

Inclisiran as an alternative treatment for Hypercholesterolemia

Jorge Andrés Ojeda Villota ^{1,*}, Javier Alfredo Pérez Martínez ², Luis Alberto Burgos de Moya ³, Rodrigo Alfonso Chavez Vega ⁴, Roxana Rivera Valencia ⁵, Laura Melissa Medina Medina ⁶, María Paula González Rodríguez ⁷ and Ingrith Tatiana Poveda Castillo ⁸

¹ Internist, Universidad Metropolitana, Barranquilla.

² Internist, Universidad Libre, Barranquilla.

³ Internist, Universidad Simón Bolívar, Barranquilla 0000-0001-7933-6436.

⁴ General Physician, Universidad Del Sinú Cartagena.

⁵ General Physician, Universidad de Carabobo, Venezuela.

⁶ General Physician, Universidad Industrial de Santander, Bucaramanga.

⁷ General Physician, Universidad Simón Bolívar.

⁸ General Physician, Fundación Universitaria Juan N Corpas.

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Abstract

Hypercholesterolemia (CH) is defined as the elevation of serum cholesterol levels, especially low-density lipoprotein (LDL) cholesterol, which is considered to be one of the most relevant risk factors for triggering cardiovascular disease, for This is vitally important to start treatment, there are several highly useful pharmacological groups for lipid-lowering therapy, among them we highlight the PCSK9 inhibitors, among the molecules that are part of this group we find inclisiran, this being a structure that promises a lot in regarding the management of hypercholesterolemia.

Keywords: Include; Treatment; Hypercholesterolemia; LDL elevation; PCSK9 inhibitors

1. Introduction

In recent years, atherosclerosis cardiovascular disease (CVD) has stood out as one of the main cause of death worldwide, this being an endothelial lesion that begins with the formation of lipid plaques, which is accompanied by a targeted chronic inflammatory response to the most sensitive area of the affected vascular wall, this process has constantly been associated with hypercholesterolemia which is characterized by elevated serum cholesterol levels, especially low-density lipoprotein (LDL) cholesterol, which is considered to be one of the most relevant risk factors for triggering cardiovascular disease, so many studies have been carried out that describe what action should be taken to manage hypercholesterolemia, there are different pharmacological groups designed for lipid-lowering therapy, but within In this group there are drugs that do not meet the requirements or are not tolerated by the pa This is why the need arises to modify the treatment and therefore innovate with molecules that are optimal for therapy [1,2, 3].

2. Methodology

This is a study aimed at a narrative review, it was carried out through the selection of original articles, available research reviews, written in English and / or Spanish, through recognized databases such as pubmed, scielo, science direct, wiley, plos one. Regardless of its year of publication, using the search terms include, treatment, hypercholesterolemia, LDL

* Corresponding author: Jorge Andrés Ojeda Villota
Internist, Universidad Metropolitana, Barranquilla.

elevation, PCSK9 inhibitors. A search criterion was not established for a defined language, however, all the articles containing the corresponding information and of great importance for conducting our review were selected.

3. Results

Cholesterol is a vitally important molecule, at the cellular level these make up the cell membranes and participate in the metabolism of certain hormones. Because it is an insoluble structure in aqueous solutions, so it must be transported in the bloodstream, there are particles called lipoproteins which fulfill this function, there are several types of proteins within them are high density lipoproteins (HDL), low density (LDL) and very low density, depending on which protein of each cholesterol molecule it is thus possible to establish whether it is harmful (LDL) or if on the contrary it is protective (HDL) [4, 5, 6].

Hypercholesterolemia (CH) is defined as an increase in circulating lipoproteins, which is reflected as an increase in serum cholesterol levels, this is due to an increase in the production or deficiencies in the process of metabolizing lipid proteins, this clinically is going to be characterized by elevation of total cholesterol levels above 200 mg / dl and LDL-cholesterol above 130 mg / dl. (Table 1) [7, 8].

Table 1 Normal cholesterol values

Total cholesterol	Less than 200 mg / dl (a level of more than 200 may indicate a higher risk of heart disease)
Cholesterol HDL	More than 40 mg / dl in men and 50 mg / dl in women
Cholesterol LDL	Less than 130 mg / dl (people with heart disease or diabetics must have less than 100 mg / dl)

HC is generally caused by a large intake of foods rich in fat, it can be secondary to metabolic disorders such as diabetes, hypothyroidism and Cushing's syndrome; it can also be genetic in the case of familial hypercholesterolemia and medications can also be a cause within them, we can highlight contraceptives, hormonal therapies, the occasional diuretic or beta-blockers [9]. Generally it does not have specific clinical manifestations, this can occur with dizziness, headaches, nausea, among other symptoms [10].

