trial (i.e. early sphincterotomy may reduce disease severity in predicted severe acute necrotizing pancreatitis), the use of composite measure at 6 months is acceptable as it provides a complete assessment of severity during the entire course of acute pancreatitis.

The use of elevated alanine transaminase as the sole criterion to diagnose biliary pancreatitis in a considerable number of patients is also of concern. Previous studies included these criteria along with the presence of other evidence of gallstone disease including either elevated serum bilirubin or alkaline phosphatase when imaging failed to show evidence of gallstone/sludge.[7,8] Further, patients in the ERCP group had higher SIRS scores and C-reactive protein (CRP) at admission. These baseline differences could have masked the possible benefit of ERCP as sicker patients were included in the intervention arm, which might impact the results. This is especially so because in a substantial number of patients (19%) in the ERCP group, the procedure could not be done. The reason for technical failure was large periampullary diverticulum in 3 patients and complications of pancreatitis including periampullary oedema and respiratory failure in 7 patients. Eventually, in the ERCP arm, there was imbalance for these two reasons: failure to complete the procedure and higher SIRS rates that could have impacted the primary outcome. In such a situation, a per-protocol analysis should also have been done. The authors had committed this in the statistical plan, but this analysis was not provided.

In view of these concerns, we believe that the final word on the role of early ERCP in acute pancreatitis has not yet been said. Future studies should address these concerns about patient selection and selection of appropriate outcome measures before the role of ERCP in this group of patients can be defined.

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Future pharmacotherapy for non-alcoholic steatohepatitis

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semaglutide in non-alcoholic steatohepatitis. *N Engl J Med* 2020;**384:**1113–24. doi: 10.1056/NEJMoa2028395.

SUMMARY

This was a 72-week, double-blind phase 2 randomized controlled trial involving patients with histologically proven non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score ≥4 and F1–F3 fibrosis. Three hundred and twenty patients with (62%) or without (38%) diabetes mellitus (DM) were randomized to receive daily subcutaneous injection of semaglutide at a dose of 0.1 mg (*n*=80), 0.2 mg (*n*=78) or 0.4 mg (*n*=82) or placebo (*n*=80 patients). The primary end-point of resolution of NASH without worsening of fibrosis was observed in a significantly higher proportion of those who received 0.4 mg of semaglutide (59%) compared to placebo (17%, p<0.001); the highest efficacy ever shown by any drug in resolution of NASH. However, there was no difference in the attainment of the secondary end-point of improvement in fibrosis by at least one stage without worsening of NASH between the semaglutide arm and placebo. Semaglutide was also associated with a dose-dependent reduction in body weight ranging from 5% to 13% in those who received 0.1 and 0.4 mg, respectively. In comparison, the average weight loss in the placebo arm was only 1%. Importantly, the decrease in body weight, which was observed in the initial 28–44 weeks of semaglutide therapy, was sustained over the remaining duration of the study. Overall, semaglutide was well tolerated. The most common adverse effects with semaglutide included gastrointestinal disturbances such as nausea, vomiting, anorexia, constipation and abdominal pain, which led to drug discontinuation in 4% of patients. However, overall drug discontinuation rates were comparable between semaglutide (7%) and placebo (5%). Although an increase in serum amylase and lipase was observed in those receiving semaglutide, there was no incidence of acute pancreatitis. Three patients developed malignancies during the study, all of whom were receiving semaglutide.

COMMENT

NAFLD refers to the excessive accumulation of fat in the liver in the absence of considerable alcohol intake or other alternate aetiologies.[1] Rapid adoption of urban lifestyles with sedentary habits and easy access to calorie-dense foods, together with the ongoing global epidemic of DM and obesity, have led to the emergence of NAFLD as a substantial public health problem. Indeed, almost a fourth of the world's population is afflicted by NAFLD.[2] In India, the prevalence of NAFLD has been reported to vary from 9% to 53%, with a higher prevalence in urban areas compared to rural areas.[3] An Indian position paper on NAFLD had estimated that there are more than 25 million Indians with NAFLD who are at risk of developing progressive liver disease.[4] NAFLD is a spectrum consisting of non-alcoholic fatty liver (NAFL) or simple steatosis, NASH, NASH with significant fibrosis, NASH-related cirrhosis and NASH-related hepatocellular carcinoma (HCC). NASH is more progressive than NAFL; the differentiation thus being important both from prognostic and treatment point of view. Recent data from India suggest that a considerable number of patients with NAFLD present with NASH and fibrosis and NASH is an important cause of cirrhosis and HCC.[5,6] In addition to being responsible for liver-related morbidity and mortality, NASH is associated with increased risk of atherosclerosis, cardiovascular disease, type 2 DM, chronic kidney disease and extrahepatic malignancies.[7,8]

