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Review Article

Atherogenic Dyslipidemia: What's New

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Abstract

Currently, new classes of lipid-lowering drugs have been developed. Some of them are available for clinical practice. The convertase intended / kexintype pro-proteina 9 (PCSK9) inhibitor increases the expression of the Low Density Lipoprotein (LDL) receptors on hepatocytes through improved recycling of LDL receptor. Now is accepted that Statins have proven to be a very effective and safe treatment in many and various types of studies including controlled, clinical trials and treatment of first line against the atherogenic dyslipidemia. However and to weights of a treatment optimal with Statins, 60% to 80% of risk cardiovascular residual persists. Thus, patients with Familial Hypercholesterolemia with a very high level of cholesterol in Lipoproteins of Low Density (LDL-C) and patients who do not tolerate or do not respond to Statins are other barriers to treatment with Statins. The inhibitor of PCSK9 recently showed results promising of down in form significant C-LDL in the Hypercholesterolemia Family (HF) of them patients of the phase of trials to long term III. MTP inhibitor and against ApoB antisense oligonucleotide were approved for the treatment of homozygous familial hyperlipidemia but it still needs more evidence strengthened by the hepatic safety as hepatosteatosis.

Introduction

Atherosclerotic Cardiovascular Disease (ACVD) is the leading cause of death in the world, and Mexico is no exception to this pandemic. It is considered, in addition, the main burden of health care around the world, regardless of different ethnic groups. Dyslipidemia characterized by high levels of atherogenic lipoprotein including Cholesterol Lipoproteins of Low Density (LDL-C), is known as the main risk factor for ACVD [1]. Statins, 3-Hydroxy-3-methylglutaryl-Coenzyme A reductase, effectively block the hepatic synthesis of cholesterol and reduces LDL-C enough up to 50% from baseline in accordance with the power of Statins [2].

During the last decades, Statins have been the cornerstone of the medical treatment of Dyslipidemia. Statins reduce CVD risk by 15% to 37%, but a residual from 60% to 80% of CVD risk continues to be observed [3]. These remaining CVD risks have been recognized as favoring the vascular event in approximately 20% of patients with coronary heart disease even under optimal treatment with Statins [4]. At the Mexican Institute of Social Secuirity for more than one decade led by atherosclerotic disease cardiovascular disease is the leading cause of death regardless of age and gender group (Figure 1) (Table 1).

The underlying risk factors include Obesity, Hypertension, Diabetes, Smoking and Dyslipidemia. Nevertheless the great effort to control these factors, the elevated prevalence and incidence is still as the great challenge for the next decades in Mexico as well the rest of the World.

Familial Hypercholesterolemia is a genetic disorder caused by mutation of the gene for the receptor of Low Density Lipoproteins (LDLR), Apolipoprotein B (ApoB) gene or the gene of the pro-protein convertase subtisilin/kenin type 9 (PCSK9) with a prevalence of 1 in 300 to 500 people in heterozygous and 1 in 1,000,000 people by the most severe homozygous form [5]. These genetic defects cause the significant elevation of blood levels of cholesterol LDL (LDL-C), which are translated in the early development of coronary artery disease and higher mortality. Familial Hypercholesterolemia is a genetic disorder caused by mutation of the gene for the receptor of Low Density Lipoproteins (LDLR), Apolipoprotein B (ApoB) gene or the gene of the pro-protein convertase subtisilin/kenin type 9 (PCSK9) with a prevalence of 1 in 300 to 500 people in heterozygous and 1 in 1,000,000 people by the most severe homozygous form. These genetic defects cause the significant elevation of blood levels of cholesterol LDL (LDL-C), which are translated in the early development of coronary artery disease and higher mortality [5].
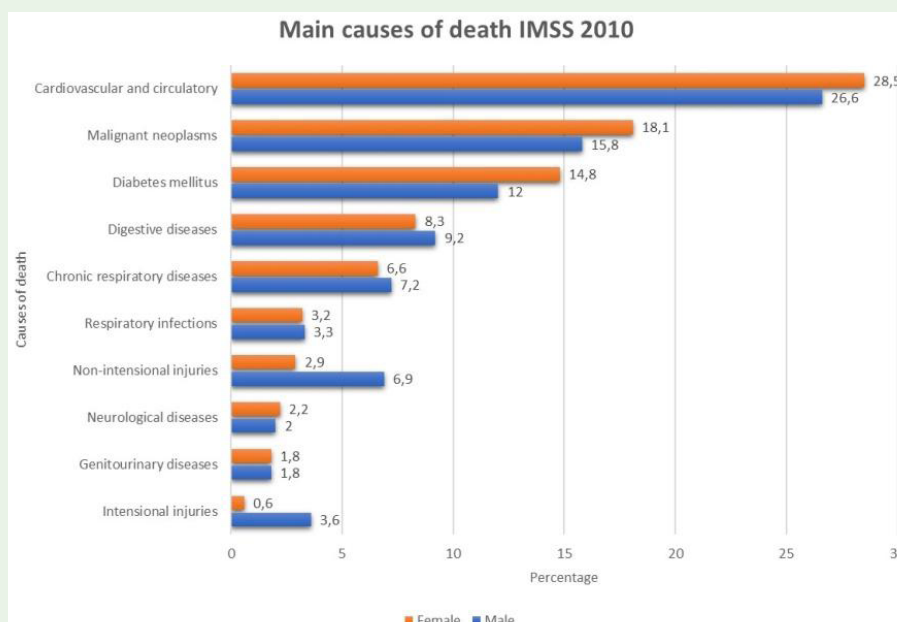
Figure 1: Changes in Mean Facial (± S.E.) Width-to-Height Ratios of Major League Baseball Players Active 1870-1989.

