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SPECIAL ARTICLE

The future is now: promising therapies

El futuro es ahora: terapias prometedoras

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Abstract

Statins do not always allow the recommended goals to be met. Recent and future options for dyslipidemias are reviewed.

***Triglycerides:** Pemafibrate affects triglycerides and HDL-C but has not yet shown changes in hard outcomes. Ethyl icosapentate reduced events, probably due to an anti-inflammatory effect.*

***LDL cholesterol:** Inclisiran, a synthetic small interfering RNA (siRNA), reduces LDL-C up to 83%. Confirmation of MACE reduction is lacking.*

***PCSK9:** MK-0616 is in Phase IIb. Gemcabene inhibits cholesterol and fatty acid synthesis and has anti-inflammatory properties.*

***ANGPTL3:** Evinacumab reduces triglycerides and LDL-C and is already approved for homozygous familial hypercholesterolemia. ARO_ANG3 is in Phase II.*

***Gene therapy:** Two strategies have been successfully used: gene transfer and gene editing.*

***Lp(a):** Pelacarsen, in Phase II, interferes with Lp(a) production. Olpasiran prevents Lp(a) assembly, with reductions of up to 95%. SLN360 can prevent Lp(a) production by up to 98%.*

***Keywords:** siRNA; ANGPTL3; gene therapy; PCSK9.*

Resumen

Las estatinas no siempre permiten lograr las metas recomendadas. Se revisan opciones recientes y futuras para las dislipidemias.

***Triglicéridos:** el pemafibrato tiene un efecto en triglicéridos y cHDL, pero aún no demuestra cambios en desenlaces duros. El icosapento de etilo redujo eventos, probablemente por un efecto antiiflamatorio.*

***Colesterol LDL:** el inclisirán, un ARN pequeño de interferencia sintético (ARNpi), reduce el cLDL hasta en 83%. Falta confirmación de reducción en MACE.*

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PCSK9: *el MK-0616 está en fase IIb. El gemcabene inhibe síntesis de colesterol y de ácidos grasos, y es antiinflamatorio.*

ANGPTL3: *evinacumab reduce triglicéridos y c.LDL; ya ha sido aprobado para hipercolesterolemia familiar homocigota. El ARO_ANG3 está en fase II.*

Terapia génica: *se han utilizado con éxito dos estrategias: la transferencia y la edición de genes.*

Lp(a): *Pelacarsén, en fase II, interfiere la producción de Lp(a). Olpasirán evita el ensamblaje de Lp(a), con reducciones hasta del 95%. El SLN360 puede evitar la producción de Lp(a) hasta en un 98%.*

Palabras clave: *ARN pequeño de interferencia; ANGPTL3; terapia génica, PCSK9.*

Low-density lipoprotein (LDL) cholesterol is the protagonist of atherosclerosis, not only due to its pathophysiological role but also as the main therapeutic target. Despite very solid evidence in favor of statins, these do not achieve the recommended goals in up to 67% of the patients who take them, according to data from the PINNACLE Registry presented at the American Heart Association Congress in 20191. In this study, which evaluated 1.9 million patients with atherosclerotic cardiovascular disease, 21.1% of the patients had not received any lipid-lowering drug and 84.5% had not reached the LDL-C target of less than 70 mg/dl. This same study showed that females, African Americans and hypertensive patients had less chance of reaching the goals.

It is vitally important to have more potent drugs available for cases that require them, ideally with different mechanisms of action than statins, and that can be combined with them, if necessary. Also, drugs that can be used in people with true statin intolerance.

Triglyceride reduction and increased HDL cholesterol

While the initial studies emphasizing triglyceride reduction and increased HDL-C showed positive effects (the Helsinki Heart Study[2], with gemfibrozil, had a 34% reduction in the incidence of coronary disease, and VA-HIT[3], also with gemfibrozil, a 22% reduction in the relative risk of the combined outcome of non-fatal myocardial infarction or coronary death), subsequent studies in which the patients were already on statins and other medications (renin-angiotensin system modulators or beta blockers, among others) showed no net benefit (FIELD[4], with fenofibrate, which did not reduce the risk of the primary outcome of coronary events; ACCORD[5], with fenofibrate plus simvastatin, versus simvastatin alone, did not reduce the risk of fatal cardiovascular events, myocardial infarction or non-fatal stroke and others). These were collected in Jakob's systematic review and meta-analysis[6], which concluded that fibrates reduced the risk of cardiovascular and coronary events in primary prevention, but that the effect was modest (RRR < 1%) and that there was low-quality evidence that fibrates had no effect on all-cause mortality or non-cardiovascular mortality.

