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REVIEW

Therapeutic management of hyperlipoproteinemia (a)

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Abstract

Cardiovascular disease (CVD) has consistently been the leading cause of death worldwide. Several clinical and epidemiological studies have demonstrated that an elevated plasma concentration of lipoprotein (a) [Lp(a)] is a causative and independent major risk factor for the development of CVD, as well as calcific aortic valve stenosis. Thus, the therapeutic management of hyperlipoproteinemia (a) has received much attention, as significant reductions in Lp(a) levels may, potentially, favorably affect cardiovascular risk. Aspirin, niacin, estrogens, and statins, which act on different molecular pathways, may be prescribed to patients with mild or modest elevations of Lp(a) levels. Other therapeutic interventions, such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, Lp(a) apheresis, and the novel antisense oligonucleotides APO(a)-Rx and APO(a)-LRx, which are being evaluated in ongoing clinical trials, have provided some promising results and can potentially be used in severe cases of hyperlipoproteinemia (a). This review aims to present and discuss the current clinical and scientific data pertaining to the therapeutic options for the management of hyperlipoproteinemia (a).

Keywords: cardiovascular disease, cardiovascular risk, hyperlipoproteinemia (a), lipoprotein (a), therapeutic management.

Citation

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Introduction

Cardiovascular disease (CVD) remains the main cause of morbidity and mortality worldwide. An estimated 92.1 million US adults had at least one type of CVD in 2014, and 43.9% of the US adult population is projected to have some form of CVD by 2030.[1] Epidemiological data have revealed that there is a significant, independent, continuous, causative association between lipoprotein (a) [Lp(a)] plasma concentrations and risk for CVD, including coronary artery disease (CAD),[2–4] stroke,[3,4] peripheral artery disease,[4] calcific aortic valve stenosis,[5–7] heart failure,[8] and venous thromboembolism.[9]

Lp(a) is a plasma lipoprotein consisting of a cholesterol-rich low-density lipoprotein (LDL) particle with one molecule of apolipoprotein B-100 and an additional high molecular weight glycoprotein, apolipoprotein (a) [Apo(a)], which is covalently attached via a single disulfide bond. Apo(a), which is encoded by the *LPA* gene, is synthesized exclusively by the liver, and it is structurally homologous with plasminogen, being also accountable for specific characteristics of Lp(a). Lp(a) concentrations in the bloodstream are relatively independent of age and gender across people of different ethnicities and are >90% genetically determined. The strict genetic control of Lp(a) in the bloodstream is mainly explained by the presence of a size polymorphism of Apo(a), caused by a variable number of kringle IV type 2 (KIV-2) repeats in the *LPA* gene. This polymorphism results in a variable number (from 2 to >40) of 5.6 kb repeats, associated inversely with plasma Lp(a) levels. Thus, the fewer the repeats in the Apo(a) gene, the higher the plasma levels of Lp(a). Furthermore, the rate of Lp(a) production by the hepatocytes also contributes to the regulation of Lp(a) plasma levels. It is worth mentioning that the catabolism of Lp(a) is still not well understood; however, evidence supports that the kidney may play a major role.[10,11] In addition, evidence also indicates that a unique physiological role of Lp(a) is to bind and transport proinflammatory oxidized phospholipids in plasma, which may explain the increased risk of atherosclerosis and CVD conferred by hyperlipoproteinemia (a).[12] Apart from its proatherogenic effects, Lp(a) may exert several other detrimental CV effects, such as modulation of platelet aggregation, reduction in fibrinolysis, recruitment of inflammatory cells, and induction of vascular remodeling.[13]

A threshold value that is commonly used to define hyperlipoproteinemia (a) in clinical studies and in practice is an Lp(a) level >30 mg/dl. The prevalence of hyperlipoproteinemia (a) is fairly common. In a large study, which analyzed Lp(a) levels in 531,144 subjects from a referral laboratory in the United States, 35% of patients had Lp(a) levels >30 mg/dL, and 24% of patients had Lp(a) levels >50 mg/dL.[14] In Europe, the incidence of Lp(a) levels >30 mg/dL is estimated to be between 7% and 26% in the general population. In a study, which reviewed the Lp(a) concentrations of 52,898 consecutive patients with CVD, admitted to a hospital in Germany, levels of Lp(a) >30 mg/dL were found in 26.6% of the patients.[15]

