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Fast Decline of Low-Density Lipoprotein Cholesterol after a First Dose of Inclisiran: A Case Report

Kinz W[1], Schnetzer L[2]*, Fraunberger P[3,4] and Drexel H[1,2,4]

[1]*Department of Internal Medicine & Intensive Care, County Hospital Bregenz, Bregenz, Austria*

[2]*Vorarlberg Institute for Vascular Investigation & Treatment (VIVIT), Dornbirn, Austria*

[3]*Medical Central Laboratories, Feldkirch, Austria*

[4]*Vorarlberger Landeskrankenhausbetriebsgesellschaft, Feldkirch, Austria*

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***Corresponding author:** Laura Schnetzer, Vorarlberg Institute for Vascular Investigation & Treatment (VIVIT), Campus V, Stadtstraße 33, 6850 Dornbirn, Austria, Email: laura.schnetzer@vivit.at

Abstract

Background: Inclisiran is a novel PCSK9 reducing drug acting via siRNA. Its advantage for adherence is a long action allowing for only twice-a-years' administration. However, study development programs did not investigate the early slope of lipid decrease, which nevertheless, would be of high interest because a faster lowering of LDL-C could lead to a better outcome for the patient. Therefore, in this case report, a close-meshed analysis of lipid effects after inclisiran administration is reported.

Patient information: An 84-year-old male patient was admitted to our hospital because of acute decompensated heart failure. His medical history included coronary artery disease and several cardiovascular risk factors, including hypercholesterolemia.

Findings: Due to an intolerance to three different statins the patient was not willing to take any oral lipid lowering therapy, thus he received inclisiran. His baseline LDL-C was 174mg/dL, and he received an initial subcutaneous dose of 284mg of inclisiran; LDL-C dropped to 138mg/dL (-21%) after five days, to 101mg/dL (-42%) after 10 days, 79mg/dL (-55%) after two weeks and 77mg/dL (-56%) after three weeks. The reduction of total cholesterol and apo-lipoprotein B ran approximately parallel to the course of LDL-C.

Conclusion: Inclisiran exerts a prompt lipid lowering effect after a first subcutaneous administration; LDL-C as well as total cholesterol and apo-lipoprotein B steadily decrease for two weeks before flattening. This comparably fast LDL-C reduction is one further strength of this new drug. From our data we conclude that, as early as two weeks after administration, the effect of the drug can be assessed.

Keywords: Kinetics; LDL cholesterol; Total cholesterol; Hyperlipidemia; Pharmacotherapy; Cardiovascular

Abbreviations: Apo-A: Apo-Lipoprotein A; Apo-B: Apo-Lipoprotein B; HDL-C: High-Density Lipoprotein-Cholesterol; LDL-C: Low-Density Lipoprotein-Cholesterol; PCSK9: Proprotein Convertase Subtilisin/Kexin type 9; siRNA: Small Interfering Ribonucleic Acid

Introduction

With the introduction of intense lipid lowering therapy, major interest has risen on the time course of low-density lipoprotein-cholesterol (LDL-C) lowering by statins, ezetimibe, bempedoic acid, PCSK9 (proprotein convertase subtilisin/kexin type 9) antibodies as well as the siRNA (small interfering ribonucleic acid) inclisiran.

In cardiology and vascular medicine, the velocity of the decrease is now an important topic due to the hypothesis that the faster LDL-C is lowered the better is the outcome of the patient, particularly with acute coronary syndrome and acute peripheral artery disease including critical ischemia [1,2]. From phase 3 studies and clinical trials we usually do not get close meshed data of LDL-C.

The aim of this report was to provide such a time course of LDL-C in an elderly patient. A second aim was to determine whether LDL-C measurements are necessary or if total cholesterol readings are sufficient to describe the time course of the effect. We had the opportunity to study the time course of LDL- and total cholesterol as well as of apo-lipoproteins after the application of the new PCSK9 siRNA inclisiran in a statin intolerant patient.

Case Report

We report on an 84-year-old male patient who was admitted to the medical department of the Bregenz County Hospital due to acute decompensated heart failure. Among his known diagnoses are the following noteworthy:

i. Triple vessel coronary heart disease with three bypass grafts (five years prior)

ii. A NSTEMI (three years prior) with implantation of two drug-eluting stents and a type IV myocardial infarction a few weeks post intervention

iii. Peripheral arterial occlusive disease was grade I according to the Fontaine classification

iv. Cardiovascular risk factors: hypercholesterolemia, diabetes mellitus type two and arterial hypertension.

The patient belonged to the very high-risk category, therefore, despite of his old age, an intensive lipid lowering therapy was pursued as a secondary prevention measure and due to an LDL-C of 174mg/dL, total cholesterol of 238mg/dL and triglycerides of 143mg/dL. He was not willing to take an oral lipid lowering therapy, as the medication with three different statins had always led to typical muscle pain which regularly resulted in discontinuation and resolved thereafter. The patient was therefore offered subcutaneous inclisiran twice yearly and was willing to adhere to this medication. He gave informed consent to the treatment with 284mg of inclisiran as a first dose. The drug had been approved in Austria and was reimbursed to the patient. The patient was not in a study, this is a mere clinical report.

