Letter to the Editor

PCSK9 administration ameliorates non alchoholic fatty disease in patients with heterozygous familial hyperlipidemia

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Dear Editor
Non-alcoholic fatty liver disease (NAFLD) steatosis of the liver progressing to steatohepatitis (NASH) associated with inflammation, fibrosis, cirrhosis, and in some cases hepatocellular carcinoma [1]. NAFLD is a cause of a worldwide growing epidemic, and is related to obesity and insulin resistance (IR) [1]. NAFLD patients are at increased risk of liver-related as well as cardiovascular disease (CVD) morbidity and mortality, while NAFLD is the second cause of liver transplantation [1].

Proprotein convertase subtilisin kexin 9 (PCSK9) binds the low-density lipoprotein (LDL) receptor at the surface of hepatocytes, thereby preventing its recycling and enhancing its degradation in endosomes/lysosomes, resulting in reduced LDL-C clearance [2]. Gain-of-function PCSK9 variants lead to higher LDL-C and increased risk of CVD; loss-of-function PCSK9 variants are associated with reductions in both LDL-C and CVD risk [2]. PCSK9 inhibitors (PCSK9i), human antibodies, are used to reduce LDL-C on top of high doses of potent statins plus ezetimibe, mainly in patients with heterozygous familial hyperlipidemia (HeFH) [3].

After the successful use of statins for the treatment of NAFLD [4], we tried to investigate the effect of PCSK9 on NAFLD in HeFH patients. We randomized 40 patients with HeFH either to evolocumab (140 mg/14d subcutaneously) or to alirocumab (150 mg/14d subcutaneously). From these, 13 patients had NAFLD (diagnosed with abdominal ultrasound and magnetic resonance imaging). From these 6 had NASH diagnosed with elastography. Serum transaminases were normal in 5/13 patients, while gamma glutamyl transferase was increased in all participants (92±18 IU/L). After one year of treatment with either of the PCSK9s, NAFLD/NASH was completely ameliorated without steatosis, inflammation, or fibrosis. No patient presented with cirrhosis. These patients, besides CVD risk reduction with PCSK9i, had an improvement of liver structure and function, an additional problem to those exposed at liver related or CVD risk.

In 201 consecutive patients biopsy confirmed NASH, it was shown that circulating and hepatic PCSK9 increases with hepatic fat accumulation and
correlates with the severity of steatosis (p=0.04), independently of metabolic confounders and liver damage [5]. Moreover, from 13 HeFH patients 10 had metabolic syndrome (MetS) or diabetes (IR) [6]. NAFLD/NASH is considered the liver expression of IR[7,8]. Thus, if you reduce IR with a PCSK9i, besides its other actions mentioned above, you expect to have a beneficial clinical result [6]. In a study that included 137 adults it was shown that PCSK9 correlated positively with IR (r=0.425, p<0.001) [6]. Multiple regression analysis revealed that the strongest predictor of PCSK9 was IR (p<0.001), waist circumference (p<0.001), and triglycerides (p=0.013)[6].

Overall, it seems that PCSK9i have a beneficial effect on NAFLD/NASH related to direct effects on the liver and to the reduction in IR. This should be verified by larger studies and in this case it will have clinical implications. For example in the ODYSSEY Outcomes trial [9] total mortality was reduced by 15% (p=0.029), while CVD mortality was not reduced. It is not impossible that a part of total mortality reduction could be attributed to reduction of liver-related mortality. This also needs confirmation by larger studies.

Conflict of interest
This paper was written by the authors without any professional writer help and with no conflict of interest regarding the issue analyzed whatsoever.

References


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