White Paper

Exploring the NASH Clinical Trial Landscape in India

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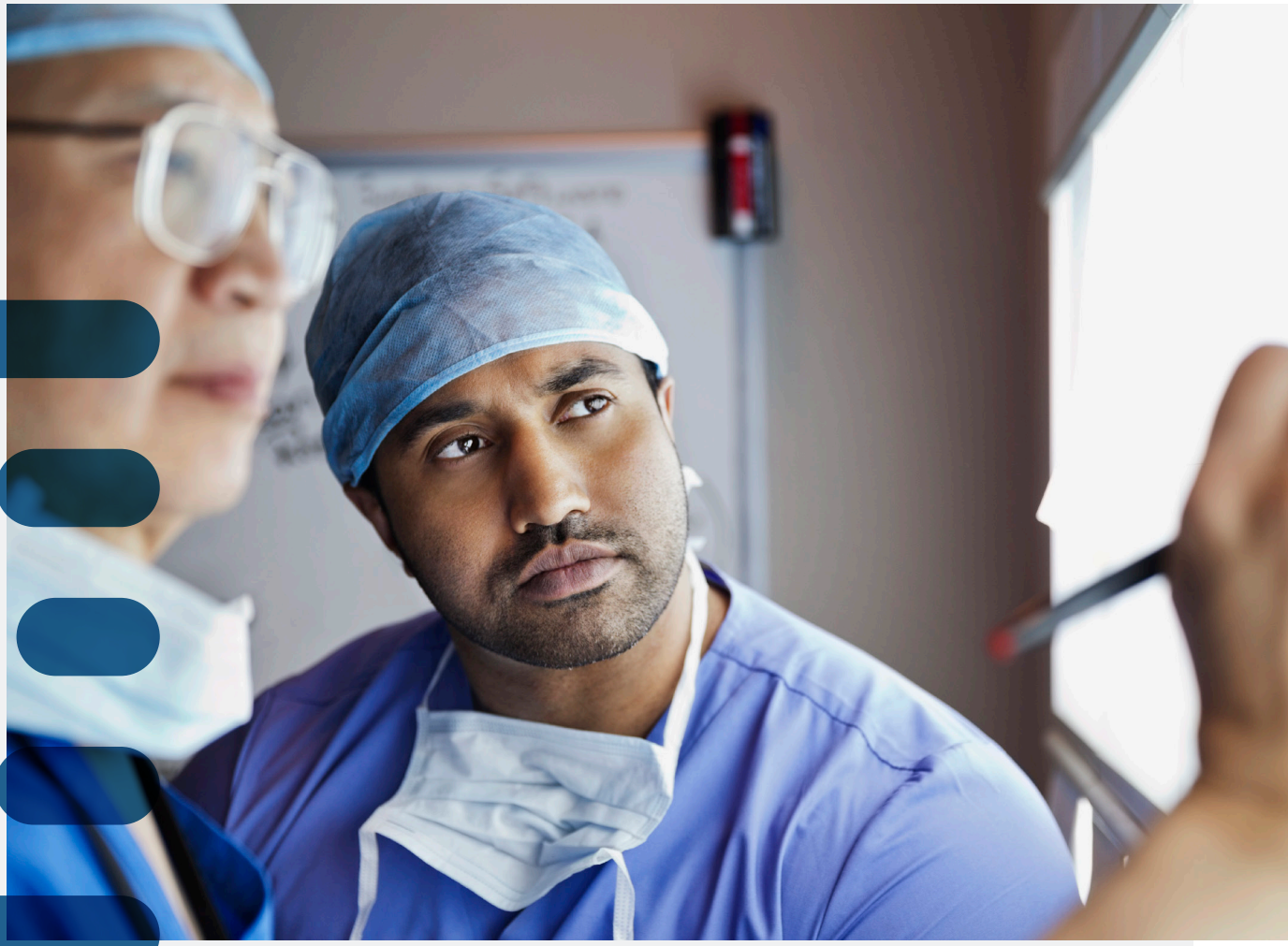

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease worldwide and non-alcoholic steatohepatitis (NASH), its progressive form, is rapidly becoming the leading cause of end-stage liver disease and liver transplantation. There is a huge unmet need in the management of NAFLD and NASH. The key challenge is that NAFLD/NASH remains to be an under recognized disease despite its increasing prevalence, and early diagnosis is crucial to reduce the risk of progression and its consequent complications. Another major concern is the lack of approved NASH therapy and to address this issue, there has been a global surge in clinical trials. However, NASH clinical trials have encountered challenges related to patient recruitment and retention, lack of validated noninvasive diagnostic tests, and the effect of placebo response on trial outcomes. Measures to improve the NAFLD and NASH clinical trial environment can help accelerate the approval and availability of better treatment options for NASH.

