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(REVIEW ARTICLE)

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An Overview on a new generation LDL-C lowering drug: Inclisiran and its market forecast

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Abstract

Inspite of the broadly available efficacious lipid-lowering drugs, atherosclerotic cardiovascular disease still remains a universal health issue. LDL-C represents an essential part in pathological process of atherosclerotic disease. High concentrations of plasma have been correlated with 50-70 % increase in progression of atherosclerotic plagues in patients with or without undistinguished cardiovascular risk. FDA has approved Novartis Leqvio (Inclisiran) first -in class siRNA to lower cholesterol and maintain it low with two doses a year. Inclisiran is a small interfering RNA (siRNA) molecule, targeting the hepatic production of PCSK9 results in lowering of LDL.

The review displays the current scientific information referring to inclisiran as a new favourable weapon in the control of hypercholesterolemia and insights to its global market forecast.

Keywords: Atherosclerotic; Hypercholesterolemia; LDL-C; Inclisiran; siRNA; PCSK9; Global market

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death globally, claiming an estimated 17.7 million lives in 2015 alone, which accounts for approximately 31% of all deaths worldwide [1]. One of the primary risk factors associated with CVD is hypercholesterolemia, where elevated levels of low-density lipoprotein cholesterol (LDL-C) significantly elevate the likelihood of developing cardiovascular complications. The profound impact of LDL-C reduction on lowering cardiovascular risk has been unequivocally established in both primary preventions, where interventions aim to prevent initial onset, and secondary prevention, which focuses on individuals with existing CVD, underscoring the critical role of managing cholesterol levels in mitigating CVD risk [2,3].

Dyslipidaemia, characterized by abnormal lipid levels, is a modifiable risk factor that plays a pivotal role in the development and progression of atherosclerosis, a key contributor to CVD. Complementing lifestyle modifications that promote heart health, the adoption of lipid-lowering therapies remains a fundamental strategy in reducing CVD risk. By targeting dyslipidaemia through pharmacological interventions that effectively regulate lipid profiles, individuals can address a significant aspect of CVD prevention and management, emphasizing the importance of a comprehensive approach in combating this prevalent and life-threatening condition [4].

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Inclisiran, a key small interfering RNA molecule, belongs to the siRNA group characterized by its 20-30 nucleotide RNA structure, serving as vital regulators within the intricate framework of eukaryotic genomes. Recently, there has been a surge in recognizing the pivotal role of siRNAs in modulating gene expression and controlling biological functions. A notable application of the siRNA molecule lies in the targeted reduction of PCSK9 levels, showcasing its therapeutic potential. This siRNA's mechanism leverages the widely studied RNA interference (RNAi) pathway, employing its interaction with the RNA-induced silencing complex (RISC) within cells. Through such interaction, the siRNA molecule facilitates the specific cleavage of messenger RNA (mRNA) molecules encoding PCSK9, thus modulating its expression and downstream effects. This strategic approach demonstrates the precision and efficacy of utilizing siRNA technology to intervene at a molecular level, offering opportunities for innovative therapies and in-depth exploration of gene regulation mechanisms [2,5].

Inclisiran, sold under the brand name Leqvio, is a medication used for the treatment of high low-density lipoprotein (LDL) cholesterol and for the treatment of people with atherosclerotic cardiovascular disease (ASCVD), ASCVD risk-equivalents, and heterozygous familial hypercholesterolemia (HeFH). It is a small interfering RNA (siRNA) that acts as an inhibitor of a proprotein convertase, specifically, inhibiting translation of the protein PCSK9 [4].

2. Drug Profile

Inclisiran, a small interfering RNA (siRNA) molecule is intended to target PCSK9 (proprotein convertase subtilisin/kexin type 9), a protein that controls blood cholesterol levels. Inclisiran is intended to lower low-density lipoprotein cholesterol (LDL-C), also known as "bad" cholesterol, by blocking PCSK9 [2,6].

Inclisiran is a novel small interfering RNA (siRNA) that reduces PCSK9 production in the liver and lowers plasma LDL-C levels. It is administered twice-yearly (after initial and 3-month doses) via subcutaneous injection by a healthcare professional [7,8]. It has demonstrated encouraging outcomes in clinical trials concerning LDL-C levels. This medication may prove advantageous for individuals who have not been able to reach their desired cholesterol levels with existing lipid-lowering treatments such as statins or who have encountered negative side effects from them [9]. The approval of inclisiran is mentioned in Figure 1.