However, it is worth emphasizing that the measurement of Lp(a) levels is not included in the standard lipid profile, and thus it is difficult to effectively detect all subjects with hyperlipoproteinemia (a), who would potentially benefit from treatment. The 2016 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the Management of Dyslipidaemias recommend that measurement of Lp(a) levels should be systematically considered in individuals with high CVD risk or a strong family history of premature atherothrombotic disease. In addition, Lp(a) measurement should also be considered in patients with intermediate-to-high risk for CVD. According to the ESC/EAS guidelines, the risk conferred by Lp(a) is regarded as significant when Lp(a) levels are >50 mg/dL.[16] Measurement of Lp(a) for screening or diagnostic purposes needs to be performed only once, as there are no significant fluctuations in Lp(a) values over time. This is because, as mentioned earlier, >90% of circulating Lp(a) levels are genetically determined.[17]

As hyperlipoproteinemia (a) is an established independent, causative risk factor for CVD, it becomes well understandable that the identification of therapeutic interventions that would lower Lp(a) levels is very important with the hope that this would also lead to reduction of the risk for CVD. Our review aims to present and discuss the current clinical and scientific data pertaining to the therapeutic options for the management of hyperlipoproteinemia (a).

Aspirin

Aspirin (acetylsalicylic acid) is one of the most widely used medications of all time, prescribed for the treatment of various diseases. Aspirin exerts mainly antiplatelet and anti-inflammatory actions by inhibiting the activity of the two isoforms of the enzyme cyclooxygenase (COX), namely COX-1 and COX-2. COX-1 leads to the formation of prostaglandins that protect the stomach mucosa from damage by hydrochloric acid, whereas thromboxane A2 (the major product of platelet COX-1) promotes platelet aggregation.[18] COX-2 is upregulated by proinflammatory mediators, and its products cause several symptoms, such as swelling, pain, and fever.[19] On the other hand, aspirin has also been shown to exert a favorable effect in hyperlipoproteinemia (a).

In a small trial in Japan, which included 70 patients with CAD or cerebral infarction, low-dose aspirin therapy (81 mg daily) for 6 months led to a significant reduction of Lp(a) levels by 18.3% in the subset of patients with a baseline Lp(a) level >30 mg/dL. In contrast, no significant changes in Lp(a) levels were observed in the subset of patients with low baseline Lp(a) levels (<30 mg/dL).[20]

In another small trial of 25 patients with ischemic stroke in northern India, 4 weeks of daily treatment with 150 mg of aspirin provided similar favorable results, as it lowered Lp(a) plasma values by 46.24%. Again, patients with higher baseline Lp(a) levels (>25 mg/dL) showed greater decline, as compared with those with Lp(a) levels <25 mg/dL (55.63 *versus* 26.63%, respectively).[21]

Furthermore, the Women's Health Study evaluated the effect of low-dose aspirin therapy (100 mg orally on alternate days) on carriers of rs3798220, a minor allele variant of Apo(a), which has been shown to be associated with elevated plasma levels of Lp(a) and increased risk for CVD. In this study, which had a follow-up period of 9.9 years, median Lp(a) levels in heterozygous and homozygous carriers of rs3798220 were found to be 8 and 15 times higher, respectively, than the Lp(a) levels in non-carriers. Carriers of this rare variant had also a significantly increased risk of major adverse cardiovascular events (MACE) compared to non-carriers [hazard ratio (HR), 2.21]. Aspirin treatment effectively and significantly reduced this increased risk of future CV events by 56%.[22] Of note, however, a review questioned the results of the Women's Health Study, as the number of events was small and there was not a definitely identified mechanism linking aspirin with Lp(a).[23] Notwithstanding, based on in vitro studies in human hepatocytes, the main proposed molecular mechanism by which aspirin reduces Lp(a) is reduction of Apo(a) production from hepatocytes *via* reduction of the transcriptional activity of Apo(a) gene with suppression of Apo(a) mRNA expression.[24] However, further investigation is needed to definitely confirm this mechanism.