Pemafibrate

Pemafibrate is a selective PPAR α modulator, with a better effect than fibrates on triglycerides and HDL-C, which makes it a potential candidate for controlling residual risk in patients who have taken statins and other medications to control LDL-C. The study by Yamashita[7], which grouped the results of studies in dyslipidemic patients with or without a combination with statins found 45.1, 48.5 and 50.0% reductions in triglycerides at week 12, depending on the dose used, compared with placebo. Furthermore, the treatment group had a similar incidence of adverse events as the placebo group, even in patients with kidney failure, as this drug is eliminated by the liver.

As in all cases, lipid lowering is an intermediate result of a lipid-lowering agent, and its effect should be evaluated in hard outcomes. The PROMINENT[8] study evaluated the effect of pemafibrate vs. placebo on cardiovascular outcomes in patients with diabetes, triglycerides between 200 and 499 mg/dl and HDL-C ≤ 40 mg/dl. Two cohorts were evaluated, one in primary prevention and the other in secondary prevention. Ninety-six percent of the patients were on statins (and more than two-thirds were on high-intensity statins). Compared with placebo, the pemafibrate group achieved a 26.2% reduction in triglycerides and a 5.1% increase in HDL-C. However, there was no reduction in the incidence of the primary outcome (composed of non-fatal myocardial infarction, ischemic stroke, coronary revascularization or cardiovascular death). The patients who received pemafibrate had a higher incidence of renal events and venous thromboses, as well as a lower incidence of nonalcoholic fatty liver.

Although there was a reduction in remnant cholesterol (-25.6% compared with the placebo group), the levels of non-HDL cholesterol did not change substantially (-0.2%), there was a modest change in ApoB (+4.8%) and the LDL-C levels increased (12.3%). The finding of increased ApoB and LDL-C may be one of the explanations of the study results, as the reduction in proatherogenic particles and non-remo-

deling of TG-rich particles is essential to achieving an effect on events. The other important explanation is the protective effect of statins, which almost all patients were taking, and which may have made it difficult for pemafibrate to show an additional effect. This same reasoning has been proposed to explain the poor results of studies like FIELD and ACCORD.

In addition, the authors of PROMINENT propose that pemafibrate may have led to greater efficiency in the conversion of LDL remnants by stimulating lipoprotein lipase activity, which would explain the reduction in remnants and increase in LDL-C and ApoB, and no change in non-HDL cholesterol. Therefore, for medications targeting triglycerides to be effective, they must be able to increase triglyceride-rich remnant clearance (ApoB reduction is a marker of this effect) rather than simply convert the remnants to LDL.

This concept is reinforced by the results of two studies, REDUCE-IT[9] with icosapent ethyl, which showed a significant reduction (-25%) in the primary outcome not explainable by the modest reduction in triglycerides (-18.3%), and STRENGTH[10] with omega-3 fatty acids, which showed no changes in ApoB nor in the incidence of cardiovascular events. The possible effect of the use of mineral oil as a placebo in the REDUCE-IT study[11] still needs to be clarified, which could explain the results.

The potential role of pemafibrate and fibrates in atherosclerotic disease control has not been definitively established either, although their triglyceride reduction and HDL-C boosting profile makes them potential candidates for patients with residual risk due to high non-HDL cholesterol.

Inclisiran

The effectiveness and safety of PCSK9 inhibitor monoclonal antibodies have been clearly demonstrated, prompting research into medications with PCSK9 as their therapeutic target. Inclisiran is a recent medication which inhibits PCSK9 production through a different mechanism than that of alirocumab or evolocumab: this is a long-acting synthetic small interfering RNA (siRNA) which causes substantial and sustained LDL-C reduction over time (up to six months after one or two doses).

Small interfering RNA binds to the RNA-induced silencing complex (RISC)[12], which allows it to excise the messenger RNA which codes for PCSK9 production, leading to reduced production (Fig. 1). The effect is especially useful when the medication is combined with statins which upregulate PCSK9 production[13]. Studies show that inclisiran causes an ~74% reduction in circulating PCSK9 (with a 300 mg subcutaneous dose), which can be sustained up to day 180 (> 50%). With multiple doses, the reduction may reach ~83% (500 mg), which also remains above 50% at 180 days. This sustained reduction allows it to be administered every three or six months.

Unlike monoclonal antibodies, which affect PCSK9 regardless of its source (liver, small intestine or kidney), inclisiran is only aimed at hepatic PCSK9 production.

