Effects of mipomersen, an apolipoprotein B100 antisense, on lipoprotein (a) metabolism in healthy subjects

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Abstract Elevated lipoprotein (a) [Lp(a)] levels increase the risk for CVD. Novel treatments that decrease LDL cholesterol (LDL-C) have also shown promise for reducing Lp(a) levels. Mipomersen, an antisense oligonucleotide that inhibits apoB synthesis, is approved for the treatment of homozygous familial hypercholesterolemia. It decreases plasma levels of LDL-C by 25% to 39% and lowers levels of Lp(a) by 21% to 39%. We examined the mechanisms for Lp(a) lowering during mipomersen treatment. We enrolled 14 healthy volunteers who received weekly placebo injections for 3 weeks followed by weekly injections of mipomersen for 7 weeks. Stable isotope kinetic studies were performed using deuterated leucine at the end of the placebo and mipomersen treatment periods. The fractional catabolic rate (FCR) of Lp(a) was determined from the enrichment of a leucine-containing peptide specific to apo(a) by LC/MS. The production rate (PR) of Lp(a) was calculated from the product of Lp(a) FCR and Lp(a) concentration (converted to pool size). In a diverse population, mipomersen reduced plasma Lp(a) levels by 21%. In the overall study group, mipomersen treatment resulted in a 27% increase in the FCR of Lp(a) with no significant change in PR. However, there was heterogeneity in the response to mipomersen therapy, and changes in both FCRs and PRs affected the degree of change in Lp(a) concentrations. Mipomersen treatment decreases Lp(a) plasma levels mainly by increasing the FCR of Lp(a), although changes in Lp(a) PR were significant predictors of reductions in Lp(a) levels in some subjects.—Nandakumar, R., A. Matveyenko, T. Thomas, M. Pavlyha, C. Ngai, S. Holleran, R. Ramakrishnan, H. N. Ginsberg, W. Karmally, S. M. Marcovina, and G. Reyes-Soffer.

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Lipoprotein (a) [Lp(a)] is a lipoprotein particle similar in lipid and protein composition to LDL. It is present in plasma mainly in the density range of 1.019 to 1.20 g/ml and has recently been described as a carrier of proinflammatory oxidized phospholipids (1). The hallmark of the particle is apo(a) bound to apolipoprotein B100 (apoB) by a disulfide linkage between cysteine 4326 in apoB and cysteine 4057 in apo(a) kringle IV type 9 (2). Apo(a) is highly glycosylated and is variable in length depending on the number of repeats of kringle IV type 2, which range from 3 to greater than 40 (3). Mendelian randomization (4, 5) and epidemiological cohort studies (6, 7) have shown an increase in CVD risk in individuals with smaller apo(a) isoforms and higher plasma levels of Lp(a). In a meta-analysis of 36 prospective studies with 126,634 participants, a linear relationship was found between Lp(a) levels and CVD risk (7, 8). These studies, together with the potential for marked reductions in Lp(a) by novel LDL cholesterol (LDL-C) and apo(a)-specific lowering treatments (9–13), have reignited interest in pathways that regulate plasma Lp(a) levels (14).

Mipomersen is an apoB antisense oligonucleotide approved for the treatment of patients with homozygous

Abbreviations: CUMC, Columbia University Medical Center; FCR, fractional catabolic rate; LDL-C, LDL cholesterol; Lp(a), lipoprotein (a); PR, production rate; TG, triglyceride.

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familial hypercholesterolemia. In clinical trials, cohorts treated with mipomersen have shown decreases in LDL-C in the range of 25% to 39% (15) as well as reductions in Lp(a) of 21% to 39% (11). We studied the effects of a submaximal dose (16, 17) of mipomersen on apoB metabolism in healthy volunteers and found that although mipomersen treatment for 7 weeks significantly reduced the levels of apoB in VLDL, IDL, and LDL by 29%, 25%, and 42%, respectively, it did so without reducing the hepatic secretion of VLDL apoB or VLDL triglycerides (TGs). Rather, mipomersen increased the fractional catabolic rates (FCRs) of VLDL, IDL, and LDL apoB as well as the direct removal of VLDL apoB. Parallel studies in mice and hepatocyte cell models led us to conclude that human liver synthesizes excess apoB and degrade whatever exceeds the amount required to maintain hepatic homeostasis by transporting lipids out of the liver in VLDL. Thus, in individuals with normal hepatic lipid metabolism, submaximal inhibition of apoB synthesis does not necessarily result in lower rates of VLDL secretion (17).