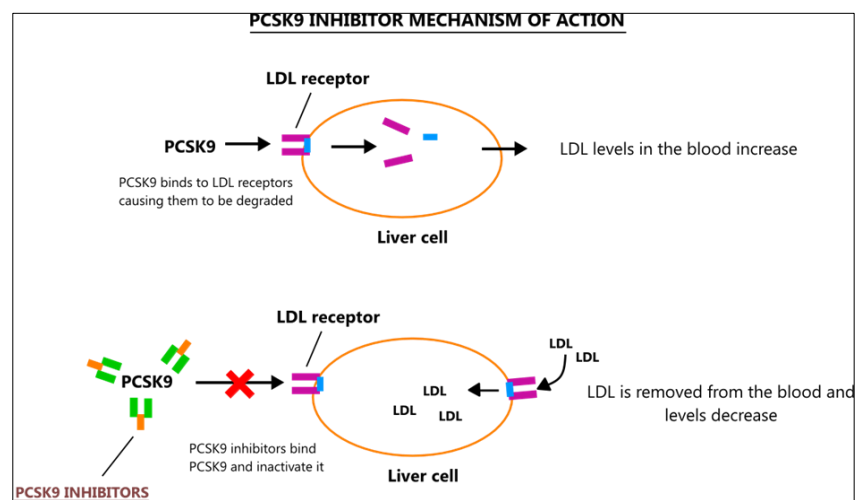


Figure 1 Mechanism of action of PCSK inhibitors

The hyperlipidemia management scheme generally begins with lifestyle changes such as modifying the diet and performing aerobic exercise, drug therapy can also be established, but this will depend on the serum cholesterol levels and the associated comorbidities of each patient [11, 12]. Each pharmacological group has its characteristics, because they must be formulated depending on the patient's requirements. There are drugs that have the ability to lower LDL cholesterol or raise HDL cholesterol [13, 14].

Statins decrease the synthesis of cholesterol at the liver level through the inhibition of exercise of HMG-CoA reductase, which proportionally generates a decrease in cholesterol levels, they are a fundamental part of the management to

reduce LDL cholesterol and the prevention of cardiovascular disease, it is even used in patients who have already presented a cardiovascular event, a recent study was carried out that mentioned the effectiveness of these molecules but it has become a challenge to increase adherence to long-term treatment, on the other hand there are also other pharmacological groups that are very effective for the management of CH [15].

Inhibitors of the proprotein convertase subtilisin / kexin type 9 (PCSK9) are relatively new drugs that have proven to be very effective, they provide an accessory way to lower LDL-cholesterol levels by increasing the availability of LDL receptors (LDLR) at the level of the liver cells, which generates a constant activity of the receptors, which allows to increase the uptake and collect the LDL from the plasma. (Figure 1) [16, 17].

Patients with spontaneous functional PCSK9 deficiency have reduced LDL-cholesterol levels and lower long-term cardiovascular risk. At the beginning of the 21st century, a spontaneous increase in the function of PCSK9 was described as one of the causes of familial hypercholesterolemia. Statin treatment has been shown to increase the function of PCSK9, causing it to escape and weakening its lipid-lowering effect [18, 19, 20].

Within the group of PCSK inhibitors, we find the inclisiran, This is a small small molecule of interfering RNA (siRNA), which increases the amount of LDLR at the level of the membranes of hepatocytes, by inhibiting the transcription of PCSK9, cataloging this As a promising drug for the management of GH, it was approved by the European Union at the end of 2020, to be used in the adult population that requires it, these regulatory entities established recommendations to start treatment with iPCSK9, the first to be It was suggested that the patient had a high cardiovascular risk, followed by cholesterol levels that persist on the rise despite changes in lifestyle, diets, aerobic exercises and having reached the maximum tolerable statin dose, in some guidelines prior therapy is suggested with ezetimibe to try to control LDL-cholesterol before starting treatment with iPCSK9, also other literature talks about other indications conditions, such as heterozygous and homozygous familial hypercholesterolemia (FH), mixed dyslipidaemia, and statin intolerance [21, 22, 23].

Studies evaluating the safety and side effects of PCSK9 siRNA have been documented and established that it has no serious side effects, but it can trigger mild-moderate effects such as flu-like symptoms, myalgias, arthralgias, headaches, and diarrhea [24]. In addition to being a safe therapy, it offers an advantage compared to other therapies, which is the administration scheme, which is to apply subcutaneous injections once or twice a month, thus favoring therapeutic adherence [25].

4. Discussion

IPCSK9 have been studied by numerous clinical trials evaluating the efficacy, safety and side effects of this, in these studies patients with high-risk cardiovascular disease, heterozygous and homozygous familial hypercholesterolemia, mixed dyslipidemia, persistence of levels were included. High LDL cholesterol despite previous management with statins and receiving the maximum possible dose of therapy and statin intolerance. iPCSK9 are effective drugs, which showed significant effects on low-density lipoprotein cholesterol levels, even more than 60% of the studied population showed the expected results, in other investigations they have described a significant decrease in LDL-cholesterol at 180 days after starting therapy, PCSK9 levels were also markedly reduced at 180 days among patients who received inclisiran, which allowed a large part of the patients to achieve a therapeutic goal.

5. Conclusion

The anti-PCSK9 monoclonal antibody represents a new category of treatment designed to significantly lower LDL-C in patients at high cardiovascular risk who have been treated with statins alone or in combination with ezetimibe. People who reach the goal and whose patients are intolerant or contraindicated the use of statins. Clinical evidence demonstrates its efficacy and safety, in addition to the convenience of infrequent dosing, as well as the cardiovascular benefits of these new therapies.

Compliance with ethical standards

Disclosure of conflict of interest

The authors do not declare conflicts of interest

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