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INCLISIRAN: A SYSTEMATIC REVIEW OF THE BENEFITS OF PROMISING LIPID-LOWERING IN THE TREATMENT OF DYSLIPIDEMIAS

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Abstract: Objective: To evaluate the reduction of negative outcomes and increase in survival with the new lipid-lowering therapy on the market, as well as its superiority in relation to other drugs, having as a fundamental principle of management the reduction of LDL cholesterol levels. **Methods:** An integrative review was carried out, using as criteria the search in the National Library of Medicine (PubMed) and Scientific Electronic Library Online (SciELO) databases using the descriptors (i) inclisiran (ii) PCSK9, (iii) dyslipidemias with the Boolean operator "AND". Studies published from 2018 to 2022 were included. **Results:** The approved inclisiran has been shown to reduce LDL cholesterol levels by more than 50%, it also brings as a positive point the factor of durability of the therapy, being proposed as a vaccine for patients with dyslipidemia, the which is an immeasurable advance in cardiology and endocrinology in recent years, not requiring daily doses of medication, which facilitates therapeutic adherence and the reduction of cardiovascular outcomes. With adverse effects, 4.69% of patients who received inclisiran reported an injection site reaction, all reactions were transient, there was no evidence of liver, kidney, muscle or platelet toxicity. **Final considerations:** PCSK9 inhibitors are a welcome addition to our approaches to reducing LDL-C and cardiovascular events in patients with high levels of dyslipidemia and refractory to conventional treatments.
Keywords: Dyslipidemia; Inclisiran; PCSK9.

INTRODUCTION

Low-density lipoprotein (LDL-C) is a major causal factor for atherosclerotic cardiovascular disease (CVD), with cumulative exposure to LDL-C over the individual's lifetime crucial to CVD development (KALLEND D et al., 2022).).

Since the risk of atherosclerotic cardiovascular disease is determined by the degree and duration of an elevated LDL cholesterol level, the goal of management must be initiation of therapy to reduce LDL cholesterol levels, statins are considered essential in global guidelines for the management of care for patients with clinically manifest coronary artery disease (WRIGHT et al., 2020).

However, many patients do not achieve optimal LDL-C reduction or experience cardiovascular events despite statin therapy. Initial therapeutic approaches to reducing circulating levels of PCSK9 focused on the use of monoclonal antibodies. This approach sequesters all of the PCSK9 from the reticuloendothelial system, thus preventing it from binding to the LDL receptor. Circulating PCSK9 is derived almost entirely from the liver; therefore, therapeutic approaches that target the hepatic production of PCSK9 may offer an alternative to the use of monoclonal antibodies (KASTELEIN et al., 2018).

Monoclonal antibodies directed against proprotein convertase subtilisin-kexin type 9 (PCSK9) have been shown to reduce LDL cholesterol levels by more than 50%, but require administration every 2 to 4 weeks. Phase 2 studies show that a biannual injection of inclisiran, a small interfering RNA, was shown to inhibit hepatic synthesis of PCSK9 in adults with heterozygous familial hypercholesterolemia (WRIGHT et al., 2020).

Inclisiran is an experimental, chemically synthesized siRNA molecule that produced sustained silencing of hepatocyte-specific and PCSK9-specific RNA in healthy volunteers up to 84 days after administration. Novel approaches involving monoclonal antibodies that interfere with PCSK9-LDLR interaction or RNA interference preventing PCSK9 synthesis are associated with substantial LDL-C declines among individuals with suboptimal LDL-C levels despite being on optimal background therapy with statins with or without other lipid-lowering agents. Pharmacological inhibition of PCSK9 has a favorable safety profile, but long-term safety still needs to be proven (KARAKAS et al., 2018).

Therefore inclisiran may represent a new and potent therapeutic option for patients with elevated LDL-C who are unable to tolerate statins. There is the possibility that we are facing a presumptive vaccine for dyslipidemia, with the ultimate purpose of lipid-lowering therapy to reduce the risk of atherosclerotic cardiovascular disease (CVD) (LEITER et al., 2020).

REVISION

INCIDENCE AND PREVALENCE OF DYSLIPIDEMIAS

With the change in lifestyle and eating habits in recent decades, a significant increase in metabolic, cardiovascular and cerebrovascular disorders in the population can be noticed. Currently, dyslipidemias generate major disorders for public health, since it is the main risk factor for atherosclerotic cardiovascular diseases.(9) In addition to the hereditary lipid syndromes that significantly increase cardiovascular risk events. (DONALD et al., 2022)

According to the 2021 update of the Brazilian Guidelines on Familial Hypercholesterolemia, the prevalence of the disease is 1:200 to 1:300 in heterozygous FH (HeFH) and 1:160,000 to 1:300,000 in homozygous FH (HoFH). FH is a common genetic cause of early coronary heart disease, due to exposure to high concentrations of LDL-c. About 85% of men and 50% of women can have a coronary event before reaching age 65. Approximately 200,000 people/year worldwide die from premature coronary heart disease due to appropriate treatments.

