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Editorial

Inclisiran: A knight in shining armor?

Statins were the first "knight in shining armor" to rescue millions from the ill effects of atherosclerotic cardiovascular disease (ASCVD). Yet, 10–20% of patients do not tolerate statin therapy and significant residual cardiovascular risk due to elevated low-density lipoprotein cholesterol (LDL-C) remains in statin-treated patients [1]. The identification of PCSK9 as a therapeutic target and the development of two monoclonal antibodies (mAb) targeting PCSK9, alirocumab and evolocumab, has revolutionized the treatment of dyslipidemia by providing effective non-statin alternatives for patients unable to tolerate statin therapy or achieve desired LDL-C levels with maximum tolerated statin therapy [2]. However, the uptake of PCSK9 mAbs in clinical practice has been slowed due to their cost, lack of robust data showing a mortality benefit, and hesitancy from some patients to perform bi-weekly or monthly self injections [3].

Inclisiran is a novel, small-interfering double-stranded RNA (siRNA) molecule directed against intracellular PCSK9 mRNA in the hepatocyte that essentially "silences" PCSK9 synthesis and reduces intra- and extracellular PCSK9 levels [4]. Without PCSK9 to facilitate LDL receptor degradation, the LDL receptors recycle to the hepatocyte surface to continue clearing LDL from the circulation. A major practical advantage of inclisiran is it can be administered less frequently than PCSK9-mAbs since the silencing complex is active even after mRNA degradation. After an initial and 90-day dose, inclisiran only requires administration every six months thereafter.

The meta-analysis by Cicero [5] and colleagues assessed the efficacy and safety of inclisiran using data from five randomized, placebo-controlled trials. Inclisiran significantly reduced serum PCSK9 levels (−78.23%), LDL-C (−45.48%), apoB (−34.58%), and Lp(a) (−20.9%) compared to placebo. In an exploratory endpoint, pooled data from 3 clinical trials found a 26% lower risk of MACE with inclisiran compared to placebo but this is merely speculative. Injection site reactions and bronchitis were the only discernible adverse effects compared to placebo. This meta-analysis builds on previous reports of inclisiran's efficacy and safety using more robust methodology and a larger sample size. The lipid-lowering efficacy and short-term safety of inclisiran are well documented and substantiated by the meta-analysis conducted by Cicero and colleagues. However, many unanswered questions remain before we can "knight" inclisiran as a preferred non-statin option in high-risk patients.

The primary question regarding inclisiran is whether it reduces MACE and while the exploratory analysis is encouraging, we'll have to wait until the ORION-4 trial (NCT03705234) is completed in 2026 to know definitively. Mechanistically speaking and based on the data we have with the PCSK9 mAbs [2], it would seem likely that inclisiran would reduce MACE. There is, however, a notable difference between the 50 to >60% LDL-C reduction observed with the PCSK9 mAbs compared to the more modest 45% reduction reported in this meta-analysis. This difference in LDL-C lowering potency could impact the effectiveness of inclisiran on reducing MACE.

Another important consideration is long-term safety as siRNA technology remains relatively new as the US Food and Drug Administration (FDA) only approved the first siRNA therapy in 2018. Significant research and development have been needed to address concerns related to stability, potential for immune activation, risk of nanotoxicity, and target affinity [6]. To date, injection site reactions and bronchitis are the primary adverse effects reported with inclisiran; however, the follow up in clinical trials has been limited to ~18 months. Injection-site reactions also occur with the PCSK9 mAbs but this may be less of a concern with inclisiran given its less frequent administration. A higher incidence of bronchitis was noted in the meta-analysis by Cicero and colleagues, which has also been reported with the PCSK9-mAbs as well, but the clinical significance of this is unclear.

Based on the data we have; how should clinicians use Inclisiran? Inclisiran is currently FDA approved for use in patients with heterozygous familial hypercholesterolemia (HeFH) or clinical ASCVD who require additional LDL-C lowering (Fig. 1). Unlike PCSK9 mAbs, inclisiran must be administered by a healthcare professional as this is how it was administered in clinical trials. This may facilitate better follow-up with patients and clinician assurance of adherence. Of course, this will require healthcare systems and clinics to develop processes for purchasing and administering inclisiran. The administration frequency of inclisiran may be preferred by patients unable or unwilling to self-administer a PCSK9 mAb every 2 to 4 weeks, and those who experience injection site reactions with the PCSK9 mAbs. Until the ORION-4 data are available, however, inclisiran is merely a more convenient option than the PCSK9 mAbs, which should still be preferred given their more robust evidence base.