High doses of Statins are the first choice of treatment for these patients, but even with a maximum intensity of statin therapy only 20% of patients with Familial Hypercholesterolemia tend to achieve the optimal goal of LDL-C [5]. In addition, a subgroup of patients is intolerant to therapy with Statins at high doses due to adverse effects, including myotoxicity or hepatotoxicity.

Resins, Fibrates, niacin, bile acids, and Ezetimibe hijackers have been approved as agents not Statins for the treatment of Dyslipidemia [6]. Each class of drug Statin showed no significant improvement in lipid profiles and all have a different effect in subtractions from composition of lipoproteins in the blood, such as elevation of cholesterol (HDL-C) high-density lipoprotein. However, none of these agents to demonstrated a reduction of the additional risk of EAC when added to statin therapy. Only Ezetimibe showed significant reduction in cardiovascular events in the recent randomized clinical trial: IMPROVE-IT, combining simvastatin and simvastatin monotherapy comparison more Ezetimibe [7].

There has been a consistent need of how we could optimize the treatment for patients with increased risk of CAD. There are still many percentages of patients who exist to request new combination of drugs beyond the treatment with only Statins. In this review, we will discuss four new drugs developed to treat Dyslipidemia, PCSK9 inhibitor,

Table 1: Prevalence of cardiovascular risk factors in Mexico (National Register 2016**).**

%	All (n=18,979)	STEMI (n=13,990)	ACS (n=4,989)
Smoking	47.4	49.1	42.3
Hypertension	62.0	58.3	72.2
Diabetes	46.2	45.5	48.2
Dyslipidemia	36.9	35.3	41.4

STEMI: ST-Elevation Acute Myocardial Infarction; **ACS**: Acute Coronary Syndromes.
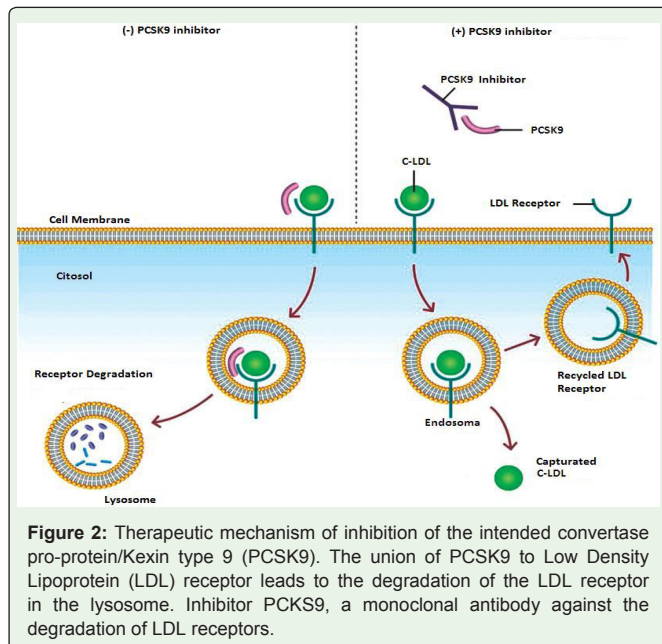
inhibitor of protein transport of triglycerides microsomal (MTP), the Mimetic apolipoprotein A1 (ApoA1), and the Oligonucleotide antisense against ApoB including its mode of actions and results of preclinical and clinical studies.

