Effect of IL-6 Inhibition on Lipoprotein(a) Levels: A Systematic Review and Meta-Analysis

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BACKGROUND

- Experimental studies suggest that **interleukin-6 (IL-6)** inhibition may reduce atherosclerotic cardiovascular disease (ASCVD) risk via mechanisms such as reducing endothelial activation, leukocyte recruitment, foam cell formation, plaque rupture, and hepatic synthesis of prothrombotic proteins (Figure 1).[1]

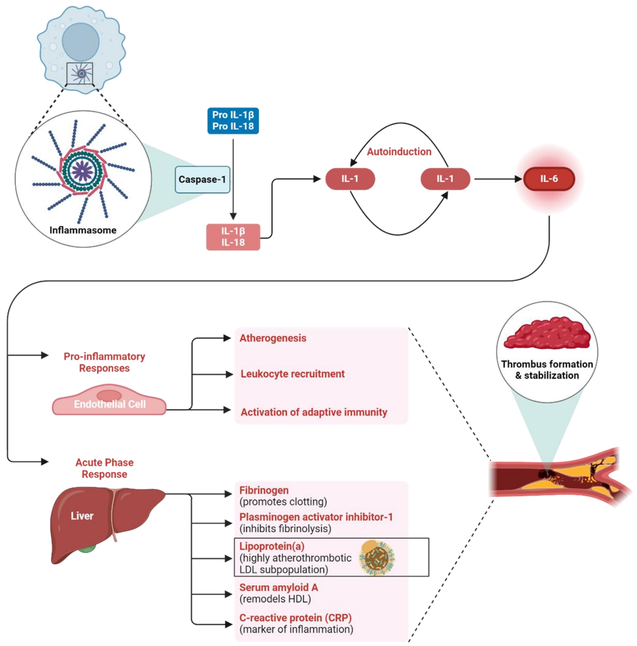

Figure 1. Mechanisms of IL-6 in ASCVD.

- Importantly, IL-6 inhibition may decrease hepatic apolipoprotein(a) [apo(a)] synthesis, lowering levels of lipoprotein(a) [Lp(a)], a highly atherogenic lipoprotein.[2]
- The promoter region of the *LPA* gene encoding for apo(a) contains a functional IL-6 response element (CTGGGA) that upregulates apo(a) expression (Figure 2).[3]
- Higher levels of Lp(a) were observed in individuals with elevated IL-6 levels in a population cohort in Germany (n=1,153).[2]
- Transcriptomic analysis of human liver biopsies (n=57) showed a correlation between gene expression of *LPA* and IL-6 response genes.[2]

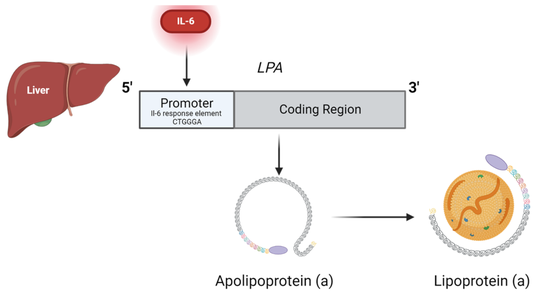

Figure 2. Effect of IL-6 on Lp(a).

- Ongoing Phase 2 and Phase 3 (NCT06362759, NCT05021835, NCT06118281, NCT05485961) trials are evaluating anti-IL-6 monoclonal antibodies (mAbs) in patients with established ASCVD or at high-risk of ASCVD.
- **Objective: We conducted a systematic review and meta-analysis to quantify the effect of anti-IL-6/IL-6 receptor (IL-6R) mAbs on Lp(a) levels.**

