RNA Interference for the Masses? siRNA Targeting PCSK9 Promises Prevention of Cardiovascular Disease

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UNTIL NOW, ANTISENSE oligonucleotides and small interfering RNAs (siRNAs) have been approved for rare severe progressive diseases where no other treatment options exist, such as spinal muscular atrophy [1–3], transthyretin amyloidosis [4,5], Duchenne muscular dystrophy [6,7], familial chylomicronemia [8], and acute intermittent porphyria [9]. The bar for treatment in these cases is relatively low because patients have had no other options.

But now, an oligonucleotide is emerging as a competitive option in a very different situation: for *prevention* of cardiovascular disease, perhaps many years before any symptoms arise, and in broad populations. This compound is inclisiran, an siRNA-based inhibitor of the expression of proprotein convertase subtilisin/kexin type 9 (PCSK9) [10,11]. Inhibition of PCSK9 expression causes robust reduction of plasma low-density lipoprotein (LDL) cholesterol, an established risk factor for cardiovascular disease. People with loss of function mutations in *PCSK9* have a marked reduction in coronary events associated with strikingly low levels of plasma LDL [12,13].

The Medicines Company presented favorable results from ORION 11, the first Phase III clinical trial of inclisiran, at the European Society of Cardiology's September 2019 congress in Paris. Equally compelling results were presented from two additional Phase III trials (ORION 9 and 10) at the November 2019 American Heart Association meeting in Philadelphia. In total, the ORION 10 and 11 trials enrolled >3,000 patients with atherosclerotic cardiovascular disease, whereas ORION 9 enrolled 482 patients with heterozygous familial hypercholesterolemia [14].

Patients were given a subcutaneous injection of 300 mg inclisiran on day 1, day 90, and then every 6 months. The impressive duration of effect of this compound, and its relationship to chemical modifications of the siRNA, has been previously discussed [11].

For a drug to be used in primary prevention—that is, to be administered to patients starting many years before adverse symptoms are expected—it must have a scrupulously clean safety profile. And this is doubly true in a context where other safe drugs are already available for the same goal. Previous advanced clinical trials on oligonucleotides—including other GalNAc-conjugated siRNAs—have encountered unexpected toxicity issues in Phase III trials. Thus, one of the most im-

portant results from these three trials is that inclisiran has a very clean safety profile. Moreover, these three Phase III trials enrolled patients who were in less than ideal health. Against that background, the results are even more remarkable: The only adverse events that were more common in the inclisiran group than in the placebo group were mild injection site reactions, which physicians compared with an insect bite, that occurred in ~3% of inclisiran injections.

Inclisiran also showed robust LDL-lowering efficacy in Phase III. The same 300-mg dose was given to all patients regardless of weight or baseline LDL levels. And interestingly, almost all patients, again irrespective of weight or baseline LDL level, showed a reduction in plasma LDL of just >50%. This drop, if sustained by remaining on therapy for the long-term, would be expected to produce a profound improvement in cardiovascular outcomes. That said, clinical data on long-term cardiovascular outcomes with inclisiran treatment (as well as longer-term safety) will have to await the results of an ongoing 15,000-patient 5-year trial (ORION 4).

The reduction of plasma LDL levels is a competitive therapeutic space, with approved drugs, including widely available and low-cost statins as well as two antibody-based PCSK9 inhibitors, Amgen's Repatha (evolocumab), and Sanofi-Regeneron's Praluent (alirocumab). The most potent statins, atorvastatin and rosuvastatin, in their highest doses, reduce LDL as much as 50% although there is significant variability. Similarly, the antibody-based PCSK9 inhibitors presently available lower LDL between 40% and 60% [15]. Both inclisiran and PCSK9 antibodies showed this 50% reduction on top of maximally tolerated statin treatment.

The American Heart Association guidelines have been adjusted based on the increasing evidence that lower LDL levels are better. The newest guidelines recommend LDL levels <70 for those with significant disease or very high risk, but there is evidence that the cardiac risk benefit of reducing LDL levels continues down to very low LDL levels. Many cardiologists would now prefer an LDL <50, or even lower for patients with recurrent disease or who are exceptionally high risk. When used together with statins, it is now common to see patients with LDL levels <20 and even <10 mg/dL, and no adverse effects of these very low levels have so far been found [16]. It almost begs the question of

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what LDL is good for, given that patients seem to thrive with astonishingly low levels of this factor.

A twice-yearly injection raises interesting questions about patient compliance. Antibody-based PCSK9 inhibitors are self-injected once every 2 weeks, and patients seem to have no problem with this. But for a twice-yearly injection, it might be better to have this done in a physician's office at the intervals required. Perhaps a formal reminder system—for both the patient and the physician—could be put into place.

One of the curious things about statins is that for unclear reasons they have acquired an Internet-driven bad reputation. In controlled trials there is very little difference in side effects between the real statin and the placebo, but in the real world the incidence of apparent statin intolerance is always higher than what is seen in studies. Yet in the experience of the University of Massachusetts lipid clinic, patients who were seen because of statin intolerance rarely show the same side effects with a PCSK9 inhibitor and interestingly, they seem to prefer the biweekly self-injection over daily oral pills. So particularly with the twice-a-year injection of inclisiran, and increasing evidence of long-term safety, it might not be surprising to see such a medication becoming more popular than statins themselves.

Along with the far fewer injections required, what will make this medication even more competitive would be a low price. When the PCSK9 inhibitors came on the market they were formidably expensive, but the price has dropped considerably for the past several years, and it has become much easier to use PCSK9 inhibitors more liberally. It will be interesting to see the price point of inclisiran, if approved.

Based on the favorable Phase III results and their implications for inclisiran's commercial prospects, Novartis made a US \$9.7 billion acquisition of the Medicines Company within a week of the presentation of the Phase III trials.

Inclisiran is an siRNA delivered by conjugation with a trivalent GalNAc moiety; this sugar-based ligand triggers productive internalization by hepatocytes [17–20]. After years of development, clinical success for GalNAc drugs has come quickly: just days after the Medicines Company presented their Phase III results at the American Heart Association meeting in Philadelphia, the Food and Drug Administration approved a different GalNAc conjugate, the first to be approved: Alnylam's Givlaari (givosiran) that silences aminolevulinic acid synthase I for the treatment of acute intermittent porphyria [9].

In summary, in a true milestone for the field of oligonucleotide therapeutics, the favorable clinical results on inclisiran suggest that oligonucleotides should no longer be considered to be suited only for rare and severe diseases, or that they can only be sold with a high price tag. These data show that oligonucleotides can play a valuable role in additional areas of the drug market—(1) larger patient populations at lower cost, and (2) preventive medicine—reducing risk factors that would otherwise lead to adverse outcomes in a subset of the population. To do either of those things, they need a perfectly clean safety profile. Thus, these positive Phase III results for inclisiran represent an important milestone for the field of oligonucleotide therapeutics, and may also represent an important milestone in treating cardiovascular disease.

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