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SMALL INTERFERING RNA DRUGS IN TREATMENT OF DYSLIPIDEMIA

Annotation. Inclisiran is the first example of an approved synthetic small interfering RNA (siRNA) drug for treating familial hypercholesterolemia. This review describes the scientific basis of RNA silencing, and critically evaluates the evidence relating to inclisiran, a small interfering RNA against proprotein convertase subtilisin kexin 9 (PCSK9).

Keywords: Inclisiran, LDL cholesterol, Dyslipidaemia, Atherosclerosis

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МАЛАЯ ИНТЕРФЕРИРУЮЩАЯ РНК В ЛЕЧЕНИИ ДИСЛИПИДЕМИИ

Аннотация. Профилактика сердечно-сосудистых заболеваний (ССЗ) и, в частности, гиполипидемические препараты — это история большого успеха современной медицины. Альтернативный подход заключается в том, чтобы нарушить выработку белков посредством подавления активности рибонуклеиновой кислотой (РНК), что приводит к длительному нокдауну определенных биологических молекул. В этом обзоре описывается научная основа сайленсинга РНК

и критически оцениваются доказательства, касающиеся инклизирана, малой интерферирующей РНК против пропротеинконвертазы субтилизина кексина 9 (PCSK9).

Ключевые слова: инклизиран, холестерин ЛПНП, дислипидемия, атеросклероз.

The siRNA molecule inhibits the expression of PCSK9 by binding to the host mRNA strand encoding for the protein, causing it to cleave and degrade. This reduces the availability of the PCSK9 enzyme, which would otherwise block LDL receptors from initiating ingestion of LDL particles from the extracellular fluid. Inclisiran can therefore reduce blood concentration of LDL, with measurable clinical effects. RNA interference (RNAi), as the biological basis for a subcategory of gene therapy, is a highly precise approach to suppressing the expression of specific genes [5]. This pathway is a cellular mechanism for defending against the effects of foreign genetic material being introduced into an organism, for example, through infection with a virus. RNAi can be exploited pharmaceutically to target and suppress genes that have been associated with diseases, with the added benefit of greater personalisation of therapeutics through sequence specificity [6]. RNAi can be achieved by two types of small double stranded RNA molecule, namely small interfering RNA (siRNA) and microRNA (miRNA), both of which suppress gene expression according to their specific sequence albeit in slightly different ways: miRNA mediates the repression of mRNA translation, whereas siRNA mediates mRNA degradation. These differences provide a range of therapeutic possibilities, with the potential for one miRNA drug to target a number of different selected genes together, whereas an siRNA drug is able to target a single specific gene of interest. The focus of this review is on siRNA technology. Once in the cytoplasm of a

hepatocyte, the double stranded siRNA drug inclisiran is uncoiled into two single, short RNA strands, one of which acts as the guide strand whilst the other becomes the passenger, which has no further role to play and is degraded [7].

The inclisiran guide strand becomes bound to the RNA-induced silencing complex (RISC) and then pairs with the complementary mRNA strand for PCSK9. The RISC argonaute enzymes then cleave the PCSK9 mRNA sequence where it is boundto the corresponding inclisiran guide strand, effectively silencing the PCSK9 gene. With a reduced synthesis of the PCSK9 protein, LDL-C concentration in the blood plasma is reduced. Following mRNA cleavage, the inclisiran/RISC complex remains intact and retains its activity for further interference with gene expression of PCSK9, meaning that a single siRNA inclisiran molecule has some considerable long-term efficacy. Although only a small percentage of inclisiran administered becomes active in the hepatocytes, that which forms part of an inclisiran/RISC complex has a very long half-life allowing dosing in patients to be months a part [4].

RNA drugs are large molecules, when compared with typical small-molecule compounds, and also carry a negative electrical charge—both properties decrease the likelihood of entering the cell across the lipid bilayer. Therefore, lipid nanoparticle encapsulation helps to overcome these drawbacks and aids intracellular delivery [4]. And because the liver is the primary filter for nanoparticles [5], it is possible to design novel siRNA drugs for dyslipidemia that can target hepatocytes through this means [6]. Chemical conjugation is another method that has been employed to improve the stability and delivery of siRNAs. A covalently bound conjugate allows the siRNA drug to be targeted to specific tissues or cells by binding to a cell surface receptor, followed by entry through receptor-mediated endocytosis. Following on from ALN-PCS, an siRNA for PCSK9, known as ALN-PCSsc,

was conjugated with N-acetylgalactosamine (GalNAc), which allowed the drug to target hepatocytes via the asialoglycoprotein receptor. The siRNA in inclisiran is also conjugated with GalNAc, building on this earlier approach.

Inclisiran has been evaluated in a range of clinical trials, including secondary prevention populations, high risk primary prevention and individuals with homozygous FH (HoFH) or heterozygous FH (HeFH) [8]. Characteristics of ongoing and completed trials are summarized n , with their results (where available). Pooled analyses of currently available data are reassuring with respect to the safety and efficacy of inclisiran. A patient-level pooled analysis including 3,660 patients from three ORION trials has recently been published. The analysis included data from patients with familial hypercholesterolemia (ORION-9), ASCVD (ORION-10) and ASCVD risk equivalents (ORION-11); 92% of subjects were taking statin therapy and 14% were using ezetimibe. Patients were injected with inclisiran or placebo at baseline, after 3 months and then every 6 months. At 510 days, LDL-C was found to be reduced by 50.7% in the inclisiran group, after correction for placebo. Adverse effects included bronchitis and mild injection site reactions. A pre-specified safety analysis of the ORION-1 trial (501 patients) focused on hematological variables during a year of follow-up. A particular advantage of inclisiran over other lipid-lowering therapies is the fact that it can be safely used in patients with mild (CrCl 60–89 mL/min), moderate (CrCl 30–59 mL/min) or severe CrCl 30–59 mL/min) renal function impairment, without the need for dose adjustment, thereby addressing an unmet need, particularly in the secondary prevention of cardiovascular disease.

Polish guidelines recommend that inclisiran may be considered in patients with ASCFD or FH who do not achieve lipid targets on statin and ezetimibe, in statin intolerance and in very high-risk primary prevention patients who do not adhere to, or consent to, other lipid-lowering therapies.

In the UK, the National Institute for Health and Care Excellence (NICE) is currently evaluating inclisiran for the treatment of primary hypercholesterolemia or mixed dyslipidemia. Current recommendations and marketing approvals are based on the data showing robust long-term reduction of circulating LDL-C by inclisiran.

Conclusions. Whilst inclisiran is the first drug in its class for dyslipidemia, it is unlikely to be the only one since RNA inhibition offers, at least theoretically, the opportunity to target any gene of interest. The siRNA templates are already established, and therefore, it is a simple step to modify the sequence of nucleic acids to a specific target mRNA. Other proteins associated with plasma lipid homeostasis, particularly if they are functional in the liver, are therefore likely to be included in research and development programs using this technology. An orally available antisense oligonucleotide for PCSK9 has recently demonstrated promise in preclinical studies, and RNA silencing is currently under investigation to target a range of proteins implicated in the pathophysiology of atherosclerosis.

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