In this same cohort of participants, we observed a 24% reduction in plasma Lp(a) levels, and this raised the question whether our findings regarding the effects of mipomersen on apoB metabolism could provide insights into the mechanisms regulating Lp(a) production and clearance from the circulation. For example, was spare apoB necessary for Lp(a) assembly, and would reductions in Lp(a) levels be the result, therefore, of reduced apoB synthesis and thus Lp(a) secretion? Alternatively, would we find an increased FCR (in parallel with the increase in the FCR of LDL apoB) as the basis of the decrease in Lp(a) levels? Although we were unable to definitively provide a mechanism for the mipomersen-mediated increase in the FCR of LDL apoB (17), would we find a similar increase in the FCR of Lp(a), suggesting that the LDL receptor may be involved in the clearance of both lipoproteins, as recently observed with PCSK9 inhibition (18, 19)?

Materials and Methods

Study population

We enrolled 29 participants in the parent study, and 17 completed the protocol (17). The study was conducted at the Columbia University Medical Center (CUMC) and approved by the CUMC Institutional Review Board. All participants gave informed consent before enrolling in the study. An examination of the effects of mipomersen on the metabolism of Lp(a) was an exploratory study added to the parent protocol. Due to limitations in the sensitivity of the LC/MS/MS method used, we were able to examine the kinetics of apo(a) in only 14 of the 17 participants who completed the parent study. Supplemental Table S1 presents Lp(a) plasma levels and isoforms in the complete cohort. The three participants with very low Lp(a) plasma levels who were not included in the Lp(a) kinetic analyses are denoted. These levels were below the limit of confidence for our MS analysis of enrichment.

Research protocol

Complete details of the study protocol have been previously published (17). In brief, we performed a single-blind, two-period, linear, placebo-controlled phase I study in healthy volunteers. The study design was chosen due to the long half-life of the compound, which in a randomized crossover design might create issues with the retention of study subjects due to the need for a very long washout period. Similar single-blind, linear, placebo-controlled studies have been performed by our group (13, 18). Participants were not taking medications known to affect lipid metabolism and had normal plasma glucose levels and normal hepatic and renal function. Subjects received three weekly subcutaneous doses of placebo followed by seven weekly doses of 200 mg mipomersen. The safety data for this study have been published (17). Stable isotope studies were performed at the end of the three-placebo treatment period as well as after the end of seven weekly doses of mipomersen.

Inpatient study

Participants were admitted to the inpatient unit of the Irving Institute for Clinical and Translational Research at CUMC. Fasting blood was obtained on day 1. All day 1 meals, which followed American Heart Association guidelines for a healthy diet, were provided at the unit. Isocaloric low-fat liquid meals were started at 1 AM on day 2, 8 h prior to the administration of stable isotopes, and continued every 2 h for the next 32 h to maintain steady-state lipoprotein kinetics throughout the turnover study. At 9 AM on day 2, participants received a priming dose of [5,5,5,2H3](d3)-leucine (10 umol/kg body weight) followed by a constant infusion of d5-leucine (10 umol/kg body weight/h) for 15 h. Blood samples were collected at 0, 2, 4, 6, 8, 10, 12, and 15 h, and plasma was isolated and stored at −80°C until further analysis. We analyzed apo(a) flux in the D:1.019−1.063 g/ml (LDL) fraction isolated by ultracentrifugation. This density range contains the majority of Lp(a) particles in plasma (20).

