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Saroglitazar for the Treatment of NASH: The Peroxisome Proliferator-Activated Receptor Story Goes On!

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Despite intensive research, no drug to date has been approved for the management of NAFLD, and many clinical trials have failed, including some recent large phase 3 trials. This has in part to do with the complex disease pathophysiology, which is only partially unraveled.[1] Furthermore, the disease is embedded in a set of metabolic drivers, creating an environment of metabolic and inflammatory stress. As a result, NAFLD is not an isolated liver disease, and treatment needs to take into account the extrahepatic drivers of disease progression, of which the adipose tissue dysfunction is a pivotal one.[2]

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that are key regulators of glucose and lipid homeostasis as well as inflammation and fibrogenesis.[3] This makes them interesting targets for pharmacotherapy. Three different PPAR isotypes (α, β/δ, γ) exist, and their expression and function differ according to the organ and cell type (Fig. 1). Drugs targeting PPARs have hence the potential to target both intrahepatic and extrahepatic sites, depending on their characteristics: PPAR drugs can substantially differ in target engagement, even if they belong to the same molecular class and/or target the same isotype. This is best documented for PPARα agonists, a phenomenon called selective PPAR modulators. This implies that every PPAR agonist needs to be evaluated individually on top of class effects.

In the current issue, Gawrieh et al. present the results of saroglitazar, a dual PPARα-γ agonist, on noninvasive markers of NAFLD disease severity after 16 weeks of treatment.[4] The concept of a dual, or even triple/pan, PPAR agonist is interesting, because tackling several mechanisms (metabolic/inflammatory/fibrogenic) at several sites (hepatic/extrahepatic) theoretically has the potential of resulting in superior efficacy compared with mono-agonists. Preclinical evidence supports this concept,[5] although clinical head-to-head comparisons are lacking and comparison across trials needs caution. Combination of targets might also, by allowing lower affinity for the individual isotypes and/or by counteracting side effects of single agonists, reduce side effects. Again, there are no head-to-head comparisons to prove these conceptual considerations, but comparison of the data of different compounds can provide some insights.

Beyond a substantial amount of preclinical data, hepatic PPARα expression has been shown to inversely correlate with disease severity and to improve on disease improvement.[6] PPARα mono-agonists have been poorly studied, but the PPARα-δ dual agonist elafibranor showed some favorable effects in phase 2.[7] This was not confirmed in phase 3, but these data are not fully released yet and merit an in-depth analysis. PPARγ

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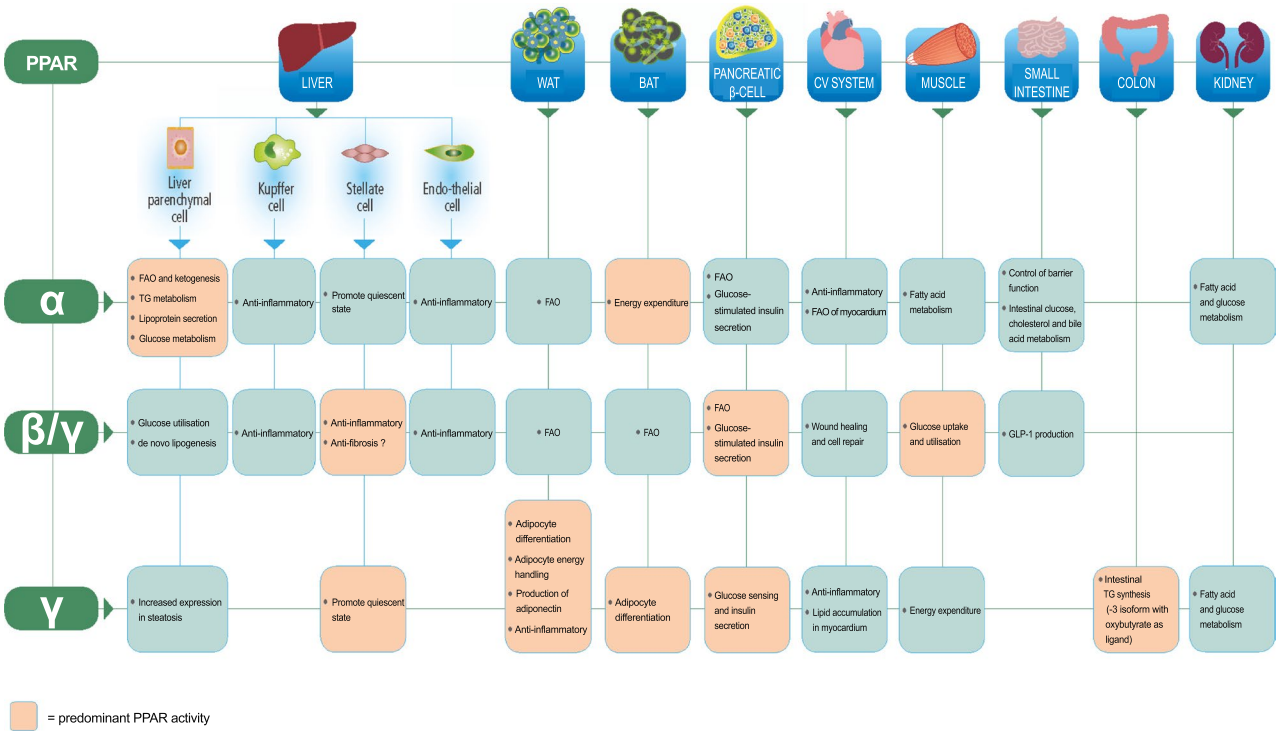