METHODS

- We searched PubMed, Cochrane Library, and Embase databases for studies published up to June 30, 2024, that reported changes to Lp(a) levels over time following repeat doses of anti-IL-6/IL-6R mAbs and a comparator. Of the 96 studies identified, 33 duplicate records and 54 ineligible records were removed leaving a total of 10 studies.
- The **primary analysis** employed a random-effects meta-analysis to compare the impact of IL-6 inhibitors on Lp(a) levels with the comparator group in studies that included both arms. We analyzed the treatment effects at two time points: 2-3 months and 6 months. **Secondary analyses** included a pre-post analysis of the impact of IL-6 inhibitors on Lp(a) levels before and after the intervention, also at 2-3 months and 6 months.
- Standardized mean differences (SMD) and 95% confidence intervals (95% CI) were calculated for the absolute change in Lp(a) levels. SMD values were characterized as small (0.2-0.5), medium (0.5-0.8), and large (>0.8). Studies reporting medians and interquartile ranges (IQR) were converted to means and standard deviations (SD) using methods described by Wan et al.[4] If standard errors (SE) were given, we estimated the SD by SD = SE x sqrt(n), where n is the number of subjects. For studies with multiple treatment arms of the same agent, all arms were combined using formulas from the Cochrane Handbook.
- Heterogeneity was quantified from the I^2 statistic and characterized as moderate (30-60%), substantial (50-90%), and considerable (75-100%).
- Sensitivity analyses were performed using the leave-one-out method, removing one study at a time and repeating the analysis for all studies.

RESULTS

- Our analysis included ten studies with 1,201 total participants (876 rheumatoid arthritis, 325 chronic kidney disease) receiving either an anti-IL-6/IL-6R mAb (311 tocilizumab, 153 sarilumab, 247 ziltivekimab) or comparator (78 placebo, 412 tumor necrosis factor inhibitor).
- The mean age across the study was 50-70 years, with 25-100% women. The follow-up duration ranged from 2-12 months. Average Lp(a) levels were 65.7 (SD 89.5) nmol/L among 325 participants and 25.7 (SD 32.8) mg/dL among 876 participants.

Table 1. Summary of studies included within the meta-analysis.

Study	Study type	Number of patients	Age, years	Female sex, %	Underlying condition	IL-6/IL-6R antibody	Comparator	CRP (mg/L)	Follow-up	Lipoprotein(a)
Gabay 2016 (ADACTA)	RCT	324	53-54	80-82	Rheumatoid arthritis	Tocilizumab	Adalimumab	25-26	8 weeks	22-26 mg/dL
Lee 2016 (MEASURE)	RCT	20	59	100	Rheumatoid arthritis	Tocilizumab	Placebo	12.8	12 weeks	30 mg/dL
Virone 2019 (ROC)	RCT	203	57	82	Rheumatoid arthritis	Tocilizumab	TNF inhibitor	8.5	24 weeks	10-15 mg/dL
Gabay 2020 (MONARCH)	RCT	307	50-53	79-84	Rheumatoid arthritis	Sarilumab	Adalimumab	17.4-23.6	12, 24 weeks	17.9-23.6 mg/dL
Ridker 2021 (RESCUE)	RCT	264	66-70.0	44-55	Non–dialysis-dependent CKD	Ziltivekimab	Placebo	5.5-5.8	12 weeks	37-50 nmol/L
Pergola 2021	RCT	61	58-64	25-56	Hemodialysis-dependent CKD, anemia	Ziltivekimab	Placebo	4.0-13.2	12 weeks	22-64 nmol/L
Ferraz-Amaro 2019	OBS	27	52	88	Rheumatoid arthritis	Tocilizumab	None	8.8	3, 6, 12 months	29 mg/dL
Schultz 2010	OBS	11	51	64	Rheumatoid arthritis	Tocilizumab	None	–	1, 3 months	35 mg/dL
Benucci 2013	OBS	16	56	100	Rheumatoid arthritis	Tocilizumab	None	3.8	6 months	28 mg/dL
Pierini 2021	OBS	28	61	89	Rheumatoid arthritis	Tocilizumab	None	3.9	3 months	48 mg/dL

OBS, prospective observational, CKD, chronic kidney disease; CRP, C-reactive protein; ESRD, end-stage renal disease; RCT, randomized controlled trial; TNF, tumor necrosis factor.

Primary Analysis

- Four comparative studies with 2-3-month follow-up data were pooled (n=915) for a total of 534 participants receiving anti-IL-6/IL-6R mAb therapy vs 381 receiving the comparator (Figure 3A).
- Two comparative studies with 6-month follow-up data (n=450) were pooled for a total of 200 participants receiving anti-IL-6/IL-6R mAb therapy vs 250 receiving the comparator (Figure 3B).
- A randomized controlled Phase 2b trial of clazakizumab was recently published and not included in this analysis.[5] They reported a 37-52% decrease in Lp(a) in patients with end-stage kidney disease receiving clazakizumab 2.5, 5, or 10 mg IV once every four weeks for 12 weeks.
- Pooled analysis indicated a reduction in Lp(a) at (A) 2-3 months with an SMD of -0.49 (95% CI -0.73 to -0.24, p<0.001) and at (B) 6 months with SMD of -0.97 (95% CI -1.16 to -0.77, p<0.001).

