Perspective

Lipoprotein(a) and inhibitors of proprotein convertase subtilisin/kexin type 9

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Abstract: Lipoprotein(a) [Lp(a)] has been identified as a risk factor for cardiovascular disease. Lp(a) levels are also high under certain clinical conditions, including familial hypercholesterolemia and high blood low-density lipoprotein (LDL) cholesterol levels. Few effective generic therapies for modulating Lp(a) have been developed. However, new therapies involving inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) using monoclonal antibodies have markedly reduced the blood LDL levels—and the Lp(a) levels as well. Much attention has therefore been focused on this therapy and its utility. The mechanism by which PCSK9 inhibitors reduce the Lp(a) levels remains unclear. We here describe the effects of PCSK9 inhibitors on Lp(a) and discuss potential mechanisms and perspectives of this topic.

Keywords: Apolipoprotein(a) [apo(a)]; apolipoprotein B (apoB); familiar hypercholesterolemia; LDL receptor; LDL receptor-related protein (LRP); scavenger receptor (SR)

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Introduction

A variety of lipoproteins are involved in cardiovascular health, and low-density lipoprotein (LDL) is well-established as a risk factor for cardiovascular disease (1,2). Lipoprotein(a) [Lp(a)] is a unique lipoprotein particle with a composition similar to that of LDL, including apolipoprotein (apo) B-100, which is bound to apo(a) (a glycoprotein) by a disulfide bridge (3-5). Apo(a) contains a specific sequence, such as kringle IV, similar to plasminogen (a fibrinolytic molecule) (3-5). Although the patho-biological role of Lp(a) is not completely clear, Lp(a) is considered to be a contributor to atherothrombosis on the basis of its LDL-like property and its competitive homology to plasminogen (3-5). Indeed, epidemiological and clinical studies have shown a high Lp(a) level to be a risk factor for cardiovascular disease (i.e., coronary heart disease, aortic aneurysm, peripheral artery disease, ischemic stroke) (5-9).

The general consensus holds that the Lp(a) level is primarily determined genetically by the *LPA* gene sites responsible for the encoding of apo(a), and the Lp(a) level does not necessarily parallel the level of other lipoprotein species (3-5). Of interest, the Lp(a) level is reported to be elevated under certain clinical conditions, such as in patients with familial hypercholesterolemia (10-12). Furthermore, it has been reported that a high Lp(a) state is prevalent when the LDL cholesterol level is high in patients with acute coronary syndrome (13). However, typically, Lp(a) is not considerably changed by disease burden, lifestyle modifications or drug agent interventions (14,15). Under current generic therapeutic strategies, some reduction in the Lp(a) level may be achieved when using certain drug

agents prescribed orally, such as nicotinic acid and tibolone (5,16,17). Among these agents, nicotinic acid is the only lipid-modulating drug (16). Thus, given that a high Lp(a) level is a cardiovascular risk factor and no effective therapies to reduce Lp(a) have existed, the strict control of other risk factors for cardiovascular disease (e.g., obesity, smoking, physical inactivity, hyper-LDL-cholesterolemia) rather than Lp(a) itself is recommended (5).

Lp(a) reduction by proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

This situation has recently begun changing with the introduction of innovative new therapies involving inhibitors of PCSK9 using its monoclonal antibodies (18,19). PCSK9 is an enzyme of the proteinase K subfamily of subtilisin-related serine endoproteases (18,19) and is synthetized chiefly in the liver and then, circulates in the blood, binding to the extracellular domain of the LDL receptor in the liver. Within the liver tissue, the complex of PCSK9 and LDL receptor is internalized through endocytosis. PCSK9 binds to the LDL receptor in the sorting endosome, and the LDL receptor is degraded instead of being recycled. Thus, the disruption of PCSK9 in the recycling of the LDL receptor leads to a reduction in the available LDL receptor, which consequently leads to a high level of LDL in the blood. Degradation of the LDL receptor is thus a promising therapeutic target, and therapies involving inhibitors of PCSK9 have been actively applied to reduce LDL levels (18,19).

