Effect of dalcetrapib, a CETP modulator, on non-cholesterol sterol markers of cholesterol homeostasis in hamsters and healthy subjects

Eric J Niesor1, Evelyne Chaput1, Andreas Staempfl1, Denise Blum1, Michael Derks1, David Kallend1
1F. Hoffmann-La Roche Ltd, Basel, Switzerland

Objective: High levels of HDL-C in man correlate with elevated plasma markers of cholesterol absorption and reduced markers of cholesterol synthesis. The effect of dalcetrapib, a cholesteryl ester transfer protein (CETP) modulator, on markers of cholesterol homeostasis was compared to torcetrapib in hamsters, and assessed in man.

Methods: The effect of dalcetrapib and torcetrapib, ± ezetimibe, on plasma non-cholesterol sterols, lathosterol and desmosterol (cholesterol synthesis markers) and campesterol, β-sitosterol and cholestanol (intestinal cholesterol absorption markers) was compared in hamsters, along with the effect of dalcetrapib on cholesterol absorption. In a randomized, open-label, crossover study, 22 healthy subjects were administered: dalcetrapib 900mg, ezetimibe 10mg, dalcetrapib 900mg + ezetimibe 10mg over three 7-day periods, and levels of the plasma non-cholesterol sterol markers measured.

Results: HDL-C was raised by dalcetrapib (49%, $p=0.04$) and torcetrapib (72%, $p=0.003$) in hamsters. Unlike torcetrapib, dalcetrapib increased markers of cholesterol absorption; synthesis markers were unaffected by either treatment. Dalcetrapib did not change $^3$H-cholesterol intestinal absorption but favored its distribution in the HDL vs non-HDL fraction. In man, dalcetrapib increased campesterol (27%, $p=0.001$), β-sitosterol (32%, $p<0.001$), and cholestanol (12%, $p=0.03$; in ratio to cholesterol). Co-administration with ezetimibe reduced campesterol by 11% ($p=0.02$); β-sitosterol and cholestanol were unaffected. Lathosterol and desmosterol were unchanged with dalcetrapib, but increased with ezetimibe alone (56–148%) or combined with dalcetrapib (32–38%; both $p<0.001$).

Conclusion: Dalcetrapib represents the first HDL-raising intervention to specifically increase markers of cholesterol absorption, without affecting markers of synthesis, most likely reflecting nascent HDL lipidation by enterocyte basolateral ABCA1.