arrive at an optimal tailored treatment plan to minimize individual ASCVD risk (17). Adherence to therapy was similar to that in clinical studies, and we observed therapy interruption in only 1 patient after the first dose of inclisiran, but not due to adverse effects. Furthermore, liver tests after starting treatment with inclisiran were comparable to baseline levels.

In conclusion, consistent with clinical trials and other studies in real clinical practice, our findings support that inclisiran has a favorable safety profile and can be an effective means of achieving LDL-C target values in patients at very high CV risk, which we achieved in 63.4 % of patients, compared to 0 % with LDL-C > 2.6 mmol/L based on inclusion criteria.

Limitations

This study has several limitations, most of which are characteristic of observational studies. The study is based on information reported by patients, and we did not measure drug (or metabolite) concentrations. Therefore, we cannot exclude the possibility that in some patients, the varying changes in LDL-C, particularly after the second and subsequent injections of inclisiran, may have been due to non-adherence to accompanying lipid-lowering therapy. The cohort was also highly heterogeneous and included patients with various diagnoses, albeit at very high CV risk, on different baseline lipid-lowering therapies. Finally, in this study, we did not distinguish between patients taking a statin and those receiving combination therapy with a statin and ezetimibe. This factor may have influenced the interpretation of the results, although the primary aim of this study was to highlight the fact that the addition of inclisiran to the initially initiated lipid-lowering therapy led to a more pronounced reduction in LDL-C and Lp(a). Despite the study's limitations, our data provide valuable insights into the effectiveness of inclisiran and the management of patients in real clinical practice in Slovakia.

Conclusions

Based on the results of this observational study describing experiences with inclisiran from a single center, we assume a comparable effect of administration as in clinical studies with nearly 100% adherence and without significant adverse effects. The overall management of patients receiving inclisiran therapy is straightforward, requiring no complex administration; the costs for ordering the therapy arise in the outpatient setting only after reimbursement by the health insurance company (with an invoice maturity of 60–75 days). Due to favorable indication criteria, the therapy is generally accessible, and administration is not limited to specialized centers. The therapy guarantees the achievement of target LDL-C values in over 63.4 % of patients, for whom we would not have reached target LDL-C values without this therapy. We anticipate that the availability and potential widespread implementation of this therapy in patients with very high CV risk could lead to better management of hyperlipidemia and significant reductions in CV morbidity and mortality. Since this is a pilot observational study with limitations regarding sample size, we expect the contribution of additional larger studies that would examine the more comprehensive effects of hypolipidemic therapy with inclisiran, involving multiple centers and a broader patient group.