Results

In the days after the administration of inclisiran, regular blood was drawn daily for clinical reasons. The lipid profile included determination of LDL-C as well as high density lipoprotein (HDL)-C, total cholesterol, triglycerides, Apo-A1 and Apo-B. LDL-C was determined by a direct method [3,4], details of the analytical methods have been published earlier [5].

The results over three weeks are displayed in Figure 1 and 2. Figure 1 depicts the course of LDL- and total cholesterol. A reduction from initially 174mg/dL LDL-C to 138mg/dL (-21%) was observed after five days. The LDL-C further dropped to 101mg/dL (-42%) after 10 days, 79mg/dL (-55%) after two weeks and 77mg/dL (-56%) after three weeks. The reduction of total cholesterol paralleled the course of LDL-C. As shown in Figure 2, a reduction of Apo-B, consistent with the reduction of LDL-C is evident, triglycerides also display a slight reduction, whereas HDL-C and Apo-A do not change. The patient tolerated the medication well and experienced no adverse effects. After the discharge from hospital, the patient was re-evaluated over the span of one year during further admissions to the hospital because of recurrent decompensated heart failure. During this year the cholesterol parameters stayed around the level of day 22.

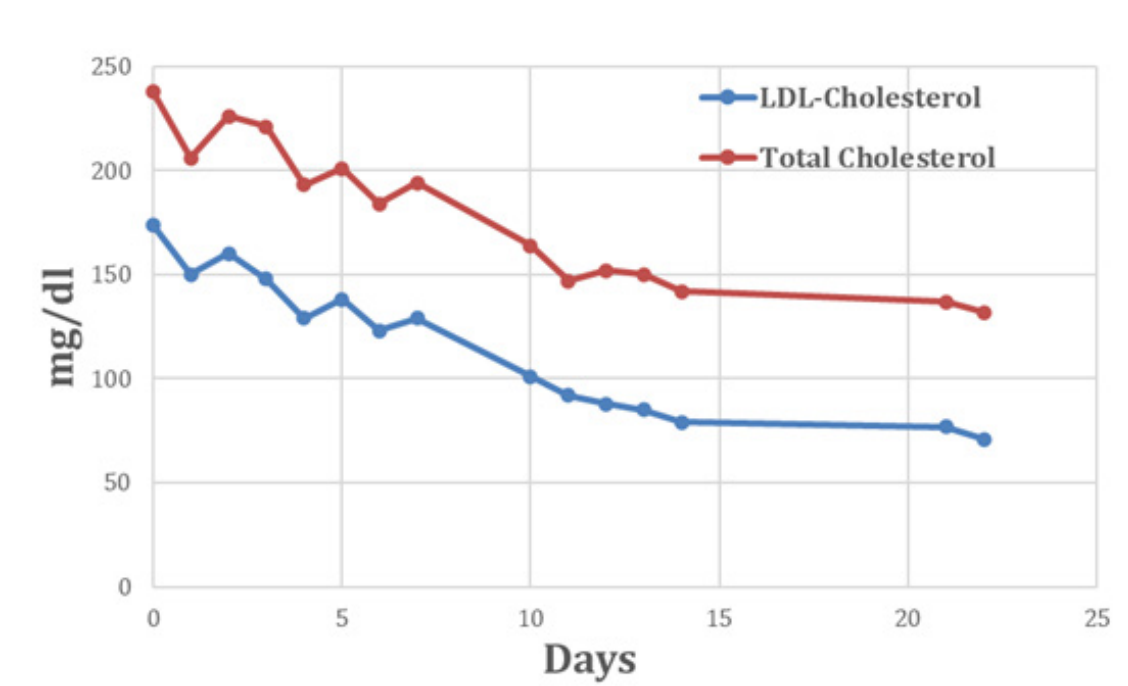

Figure 1: Therapeutic efficacy of inclisiran therapy (administered at day 0) in lowering LDL- and total cholesterol in a patient after an acute coronary syndrome. LDL = low density lipoprotein.

