Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 32 Suppl. 3
July-September 2021

doi: 10.35366/100802

Present and future of the hypolipidemic treatment, new molecules in sight

Presente y futuro del tratamiento hipolipemiante, nuevas moléculas a la vista

Úrsula Medina, MD, PhD* Rafael Almendra-Pegueros, RD, BSc‡
Antonio Gordillo-Moscoso, MD, PhD*

INTRODUCTION

In Mexico, despite dietary and pharmacological interventions, dyslipidemias represent a public health problem, the most prevalent are elevated LDL-C and hypoalphalipoproteinemia, highlighting the phenotype of elevated triglycerides/low HDL-C in men and women between 40 and 59 years old (43.3% and 43.7%, respectively). However, it is even more alarming, the low number of patients under treatment, of only 3.7%.[1]

Therefore, considering the substantial risk of associated cardiovascular events, it is necessary to perform an analysis of current and emerging therapies. In this way, it is intended to identify those with therapeutic potential, that have regulatory approval, quality control necessary in the development of any drug and that may in the future be accessible to the population.[2]

DEVELOPMENT OF NEW DRUGS

The development of new drugs starts with an exhaustive search of new molecules, that can interact with receptors, enzymes, proteins, and genes involved in the physiopathology of dyslipidemia. These molecules could be considered as molecules candidates for hypolipidemic treatment.

The process for considering a molecule as a New Molecule Candidate (NMC), from discovery to market can last more than 12 years *(Figure 1)*. It is crucial to consider the necessary economic investment that is required for the development that increases as the discovery and development processes become more complex. This is point to consider in the decision-making for the implementation of new pharmacological therapies since if the cost/benefit is high (not adequate), patient will not achieve an adequate attachment and therefore, success rate will be reduced.[3]

DISCOVERY PHASE

At this stage, study objective is defined and a new NMC is proposed. This can be based on 1) efficacy similar to other drugs authorized, 2) genetic evidence of interaction in the disease, 3) involvement in components of a specific physiopathology and, 4) selective analysis of synthesized compounds capable of interact with a therapeutic target.

DEVELOPMENT OR PRE-CINICAL PHASE

Once NMC have been postulated, they must demonstrate specific efficacy and safety characteristics according to the molecule type (chemical, biological, biotechnological). Pharmacokinetic properties should be reproducible and demonstratable in multiple laboratory trials, at different therapeutic doses, in different study models (in vitro, animal models), under conditions as physiologically similar to the specific pathology and should provide information on the occurrence of adverse effects, before starting human testing. NMC whose effects become reproducible

* Laboratorio de Investigación Traslacional en Farmacología, Facultad de Medicina, Universidad Autónoma de San Luis Potosí. Mexico.
‡ Escuela de Ciencias de la Salud, Universidad del Valle de México, Campus San Luis Potosí. Mexico.

Received:
03/07/2021
Accepted:
12/07/2021

How to cite: Medina Ú, Almendra-Pegueros R, Gordillo-Moscoso A. Present and future of the hypolipidemic treatment, new molecules in sight. Cardiovasc Metab Sci. 2021; 32 (s3): s225-s230. https://dx.doi.org/10.35366/100802

and meet the above conditions must submit a results report and starts the clinical phase to seek approval from major regulatory agencies (FDA, EMA, COFEPRIS).

However, the lack of trial reproducibility is the main limitation. Around 90% of NMC do not meet these requirements and have pharmacokinetic/pharmacodynamic deficiencies, in vitro/in vivo toxicity, or lack of efficacy and therefore they are not promoted to the next stage of development.

CLINICAL PHASE

This phase consists of four stages and involves human testing. Phase I is performed in a small group of healthy volunteers (< 100). The objective of phase I is to determine signs of acute toxicity. The average time is around six to 12 months. Main limitation of this phase is the recruitment of study subjects since they are usually young men with weight and average size (170 cm/70 kg).