Based on the previous discussion, aspirin therapy may be an option for patients with elevated levels of Lp(a) and high risk for or established CVD, as it is commonly administered in those patients for its antiplatelet effects to reduce adverse CV events. However, the effect of aspirin on Lp(a) levels will need to be further evaluated in prospective, randomized, controlled trials that will include a large number of subjects with hyperlipoproteinemia (a).

Niacin

Niacin (nicotinic acid) has been used for decades as a lipid-lowering drug. Its mechanism of action is not well understood.[25] A meta-analysis of 30 randomized controlled trials showed that treatment with niacin leads to a 20% reduction in triglycerides (TG), a 14% reduction in LDL cholesterol (LDL-C), and a 16% increase in high-density lipoprotein (HDL) cholesterol (HDL-C).

In addition, niacin monotherapy was also associated with an 11% reduction of CV mortality and a 27% decreased risk of major coronary events.[26] On the other hand, niacin does not increase ATP-binding cassette transporter A1 (ABCA1)-specific cholesterol efflux,[27] nor does it favorably affect the antioxidant capacity of HDL or the small dense LDL apolipoprotein B (ApoB) concentration[28] in statin-treated patients. Thus, despite an increase in circulating HDL-C, niacin may not improve HDL functionality, which has been shown to be a far more significant marker of the cardioprotective effect of HDL than the absolute HDL-C plasma concentration *per se*.[29]

Niacin therapy has also been shown to decrease levels of Lp(a). A meta-analysis of 14 randomized, placebo-controlled clinical trials showed a significant 22.9% reduction of Lp(a) levels following extended-release niacin (ERN) therapy, which did not appear to be dose-related.[30] Data from a randomized, crossover, controlled study demonstrated that the ERN-induced reduction of Lp(a) levels was related to a 50% decrease of Apo(a) production rate, apparently due to increased retention of Apo(a) at the hepatocyte surface and/or direct inhibition of transcription of the Apo(a) gene, although this effect was partially compensated by a 37% decreased Apo(a) catabolism.[31]

However, recent clinical evidence demonstrated that niacin, co-administered with statins in patients with CVD, not only failed to improve cardiovascular outcomes but was also associated with an increased risk of adverse events.[32,33] Thus, the use of niacin in current clinical practice has been significantly limited. Furthermore, the niacin-induced Lp(a) reductions have been shown to be proportional to the Apo(a) isoform size. Thus, the potential benefits of niacin-induced Lp(a) reductions on CV risk are likely to be small and would not be expected to outweigh the adverse effects of niacin.[34]

Estrogen/hormone replacement therapy

An early observation over the past few decades was that premenopausal women have a reduced incidence of CVD relative to men of a similar age, apparently due to the cardioprotective effects of estrogen.[35] The atheroprotective effects of estrogen are attributed to the favorable effect on the lipid profile (increase in HDL-C and reduction of LDL-C), as well as to the direct actions of estrogen on blood vessels, mainly mediated by an increase in the bioavailability of endothelial-derived nitric oxide and subsequent relaxation of vascular smooth muscle cells and vasodilation.[35,36]

Given the above, the concept of estrogen administration for the improvement of cardiovascular outcomes existed for many years; however, it failed to prove its clinical benefit in large, multicenter, randomized controlled trials.[37,38]

Nevertheless, there is extensive clinical evidence demonstrating the favorable effects of estrogen and/or hormone replacement therapy (HRT) on hyperlipoproteinemia (a).

A meta-analysis of 107 trials, which evaluated the effect of HRT on several metabolic, inflammatory, and thrombotic components in postmenopausal women, revealed that HRT produced a mean reduction of 25% on circulating Lp(a) levels.[39] Another trial showed that among 27,736 initially healthy women, Lp(a) values were 19% lower among those taking HRT. Of note, in this trial, use of HRT significantly attenuated the predictive value of Lp(a) levels on CVD risk.[40]

The Heart and Estrogen/progestin Replacement Study (HERS) was a randomized, blinded, placebo-controlled secondary prevention trial that evaluated the effect of HRT (oral conjugated equine estrogen plus medroxyprogesterone acetate) on the risk of subsequent coronary heart disease (CHD) events in 2763 postmenopausal women with established CAD. After a mean follow-up period of 4.1 years, it was shown that HRT not only failed to reduce the overall rate of CHD events but it was also associated with an increase in the rate of thromboembolic events.[37] Notwithstanding, in this trial, HRT exerted a more favorable effect (compared to placebo) in women with high initial Lp(a) levels than in women with low Lp(a) levels at baseline. Furthermore, the subset of women on HRT who achieved substantial reductions in Lp(a) by more than 8.8 mg/dL had a significant reduction in the risk for CHD events, as compared with women who had smaller reductions in Lp(a) levels.[41]