Lifestyle interventions and control of metabolic risk factors remain the mainstay of treatment in NAFLD. Pharmacotherapy in NAFLD is usually reserved for patients with NASH or those with fibrosis. However, the pharmacotherapeutic options are limited for such patients; to the extent that not even a single drug is approved by the Food and Drug Administration in the United States for the treatment of NASH. Based on the clinical trials, most of the scientific societies do recommend the use of pioglitazone (peroxisome proliferator-activated receptor-gamma [PPAR-γ] receptor agonist) and vitamin E (antioxidant) in biopsy-proven patients with NASH.[1,4] Based on the real-world and histological data, the Drug Controller General of India has approved saroglitazar, a dual PPAR α/γ agonist for the treatment of patients with NASH with F1–3 fibrosis.[9] However, none of the three drugs have been shown to be effective in improving hepatic fibrosis and may even have limited efficacy for resolution of NASH. Moreover, the long-term safety of vitamin E and pioglitazone is also in question. Hence, new drugs are needed to treat patients with NASH.

The pathogenesis of NAFLD/NASH involves multiple pathways, and a large number of drugs targeting various pathways are being evaluated for the treatment of NASH and are in various phases of clinical trials.[10] Glucagon-like peptide-1 (GLP-1) receptor agonists are one such class of drugs being evaluated for the treatment of NASH. GLP-1 and gastric inhibitory peptide belongs to the category of hormones called the 'incretin' hormones that are produced by the intestinal mucosa in response to oral intake of nutrients that enhance glucose-stimulated insulin secretion and lower blood glucose levels. The therapeutic use of native GLP-1 is limited by its very short half-life and rapid degradation by dipeptidyl peptidase-4 (DPP-4). Several long-acting GLP-1 analogues that are resistant to degradation have been developed to have long GLP-1 insulinotropic activity. Available GLP-1 receptor agonists include dulaglutide, exenatide, liraglutide and semaglutide.

GLP-1 receptor agonists have been shown to decrease insulin resistance and reduce body weight.[11] Further, in patients with DM, they have been shown to improve cardiovascular outcomes, which are the most common cause of mortality in NAFLD.[12] Although the expression of GLP-1 receptors in the liver is debatable, GLP-1 receptor agonists have been shown to reduce hepatic lipotoxicity, endoplasmic reticulum stress and hepatic inflammation in patients with NASH, which may be partially attributed to weight loss and improvement in insulin resistance.[13] Because of the protective cardiovascular profile, improvement in insulin resistance and weight reduction, GLP-1 receptor agonists are attractive candidates for the treatment of NASH where metabolic syndrome and insulin resistance are central in the pathogenesis.

In an earlier phase 2 study (LEAN trial), liraglutide, another GLP-1 receptor agonist was shown to significantly improve resolution of NASH (39% *v* 9%) with decrease in progression of fibrosis as compared to placebo in a small number of patients.[14] However, semaglutide has certain pharmacokinetic advantages over liraglutide, which may make it more suitable for long-term treatment. Structurally, semaglutide resembles liraglutide with the notable exception of α-amino butyric acid instead of alanine in the second amino acid position. This makes semaglutide resistant to degradation by DPP-4. The fatty acid side chain in semaglutide is more tightly bound, which further decreases elimination.[15] As such, the half-life of semaglutide is 165 hours, which permits once weekly administration.[16] An oral formulation of semaglutide containing sodium-N-amino-caprylate to facilitate gastric absorption has been introduced.[17] In addition to its efficacy, the ease of oral pill or weekly injection of semaglutide

would be a boon for the ever-increasing patients with NASH in India and globally. However, further studies would be required to confirm the efficacy of once weekly injection or oral formulations of semaglutide in NASH. Given the complex and multifactorial pathophysiology of NAFLD/NASH, combining drugs acting via different mechanisms appears to be a rational and attractive option. In that direction, semaglutide is being evaluated in combination with cilofexor (non-steroidal farnesoid X receptor agonist) and/or firsocostat (acetyl-CoA carboxylase inhibitor).

With such impressive results in a phase 2 study, all eyes would now be on the phase 3 clinical trial of semaglutide in NASH, hoping that it not only replicates its results of NASH resolution as shown in phase 2 study but also shows improvement in hepatic fibrosis, which is the key determinant of outcome in NASH. Even though previous studies using semaglutide in patients with DM did not report the occurrence of malignancy,[18] this would require a closer watch in future studies.

Finally, there is no denying that a granular understanding of NAFLD/NASH pathophysiology is opening the doors to the clinical evaluation of various novel drugs. The future of NASH pharmacotherapy looks promising.

Conflicts of interest. None declared

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