Reduced fasting and postprandial triglyceride levels by alirocumab in male diabetes patients on intensive insulin treatment by improved chylomicron metabolism

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Introduction

- Type 2 Diabetes Mellitus (T2DM) is associated with an increased risk for cardiovascular disease, atherogenic dyslipidemia and postprandial hyperlipidemia.
- Statins have shown to improve diabetic dyslipidemia.
- The effects of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors on postprandial lipemia in T2DM have not been evaluated in detail.

Methods

A randomized, 1:1, double-blind, proof-of-concept study in which 12 male patients with T2DM on intensive insulin regimen were allocated to 6 weeks of biweekly subcutaneous alirocumab (150 mg) or placebo. Postprandial lipemia was assessed before and after an intervention using an 8-hrs standardized oral fat loading test. Vascular function was assessed by measurement of fasting pulse wave velocity (PWV) and pulse wave augmentation index (Aix).

Results

Table 1. Baseline characteristics

	Total (n=12)	Alirocumab (n=6)	Placebo (n=6)
Age (years)	62.6 ± 7.8	61.5 ± 9.9	63.7 ± 5.6
Body mass index (kg/m ²)	32.8 ± 5.6	31.5 ± 6.0	34.1 ± 5.5
Waist circumference (cm)	110 ± 21	107 ± 25	113 ± 19
Systolic blood pressure (mmHg)	134 ± 11	133 ± 12	135 ± 10
Fasting glucose (mmol/L)	8.5 ± 1.9	8.3 ± 2.3	8.6 ± 1.7
Glycated A1c (mmol/mol)	65.6 ± 8.7	63.5 ± 7.7	65.5 ± 10.9
LDL-C (mmol/L)	1.9 ± 0.5	1.9 ± 0.5	2.0 ± 0.5
Plasma TG (mmol/L)	1.89 (0.92-2.87)	1.75 (0.86-2.59)	2.64 (1.69-3.59)
Apo B (g/L)	0.85 ± 0.20	0.82 ± 0.15	0.89 ± 0.25
Apo B48 (mg/L)	12.9 (4.4-21.4)	9.3 (0.0-19.2)	18.8 (8.2-29.4)

No significant differences between intervention groups

Abbreviations: Apo, apolipoprotein; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides

Fasting levels of total cholesterol (median change compared to baseline -28.2%; $p < 0.001$), LDL-C (-39.5%; $p < 0.001$) and apo B (-50.7%; $p < 0.001$) were significantly changed after six weeks of treatment with alirocumab versus placebo.

► A median -24.7% ($p = 0.02$) change compared to baseline in fasting triglycerides and a median -35.9% ($p = 0.04$) change in apo B48 levels compared to baseline was observed between alirocumab (red bar) and placebo (blue bar).

Figure 1. Mean (standard error of the mean) of TG and apo B48 levels during an oral fat load with alirocumab at baseline (red open square) and after treatment (red closed square) and placebo at baseline (blue open circle) and after treatment (blue closed circle).

Postprandial (incremental area under the curve) responses of total cholesterol (median change compared to baseline -28.2%; $p < 0.001$), apolipoprotein B (-48.6%; $p < 0.001$) and HDL-C (+4.2%; $p = 0.04$) changed after six weeks of treatment with alirocumab compared to placebo.

Fasting pulse wave velocity was reduced after six weeks of alirocumab versus placebo (median change compared to baseline -7.9%; $p = 0.03$). There were no changes in postprandial vascular function (both PWV and Aix).

Conclusion

Alirocumab lowered both fasting and postprandial TG levels in male patients with T2DM by reducing levels of circulating chylomicrons and their remnants. In addition, an improved vascular elasticity was found. This may contribute to cardiovascular protection in T2DM in addition to LDL-C lowering by these compounds.