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The wind of change – PCSK9 inhibitors in hypolipidemic treatment. The Polish perspective

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ABSTRACT

Introduction and aim. Cardiovascular diseases are the main cause of mortality in the world. One of the alterable risk factors of ischaemic heart disease is dyslipidemia. Discovery and usage of a new group of drugs - PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors lead to a decrease of LDL-C (low-density lipoprotein cholesterol) levels in patients who are resistant to standard hypolipidemic therapy. The aim of this paper is to introduce PCSK9 inhibitors and describe their usage in medicine.

Material and methods. A review of the available literature was performed by searching the PubMed and GoogleScholar databases using the following key words: PCSK9 inhibitors; alirocumab; evolocumab; inclisiran.

Analysis of the literature. According to the European Society of Cardiology guidelines for dyslipidemias from year 2019, the main aim of dyslipidemia treatment is LDL-C reduction to target values depending on patient risk levels. It may be achieved in 2 ways, namely, by lifestyle modification or by pharmacological treatment with statins, fibrates and cholesterol absorption inhibitors. However, a therapy with PCSK9 inhibitors may be considered the most effective in certain groups of patients. Evolocumab and alirocumab are 2 representatives of those new drugs, which are allowed for use in 3 scenarios – in patients with familial hypercholesterolemia, in those with high risk of cardiovascular incident, and in those with statin intolerance. The major advantage of the aforementioned drugs is their safety. Since 2021 inclisiran (the first drug in siRNA class) is available for use as a new type of PCSK9 blocker.

Conclusion. PCSK9 inhibitors can be life-saving for patients with a high risk of cardiovascular incidents associated with an elevated level of LDL-C. They reduce LDL-C

more efficiently and have fewer side effects in comparison with the other hypolipidemic drugs. Therefore, PCSK9 inhibitors play a very important role in the lipid-lowering treatment.

Key words. PCSK9 inhibitors; familial hypercholesterolemia; alirocumab; evolocumab; inclisiran

Introduction

Cardiovascular diseases are the main cause of death, both, in Poland and all over the world. One of the modifiable risk factors of ischaemic heart disease are lipid disorders.¹ According to the 2011 NATPOL survey (*Ogólnopolskie Badanie Rozpowszechnienia Czynników Ryzyka Chorób Układu Krążenia NATPOL 2011*) lipid metabolism disorders concern 61% of the Polish population and only 8% of the patients are being treated effectively.² Interventional strategy (i.e. lifestyle modification vs. pharmacotherapy) depends on the total cardiovascular risk and the low-density lipoprotein cholesterol (LDL-C) level.² According to the European Society of Cardiology (ESC) 2019 guidelines regarding lipid disorders, the goal of dyslipidemia treatment is a reduction of LDL-C levels to target values, as follows:

- as secondary prevention in patients with very high cardiovascular risk, $\geq 50\%$ reduction of LDL-C levels compared to baseline and a target LDL-C level value of < 1.4 mmol/l (< 55 mg/dl) are recommended – recommendation class I, level of evidence A;

- as primary prevention in very high-risk patients without familial hypercholesterolemia (FH), $\geq 50\%$ reduction of LDL-C levels compared to baseline and a target LDL-C level value of < 1.4 mmol/l (< 55 mg/dl) are recommended – recommendation class I, level of evidence C;
- as primary prevention in very high-risk patients with FH, $\geq 50\%$ reduction of LDL-C levels compared to baseline and a target LDL-C level value of < 1.4 mmol/l (< 55 mg/dl) are recommended – recommendation class IIa, level of evidence C;
- in high-risk patients, $\geq 50\%$ reduction of LDL-C levels compared to baseline and a target LDL-C level value of < 1.8 mmol/l (< 70 mg/dl) are recommended – recommendation class I, level of evidence A;
- in moderate-risk patients, LDL-C level of < 2.6 mmol/l (< 100 mg/dl) should be considered as a target value – recommendation class IIa, level of evidence A;
- in low-risk patients, LDL-C level of < 3.0 mmol/l (< 116 mg/dl) may be considered as a target value – recommendation class IIb, level of evidence A.

Furthermore, a new group of extremely high risk patients has been distinguished. It includes those with Atherosclerotic Cardiovascular Disease (ASCVD), who suffered a second cardiovascular event within the previous 2 years (not necessarily of the same kind as the first one) despite of a highest tolerable dose of statins treatment. For this group LDL-C level of $< 1,0$ mmol/l (< 40 mg/dl) should be considered – recommendation class IIb, level of evidence B.³

The “baseline LDL-C level” concerns LDL-C levels in an individual who is not taking any hypolipidemic medication.