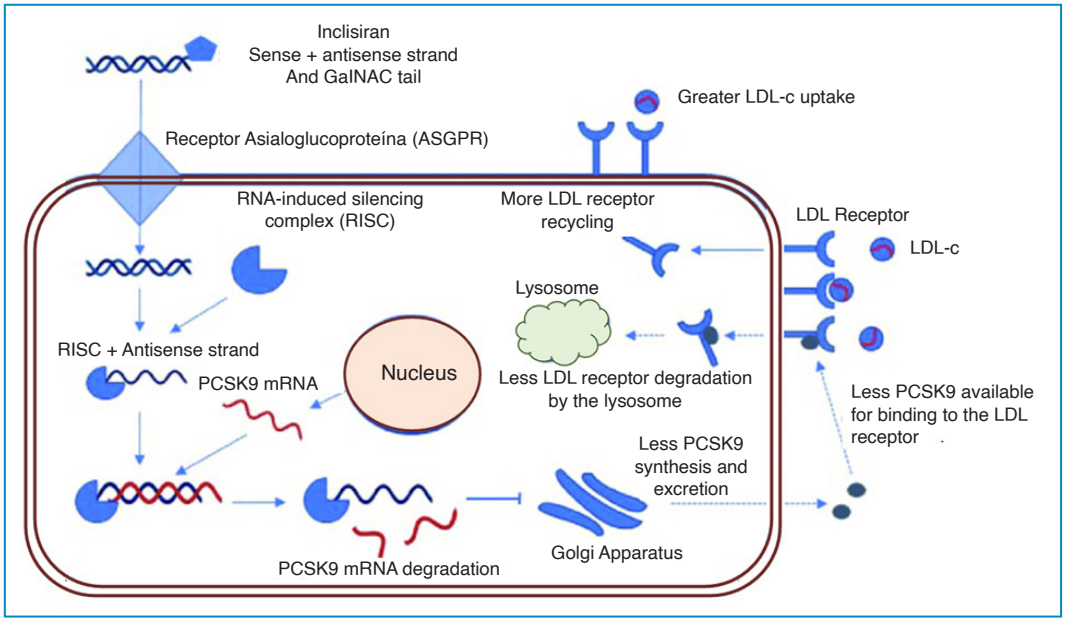

Figure 1. Mechanism of action of inclisiran.
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Studies in all phases have shown that inclisiran is safe, and its adverse events have been mild or moderate[14]. However, the treatments employing siRNA are very new and long-term safety data is still lacking.

Some studies have suggested an increase in blood sugar and HbA1c levels, especially in the first months of use, and although it has not been clearly shown to increase the risk of diabetes[15], there is a suggested mechanism of action: higher glucose levels and a greater risk of diabetes mellitus were found in mice with loss of PCSK9 function; likewise, genetic deletion of PCSK9 was associated with glucose intolerance[16].

The inclisiran effectiveness and safety studies are collected in the ORION program.

A joint analysis of the Phase III ORION studies[17] showed a reduction in PCSK9 levels compared with the baseline, a -68.2 to -29.5% reduction in total cholesterol, -42.8% in non-HDL cholesterol, -40.2% in ApoB and -20.0% in Lp(a). The average percent LDL-C reduction was 50.6%.

This same study, which included patients with heterozygous familial hypercholesterolemia, atherosclerotic disease and atherosclerotic disease risk equivalent, on maximum statin doses, prespecified the exploratory outcomes of major cardiovascular events (MACE) like non-allocated cardiovascular death, cardiac arrest, non-fatal myocardial infarction, and fatal and non-fatal stroke. A significant reduction in MACE was achieved (OR = 0.74; 95% CI = 0.58-0.94), but not in fatal or non-fatal myocardial infarction (OR = 0.80; 95% CI = 0.50-1.27) or fatal or non-fatal stroke (OR = 0.86; 95% CI = 0.41-1.81). These results are promising but must be confirmed with longer-lasting studies.

The network meta-analysis by Wang et al., using the available ORION studies[18], showed significant changes (reduction) in LDL-C, but not in triglycerides or HDL-C. The adverse events were nasopharyngitis, headache and musculoskeletal pain, with no statistically significant difference compared to the placebo group.

Inclisiran is a promising option for treating patients with atherosclerotic cardiovascular disease, due to its effectiveness and safety profile. Data is lacking on clinical event effects.

MK-0616

This is a macrocyclic peptide which inhibits PCSK9, with the novelty of being orally administered. It binds to PCSK9 and prevents its interaction with LDL receptors, preserving them and achieving LDL-C reduction through greater receptor availability. A Phase IIb study in patients with hypercholesterolemia and atherosclerotic cardiovascular disease (or > 5% cardiovascular risk)[19] already concluded, and a Phase III clinical trial in patients with moderate renal impairment is in the data collection stage[20]. In the first study, with 381 randomly assigned participants, all the MK-0616 doses showed statistically significant differences ($p < 0.001$) in the least squares mean percent change in LDL-C after up to eight weeks of treatment versus placebo: -41.2% (6 mg), -55.7% (12 mg), -59.1% (18 mg) and -60.9% (30 mg). There was no statistical difference in the incidence of adverse events compared with the placebo (39.5 to 43.4% with the different doses and 44.0% with placebo).

Gemcabene

This is a novel lipid-lowering drug whose action does not depend on LDL receptors, which makes it especially useful in patients who do not respond well to statins, ezetimibe or PCSK9 inhibitors, as occurs in patients with homozygous familial hypercholesterolemia.