In phase II, the drug is administered in groups of patients with an early stage of the study pathology (100-200). The objective is to verify the effectiveness of the candidate drug in the proposed pathology. It is usually performed by comparing the new formulation against placebo or the current therapeutical gold standard. The average development time is two to three years. The main limitations are the tests are performed realized in patients in the early stages of pathology evolution and without previous data of failure to standard treatment.

Phase III is carried out in multiple research centers, in different populations (100-1,000), with a diversity of characteristics. The objective is to verify safety and efficacy profiles and detect toxicity not previously manifested. The average development time of this phase is three to five years because it depends on specific selection criteria. The last phase (phase IV) is performed after authorization of the drug. The main objective is to perform pharmacovigilance and detect rare and long-term adverse effects.

Despite the high investment in the development of new pharmacological agents, many of them have failed. To improve the translational pharmacology scope, Horvath P et al, 2016 proposes that before seeking a new goal or proposing a new pharmacological target, the following points must be reviewed: 1) adequate cell lines or preclinical models, 2) population where they will be developed, 3) improve statistical and methodological robustness in both previous points and 4) safety and toxicity problems because cardio or hepatotoxic effects are mainly evidenced in post-authorization phase.

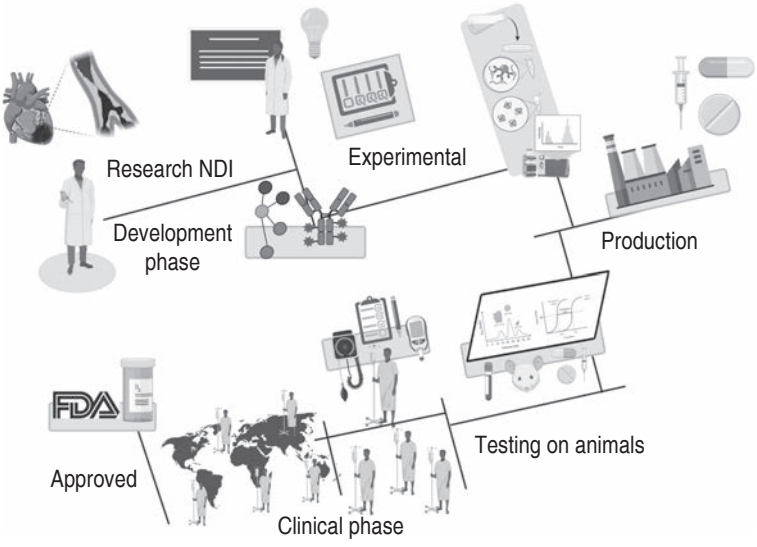

Figure 1: Drug development phases.

THERAPEUTIC TARGET MOLECULES: THEIR USEFULNESS AND SEARCH

The descriptive work on the cholesterol cycle and its relationship to atherosclerotic disease in subjects with homozygote familial hypercholesterolemia, carried out by Goldstein and Brown in 1970, in conjunction with reports from the Framingham Study, determined the importance of lowering serum cholesterol levels for the prevention and treatment of vascular atheromatic disease.[4] Dietary changes demonstrated little effect on cholesterol level in family hypercholesterolemic patients, leading to an increased interest in endogenous cholesterol synthesis at liver level as a cause of pathological serum lipids increase.

The first pharmacological approach to reduce serum lipids was the use of dietary fibers and fat-absorbing resins that decrease

cholesterol absorption at the intestinal level. It's non-specific and modest antilipidemic effect was associated with significant adverse effects at gastrointestinal level.

In 1980, a molecule to specifically alter serum cholesterol levels by interfering with its synthetic pathway was used. Akira Endo et al[5] described the effects of the compound **ML-236B** (lovastatin-competitive inhibitor of the 3-hydroxy-3-methyl glutaryl CoA reductase enzyme), in subjects with primary hypercholesterolemia. An average of 27% reduction in serum cholesterol levels was observed. Since then, the strategy to decrease cholesterol levels and particularly its most atheromatous subfraction: low-density cholesterol (LDL-C), has focused on identifying key proteins in exogenous, endogenous, and reverse phases of the cholesterol cycle. The basis for such therapeutic orientation is that a specific blockage or functional alteration, will result in a reduction in serum concentrations. This blockage will prevent the formation of obliterating atheroma and/or decrease its size in a long-term form.