PCSK9 Inhibitors

PCSK9, pro-protein convertase intended / Kexin type 9 is a key protein in the regulation of the metabolism of cholesterol that acts mainly through the increase in receptor (LDLR) low-density lipoprotein degradation in liver. "Gain of function" mutations of PCSK9 are a genetic cause of autosomal dominant hypercholesterolemia. In contrast, the "loss of function" mutations were associated with low levels of LDL-cholesterol (LDL-C) and the reduction of the risk of coronary heart disease. To the extent that these "loss of function" mutations do not induce harmful effects, inhibition of PCSK9 is a new interesting strategy to reduce plasma concentrations of LDL-C.

PCSK9 is a serine protease that plays a central role in the metabolism of cholesterol in the liver through the improvement of receptors (LDLRs) LDL degradation [8]. The LDL receptor can be recycled or degraded in the Lysosomal process after internalization. Circulating PCSK9 binds to receptors LDL directing them towards the lysosome, improving its clearance in the hepatocyte to degradation, and prevents the LDLRs recycling back to the cell surface after internalization [9]. Therefore, to block PCSK9, PCSK9 inhibitors can reduce the LDLRs degradation and increases the surface expression of the LDLRs, which in turn improves the LDLRs recycling and reduces the level of LDL cholesterol (Figure 2) [10].

Several approaches have been proposed to inhibit PCSK9, including antibody monoclonal antibody, small RNAI, antisense oligonucleotides, and Mimetic peptides [11]. Among them, against PCSK9 fully humanized monoclonal antibody showed successful human data.

Figure 2: Therapeutic mechanism of inhibition of the intended convertase pro-protein/Kexin type 9 (PCSK9). The union of PCSK9 to Low Density Lipoprotein (LDL) receptor leads to the degradation of the LDL receptor in the lysosome. Inhibitor PCKS9, a monoclonal antibody against the degradation of LDL receptors.

Specific agents PCSK9 in development

In mice lacking with PCSK9, is significantly reduced the accumulation of cholesterol esters in the lesion of aortic atherosclerosis. In comparison, the over expression of PCSK9 induced excess burden of atherosclerosis [12]. But in mice deficient of the LDLR, download or on Express to PCSK9 had no significant effect on the accumulation of esters of cholesterol and the size of atherosclerotic plaque. This study strongly suggests that the process by which PCSK9 improves atherosclerosis is mediated mainly by its action on the LDLR [12]. Guinea Pigs cloned and created for the transposition of a gain of function mutation of human PCSK9, a model for Familial Hypercholesterolemia had a significant increase in aortic atherosclerosis in comparison with their counterparts in wild type [13].

Clinical application

Among the various approaches to PCSK9 inhibition, data from studies in humans are only available for the monoclonal antibody against PCSK9. In phase II studies, the two most advanced in development (Alirocumab and Evolocumab) monoclonal antibodies decreased atherogenic lipoproteins very effectively and these drugs were well-tolerated in humans.

A trial of 77 patients with heterozygous Familial Hypercholesterolemia, Alirocumab reduced LDL-C of 29% to 43% with an injection of 150 to 300 mg every 4 weeks and 68% for injection 150 mg every 2 weeks. In addition, the higher dose of Alirocumab, 150 mg every 2 weeks, showed a significant increase in HDL-C and ApoA1 at 6.5% and 8.8%, respectively, as the ApoB and cholesterol decrease non-HDL [14]. In the GAUSS trial which investigated the efficacy and safety of Evolocumab in 160 patients intolerant to statins, Evolocumab induced a decrease in significant dose levels of LDL cholesterol from 40.8% to 50.7% in comparison with the basevalue [15].

In addition, the combination of Evolocumab and Ezetimibe showed an almost 63% reduction in LDL-C. The result of a large phase III Alirocumab study has been recently reported. In the trial involving 2,341 patients receiving maximum tolerated dose of statins, Alirocumab reduced the LDL-C by 62% compared to the base line and the effect remained for 78 weeks of prolonged treatment [16].