The secondary therapeutic target is to decrease the levels of apolipoprotein B (ApoB) and the non-HDL (non-high-density lipoprotein) cholesterol. The advantage of the ApoB and the

non-HDL cholesterol levels assessment is the reduced occurrence of diagnostic errors associated with high concentrations of the triglycerides (TG) in plasma.⁴

Aim

The aim of this paper is to present the new types of lipid-lowering drugs and their exceptional effectiveness in cholesterol reduction, compared to the methods applied so far, and to emphasise the relevance of this matter.

Material and methods

A review of the available literature was performed by searching the PubMed and GoogleScholar databases using the following key words: PCSK9 inhibitors; familial hypercholesterolemia; alirocumab; evolocumab; inclisiran.

Analysis of the literature

Non-pharmacological approach in dyslipidemia

All patients qualified for the pharmacological lipid-lowering treatment require additional non-pharmacological therapy. Healthy lifestyle, concerning the diet, weight control, physical exercise, and tobacco avoidance, optimises patients' lipidaemic profile and, therefore, decreases their cardiovascular risk. Among the general recommendations are the following:

- caloric supply adjusted to energetic needs;
- fruit (min. 200 g/day), vegetable (min. 200 g/day), non-salted nuts (30 g/day), wholegrain bread and omega-3-rich fish (twice a week) consumption;
- reduction of saturated fats consumption and replacement of those with mono- and polyunsaturated fatty acids;
- consumption of carbohydrates rich in fibre (especially the soluble one);
- reduction of salt consumption to < 5 g/day;

- reduction of ethanol consumption to < 100 g/week in women and men;
- reduction of artificially-sweetened beverages and foods consumption;
- 2,5 - 5 hours of moderate physical activity per week or 30-60 min in majority of the days;
- healthy weight achievement and maintenance - BMI 20–25 kg/m², abdominal circumference < 80 cm in women and < 95 cm in men;
- avoidance of tobacco exposition of any kind.⁵

Pharmacological treatment

1) Statins

Inhibition of the 3-Hydroxy-3-methylglutaryl coenzyme A reductase, one of the key enzymes in cholesterol synthesis, results in LDL-C reduction by 30-60% on average, TG reduction by 20-45% and HDL (high-density lipoprotein) increase by 5-15%. Statins decrease the morbidity and mortality caused by cardiovascular diseases.⁶

2) Fibrates

The alpha-receptors agonists activated by the peroxisome proliferators work through the transcription factors. Fibrates increase the lipoprotein lipase activity by enhancing fatty acid oxidation and decreasing TG synthesis in the liver. Furthermore, they increase the apolipoprotein AI and AII production, which belong to HDL group. Fibrates decrease TG levels by 30-50% on average and increase HDL cholesterol levels by 5-10%.⁶ Additionally, the pleiotropic anti-inflammatory, antioxidant and anticlotting effect of both statins and fibrates is of significant importance.⁷

3) Cholesterol absorption inhibitors

Ezetimibe inhibits cholesterol absorption in small intestine, which decreases its influx to the liver. As a result, LDL receptor expression of hepatocytes increases, thanks to which

“endogenous” LDL-C is being absorbed in greater quantities. Combined statin/ezetimibe therapy results in further decrease of LDL levels by 25%. Due to their low availability and the caused adverse effects, nicotinic acid (niacin) and bile acid sequestrants play a less significant role in the treatment.⁶

The drugs that are setting a new direction in the pharmacotherapy of dyslipidemia are PCSK9 inhibitors.

What are PCK9 inhibitors?

Historical overview:

- year 2003:
 - proprotein convertase subtilisin/kexin type 9 (PCSK9) was described by Nabil G.Seidah (Canada). Its first name: NARC-1 (neural apoptosis-regulated convertase) - a group of scientists from Paris (Abifadel et al.) described the correlation between the PCSK9 gene mutation and the FH.

- year 2015:
 - the first representative - alirocumab - was accepted for clinical use by the FDA (The United States Food and Drug Administration).

PCSK9 is a protein synthesised mainly by the liver, with the enzymatic activity of a serine protease. Additionally, it is expressed in lesser quantities in the intestines, the kidneys and the brain. Its gene is located on the chromosome 1.⁸

The PCSK9 protein binds to the LDL-C receptor (LDLR) on the liver cell surface and, together with LDL-C, enters the cell in the process of endocytosis, subsequently mediating the lysosomal degradation of this complex. Consequently, the number of the LDLR is being

decreased, both, on the liver cell surface and those circulating in blood, which leads to LDL-C level elevation.^{9,10}

