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Development pathways and trial design for liver cirrhosis secondary to NASH.

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Liver cirrhosis is a worldwide health problem that is associated with various complications and high mortality. It can be a consequence of different causes, such as high alcohol consumption, non-alcoholic steatohepatitis (NASH), viral hepatitis B, C or D, cholestatic diseases, metabolic diseases and others. More than 1.3 million deaths worldwide annually are attributable to liver cirrhosis.

Liver cirrhosis due to NASH is currently an important and increasing indication for liver transplantation in the US. In fact, the global incidence of liver cirrhosis caused by NASH increased ~106% from 1990 to 2017,[1] partly due to population growth and aging, but also secondary to the increase in obesity around the world. The incidence varies by gender (higher in males than females); increases with age and by prevalence of additional risk factors (metabolic syndrome); and by sociodemographic factors. The impact of viral hepatitis B and C on the need for liver transplantation and as a cause of significant morbidity and mortality is expected to be attenuated and overtaken by that of NASH in the near future. In fact, a tsunami of patients with cirrhosis secondary to NASH is expected over the next decade. Even in some geographic areas with populations that typically have low body mass index (e.g., Japan, China, Singapore) there is still an increasing incidence of NASH, indicating that there are other cofactors contributing to the onset and progression to cirrhosis in these patients.

There are several challenges faced when conducting clinical trials in patients with cirrhosis secondary to NASH. This white paper provides a framework for sponsors looking to develop new treatments for this growing problem and addresses the following key areas:

- Combination of biomarkers for early identification of NASH with cirrhosis
- Developmental pathways for clinical trials in cirrhosis populations
- Identification of the appropriate target populations
- Surrogate and clinical outcome endpoints in clinical trials in populations with cirrhosis

NASH-related cirrhosis requires a combination of biomarkers for early identification

Data suggest that many patients with early liver cirrhosis are undiagnosed. A recent study reported that the majority of patients with cirrhosis secondary to NAFLD are diagnosed incidentally and that these patients are more likely to have advanced liver disease and hepatocellular carcinoma (HCC) at initial presentation.[2] High transaminase levels are a frequent reason for referral to hepatologists. However, transaminases may be normal in patients with compensated cirrhosis and thus lead to a delay in the diagnosis.[3] In order to evaluate transaminase levels in patients with suspected NASH cirrhosis, we performed an analysis using Labcorp patient-level data in ~22,000 patients with NASH Fibrosure Tests suggesting liver cirrhosis (Fibrosure score >0.74). After excluding any ICD10 code indicating liver disease (viral hepatitis, alcoholic steatohepatitis, etc.), median ALT levels were 31 and 38 IU/l in females and males, respectively, therefore confirming that most patients with NASH cirrhosis defined by this non-invasive test have ALT levels below the reference ranges. Thus, other more sensitive biomarkers for early diagnosis are required. It has been suggested that the FIB4 panel (determined by values of age, AST, ALT, platelet count) is a more sensitive marker for the presence of advanced fibrosis and cirrhosis than transaminases. Consistent with previous data, median FIB4 levels were 3.34 in the analysis of this population. Therefore, as suggested by clinical guidelines,[4] performing FIB4 in patients at risk of NAFLD can facilitate the identification of this patient population.

Developmental pathways for cirrhosis clinical trials

The approval of all drugs in the US is based on the need to demonstrate substantial evidence of efficacy in the treated group versus a control group. Endpoints should measure how the persons feel, function or survive (e.g., clinical benefit). The overall risk and benefit of each investigational product is taken into account in the approval decision. The EU, England and Japan have similar requirements for drug approval.

The FDA and EU also allow approval of drugs based on *validated* surrogate endpoints. These endpoints are supported by robust evidence that the surrogate endpoint is associated with clinical outcomes (e.g., hypertension is a validated surrogate for cardiovascular outcomes and sustained viral response [SVR] is a validated endpoint for chronic hepatitis C).