Determination of stable isotope enrichment of apo(a)

Apo(a) enrichment with d5-leucine was measured as described by Zhou et al (21). In brief, 200 μl of the LDL fraction isolated from plasma was desalted, reduced with dithiothreitol, alkylated with iodoacetamide, and digested using trypsin. A multiple reaction monitoring method was used to monitor the following precursor product ion transitions to a peptide specific to apo(a) (LFLEPTQADALLK): 786.7 > 1069.7 (M0) and 788.2 > 1069.7 (M3). Two microliters of the digested samples were analyzed using a nanoAcquity ultra-performance LC system coupled with an ion key source integrated to a Xevo TQS triple quadrupole tandem mass spectrometer (Waters, Milford, MA). The separation was achieved using an iKey Peptide BEH C18 separation device (130 Å, 1.7 μm, 150 μm × 100 mm) maintained at 60°C. The gradient was 90% A (0.1% formic acid in water)/10% B (0.1% formic acid in acetonitrile) ramped linearly to 10% A at 6 min, held for 3 min, and then re-equilibrated to initial conditions (total run time: 12 min; flow rate: 3 μl/min). The multiple reaction monitoring transitions were monitored with a collision energy of 24 eV.

Plasma Lp(a) and Lp(a) isoform measurements

Lp(a) is measured by a monoclonal antibody sandwich ELISA using monoclonal antibodies developed and characterized at the Northwest Lipid Metabolism and Diabetes Research Laboratory at the University of Washington. The first monoclonal antibody, bound to the solid phase, is specific to an epitope present in the apo(a) kringle IV type 2 identical repeats, whereas the detecting monoclonal antibody is directed to an epitope present only in kringle IV type 9. For this reason, the quantification of Lp(a) by this assay is not affected by the apo(a) size polymorphism. The value to the assay calibrator is traceable to the World Health Organization-International Federation of Clinical Chemistry and
Laboratory Medicine reference material PRM-2B, and the values are expressed in nmol/l. It has been demonstrated that Lp(a) contains one molecule of apo(a) per particle, and therefore the values in nmol/l indicate the number of Lp(a) particles per liter (22, 23). The apo(a) isoforms were measured with electrophoresis and immunoblotting (24).

**Modeling of apo(a)**

The apo(a) enrichment data were modeled as previously described (13). The apo(a) enrichment curves are presented in supplemental Fig. S1. Briefly, we estimated apo(a) FCR by fitting the leucine enrichment data in the apo(a) protein using a single-pool model, with the precursor enrichment set as the VLDL apoB enrichment plateau estimated with our apoB model (17). The apo(a) production rate (PR) in nmol/kg/day was calculated as the product of apo(a) FCR (in pools/day), and the molar pool size per kilogram of body weight of apo(a), which is the apo(a) concentration (nM) multiplied by the plasma volume (estimated as 0.045 l/kg body weight).

**Statistical analysis**

The corresponding authors had full access to all of the data and take responsibility for its integrity and the data analysis. The effects of mipomersen on lipid and lipoprotein levels and on apo(a) FCR and PR were analyzed by paired *t*-tests on absolute values or by a one-sample *t*-test of percentage changes. Associations between pairs of variables were assessed by Pearson correlations. The joint effect of changes in synthesis (PR) and clearance (FCR) on plasma level changes was studied by multiple regression. The association between one of two independent variables, $x_1$, and the dependent variable $y$ was displayed graphically by subtracting from each subject’s $\gamma$ the slope of the other independent variable, $b_2$, multiplied by $x_2 - M_2$, where $M_2$ is the study mean of $x_2$, that is, $\gamma - b_2(x_2 - M_2)$ versus $x_1$.

**RESULTS**

We examined the metabolism of Lp(a) in 14 volunteers who completed the parent study of the effects of mipomersen on apoB metabolism. Demographic data for the entire cohort have been published previously (17); the data for the 14 subjects in the present study are depicted in Table 1.

**Plasma lipid and apoB levels**

Mipomersen treatment for 7 weeks reduced levels (mean ± SD) of total cholesterol by 21.4 ± 11% (160.4 ± 19.7 vs. 125.3 ± 20.3 mg/dl), triglycerides by 17 ± 16% (113.2 ± 51.8 vs. 89.8 ± 31.5 mg/dl), LDL-C by 39 ± 15% (95.7 ± 21.4 vs. 59.0 ± 19.3 mg/dl), and apoB by 38 ± 16% (72.4 ± 17.8 vs. 44.1 ± 13.0 mg/dl). LDL cholesterol increased by 19 ± 16% (42.1 ± 15.1 vs. 48.4 ± 15.2 mg/dl) (Table 2). These changes were similar to those published for the complete cohort (17).