Disease burden

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide with a prevalence of 24%.[1,2] It is estimated that the prevalence of NAFLD will increase by 21% by 2030, from 83.1 million in 2015 to 100.9 million, while prevalence of fibrotic NASH will increase by 63% from 16.52 million to 27.00 million cases and there would be around 178% rise in liver-related mortality in the same time period.3 The incidence and prevalence of NAFLD in India is comparable to global figures; seen commonly in ages 30 to 50 years. Around 5% of the patients diagnosed with NAFLD would probably have NASH.[4] In India, NAFLD is not only a concern for obese or patients with DM, it has been observed that NAFLD can develop in the absence of obesity, which is termed as “lean” NAFLD.[5] In a prospective epidemiological study carried out in a rural area of West Bengal, India, 75% of NAFLD subjects belonged to the non-obese group, with an average BMI <18 and fasting blood glucose that is slightly above 100 mg/dl.[6,7]

Diagnosis and treatment of NASH: An unmet need

NASH is still an underrecognized disease. Increasing awareness of this disease in the general population and among primary care physicians (PCPs) is essential to allow for a structured referral pathway and early detection.

Currently, there are no standard screening recommendations for NAFLD and NASH globally.

- Routine screening for NAFLD in high-risk patients attending primary care, diabetes or obesity clinics is not recommended by the American association for

the study of liver diseases (AASLD) guidelines due to uncertainties surrounding diagnostic tests and treatment options.[8]

- The European guidelines allows screening for NAFLD in the population at risk with context of the available resources.[9]
- There are no established screening guidelines for NAFLD in India. As the majority of noncirrhotic NAFLD and NASH patients are asymptomatic, the diagnosis of fatty liver is usually made based on an incidental finding on ultrasound and/or elevated liver enzymes. Further investigation may reveal the presence of metabolic syndrome such as central obesity, dyslipidemia, and diabetes. Patients may have normal liver enzymes and remain undiagnosed. Diagnostic modalities are directed to confirm the presence of fatty liver and determine the severity of liver disease.[10]

As regards patient pathway, NAFLD is managed in the primary healthcare setting and referrals are not common. Most patients seen by specialists are generally walk-in patients as patients may have tests done upon request and seek hepatology consult directly only for incidental finding of elevated liver enzymes or fatty liver on ultrasound. There is general lack of awareness of NASH and its complications or its long-term consequences among patients and PCPs alike.[11]

Globally, there is no established consensus on the optimal management of NASH and no approved pharmacologic therapy; however, being a metabolic disorder, patients are monitored and managed holistically for other abnormalities including obesity, diabetes, and dyslipidemia. Targeted treatment options in India consist of the use of either pioglitazone, vitamin E, metformin or ursodeoxycholic acid (UDCA) in patients with histological evidence of NASH; however, these are not approved therapies and hence there is a huge unmet need for effective treatment options for NASH patients with advanced fibrosis who have the highest rates of liver-related morbidity and mortality.[12] In addition, the optimal duration of therapy is unknown and there is no clear evidence to support the frequency of follow-up. Alternative systems of medicine like Ayurveda, Homeopathy, Yoga, herbal remedies are likewise available in India for the treatment of fatty liver or NAS.

It is essential that physicians follow an individualized approach to management of NAFLD and NASH, taking into consideration the patient's co-morbidities, disease severity, availability and costs of diagnostic modalities and treatment options in the local setting as well as patient preference.

Conducting NASH clinical trials in India

As there is no approved therapy for NASH, there is a global surge of clinical trials with drugs targeting lipid metabolism, inflammation, and fibrosis.[13] India has participated in trials on a PPAR agonist and ASK1-inhibitor for NASH.[5]

- Despite a high prevalence of NAFLD, identifying and recruiting patients with histologically confirmed NASH is a challenge, and this contributes to concerns on patient recruitment. Most patients with NAFLD are usually asymptomatic, or may present with non-specific signs and symptoms such as fatigability, heaviness, and discomfort on the right side of the upper abdomen.[4] It is, therefore, a challenge to convince asymptomatic patients who feel healthy to undergo invasive diagnostic biopsy for a disease that does not cause any signs and symptoms at the onset.
- It is important to identify sites that have a multidisciplinary approach to management of NAFLD, and a robust referral system from PCPs, endocrinologists and gastroenterologists/ hepatologists, including other relevant specialties. However, there is a general lack of disease awareness even among PCPs, and there is also no established referral pathway in India to identify these patients, resulting in a large number of unrecognized fatty liver patients who are not referred for further specialist management, thus contributing to

underdiagnosis of the disease.[16,17]

- Majority of NASH therapeutic trials require liver biopsy to establish the diagnosis of NASH and fibrosis stage at baseline, as well as to confirm treatment response.[18,19] A second or even a third biopsy is required during and at the end of a trial to assess disease progression and trial endpoints. Convincing patients to undergo a liver biopsy is challenging, due to the inherent risks associated with an invasive procedure. Moreover, the results from the biopsy will not alter disease management due to lack of specific treatment.[7] This is a major reason for patients' refusal to undergo the procedure in India as in other countries. In addition, the procedure has a risk of sampling errors where required histological parameters may not be present in the sample as well as discordance between local and central reader in the interpretations of the primary biopsy and between pre and post biopsy samples, as much as 26% in one study.[19] These may result in screen failures with a negative impact on site engagement and consequently, enrolment rates.[20]

- Recent advances in technology have produced newer and better imaging modalities for assessing fatty liver and fibrosis such as magnetic resonance imaging derived proton density fat fraction (MRI-PDFF) and MR elastography and are being used in early-phase NASH trials to measure liver fat content and fibrosis stage. [21,18] These are available in a few specialized centers; however, prohibitive costs and lack of reimbursements for these procedures may limit their use, except when required for clinical trials.

