What is non-alcoholic steatohepatitis (NASH)?

More than just a liver disease

Liver diseases are highly complex conditions driven by multiple pathways[1]; they are typically poorly understood, frequently overlooked and associated with a high unmet patient need worldwide. While there have been significant medical advances in viral hepatitis, non-viral liver diseases, characterized by liver inflammation and fibrosis that are often asymptomatic, have limited therapeutic options causing an increasing global chronic disease burden.

One such example is non-alcoholic fatty liver disease (NAFLD). The obesity epidemic has impacted the prevalence of NAFLD across all ages globally[2,3]. If left untreated, over time fat build-up in the liver triggers a cycle of chronic inflammation which develops into non-alcoholic steatohepatitis (NASH) with associated fibrosis (scarring of the liver). There are currently no approved treatments for NASH, and the condition is predicted to become the leading cause of liver transplant in developed countries by 2020[4]. The prevalence of NAFLD in Western countries is 20-30%, and it is estimated that 2-3% of the western population has NASH[5].

NASH: A silent disease

NASH is a more severe, progressive form of NAFLD[6] with generally no, or only a few, non-specific signs or symptoms. If the liver damage continues long-term, it can result in advanced fibrosis (scarring of the liver), called cirrhosis, where patients may experience symptoms such as nausea, fatigue and weight loss; with further complications leading to portal hypertension, enlarged blood vessels, enlarged spleen, mental confusion and even kidney or lung failure[7]. Cirrhosis leads to an increased risk of developing a type of liver cancer called hepatocellular carcinoma (HCC), as well as liver failure and, barring a transplant, significant morbidity and death[7].

Most people who have NASH are aged on average between 40 to 50 years[5], however increasing numbers of teenagers and young adults are being diagnosed[8]. Studies also suggest that people with NAFLD have a greater chance of developing cardiovascular disease and this is also one of the most common causes of death from NASH[9]. Risk factors include[10]:

- **Obesity**, particularly if the individual has a large waist size
- **High levels of fats** (triglycerides) or abnormal levels of cholesterol in the blood
- **Having a metabolic syndrome** group of traits linked to being overweight and obese, including large waist size, high levels of triglycerides in your blood, low levels of HDL cholesterol in your blood, high blood pressure and higher than normal blood glucose levels
- **Type 2 diabetes**

Reaching a diagnosis

Whilst NAFLD can be diagnosed through various imaging techniques, a definitive NASH diagnosis requires an invasive liver biopsy[11]. The lack of non-invasive biomarkers in NASH represents an unmet need in supporting diagnosis of liver diseases and treatment development.

Treatment goals: An urgent need for new treatment options for NASH patients

As liver conditions, such as NASH, are highly complex and differ between patients, developing effective treatments requires collaboration across a number of areas of expertise.

Currently no approved treatments for NASH exist, although studies have demonstrated that Vitamin E and treatments for Type 2 diabetes show some improvements in NASH[12,13],

ultimately if cirrhosis develops, a liver transplant may be required[7]. Treating the conditions associated with NASH, with the aim of reducing liver inflammation, include[13]:

- Diet and weight loss
- Regular exercise
- Avoid significant alcohol

Novartis: Growing liver portfolio to target multiple pathways involved in NASH progression

Novartis is investing in a deep pipeline, spanning different stages of liver diseases, through both external collaborations and in-house research. The aim is to further scientific knowledge, accelerate treatment development and, ultimately, improve patient outcomes in the treatment of NASH.

Novartis currently has two farnesoid X receptor (FXR) agonists in global clinical studies. One of the most advanced investigational compounds is a liver-specific potent, non-bile acid FXR agonist, LJN452 (Tropifexor), which has received Fast Track designation from the FDA in 2016 and is in Phase II of clinical development. FXR agonists work by regulating the bile acid levels in the liver, and reducing fat build up (steatosis), inflammation, thickening and scarring in the liver. Tropifexor is being investigated as a mono therapy option, as well as in combination with Allergan's Cenicriviroc (CVC).

Novartis and Conatus Pharmaceuticals Inc. are jointly developing emricasan, an investigational, first-in-class, pan-caspase inhibitor which works by inhibiting pathways that result in cell death (apoptosis) and inflammation. Emricasan has received FDA Fast Track designation and if clinical development progresses positively, Novartis aims to conduct Phase III studies of emricasan to assess its potential as both a monotherapy and potentially an FXR agonist combination therapy option.

These new investigational agents are being evaluated in ongoing clinical trials.

References

1. Zhou WC, Zhang QB, Qiao L. Pathogenesis of liver cirrhosis. World J Hepatol. 2014;20(23):7312-7324.
2. Temple JL, et al. A Guide to Non-Alcoholic Fatty Liver Disease in Childhood and Adolescence. Int J Mol Sci. 2016;17(6): 947.
3. Vos M, et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children. J Pediatr Gastroenterol Nutr. 2017;64(2):319-334.
4. Canbay a et al. NASH Cirrhosis - the New Burden in Liver Transplantation: How Should It Be Managed? Visc Med. 2016 Aug; 32(4): 234–238.
5. National Institute for Clinical Excellence (NICE). Non-alcoholic fatty liver disease (NAFLD): assessment and management Available at: https://www.nice.org.uk/guidance/ng49/chapter/context Last accessed: March 2018.
6. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34(3):274-85.
7. National Institute of Diabetes and Digestive and Kidney Diseases. Cirrhosis. Available at: https://www.niddk.nih.gov/health-information/liver-disease/cirrhosis Last accessed: March 2018
8. Lerret SM, et al. Predictors of Nonalcoholic Steatohepatitis in Obese Children. Gastroenterol Nurs. 2011;34(6):434–437.
9. Azzam, H, Malnick, S. Non-alcoholic fatty liver disease – the heart of the matter. World J Hepatol. 2015;7(10):1369-1376.
10. National Institute of Diabetes and Digestive and Kidney Diseases. Symptoms and Causes of NAFLD and NASH. Available at: https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash/symptoms-causes Last accessed: March 2018.
11. National Institute of Diabetes and Digestive and Kidney Diseases. Diagnosis of NAFLD and NASH. Available at: https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash/diagnosis Last accessed: March 2018.
12. Sanyal AJ, et al. Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis. N Engl J Med. 2010;362:1675-1685.

13. National Institute of Diabetes and Digestive and Kidney Diseases. Treatment of NAFLD and NASH. Available at: https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash/treatment Last accessed: March 2018.