Current evidence does not justify postmenopausal HRT for primary or secondary prevention of CVD.[37,38,42] As a result, the favorable use of estrogen/HRT in the treatment of hyperlipoproteinemia (a) is only restricted for women who have an indication to take HRT for a gynecological disease. It is worth mentioning that certain other estrogen-related agents, such as tibolone and tamoxifen, are being evaluated for their effect on Lp(a). Tibolone is a synthetic steroid with estrogenic, progestogenic, and androgenic properties, which has been shown to cause significant decreases in Lp(a) levels.[43] In a systematic review and meta-analysis of 12 studies including a total of 1009 patients, treatment with tibolone led to a 25.28% mean reduction in Lp(a) levels in postmenopausal women.[44] In another systematic review and meta-analysis, it was shown that treatment with tamoxifen, a selective estrogen receptor modulator widely used in the treatment of breast cancer, led to a statistically significant reduction in Lp(a) levels [standardized mean difference (SMD) −0.41; 95% confidence interval (CI): −0.68 to −0.14; p=0.003].[45] However, the impact of the tibolone- and tamoxifen-induced Lp(a) reductions on CVD risk remains to be explored in future trials.

Statins

Statins are currently the cornerstone for the treatment of hypercholesterolemia, substantially decreasing both LDL-C and risk for CVD in both primary and secondary prevention.[46] In recent years, there was a concept that reductions of LDL-C <70 mg/dL would also favorably counteract the atherogenic properties of Lp(a). However, today, it is known that this was a

false assumption, as elevated Lp(a) levels are an independent major risk factor for CVD, leading to increased atherosclerosis burden and residual risk, even in patients who achieve LDL-C levels <70 mg/dL.[17,47–51] Furthermore, the LDL receptor (LDLR) plays only a modest role in the clearance of Lp(a).[17]

Treatment with statins does not reduce Lp(a) levels. This is because, as mentioned earlier, the LDLR plays a minimal, if any, role in Lp(a) clearance. In fact, some reports show that statins may actually increase Lp(a) levels by roughly 10–20%.[17,52,53] Actually, in a subject-level meta-analysis from six randomized trials, which included 5256 patients (3885 on statin and 1371 on placebo), statin therapy led to a mean percent increase of Lp(a) levels from baseline ranging from 8.5% to 9.6%. More specifically, atorvastatin increased Lp(a) levels by 18.7–24.2%, and pravastatin increased Lp(a) levels by 11.6–20.4%. Furthermore, incubation of HepG2 hepatocytes with atorvastatin resulted in an increase in expression of LPA mRNA and Apo(a).[52]

As statin therapy does not exert a favorable effect on Lp(a), the main rationale for the use of statins in hyperlipoproteinemia (a) is the reduction of the overall risk for CVD, through reduction of its LDL-dependent portion, in patients that have an overall increased CVD risk due to the elevated Lp(a) levels. In fact, evidence clearly demonstrates that the efficacy of statins in reducing CVD is similar among subjects with high or low Lp(a) concentrations.[50]

Proprotein convertase subtilisin/kexin type 9 inhibitors

Undoubtedly, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which are human monoclonal antibodies directed against PCSK9, have emerged as a key lipid-modifying therapy. PCSK9 binds to the LDLR and targets the receptors for lysosomal degradation, thereby reducing their recycling and decreasing the removal rate of circulating LDL-C.[54,55] Therefore, pharmacological inhibition of PCSK9 leads to upregulated expression of LDLR, thus reducing circulating LDL-C levels. In fact, clinical evidence has shown that PCSK9 inhibitors reduce LDL-C levels by approximately 60% and significantly improve CV outcomes.[56,57]