The discovery of this mechanism was accidental and regarded two groups of patients - those with very high LDL-C levels, diagnosed with autosomal dominant hypercholesterolemia - gain of function mutation of the PCSK9 protein; and those with very low LDL-C levels (< 20 mg/dl) - loss of function mutation, where the nonfunctioning PCSK9 protein is not binding to LDLR, which results in the receptors resurfacing and effectively reducing the LDL-C. It was an inspiration for further investigations of diverse ways to inhibit the PCSK9 protein (by monoclonal antibodies or by RNA interference), which could aid the statins in the efficient LDL-C reduction.⁹

Familial hypercholesterolemia

The PCSK9 gene mutation, resulting in an increased PCSK9 protein activity, is one of the main mutations responsible for the FH occurrence. As can be seen from the following statistics:

- 1:500 – 1:200 are the heterozygotic FHs (LDL-C usually within 5-14 mmol/l);
- 1:300000 – 1:160000 are the homozygotic FHs (no LDLR activity, LDL-C may significantly surpass 13 mmol/l, coronary artery disease is estimated to occur at 10 years of age and acute coronary syndrome by 20 years of age);
- 10 000 000 affected patients; 190 000 patients in Poland;
- 100 times greater risk of mortality;
- signs and symptoms of coronary disease in 50% of patients before 55 years of age.^{9,11,12}

How was the knowledge of PCSK9 inhibitors used in the context of the FH and the high cardiovascular risk?

PCSK9 inhibitors are a new alternative in hypolipidemic treatment. They are a perfect choice for the patients, in whom the targeted LDL-C levels cannot be achieved with the standard treatment, as well as in those who cannot use statins due to the severe side effects.

The monoclonal antibodies against PCSK9 - evolocumab and alirocumab belong to this group. They were used in studies on 3 different types of patients, namely, those with high cardiovascular risk, those with FH and those with statin intolerance.^{9,13} They were proven to be highly effective in reducing LDL-C levels (by 45-65% compared to placebo, depending on the group of patients, and by approximately 35-45% compared to the ezetimibe therapy) and allowed to achieve the therapeutic goals in as many as 80-90% of the subjects. Furthermore, they regulate the levels of other lipid profile parameters, effectively reducing the non-HDL-C (by approximately 50% on average, compared with placebo), apoB (approx. 50%), TG (15–20%) and lipoprotein(a) (Lp(a), approx. 25%) levels, as well as, increasing the HDL-C (5–10%) and apoA1 (3–5%) levels.^{9,13,14} The available research shows that PCSK9 inhibitors used in monotherapy can lower the LDL-C levels by 60% on average, and by up to 85% in polytherapy with statins and ezetimibe.⁹ Evolocumab and alirocumab were approved for use by the FDA and European Medicine Agency (EMA) in the following cases:

- 1) in adults with primary hypercholesterolaemia (heterozygous familial and non-familial);
- 2) in mixed dyslipidemia as the diet complementation:
 - a) in combined therapy with a statin or a statin and another lipid-lowering drug in patients in whom the target LDL-C concentration cannot be achieved with the highest well-tolerated statin dose;
 - b) in monotherapy or combined with another lipid-lowering agent in statin-intolerant patients or for whom statin use is contraindicated.

Evolocumab – according to the TAUSSIG and TESLA studies, it should be considered in combination with other hypolipemising drugs in patients of more than 12 years of age with the homozygous FH.^{9,14}

The FOURIER¹⁵ (evolocumab) and ODYSSEY OUTCOMES¹⁶ (alirocumab) studies proved the great effectiveness of both PCSK9 inhibitors in the context of reducing the main endpoint (cardiovascular events) by 15%, and showed that alicumab can additionally significantly reduce the number of deaths regardless of the cause (also by 15%).⁹ Sub-analyses in subgroups of patients who suffered a myocardial infarction with stroke; several cardiovascular events; an epidemiologically recent myocardial infarction; a myocardial infarction with concomitant peripheral vascular disease or multifocal atherosclerosis; a myocardial infarction with other risk factors, namely diabetes, elevated hsCRP, Lp(a), or with different baseline LDL-C levels, or finally in patients with a long follow-up period (> 3 years), not only showed significant effectiveness of PCSK9 inhibitors¹⁶, but also were a starting point for identifying patients at extreme cardiovascular risk and creating a reimbursement program that has been available in Poland for the patients with FH since the 1st of November 2018, and, subsequently, since the 1st of November 2020 for those who suffered a myocardial infarction.⁹ Currently, treatment for patients with FH with LDL-C > 100 mg/dl (2.5 mmol/l) is available, with a prior 3-month therapy with statins and ezetimibe.⁹