It is a dual modulator of ATP-citrate lyase which lowers acetyl-coenzyme A levels and, therefore, HMG-CoA levels, leading to a reduction in cholesterol and AMP-activated protein kinase synthesis, and inhibits both cholesterol and fatty acid synthesis determined by 14C-acetate uptake in the hepatocytes, an additional effect of PPAR-alpha activation[21]. Furthermore, it reduces C-reactive protein, both isolated as well as combined with statins[22], which demonstrates its anti-inflammatory properties.

In general, it has sustained effects on LDL-C reduction (-30%) when used in patients already on lipid-lowering therapy[23], which makes it useful as an additional therapy in the treatment of familial hypercholesterolemia. The study by Ballantyne et al.[24] showed a reduction in LDL-C (-26.6%), non-HDL cholesterol (-23.0 5), ApoB (-22.1%), total cholesterol (-17.1%), triglycerdies (+1.5%), HDL-C (+4.4%), Lp(a) (+6.0%) and usCRP (-20%).

Gemcabene is still in Phase II studies and the review of additional data on carcinogenicity, requested by the FDA, is still pending.

ANGPTL3 inhibitors

A new therapeutic tool appeared with the discovery that patients with loss of function of the angiopoeitin-like protein (ANGPTL3) gene, which is a negative regulator of lipoprotein lipase activity, had lowered triglycerides, LDL-C and HDL-C, as well as a reduced risk of coronary disease[25,26]. It was also shown that loss-of-function variants in LPL were accompanied by an increased risk of coronary disease[27]. An antisense oligonucleotide targeting ANGPTL3 mRNA (vupanorsen)[28] has been tested, along with a monoclonal antibody.

In a Phase II study, vupanorsen showed significant reductions in triglycerides (36, 53 and 47%, accor-

ding to the dose) and ANGPTL3 (41, 59 and 56%). The highest dose showed a 58% reduction in ApoC-III, -38% in remnant cholesterol, -19% in total cholesterol, -18% in non-HDL cholesterol, -24% in HDL-C and -9% in ApoB. The results of the TRANSLATE-TIMI 70 study, in which the goals of statistically significant reduction in non-HDL cholesterol, triglycerides and ANGPTL3 were met, found a modest reduction in LDL-C levels, increased transaminases and the onset of hepatic steatosis, and therefore the clinical development program for vupanorsen was stopped[29].

Evinacumab is a human monoclonal antibody against ANGPTL3 which, in healthy volunteers, produced up to 76% triglyceride reduction, with up to -23% for LDL-C and -18.4% for HDL-C[30]. Triglyceride reduction is due in part to disinhibition of LPL, with the consequent hydrolysis of triglyceride-rich lipoproteins[31], while the reduction in HDL-C is due to disinhibition of endothelial lipase[32]. The change in LDL-C is unclear, but in studies in mice with LDL receptor deficiency it was found to be unrelated to the LDL receptor, which suggests its potential use in patients with homozygous familial hypercholesterolemia.

In a pilot study of nine patients with homozygous familial hypercholesterolemia, evinacumab showed a -46.8% LDL-C reduction in those who also underwent apheresis or lipid-lowering treatment, sustained (-43.4%) over an extension period without apheresis. It was well tolerated and there were no major adverse events or significant changes in hepatic or muscular enzymes[33].

In the HELPISE HoFH study of 65 patients with homozygous familial hypercholesterolemia who were on at least three lipid-lowering therapies (94% statins, 77% high-intensity; 75% ezetimibe; 25% lomitapide; 77% PCSK9 inhibitors and 34% apheresis), LDL-C was lowered by 49% consistently with the different therapies. This almost 50% reduction leads to the expectation of a reduction in the risk of major adverse events (MACE). Evinacumab was effective in patients with a deficit of LDL receptors (negative-negative), as well as in those with residual receptor activity[34]. In secondary outcomes, there were significant reductions in both ApoB (-36.9%) and non-HDL cholesterol (-51.7%) and total cholesterol (-48.4%); in addition, the adverse events were similar to those of the placebo group[35]. This drug is currently approved by the FDA for treating homozygous familial hypercholesterolemia.

ARO-ANG3

This is a small interfering RNA against ANGPTL3 which was evaluated in a Phase II study in patients with mixed dyslipidemia, and showed a 60% reduction in triglycerides, a dose-dependent reduction in LDL-C up to 32%, as well as a reduction in ApoB and remnant cholesterol. An additional benefit was documented in the dose-dependent reduction in liver fat, measured by magnetic resonance, without transaminase elevation, contrary to what happened with vupanorsen[36].

Gene therapy with CRISPR/Cas9

While it is true that most patients with dyslipidemias can be controlled with statins and lifestyle changes, in special cases (He FH and Ho FH, patients with very high cardiovascular risk or those with true statin intolerance), drug combinations are required. In this context, a frequent problem is lack of adherence to treatment, which is why the PCSK9 modulating therapies have offered relief.