For serious and life-threatening diseases with an unmet medical need, the agencies allow an "Accelerated Approval" (FDA) or "Conditional Approval" (EMA) pathway based on surrogate endpoints that are considered "*reasonably likely* to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is *reasonably likely* to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)."[5]

For trials in populations with noncirrhotic NASH, the agencies have accepted slowing of progression of clinical outcomes (death, transplant and decompensation events). Though both agencies include the accelerated/conditional approval pathway in clinical trials for a population with noncirrhotic NASH, the suggested marketing authorization trials in the FDA Draft Guidance for Clinical Trials in Patients with Compensated Cirrhosis Secondary to NASH recommends clinical outcome data in order to reach marketing authorization.[6,7]

The FDA has stated in meetings that parallel programs for one IP in both patients with cirrhosis and in patients without cirrhosis due to NASH could facilitate a "final" approval for both subpopulations, based on demonstration of clinical benefit in a compensated cirrhosis and demonstration of improvement in the histopathologic surrogate endpoint in the noncirrhotic population. However, this statement has not yet been published in a guidance document. It is important to note that resolution of fibrosis (a histopathologic endpoint) may take years to achieve. This was demonstrated in a recent publication in which significant weight loss did not improve advanced fibrosis in a population of obese patients with stage 3 or stage 4 fibrosis due to NASH.[8]

Identification of the appropriate target populations

Since there are many inciting triggers associated with the development of NASH with fibrosis, including those of cellular stress, insulin resistance, metabolic derangement, inflammation and fibrogenesis, it becomes difficult to assess the impact of a single compound being studied on the natural history of the disease. The future of treatments for NASH with liver fibrosis will likely include combination therapies directed at targeting both the underlying metabolic disorder, as well as the resultant fibrosis associated with the disease.

For all clinical trials in NASH populations, patients' comorbidities should be treated, and stable medication regimens should be in place for several months prior to enrollment. Additionally, hepatic impairment studies will need to be performed early in drug development, especially for drugs that are partially or completely metabolized via bile.

In studies targeting patients with compensated cirrhosis due to NASH, one of the key challenges is the attribution of NASH as the etiology of cirrhosis and the trial eligibility criteria. The target population with cirrhosis secondary to NASH has been defined in a recent article published by the Liver Forum,[9] but there is still lack of clarity regarding attributing the liver disease to NASH for those patients in whom the histologic evidence is no longer present (i.e., burned-out cirrhosis). Additionally, for a given Child-Pugh stage of cirrhosis (A, B or C), there may be significant disparities of liver function, despite similar laboratory results and clinical exam.[10]

Patients with compensated cirrhosis encompass both those with and without portal hypertension (PHT). It is important to match the mechanism of action (MOA) of the investigational product (IP) with the target population, as it may not be effective to treat patients with PHT with anti-fibrotic drugs alone. The population selected should be likely to respond to the IP. PHT can be suspected by many noninvasive tests (e.g., platelet count, venous collaterals on an imaging study, esophageal varices seen on endoscopy, Fibroscan kPa >20), as well as direct, invasive measures (hepatic venous pressure gradient [HVPG]). It is critical that drugs are developed that directly impact the hemodynamic changes in PHT to meet the needs of this growing population. Additionally, it needs to be taken into account that non-invasive tests are static and measure a point in time, rather than the dynamic continuum of cirrhosis, as described by Garcia-Tsao and Friedman.[11]

Enrichment strategies, aimed at identifying a more homogenous group of patients will be important tools in designing future clinical trials in cirrhosis due to NASH. Such strategies, based serum biomarkers (Pro C-3 or NIS-4,[12,13] ELF[14]), imaging biomarkers (e.g., elastography,[15] MRI-cT1[16]) and other assessments of liver functional capacity (e.g., HepQuant Tests)[17,18], may decrease the variability (noise) in these trials that make interpretation of data less difficult.

Recent data also suggest that application of machine learning technology may also allow for identification of patients at higher risk for rapid progression of NASH.[19] It should be noted, however, that these enrichment strategies may have implications on the final labeling claim for a compound.

Surrogate and clinical outcome endpoints in trials in populations with cirrhosis

For clinical trials in patients with cirrhosis secondary to NASH, the FDA and EMA request that trials be performed to clinical outcomes, with a primary composite endpoint showing improvement in decompensated events (variceal bleeding, ascites, encephalopathy, MELD change from ≤ 12 to ≥ 15, liver transplantation, and all-cause mortality). The EU adds development of hepatocellular cancer to the list of clinical outcomes endpoints.