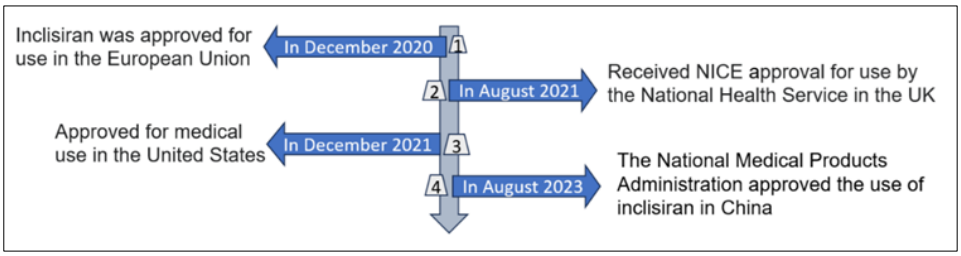

Figure 1 Updated approval of Inclisiran

3. Mechanism of action

The mechanism of action of inclisiran involves targeting the PCSK9 (proprotein convertase subtilisin/kexin type 9) pathway, which plays a vital function in controlling the body's metabolism of cholesterol as shown in Figure 2 [9,10].

- **PCSK9 Pathway:** The PCSK9 pathway involves a protein (PCSK9) produced by the liver that binds to LDL receptors and reduces their numbers, leading to higher levels of LDL cholesterol in the bloodstream and an increased risk of cardiovascular diseases [11].
- **Inhibition of PCSK9 mRNA**: Inclisiran works by blocking the production of PCSK9 protein by targeting its messenger RNA (mRNA). This prevents the mRNA from being translated into PCSK9 protein [12].
- **Reduction of PCSK9 Protein:** Inclisiran therapy reduces the production of PCSK9 protein, which in turn leads to more LDL receptors being available on liver cells. This allows for more efficient removal of LDL cholesterol from the blood.
- **Enhanced LDL Clearance:** An increase in LDL receptors helps liver cells remove LDL cholesterol from the blood, which lowers LDL cholesterol levels and reduces the risk of cardiovascular events like heart attacks and strokes.

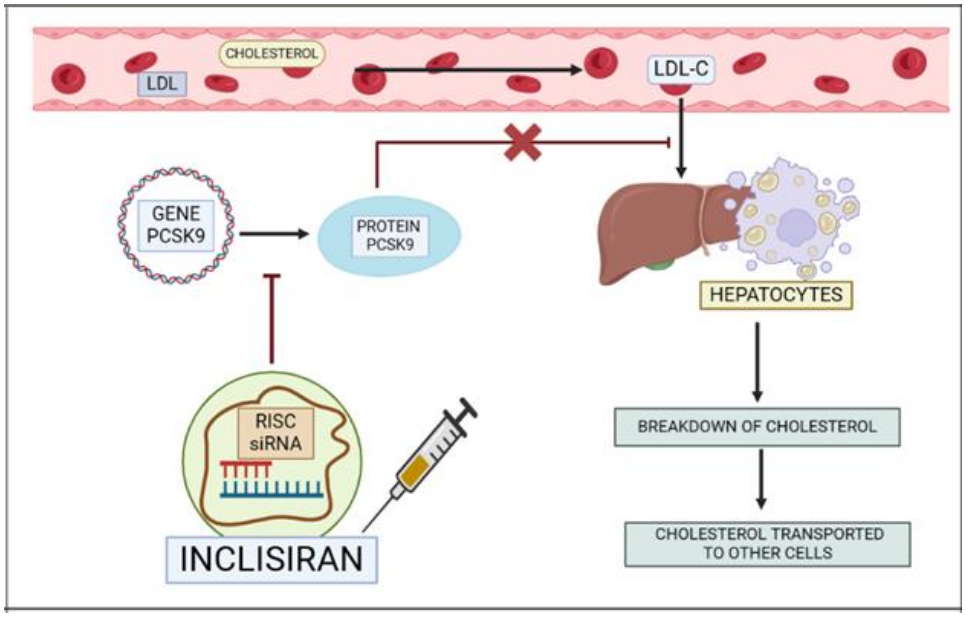

Figure 2 Mechanism of action of Inclisiran

4. Pharmacokinetics:

Inclisiran is administered via subcutaneous injection, and its absorption into the bloodstream follows the typical pathway for subcutaneously administered drugs [4,5]. Here's an overview of the absorption process:

4.1. Absorption

Inclisiran is a subcutaneous injection used to inhibit PCSK9 production in the liver, bypassing the first-pass effect. Its pharmacokinetic profile depends on absorption into the bloodstream, with specific properties varying based on dose, injection site, and patient characteristics. It has a prolonged duration of action, allowing for less frequent dosing and subcutaneous administration allows for less frequent dosing compared to oral medications [5].

