

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Trials of obeticholic acid for non-alcoholic steatohepatitis

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1523033> since 2015-08-24T10:56:21Z

Published version:

DOI:10.1016/S0140-6736(15)61198-9

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)



UNIVERSITÀ DEGLI STUDI DI TORINO

This Accepted Author Manuscript (AAM) is copyrighted and published by Elsevier. It is posted here by agreement between Elsevier and the University of Turin. Changes resulting from the publishing process - such as editing, corrections, structural formatting, and other quality control mechanisms - may not be reflected in this version of the text. The definitive version of the text was subsequently published in [*Lancet. 2015 Jul 4;386(9988):27. doi: 10.1016/S0140-6736(15)61198-9*].

You may download, copy and otherwise use the AAM for non-commercial purposes provided that your license is limited by the following restrictions:

- (1) You may use this AAM for non-commercial purposes only under the terms of the CC-BY-NC-ND license.
- (2) The integrity of the work and identification of the author, copyright owner, and publisher must be preserved in any copy.
- (3) You must attribute this AAM in the following format: Creative Commons BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/deed.en>), *doi: 10.1016/S0140-6736(15)61198-9*

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

RUNNING TITLE: OCA and NASH

Giovanni Musso¹M.D., Maurizio Cassader² Ph.D. Roberto Gambino² Ph.D.

¹*Gradenigo Hospital, Italy*

²*Department of Medical Sciences, University of Turin, Italy*

Corresponding author:

Giovanni Musso

Gradenigo Hospital

Corso Regina Margherita 8,

10132 Torino, Italy.

Phone: +39-11-3475944237

Fax: +39118151320

E-mail: giovanni_musso@yahoo.it

Word count: 399

KEY WORDS: NASH, OCA, FXR

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 β -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 treatment³. 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 than in non-diabetic individuals⁴, 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.

ACKNOWLEDGEMENTS

Author Contributions.

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.

Giovanni Musso has no present or past conflict of interest or financial relationship to disclose. No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Roberto Gambino has no present or past conflict of interest or financial relationship to disclose. No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Maurizio Cassader has no present or past conflict of interest or financial relationship to disclose. No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Funding source. This manuscript was written without any funding source, nor has any author received payment from any pharmaceutical company or other agency to write this article.

REFERENCES

- ¹ Neuschwander-Tetri B, Loomba R, Sanyal AJ, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial *The Lancet* in press, corrected proof, available online Nov 7th 2014 doi:10.1016/S01406736(14)61933-4
- ² Mudaliar S, Henry RR, Sanyal AJ, et al. Efficacy and safety of the farnesoid X receptor agonist obeticholic acid in patients with type 2 diabetes and nonalcoholic fatty liver disease. *Gastroenterology*. 2013;145: 574-82.
- ³ Musso G, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. *Diabetologia*. 2012;55: 885-904
- ⁴ Ma H, Patti ME. Bile acids, obesity, and the metabolic syndrome. *Best Pract Res Clin Gastroenterol*. 2014;28: 573-83