Due to the liver's central role in lipid regulation (transplantation significantly improves LDL-C levels in patients with Ho FH), research has focused on developing liver-targeted therapies. There have been recent advances in gene transfer or editing which have already proven useful in various conditions such as hemophilia, Wilson's disease and familial hypercholesterolemia[37].

The two main strategies which have been used are gene transfer and gene editing. In transfer, copies of functional genes are inserted into the cell through viral vectors, using adenoassociated recombinant viruses (AAV), which cannot replicate and have a very weak ability to integrate into the patient's DNA[38]. This treatment already has an approved therapy for managing one form of hereditary retinal dystrophy and another for spinal muscular dystrophy in children.

Gene editing seeks to directly repair DNA genes, combining a delivered editing system with the cells' own DNA repair mechanisms. Once achieved, these changes persist both in the RNA as well as in the proteins produced and cannot be reversed, as they become permanent, which demands a very rigorous and comprehensive evaluation of their safety[39].

The risks are not minor: there is a possibility of an immune response to the viral vectors or their integration into the genome, as well as the production of autoantibodies against the new protein. Furthermore, these therapies should be limited to somatic cells due to the risk that, if they affect germ cells, the changes could be passed on to future generations.

The Clstered Regularly Interspaced Short Palindromic Repeats (CRISPR/Cas9) system allows the receptor organism's DNA to be edited. It uses an endonuclease-associated RNA molecule (Cas9). The RNA guides the Cas9 molecular scissors to the exact mutation site for them to cut at the site marked by the PAM (protospacer). Once the DNA strands are cut, cellular repair mechanisms are used and the exogenously added DNA is used by the same cell to repair it precisely and specifically (Fig. 2).

Typically, these tools are limited to treating monogenic diseases, and familial hypercholesterolemia is an excellent example, although, perhaps in the future, several therapeutic targets may be combined to make personalized genetic editing cocktails.

In an interesting proof of concept study[40], fibroblasts were taken from the skin of patients with homozygous familial hypercholesterolemia and treated with CRISP/Cas9 and a repair template. Eighty-three percent of the enriched clones showed correction of both alleles and differentiated into hepatocyte-like cells. These corrected cells expressed LDL receptors and internalized LDL.

Several entities could be targeted with these therapies, specifically FH related to PCSK9 gene mutations, but also in patients with recessive autosomal disorders of the LDL receptor adaptor (LDLRAP1), or ABCG8/G5 sitosterolemia, familial chylomicronemia syndrome (APOC2, APOA5, LMF1, LPL, GPIHBP1) and LCAT deficiency or abetalipoproteinemia (MTTP).

Other options

Several therapeutic options are being studied, either in preclinical or initial clinical phases. A few preliminary studies evaluate the effect of a molecule derived from nitric oxide, which could have an effect on PCSK9 activity[42]; other, more advanced studies target Lp(a), with molecules like pelacarsen, oplasiran, SLN360 and LY3819469, based on RNA technology.

Pelacarsen

In a Phase II dose-finding clinical trial with a placebo comparator, pelacarsen, an antisense oligonucleotide which interferes with the production of Lp(a), caused a dose-dependent reduction in Lp(a) of 35, 56, 58, 72 and 80%. The Lp(a) levels returned to their baseline levels 16 months after stopping the medication. Reductions were also found in ApoB and oxidized phospholipids (OxPL-apo(a) and OxPL-apoB), associated with the proinflammatory effects of Lp(a). The most common adverse event was a reaction at the injection site[43].

The effects are promising, especially considering that these results were obtained in patients with controlled LDL-C, most of whom were on statins and 20% on PCSK9 inhibitors.

The Assessing the Impact of Lipoprotein (a) Lowering With Pelacarsen on Major Cardiovascular Events in Patients With CVD (HORIZON) Lp(a) study is an ongoing Phase III clinical trial which began in December 2019 and will evaluate the effect on cardiovascular events in 8,000 patients, over 4.25 years. The primary outcomes are time elapsed to the first MACE in those with at least 70 mg/dl and at least 90 mg/dl. The results are expected in 2025.

Olpasiran

This is a small interfering RNA which prevents Lp(a) assembly in the hepatocyte, leading to a marked reduction in circulating Lp(a). In a study of heal-

