NASH-new therapeutic options for the unmet need

Non-alcoholic fatty liver disease (NAFLD) constitutes a spectrum of disease, characterized by excessive accumulation of fats in the hepatocytes. Broadly classified as Non-alcoholic fatty liver (NAFL) and Non-alcoholic steatohepatitis (NASH), NAFLD is often associated with insulin resistance, obesity, dyslipidemia, type 2 diabetes, and cardiovascular disease.

NASH represents the most severe form of NAFLD and involves inflammation and cell injury with or without fibrosis which may further progress to cirrhosis and ultimately hepatocellular carcinoma.

As far as the pathophysiology of NASH is concerned, data shows that a plethora of events with simultaneous origins from the liver, adipose tissue, and the gastrointestinal tract are responsible. Insulin resistance, the main consequence of obesity and metabolic syndrome, leads to fat buildup in the liver. But the real culprit is oxidative stress which causes peroxidation of the hepatocyte lipid membrane and ultimately leads to progressive disease or NASH. Variance amongst the proinflammatory and anti-inflammatory adipokines and adipocytes induced cytokines are other additional mechanisms held responsible.

NASH is a leading cause of liver-related morbidity and mortality worldwide and is poised to be the leading cause of liver transplants by 2020. Despite the enormous burden to global healthcare system and debilitating consequences for patients, there are currently no FDA approved pharmacological therapies specially catering to NASH. As a matter of fact, serious concerns have been generated to develop effective treatment strategies for NASH throughout the medical community.

The current therapeutic recommendations for NAFLD/NASH as per the American Association for the study of liver disease (AASLD) includes lifestyle modification-weight loss, thiazolidinediones-Pioglitazone, Antioxidants-Vitamin E, ursodeoxycholic acid (UDCA) and bariatric surgery. Amongst this, Vitamin E and thiazolidinediones are highly recommended, however, long-term safety concerns limit their potential use.

Innovative therapies-Need of the hour!

With a multitude of pathways responsible for the development of the disease, effective treatment strategies, that can manage the complex pathophysiologic processes of NASH is the need of the hour. Lack of approved treatments and a large patient pool is driving research and innovation in the biopharmaceutical industry towards this highly unmet medical need. Due to its classification as a medical condition of an unmet therapeutic need, FDA has conferred an accelerated approval pathway to medications showing promising benefits in NASH.

Due to an increasing understanding of the various molecular pathways responsible for the progression of NASH, a number of novel therapeutic agents are being evaluated to effectively combat this dreaded disease. Non-availability of an approved pharmacotherapy has led 'big pharmas' and other companies to treat NASH as a unique economic opportunity with analysts estimating the size of the global market for NASH treatments to be $35 to $40 billion by 2025.

A snapshot of the various mechanisms utilized by prospective companies

1. Drugs targeting hepatic fat accumulation
    - Peroxisome proliferator-activator receptors agonists
    - Farnesoid X receptor agonists
    - Inhibitors of de novo lipogenesis- ACC (Acetyl-CoA carboxylase) inhibitor
    - Fibroblast growth factor-21 analogs
2. Drugs targeting oxidative stress, inflammation, and apoptosis
    - Apoptosis signaling kinase 1 (ASK1) inhibitor
    - Irreversible caspase inhibitor
3. Drugs targeting intestinal microbiomes and metabolic endotoxemia
4. Drugs targeting hepatic fibrosis
    - CCR2 and CCR5 (Cysteine-cysteine motif chemokine receptor-2/5) receptor antagonist
    - Galectin 3 antagonist

The frontrunners in NASH therapy- Who will win the race?

Various investigational drugs work on diverse mechanism of action and all are at different stages of clinical development. Amongst the competitors, few have managed to enter phase III clinical trials and can certainly be addressed as the frontrunners in this race. The list of promising contenders includes Obeticholic Acid (Intercept), Elafibranor (Genfit), Cenicriviroc (Allergan/Tobira) and Selonsertib (Gilead).

A farnesoid X receptor (FXR) agonist, obeticholic acid leads the race in approval for NASH. It is currently being evaluated in two phase 3 trials-REGENERATE (for the treatment of non-cirrhotic NASH) and REVERSE (NASH patients with compensated cirrhosis). Obeticholic Acid has also been granted breakthrough therapy designation by FDA for the treatment of NASH with liver fibrosis.

On the other hand, Genfit's elafibranor is a dual-PPAR alpha/delta agonist and has demonstrated reversal of NASH without worsening of fibrosis in post-hoc analysis of data from phase 2 trial. Elafibranor also demonstrated excellent safety and tolerance profile and also provided outstanding cardio-protective benefits.

Cenicriviroc is a chemokine receptor (CCR2/5) antagonist. These receptors are intricately involved in the inflammatory and fibrogenic pathways in NASH. Due to its dual targeting mechanism, cenicriviroc if approved is expected to play a pivotal role in the treatment of

adults with NASH-associated liver fibrosis. It is currently being evaluated in the phase III AURORA trials.

Gilead's selonsertib is an inhibitor of Apoptosis Signaling Kinase 1 (ASK1). ASK1 is involved in inflammation, cell death and fibrosis in settings of increased oxidative stress, which is associated with the pathogenesis of NASH. By blocking ASK1, selonsertib has shown a reduction in liver fibrosis associated with NASH.

Not far behind in the race are drug candidates in the phase 2 trials. The list includes Emricasan (Conatus Pharmaceuticals), GR-MD-02 (Galectin Therapeutics), Aramchol (Galmed), IMM-124E (Immuron) and MGL-3196 (Madrigal).

Harnessing the power of combination therapies

Given the complex and multifactorial nature of NASH, combination therapy seems to be a logical strategy which can be employed by prospective NASH focussed companies. Novartis is expecting to combine its FXR agonist, tropifexor (LJN452) with Allergan's cenicriviroc. Novartis is also planning to test a combination of tropifexor with emricasan- an irreversible caspase inhibitor. Gilead Sciences is also focussing on combination therapy to treat NASH fibrosis. Encouraging results were obtained in a proof-of-concept study combining selonsertib (formerly GS-4997) plus GS-0976 (ACC inhibitor) or GS-9674 (FXR agonist). The regimens containing GS-0976 (combined with selonsertib or as monotherapy) produced the greatest changes in liver fat content. Patients receiving the combination also experienced the greatest reduction in a protein called lumican, a marker of fibrogenesis (formation of scar tissue).

Future prospects

With a therapeutic pipeline boosting of numerous investigational drugs in various phases of development, the highly untapped NASH market is certainly on its way to a promising therapy option. Owing to the chronic nature of the disease, the main goal of any NASH therapy should be to justify its cost/effectiveness model in the long run. Drugs targeting later stage of fibrosis and cirrhosis, where the risk of cancer development/liver failure is highest, would likely gain more acceptances from the payers.

As liver biopsy is the current gold standard for disease diagnosis, another aspect to be considered is the development of better screening methods for patient identification and treatment efficacy. Specific biomarkers may improve diagnosis and can also help to monitor/stage the disease.

With potential drugs in phase 3 studies, there is hope that the next few years will definitely roll out a suitable therapy option in clinical practice. However, cost-effectiveness and patient-centered benefits will certainly play a pivotal role in the whole process.