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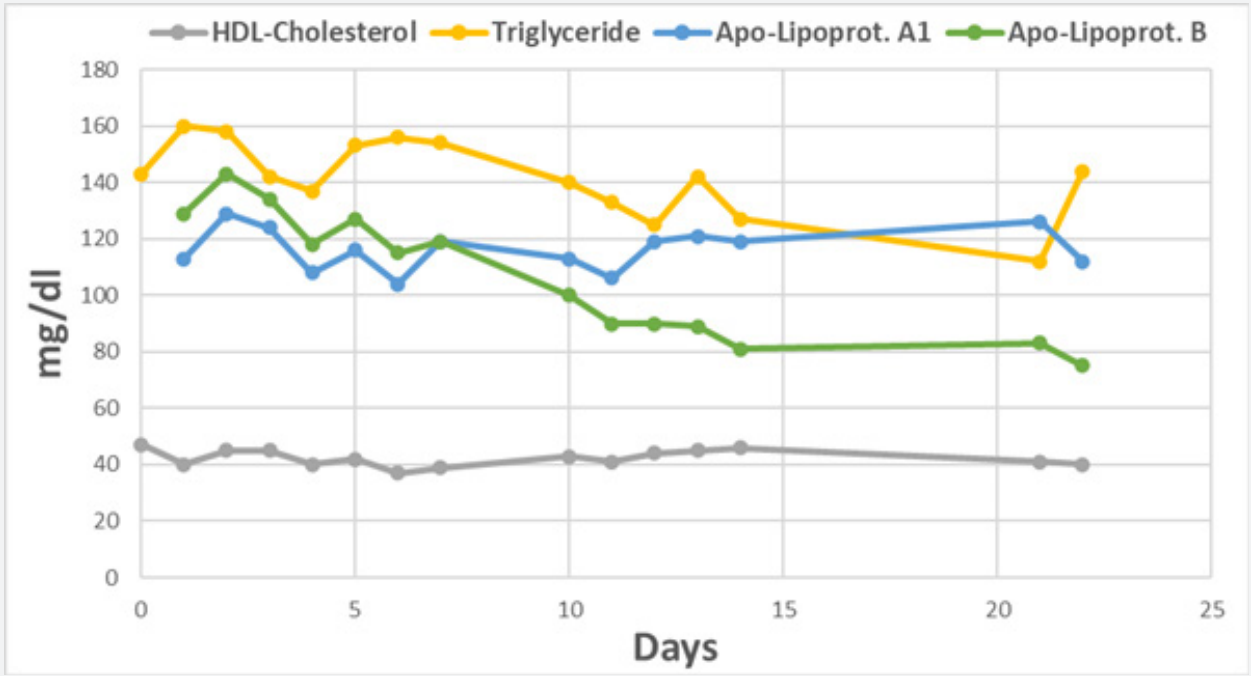

Figure 2: Different lipid parameters measured after the application of inclisiran (day 0) in the same patient as in Figure 1. HDL=high density lipoprotein.

Discussion

Inclisiran is a promising new lipid lowering drug. We could demonstrate the close-meshed time course of the most important lipids in the first three weeks after the administration of inclisiran in an elderly patient. Our data are novel in demonstrating a fast reduction of LDL-C within the first two weeks after the first subcutaneous administration of the drug.

No such data have been reported from the development program of the drug:

In the ORION trials [6-14], the first measurements were only taken after several weeks, whereas our data describes the early course with numerous readings and shows a steady decline of LDL-C during the first two weeks with a plateau thereafter. An early assessment of the efficacy of the therapy is necessary, as a fast lowering of the lipids is expected to lead to a better outcome of the patient [1]. Table 1 shows a comparison of different lipid lowering drugs concerning their LDL-C lowering capacity and duration until this reduction is obtained.

Table 1: Comparison of different lipid lowering drugs concerning their LDL-C Lowering Capacity and Duration until this reduction is obtained. PCSK9= Proprotein Convertase Subtilisin/Kexin Type 9, siRNA=Small Interfering Ribonucleic Acid, LDL-C=Low Density Lipoprotein-Cholesterol.

Drug class	Proportional LDL-C lowering compared to placebo	Maximum duration of therapy to attain the respective LDL-C reduction
Moderate-intensity statin	-30%	4 weeks [15]
High-intensity statin	-50%	4 weeks [15]
Ezetimibe	-20%	6 weeks [16]
PCSK9 antibodies	-60%	1-4 weeks [17]
Bempedoic acid	-20%	4 weeks [18]
PCSK9 siRNA	-50%	2-4 weeks [19]

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Furthermore, we could show that total cholesterol gives a good approximation of LDL-C after administration of inclisiran. However, our data is based solely on the measurements from a single patient and therefore must be interpreted with caution. Further research, including more patients is necessary to confirm our result.

In conclusion, it can be stated that inclisiran exerts a prompt lipid lowering effect after administration, LDL-C as well as total cholesterol steadily decrease for two weeks before flattening. This comparably fast LDL-C reduction is one further strength of the new drug inclisiran. From our data we conclude that as early as two weeks after administration the effect of the drug can be assessed. This allows for the early decision whether additional therapy is necessary to attain the goal of the target LDL-C.

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Author Contributions

WK and HD contributed to the study conception and design. Material preparation and data collection were performed by HD and WK, analysis by PF. The figures and tables were prepared by HD. All authors contributed to the interpretation of the data. The first draft of the manuscript was written by HD and LS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of Interests

The VIVIT research institute was supported by the State Government of Vorarlberg (Bregenz, Austria), which, however, exerted no influence on the present work in any way. Apart from that, the present study did not receive any financial support or grant from funding agencies in the public, commercial, or not-for-profit sectors. No potential conflicts of interest relevant to this article was reported by any author.

Ethical Approval and Data Availability

The study was conducted according to the principles of the Declaration of Helsinki. Informed consent for the publication was provided by the patient to WK and HD. All relevant data was presented in the case review. For further inquiries please contact the authors.

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