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Entering the GOLDEN Age for Therapies in NASH


The burden from nonalcoholic fatty liver disease (NAFLD) is increasing rapidly,1 as reflected in referrals to hospital specialists as well as consideration for liver transplantation,2 and yet there are no licensed therapies for this condition. In this edition of Gastroenterology, Ratziu et al3 report on the efficacy of GFT505, a dual peroxisome proliferator-activated receptor (PPAR)-α and -δ agonist, in a well-conducted phase II study in patients with nonalcoholic steatohepatitis (NASH). GFT505 has been shown previously to have potent activity in preclinical models of NAFLD, reducing hepatic lipid accumulation as well as decreasing expression of proinflammatory and profibrotic genes.4 The PPAR-α receptor is highly expressed in rodent hepatocytes where, after agonism, it prevents accumulation of triglycerides through an induction of genes involved in mitochondrial and peroxisomal fatty acid β-oxidation.5 However, GFT505 was still able to decrease steatosis and liver inflammation in a PPARα knockout mouse fed a Western diet and with a more pronounced antifibrotic effect.4 The latter suggests that PPAR-δ agonism may mediate much of the antifibrotic effect of GFT505, which is supported by the high levels of PPAR-δ expression in hepatic stellate cells, which are known to increase further during hepatic stellate cell activation and liver fibrosis.6 The effects of PPAR-δ agonism on steatosis and inflammation can also be explained by its ability to stimulate hepatic fatty acid β-oxidation and its induction of macrophages to adopt an alternative antiinflammatory M2 phenotype.7 Early phase clinical studies supported the efficacy of GFT505 as demonstrated by an improvement in liver biochemistry when administered to patients with type 2 diabetes. These studies also provided important insights on the mechanism of action of GFT505, demonstrating improvements in peripheral and hepatic insulin sensitivity with associated decreases in plasma free fatty acid levels.8
<table>
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<th>Trial</th>
<th>Duration of Treatment</th>
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<th>Result</th>
<th>Definition of Resolution of NASH</th>
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<tr>
<td>PIVENS13</td>
<td>96 weeks</td>
<td>↓ by ≥1 point in ballooning AND no ↑ in fibrosis AND either a ↓ in NAS to ≤3 or a ↓ in NAS by ≥2 points with ≥1 point ↓ in either lobular inflammation or steatosis.</td>
<td>Placebo 19% vitamin E 43% (P = .001)</td>
<td>Pattern recognition: resolution of definitive NASH</td>
<td>Placebo 21% vitamin E 36% (NS)</td>
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<td></td>
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<td></td>
<td>Pioglitazone 34% (NS)</td>
<td></td>
<td>Pioglitazone 47% (P = .001)</td>
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<td>FLINT14</td>
<td>72 weeks</td>
<td>↓ by ≥2 points in NAS AND no ↑ in fibrosis</td>
<td>Placebo 21% Obeticholic acid 45% (P = .001)</td>
<td>Pattern recognition: resolution defined as either not NAFLD, or NAFLD but not NASH</td>
<td>Placebo 13% Obeticholic acid 22% (P = .08)</td>
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<td>EPA-E19</td>
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<td>Placebo 40% EPA-E 1800 mg 37% (NS)</td>
<td>Not included</td>
<td>Not included</td>
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<td>EPA-E 2700 mg 35.9% (NS)</td>
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<td>LEAN10</td>
<td>48 weeks</td>
<td>Resolution of NASH without worsening of fibrosis</td>
<td>Placebo 9% Liraglutide 39% (P = .02)</td>
<td>Defined as disappearance of hepatocyte ballooning.</td>
<td>Was the primary endpoint</td>
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<tr>
<td>GOLDEN3</td>
<td>52 weeks</td>
<td>Reduction to zero in any one of ballooning, lobular inflammation or steatosis with no worsening in fibrosis</td>
<td>Placebo 17% Elafibranor 80 mg 23%</td>
<td>Resolution defined by a score of B0 and lobular inflammation score of 0/1 without worsening of fibrosis</td>
<td>Placebo 12% Elafibranor 80 mg 13% (P = .045)</td>
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<tr>
<td></td>
<td></td>
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<td>Elafibranor 120 mg 21%</td>
<td></td>
<td>Elafibranor 120 mg 19% (P = .045)</td>
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<tr>
<td>CENICRIVIROC</td>
<td>104 weeks⁹</td>
<td>↓ in NAS by ≥2 points with contribution from more than one domain AND no ↑ in fibrosis</td>
<td>In progress</td>
<td>Pattern recognition: resolution of NASH without worsening of fibrosis</td>
<td>In progress</td>
</tr>
</tbody>
</table>

NAFLD, nonalcoholic fatty liver disease; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis; NS, not significant.

⁹Worsening in fibrosis was defined by an increase in 1 stage of fibrosis as per the Kleiner fibrosis classification.

This did not include any stipulation about absence of worsening in fibrosis.

³Worsening in fibrosis defined as either progression to stage 3 or stage 4 (if stage 3 at baseline) in the Kleiner fibrosis classification.

This represented a post hoc analysis of a modified definition of the primary endpoint.

