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A Review of Pharmaceutical and Clinical Studies of the Cholesterol-Lowering Drug PCSK9 Inhibitor Inclisiran

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Abstract:

Hypercholesterolemia can lead to atherosclerosis, which in turn can cause a range of cardiovascular and cerebrovascular diseases. As the first drug approved by the US Food and Drug Administration in 2021 to lower low-density lipoprotein cholesterol through siRNA therapy, inclisiran's sustained potent lipid-lowering effect and safety profile make it a promising treatment option for dyslipidemia. This article reviews the latest research progress on the mechanism of action, pharmacokinetic properties, efficacy, and safety of inclisiran. It also briefly explains its unique clinical administration method, aiming to provide a reference for the clinical use of inclisiran.

Keywords:

Inclisiran
Proprotein Convertase Subtilisin/Kexin Type 9 inhibitors
siRNA therapy
Low-density lipoprotein cholesterol

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1. Introduction

In the development and progression of atherosclerosis, high levels of low-density lipoprotein cholesterol (LDL-C) are one of the high-risk factors for atherosclerosis [1]. Taking atherosclerotic cardiovascular disease (ASCVD) as an example, among the ASCVD population in China, the treatment rate with lipid-lowering drugs is 14.5%, and the LDL-C target achievement rate is only 6.8% [2,3]. The latest Chinese guidelines for lipid management still recommend LDL-C as the primary target for lipid intervention and statins as the preferred drug to lower LDL-C levels [4,5]. However, there is still a significant gap between the LDL-C target achievement rate and statin treatment rate in high-risk and very high-risk populations than the guidelines' recommendations. Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors can not only significantly reduce LDL-C levels but also significantly delay and reverse the progression of atherosclerotic plaques [6]. However, anti-PCSK9 monoclonal antibodies have a short duration of action and

require relatively frequent subcutaneous administration, leading to a risk of low patient compliance [7]. Inclisiran is the first siRNA drug approved for the treatment of hypercholesterolemia or mixed dyslipidemia [8,9], and its unique administration schedule is expected to increase patient compliance. The following is a review of the latest clinical research progress on the mechanism of action, pharmacokinetic properties, efficacy, safety, usage, and dosage of inclisiran.

2. Mechanism of action to reduce serum LDL-C levels

The low-density lipoprotein receptor (LDL-R) in the human body transports LDL-C into hepatocytes for decomposition. PCSK9 prevents the recirculation of LDL-R back to the hepatocyte membrane, increasing serum LDL-C levels [10]. Inclisiran binds to the RNA-induced silencing complex within cells, participating in the natural pathway of RNA interference. It activates ribonuclease to specifically cleave PCSK9 mRNA, thereby blocking the expression of the PCSK9 gene, increasing the recirculation and expression of LDL-R on hepatocytes, and achieving the effect of lowering blood lipids. Unlike monoclonal antibodies that can only reduce extracellular PCSK9 levels, inclisiran can reduce both intracellular and extracellular PCSK9 levels [11]. The RNA-induced silencing complex remains active after mRNA degradation, so theoretically, the lipid-lowering effect of inclisiran is long-lasting [12,13]. This drug utilizes a specific binding and degradation mechanism of PCSK9 mRNA precursors, complementing the currently available lipid-lowering drugs on the market [14].

3. Pharmacokinetic properties

Within the dose range of 24 to 756 mg, single subcutaneous administrations of inclisiran demonstrate pharmacokinetic properties that are roughly proportional to the dose. Peak plasma concentrations are reached approximately 4 hours after administration, and the drug is almost completely cleared from the circulation within 24 hours after subcutaneous injection. Multiple administrations do not result in drug accumulation. In healthy adults, the apparent volume of distribution is approximately 500 L after a single subcutaneous injection of 284 mg [15]. The pharmacodynamic effects and safety of inclisiran are similar in subjects with normal renal function and those with renal impairment, so no adjustment of the inclisiran dose is required for these patients. However, there is a temporary lack of clinical data on the use of inclisiran in patients with acute kidney disease, those who have received kidney transplants, and those requiring hemodialysis [16–18]. Inclisiran is generally safe and well-tolerated in patients with mild/moderate hepatic impairment. Compared to patients with normal liver function, the pharmacokinetic exposure is up to 2 times higher, while the pharmacodynamic effect remains relatively unchanged, so no dose adjustment is necessary [17].