However, both the FDA and EMA have allowed trials in populations with cirrhosis secondary to NASH to move forward using accelerated approval pathways and a surrogate (interim) analysis of improvements in cirrhosis (regression from fibrosis stage 4 [cirrhosis] to stage 3 [bridging fibrosis]). To date, no drugs have been successful in achieving marketing approval in patients with cirrhosis due to NASH. This may be secondary to lack of homogeneity and specificity of the target populations (patients with PHT were included in these trials), and the single, anti-fibrotic or anti-inflammatory MOA of the drugs used in these trials.

Enrichment of the compensated cirrhotic NASH population with a high probability of developing a clinical outcome can be considered when designing a trial in this population. However, it is more important that trial design takes into account the MOA of the IP.[20] Assessing the efficacy (proof-of-concept) in the population targeted will be important as the effects of portal hypertension may negate the effects of an anti-fibrotic agent used alone.[21] The measurement of hepatic venous pressure gradient (HVPG) can be helpful in drug development, but this technique is invasive, operator-dependent, and carries risk, therefore indirect estimates of portal pressure are needed to assess efficacy of potential IPs. There is a wealth of literature on this topic, but no clinical trials using these non-invasive tests have been performed as of yet.[21,22,23] Further qualification and validation of non-invasive testing and functional biomarkers, along with machine learning strategies, should allow for more precise risk stratification of this complicated group of patients.

Trials in patients with decompensated cirrhosis are especially challenging to perform, and most have targeted specific decompensation events or complications of cirrhosis (e.g., rifaximin for treatment of hepatic encephalopathy and band ligation for esophageal varices). The few trials that have attempted to target treatment of fibrosis in advanced NASH cirrhosis patients have not been successful. These very advanced patients may no longer be responsive to an anti-fibrotic drug therapy alone. Drugs that specifically target portal hypertension, or a combination of drugs that treat both the fibrosis and the portal hypertension, may be needed in this group of patients.[24] More data is clearly necessary to address these important issues.

Summary

There is a high unmet medical need for treatments for patients with cirrhosis secondary to NASH, and the number of these patients is projected to increase substantially over the next decade. Although there has been tremendous progress in the design of clinical trials, and regulatory agencies are willing to facilitate efficacious drugs to be approved for these patients, there are still several challenges in clinical development in patients with cirrhosis due to NASH.

Most of these patients will likely require a drug or combination of drugs to treat the complexities of cirrhosis. Targeting the correct population that will respond to the MOA of the IP is imperative. In addition, there is a high need for sensitive and specific non-invasive tests (NITs) that can replace "reasonably likely" surrogates (i.e., histopathology) for accelerated approval, as well as validated surrogate endpoints to replace long-term clinical outcomes in cirrhotic patients due to NASH.

While a cure and subsequent reversal of cirrhosis would be ideal, slowing of disease progression would likely be acceptable to physicians, patients and regulatory agencies for drug approval. Additionally, much work still needs to be done to understand the long-term natural history of NASH cirrhosis, the identification of those individuals with high likelihood of progression of their disease, and those with a likelihood of response to a given therapy.

