CHAPTER

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NASH: Do we Really have an Effective Treatment?

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) constitutes the spectrum of liver disease encompassing varying degrees of steatosis, inflammation, hepatocellular injury and fibrosis. NAFLD is considered to be the hepatic component of metabolic syndrome (MS) in view of the close association between these two conditions. The histological spectrum of NAFLD ranges from non-alcoholic fatty liver (NAFL) which is characterized by presence of steatosis accompanied by mild or no inflammation to non-alcoholic steatohepatitis (NASH) which is accompanied by inflammation and hepatocyte ballooning with or without associated fibrosis. NAFLD has been defined as the accumulation of fat in the liver in the absence of recent or ongoing intake of significant amount of alcohol. The significant amount of alcohol has been defined variably but a cut-off of intake up to 20 g/day seems reasonable both for males and females.

The natural history of NASH tends to parallel the more aggressive histological picture, with prospective cohort studies demonstrating a higher rate of morbidity and mortality compared to NAFL, particularly when fibrosis is present. Patients with NAFLD are not only at an increased risk for liver related mortality but are also predisposed to an increased incidence of diabetes mellitus (DM) and cardiovascular risk on follow-up.

Insulin resistance (IR) is a key component involved in the pathogenesis of NAFLD and various studies have depicted a high prevalence of IR (7-55%) among Asian-Indians residing in India. It has also been demonstrated that Indians have a higher IR and hepatic triglyceride content when compared to other races suggesting that Indians are highly prone to develop NAFLD. Recent evidence indicates that hepatic fat content of Asian- Indians is almost twice in amount for similar body mass index (BMI) when compared to white Caucasians. In the general population of India, the prevalence of NAFLD is documented to be around 9-35% and this higher prevalence of NAFLD and the inter-ethnic difference noted is believed to be linked not only to factors relating to lifestyle but also to a strong underlying genetic predisposition. Among the various reasons postulated, polymorphisms of apolipoprotein C3 (APOC3) gene may be a phenomenon which is peculiar to Asian- Indians. It has been noted that Asian-Indians are less obese than their Western counterparts and this could be allowing a higher phenotypic expression of the APOC3 genetic polymorphism. Data has also suggested that iron overload and HFE gene mutations do not play a significant role in the pathogenesis of NAFLD in patients in India which is in sharp contrast to the patients in the West. Even though NAFLD is growing to be an important cause of cryptogenic cirrhosis and hepatocellular carcinoma (HCC) in patients in India, it is noted that the histologic severity is often less at presentation when compared to data from the West.

As mentioned earlier, NAFLD is a broad term encompassing simple steatosis (NAFL), NASH, NASH-related cirrhosis, and NASH-related HCC. The differentiation between NAFL and NASH is of utmost importance in determining the prognosis, risk of progression, need for pharmacological treatment and for assessing the liver-related and cardiovascular morbidity and mortality, which occurs more commonly in patients with NASH than in those with NAFL. NASH is usually a histologic diagnosis except in scenarios where hepatic fibrosis is diagnosed with the help of non-invasive modalities like Transient Elastography (Fibroscan). Suggested algorithm for the workup of patients with NAFLD has been depicted in Figure 1.

TREATMENT OF NON-ALCOHOLIC FATTY LIVER DISEASE

Treatment of NAFLD/NASH is one of the most challenging fields in Hepatology today with lot of research going on in finding the new drugs in the treatment of such patients. The vital aspect underlying the therapeutic modalities in patients with NAFLD have centred around various risk factors associated with the disease. The various strategies involved in the management of patients with NAFLD include lifestyle modifications such as weight loss and exercise, treatment of risk factors such as control of DM, control of hyperlipidemia, hypertension and using various pharmacologic interventions to target the basic pathogenetic mechanisms involved with the progression of the disease.

We describe below the available effective treatment modalities for patients with NAFLD/NASH and also the drugs which are in pipeline and would be available for clinical use in near future.

LIFESTYLE MODIFICATIONS & WEIGHT REDUCTION

Patients with NAFLD irrespective of their current body weight should be advised active lifestyle modifications in the form of regular exercise. Those patients who are overweight and obese should be encouraged to lose weight. Hepatic triglyceride content is shown to decrease with a 3%-5% weight loss; however randomized controlled studies have demonstrated that necroinflammation