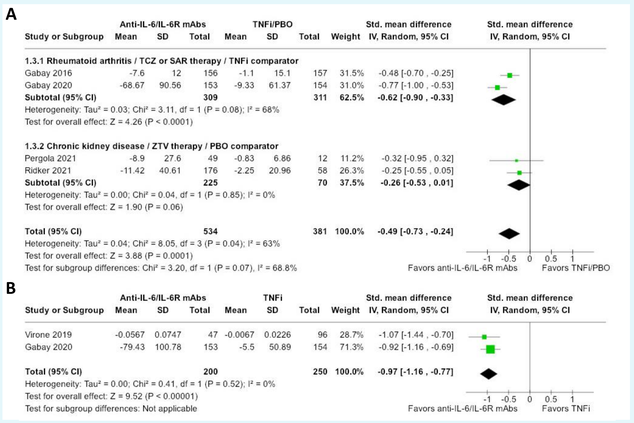

Figure 3. Changes in Lp(a) in controlled studies of anti-IL-6/anti-IL-6R mAbs.

Secondary Analysis

- Eight studies (n=648) provided the data necessary to compare pre- to post-treatment Lp(a) levels at 2-3 months following anti-IL-6/IL-6R mAb therapy (Figure 4A)
- Four studies (n=243) had 6-month follow-up data (Figure 4B).
- One study (Ferraz-Amaro, 2019) reported Lp(a) levels at 12 months, showing an absolute reduction of -6 (IQR: -33 to 0 mg/dL) mg/dL in patients receiving anti-IL-6/IL-6R mAb therapy.
- Pooled analysis indicated a reduction in Lp(a) at (A) 2-3 months with SMD of -0.29 (95% CI -0.44 to -0.14) and at (B) 6 months with SMD of -0.33 (95% CI -0.51 to -0.15, p<0.001).

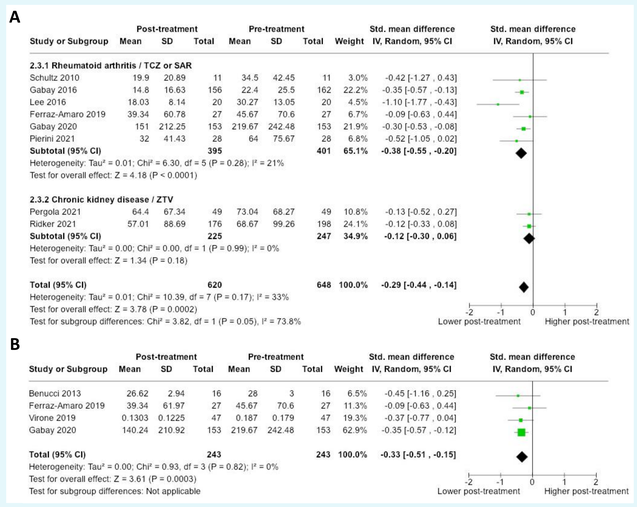

Figure 4. Changes in Lp(a) in studies of anti-IL-6/anti-IL-6R mAbs.

CONCLUSIONS

- This meta-analysis indicated moderate to large reductions in Lp(a) levels with anti-IL-6/ IL-6R mAbs versus controls.
- Limitations included:
  - Differences in Lp(a) units across studies (nmol/L vs. mg/dL)
  - Inability to report percent changes in Lp(a) due to inconsistent reporting or incomplete data.
- Further studies are needed to examine the effect of IL-6 inhibition specifically in patients with elevated levels of Lp(a).

DISCLOSURES

- SM and RM have no interests to disclose. EdG, JW, and YC are employees of Tourmaline Bio, Inc. MDS is supported by institutional grants from Amgen, Arrowhead, Boehringer Ingelheim, 89Bio, Esperion, Novartis, Ionis, Merck, New Amsterdam, and Cleerly; has participated in scientific advisory boards with Amgen, Agepha, Ionis, Novartis, New Amsterdam, and Merck; and has served as a consultant for Ionis, Novartis, Regeneron, Aidoc, Shanghai Pharma Biotherapeutics, Kaneka, Novo Nordisk, Arrowhead, and Tourmaline.

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