REFERENCES

1. Vardas P, Townsend N, Torbica A, et al. European Society of Cardiology: cardiovascular disease statistics 2021. Eur Heart J. 2022;43(8):716-799.
2. Štatistický úrad SR. Najčastejšie príčiny úmrtia obyvateľov SR [Internet]. 2023 [cited 25-01-02]. Available from: https://statdat.statistics.sk/.
3. Český statistický úřad. Smrt v datech [Internet]. 2023 [cited 25-01-02]. Available from: https://statistikaamy.csu.gov.cz/.
4. Baigent C, Blackwell L, Emberson J, et al. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670-1681.
5. Nicholls SJ, Kataoka Y, Nissen SE, et al. Effect of evolocumab on coronary plaque phenotype and burden in statin-treated patients following myocardial infarction. JACC Cardiovasc Imaging. 2022;15(7):1308-1321.
6. Khvorova A. Oligonucleotide Therapeutics - A New Class of Cholesterol-Lowering Drugs. N Engl J Med. 2017;376(1):4-7.
7. Raal FJ, Kallend D, Ray KK, et al. Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia. N Engl J Med. 2020;382(16):1520-1530.
8. Alonso R, Arroyo-Olivares R, Muñiz-Grijalvo O, et al. Persistence with long-term PCSK9 inhibitor treatment and its effectiveness in familial hypercholesterolaemia: data from the SAFEHEART study. Eur J Prev Cardiol. 2023;30(4):320-328.
9. A Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People With Cardiovascular Disease (ORION-4). Available from: https://clinicaltrials.gov/ct2/show/NCT03705234. Accessed: November 16, 2024.
10. Ray KK, Stoekenbroek RM, Kallend D, et al. Effect of 1 or 2 doses of inclisiran on low-density lipoprotein cholesterol levels: one-year follow-up of the ORION-1 randomized clinical trial. JAMA Cardiol. 2019;4(11):1067-1075.
11. Ray KK, Troquay RP, Visseren FI, et al. Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial. Lancet Diabetes Endocrinol. 2023;11:109-119.
12. Raal FJ, Kallend D, Ray KK, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. N Engl J Med. 2020;382(16):1520-1530.
13. Katsiki N, Vrablik M, Banach M, et al. Inclisiran, low-density lipoprotein cholesterol and lipoprotein (a). Pharmaceuticals (Basel). 2023;16(4):577.
14. Padam P, Barton L, Wilson S, et al. Lipid lowering with inclisiran: a real-world single-centre experience. Open Heart. 2022;9(2):e002184.
15. Basile C, Gargiulo P, Merlini PA, et al. Efficacy and safety of inclisiran in real-world practice: insights from the Cholinet registry. Eur Heart J. 2023;44(Suppl 2):ehad655-2812.
16. Wright RS, Raal FJ, Koenig W, et al. Inclisiran administration potently and durably lowers LDL-C over an extended-term follow-up: the ORION-8 trial. Cardiovasc Res. 2024; 120(12):1400-1410.
17. Makhmudova U, Schatz U, Perakakis N, et al. High interindividual variability in LDL-cholesterol reductions after inclisiran administration in a real-world multicenter setting in Germany. Clin Res Cardiol. 2023;112(11):1639-1649.
18. Mulder JWCM, Galema-Boers AMH, Roeters van Lennep JE. First clinical experiences with inclisiran in a real-world setting. J Clin Lipidol. 2023;17(6):818-827.
19. Lagace TA. PCSK9 and LDLR degradation: regulatory mechanisms in circulation and in cells. Curr Opin Lipidol. 2014;25(5):387-393.
20. Dong B, Wu M, Li H, et al. Strong induction of PCSK9 gene expression through HNF1alpha and SREBP2: mechanism for the resistance to LDL-cholesterol lowering effect of statins in dyslipidemic hamsters. J Lipid Res. 2010;51(6):1486-1495.
21. Bao X, Liang Y, Chang H, et al. Targeting proprotein convertase subtilisin/kexin type 9 (PCSK9): from bench to bedside. Signal Transduct Target Ther. 2024;9(1):13.
22. Patnaik S, Pollevick ME, Lara-Breitinger KM, et al. Inter-individual variability in lipid response: a narrative review. Am J Med. 2022;135(12):1427-1433.e7.
23. Ray KK, Bruckert E, Peronne-Filardi P, et al. Long-term persistence with evolocumab treatment and sustained reductions in LDL-cholesterol levels over 30 months: final results from the European observational HEYMANS study. Atherosclerosis. 2023;366:14-21.
24. Vonbank A, Drexel H, Agewall S, et al. Reasons for disparity in statin adherence rates between clinical trials and real-world observations: a review. Eur Heart J Cardiovasc Pharmacother. 2018;4(4):230-236.
25. Arnold N, Koenig W. PCSK9 Inhibitor Wars: How Does Inclisiran Fit in with Current Monoclonal Antibody Inhibitor Therapy? Considerations for Patient Selection. Curr Cardiol Rep. 2022;24(11):1657-1667.
26. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376(18):1713-1722.
27. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med. 2018;379(22):2097-2107.
28. Bittner VA, Schwartz GG, Bhatt DL, et al. Alirocumab and cardiovascular outcomes according to sex and lipoprotein(a) after acute coronary syndrome: a report from the ODYSSEY OUTCOMES study. J Clin Lipidol. 2024;18(4):e548-e561.
29. Ying Q, Chan DC, Watts GF. New Insights Into the Regulation of Lipoprotein Metabolism by PCSK9: Lessons From Stable Isotope Tracer Studies in Human Subjects. Front Physiol. 2021;12:603910.
30. Libby P, Ridker PM. Inflammation and atherosclerosis: role of C-reactive protein in risk assessment. Am J Med. 2004; 116(Suppl 6A):S9-S16.
31. Landmesser U, Conde LG, Wright RS, et al. Effect of inclisiran on haematological and immunological biomarkers: a pooled analysis of ORION-9, -10, and -11 trial data. Atherosclerosis. 2021;331:E37.