As with most novel therapies, a major limitation to inclisiran will be its cost, which is currently $3250 per dose in the United States [7]. Furthermore, inclisiran is being launched under the "Buy-and-Bill" model where the drug is purchased by the healthcare system or clinic and administered in the office. Clinicians desiring access to inclisiran for their patients will have to navigate local Pharmacy & Therapeutics committees and third-party payors, which may delay implementation and availability of inclisiran. Alternative access options may include pharmacies or infusion centers, but similar barriers are likely to be present [8]. The Institute of Clinical and Economic Review (ICER) concluded that the similarity in mechanism and effects on LDL-C between inclisiran and the PCSK9 mAbs provides a high certainty of a small net health benefit that could be more substantial pending results of

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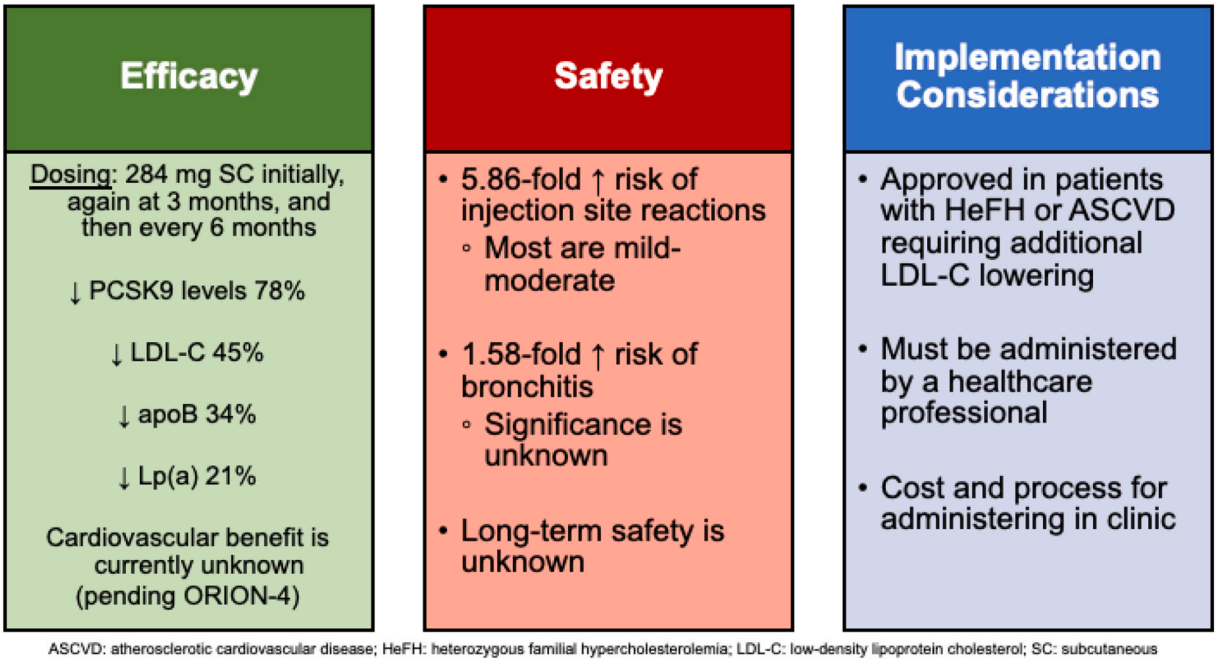

Fig. 1. Inclisiran: Efficacy, safety, and implementation considerations.

the ORION-4 trial [9].

Although there are many unanswered questions with inclisiran, it's important to recognize the significance of inclisiran from a scientific perspective. Inclisiran is only the fourth siRNA therapy approved by the FDA and the first in cardiovascular medicine. We are now in an era of more precise therapeutic options that may lead to more predictable efficacy and safety, and improved adherence over time. However, this progress will stall if we're unable to solve issues around cost and accessibility and such novel therapies as inclisiran will be limited to those with the means to pay for them. The real "knight in shining armor" will be whoever figures out how to produce these therapies more efficiently and less costly to ensure equal access to all.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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