On the other hand, post hoc, Alirocumab analysis showed a reduction in the rate of adverse cardiovascular events compared with placebo (hazard ratio, 0.52; 95% confidence interval, 0.31 to 0.90) [16]. The result of the Evolocumab long term extension study also showed consistent LDL-C reduction up to 48 weeks of treatment, and reduced it cardiovascular events in approximately 1 year of treatment (risk ratio, 0.47; interval of) (the 95% confidence, 0.28 to 0.78) [17].

The are key points to take in account from the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) update on practical clinical guidance for pro-protein convertase subtilisin/kexin type 9 (PCSK9) inhibition in patients with atherosclerotic cardiovascular disease (ASCVD) or in familial hypercholesterolemia (FH) [18]:

A. In the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial of Evolocumab (a fully human monoclonal PCSK9 antibody) in 27,564 patients with ASCVD, low-density lipoprotein cholesterol (LDL-C) levels were lowered by 59% (from mean 93 mg/dl to 55 mg/dl) and significantly reduced the risk of major CV events (absolute event rates 9.8% vs. 11.3% on placebo over 2.2 years, relative risk reduction of 15%).

i. The clinical benefit of treatment was due to reduction of nonfatal events, largely driven by reduction in Myocardial Infarction (MI) and coronary revascularization. This benefit was generally consistent across all major patient subgroups, including age, sex, and type of clinical presentation of ASCVD (Coronary Artery Disease [CAD] with history of MI, ischemic stroke, and symptomatic peripheral arterial disease [PAD]), and accrued over time. When adjusted for duration of treatment, the results from FOURIER were superimposable with those observed with statin therapy.

B. While there was no significant benefit on CV and all-cause mortality, the findings are consistent with a meta-analysis of four high versus low-dose statin trials that found a reduction mainly in nonfatal CV events in patients allocated to the high-dose regimen. Moreover, while reduced mortality was observed in earlier statin placebo-controlled trials, this was only seen after prolonged treatment and not after 2.2 years against a background of contemporaneous, predominantly high-dose statin therapy as in the FOURIER trial. It will be of great interest to see whether longer follow-up of patients treated with a PCSK9 inhibitor results in reduction in mortality.

C. As exemplified by FOURIER, patients with documented clinical ASCVD are at very high CV risk, with an annual absolute risk of a major CV event >3%. The recommended first approach to the management of elevated LDL-C levels in these patients is intense statin therapy. Clinicians should allow sufficient time to achieve the maximum tolerated regimen of statin therapy with concomitant ezetimibe, depending on clinical judgement and local guidance.

D. On the basis of currently available evidence, the Task Force recommends that a PCSK9 inhibitor should be considered in the following:

   i. Patients with ASCVD, by definition at very high risk, who have substantially elevated LDL-C levels despite maximally tolerated statin with or without ezetimibe therapy, and thus are considered at particularly high risk of an adverse prognosis.

   ii. Patients with ASCVD and at very high risk who do not tolerate appropriate doses of at least three statins and thus have elevated LDL-C levels.

   iii. FH patients without clinically diagnosed ASCVD, at high or very high CV risk, and with substantially elevated LDL-C.

E. Additional indices of risk severity are defined for patients with clinical ASCVD including concomitant presence of FH; diabetes mellitus with target organ damage or with a major risk factor such as marked hypertension; severe or extensive ASCVD; or rapid progression of ASCVD (repeated acute coronary syndrome, unplanned coronary revascularizations, or ischemic stroke within 5 years of the event). For FH patients without clinical ASCVD, additional indices of risk severity are diabetes mellitus with target organ damage or with a major risk factor such as marked hypertension; lipoprotein (a) >50 mg/dl; major risk factors such as smoking, marked hypertension; >40 years without treatment; premature ASCVD (<55 years in males and <60 years in females) in first-degree relatives; and imaging indicators of increased risk.

F. The Task Force recommends an LDL-C threshold for consideration of PCSK9 inhibitor treatment of 140 mg/dl, despite statin with or without ezetimibe therapy or inability to tolerate appropriate doses of at least three statins. Reduction of LDL-C levels by 50% with this treatment offers the possibility of attainment of the guideline-recommended LDL-C goal or 70 mg/dl, resulting in >1% annual reduction in absolute CV risk. In addition, the presence of additional indices of risk severity, such as rapidly progressive ASCVD, in particular after an ACS, diabetes mellitus, or complex multivessel or polyvascularatherosclerotic disease, exacerbates absolute risk and would qualify for lowering the LDL-C threshold to 100 mg/dl.

