Currently treatment options for Non-Alcoholic Steatohepatitis (NASH), the aggressive form of non-alcoholic fatty liver disease (NAFLD) and one of the commonest causes of cirrhosis worldwide, are mainly limited to promotion of life style changes in diet and exercise habits as well as to control of comorbidities such as type 2 diabetes mellitus and dyslipidemia. With regard to pharmacotherapy, the armamentarium to treat NASH is rather limited and currently only vitamin E and pioglitazone are recommended in selected patients although their long-term benefit has not been demonstrated and some caution has been recommended due to potentially unwanted side-effects of these drugs. Indeed, several additional agents are in the therapeutic pipeline and are currently being tested in controlled trials as can be checked in open databases such as ClinicalTrials.gov (https://clinicaltrials.gov). The therapeutic targets being tackled are diverse and derive from recent basic and clinical research that had identified factors involved in NASH pathogenesis and progression. Among these factors are insulin resistance (IR), adipokine/cytokine imbalance, excessive oxidative stress, dysregulation of both lipid and carbohydrate metabolism and ongoing fibrogenesis. Most of the above mentioned factors are directly or indirectly regulated by the farnesoid X receptor (FXR), a nuclear hormone receptor regulated by bile acids (BAs), thus rendering the agonism of this receptor a potentially useful pharmacological target to treat NASH. This contention had previous support from pre-clinical studies and the recent publication of the FLINT study, a multicenter, randomized and placebo controlled trial examining the effects of obeticholic acid (OA), a synthetic FXR agonist, in patients with steatohepatitis opens windows of hope about counting with effective drugs for treating NASH.

Before getting into details on the trial itself, a word about the molecular pathways on which FXR agonists could exert potentially beneficial effects in NASH is in order.

In the last decade, BA have emerged as key metabolic modulators due to their ability to act as ligands of nuclear and membrane receptors. After the seminal reports demonstrating that FXR acts as an intracellular sensor for BA and that its deficiency determines important alterations in lipid and carbohydrate metabolism a wealth of information has accumulated regarding the critical role of FXR in a variety of cellular processes in different tissues mainly in the liver and intestine. As a transcription factor, when FXR is activated by a ligand (i.e. the natural bile acid chenodeoxycholic acid or the synthetic compound OA) heterodimerizes with a partner nuclear receptor, the retinoid X receptor, the retinoid X receptor α, and then translocates to the nucleus regulating the expression of multiple target genes. One of these genes is the short heterodimer partner, SHP that controls the expression of cholesterol 7α-hydroxylase (CYP7A1), the key enzyme in BA synthesis. Through this pathway, along with controlling BA import and export through the regulation of membrane transporters, FXR regulates intracellular BA levels, which is critical for preventing hepatocyte injury and death. Details of all additional target genes of FXR signaling is beyond the scope of this commentary and can be found elsewhere, but among those hepatic FXR targets that relevant to NASH pathophysiology the following deserve to be mentioned:

1. Sterol regulatory element-binding transcription factor 1 (SREBP1c) which controls novo lipogenesis, a process up-regulated in patients with NASH, is down-regulated by FXR.
2. Peroxisome proliferator-activated receptor (PPAR)-α that controls the cellular utilization of fatty acids is up-regulated by FXR.

3. Phosphoenolpyruvate carboxykinase (PEPCK) a key enzyme of gluconeogenesis that has been shown to be down-regulated by BA.

4. NF-κB a transcription factor that orchestrates inflammation which activity and signaling is reduced by FXR agonists.

In addition, at the level of ileal enterocytes, FXR controls the secretion from the intestine of an important enterokine, Fibroblast Growth Factor-19 (FGF-19, FGF-15 in mice) that controls hepatic BA synthesis and seems to be important metabolic actions. Finally, it must be also mentioned that FXR agonism have shown to be anti-fibrogenic in some preclinical models. Thus, the critical roles of FXR in BA synthesis as well as in liver energy homeostasis and inflammation and possibly fibrosis led to the active search of agents to pharmacologically modulate these pathways, with OA being the first-in-class FXR agonist to be tested in clinical trials.