4.2. Distribution

The drug is designed to inhibit PCSK9 production, targets liver cells and may bind to plasma proteins, affecting its distribution, metabolism, and elimination. Its pharmacokinetic profile is influenced by its liver selectivity, which affects PCSK9 production, making understanding its distribution crucial for optimizing therapeutic efficacy. Its selective targeting of hepatocytes and long-lasting action contribute to its efficacy [4].

4.3. Metabolism

This synthetic RNA molecule, does not undergo cytochrome P450 metabolism in the liver, unlike many small-molecule drugs. Its stable siRNA molecule selectively targets PCSK9 mRNA, leading to its degradation within the cell. Inclisiran inhibits PCSK9 synthesis in hepatocytes, but unbound inclisiran or its breakdown products may be excreted via renal clearance, likely contributing minimally to overall elimination [13].

4.4. Elimination

Inclisiran is eliminated through hepatic clearance, targeting hepatocytes to inhibit PCSK9 protein production. It is broken down in hepatocytes through RNA metabolism and degradation, targeting PCSK9 messenger RNA. Its breakdown products may be excreted from the liver. Unbound inclisiran or its breakdown products may be excreted via the kidneys, but their contribution is minimal compared to hepatic clearance.

5. Side effects

The side effects of inclisiran are shown in Figure 3.

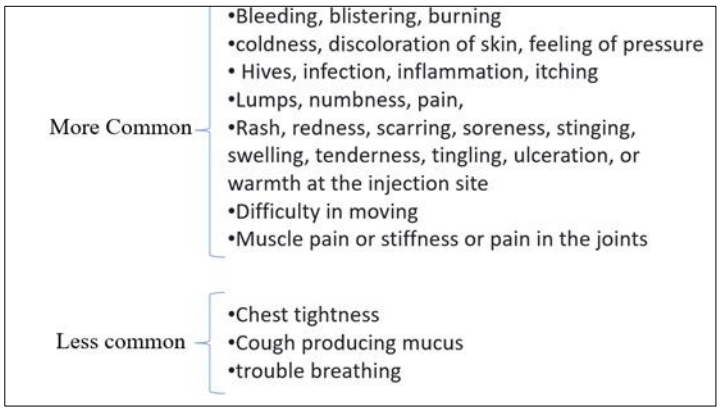

Figure 3 Side effects of Inclisiran

6. Future Prospects

Currently the implication of inclisiran, a novel medication, has been widely adopted within populations at risk of cardiovascular events. This new drug has been specifically designed to provide sustained lipid-lowering effects, making it a promising option for individuals with cardiovascular risk factors. The unique dosing regimen of inclisiran is believed to contribute to improved medication compliance and overall therapeutic outcomes. Despite its potential benefits, inclisiran does face challenges including concerns related to its safety profile, efficacy, cost-effectiveness, and availability. Furthermore, there remains a need to better understand how inclisiran interacts with other drugs and its synergistic effects in clinical practice. The future role of inclisiran in cardiovascular care will heavily rely on continuous advancements in our understanding of how it works in reducing LDL cholesterol through PCSK9 inhibition, as well as its cost-effectiveness in comparison to existing treatment options. A brief report on inclisiran is shown in Figure 4.