Identification and validation of these proteins as modifiable targets allows performing designs and simulations *in silico*, biochemical or molecular synthesis, or genetic engineering techniques initially tested in cell or tissue cultures, natural and chimeric animal models and follow the processes previously described in this review.

To this point, several proteins with potential use as therapeutic targets have been found. Here the most important under investigation, as well as the lipid cycle phase in which they exert their function are described:

Apolipoprotein E (APO-E): internal ligand of the LDL receptor, participates in metabolic regulation of lipoproteins, through the transport of lipids to and from different tissues. Participates in exogenous and endogenous phases of the cholesterol cycle.

Apolipoprotein A1 (APO-A1): participates in the formation and molecular structure of HDL cholesterol, activates the enzyme lecithin cholesterol acyl transferase (LCAT), and stimulates reverse transport of cholesterol.[6]

ATP-citrate-lyase (ACLY): participates in cholesterol synthesis. This enzyme catalyzes conversion of citrate and coenzyme A to acetyl Co-A; condensation of three molecules of Acetyl Co-A generate the 3-methyl-glutaryl coenzyme A, which in successive steps will generate mevalonate and finally the cholesterol molecule.

Proprotein convert subtilisin/kexin type 9 (PCSK9): liver origin protein. In the hepatocyte membrane, it joins to the LDL receptor (LDLR), the LDLR-PCSK9 complex is internalized to the cytoplasm in endosomes/lysosomes, allowing the degradation of LDLR, preventing its recycling and decreasing LDL-cholesterol clearance.[7] It participates in the endogenous and exogenous phases of cholesterol.

INNOVATIVE MOLECULES IN DEVELOPMENT

Since its creation in 1997, the registration ClinicalTrials.gov has allowed to follow the process of new drugs development, recording phase I, II, and III studies of new molecules, as well as other processes or developments that do not relate to drugs.[8] Assignment of a registration number allows to track the evolution of a study and facilitates but does not ensure, publication in academic journals and subsequent authorization by the U.S. Drug Administration (FDA).

A systematic search was done using the words, «Hypercholesterolemia» and «Early phase I, II, III». Twenty-eight «innovative» molecules were identified at different stages of development.

Of the innovative molecules identified, nine are new recombinant anti-PCSK9 antibodies, with small modifications to those currently authorized. The first antisense oligonucleotide molecule with extensive improvements to previous anti-PCSK9 drugs was suspended by significant immunological adverse reactions. Showing the difficulties to design biotechnological drugs. One identified development includes a prosthetic drug without biological antibody activity created to bind to PCSK9 to prevent its digestion. Two developments in this group attract powerful attention, although they are in early stages of

Table 1. Characteristics of approved innovative molecules.

Molecule	Lomitapide	Mipomersen	Permafibrate	Inclisiran	Bempedoic Acid
Approval year	2012	2013	2017	2020	2020
Indication	Familial Hypercholesterolemia	Familial Hypercholesterolemia	Familial Hypercholesterolemia and hyperlipidemia	Familial Hypercholesterolemia	Familial Hypercholesterolemia
Route of administration	Oral	Subcutaneous	Oral	Subcutaneous	Oral
Dosage	5mg/day	200mg/week	0.1mg/12hours	300mg/6 months	180mg/day

development: an oral administration PCSK9 inhibitor and a vaccine created with RNA coding a PCSK9 blocker protein that would have subcutaneous application every three months.

