MRI-PDFF Response (MGL-3196 and Placebo treated) Predicts Reductions in Ballooning and Inflammation Components in NAS and NASH Resolution in a 36-Week Phase 2 Serial Liver Biopsy Study

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INTRODUCTION

MGL-3196 is a liver-directed, orally active, highly selective THR-β agonist which may reduce NASH by increasing hepatic fat metabolism and normalizing liver function (Fig 1). In a 12-wk interim and 36-wk final analysis of the serial liver biopsy study, MGL-3196 treated patients had reduced liver fat on MRI-PDFF compared with Placebo (pbo) patients and more MGL-3196 (60%) treated than pbo (18%) patients showed at least 30% reduction in hepatic fat (PDF response) (p<0.0001). NASH resolution on liver biopsy at 36 Weeks was observed in 39% of MGL-3196 patients who were MRI-PDFF responders at Wk 12 (P<0.001).1 We assessed whether response and magnitude of response PDF in Week 12 in pbo or MGL-3196 patients predicted ALT improvement and histologic response on liver biopsy at Week 36.

METHODS

MGL-3196-05 (NCT02912260) was a 36-wk multicenter, randomized, double-blind, pbo-controlled Serial MRI-PDFF, paired liver biopsy study in adults with biopsy-confirmed NASH (NAS≥4, F1-F3) and hepatic fat fraction ≥20%, assessed by MRI-PDFF (Fig 2, Table 1). At 36 weeks 107 paired liver biopsies, 73 drug-treated, 34 pbo were assessed (Fig 3). NAS component, correlation and responder analyses were conducted to examine the predictive power of MRI-PDFF response on histologic response of NAS components and ALD reduction in pbo and MGL-3196 patients.

RESULTS

In MGL-3196 patients, week 12 MRI-PDFF response (≥30% fat reduction) versus non-response predicted NASH resolution at Week 36 (p<0.001. Fig 4-5A, B). MGL-3196 PDF and/or steatosis responders compared with MGL-3196 non-responders were more likely to show a reduction in other components of NAS (ballooning, inflammation) (OR 8.86, p=0.0036). In MGL-3196 patients, Week 12 PDF response correlated with improvement in inflammation and ballooning components of NAS (0.42, Fig 6A), and reduction in NAS (0.42) Steatosis grade change underpredicted the MRI-PDFF response (Fig 6B). Particularly in patients with Grade 1 steatosis at baseline, pbo patients with ≥5% weight loss were likely PDF responders (71%, p=0.007). In pbo patients PDF response correlated with weight loss (0.58), which predicted inflammation and ballooning responses (Fig 7. 0.58). In pbo patients with <3% weight loss, a 1 pt. ballooning reduction was unrelated to any benefit, and not associated with improvement in steatosis, inflammation, fibrosis or ALT (Fig 8). Steatosis was further assessed by Second Harmonic Generation q(steatosis), which provides a continuous variable steatosis score, correlated well with pathologist steatosis score (Fig 9A) and MRI-PDFF (Fig 9B), and in the absence of MRI-PDFF assessment, provides a potential opportunity to provide a more accurate assessment of hepatic steatosis and change in steatosis than the pathology steatosis score.

CONCLUSIONS

• In both MGL-3196 and placebo treated patients, MRI-PDFF response correlated with reduction in ballooning and inflammation scores on liver biopsy and was strongly associated with NASH resolution.
• In pbo, but not MGL-3196 patients, most of the response was driven by weight loss.
• These data support the contention that reduction of hepatic fat is a critical component of NASH improvement and resolution.

DISCLOSURES

1Hepatology Nov 2018. AASLD Liver Meeting 2018. In a Placebo Controlled 36 Week Phase 2 Trial: Treatment with MGL-3196 Compared to Placebo Results in Significant Reductions in Hepatic Fat (MRI-PDFF), Liver Enzymes, Fibrosis Biomarkers, Atherogenic Lipids, and Improvement in NASH on Serial Liver Biopsy.

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