Commentary

# Is it necessary to target lipid metabolism in different organs for effective treatment of NASH?—the results of the Pan-PPAR Lanifibranor trial

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*Comment on:* Francque SM, Bedossa P, Ratziu V, *et al.* A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH. N Engl J Med 2021;385:1547-58.

Submitted Dec 29, 2021. Accepted for publication Feb 15, 2022.
doi: 10.21037/hbsn-21-569
**View this article at:** https://dx.doi.org/10.21037/hbsn-21-569

Nonalcoholic fatty liver disease (NAFLD) is a metabolic disease associated not only to alteration in lipid metabolism but also to insulin resistance and impaired glucose metabolism that can progress to more severe forms, like nonalcoholic steatohepatitis (NASH). Moreover, NAFLD and NASH are highly prevalent in patients with type 2 diabetes.

Subjects with NAFLD/NASH are insulin resistant, particularly in adipose tissue where insulin does not limit lipolysis (1). This results in high levels of circulating non-esterified fatty acids (NEFAs) being absorbed and esterified into triglycerides (TG) by the liver, aided by high insulin concentrations.

There is no approved pharmacological treatment for NAFLD/NASH, although several drugs are currently in the pipeline (2). It is now clear that the most effective drugs for noncirrhotic NASH are those that not only ameliorate steatosis and inflammation, but also have major metabolic effects, in particular on lipid metabolism. Among the drugs that target lipid metabolism are the peroxisome proliferator-activated receptor (PPAR) agonists which have been shown to be effective for the treatment of NASH and have important metabolic effects (2).

PPARs are transcription factors of the nuclear receptor family. Three PPAR isotypes have been identified, PPAR-α, PPAR-γ and PPAR-β/δ, differentially expressed in tissues and cell types with different functions (*Figure 1*). They are differently expressed in the organs and impact different pathways and mechanisms involved in NASH and fibrosis progression (*Figure 1*). PPAR-α is highly expressed in liver where it controls lipid transport and metabolism, activates mitochondrial function, promotes peroxisomal fatty acid β-oxidation and ketogenesis. Subjects with NAFLD have lower hepatic expression of PPAR-α that associates with the severity of liver fibrosis (3) and reduced hepatic unsaturated fatty acids that are among the main activators of PPAR-α (4). PPAR-γ is highly enriched in adipocytes and macrophages much less in liver, although its hepatic expression was found increased in subjects with obesity (5), where it promotes lipogenesis, fatty acid re-esterification and TG accumulation. PPAR-δ is ubiquitously expressed with action on both glucose and lipid metabolism, including fatty acid oxidation mainly in extrahepatic organs. Thus, several PPAR agonists have been tested in patients with NAFLD/NASH (as single PPAR or multiple PPAR agonists) (2).

Francque *et al.* have recently published the results of the Phase 2b trial with the pan-PPAR (PPAR-α/γ/δ) agonist Lanifibranor [Phase 2b Study in NASH to Assess IVA337 (NATIVE), NCT03008070] (6). The study included 247 patients that were randomly assigned to receive 1,200 mg/day (n=83) or 800 mg/day (n=83) of Lanifibranor or placebo (n=81) for 24 weeks. The primary endpoint was the decrease of ≥2 points of NASH activity (SAF score that combines hepatocellular inflammation and ballooning) and as secondary endpoints NASH resolution without worsening and with improvement of fibrosis. The primary endpoint was achieved in approximately half of patients treated with Lanifibranor (55% and 48% if treated with 1,200 and

