INCLISIRAN: A NOVEL LDLc LOWERING TREATMENT AFFECTING PCSK9 ACTIVITY

SUMMARY

- **Inclisiran is a "new-in-class" small interfering RNA (siRNA) twice-yearly injectable LDLc lowering treatment manufactured by drugs company Novartis**.
    - Inclisiran **inhibits the production of PCSK9 by liver cells**. PCSK9 up-regulates the degradation of LDL-receptors (LDL-Rs). Less PCSK9 means more LDL-R at the surface of hepatocytes and increased processing of LDLc out of blood serum thus lowering circulatory LDLc.
    - Other LDLc lowering medication target PCSK9 but **only inclisiran directly inhibits PCSK9 production**.
- *Preliminary results* of a phase III study of inclisiran involving 1617 patients who had elevated LDL cholesterol concentrations despite taking the maximum dose of statins **showed a 50% reduction of LDLc in treated vs placebo patient with a similar and acceptable side-effect profile**[1].
- **Inclisiran is to be evaluated as part of a large-scale NHS clinical trial expected to start later this year**[2]. The details of the trial and of patient eligibility criteria should the trial be successful are not yet know.
- NHS England will seek an expedited agreement from the National Institute for Health and Care Excellence's (NICE) approval programme and **will agree a population-level commercial arrangement with the company to make it "widely available" to patients as soon as 2021**. The details of this agreement are not known.
- **Presently, the treatment is likely to be reserved for patient already (but sub-optimally) managed on high-intensity statins/ezetimibe (as opposed to being offered first line as a treatment alternative)**[3].
- There **are concerns about the transparency of the NHS/Novartis agreement** and joint large-scale clinical tria,l **and the long-term safety and effectiveness of inclisiran**[4].

WHAT IS PCSK9?

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme in the proprotein convertase family of proteins –it functions to activate other proteins. In the context of lipid homeostasis, PCSK9 modifies the "recycling" of the LDL-R[5]. When LDLc binds the LDL-R at the surface of hepatocytes, the resulting complex is internalised within an endosome. PCSK9 binds the LDL-R:LDLc complex and commits the whole LDL-R:LDLc:PCSK9 complex to destruction by lysosomal degradation, i.e. the number LDL-Rs on the cell surface is reduced.

HOW DO PCSK9-INHIBITING MEDICATIONS WORK?

If PCSK9 does not bind the LDL-R:LDLc complex, upon endosomal internalisation, the LDLc:LDL-R complex is again processed by endosomal degradation **but the LDL-R is recycled back to the cell surface**[5,6]. So if the activity of PCKS9 is reduced –either by direct inhibition or by reduced production– more LDL-Rs are available to take-up LDLc from blood serum and thus reducing circulating LDLc.

Three medication target PCSK9 activity: alirocumab (Praluent) and evolocumab (Repatha) and inclisiran. The two former medications are monoclonal antibodies to PCSK9 (which stop it from binding to LDL-R). Inclisiran is a siRNA which inhibits the synthesis of PCSK9 in the first place by "blocking" the mRNA encoding it –this is a new way of treating raised cholesterol and, at present, **inclisiran is the only such medication**.

In August 2020, the NEJM published phase 3 clinical trial showing promising results for evinacumab, a new-in-class monoclonal antibody against angiopoietin-like 3 (ANGPTL3) with a 47% reduction in LDLc in homozygous FH patients on maximum doses of other background lipid-lowering therapies[7].

DOES INCLISIRAN WORK?

It would seem so. The initial results of the ORION-11 stage III clinical trial were presented at the European Cardiology Society's 2019 congress in Paris[1]. The double-blind trial involved 1617 patient with elevated low-density lipoprotein cholesterol (LDL-C) despite maximum tolerated therapy (statin and/or ezetimibe) randomised to treatment with inclisiran or placebo administered by injection on day 1, day 90, day 270, and day 450.

Results are well summarised by the concomitant American College of Cardiology's news report[8]:

"For the primary endpoint of percent change in LDL-C from baseline to Day 510 there was a 49 percent reduction with inclisiran and a 4 percent increase with placebo, for a 54 percent between-group difference (p<0.00001).

The safety profile of inclisiran was similar with placebo, with a similar rate of treatment-emergent adverse and serious events in both groups. […]

In the inclisiran and placebo groups, respectively, the rate of cardiovascular death was similar (1.1 percent and 1.2 percent), but the rate of fatal or nonfatal myocardial infarction and stroke was lower (1.5 percent vs. 3.7 percent) and this was primarily driven by a lower rate of fatal or nonfatal myocardial infarction (1.2 percent vs. 2.7 percent)." The main adverse event recorded was transient and manageable redness at the site of injection.

On the basis of the trial, the DHSC and its putative trial partners have stated that: **"Early results from clinical trials suggest that if inclisiran is given to 300,000 patients annually, it could help prevent 55,000 heart attacks and strokes, and has the potential of saving 30,000 lives in the next 10 years.[2]"**

WHAT IS NHS' INVOLVEMENT IN THIS?

It is two-fold[2]:

1. NHS England and NIHR, alongside Oxford University's Nuffield Department of Population Health (NDPH) and Novartis will lead a large-scale clinical trial.
2. It will seek a population-level commercial arrangement to make the medication widely available.

So the NHS will help further test the drug and, if inclisiran is confirmed effective, the NHS will presumably be offered the medication by Novartis at an appropriately discounted price. There have been concerns about this unusual public-private alliance not least because "Inclisiran is not yet approved by any regulatory body worldwide, and there is currently no reliable publicly available evidence on its effect on cardiovascular disease or long term safety and cost effectiveness"[4].

WHO WILL BE IN THE TRIAL? WHO WILL BE ELLIGIBLE FOR TREATMENT WITH INCLISIRAN? This is not known at present. It is worth considering the comments of a couple of experts in CVD prevention[3]:

Dr Riyaz Patel, Associate Professor and Consultant Cardiologist, Clinical lead for the CVD Prevention Service, Barts Health NHS Trust:

- "What is different here is that **[inclisiran] will be evaluated as it is being used**, which is acceptable as it is proven to be safe but also because data in recent years has shown that however you lower cholesterol the benefit will be the same."
- "Whether [inclisiran] will save 30,000 lives depends on many factors. It is an estimate based on extrapolation from existing data with multiple assumptions."
- "Also, [inclisiran] was used only in people who were maximally treated already with statins or other drugs – so this was very much an add-on to help people lower their cholesterol when it remained high on treatment […] **Patients should not expect this new drug to replace statins for the foreseeable future.**"

Prof Naveed Sattar, Professor of Metabolic Medicine, University of Glasgow:

"Doctors are excited by inclisiran and the potential to 'vaccinate' against high cholesterol in some patients, with obvious benefits to compliance and uptake. However, many would also like to see longer term safety data from ongoing trials and to be told the cost of this new drug before they consider implications for care."

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