G. In addition, further risk assessment imaging may help to identify those patients with severe and/or extensive ASCVD who are at particularly high risk. These include carotid artery plaque (defined as either focal wall thickening >50% compared with the surrounding vessel wall or a focal region with an intima-media thickness measurement >1.5 mm); coronary artery calcium score >400; or extent, severity, location, and composition of plaque on coronary computed tomography angiography.

H. Monitoring treatment includes monitoring the LDL-C lowering response to statin and ezetimibe at 4 weeks and checking adherence before considering a PCSK9 inhibitor, as well as assessing the LDL-C lowering response to the PCSK9 inhibitor at 2 weeks after first injection of either the monthly or 2-weekly regimen (before the next injection).

I. The Task Force did not provide discussion of cost-effectiveness. However, they stressed that absolute CV risk together with absolute LDL-C levels are the key determinants of the number needed to treat (NNT) to prevent a CV event. In patients with ASCVD, who have substantially elevated LDL-C levels despite maximally tolerated statin plus ezetimibe therapy, or inability to tolerate statins, data from the FOURIER trial suggest that adding a PCSK9 inhibitor to lower LDL-C levels by 50% might be expected to reduce the 5-year NNT to <30 in patients with a baseline LDL-C <140 mg/dl. It would be presumptive to model the impact of adding a PCSK9 inhibitor on the NNT until longer-term follow-up data are available to assess the potential of these treatments to modify the trajectory of ASCVD.

J. Gaps in knowledge concerning PCSK9 inhibitor therapy include:

   i. Inter-individual variability in LDL-C lowering response to Alirocumab and Evolocumab.

   ii. Dedicated trials in patients with recent (<1 month) CV events.

   iii. Impact of PCSK9 inhibition in patients with chronic kidney disease (not requiring dialysis).

   iv. Long-term efficacy and safety of PCSK9 inhibitors in clinical use.

   v. Long-term safety of very low LDL-C levels.

   vi. Long-term impact of PCSK9 inhibition on disability and CV mortality.

   vii. Long-term evaluation of risk for type 2 diabetes.

   viii. Impact of sustained and marked LDL-C lowering to very low levels on plaque composition and stability.

   ix. Long-term impact of reduction in elevated lipoprotein (a) with PCSK9 inhibition.

   x. Cost-effectiveness of PCSK9 inhibition added to maximally tolerated statin with or without ezetimibe therapy.

The ESC/EAS guidelines are for the most part supported by evidence [18]. However, the complexity of the decision trees which encourage further expensive testing in patients with known ASCVD, and failure to reduce the LDL-C to <140 mg/dl with maximal statin + ezetimibe, is more stringent than presently accepted by most third-party payers in the United States prior to FOURIER trial results-particularly strict considering that the treatment benefit in FOURIER was present in patients with an LDL-C <70 mg/dl on maximally tolerated statin therapy. Similarly, approval for patients with FH without ASCVD is an LDL-C >100 mg/dl despite maximal tolerated doses of statin + ezetimibe and >70 mg/dl with ASCVD or high risk defined as elevated Lp (a), high level of high-sensitivity C-reactive protein, and high coronary calcium score.

Microsomal Trygliceride Transfer Protein inhibitor (MTTPi)