Lp(a) plasma levels decreased in 11 of the 14 subjects analyzed (supplemental Table 1). Baseline median levels (interquartile range) were 56.3 nmol/l (41.9, 116.4) and decreased to 52.1 nmol/l (25.8, 101.6) after 7 weeks of mipomersen treatment. There was a significant reduction in Lp(a) plasma levels (mean ± SD) of 21.4 ± 26.3 nmol/l (P = 0.01) (Table 3). A similar reduction of 22.9 ± 26.2 nmol/l (P = 0.002) in Lp(a) was observed in the 17 participants in the parent study (supplemental Table S1). As expected, the baseline levels of Lp(a) were inversely related to isoform size (supplemental Fig. S2). There were also significant relationships between the size of the predominant apo(a) isoform and the mipomersen-mediated percentage change in Lp(a) (supplemental Fig. S3) and between baseline Lp(a) level and the percentage change during mipomersen treatment (supplemental Fig. S4).

The mean reduction in Lp(a) of 21.4% in the 14 subjects after 7 weeks of treatment with mipomersen was also accompanied by a 26.6 ± 36% increase in the FCR of apo(a) (0.14 ± 0.05 pool/day at baseline vs. 0.17 ± 0.06 pool/day on mipomersen; P = 0.016) (Table 3). In contrast, the mean change in the PR of apo(a) after mipomersen therapy in the 14 subjects was −0.5 ± 45.8% (0.44 ± 0.19 nmol/kg/day at baseline vs. 0.45 ± 0.30 nmol/kg/day on mipomersen; P = 0.97) (Table 3). Individual FCRs and PRs for Lp(a) are presented in supplemental Table S2. The ranges in FCR and PR from this population are similar to our previous cohorts (13, 18).

There was a strong trend for a relationship between baseline levels of Lp(a) and baseline apo(a) FCRs (Fig. 1A) and a significant correlation between baseline Lp(a) levels and baseline PRs of Lp(a) (Fig. 1B). However, changes in Lp(a) FCRs were not related to changes in Lp(a) levels (Fig. 2A). In contrast, and despite the absence of a significant change in the mean apo(a) PR for the entire group, changes in PR correlated positively and significantly with

### Table 1. Baseline characteristics

| Gender, n (%) | Males, 7 (50) | Females, 7 (50) | Mean age ± SD: 46.6 ± 14 years |
|--------------|-------------|----------------|-----------------------------|
| Race, n (%)  | White, 4 (29.4) | Black, 7 (50) | Hispanic, 2 (14) | Asian, 1 (7) |

### Table 2. Effects of subcutaneous administration of 150 mg mipomersen on plasma lipids and lipoproteins

|                      | Placebo (mg/dl) | Mipomersen (mg/dl) | Change (%) | P   |
|----------------------|----------------|-------------------|------------|-----|
| Total cholesterol    | 160.4 ± 19.7   | 125.5 ± 20.3      | −21.4 ± 11 | <0.001 |
| HDL cholesterol      | 42.1 ± 15.1    | 48.4 ± 15.2       | 19.1 ± 16.2 | <0.001 |
| LDL-C                | 95.7 ± 21.4    | 59.0 ± 19.3       | −38.5 ± 15.4 | <0.001 |
| TGs                  | 113.2 ± 51.8   | 89.8 ± 31.5       | −16.8 ± 15.8 | <0.01  |
| apoB                 | 72.4 ± 17.8    | 44.1 ± 13.0       | −38.1 ± 16  | <0.001 |

Values are means ± SDs.
TABLE 3. Effects of mipomersen on Lp(a) plasma levels and the kinetics of apo(a)

|                | Placebo | Mipomersen | Change (Mean %) | Change (SD) | p   |
|----------------|---------|------------|-----------------|-------------|-----|
| Lp(a) (nmol/l) | 56.3 (44.5, 106.8) | 52.1 (26.4, 92.4) | −21.4 | 26.3 | 0.01 |
| apo(a) FCR (pools/day) | 0.14 ± 0.05 | 0.17 ± 0.06 | ±26.6 | 36.0 | 0.016 |
| apo(a) PR (nmol/kg/day) | 0.44 ± 0.19 | 0.45 ± 0.30 | ±0.5 | 45.8 | ns   |