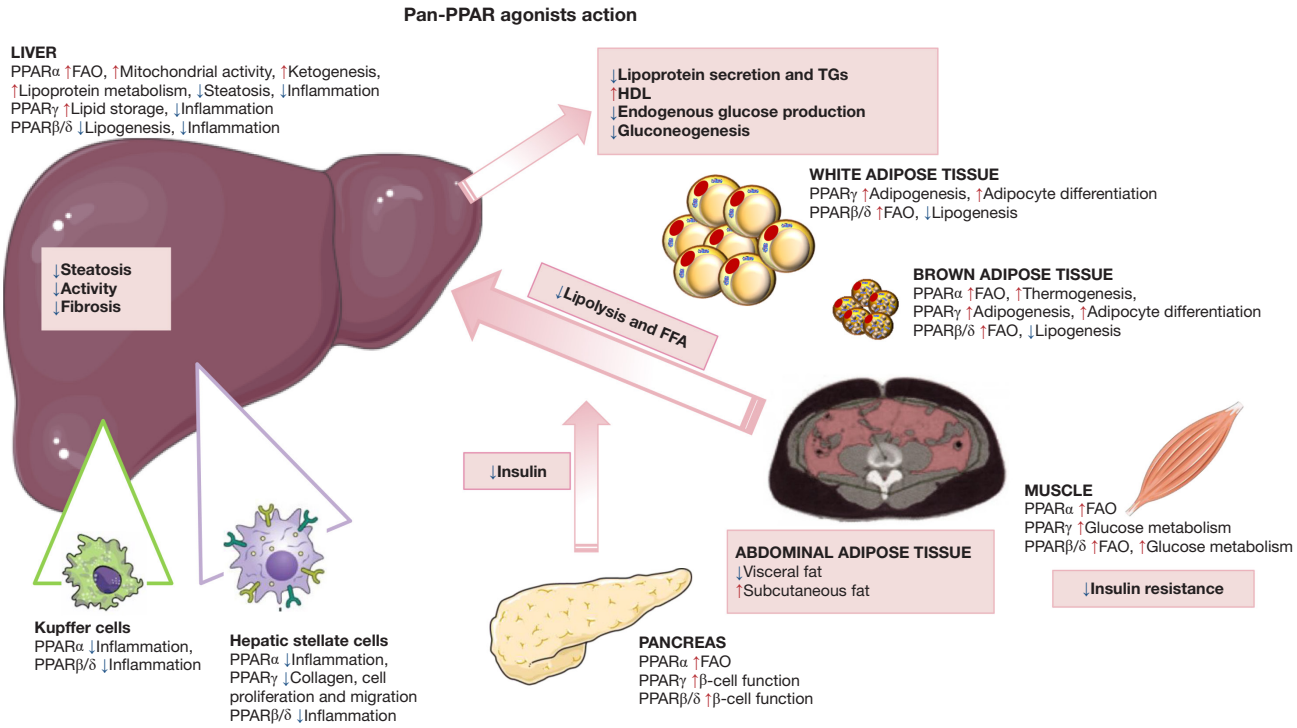


**Figure 1** The complex role of PPARs in liver and peripheral organs, and their involvement in NASH and liver fibrosis. Three PPAR isotypes have been identified, PPARα, PPARγ and PPARβ/δ, differentially expressed in tissues and cell types with different functions (red and blue). Effects of treatment with PPAR agonists (single PPAR or multiple PPAR activation) are shown (in the pink boxes). In NASH, PPARs agonists improve lipid metabolism by modulating lipid fluxes (lipolysis, lipogenesis and lipoprotein secretion), regulating the transport and oxidation of fatty acid. They also reduce insulin resistance by decreasing hepatic glucose production and increasing peripheral glucose uptake. In addition, they reduce inflammation in the liver and the whole body. Taken together, the three PPAR isotypes improve NASH and fibrosis by targeting the multiple pathways involved in the development of NASH and its progression. FAO, fatty acid oxidation; HDL, high density lipoproteins; PPAR, peroxisome proliferator activated receptor; TG, triglyceride; FFA, free fatty acid.

800 mg/day respectively) compared with one third of patients treated with placebo (33%; P=0.007 and P=0.07 *vs.* 1,200 and 800 mg/day respectively).

The composite end point, resolution of NASH and improvement in fibrosis stage ≥1 point, unique to this trial, occurred in 35% and 25% of subjects in the 1,200 and 800 mg Lanifibranor groups, respectively, *vs.* 9% in the placebo group. Furthermore, Lanifibranor reduced glycated hemoglobin (HbA1c) by 0.4% in the 1,200 mg Lanifibranor group (from 6.1% to 5.7%, *vs.* +0.1% in placebo; by 0.7% in patients with diabetes), triglyceride, insulin, apolipoprotein A1 and increased HDL cholesterol and adiponectin.

The mechanisms that explain the improvement in NASH after activation of PPARs receptors include the reduction in lipolysis and fatty acids to the liver in combination with lower insulin levels, due to the amelioration of insulin resistance in all tissues, and higher fatty acid oxidation (*Figure 1*). Moreover, Lanifibranor improved the lipoprotein profile with the potential of improving cardiovascular outcomes, which are still the leading cause of death in patients with non-cirrhotic NASH.