The FLINT (FXR Ligand Obeticholic Acid in NASH Treatment) trial was a phase 2b randomized controlled trial conducted in several medical centers in the USA as part of the collaborative efforts made by the NASH Clinical Research Network (NASH CRN), which is an NIH-sponsored network devoted to conduct studies focused in the etiology, contributing factors, natural history, complications, and therapy of NASH. The study involved 283 non-cirrhotic biopsy-proven NASH patients allocated to receive either 25 mg OA daily (n = 141) or placebo (n = 142) for 72 weeks. The study was carefully designed and the complete protocol is available online (https://jhuccs1.us/nash/open/protocols/FLINT/FLINTProtocol_May2013.pdf). The primary outcome was histological improvement of NASH assessed by the change in NAFLD activity score (NAS) in 2-points. Additional outcomes considered were serum levels of liver enzymes, hepatic lipid content assessed by MRI, insulin resistance and serum lipids. In the primary intention-to-treat analysis, 45% (50 of 110) of patients in the OA group showed improved liver histology compared with 21% (23 of 109) in the placebo group (P = 0.002). In addition, patients receiving OA showed statistically significant improvements in individual features of inflammation and fibrosis. Although these histologic improvements configured a trend toward NASH resolution, the proportion of patients achieving this endpoint did not differ between those receiving placebo and those receiving OA. In addition to histological findings significant reductions in serum liver enzymes levels were found in the treatment group as well as a modest (-2 kg) weight loss and a small decrease in systolic blood pressure. In addition, somewhat unexpectedly OA treatment was associated to increased serum levels of insulin and a higher HOMA index suggesting a higher IR in OA treated subjects. Finally, patients who received OA showed significant changes in serum lipids consisting in an increase of 6 mg/dL in total serum cholesterol levels, an increase of 8.5 mg/dL in LDL cholesterol and a modest (0.8 mg/dL) but significant reduction in HDL cholesterol (p = 0.01). Medical management for dyslipidemia was instituted during although dose information was not reported.

OA was generally well tolerated. The only adverse event occurring more frequently in patients receiving OA was pruritus which was also observed in and earlier trial in patients with primary biliary cirrhosis. However, in the FLINT trial pruritus was easily managed and rarely associated to the need of drug discontinuation.

Results of the FLINT trial are indeed promising since significant improvement in liver histology is considered a “hard endpoint” in the field of NASH. Fibrosis improvement (35% of OA-treated patients regressed by one stage or more vs. 19 in the placebo group) OA treated patients is particularly encouraging, since this has not been shown with other compounds tested in controlled trials such as vitamin E and pioglitazone.

Of note, liver fibrosis is closely related to both overall and liver-related mortality in patients with NAFLD. However, it remains unproven if this change in the fibrosis degree really translates into beneficial effects in terms of survival. The same stands true for the observed decrease in NAS score. Moreover, the significance of the observed changes in the serum lipid profile on cardiovascular outcomes need to be explored in more detail as well as the therapeutic strategy to treat dyslipidemia in patients receiving OA as safety concerns could arise from interaction between this agent and lipid-lowering therapies.

Where do we stand after this study with regard to NASH therapy? Although the FLINT trial represent a step forward in the field, we now need, as it is usual in the arena of pharmacotherapy, further and larger studies in order to confirm the current findings refine some of the observations to prove their clinical relevance and establish the long-term safety of OA in NASH.
In the age of better hepatitis C virus therapy and the rapid rise in the prevalence of NASH, novel targeted approaches for the latter are being actively developed and tested by pharmaceutical companies. In fact, as mentioned above, a number of other agents (the PPAR α/δ agonist GFT-505, the fatty acid-bile acid conjugates arachamil, the inhibitor of lysyl oxidase-like-2 simtuzumab and the chemokine receptors antagonists cenicriviroc among others) are currently under study in phase 2 or 3 trials. Hopefully, some of these agents will undergo a successful transition from the bench into the clinic and we will count with safe and effective agents to treat NASH patients in the near future.

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CONFLICT OF INTEREST

The authors declare not to have conflict of interests related to this scientific work.

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