Lp(a) levels are expressed as medians with interquartile ranges. FCRs and PRs are presented as means ± SDs. ns, nonsignificant.

changes in Lp(a) levels (Fig. 2B). In an effort to further understand the relationships of both PR and FCR with changes in Lp(a) concentrations, we performed a multiple regression of change in Lp(a) level from mipomersen treatment and found a significant effect for both change in PR (P = 0.001) and FCR (P = 0.02). The results of the regression analysis (Fig. 2C) demonstrate a strong inverse relationship between Lp(a) change when we adjusted for the effect of change in PR versus change in FCR.

**DISCUSSION**

Lp(a) is an apoB-containing lipoprotein that increases the risk of CVD. Despite in vivo studies of Lp(a) metabolism spanning almost 50 years, the regulation of plasma levels of this unique lipoprotein remains incompletely defined (14). Early investigations suggested that an individual’s baseline level of Lp(a) was determined mainly by production and not clearance (25, 26). Those findings were supported in initial studies of the effects of drugs on Lp(a) metabolism. Thus, reductions in Lp(a) concentrations during estrogen therapy as well as niacin therapy were due to lower Lp(a) PRs (27, 28). However, there is discordance in the effect of these treatments on apoB production, with estrogen therapy increasing (29) and niacin therapy reducing (28) VLDL apoB secretion. These results indicate a lack of concordance, at least in these two instances, between the regulation of the assembly of apoB lipoproteins with and without apo(a) as a component.

Our current findings demonstrate that treatment with mipomersen, an antisense oligonucleotide to apoB, caused a 21% decrease in plasma Lp(a) levels that was associated with a 27% increase in the mean FCR of Lp(a), with no effect on the mean Lp(a) PR in the overall group of subjects. However, there was significant heterogeneity in the effects of mipomersen on Lp(a) metabolism. Despite this heterogeneity, there are two potentially important insights about Lp(a) metabolism that can be gleaned from the overall results. The first is that the increase in Lp(a) FCR observed was similar to the 30% increase in the FCR of LDL apoB we found in the parent study of the effects of mipomersen on the metabolism of VLDL, IDL, and LDL (17). These concordant results support a role for the LDL receptor in the clearance of Lp(a) from plasma, although in the parent study, experiments with mice and hepatoma cells did not demonstrate changes in LDL receptor function (17). Moreover, a systematic review of the Lp(a) kinetic studies do not point to a major role of the LDL receptor in Lp(a) metabolism (14). Additionally, although the PCSK9 inhibitor alirocumab reduced Lp(a) levels by 19% in association with a 25% increase in FCR, it simultaneously increased the FCR of LDL apoB by 80% (18). Such results are best explained by multiple receptors for Lp(a), with the LDL receptor playing only a modest role. Adding uncertainty to the role of the LDL receptor are our findings that the cholesterol ester transfer protein inhibitor anacetrapib reduced LDL apoB levels by 18% concomitant with an increase in FCR of 27% (30) but reduced Lp(a) levels by 34% without any change in FCR but a reduction of 41% in apo(a) PR (13). Watts et al. (19) recently reported results of a stable isotope study of the effects of a second PCSK9 inhibitor, evolocumab, versus placebo on Lp(a) metabolism in which they did not find effects on the clearance of apo(a) but rather demonstrated that the reduction in Lp(a) levels observed were due to decreased Lp(a) PR. It is not clear why these results differ from ours with alirocumab, although evolocumab was studied in a population of white males with Lp(a) levels lower (32.4 nmol/l) than in those in our mixed-gender and mixed-race study group (56.3 nmol/l). Additionally, the evolocumab study was conducted with subjects in a fasting state, whereas we conducted our study with a constant steady-state supply of nutrients.