In addition, one drug classified as anti-angiogenic is developing as a hypolipidemic agent by blocking the angiopoietin-3 receptor. Another molecular mechanism under development is the creation of mimetic peptides of apolipoproteins B and E, that block lipid receptors and decrease levels of LDL-C. A mimetic molecule of Apo-1 increases lipid uptake by HDL-C. Two other anti-senses oligopeptides (siRNA), which block the expression of angiopoietin-3 are in their first stage of development.

Synthetic molecules, although in a smaller proportion, are represented by a nicotinic acid receptor agonist, two beta-hydroxysteroid dehydrogenase inhibitors, and a cholesterol ester transferring protein (CEPT) inhibitor.

It is notable that, of these 28 prospects, most are reported on Clinicaltrials.gov as completed. Less than 15% of those have reported results and fewer have been published. This phenomenon diminishes the credibility of the control that motivated the register.

Finally, 19 molecule development projects located were suspended for different causes. Some causes of this suspension are ineffectiveness, important adverse events (liver damage, kidney damage, or increased cardiovascular events), up to a case of interruption without specifying details by the production company despite having authorization for its marketing. These projects are published even less frequently.

INNOVATIVE APPROVED MOLECULES

After a search in PubMed with the following keywords: *Hyperlipidemias*, *Drugs-Investigational*, *Drug Approval*, and *Drug Development* and using the last 10 years and human species as filters, one hundred and forty-eight articles were obtained, after revision of title and abstract, 50 articles about currently approved molecules were maintained. Finally, 24 articles were included in this review.

Lomitapide: is a selective microsomal triglyceride transfer protein inhibitor for lowering LDL-C levels in adults with familial hypercholesterolemia *(Table 1)*.[9] Lomitapide binds to and suppresses microsomal triglyceride transfer protein (MTP), producing lipoproteins that contain apo-B in the hepatocytes and the enterocytes leading to a decrease in the generation of very-low-density lipoprotein (VLDL) and chylomicrons and hence decreasing LDL-C levels in plasma. It is effective in reducing LDL-C, alone (35% reduction in LDL-C), or in combination with ezetimibe, fenofibrate, and atorvastatin (66% reduction in LDL-C). Similarly, it has been observed that under these schemes reductions of up to 50% of serum triglyceride levels and up to 3% of weight loss is achieved.[10] Several studies make such observations; however, report of adverse events is important.

In phase II and III clinical studies, about 90% of the population suffers from gastrointestinal discomfort, 30% report diarrhea, nausea, vomiting, and dyspepsia. About 20% report abdominal pain, discomfort, gases and flatulence.[10] It is important to add that in

some cases, side effects are those related to hepatic transaminases elevation (approximately 30% of patients, this is a reversible situation within two weeks of drug discontinuation) and accumulation of liver fatty tissue, situations to be considered in clinical use.

Mipomersen: second generation oligonucleotide antisense drug for Apo-B, approved for treatment of family hypercholesterolemia in patients over 12 years, by weekly subcutaneous injections of 200 mg. Mipomersen binds to the region-specific segment encoding RNAm for apo-B, reducing the translation of RNAm into protein by multiple mechanisms including, activation of RNase H-mediated degradation of the cognate mRNA, thus dissipating the synthesis of ApoB in the liver and its transport.

It use has achieved a 25% reduction in LDL-C levels. Similarly, changes in lipid metabolism indicators such as total cholesterol, and APO-B have been observed.[11] However, certain adverse effects were identified, including reaction in the area of application of the drug (84%), flu symptoms (30%), and the elevation of hepatic transaminases (up to 40%). For that reason, the FDA alert about the non-free use of mipomersen. Current use require that patients consuming it receive a follow-up from pharmaco-surveillance in an close manner.[10]

Permafibrate: is a highly selective peroxisome proliferator activated receptor (PPAR)-α, developed for the treatment of hyperlipidemias. Permafibrate is > 2,500 times more efficient than fenofibrate with reduced adverse effects. The mechanism of action is the reduction of triglyceride-rich protein (TLR), acting together in lipoprotein metabolism in the liver, small intestine, as well as macrophages.