References

1. GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* 2020; 5: 245-66.
2. Bertot LC, Jeffrey GP, Wallace M, et al. Nonalcoholic fatty liver disease-related cirrhosis is commonly unrecognized and associated with hepatocellular carcinoma. *Hepatology Communications* 2017; 1:53-60.
3. Mofrad P, Contos MJ, Haque M, Sargeant C, Fisher RA, Luketic VA, et al. Clinical and histologic spectrum of non-alcoholic fatty liver disease associated with normal ALT values. *Hepatology* 2003; 37:1286-1292.
4. European Association for the Study of Obesity (EASO): Clinical practice guidelines for the management of non-alcoholic fatty liver disease. *Diabetologia* 2016; 59: 1121-1140.
5. FDA guidance for industry: expedited programs for serious conditions—drugs and biologics. Published 2014. Accessed 2022. https://www.fda.gov/media/86377/download.
6. Non-alcoholic steatohepatitis with compensated cirrhosis: Developing drugs for treatment. Guidance for Industry. US Department of Health and Human Services, Food and Drug Administration. Center for Drug Evaluation and Research (CDER) 2019:1-8. https://www.fda.gov/media/127738/download.
7. Reflection paper on regulatory requirements for the development of medicinal products for chronic, non-infectious liver diseases (PBC, PSC, NASH). EMA/CHMP/299976/2018.
8. Lassailly G, Caiazzo R, Wandji LC et al. Bariatric surgery provides long-term resolution of non-alcoholic steatohepatitis and regression of fibrosis. *Gastroenterology* 2020;159 (4):1290-1301.
9. Noureddin M, Chan JL, Barradas K et al. Attribution of non-alcoholic cirrhosis as an etiology of cirrhosis for clinical trials eligibility: recommendations from the multi-stakeholder liver forum. *Gastroenterology* 2020; 159(2): 422-427.
10. Everson G. DSI quantifies functional range over the spectrum of chronic liver disease. *HepQuant*, 2021: data on file.
11. Garcia-Tsao G, Friedman S, Iredale J, Massimo Pinzani. Now there are many (stages) where before there was one: in search of a pathophysiological classification of cirrhosis. *Hepatology* 2010; 51 (4); 1445-9.
12. Nielsen MJ, Thorburn D, Leeming DJ, et al. Serological markers of extracellular matrix remodelling predict transplant-free survival in primary sclerosing cholangitis. *Aliment Pharm Ther* 2018; 48 (2): 179-189.
13. Harrison S, Ratzui V, Boursier J, et al. A blood-based biomarker panel (NIS4) for non-invasive diagnosis of non-alcoholic steatohepatitis and liver fibrosis: a prospective derivation and global validation study. *Lancet Gastroenterology and Hepatol* 2020; 5(11): 970-985.
14. Harrison SA, Abdelmalek MNF, Caldwell S, et al. Simtuzumab is ineffective for patients with bridging fibrosis or compensated cirrhosis caused by non-alcoholic steatohepatitis. *Gastroenterology* 2018; 155 (4);1140-1153.
15. Han MA T, Vipani A, Noureddin N, et al. MR elastography-based liver fibrosis correlates with liver events in non-alcoholic fatty liver patients: a multicentre study. *Liver International* 2020; https://onlinelibrary.wiley.com/doi/10.1111/liv.14593.
16. Dennis A, Kelly MD, Fernandes C, et al. Correlations between MRI biomarkers PDFF and cT1 with histological features of non-alcoholic steatohepatitis. *Front Endocrinol* 2021; 11: https://www.frontiersin.org/articles/10.3389/fendo.2020.575843/full.
17. Fallahzadeh MA, Hansen DJ, Trotter JF, et al. Predicting clinical decompensation in patients with cirrhosis using Hepquant SHUNT test. *Aliment Pharmacol Ther* 2021; 53 (8): 928-938.
18. Fallahzadeh MA, Hansen DJ, Trotter JF, et al. Predicting clinical decompensation in patients with cirrhosis using Hepquant SHUNT test. *Aliment Pharmacol Ther* 2021; 53 (8): 928-938.
19. Fallahzadeh MA, Hansen DJ, Trotter JF, et al. Predicting clinical decompensation in patients with cirrhosis using Hepquant SHUNT test. *Aliment Pharmacol Ther* 2021; 53 (8): 928-938.
20. Non-alcoholic steatohepatitis with compensated cirrhosis: developing drugs for treatment. Guidance for Industry. US Department of Health and Human Services, Food and Drug Administration. *Center for Drug Evaluation and Research (CDER)* 2019:1-8. https://www.fda.gov/media/127738/download.
21. Garcia-Tsao G, Bosch J, Kayali Z, et al. Randomized placebo-controlled trial of emricasan for non-alcoholic steatohepatitis-related cirrhosis and severe portal hypertension. *J Hepatol* 2020; 72: 885-895.
22. Frenette C, Kayali Z, Mena E et al. Emricasan to prevent new decompensation in patients with NASH-related decompensated cirrhosis. *J Hepatol* 2021 Feb; 74(2):274-282
23. Caussy C, Reeder SB, Sirlin CB & Rohit Loomba. Non-invasive, quantitative assessment of liver fat by MRI-PDFF as an endpoint in NASH trials. *Hepatology* 2018; 68(2);763-772.
24. Hai Y, Chong W, Eisenbrey JR. Network meta-analysis: non-invasive imaging modalities for identifying clinically significant portal hypertension. *Dig Dis Sci* 2021: https://link.springer.com/article/10.1007/s10620-021-07168-y.

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