(ASSAD et al., 2021).

CLASSIFICATION

Dyslipidemias can be classified into hyperlipidemias, where we find high levels of lipoproteins and hypolipidemias in which the levels are reduced, are classified according to their etiology as primary and secondary. Where the underlying disorder is genetic in primary dyslipidemias and in secondary dyslipidemia, it comes from inadequate lifestyle, medication use and the individual's morbid conditions (AFIUNE, et al., 2018).

The laboratory classification is of great importance because it stipulates the reference values to which they serve for diagnosis and monitoring of the treatment of patients with dyslipidemias, being a fundamental tool to verify if the patient is within the stipulated target for their cardiovascular risk (AFIUNE, et al., 2018).

The phenotypic classification is currently little used due to the low contribution to the diagnosis of the etiology, but it is based on the patterns of lipoproteins, associated with high concentrations of cholesterol and triglycerides, not taking into account HDL-C cholesterol (AFIUNE, et al., 2018).

DIAGNOSIS

As an essential tool, laboratory tests serve both for diagnosis and monitoring of dyslipidemic patients (AFIUNE, et al., 2018).

Isolated hypercholesterolemia	Isolated increase in LDL-c (LDL-c ≥ 160 mg/dL).
Isolated hypertriglyceridemia	Isolated increase in triglycerides (TG ≥ 150 mg/dL or ≥ 175 mg/dL, if sample taken without fasting).
Mixed hyperlipidemia	Increase in LDL-c (LDL-c ≥ 160mg/dL) and TG (TG ≥ 150mg/dL or ≥ 175 mg/dL, if the sample is obtained without fasting)).
HDL-c low	HDL-c reduction (men < 40 mg/dL and women < 50 mg/dL)

TABLE 1 - LABORATORY CLASSIFICATION (Prepared by the authors).

For the diagnosis of FH, clinical/biochemical screening must be performed and, if possible, as a definitive method, genetic testing (analysis of the LDLR, ApoB and PCSK9 genes) is necessary, which is the reference standard for the diagnosis of familial hypercholesterolemia (AFIUNE, et al., 2018).

CARDIOVASCULAR RISK STRATIFICATION

There are algorithms for assessing cardiovascular risk, but the one recommended by the Brazilian Guideline on dyslipidemia and prevention of atherosclerosis is the Global Risk Score (ERG), which estimates the risk of cardiovascular outcomes in 10 years, can be used both in patients undergoing treatment lipid-lowering or not in individuals who were not classified in the very high or high risk conditions, where they are classified later according to the risk obtained (MICHEL, 2021).

For patients who are not using lipid-lowering drugs, those who have significant atherosclerotic disease, that is, who have a vascular occlusion greater than or equal to 50% in the arterial territory, are considered to be at very high risk, and high-risk patients

are those who have atherosclerosis. diagnosed subclinical disease, patients with aortic aneurysm, chronic kidney disease undergoing dialysis, those with LDL-C greater than or equal to 190 mg/dl and patients with type 1 or 2 DM with LDL-C between 70-189 mg/dl with risk stratifiers (ER) or subclinical atherosclerotic disease (DASC). Patients considered at intermediate risk are those whose ERG is between 5 and 20% in males and between 5 and 10% in females or diabetics without the criteria for DASC or RE and low risk male and female patients with risk in 10 years < 5%, calculated by the ERG (AFIUNE, et al., 2018).

THERAPEUTIC GOALS TO REDUCE LDL-C AND NON-HDL CHOLESTEROL IN PATIENTS WITH OR WITHOUT HYPOLIPEMIATING THERAPY

WITHOUT STATIN		WITH STATIN	
RISK	REDUCTION %	LDL-C GOAL (mg/dl)	GOAL OF NOT HDL (mg/dl)
VERY HIGH	> 50 %	<50	< 50
HIGH	>50%	<70	< 70
INTERMEDIARY	30-50%	< 100	<100
LOW	> 30%	< 130	<130

TABLE 2- THERAPEUTIC GOALS FOR REDUCTION OF LDL-c AND NON-HDL CHOLESTEROL IN PATIENTS WITH OR WITHOUT HYPOLIPEMIATING THERAPY (DESIGNED BY THE AUTHORS)

MACRO AND MICROVASCULAR COMPLICATIONS

Dyslipidemia is considered as one of the main determinants in the occurrence of cardiovascular and cerebrovascular diseases, among them atherosclerosis, which consists of the thickening and loss of elasticity of the artery walls, acute myocardial infarction and stroke. However, dyslipidemia and SAH are identified as multifactorial and prevalent diseases in the population that generate lesions systemically according to the chronicity of the condition, thus being a condition that requires strict control (KASTELEIN et al., 2018).