Moreover, it is worth noting that the EVOPACS and EVACS studies on evolocumab^{18,19} and the VCU-AlirocRT study on alicumab²⁰ proved the effectiveness of PCSK9 inhibitors used immediately after an acute coronary syndrome (ACS), which resulted in a new recommendation in the latest ESC/EAS 2019 guidelines - to start the PCSK9 inhibitors treatment already during the hospitalisation (recommendation level IIa C).⁹ The EVACS study showed that the usage of evolocumab immediately after an ACS was associated with a significant reduction in LDL-C already after 3 days (to average concentration of 1.3 mmol/l),

and to less than 1 mmol/L (40 mg/dL) after 4–7 days of use, compared to the control group. This early therapy resulted in achieving the target LDL-C level of less than 55 mg/dl in 65.4% of the patients at discharge, and more than 85% of the patients 30 days into the treatment.^{9,19}

PCSK9 inhibitors safety

Thus far, results of the clinical trials regarding the safety of the PCSK9 inhibitors have been favourable. The important advantage of the PCSK9 inhibitors, over the other lipid-lowering drugs, is their better tolerance. Furthermore, they cause significantly less muscular symptoms compared to statins, while skin complications (resulting from subcutaneous administration of monoclonal antibodies) are not notably more common in the patients using the PCSK9 inhibitors than in those using other drugs. The most common side effects reported during the treatment were: myalgia (27.2%), back pain (12.2%), nasopharyngitis (9.3%), headache (9.2%), upper respiratory tract infections (9%), flu-like symptoms (7.5%), arthralgia (7%) and increased alanine aminotransferase (ALAT) and/or aspartate aminotransferase (AST) levels up to 3 times above the upper limit (6%).²¹ Treatment during pregnancy is, however, not recommended, unless the woman's clinical condition requires therapy with alirocumab (category C).²²

Routes of administration

The available medications are administered parenterally in subcutaneous injections:

- Alirocumab (trade name Praluent) - 1 ml solution (75mg and 150mg - different strengths) intended for use once every two weeks or 300 mg once a month.²²
- Evolocumab (trade name Repatha) - solution of 140 mg/ml pre-filled 1 ml syringe, recommended doses: 1x140 mg / 2 weeks or 420 mg/month (in homozygous FH 420 mg / 2 weeks).

Treatment limitations

The PCSK9 inhibitors are very potent in reducing, both, LDL-C levels and, when combined with a statin and/or ezetimibe, the risk of cardiovascular events. However, due to the cost of the treatment and the limited data on their long-term safety, they may be deemed cost-effective solely in patients at very high risk of atherosclerotic cardiovascular disease solely. Furthermore, in countries with limited health care resources the therapy may not be possible whatsoever.³

Inclisiran – new treatment possibilities

Inclisiran is the first drug in the siRNA (small interfering RNA) class, which in 2021 was registered for use in Europe - to reduce cholesterol, with two doses per year.²⁴ It works by interfering with RNA, thereby reducing the production of the PCSK9 protein, which results in reduction of the LDL-C levels. The drug was registered based on the results of the ORION clinical program, in which it was proven that it reduces LDL-C levels by up to 52% in patients with elevated LDL-C levels despite of the therapy with maximal well-tolerated dose of statins. With only two doses yearly - the second one 3 months after the initial one, it facilitates long-term treatment compliance.²⁴⁻²⁶ Inclisiran is approved for treatment in adults with primary hypercholesterolemia (heterozygous familial or non-familial) or mixed dyslipidemia in combination with a statin or a statin and another lipid-lowering drug in the following scenarios: when the LDL-C level goal cannot be achieved with the highest well-tolerated statin dose (in monotherapy or in combination with other lipid-lowering agent), in statin-intolerant patients, and in those for whom statins are contraindicated. In three clinical trials with patients taking inclisiran, a reduction in LDL-C was observed in each 6-month period prior to the following dose. The drug was well tolerated in the phase III trials.²⁴

Conclusion

Dyslipidemia (especially the high LDL cholesterol blood levels) is an important risk factor of ischaemic heart disease - one of the main mortality causes around the world. PCSK9 inhibitors are a new type of drugs - a step forward in dyslipidemia treatment and ischaemic heart disease prevention thanks to their distinct efficacy in the LDL cholesterol levels reduction. Importantly, the aforementioned drugs are safe, well-tolerated and their combination with other medicaments, including statins, is possible. Consequently, they are revolutionary in treating patients in whom other hypolipemising drugs were unsuccessful in optimising the LDL cholesterol levels.

Declarations

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Author contributions

Conceptualisation, N.I.; Methodology, P.Z.; Software, M.S.; Validation, D.M.; Formal Analysis L.A.; Investigation, P.Z.; Resources, M.S.; Data Curation, D.M.; Writing – Original Draft Preparation, N.I.; Writing – Review & Editing, N.I., M.S.; Visualisation, P.Z.; Supervision, D.M.; Project Administration: N.I., L.A.

Conflicts of interest

Authors have no conflicts of interest to declare.

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