Apart from their beneficial effect on LDL-C, PCSK9 inhibitors also decrease Lp(a) plasma concentrations. In a pooled analysis of data from 1359 patients in four phase 2 trials, the PCSK9 inhibitor evolocumab was shown to cause significant mean dose-related reductions in Lp(a) levels of 24.5–29.5% (depending on the dosing regimen), as compared with placebo.[58] In another randomized, double-blind, placebo-controlled phase 3 clinical trial (FOURIER trial), after 48 weeks of treatment, evolocumab decreased the concentration of Lp(a) by a median of 26.9%.[56] It is worth mentioning that patients with higher baseline Lp(a) levels tended to derive greater clinical benefit from PCSK9 inhibition with evolocumab. More specifically, evolocumab reduced the risk of death from CHD, myocardial infarction, or urgent revascularization by 23% in patients with a baseline Lp(a) above the median of 37 nmol/L and by 7% in those with a baseline Lp(a) below the median. Coupled with the higher baseline risk, the absolute risk reductions were 2.49% and 0.95% in patients with a baseline Lp(a) above and below the median, respectively.[59] This important finding was very recently corroborated in another trial, which examined the effect of Lp(a) lowering by another PCSK9 inhibitor, alirocumab, in the ODYSSEY OUTCOMES trial.[57] It was clearly shown that patients with a recent acute coronary syndrome (ACS) who had higher baseline Lp(a) levels derived a greater absolute reduction in MACE from treatment with alirocumab, which suggested that Lp(a) could be a therapeutic target in selected patients after recent ACS.[60]

However, there is some evidence showing that marked reductions in Lp(a) levels, larger than those attained with PCSK9 inhibitors, would be required for a CV benefit to be realized. In a large mendelian randomization analysis, it was shown that marked absolute reductions in Lp(a) levels of approximately 100 mg/dL may be required to produce a clinically meaningful reduction in the risk of CHD, similar in magnitude to what can be achieved by lowering LDL-C level by 1 mmol/L (38.67 mg/dL).[61] The results of this study were corroborated by a recent pooled analysis of alirocumab phase 3 trials, which showed that Lp(a) reductions were not significantly associated with MACE independently of LDL-C reductions and thus reducing the risk of MACE by targeting Lp(a) may require greater reductions in Lp(a) with more potent therapies and/or higher baseline Lp(a) levels.[62]

The mechanism by which PCSK9 inhibitors decrease levels of Lp(a) has not been clearly elucidated. However, it has been suggested that PCSK9 monotherapy lowers the plasma Lp(a) pool size by decreasing the production of Lp(a) particles, whereas PCSK9 inhibition in combination with statins lowers the plasma Lp(a) pool size by accelerating the catabolism of Lp(a) particles.[63]

To date, despite the favorable effects of PCSK9 inhibition on Lp(a), PCSK9 inhibitors are not yet approved by the United States Food and Drug Administration (FDA) for the treatment of hyperlipoproteinemia (a).

Lipoprotein (a) apheresis

Lipoprotein apheresis (LA) involves the physical removal of lipoproteins from the blood and is employed in patients who cannot achieve acceptable plasma lipoprotein levels despite appropriate lifestyle changes and pharmacologic lipid-lowering interventions.[64] In general, LA is a lifelong therapy. It is an invasive therapeutic method and venous puncture problems may arise, particularly in female patients. In addition, hypotensive episodes may occur during LA, and there is a risk of bleeding due to the use of anticoagulation that is needed during LA sessions. Notwithstanding, LA has been in general accepted as a safe therapeutic approach.[65] LA still plays a significant role in the management of patients with

homozygous familial hypercholesterolemia (FH), as well as in the management of some patients with other severe drug-resistant dyslipidemias and established CVD. As it was mentioned earlier, Lp(a) has been recently identified as an important, independent, causative risk factor for CVD and thus LA has been used to reduce plasma Lp(a) levels in patients with marked Lp(a) elevations and CVD.[66] It should be noted, however, that LA removes Lp(a) and LDL simultaneously, which makes it hard to distinguish the beneficial effects of Lp(a) and LDL-C lowering.[11,67]