MTTPi is expressed predominantly in the liver cells and enterocytes, whose action is required in the synthesis of lipoproteins containing ApoB. TMP makes transfers of phospholipids, triglycerides (TG) and esters of cholesterol to the ApoB in endoplasmic reticulum and plays a fundamental role in synthesis of lipoproteins of Very Low Density (VLDL) and chylomicrons in the liver and the intestine [19]. TMP inhibition reduces the synthesis and secretion of VLDL in the liver by inhibiting lipidation of ApoB (Figure 3) [20].
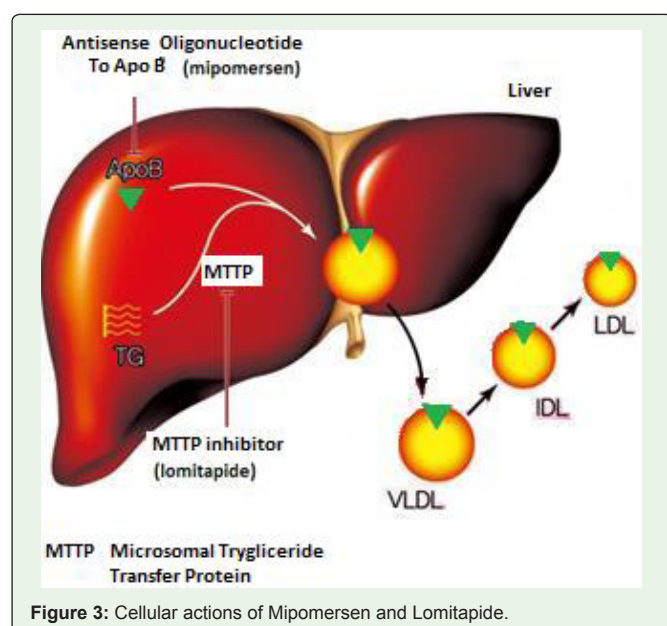
Antisense Oligonucleotide
To Apo B (mipomersen)

Liver

ApoB

MTTP

TG

MTTP inhibitor
(lomitapide)

VLDL

IDL

LDL

MTTP Microsomal Trygliceride
Transfer Protein

Figure 3: Cellular actions of Mipomersen and Lomitapide.

Inhibition of MTTP can reverse the increase in hepatic production and secretion of VLDL caused by insulin resistance. On the other hand, inhibition of MTTP in enterocytes may contribute to the reduction in the level of TG in plasma by the absorption of dietary fat reduction through chylomicrons. Orally active molecule MTTP inhibitor, Lomitapide, has been developed and approved for the treatment of homozygous Familial Hypercholesterolemia [21].

Pre-clinical phase

In an initial study, the treatment of hamsters with Lomitapide 7 days produced a dose-dependent reduction both in VLDL and LDL-C in the range from 19% to 89% and TGL in the range of 8% to 49%. However, a concomitant decrease in HDL-C levels, especially at higher doses, it was noted. The same study also investigated the effectiveness of Lomitapide in rabbits Watanabe homozygous hyperlipidemic as an atypical model of the homozygous familial hypercholesterolemia. After the administration of Lomitapide for 2 weeks, the level of lipoproteins containing ApoB-it normalized [22].

The administration of single dose of Lomitapide reduced fat rat Zucker, a genetic model of diabetic Dyslipidemia and metabolic syndrome, the serum level of TG in 35% and 47% to 0.3 and 1 mg / kg dose. The long duration of treatment also showed significant decrease in serum levels of TG (71% to 87%), acid fatty not esterified (33% to 40%), and the LDL-C (26% to 29%) [23].

Clinical impact

In a phase III trial of 29 patients with homozygous Familial Hypercholesterolemia with basal media of LDL-C 336 mg / dl despite therapy after lowering, Lomitapide reduced LDL-C in 50% at 26 weeks of treatment and 38% at 52 weeks of treatment or [24]. The levels of HDL-C was significantly reduced by 12% at 26 weeks, but returned to the levels prior to the treatment to 78 weeks [24].

The most common adverse effects are diarrhea, nausea, and abdominal pain [4]. In the early phase clinical studies, Lomitapide

increased hepatic content of TGL in a manner dependent on the dose, presumably due to inhibition of PTM hepatic [6] and capture of VLDL in the liver. In a phase III trial, 10 patients showed elevated liver enzymes and settled with the modification of the dose. The results of this study showed acceptable risk-benefit profile and Lomitapide was approved for the treatment of homozygous Familial Hypercholesterolemia by the US Food and Drug Administration (FDA) [21].

Oligonucleotide anti sense against apolipoprotein B

The ApoB is the main structural protein of lipoprotein atherogenic (apo-B containing lipoprotein). It has a key role in the assembly and secretion of VLDL in the liver [25]. The plasma concentration of ApoB is a reliable index of the total number of atherogenic, such as dense and small LDL lipoproteins. Mipomersen is an oligonucleotide synthetic antisense 20 nucleotides that can be joined through the ApoB mRNA complementary sequences of interaction [21]. The hybridization of Mipomersen ApoB RNAm target creates a substrate to RNase H1, resulting in the decrease of the level of RNAm ApoB and production of protein ApoB [21].