4. Clinical efficacy

The ORION project globally evaluated the efficacy and safety of inclisiran through studies on high-risk ASCVD and familial hypercholesterolemia populations. In the ORION-1 study (a randomized, double-blind, placebo-controlled, multicenter Phase 2 study), patients with ASCVD and elevated LDL-C levels despite statin therapy received single or repeated subcutaneous injections of inclisiran at 100, 200, 300, or 500 mg. The results showed significant ($P < 0.001$) and sustained reductions in LDL-C and PCSK9 levels. The regimen of 300 mg of inclisiran administered on Day 1 and Day 90 achieved the best results, with LDL-C and PCSK9 levels reduced by 52.6% and 69.1%, respectively, after 180 days [19]. After one year of follow-up in ORION-1, a single 300 mg subcutaneous injection of inclisiran reduced LDL-C by 50.9%, 38.6%, and 19.0% at 2, 6, and 12 months, respectively. With an additional injection at 3 months, LDL-C levels were reduced by 55.5%, 52.5%, and 31.4% at 5, 6, and 12 months, respectively [19,20]. This suggests that the optimal initial treatment dose is two 300 mg subcutaneous injections of inclisiran on Day 1 and Day 90, followed by maintenance therapy with injections every 6 months. Additionally, patients treated with inclisiran in this study had lower levels of non-HDL cholesterol, lipoprotein(a), and apolipoprotein B, and higher levels of HDL cholesterol [21].

The key trials evaluating the efficacy of inclisiran are ORION-9, ORION-10, and ORION-11 (multicenter,

double-blind, randomized, placebo-controlled Phase 3 trials). ORION-9 mainly included 482 patients with heterozygous familial hypercholesterolemia who were receiving statin therapy but still had high LDL-C levels (≥ 100 mg/dL). Patients were randomly assigned to receive 300 mg of inclisiran or placebo via subcutaneous injection on Day 1, Month 3, Month 9, and Month 15. At Day 540, LDL-C levels were reduced by 39.7% in the inclisiran group compared to an 8.2% increase in the placebo group [22-24]. ORION-10 and ORION-11 included 1,561 ASCVD patients and 1,617 ASCVD or ASCVD-risk equivalent patients (LDL-C ≥ 70 mg/dL), respectively. They received 300 mg of inclisiran or placebo subcutaneously on Day 1, Month 3, and then every 6 months. At Day 510, LDL-C levels were reduced by 52.3% in ORION-10 and 49.9% in ORION-11 compared to the placebo group [25]. These three trials confirm the effective and durable LDL-C reduction achieved by inclisiran.

4.1. Long-term efficacy

In the ORION-3 study, 290 patients who had previously received single or double doses of inclisiran in ORION-1 continued to receive 300 mg of inclisiran twice yearly. At Day 210, among the 277 patients evaluated, LDL-C levels decreased by an average of 47.5% from baseline (Day 1 of ORION-1) and by 44.2% from baseline to Year 4 (Day 1440 of ORION-3). PCSK9 levels decreased by an average of 69.5%, demonstrating the durable efficacy of inclisiran in reducing LDL-C and PCSK9 levels over 4 years [26]. In August 2023, the European Society of Cardiology annual meeting (ESC2023) presented clinical research from ORION-8, where some subjects received inclisiran treatment for up to 6 years. The average reduction in LDL-C levels from baseline was approximately 50%, with about 80% of patients achieving target LDL-C levels. The long-term efficacy and safety results were consistent with those of ORION-3, further confirming the sustained and potent lipid-lowering effect of inclisiran.