In a prospective, open-label, controlled 18-month study, which included 30 patients with stable CHD and Lp(a) levels >50 mg/dL, weekly treatment with Lp(a) apheresis not only decreased Lp(a) by an average of 28% after 18 months, but also caused significant regression of carotid intima-media thickness. It should be noted that the acute average decrease in Lp(a) concentration after the procedure was 73%.[68] Furthermore, in another study, it was shown that treatment with specific Lp(a) apheresis and a statin over 18 months, as compared to statin therapy alone, led to a significant reduction of the coronary and carotid atherosclerotic burden in patients with stable ischemic heart disease with baseline Lp(a) levels >50 mg/dL. In addition, levels of high-sensitivity C-reactive protein (hsCRP) were reduced by 40% in patients on Lp(a) apheresis.[69] There is also evidence suggesting that elevated Lp(a) levels are associated with a significantly increased rate of 1-year vein graft occlusions and adverse long-term cardiovascular outcomes, whereas treatment with lipoprotein apheresis improves the patency rates of vein grafts during the first year post-coronary artery bypass grafting (CABG).[70] Importantly, the results of 5 years of prospective follow-up confirmed that Lp(a) apheresis has a lasting effect on the prevention of CV events in patients with hyperlipoproteinemia (a), reducing the mean annual cardiovascular event rate by 81%.[71]

Despite the fact that Lp(a) is an important causal risk factor for CVD, and although there are only limited pharmacologic interventions to treat hyperlipoproteinemia (a), the role of LA in hyperlipoproteinemia (a) is not well defined. In the United States and the United Kingdom, increased Lp(a) *per se* is not an indication for LA and is only considered as an additional risk factor that needs to be taken into account when deciding whether LA should be used to treat elevated LDL-C levels, especially in cases of heterozygous FH. On the other hand, in Germany, increased Lp(a) levels >60 mg/dL are considered to be an indication for LA in patients with progressive CVD despite optimal management of all other risk factors including LDL-C.[66] Further research into the therapeutic options for managing elevated Lp(a) levels is expected to more definitely establish the role of LA in the management of hyperlipoproteinemia (a).

RNA-targeted therapies

As the current therapeutic management of hyperlipoproteinemia (a) is far from optimal, many new therapeutic interventions and novel targeted therapies are being evaluated in ongoing trials. APO(a)-Rx and APO(a)-LRx, which are antisense oligonucleotides (ASOs), have provided some promising results in early human trials and there is optimism that they will enter everyday clinical practice in the near future. APO(a)-Rx and APO(a)-LRx represent an elegant method for the treatment of hyperlipoproteinemia (a) and are being administered subcutaneously, inhibiting the synthesis of the atherogenic Apo(a), which is primarily synthesized in the liver, as it was mentioned earlier.[72]

In a randomized, double-blind, placebo-controlled, phase 1 clinical study, APO(a)-Rx was administered in healthy volunteers at varying doses and proved to be a safe and well-tolerated medication, as the most common adverse events were mild injection site reactions. It also provided some promising results, as six injections of APO(a)-Rx resulted in a reduction in Lp(a) levels of up to 77.8% from baseline. These reductions of Lp(a) values were also dose related, with the highest administered dose of 300 mg being the most effective treatment. Similar reductions were observed in the amount of oxidized phospholipids associated with apolipoprotein B-100 and Apo(a).[73] In another phase 2 trial, treatment with escalating-dose subcutaneous APO(a)-Rx, administered once a week for a total duration of 12 weeks in subjects with elevated Lp(a) concentrations, produced 66.8–71.6% reductions in Lp(a) levels. In a phase 1/2a trial, APO(a)-LRx proved to be a well-tolerated and potent therapy to reduce Lp(a) concentrations. Six injections of the highest administered dose of 40 mg APO(a)-LRx resulted in a 92% reduction in Lp(a) levels in healthy human volunteers. Thus, these new agents targeting the synthesis of Apo(a) may potentially assist clinicians to effectively diminish Lp(a)-mediated cardiovascular risk.[74]

Besides the aforementioned ASOs, small inhibiting RNA (siRNA) molecules targeting PCSK9 are also in development and they have shown promising initial results in the reduction of LDL-C and Lp(a).[75] In a phase 2, multicenter, double-blind, placebo-controlled trial (ORION-1 trial), treatment with inclisiran, a long-acting, synthetic siRNA directed against PCSK9, caused a reduction in LDL-C levels of up to 52.6% from baseline and a reduction in Lp(a) levels of up to 25.6% from baseline.[76] Further trials with inclisiran are expected to shed more light into its beneficial effects on Lp(a).