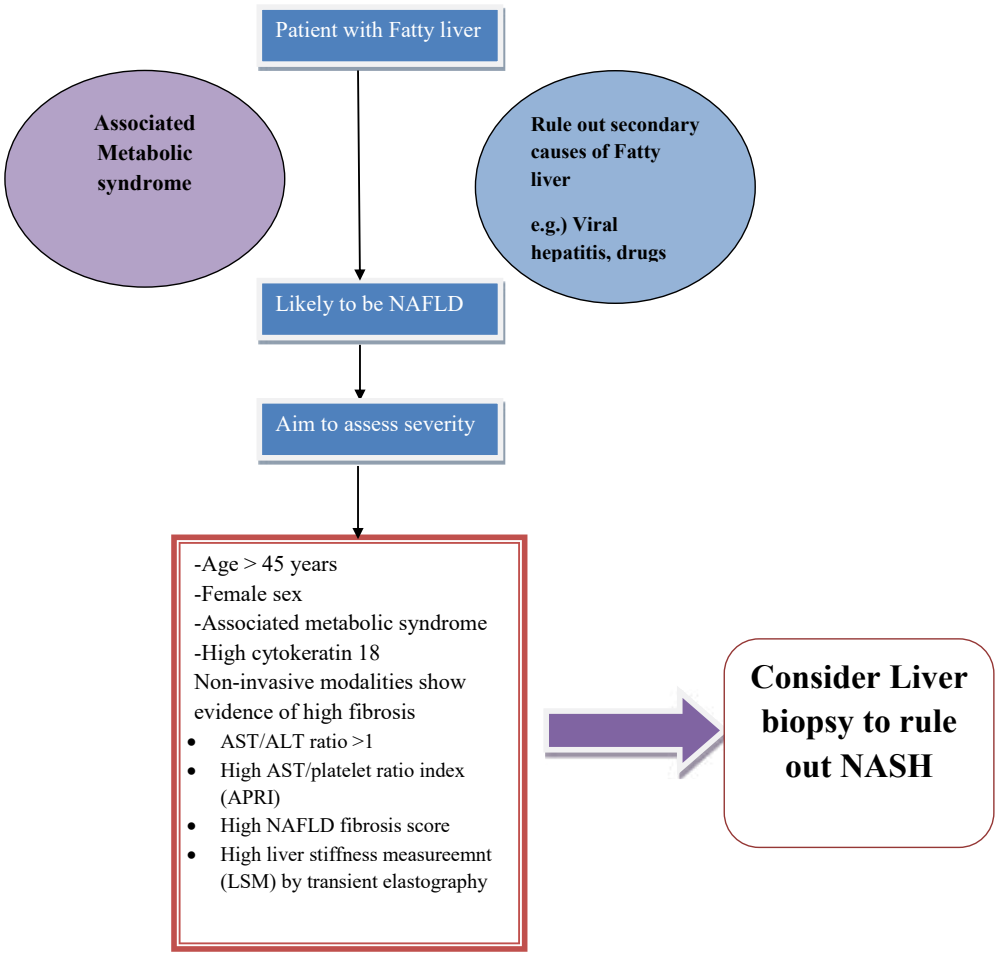

Fig.1: Diagnostic workup in patients with non-alcoholic fatty liver disease (NAFLD)

decreases in the subgroup which achieved a weight loss of about 7%-9%. In a recent study enrolling 293 patients with NASH, it was shown that a weight reduction of >10% resulted in disappearance of steatosis in 90% and regression of fibrosis in 45% of patients. The exercise regimen should consist of brisk walking, jogging, or rhythmic aerobic exercises for a minimum of 45 min, 5 days per week, to achieve a target heart rate of 60–70% of the maximal heart rate. Considering the dietary aspects in patients with NAFLD, it is imperative to mention that isolated fat restriction in patients with NAFLD is a myth and energy restriction forms the major cornerstone in decreasing the hepatic steatosis. Recently in a randomized crossover trial, a Mediterranean diet based on olive oil, nuts, fruits, vegetables, fish, legumes, dairy products, and wine was compared with a low-fat/high-carbohydrate diet for 6 weeks and it was noted that a significant reduction in hepatic steatosis was observed in patients consuming a Mediterranean diet.

There is paucity of data from India; however studies from the West have shown bariatric surgery to improve the histological components of NASH including fibrosis which improved in about 30% of patients. In severely obese patients (those with a BMI ≥ 40 or 35–40 with co-morbidities), bariatric surgery induces sustained weight loss as well as result in remission of diabetes and reduce overall long-term mortality. After a bariatric procedure, the extent of weight loss achieved appears to be associated with the reduction in liver injury and in general the gastric bypass procedure seems more effective than gastric banding as this procedure achieves a greater loss of weight. Although bariatric surgery resolves NASH in patients in whom lifestyle therapy has failed, perioperative risks limit its application. More patients may be benefitted with this modality, if BMI cut-offs are reduced in Indian patients with NAFLD.

INSULIN SENSITIZATION

As mentioned earlier, IR plays an important role in the pathogenesis of NAFLD and development of NASH. By increasing the peripheral lipolysis, IR results in increased delivery of free fatty acids to the liver, leading to excess fat and increased beta-oxidation, which worsens the oxidative stress. Few studies had suggested the role of metformin in reducing the IR and improving the aminotransferases and histological features of NASH, however a recent meta-analysis concluded metformin to be not effective in patients with NASH. Thus, The 2012 American Association for the Study of Liver Disease (AASLD) guidelines do not recommend the use of metformin in adults with NASH.