4.2. Efficacy in the Chinese population

There is relatively limited research data on inclisiran in the Chinese population. In the ORION-14 study, 40 Chinese patients were randomly assigned to receive a single subcutaneous injection of 100 mg or 300 mg of inclisiran (15 patients per group) or placebo (10 patients). The results showed that 100 mg and 300 mg of inclisiran significantly reduced PCSK9 and LDL-C levels up to Day 90, with the 300 mg dose showing better efficacy. No patients discontinued due to adverse events [27]. The Phase 3 clinical trial ORION-18, which recruited about 1,500 patients including 232 Chinese patients, is currently underway. Patients received inclisiran or placebo on Day 1, Day 90, and Day 270. Subgroup analysis of the Chinese population showed a significant reduction in LDL-C levels from baseline to Day 330, with a decrease of up to 61%. The efficacy of inclisiran in Chinese patients was similar to global results, with a trend towards better performance. The primary endpoint of this study is the percentage change in LDL-C levels from baseline to Day 510, and the results are pending. This study will provide more evidence for the efficacy and safety of inclisiran in the Asian population [28].

5. Safety

In the ORION-9, ORION-10, and ORION-11 studies, inclisiran was generally well-tolerated, with adverse event rates comparable to the placebo group. Most events were classified as mild or moderate [22,25]. A pooled analysis of these studies revealed that injection site reactions were the only adverse event reported in the inclisiran group, occurring in 5% of patients compared to 0.7% in the placebo group. These reactions were mild, moderate, transient, and no serious or persistent injection site reactions were reported [29]. In the ORION-7 trial, inclisiran was well-tolerated in patients with normal renal function and those with mild, moderate, and severe renal impairment. No dose adjustment was required for renal impairment patients at equivalent LDL-lowering levels [16].

The ORION-3 study examined the long-term tolerability of inclisiran, and found that among 284 patients (in the inclisiran monotherapy group), 79 (28%) experienced adverse events potentially related to the study drug. The most common event was an injection site reaction (16 patients, 5.6%) [26]. The results indicate that inclisiran is effective and safe for reducing LDL-C and PCSK9 levels over 4 years. It is worth noting that two

complementary Phase 3 cardiovascular clinical endpoint trials, ORION-4 and VICTORION-2/1-PREVENT, are currently underway to explore whether the LDL-C reduction achieved by inclisiran can translate into a reduction in the risk of major cardiovascular adverse events (MACE). The estimated completion date is between 2026 and 2027 [30].

6. Dosage and administration

In the European Union and the United States, the recommended dose of inclisiran is 300 mg (1 injection, 1.5 mL solution containing 284 mg of inclisiran), initially administered as a single subcutaneous injection, followed by another injection 3 months later, and then maintained with injections every 6 months for long-term treatment. The Chinese drug regulatory agency approved the marketing of inclisiran on August 23, 2023. The drug specification is 284 mg, 1.5 mL, suitable for subcutaneous injection in the abdomen. Patients receive a booster injection 3 months after the initial injection, followed by annual injections twice a year to effectively reduce LDL-C levels. Due to limited experience with inclisiran in patients with hepatic or renal impairment, it should be used with caution in patients with severe renal impairment and severe (Child-Pugh Class C) hepatic impairment. Additionally, hemodialysis should not be performed for at least 72 hours after inclisiran administration.

7. Conclusion

The role of inclisiran in the management of hyperlipidemia patients cannot be ignored. Since the Phase II clinical trial began in 2010, and its approval in Europe in December 2020 [9], despite delays caused by the global COVID-19 pandemic, inclisiran finally received FDA approval in the United States on December 22, 2021 [31]. Later, on August 22, 2023, the innovative cholesterol-lowering drug Le Kewei® (Inclisiran Sodium Injection) was approved by the National Medical Products Administration of China for the treatment of adult patients with primary hypercholesterolemia or mixed dyslipidemia. However, due to comprehensive considerations of clinical research evidence, treatment costs, and drug supply, this drug will still occupy a second- or third-line position in the short term. Statins remain the core of cholesterol-lowering therapy, with cholesterol absorption inhibitors and PCSK9 inhibitors (monoclonal antibodies) serving as important supplements. Inclisiran treatment can be considered when these drug treatments are ineffective, statin therapy cannot be tolerated, or the patient has special needs. Therefore, inclisiran still has great significance for the prevention and control of dyslipidemia in China. In the next few years, the novel siRNA lipid-lowering therapy may open up a brand new field, allowing patients to enjoy an improved quality of life brought by long-term lipid control and bringing hope to patients who have difficulty achieving lipid targets.

Disclosure statement

The authors declare no conflict of interest.

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