Evolocumab treatment reduces carotid intima-media thickness in paediatric patients with heterozygous familial hypercholesterolaemia

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Background: Familial hypercholesterolemia (FH) is characterised by high plasma levels of low-density lipoprotein cholesterol (LDL-C) and increased risk of premature atherosclerotic cardiovascular disease (ASCVD). Previous studies show that carotid intima-media thickness (cIMT) is increased in children with FH, an indicator of early ASCVD. Add-on treatment with the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, evolocumab, substantially reduced atherosclerotic lipid levels in children with heterozygous FH (HeFH) and was safe and well tolerated. The effect of evolocumab on cIMT in paediatric patients (pts) has not been investigated.

Purpose: To investigate the effect of evolocumab treatment on cIMT progression in paediatric pts with HeFH.

Methods: HAUSER-RCT was a multicenter, randomised, placebo-controlled study in which paediatric FH pts (ages 10–17 years) received monthly subcutaneous injections of evolocumab 420 mg or placebo. Of 157 pts, 150 continued to an open-label extension study (HAUSER-OLE) during which all received up to 80 weeks of monthly evolocumab 420 mg on top of stable background statin therapy. cIMT was measured by B-mode ultrasound scanning at baseline, week 24 of the RCT, and weeks 24, 48, and 80 of the OLE. cIMT was measured on anterior, lateral, and posterior imaging angles of the right and left common carotid artery. Mean thickness at each visit and mean changes from baseline were summarised by treatment received during the RCT and artery location. In addition, the largest measurements (anterior, lateral, or posterior) from a patient's left and right carotid artery were averaged to calculate a summary score.

Results: Mean baseline cIMT summary score was 0.568 mm (SD=0.06) for 46 placebo pts and 0.586 mm (SD=0.06) for 82 evolocumab pts. During the RCT, 37 placebo pts had a mean increase of 0.006 mm (SD=0.05) from baseline to week 24; in contrast, 76 evolocumab pts had a mean decrease of 0.003 mm (SD=0.05). Although this treatment group difference was not statistically significant (P=0.403), the pattern of increased cIMT for placebo and decreased cIMT for evolocumab was consistent across artery locations (Table). During the OLE, for pts who initially received placebo, mean cIMT summary score decreased by 0.019 mm (SD=0.04, n=34) from baseline to week 80 (P=0.007) (Figure). Pts who received evolocumab in both the RCT and OLE showed continued improvement during the OLE; at week 80, mean cIMT summary score decreased by 0.012 mm (SD=0.05, n=59) from baseline (P=0.067). For all pts at week 80 (n=128), the mean decrease in LDL-C from baseline was 35.3% (SD=28.0).

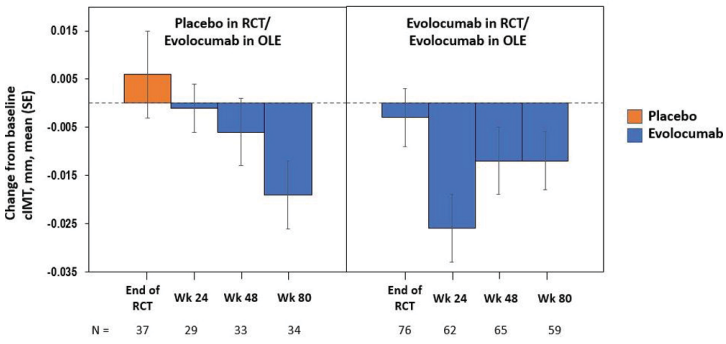
Conclusions: Open-label evolocumab treatment for up to 80 weeks led to reductions in mean cIMT. In this small sample of pts with FH, the data suggest that the addition of PCSK9 inhibition to background lipid-lowering therapy has the potential to reduce the risk of ASCVD progression and future cardiovascular events in this vulnerable paediatric population.

Table. Mean change from baseline in cIMT measurements for each treatment group during randomised treatment (24 weeks) and open-label evolocumab treatment (80 weeks).

Common carotid artery position, change from baseline, mm, mean (SD)		RCT[a] Baseline to week 24		OLE Baseline of RCT to week 80 of OLE	
		Placebo (N = 53)	Evolocumab (N = 104)	Placebo in RCT/ Evolocumab in OLE (N = 49)	Evolocumab in RCT/ Evolocumab in OLE (N = 101)
Average of largest left and largest right measurements at any position		n = 37 +0.006 (0.05)	n = 76 −0.003 (0.05)	n = 34 −0.019 (0.04)	n = 59 −0.012 (0.05)
Left artery	Lateral	n =34 +0.003 (0.08)	n = 71 −0.007 (0.07)	n = 30 −0.021 (0.07)	n = 59 −0.028 (0.07)
	Anterior	n = 33 +0.017 (0.07)	n = 67 −0.014 (0.07)	n = 31 −0.023 (0.06)	n = 52 −0.013 (0.06)
	Posterior	n = 37 +0.005 (0.06)	n = 74 +0.006 (0.08)	n = 32 −0.004 (0.05)	n = 57 −0.013 (0.08)
Right artery	Lateral	n = 37 +0.002 (0.05)	n = 74 −0.011 (0.08)	n = 33 −0.009 (0.06)	n = 57 −0.019 (0.06)
	Anterior	n = 34 +0.025 (0.08)	n = 60 −0.001 (0.06)	n = 31 −0.003 (0.05)	n = 47 −0.004 (0.07)
	Posterior	n = 34 +0.004 (0.07)	n = 73 −0.003 (0.07)	n = 28 −0.035 (0.07)	n = 59 +0.002 (0.08)

[a]First presented in Santos et al., *N Engl J Med*. 2020;383:1317–27. cIMT = carotid intima-media thickness; OLE = open-label extension; RCT = randomised controlled trial; SD = standard deviation.

Figure. Change from baseline cIMT summary score (average of largest left and right carotid artery measurements) across visits



cIMT = carotid intima-media thickness; OLE = open-label extension; RCT = randomised controlled trial; SE = standard error; Wk = week.