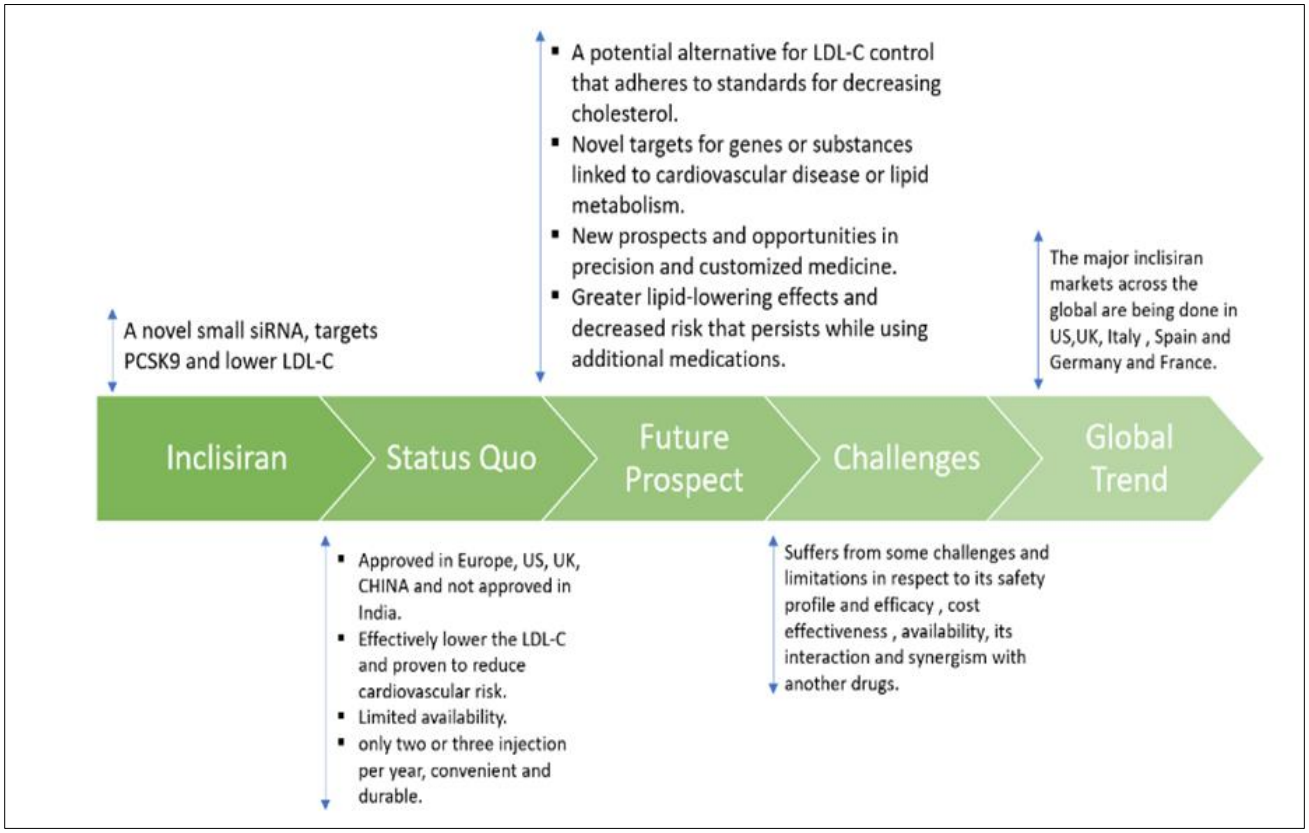

Figure 4 Brief report on Inclisiran

7. Global Trends and Market Forecast

In forthcoming years the market and concept of inclisiran is to fluctuate as a result of ongoing global research. Pharmaceutical companies in collaboration with academicians are working in order to reduce the issues and search for possibilities that might affect the supremacy of inclisiran and so its global sale is expected to reach 3 billion by 2029.The speculated global market analysis, suggests Leqvio's sales in India may reach 0.6 million by 2029 as a result of 0.02 percent dyslipidaemia [14]. As a result of sizeable research , in forthcoming year's the scenario of inclisiran is expected to change across the world which is expected in expansion of size of market for pharmaceutical companies to infiltrate more into market. The major inclisiran markets across the global are shown in Figure 5.

Figure 5 Global markets of Inclisiran

8. Conclusion

The efficacy and safety of inclisiran establishes it as a hopeful therapeutic agent in treatment of dyslipidaemia. Inclisiran has appeared as a novel hopeful therapeutical agent in the management of hypercholesterolemia. However more studies are needed to evaluate it to long- term effect and examine its clinical indications in patients. The conclusion of the review emphasizes on considerable potential of inclisiran, a useful RNA interreference domain for control of dyslipidaemia.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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