The Assembly of Very Low Density Lipoprotein (VLDL) requires the burden of triglycerides (TG) to the apolipoprotein B (ApoB) in the liver. Microsomal Triglyceride Transfer Protein (MTTP) works in this process and transfers the ApoB TG. The VLDL secreted becomes in lipoproteins of low density (LDL) in the blood stream. The Lomitapide inhibits the action of the PTM and Mipomersen inhibits the synthesis of ApoB. These two agents finally inhibit the Assembly of VLDL in the liver, resulting in decreased LDL in the blood stream. IDL, intermediate density lipoprotein [21].

Two chemical modifications were made to the structure of nucleotides of Mipomersen. Firstly, the internucleotidelink was modified chemically as a fosofotiester, which results in resistance to hydrolysis or degradation by nucleases and increase in binding to plasma proteins to facilitate the distribution and absorption of the drug. The second modification, insertion of residues of sugar metoxietilo in the first and last five positions made to Mipomersen with more stability and greater affinity [21,25].

Pre-clinical phase

Including several studies in animals such as the mouse, hamster, rabbit and monkey; oligonucleotide antisensespecific species against ApoB reduced hepatic mRNA ApoB-100, as well as serum levels of ApoB, LDL-C, and total cholesterol, in a way dependent on the dose [21]. After subcutaneous injection, Mipomersen is absorbed and distributed to tissues with higher drug concentrations in the liver and kidney easily. Mipomersen is metabolized by nucleases and the plasma elimination half-life varies from 1 to 2 months, which allows a dosage relatively rare. The system of clinical dosage for Mipomersen is weekly [21].

Clinical phase

For subjects with mild Dyslipidemia, 12 weeks of treatment with Mipomersen with doses of 50 to 400 mg every 3 weeks resulted in a reduction in LDL-C and ApoB dose-dependent by a maximum of 50% and 35%, respectively [26]. The efficacy of therapy Mipomersen in patients with Familial Hypercholesterolemia was confirmed in a

number of trials phase II and III. The phase III trial in 44 patients with heterozygous Familial Hypercholesterolemia showed significant reductions in LDL-C with a maximum of 33% and 34% reduction and ApoB.

In another phase III trial in patients with homozygous Familial Hypercholesterolemia which is already receiving the maximum tolerated dose of lipid lowering therapy, 26 weeks of treatment of Mipomersen resulted in a set reduction placebo of ApoB and LDL-C by 24% and 21% [27]. From the result of this study, Mipomersen was approved by the US FDA for the treatment of homozygous familial hypercholesterolemia. Other clinical trials in patients with primary hypercholesterolemia also showed a reduction in the dose-dependent and consistent ApoB and LDL-C with treatment of Mipomersen [28].

The most common adverse effects associated with Mipomersen are reactions at the injection site, elevation of liver enzymes and flu-like symptoms. The main security concern is the increase in hepatic accumulation of TGL presumably due to the secretion of impaired VLDL, which is the very similar mechanism of TG trapped by the PTM inhibitor. The elevations of transaminases are reversible with adjustment of the dose or even transient with continued treatment, and hepatic fat increases occurtempra and are stable in time [21]. The clinical consequences are unknown long term increase in the hepatic TG. There is still concern by periodic monitoring of liver function which should be requested in patients receiving Mipomersen [6].

Apolipoprotein A1 mimetic

The high level of serum HDL-C is a well known protective factor of coronary arterial atherosclerosis [29]. ApoA1 is the main component of apolipoprotein of HDL mature. ApoA1 takes cholesterol from macrophage by binding ATP-Cassette A1 (ABCA1) atherosclerotic lesions, resulting in reverse cholesterol transport. The central role of ApoA1 comprises the HDL-C that makes it an attractive target to modify the risk of CAD. The Mimetic ApoA1 is a class of drug designed to mimic the effect on ApoA1 and HDL-C to reverse the progression of atherosclerosis [30].

Pre-clinical phase

Several researchers have tested the effect of direct infusion of HDL or HDL recombinant with different preparations ApoA1 on atherosclerosis. In the study of animal models, the infusion of HDL or HDL recombinant showed beneficial effect and even reversal of atherosclerosis, but they were difficult to be developed as a form of manageable drug [31].