Recently, permafibrate has been approved by the FDA for the treatment of hyperlipidemias, achieving a reduction of 44.3% in triglycerides and 49.1% in cholesterol remnants. After treatment with permafibrate, the proportion of patients with triglycerides less than 150 mg/dL was 81.5%.[12] The use of permafibrate as coadjutant therapy to statins has also been shown to reduce up to 53.4% in triglycerides at doses of 0.2 mg/dL. The main role of permafibrate is the reduction of triglycerides by more than 45% after 12 to 24 weeks of administration, this reduction is comparable to the reduction achieved by fenofibrate, but with a considerable decrease in adverse effects.

In addition to these effects, the ability to reduce non-HDL cholesterol, Apo-B, ApoB48, and ApoC3, with increased HDL-C has been reported with a reduction of cardiovascular risk. Permafibrate has adverse effects of less than 5%, including nasopharyngitis, increased creatinine and uric acid, and altered liver function. Among them, no death or rhabdomyolysis has been reported.

Inclisiran: first interference RNA (siRNA) biotechnology drug, recently approved by the FDA and under current review; to reduce LDL-C levels and prevent cardiovascular events.

The reported mechanism of action is reduction of intra and extracellular production of PCSK9, from conjugation with triantennary N-acetylgalactosamine (GalNAc) that provides high-affinity binding to hepatocyte receptors, which reduce the dose and volume of drug required and the highly specific liver uptake should result in less chance of off-target effects.[13,14] Efficacy on LDL-C reduction has been demonstrated in phase II and III ORION studies, with participation of more than twenty thousand patients worldwide,[14] who were under maximum dosing of statins and/or more ezetimibe and with significant risk factors for cardiovascular disease, achieving a reduction in LDL-C of approximately 50%, allowing up to six months between doses.

Inclisiran, not only achieves LDL-C reduction, Khan et al. in a meta-analysis of three clinical trials with 3,660 patients describe that compared to placebo, it also significantly decrease ($p < 0.001$) total cholesterol (37%), ApoB (41%), non-HDL cholesterol (45%) and major cardiovascular events (24%). Despite its effectiveness, adverse effects, considered moderate, have been reported, occurring in the same proportion that in placebo group. However, there are still certain limitations that should be explored such as the comparation of inclisiran vs PCSK9 inhibitor monoclonal antibodies and the cost they will represent for health and patient services.

Bempedoic acid: it is a pro-drug rapidly absorbed by the small intestine, which allows its passage to the liver where it is activated by very-long-chain acyl-CoA synthetase 1 (ACSVL1) to ETC-1002-CoA.9, this active metabolite inhibits

adenosine triphosphate- citrate lyase (ACLY), an enzyme upstream of HMG-CoA reductase. Inhibition of ACL decreases cholesterol biosynthesis and causes an upregulation in lipoprotein receptors to increase LDL-C clearance.[15]

Efficacy of bempedoic acid was evaluated in four phase III randomized double-blind clinical trials: CLEAR Tranquility, patients with a history of statin intolerance and use of ezetimibe; CLEAR Serenity, subjects with statin intolerance but hypolipidemic therapy for primary prevention; CLEAR harmony, patients in statin therapy with maximum tolerable and CLEAR Wisdom, in patients at high cardiovascular risk and in statin therapy at tolerable maximums. A daily dose of 180 mg achieved LDL-C reduction from 12.6 (at 52 weeks of follow-up) to 23.6% (within 12 weeks of surgery). Side effects were similar in both groups. Main reported adverse events were nasopharyngitis, urinary tract infections, arthralgia, hyperuricemia, gout, decreased glomerular filtration rate, and risk of tendon rupture.[15] Despite the observed results, it is considered an expensive therapy.

CONCLUSIONS

The introduction of silico design, molecular biology, and genetic engineering in the design of new hypolipidemic drugs forces us as clinicians to be updated in new drug molecules that are a potential alternative against the process of formation of obliterating vascular atheroma.

