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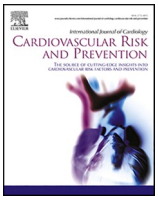

Emerging Lp(a)-Lowering therapies: Is muvalaplin a potential breakthrough?

Dear Editor,

Disclosures

All authors report no relationships that could be construed as a conflict of interest. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

CRediT authorship contribution statement

Zeeshan Afzal: Writing – review & editing, Writing – original draft, Software, Resources. **Sara Hira:** Writing – review & editing, Writing – original draft, Validation, Software, Resources. **Huili Cao:** Writing – review & editing, Supervision.

For many years, lipoprotein(a) [Lp(a)] has been regarded as a cardiovascular risk factor [1]. Aortic valve stenosis (AVS) and atherosclerotic cardiovascular disease (ASCVS) are influenced by the disturbance of lipid metabolism including Lp(a). According to increasing evidence, lowering Lp(a) remains a crucial unmet therapeutic need, especially given that the prevalence of AVS is expected to rise considerably (>300%) by 2050 [2]. As apolipoprotein(a) shares structural similarity with plasminogen and plasmin but lacks fibrinolytic activity, elevated Lp(a) levels might raise ASCVD risk through prothrombotic/anti-fibrinolytic actions and faster atherogenesis owing to Lp(a) cholesterol intimal deposition [3].

Lp(a) is formed when the apo(a) protein on an LDL-like molecule forms a molecular bond with the apo B100 protein [4]. The non-covalent binding of apo(a) Kringle IV domains 7 and 8 to residues of lysine of apo B100 in the hepatocyte and the perisinusoidal space results in the formation of a covalent disulfide bond [5].

There is an unmet demand for novel medications that particularly target Lp(a). The scientific community is not yet prepared to treat high Lp(a) levels effectively. However, various novel medications based on RNA and gene editing technologies have been investigated recently [6].

A randomized, double-blind, placebo-controlled trial of 286 patients with cardiovascular disease found that APO(a)-LRx therapy significantly decreased lipoprotein(a) levels in patients, with a mean decrease of 80% at the highest dosage of 20 mg weekly. At the highest possible cumulative dosage of 80 mg monthly, 98% of patients obtained a lipoprotein (a) level of 50 mg per deciliter or below.

No marked changes in platelet, renal, or liver function were observed, nor a between-group difference in the risk of influenza-like symptoms. The most common adverse events among patients who received APO(a)-LRx were mild injection-site reactions [7].

Another randomized, double-blinded, placebo-controlled trial of 281 patients with a history of atherosclerotic cardiovascular disease found that Olpasiran (siRNA molecule) administration significantly decreased lipoprotein(a) content in a dose-dependent way and was safe. It lowered lipoprotein(a) levels by more than 95% at higher dosages when compared to the placebo. The most frequent olpasiran-related side effect was injection-site pain.

The pharmacodynamic effects of olpasiran were maintained throughout the administration interval when the drug was administered every 12 weeks, and the trial treatment period was 48 weeks [8]. The above two trials of injectable drugs show a significant reduction in Lp(a) level, but further long trials were needed.

In competition with these two drugs, a new oral drug named Muvalaplin also shows a significant reduction in Lp(a) levels, this oral medication is a tiny molecule that inhibits the synthesis of Lp(a) by disrupting with apo(a) binding to apoB100 without interfering with plasminogen activity. After 14 days of therapy, there were no tolerability problems or major side effects. Daily dosing resulted in a dosage-dependent decrease in Lp(a) of up to 65% on day 14, with lower levels lasting up to 50 days following the final dose. The maximum dose resulted in Lp(a) trough values of 50 mg/dL or less in 93% of participants [5].

In the future, an oral agent that specifically lowers Lp(a), Muvalaplin, could provide a therapeutic alternative that may enable broader use and might be a Potential Breakthrough.

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