In 1980, a Variant arose ApoA1 called ApoA1 Milano between three Italian individuals with life long and low load atherosclerotic, despite low levels of HDL and the increase of the TG [32]. This genetic variant has a feature for the replacement of Arginine, cysteine, which allows the formation of dimers ApoA1 [33]. The ApoA1 Milano recombinant, ETC-216, was created by the combination of the mutant HDL with phospholipids to create a similar HDL particle. The effectiveness of ETC-216 has been tested in rabbits fed with cholesterol carotid arteries. After two treatments, lower doses of ETC-216 led to the reduction of the progression of the lesion and higher doses led to regression of the lesion and a significant reduction in markers associated with plaque instability [34].

The preliminary success of ApoA1 Milano and HDL recombinant

led to the development of a small peptide Mimetic ApoA1 capable of being administered orally without the need for weekly infusion therapy. This Mimetic peptide, called D-4F, was synthesized from biosynthetic and showed that it decreases the volume of atherosclerotic lesion by 79% in LDLR-null mice, despite no change in HDL in plasma [35]. Since its discovery, D-4F and its optical isomer L-4F have shown that they alter the course of cardiovascular disease in many animal models [36,37]. Studies in vitro have shown that mechanisms that D-4F decreases atherosclerosis include increased macrophage cholesterol efflux via ABCA1, increased transport of cholesterol to the liver through SR-B1, reduction of chemotaxis monocytes and membership, and the union of oxidized lipids [38].

Clinical phase

In a clinical study in patients with acute coronary syndrome, 5 weeks ApoA1 Milano infusion recombinant declined 4.2 percent atheroma volume vs., the baseline, measured by intravascular ultrasound [39]. The HDL recombinant containing ApoA1 of normal human combined with Phospholipid were also tested. The study ERASE (rHDL on atherosclerosis safety and efficacy effect), patients with SICA received HDL recombinant (CSL-112) 4 weeks, not giving rise to significant effect on atheroma or plaque volume compared with placebo [40]. However, when compared to the baseline, atheroma volume was significantly reduced by 3.4% [40].

In a trial of phase I of the small peptide Mimetic of ApoA1, coronary heart disease patients received a single dose of D-4F, which resulted in a rate significantly improved HDL-inflammatory relative to placebo [41]. L-4F showed equal to D-4F efficacy when injected intravenously. However, Watson [42] showed that patients with coronary artery disease, who received intravenous L-4F more than 7 days, did not show a significant reduction in the rate of HDL-inflammatory. Clearly, further studies pre-clinical and clinical, including clinical trials of advanced stages of mimetic ApoA1 are needed. It is too early to reach a conclusion about whether Mimetic ApoA1 may be clinically significant part of lipid lowering treatment.

Conclusion

Statin Therapy is a cornerstone in the treatment of dyslipidemia. From numerous randomized clinical trials, has been shown to be safe and effective for the prevention of future cardiovascular events. However, even so, a significant amount of residual risk of major cardiovascular event is present even under optimal treatment with Statins and it should be remembered that an important part of patients intolerant of or do not respond to therapy with Statins. Many researchers and pharmaceutical companies are involved in this field of struggle for the atherogenic Dyslipidemia and there have been many promising results from applying in real clinical practice.

PCSK9 inhibitor facilitates the uptake of LDL-C by improving recycling LDLR. Showed favourable effects of LDL-C reduction when added to statins, with acceptable safety profile and efficacy consistent long-term in large phase III trials. MTTPi and oligonucleotide against ApoB antisense inhibitor are the reduction of lipoproteins containing ApoB-, the main atherogenic lipoprotein. Lomitapide, MTTP inhibitor, and Mipomersen, against ApoB antisense oligonucleotides, have demonstrated their effectiveness in the reduction of LDL-C in the latest phase III trials for what were already approved for the treatment of patients with hypercholesterolemia homozygous

family. These two drugs are still in a major security problem, since it increases the accumulation of fat liver to trapping TG due to its pharmacological effect of the inhibition of hepatic VLDL secretion.

Long-term security profiles should be evaluated in the near future. The Mimetic ApoA1 is the more experimental class of drugs among four different classes in this review. It has been shown that altered or reversed the natural course of atherosclerosis despite the variety of level of LDL-C in preclinical studies. However, its effectiveness seems to be modest and the results are not consistent from earlier studies. A greater validation through various studies in humans is expected.

New classes of drugs beyond Statins could favor the improvement of the anti-aterosclerosis therapy. Physicians should keep your eyes on the results of next studies using new class of medications to find the best and the modality of optimal treatment for patients with Dyslipidemia.

Acknowledgement

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