Primary endpoint assessed at 52 weeks.
To assess more directly efficacy in NASH, Ratziu et al randomized 274 noncirrhotic patients with biopsy-proven NASH to either oral elafibranor (GFT505) 80 or 120 mg daily or to placebo for 52 weeks. The study did not meet its predefined primary endpoint, which was reduction of any of the components of the NAFLD Activity Score (NAS) to zero without worsening in fibrosis (progression to stage 3 or 4). However, post hoc analyses of patients with higher baseline NAS (≥4) did demonstrate superiority of the 120 mg elafibranor dose versus placebo (20% vs 11%; P = .018). Also, in response to changing recommendations for the assessment of efficacy in NASH trials, the investigators included a further post hoc analysis after completion of the study to assess the number of patients clearing NASH as defined by disappearance of ballooning together with either disappearance of lobular inflammation or the persistence of mild lobular inflammation (score of 0 or 1). As before, this had to be without worsening in liver fibrosis, although this was now defined as progression by ≥1 stage. In this latter analysis, a greater proportion of patients receiving 120 mg elafibranor met this secondary post hoc endpoint compared with those on the placebo (19% vs 12%; P = .045), with the difference being more pronounced for patients with a higher baseline NAS (≥4; 19% vs 9%; P = .013). In keeping with previous phase II studies, more than one-half of the patients in this study (51%) had F0/F1 fibrosis, raising questions about the response rate in patients with more advanced liver fibrosis, which are now becoming the focus of phase III registration trials. Notably, the efficacy of elafibranor 120 mg in patients with NAS ≥4 and F1-3 fibrosis (22% resolution vs 13%; P = .026) was also seen in patients with NAS ≥4 and F2-3 fibrosis (15% resolution vs 9% in placebo; P = .002), although in keeping with an earlier study, which suggested lower absolute response in those with advanced fibrosis.10

Primary endpoints in NASH have evolved over the past few years and have been helped by consensus guidelines such that there is now acceptance that resolution of NASH without any worsening in liver fibrosis is a standard phase 2b endpoint.11 The definition of resolution of NASH can take several forms ranging from a primarily NAS-based assessment to a more overarching gestalt assessment of the presence, or not, of NASH. Thus, despite the laudable convergence toward an accepted phase II primary endpoint, there remain challenges with the precise definition as it remains an inherently subjective assessment.12 Another strength of this study is the central reading of slides at inclusion and at the end of the study, which is necessary to decrease the impact of this subjective component on study outcome. Intuitively, an assessment by >1 pathologist would further increase confidence of any observed outcome although there are challenges in either colocating expert pathologists or transferring slides across the globe. In that regard, the use of digital photographs of sections, if and when approved by regulatory authorities, would ease some of these logistical hurdles, allowing simultaneous evaluation and discussion.

Notwithstanding the caveats around assessing histological primary endpoints in NASH, it is helpful to review the collective experience to ascertain the current reported levels of efficacy. As indicated in Table 1, a wide range of primary endpoints have been utilized in the past few years rendering it difficult to make direct comparisons of efficacy across treatments. Moreover, although many of the studies have included resolution of NASH as a secondary endpoint, no studies have included the concomitant need for no worsening in liver fibrosis. Thus, rates of NASH resolution for pioglitazone (47%),13 vitamin E (36%),13 and ursodeoxycholic acid (22%),14 where no stipulation on change in fibrosis was made, are not directly comparable with those reported for liraglutide (39%)10 or elafibranor (19%),3 where fibrosis change was also taken into account. Ultimately, it is the progression to advanced fibrosis/cirrhosis that determines the development of clinical complications of liver disease, and it remains unclear what level of impact on hepatic inflammation/NASH is required to prevent this.

Notably, the focus on NASH reflects the perception that it epitomizes the injurious process, which is at the heart of progressive disease in patients with NAFLD, and yet recent studies have presented data suggesting that clinical outcomes are predicted by the level of fibrosis rather than the presence of NASH.15,16 It is, of course, possible that these studies are potentially confounded by their retrospective nature, or that they fail to capture the dynamic nature of the presence/absence of NASH histologically, although progress in science does require consideration of challenges to accepted dogma. This uncertainty is perhaps reflected in consensus documents with input from regulatory authorities that require hard clinical endpoints or non-progression to cirrhosis for full approval of agents in NASH.11

Given the significant cardiovascular morbidity and mortality found in patients with NAFLD,17 it is important to consider the impact of any therapeutic agent on these outcomes. Elafibranor improved lipid parameters (high- and low-density lipoprotein cholesterol and triglycerides), glycemic control as well as systemic inflammatory markers such as highly sensitive C-reactive protein. Notably, there were no cardiovascular events or deaths with elafibranor, which is particularly encouraging as other studies, with similar age patients, have suggested cardiovascular event rates on placebo ranging from 12 in 8313 and 9 in 142.14 The decrease in renal function in 7 patients treated with elafibranor is a potential concern given the known association of chronic kidney disease with NASH17 and this will need to be monitored in longer term studies.

In conclusion, this study adds another therapeutic dimension for patients with NASH, and we await the outcome of pivotal phase III studies to determine its ultimate role. It is an exciting time for therapies in NASH, and although success in many other conditions has come from combinatorial therapies, most studies in NASH have examined just a single agent. As synergistic effects cannot necessarily be predicted from monotherapy studies, perhaps now is the time to take heed of previous advice10 and make the leap and undertake combination studies.
References