These effects are mediated mainly by PPAR-γ activation. While all PPARs ameliorate inflammation in both the liver and systemically, only PPAR-γ plays a key role in preventing the activation of hepatic stellate cells (HSC), a key event in fibrogenesis, and PPAR-γ activation promotes the inactivation of HSCs and regression of liver fibrosis (7). In this regard, Lanifibranor was shown to improve fibrosis, HSC phenotype and portal pressure in a preclinical model of advanced chronic liver disease (ACLD) and in liver cells of patients with ACLD (8). Weight gain was around 3kg in the highest dose of Lanifibranor compared with 5 kg previously observed with Pioglitazone probably due to the activation of PPAR-δ that increases energy expenditure and

fatty acid oxidation. However, PPAR-γ activation increases mainly the subcutaneous adipose tissue while reducing visceral fat, which is associated with the improvement in liver histology probably mediated by the reduction of visceral adipokines and NEFAs to the liver (9).

The activation of PPAR-γ appears to be crucial for the resolution of NASH as confirmed by several trials that have used Pioglitazone to improve NASH (2). Treatment with PPAR-γ agonists improve both lipid and glucose metabolism (2). Among the PPAR-γ agonists, only Pioglitazone, not Rosiglitazone, improved NASH, probably because Pioglitazone also moderately activates PPAR-α. However, it would be interesting to assess whether Pioglitazone treatment meets the main endpoint in current pharmacological studies, which is resolution of NASH without worsening fibrosis. The effects on NAFLD of PPAR-α agonists, like fibrates, were mild and controversial despite beneficial effects in preclinical studies with no effects of glucose metabolism (2,3). The phase 3 RESOLVE-IT trial with Elafibranor, a dual PPAR-α/δ agonist in development for the treatment of NASH (NCT02704403), was terminated after the detailed review of the full interim efficacy dataset failed to show differences with placebo in the pre-defined primary endpoint (NASH resolution without worsening of fibrosis).

The pan-PPAR agonist Lanifibranor at the highest dose offers another opportunity to improve histologic outcomes in patients with noncirrhotic, highly active NASH. Activating all three PPAR isotypes combines their effects on multiple organs ameliorating lipid and glucose metabolism as well as inflammation and fibrosis. The next step is the phase 3 trial which will hopefully confirm the data in a larger population.

## Acknowledgments

*Funding:* AG received the financial support from the European Union's Horizon 2020 Research and Innovation Programme under the Marie Skłodowska-Curie Grant Agreement No. 722619 (FOIE GRAS project) and Grant Agreement No. 734719 (mtFOIE GRAS project) and from the European Union's Horizon 2020 Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No. 875534 (SOPHIA project).

## Footnote

*Provenance and Peer Review:* This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

*Conflicts of Interest:* The author has completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-569/coif). The author has no conflicts of interest to declare.

*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



## References

1. Guerra S, Mocciaro G, Gastaldelli A. Adipose tissue insulin resistance and lipidome alterations as the characterizing factors of non-alcoholic steatohepatitis. Eur J Clin Invest 2022;52:e13695.
2. Gastaldelli A, Stefan N, Häring HU. Liver-targeting drugs and their effect on blood glucose and hepatic lipids. Diabetologia 2021;64:1461-79.
3. Parlati L, Régnier M, Guillou H, et al. New targets for NAFLD. JHEP Rep 2021;3:100346.
4. Forman BM, Chen J, Evans RM. Hypolipidemic drugs, polyunsaturated fatty acids, and eicosanoids are ligands for peroxisome proliferator-activated receptors alpha and delta. Proc Natl Acad Sci U S A 1997;94:4312-7.
5. Pettinelli P, Videla LA. Up-regulation of PPAR-gamma mRNA expression in the liver of obese patients: an additional reinforcing lipogenic mechanism to SREBP-1c induction. J Clin Endocrinol Metab 2011;96:1424-30.
6. Francque SM, Bedossa P, Ratziu V, et al. A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH. N Engl J Med 2021;385:1547-58.
7. Liu X, Xu J, Rosenthal S, et al. Identification of Lineage-Specific Transcription Factors That Prevent Activation of Hepatic Stellate Cells and Promote Fibrosis Resolution.

 

Gastroenterology 2020;158:1728-44.e14.
8. Boyer-Diaz Z, Aristu-Zabalza P, Andrés-Rozas M, et al. Pan-PPAR agonist lanifibranor improves portal hypertension and hepatic fibrosis in experimental advanced chronic liver disease. J Hepatol 2021;74:1188-99.
9. Gastaldelli A, Sabatini S, Carli F, et al. PPAR-γ-induced changes in visceral fat and adiponectin levels are associated with improvement of steatohepatitis in patients with NASH. Liver Int 2021;41:2659-70.

**Cite this article as:** Gastaldelli A. Is it necessary to target lipid metabolism in different organs for effective treatment of NASH?—the results of the Pan-PPAR Lanifibranor trial. HepatoBiliary Surg Nutr 2022;11(3):481-484. doi: 10.21037/hbsn-21-569