- The heterogeneous course of NAFLD/NASH affects trial outcomes where the true effect of the drug may not be apparent due to a spontaneous regression in the placebo arm. This placebo response is approximately 19% and likely related to the effect of lifestyle intervention in the control arms.[22] The "Hawthorne Effect", where the knowledge that one is being observed, or simply participating in a clinical trial alters behavior, is especially relevant in NAFLD where lifestyle change can significantly affect the underlying disease.[14] The placebo response can also be significantly affected by study design, and this relates to trial entry criteria, particularly the histological severity threshold for enrolment, and the stringency of the efficacy endpoint adopted. Most studies specify a minimum NASH grade and fibrosis stage for trial entry, and the permissiveness of the inclusion criteria can influence trial outcomes, largely by increasing the placebo response rate.[14]

Addressing the issues

- Establishing a clear patient pathway for referrals and conduct of patient awareness programs may lead to identification of more patients who can be referred to specialists for further evaluation, potentially increasing the patient pool.

- Non-invasive biomarkers are available such as APRI, FIB-4 and NFS and used widely. These biomarkers can be leveraged to potentially reduce the high percentage of screen failures due to liver biopsy by selecting patients who would likely yield positive biopsy results. However, these biomarkers have their own limitations. Further analysis is needed to evaluate whether its diagnostic performance may be affected by some clinical factors and concomitant drugs.[23] A useful strategy is to combine at least 2 non-invasive biomarkers (one imaging method such as transient elastography) to pre-screen subjects to better predict those that are likely suitable for a NASH clinical study.

- Adopting a more stringent endpoint definition for NASH resolution may reduce the placebo response rate.[14] Targeting the correct patient population by having stricter eligibility criteria as well as selecting meaningful study endpoints for each clinical trial phase may also help address the issues. An example would be a clinical trial designed to include NASH subjects with F2/F3 fibrosis to demonstrate no worsening/regression of steatohepatitis and fibrosis or a trial selecting patients with compensated cirrhosis to show no progression to decompensation based on liver-related outcome endpoints. Other meaningful endpoints include rates of

hospitalization, unscheduled clinic and emergency room visits, tests performed, and lost work days, and together with an endpoint measuring a clinically meaningful change in health status, it may provide a more comprehensive picture of an intervention's potential benefit.[15] Moreover, studies of longer duration may help to assess long term safety, durability, and benefits of various interventions on not just liver-related but cardiovascular and metabolic outcomes, which strongly contribute to the disease burden of NASH.[22] Different trial endpoints can also be utilized in early phase studies; regulatory authorities recognize this option and have allowed the utilization of non-invasive tools for diagnosis and outcomes. The US Food and Drug Administration has established regulatory pathways which incorporate non-invasive, clinical, and histologic endpoints, for phase 2 and 3 clinical development, with the expectation for post-marketing clinical outcome evaluation in phase 4 studies.[13]

Measures to enhance the clinical trial landscape of NASH in India are summarized in Table 1.

Table 1:

Factors in NASH clinical trial	Proposed measures
• Patient recruitment	• Establish a NASH patient pathway and increase awareness among physicians
• Disease awareness and patient pathway for NASH	• Patient education and multidisciplinary approach to management of patients
• Requirement for liver biopsy and discordance in biopsy interpretation between readers • Availability of new non-invasive modalities required in NASH clinical trials	• Use of multiple noninvasive biomarkers as part of prescreening to minimize biopsy-related screen failures
• High placebo response in NASH trials	• Stricter eligibility criteria to target the appropriate patient population, identify meaningful study endpoints and adopt a more stringent endpoint definition for NASH resolution

Conclusion

The rise in obesity and other lifestyle-related diseases has resulted in a significant increase in the number of NAFLD/NASH patients; however, physicians still face many challenges in managing the disease, the most basic of which is the lack of awareness of the disease and its sequelae. The lack of established guidelines in the diagnosis and management of NAFLD/NASH is likewise a critical issue that needs to be addressed, as well as the limited treatment options with no approved medications for this disease. Conducting well designed clinical trials with meaningful endpoints and less invasive procedures will accelerate the development of potentially efficacious treatments for NASH. Measures to improve the NAFLD/NASH clinical trial environment are imperative to respond to the need for more available approved therapeutic options to manage the disease.

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