Trials of obeticholic acid for non-alcoholic steatohepatitis

UNIVERSITÀ DEGLI STUDI DI TORINO

Obeticholic acid: an effective treatment for diabetic patients with non-alcoholic steatohepatitis?

RUNNING TITLE: OCA and NASH

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To the Editor:

we read with interest the results of the FLINT trial, evaluating the effect of obeticholic acid (OCA) on liver histology in non-alcoholic steatohepatitis (NASH)[1].

A remarkable yet overlooked result of this trial was the different histological response between diabetic and non-diabetic participants: among the former, liver histology improved in 53% patients with OCA vs. 19% on placebo (OR for improvement with OCA: 4.6, 95%CI=2.0-10.6, p=0.0003), while in non-diabetic patients, liver histology improved in 37% patients with OCA vs. 23% with placebo (OR: 2.0, 95%CI=0.8-4.7, p=0.12).

The impact of glucose intolerance on histological response to OCA was evident also across progressive stages of pancreatic ß-cell dysfunction, as estimated by HOMA B-cell index (online Appendix Table S2)[1]

Beside the FLINT, only another randomized trial, enrolling diabetic patients, evaluated OCA in non-alcoholic fatty liver(NAFLD)[2]. Therefore current evidence for effectiveness of farnesoid X receptor(FXR) agonists is lacking in non-diabetic individuals, a substantial proportion of NASH population.

Additionally, consistent with other randomized trials in NASH, the percentage of responders approached 50% in the FLINT, leaving a substantial proportion of patients without an effective treatment[3]. NASH is an heterogeneous conditions and diverse mechanisms of liver injury likely operate in different patient populations to promote liver disease progression. In humans, altered bile acid metabolism, which represents the rationale for using semi-synthetic bile acids, has been more convincingly demonstrated in diabetic that in non-diabetic individuals[4], thereby potentially explaining the lack of response to OCA among non-diabetic individuals in the FLINT. Hence, further assessment of FXR agonists in nondiabetic NASH is mandatory, and an approach tailored to individual metabolic profile may be required to tackle NASH epidemic.

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Giovanni Musso: conceived the article, undertook literature search and acquired data, critically analyzed the results, drafted the article, gave final approval

Giovanni Musso, as the corresponding author, had full access to all the data and takes final responsibility for the decision to submit for publication.

Maurizio Cassader: undertook literature search and acquired data, critically analyzed the results, contributed to draft of the article, gave final approval

Roberto Gambino: undertook literature search and acquired data, critically analyzed the results, contributed to draft of the article, gave final approval

Conflicts of interest.

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