INCLISIRAN: A VACCINE FOR CORONARY ARTERY DISEASE

LDL-C cholesterol control is one of the most important tools for reducing cardiovascular and atherosclerotic events, there is an advance in lipid-lowering therapies, from statins, ezetimibe, subtilisin kexin 9 protein convertase inhibitors, which reduce both LDL-C as negative cardiovascular outcomes.

PCSK9 inhibitors are today considered a poster child for advances in science, with the use of monoclonal antibodies such as Evolucumab and Alirocumab and the big star is the small interference ribonucleic acid (siRNA), which we have as an example the inclisiran that modulates and inhibits PCSK9.

Studies demonstrate the efficacy and safety of inclisiran, where it has recently been approved by the FDA (approved by the European Commission and under review by the US Food and Drug Administration). The approved inclisiran uses a trianterary ligand, which has minimal inflammatory reactions at the injection site as side effects, which strengthens its use, in addition to being a drug that can be used in patients whose side effects of statins prevent their use or their use in optimal doses leading to inappropriate treatment.

Among statin-tolerant or non-intolerant individuals, it proved to be an effective drug in the treatment of dyslipidemia, being able to reduce more than 50% of LDL-C in addition to the already reduced use of high-potency statins at optimized and tolerated doses, it also brings as a positive point, the therapeutic

durability factor, being proposed as a vaccine for patients with dyslipidemia, which is an immeasurable advance to cardiology and endocrinology in recent years, not requiring daily doses of medication, which facilitates therapeutic adherence and reduction of cardiovascular outcomes (KASTELEIN et al., 2022).

CLINICAL USE OF NEW THERAPIES

Inclisiran promises to usher in a new era in the treatment of dyslipidemias using monoclonal antibodies. Anti-PCSK9 antibodies reduce LDL-C by more than 60% and, to a lesser extent, cholesterol not bound to high-density lipoproteins or apolipoprotein B, induce a decrease of approximately 27% in lipoprotein A and triglycerides to a moderate and variable degree, in addition to increasing, in general less than 10%, HDL cholesterol and apo A1. This drug has demonstrated efficacy in relation to previously used drugs (statins, ezetimibe, resins and fibrates) (MIRANDA; BOTET,2022)

An injection of inclisiran (Lequio) was recently approved by the Food and Drug Administration (FDA) for use in adults with heterozygous FH or clinical atherosclerotic cardiovascular disease who need to lower LDL-C levels for use in conjunction with diet and statins. The approved treatment starts with an injection of 284 mg, after three months the second dose is given and follows the continued treatment once every six months (KASTELEIN et al., 2020).

IMPACT OF INJECTABLE SIRNA ON CARDIOVASCULAR OUTCOMES

Studies show that cardiovascular outcomes such as cardiac death, cardiac arrest, myocardial infarction or stroke occurred in 7.8% of patients treated with inclisiran versus 10.3% of patients treated with placebo. This lower rate was mainly driven by a reduction in IMA and stroke in patients using inclisiram.

With respect to adverse effects, 4.69% of patients who received inclisiran reported an injection site reaction, compared with 0.5% of patients who received placebo. All reactions were transient. There was no evidence of liver, kidney, muscle or platelet toxicity. Evidently, PCSK9i is a welcome addition to our approaches to reducing LDL-C and ASCVD (KALLEND D et al., 2022).

The short-term safety data for the different K9i PCS is comparable and encouraging. However, as with any other therapy, long-term observation is critical as some of the possible side effects may not have had time to manifest. For example, individuals with the PCSK9 mutation with loss of function have been shown to have an increased risk of diabetes that has not been seen so far with any of the PCSK9i. Likewise, theoretical concerns with the triternary N-acetylgalactosamine approach to siRNA have included neuropathy and thrombosis, which have also not been seen so far in the ORION studies. Finally, while there have been concerns about impaired cognition with very low LDL-C, none have been observed, at least in the short term.

FINAL CONSIDERATIONS

Therefore, the importance of therapy for dyslipidemia becomes clear, which is extremely necessary due to the high prevalence of dyslipidemias, which increases the risk of morbidity and mortality from several preventable and treatable diseases of their affections, which becomes a problem of health in the world and in our country, due to the mass involvement of the population. What became evident is the need for promotion and prevention actions in primary health care, as well as the addition of new therapies such as PCSK9 inhibitors that reduce cholesterol

levels like no other available drug, currently being considered the most potent on the market, which has been demonstrating safety in its use and as promising to become a future vaccine for dyslipidemias.

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