New therapies using monoclonal antibodies targeting PCSK9, which inhibit PCSK9 directly, have now been introduced as an effective method for reducing LDL levels (19,20). These monoclonal antibodies of PCSK9 inhibitors (i.e., alirocumab, evolocumab, bococizumab) have been shown to reduce LDL cholesterol levels by 40–70% in clinical studies in patient populations with a range of LDL cholesterol levels via different cholesterol-lowering regimens (19). In the clinical setting, PCSK9 inhibitors are combined with statins and indicated for patients with familiar hypercholesterolemia and those at very high risk of developing cardiovascular disease (including recurrent cardiovascular events) who cannot achieve target optimal LDL cholesterol levels (19,20). Patients with lipoprotein apheresis or statin intolerance can also be indicated (19,20).

Interestingly, the blood Lp(a) levels are reduced in patients treated with the PCSK9 inhibitors—up to approximately 30% in a dose-dependent fashion (21), although whether or not this Lp(a)-lowering effect was expected in the initial clinical studies is unclear. In the recognition of the clinical importance of Lp(a) in the development of cardiovascular disease and the need for methods of modulating Lp(a) levels, we believe that PCSK9 inhibitors may be a long-awaited therapy for patients with high LDL cholesterol levels plus high Lp(a) levels.

Mechanism of Lp(a) reduction by PCSK9 inhibitors

The mechanism of Lp(a) reduction observed in patients with the PCSK9 inhibitors remains unknown, and its confirmation may help clarify the Lp(a) metabolism, which remains obscure (22). Regarding potential mechanisms of Lp(a) reduction, several non-specific receptors [i.e., LDL receptor (23), LDL receptor-related protein 1 (LRP-1) (24), scavenger receptor class B type 1 (SR-B1) (25)] have been shown to mediate Lp(a) catabolism.

Lp(a) reduction via the LDL receptor is one candidate that may be involved, given the regulatory function of PCSK9 on blood LDL levels via the LDL receptor (18,19). The role of the LDL receptor in Lp(a) catabolism has been controversially reported. For example, while HMG-CoA reductase inhibitors, or statins, are widely known to be a major generic drug class that reduces blood LDL cholesterol levels via the LDL receptor in the liver, blood Lp(a) levels do not usually respond to therapy with statins, despite a reduction in the LDL cholesterol levels (15). In contrast, Lp(a) levels are high in patients with familial hypercholesterolemia (the null type of LDL receptor) (12), and Lp(a) catabolism is increased in mice overexpressing the LDL receptor (26). Of note, a recent *in vivo* experimental study on hepatic HepG2 cells and primary fibroblasts has shown that Lp(a) catabolism is reduced by PCSK9 via the LDL receptor (apoB-100 as the ligand for the receptor) (23). These findings imply that Lp(a) reduction by PCSK9 inhibitors is mediated via the LDL receptor pathway.

ApoB-100-containing lipoproteins, including Lp(a), are catabolized by LRP-1 in the liver (24), which is a candidate for Lp(a) reduction by PCSK9 inhibitors. While there are very few studies on the interaction between LRP-1 and PCSK9, a recent *in vivo* experimental study on melanoma and CHO cells has shown that PCSK9 can induce the degradation of LRP-1 (24), suggesting that Lp(a) reduction by PCSK9 inhibitors may be mediated via the LRP-1 pathway.

SR-B1 is a well-known receptor for high-density

lipoprotein, but, in fact, a multi-ligand receptor for various lipoproteins, such as LDL and Lp(a), in the liver and arterial wall tissues (25). Lipoproteins in patients with hyper-LDL cholesterolemia are often oxidized, and these oxidized LDL particles are taken up by arterial macrophages, leading to atherosclerotic pathologies (27). SR-B1 binds to oxidized LDL, and this atherosclerotic process reduces the expression of SR-B1 (28). Although the effects of PCSK9 on SR-B1 have yet to be clarified, PCSK9 facilitates the atherosclerotic process under conditions of high blood levels of LDL with oxidized LDL; therefore, an increase (removal) in the SR-B1 expression by PCSK9 inhibitors may result in Lp(a) reduction via the SR-B1 pathway.