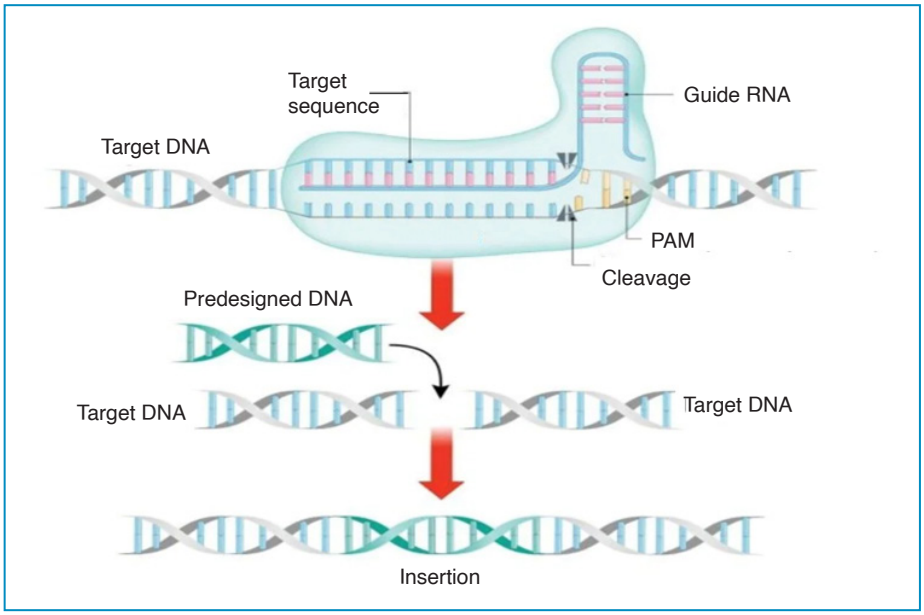

Figure 2. Genome editing.
Modificado de: Ran FA et al. Nat Protoc 2013; 8(11):2281-2308[41].

thy volunteers with elevated Lp(a), different doses of olpasiran had significant results in reducing Lp(a), between 71 and 96%, with a rapid reduction beginning on day 15 and a maximum effect between days 43 and 71, with a single dose. The values returned to baseline levels 225 days after administration[44]. There were no significant changes in kidney or liver function, platelets or laboratory markers, and a mild reaction at the injection site was the most common adverse event.

The OCEAN(a)-DOSE study is currently being carried out, evaluating several dosing strategies.

The results of the OCEAN(a)-DOSE study were recently presented, showing that patients who received olpasiran every 12 weeks had a 95% reduction in Lp(a) levels at week 36. The frequency of adverse events was no different from that of the placebo group[45]. The first patient in a randomized Phase II clinical trial, the OCEAN(a) Outcomes Trial, was randomized in December 2022.

SLN360

Similar to olpasiran, SLN360 is a small interfering RNA, specifically targeted at preventing hepatic Lp(a) production. In a study of healthy volunteers, but with elevated Lp(a) levels, 46 to 98% reductions were found depending on the dose, lasting for approximately 150 days after a single injection, with a rapid onset of action within the first two weeks, a maximum effect 30 to 60 days after application and a return to baseline at 150 days. There were no adverse events or changes in laboratory tests, nor in platelet, kidney or liver function[46].

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical responsibilities

Human and animal protection. The authors declare that no experiments were conducted on animals or humans for this study.

Data confidentiality. The authors declare that no patient data are included in this article.

Right to privacy and informed consent. The authors declare that no patient data are included in this article.

Use of artificial intelligence to generate text. The authors delcare that they have not used any type of artificial intelligence generator to draft this manuscript or create the figures, graphs, tables or their respective captions or titles.

Bibliography

1. Allen JM, Arnold SV, Lohr NL, Reisman L, Ghannam AF, Sanganalmath SK, Khan I, Iorga S, Kumbhani D. Abstract 12904: Assessing low-density lipoprotein cholesterol risk in secondary prevention patients within The PINNACLE National Outpatient Registry. Circulation. 2019;140(1):Suppl 1,Abstract 12904.
2. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. N Eng J Med. 1987;317:1237-45.
3. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, et al, for the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group*. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. N Eng J Med. 1999;341:410-8.
4. Keech A, Simes RJ, Barter P, Best J et al, for The FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005;366:1849-61.
5. The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Eng J Med. 2010;362:1563-74.
6. Jakob T, Nordmann AJ, Schandelmaier S, Ferreira-González I, Briel M, and Cochrane Heart Group. Fibrates for primary prevention of cardiovascular disease events. Cochrane Database Syst Rev. 2016(11):CD009753.
7. Yamashita S, Arai H, Yokote K, Araki E, Matsushita M, Nojima T, et al. Efficacy and Safety of pemafibrate, a novel selective peroxisome proliferator-activated receptor α modulator (SPPARMα): pooled analysis of phase 2 and 3 studies in dyslipidemic patients with or without statin combination. Int J Mol Sci. 2019;20(22):5537.
8. Pradhan AD, Glynn RJ, Fruchart JC, MacFadyen JG, Zaharris ES, Everett BM, et al., for the PROMINENT Investigators. Triglyceride lowering with pemafibrate to reduce cardiovascular risk. N Eng J Med 2022;387:1923-34.
9. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Eng J Med. 2019;380:11-22.
10. Nicholls SJ, Lincoff AM, Garcia M, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk. The STRENGTH Randomized Clinical Trial. JAMA. 2020;324(22):2268-80.
11. Ridker PM, Rifai N, MacFadyen J, Glynn RJ, Jiao L, Steg G, et al. Effects of randomized treatment with icosapent ethyl and a mineral oil comparator on interleukin-1β, Interleukin-6, C-Reactive protein, oxidized low-density lipoprotein cholesterol, homocysteine, lipoprotein(a), and lipoprotein-associated phospholipase a2: A REDUCE-IT Biomarker Substudy. Circulation. 2022;146:372-9.
12. Samuel E, Watford M, Egolum UO, Ombengi DN, Ling H, Cates DW. Inclisiran: a first-in-class siRNA therapy for lowering low-density lipoprotein cholesterol. Ann Pharmacother. 2022;57(3):317-24.
13. Fitzgerald K, Frank-Kamenetsky M, Shulga-Morskaya S, Liebow A, Bettencourt BR, Sutherland JE, et al. Effect of an RNA interference drug on the synthesis of proprotein convertase subtilisin/kexin type 9 (PCSK9) and the concentration of serum LDL cholesterol in healthy volunteers: a randomised, single-blind, placebo-controlled, phase 1 trial. Lancet. 2014;383:60-8.
14. Fitzgerald K, White S, Borodovsky A, Bettencourt BR, Strahs A, Clausen V, et al. A highly durable RNAi therapeutic inhibitor of PCSK9. N Eng J Med. 2017;376:41-51.
15. de Carvalho LSF, Campos AM, Sposito AC. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and incident type 2 diabetes: a systematic review and meta-analysis with over 96,000 patient-years. Diabetes Care. 2018;41(2):364-7.