This work offers an update on this topic, with a streamlined explanation of the process of drug developing and reviewing the pharmacological developments authorized for clinical use, that will soon be available to the cardiological group.

REFERENCES

1. Hernández-Alcaraz C, Aguilar-Salinas CA, Mendoza-Herrera K, Pedroza-Tobías A, Villalpando S, Shamah-Levy T et al. Dyslipidemia prevalence, awareness, treatment and control in Mexico: results of the Ensanut 2012. Salud Publica Mex. 2020; 62 (2): 137-146.
2. Graham I, Shear C, De Graeff P, Boulton C, Catapano AL, Stough WG et al. New strategies for the development of lipid-lowering therapies to reduce cardiovascular risk. Eur Heart J Cardiovasc Pharmacother. 2018; 4 (2): 119-127.
3. Mohs RC, Greig NH. Drug discovery and development: role of basic biological research. Alzheimers Dement Transl Res Clin Interv. 2017; 3 (4): 651-657.
4. Thompson GR. FH through the retrospectoscope. J Lipid Res. 2021; 62: 100036.
5. Yamamoto A, Sudo H, Endo A. Therapeutic effects of ML-236B in primary hypercholesterolemia. Atherosclerosis. 1980; 35 (3): 259-266.
6. van der Vorst EPC. High-density lipoproteins and apolipoprotein A1. In: Hoeger U, Harris JR, editors. Vertebrate and invertebrate respiratory proteins, lipoproteins and other body fluid proteins [Internet]. Cham: Springer International Publishing; 2020 [cited Jan 13, 2021]. pp. 399-420. (Subcellular Biochemistry; vol. 94). Available in: http://link.springer.com/10.1007/978-3-030-41769-7_16
7. Seidah NG, Awan Z, Chrétien M, Mbikay M. PCSK9: a key modulator of cardiovascular health. Circ Res. 2014; 114 (6): 1022-1036.
8. Gómez-Restrepo C, Reveiz Narváez Y. The registration of clinical trials. Rev Colomb Psiquiatr. 2008; 37 (3): 452-456.
9. Feingold KR. Cholesterol lowering drugs. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dungan K et al, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited Jan 13, 2021]. Available in: http://www.ncbi.nlm.nih.gov/books/NBK395573/
10. Sirtori CR, Pavanello C, Bertolini S. Microsomal transfer protein (MTP) inhibition-a novel approach to the treatment of homozygous hypercholesterolemia. Ann Med. 2014; 46 (7): 464-474.
11. McGowan MP, Moriarty PM, Backes JM. The effects of mipomersen, a second-generation antisense oligonucleotide, on atherogenic (apoB-containing) lipoproteins in the treatment of homozygous familial hypercholesterolemia. Clin Lipidol. 2014; 9 (5): 487-503.
12. Yamashita S, Masuda D, Matsuzawa Y. Pemafibrate, a new selective PPARα modulator: drug concept and its clinical applications for dyslipidemia and metabolic diseases. Curr Atheroscler Rep. 2020; 22 (1): 5.
13. Tomlinson B, Chan P, Zhang Y, Lam CWK. Efficacy and safety of add on therapies in patients with hypercholesterolemia undergoing statin therapy. Expert Opin Pharmacother. 2020; 21 (17): 2137-2151.
14. Kosmas CE, Muñoz Estrella A, Skavdis A, Peña Genao E, Martinez I, Guzman E. Inclisiran for the treatment of cardiovascular disease: a short review on the emerging data and therapeutic potential. Ther Clin Risk Manag. 2020; 16: 1031-1037.
15. Nguyen D, Du N, Sulaica EM, Wanat MA. Bempedoic acid: a new drug for an old problem. Ann Pharmacother. 2021; 55 (2): 246-251.

Correspondence:
Antonio Gordillo-Moscoso, MD, PhD
E-mail: gordillo@uaslp.mx