Other interventions affecting lipoprotein (a) levels

In a 12-week trial, eprotirome, a thyroid hormone analogue, caused mean reductions of Lp(a) levels from baseline by up to 43% in statin-treated patients without any evidence of adverse effects on the heart, bone, or pituitary.[77] However, further longer trials are required to confirm the beneficial effect of eprotirome on Lp(a) and to rule out potential long-term adverse thyromimetic effects.

Mipomersen, an ASO targeting ApoB, has been shown to lower levels of Lp(a) by 21–39%, mainly by decreasing the fractional

catabolic rate of Lp(a).[78] Mipomersen was approved by the FDA for the treatment of homozygous (FH). However, adverse effects leading to an increased risk of discontinuation of treatment, including injection-site reactions, hepatic steatosis, elevated liver enzymes, and flu-like symptoms,[79] exclude the widespread use of this drug for the treatment of hyperlipoproteinemia (a).

Cholesteryl ester transfer protein (CETP) inhibitors have been also shown to decrease Lp(a) levels. In two different studies, anacetrapib was shown to reduce Lp(a) levels by 23.8%[80] and 34.1%,[81] respectively. Treatment with TA-8995 (a CETP inhibitor in development) was associated with up to 36.9% reduction in Lp(a) levels from baseline.[82] The CETP inhibitor-induced decrease in Lp(a) levels appears to be due to a reduction in the Apo(a) production rate.[81] Notwithstanding, in several clinical studies, the effects of CETP inhibitors on CVD risk were shown to be detrimental, neutral, or at most slightly positive, despite a substantial increase in HDL-C levels.[83] Thus, CETP inhibitors are not currently being used in clinical practice.

The effects of fibrates on Lp(a) are mixed, as fibrates reduced Lp(a) levels in some studies but had no effect in others.[84] However, in a meta-analysis, fibrates were shown to have a significantly greater effect in reducing plasma Lp(a) concentrations than statins.[85]

In a study, which examined the effect of two bariatric surgery procedures on Lp(a), it was shown that both Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) were associated with a reduction in Lp(a) levels 1 month after the procedure. However, only RYGB was associated with a persistent reduction in Lp(a), as a 30.4% reduction in Lp(a) levels was demonstrated 6 months after RYGB.[86]

Conclusions

From the above discussion of the clinical and scientific evidence, it becomes apparent that the armamentarium for the therapeutic management of hyperlipoproteinemia (a) consists of several therapeutic options. The selection of the suitable therapy for each patient is critical. Physicians should take into account the desirable reduction of Lp(a) plasma levels, coexisting major risk factors for CVD, comorbidities, and possible side effects of the selected therapeutic intervention.

The United States National Lipid Association (NLA) has recently issued guidelines pertaining to the use of Lp(a) in clinical practice. According to NLA, Lp(a) testing would be reasonable in adults with first-degree relatives with premature atherosclerotic cardiovascular disease (ASCVD) (<55 years old in men, <65 years old in women), a personal history of premature ASCVD, primary severe hypercholesterolemia (LDL-C >190 mg/dL) or suspected FH, as well as in patients with recurrent or progressive ASCVD despite optimal lipid lowering.[87] As Lp(a) has a highly heterogeneous structure, owing to the presence of many different isoform sizes (with different molecular weights) within the population, assays reporting Lp(a) values as mass concentrations (units of mg/dL) may be subject to a bias, typically manifested as an underestimation of the levels of small Lp(a) isoforms and an overestimation of large Lp(a) isoforms. Thus, to overcome this bias, the NLA recommended that Lp(a) measurements should be performed using an immunochemical assay that is calibrated against the World Health Organization/International Federation of Clinical Chemistry and Laboratory Medicine (WHO/IFCCLM) secondary reference material and is reported in nmol/L.[87]

Nevertheless, as there are still many unanswered questions regarding the function and role of Lp(a) in CVD, evidence from ongoing and future clinical trials will shed further light to the pathogenesis of Lp(a)-mediated CV disease, as well as to the tolerability and effectiveness of novel targeted therapies. To that effect, outcome trials of APO(a)-Rx and APO(a)-LRx, which have been shown to cause a marked reduction in Lp(a) levels, are eagerly awaited and their results will provide a step forward toward the optimal therapeutic management of hyperlipoproteinemia (a).

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