FIG. 1. The complex role of PPARs in NASH and fibrosis development. The three isotypes are differentially expressed in the different tissues and cell types. The main sites of expression and the main functions are depicted. In NASH, PPARα could improve lipid metabolism by controlling lipid flux and regulating fatty acid transport as well as β-oxidation. It also reduces inflammation through its action on hepatocytes as well as reducing splanchnic inflammation and intestinal permeability. PPARα is also involved in decreasing portal pressure in the context of cirrhosis. PPARβ/δ is involved in glucose and lipoprotein metabolism and reduces insulin resistance in skeletal muscle. PPARβ/δ inhibits inflammatory macrophage phenotypes and favors the alternatively activated phenotype. PPARγ regulates insulin sensitivity within the adipose tissue and is a master regulator of HSC fate. PPARγ prevents HSC activation, which is a key event in fibrogenesis. Moreover, in the context of cirrhosis, PPARγ reduces portal pressure, splanchnic inflammation, angiogenesis, and portosystemic shunts. By acting within the different cells and organs, all together, the three PPAR isotypes impact different pathways and mechanisms involved in NASH and fibrosis progression. FAO, fatty acid oxidation; GLP-1, glucagon-like peptide 1; TG, triglyceride.

agonists, with the thiazolidinedione pioglitazone being still available, have been shown to be beneficial in terms of NASH resolution, with overall a potential signal on fibrosis improvement (but not 1 stage improvement[8]). The combined PPARα-γ agonism hence has the potential of being superior to both individual components.

The current study does not allow judging about this potential superiority, as only 16 weeks of treatment were evaluated and efficacy was only assessed based on noninvasive testing. Also, biopsy was not required for inclusion, making it impossible to have an idea about the histological disease severity at baseline. Nevertheless, the data are interesting because an extended set of noninvasive markers were assessed. There is still very little understanding of how evolution in noninvasive tests (NITs) over time correlates with evolution in histology, both in natural history and in the context of an intervention. The biopsy is challenged because of its sampling variability, but NITs are also variable, including alanine aminotransferase (ALT), which is the primary endpoint of this study. With a set of NITs, including laboratory-based and imaging tests, all pointing toward an improvement, one can feel more comfortable in concluding that the liver condition is truly improving.

As mentioned, the short duration of the study hampers comparison with other PPAR drugs, if one wishes to compare across trials, with all pitfalls of such a comparison. The elafibranor treatment period was 12 months in phase 2[7] and 18 in phase 3, most of the pioglitazone trials were of 18 months to 2 years or longer,[8] and the lanifibranor phase 2 trial was 24 weeks of treatment.[9]

The concordance in changes over time in NITs (beyond reporting the changes of NITs individually according to treatment arms) is rarely reported. In this study, using the ALT response as primary differentiator, the potential differences in effects on lipid species were analyzed, showing more pronounced improvements in lipid composition in ALT responders versus nonresponders. This is a small example of what could be the way forward in studying NITs as predictors of response, namely linking them with a specific endpoint of interest instead of an overall treatment effect without a link to the predefined response criterion.

Another important potential benefit of PPAR drugs and a potential future differentiator on the market is the impact on cardiovascular risk factors, with a potential of improving cardiovascular outcomes, which are still the main cause of death in patients with noncirrhotic NASH. Saroglitazar, as could be expected from its mode of action, substantially improved lipid profile, for which the drug has also already been approved for many years in India. The impact on glycemic control is less convincing. A more in-depth analysis of the lipid particle size and composition, including lipidomic profiling, shows an improvement on saroglitazar in multiple proatherogenic molecules beyond classical risk factors, which is an argument in favor of a translation on the long run in a reduction of cardiac events.

Finally, as for any drug, the safety profile needs to be carefully examined. Weight gain is known to occur with drugs having a PPARγ activity. Usually, this is considered a "side effect" because patients are encouraged to lose weight and weight loss is known to associate with histological improvement. Gawrieh et al. show that saroglitazar increases adiponectin levels,[4] which is also known to occur with pioglitazone and is a sign of improvement in adipose tissue function.[2] For pioglitazone, it has been shown that this also corresponds to a shift from visceral to more metabolically healthy subcutaneous fat and an improvement in the metabolic-inflammatory environment, despite the net weight gain. Also, although fluid retention and heart failure can occur in patients with pre-existing cardiac dysfunction, cardiovascular prognosis improves with pioglitazone.[10] Because the current study is a short-term study, it is difficult to judge whether the small weight gain observed with saroglitazar compares favorably with pioglitazone, but the safety data appear to be reassuring and allow for further study of the compound.

In conclusion, this study shows the positive impact of the dual PPARα-γ agonist saroglitazar on noninvasive markers of NAFLD severity and hence the potential of PPAR agonist drugs as crucial compounds in the anti-NASH armamentarium. Its superiority over mono-agonists, both in terms of efficacy as well as safety, requires a much larger study of longer duration and with an extended set of efficacy (including histology) and safety (including body composition and cardiac function) parameters.

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