16. Da Dalt L, Ruscica M, Bonacina F, et al. PCSK9 deficiency reduces insulin secretion and promotes glucose intolerance. The role of the low-density lipoprotein receptor. Eur Heart J. 2019;40(4):357-68.
17. Wright RS, Ray KK, Raal FJ, Kallend DG, Jaros M, Koenig W, et al, and for the ORION Phase III Investigators. Pooled Patient-Level Analysis of Inclisiran Trials in Patients With Familial Hypercholesterolemia or Atherosclerosis J Am Coll Cardiol. 2021;77(9):1182-93.
18. Wang Y, Wang J, Wang S. Comparative effectiveness of inclisiran 100, 300, and 500 mg in a population with hyperlipidemia: a network meta-analysis of randomized controlled trials. Am J Cardiovasc Drugs. 2018;18(4):271-82.
19. Clinical trials. A Study of the Efficacy and Safety of MK-0616 (Oral PCSK9 Inhibitor) in Adults With Hypercholesterolemia (MK-0616-008) (Internet). Clinical trials; cited 2023 Aug 15. URL: https://clinicaltrials.gov/ct2/show/NCT05261126.
20. Clinical trials. A Study of MK-0616 in Participants With Moderate Renal Impairment (MK-0616-007). (Internet). Clinical trials; cited 2023 Aug 15. URL: https://classic.clinicaltrials.gov/ct2/show/NCT05070390
21. Bisgaier CL, Essenburg AD, Barnett BC, Auerbach BJ, Haubenwallner S, Leff T, et al. A novel compound that elevates high density lipoprotein and activates the peroxisome proliferator activated receptor. J Lipid Res. 1998;39(1):17-30. Erratum in: J Lipid Res. 1998;39(6):1317.
22. Stein E, Bays H, Koren M, Bakker-Arkema R, Bisgaier C. Efficacy and safety of gemcabene as add-on to stable statin therapy in hypercholesterolemic patients. J Clin Lipidol. 2016;10:1212-22. 10.1016/j.jacl.2016.08.002.
23. Gaudet D, Durst R, Lepor N, Bakker-Arkema R, Bisgaier C, Masson L, Golden L, Kastelein JJ, Hegele RA, Stein E. Usefulness of gemcabene in homozygous familial hypercholesterolemia (from COBALT-1). Clinical Trial. Am J Cardiol. 2019;124(12):1876-80.
24. Ballantyne CM, Davidson MH, MacDougall DE, et al. Efficacy and safety of a novel dual modulator of adenosine triphosphate-citrate lyase and adenosine monophosphate-activated protein kinase in patients with hypercholesterolemia: results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. J Am Coll Cardiol. 2013;62:1154-62.
25. Dewey FE, Gusarova V, O'Dushlaine C, et al. Inactivating variants in ANGPTL4 and risk of coronary artery disease. N Eng J Med. 2016;374:1123-33.
26. Dewey FE, Gusarova V, Dunbar RL, O'Dushlaine C, Schurmann C, Gottesman O, et al. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. N Eng J Med. 2017;377:211-21.
27. Jensen MK, Rimm EB, Rader D, et al. S447X variant of the lipoprotein lipase gene, lipids, and risk of coronary heart disease in 3 prospective cohort studies. Am Heart J. 2009;157:384-90.
28. Gaudet D, Karwatowska-Prokopczuk E, Baum SJ, et al. Vupanorsen, an N-acetyl galactosamine-conjugated antisense drug to ANGPTL3 mRNA, lowers triglycerides and atherogenic lipoproteins in patients with diabetes, hepatic steatosis, and hypertriglyceridaemia. Eur Heart J. 2020;41(40):3936-45.
29. Bergmark BA, Marston NA, Bramson CR, et al. Effect of vupanorsen on non–high-density lipoprotein cholesterol levels in statintreated patients with elevated cholesterol: TRANSLATE-TIMI 70. Circulation. 2022;145(18):1377-86.