Peroxisome proliferator-activated receptors (PPAR γ) are receptors present in the nucleus which play a vital role in glucose and lipid homeostasis. The landmark study, PIVENS trial enrolled nondiabetic patients with NASH and compared pioglitazone (PPAR γ agonist) to placebo, as well as vitamin E to placebo. It was demonstrated that patients who were given pioglitazone had significant reductions in steatosis, inflammation, hepatocyte ballooning, insulin resistance, and levels of liver enzymes. However, there exists a safety concern with the use of pioglitazone, as it has shown to cause weight gain and induce congestive cardiac failure. Because of the design of the clinical trials which evaluated use of pioglitazone in NASH, most of the guidelines suggest use of this drug in non-diabetic patients with histological NASH only.

Elafibranor is the latest drug in this class and has an agonistic activity on both PPAR α and PPAR δ receptors. In the latest GOLDEN-505 trial, it was shown that elafibranor given at a dose of 120mg/day for 1 year resolved NASH without worsening fibrosis in a significantly higher number of patients when compared to those receiving placebo.

THE GLUCAGON LIKE PEPTIDE 1 (GLP1) PATHWAY

The GLP1 pathway decreases liver fatty acid accumulation through the activation of numerous genes such as PPAR α/γ which will enhance hepatic fatty oxidation, lipid export, and insulin sensitivity. In a recent randomized controlled study (LEAN study), Liraglutide (GLP1 receptor agonist) was assessed in 52 patients with NASH and DM. The investigators observed resolution of NASH in a significantly higher number of patients given liraglutide (39%) when compared to placebo (9%). This drug was also shown to have reduced the biomarkers of fibrosis, however larger studies need to be done to evaluate the ability of this drug to reduce fibrosis.

FARNESOID X RECEPTOR (FXR) PATHWAY

Obeticholic acid is an active ligand of the FXR receptor, which is a nuclear receptor actively involved in glucose, lipid and energy homeostasis. This receptor subfamily also plays a pivotal role in anti-inflammatory and anti-fibrosis pathways. In a recent landmark study, FLINT trial, it was shown that 25 mg obeticholic acid was more effective than placebo in improving liver histology in patients with NASH. In fact, fibrosis was also significantly reduced in patients who received obeticholic acid, compared to patients given placebo. Pruritis was a major side effect of this drug, reported by 20% of patients, and a major safety concern which arose was the influence of this drug in altering the lipid profile by increasing the LDL–cholesterol and lowering the levels of HDL–cholesterol.

REDUCING OXIDATIVE STRESS

Oxidative stress is known to result in chronic tissue injury, leading to increased cell death and fibrogenesis. Vitamin E is considered to be the first line pharmacotherapy for non-diabetic patients with NASH. In the previously mentioned PIVENS trial, the authors demonstrated that a daily dose of 800 mg of vitamin E given for 96 weeks reduced steatosis, lobular inflammation and hepatocellular ballooning when compared to placebo. As for pioglitazone, most of the guidelines suggest use of vitamin E in non-diabetic patients with histological NASH only. However, important safety concerns were raised with the long term usage of vitamin E, as few studies reported increased incidence of hemorrhagic stroke and prostate cancer.

REDUCING FIBROSIS

Preventing the progression of fibrosis and achieving reversal of fibrosis has become a focus of intense research in the field of hepatology. Simtuzumab is an antibody against the enzyme lysyl oxidase-like-2 (LOXL2), which is overexpressed during development of liver fibrosis. This drug is currently being evaluated in a phase 2 study enrolling patients with NASH having stage 3 and 4 fibrosis.

NOVEL APPROACHES

Recent data is pointing an altered gut microbiome in patients with NAFLD and a study done from our institute has also demonstrated small intestinal bacterial overgrowth (SIBO) in patients with NAFLD. Altered gut microbiome and SIBO can contribute to significant endotoxemia and activation of inflammatory pathways in the liver. Several strategies are being evaluated to target this gut dysbiosis (using probiotics) and downstream inflammatory pathways (using caspase inhibitors) to prevent the progression of NASH. The novel drugs in the pipeline which are being evaluated for NASH are mentioned in Table no. 1.

CONCLUSIONS

The treatment of NASH has been a focus of intensive

Table 1: New drugs in pipeline in the management of NASH

Drug	Trial	Mechanism of Action	Comments
Simtuzumab	NCT01672879	Anti-LOXL-2 antibodies	Inhibits formation and repair of extracellular matrix
Cenicriviroc	CENTAUR study	CCR2/CCR5 antagonist	Interferes with recruitment of monocytes, macrophages and HSCs upon liver injury
Emricasan	ENCORE-NF trial	Caspase inhibition	Prevents apoptosis
Sitagliptin	NCT01963845	DPP-IV inhibitors	Prevents degradation of GLP-1
GR-MD-02	NCT01899859	Galectin-3 inhibitor	Anti-fibrotic
JKB-121	NCT02442687	Toll-like receptor 4 inhibitor	Anti-inflmmatory

research in the field of hepatology with current treatment strategies aiming not only to decrease steatosis and inflammation, but also prevent the progression and promote resolution of hepatic fibrosis. However, an effective treatment would rely not only on pharmacologic interventions but also on intense lifestyle modifications in order to control the various risk factors (MS) involved in the pathogenesis and progression of this disease.

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