Independent of the LDL receptor, we should also consider the influence of apoB-100 synthesis/availability on the association of Lp(a) with PCSK9 (29,30). A study in mice investigated the effects of PCSK9 on apoB synthesis (30). Regardless of the expression of the LDL receptor, mice transduced with the PCSK9 gene exhibited an increased level of blood apoB, which may have resulted from the inhibition of intrahepatic apoB degradation (30). As Lp(a) particles consist of apoB-100, the reduction in Lp(a) levels by PCSK9 inhibitors may be due in part to less formation of Lp(a) particles via the apoB-100 synthesis pathway.

Perspectives

We must first acknowledge that the above-mentioned potential mechanisms of Lp(a) reduction in patients by PCSK9 inhibitors were basically hypothesized by experimental studies in cells and animals, an unavoidable consequence of the dearth of human studies at present. We must also note that the benefits of the Lp(a)-lowering effects of PCSK9 inhibitors have not yet been proven in a clinical setting, given that no studies have fully investigated the long-term effects of PCSK9 inhibitors on the cardiovascular disease and/or the all-cause mortality. Extremely low levels of blood Lp(a) may be detrimental in some respects (e.g., the development of certain vascular diseases and/or cancers) (5,31), although no intervention studies have been performed to examine this point.

A recent interesting meta-analysis reviewed the effect of PCSK9 inhibitors versus placebo and ezetimibe on the lipid levels and outcomes [17 randomized controlled trials in 13,083 patients randomized to PCSK9 inhibitors (n=8,250), placebo (n=3,957), ezetimibe (n=846) or ezetimibe plus PCSK9 inhibitors (n=30)] (32). The all-cause mortality was found to be reduced, with a reduction in the LDL cholesterol of 50–60% in patients who received PCSK9 inhibitors (odds ratio =0.43; 95% confidential interval, 0.22–0.82). In contrast, however, the incidence of neurocognitive adverse events was increased in these patients (odds ratio =2.34; 95% confidential interval, 1.11–4.93). We believe that the accumulation of such evidences is necessary across a wide range of studies exploring not only the biological and clinical cardiovascular aspects of Lp(a) but also the general health and cost-effectiveness of PCSK9 inhibitors (33).

None of the currently available therapeutic strategies, including PCSK9 inhibitors, reduce blood Lp(a) levels alone, instead exerting their effect concomitantly with a reduction in the blood LDL cholesterol levels. As such, the relevance of a reduction in the Lp(a) levels alone is a matter of speculation in the clinical setting. The administration of PCSK9 inhibitors to patients with normal LDL cholesterol levels but high Lp(a) levels is a matter for discussion.

In addition, the mechanisms, by which recent therapies for modulating lipoproteins, cholesteryl ester transfer protein inhibitors and hepatic thyroid analogs also reduce blood Lp(a) levels, remain unclear. However, these therapies are either in development or have been terminated for reasons such as safety and efficacy. New therapies for reducing Lp(a) are expected to be introduced in the near future, such as antisense therapy, which targets apo(a), and next-generation PCSK9 inhibitors (34-38). We think that these therapies will provide more information elucidating the Lp(a) metabolism and the clinical value of Lp(a) reduction.

Conclusions

Newly developed therapies involving the inhibition of PCSK9 using monoclonal antibodies markedly reduce the blood LDL cholesterol levels with a concomitant reduction in the blood Lp(a) levels. Since the clinical importance of Lp(a) in the development of cardiovascular disease and the need for methods of modulating Lp(a) levels have long been recognized, research on Lp(a) enters a new era with the introduction of PCSK9 inhibitors. We discussed several hypothetical mechanisms of Lp(a) reduction in patients receiving PCSK9 inhibitors, although the precise mechanism involved remains to be clarified. Future studies on this topic will help resolve this issue.

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Footnote

Conflicts of Interest: K Kotani is a member of Astellas/Amgen Biopharma, MSD. M Banach: speakers bureau: Abbott/Mylan, Abbott Vascular, Actavis, Akcea, Amgen, KRKA, MSD, Sanofi-Aventis; consultant to Abbott Vascular, Amgen, Daiichi Sankyo, Esperion, Lilly, MSD, Resverlogix, Sanofi-Aventis; grants from Valeant and Sanofi.

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