The second potential insight derives from a lack of effect of mipomersen treatment, which inhibits apoB synthesis, on the assembly of hepatic apoB with apo(a) to form an Lp(a). As noted earlier, we recently reported that a submaximal dose of mipomersen (16) did not reduce VLDL apoB secretion in the same subjects studied here (17).

**Fig. 1.** A: Relationship between baseline Lp(a) levels (nmol/L) and apo(a) FCRs in pools/day. B: Relationship between baseline Lp(a) levels (nmol/L) and apo(a) PRs in pools/day.
That result, together with data from mice and hepatoma cells, supported the presence of spare apoB in the liver that would be utilized for the assembly of VLDL only when TG secretion was needed to maintain hepatic lipid homeostasis (31). The present finding of no consistent changes in Lp(a) production during mipomersen treatment extends the concept of spare apoB in the liver to the assembly of Lp(a). Thus, our results indicate that either 1) the pool of spare apoB is so large that when apoB synthesis in partially inhibited neither VLDL nor Lp(a) assembly is affected or 2) that the apoB targeted for Lp(a) assembly is in a separate pool from the apoB targeted for VLDL assembly. Future studies examining the secretion of apoB lipoproteins when apo(a) synthesis is inhibited by 90% with specific antisense or siRNA, which would result in a state of “apoB deficiency,” may allow differentiation between these two possibilities.

Of note, in the study by Watts et al. (19), when evolocumab was administered together with atorvastatin (80 mg/day), which alone had no effects on Lp(a) level, FCR, or PR, evolocumab had a similar Lp(a)-lowering effect as observed when administered alone, but in this case the reduction was due completely to an increase in Lp(a) FCR. The contrasting metabolic effects of evolocumab, when given alone versus with atorvastatin, suggest that background metabolic differences in individuals receiving a PCSK9 inhibitor alone might affect the physiologic basis for reductions in Lp(a) levels that result from such treatment. This background metabolic heterogeneity might have played an important role in our study, where, despite clear and statistically significant group differences in the effects of mipomersen on the FCR and PR of Lp(a), there was significant heterogeneity in individual responses, with both parameters demonstrated to affect the extent of the reduction in Lp(a) observed by regression analysis. Much larger studies with significant numbers of males and females and people of different ethnic groups will be needed to provide insights into the molecular and physiologic drivers of the heterogeneous results we obtained in the present study. For example, differences in the response of individual Lp(a) isoforms to mipomersen might be one of the factors playing a role in the variability we have observed.

This study utilized samples from a parent study of the effects of mipomersen on apoB and TG metabolism (17). The study utilized a single-blind, linear, fixed-sequence design that we have used successfully in previous studies of the effects of drugs on lipoprotein metabolism (13, 17, 18, 30, 32–34). Linear sequence design studies can, however, introduce bias because of “study effect,” even when the subjects are blinded to the sequence. Unfortunately, the very long half-life of mipomersen would require several months of washout for a randomized crossover design, and that would have impeded the retention of subjects and created other problems with study logistics. The analysis of Lp(a) was performed in apo(a) from isolated LDL. However, the large majority of Lp(a) in plasma is found in this density range (20), and the FCR of apo(a) in the present study is similar to those determined in previous investigations from our group and others using plasma or other fractions as the source of Lp(a) (18, 26). Additionally, a study in which the FCR of apo(a) was determined by the rate of increase of plasma levels after physical removal of Lp(a) by apheresis reported rates nearly identical to those in the present study (35). We did not study the specific turnover of apoB within Lp(a) but assumed that the two proteins remained together, in a 1:1 ratio, from the time of entry into the circulation until the time of clearance. Our assumption was recently supported by Watts et al. (19) as well as most (27, 34, 35) but not all (33, 36) previous stable isotope studies of Lp(a) metabolism. With the increasing numbers of drug treatments that alter Lp(a) levels, additional studies will be required to better define the stability of the association between apo(a) and apoB in Lp(a) as well as the pathways by which they are cleared. Finally, our study was conducted in a small cohort that was heterogeneous in regard to race and gender. However, in our unpublished data of 43 subjects studied in three separate protocols, we have not seen an effect of race or gender on the FCR of Lp(a), our main outcome parameter in the present study.

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