30. Graham MJ, Lee RG, Brandt TA, Tai L, Fu W, Peralta R, et al. Cardiovascular and Metabolic Effects of ANGPTL3 Antisense Oligonucleotides. N Eng J Med. 2017;377:222-32.
31. Wang Y, Gusarova V, Banfi S, Gromada J, Cohen JC, Hobbs HH. Inactivation of ANGPTL3 reduces hepatic VLDL-triglyceride secretion. J Lipid Res. 2015;56:1296-307.
32. Shimamura M, Matsuda M, Yasumo H, et al. Angiopoietin-like protein3 regulates plasma HDL cholesterol through suppression of endothelial lipase. Arterioscler Thromb Vasc Biol. 2007;27:366-72.
33. Stefanutti C, Chan DC, Di Giacomo S, Morozzi C, Watts GF. Long-term efficacy and safety of evinacumab in patients with homozygous familial hypercholesterolemia: real-world clinical experience. Pharmaceuticals. 2022;15:1389.
34. Pirillo A, Catapano AL. Evinacumab: a new option in the treatment of homozygous familial hypercholesterolemia. Expert Opinion on Biological Therapy. 2022;22(7):813-20.
35. Raal FJ, Rosenson RS, Reeskamp LF, et al. Evinacumab for homozygous familial hypercholesterolemia. N Eng J Med. 2020;383(8):711-20. https://clinicaltrials.gov/ct2/show/NCT04832971.
36. Stankov S, Cuchel M. Gene editing for dyslipidemias: New tools to "cut" lipids. https://doi.org/10.1016/j.atherosclerosis.2023.01.010.
37. Mendell JR, Al-Zaidy SA, Rodino-Klapac LR, Goodspeed K, Gray SJ, Kay CN, et al. Current clinical applications of in vivo gene therapy with AAVs. Mol Ther. 2021;29:464-88.
38. Saha K, Sontheimer EJ, Brooks PJ, Dwinell MR, Gersbach CA, Liu DR, et al. The NIH somatic cell genome editing program. Nature. 2021;592:195-204.
39. Omer L, Hudson EA, Zheng S, Hoying JB, Shan Y, Boyd NL. CRISPR correction of a homozygous low-density lipoprotein receptor mutation in familial hypercholesterolemia induced pluripotent stem cells. Hepatol Commun. 2017;1:886-98.
40. Stomberski CT, Venetos NM, Zhou H, Qian Z, Collison BR, Field SJ, et al. A multienzyme S-nitrosylation cascade regulates cholesterol homeostasis. Cell Reports. 2022;41(4):1-13.
41. Ran FA, Hsu PD, Wright J, Agarwala V Scott DA, Zhang F. Genome engineering using the CRISPR-Cas9 system. Nat Protoc 2013; 8(11):2281-2308.
42. Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, et al. Lipoprotein (a) reduction in persons with cardiovascular disease. N Eng J Med. 2020;382:244-55.
43. Koren MJ, Moriarty PM, Baum SJ, et al. Preclinical development and phase 1 trial of a novel siRNA targeting lipoprotein(a). Nat Med. 2022;28:96-103. https://doi.org/10.1038/s41591-021-01634-w
44. O'Donoghue M. Reduction of Lipoprotein(a) With Small Interfering RNA: The Results of the Ocean(a)-DOSE Trial (OCEAN(a) DOSE) [Conference Presentation]. American Heart Association Scientific Sessions, 2022.
45. Nissen SE, Wolski K, Balog C, et al. Single ascending dose study of a short interfering RNA targeting lipoprotein(a) production in individuals with elevated plasma lipoprotein(a) levels. JAMA. 2022;327:1679-87. https://doi.org/10.1001/jama.2022.5050
46. Rider DA, Eisermann M, Löffler K, Aleku M, Swerdlow DI, Dames S, Hauptmann J, Morrison E, Lindholm MW, Schubert S, Campion G. Pre-clinical assessment of SLN360, a novel siRNA targeting LPA, developed to address elevated lipoprotein (a) in cardiovascular disease. Atherosclerosis 2022; 349:240-247. https://doi.org/10.1016/j.atherosclerosis.2022.03.029