Non-alcoholic Steatohepatitis: The Hidden Pandemic

Obesity has become a major public health concern worldwide. Obesity is linked to the accumulation of fat in the liver, which can be associated with hepatic inflammation. Non-alcoholic steatohepatitis (NASH) has become a major liver disease and reason for liver transplantation. Prevalence rates for NASH are up to 6.5 %. Currently, no established pharmaceutical treatment for NASH is available, and several late-stage clinical trials are ongoing to become first to market. Impacting the progress of these trials, despite the large prevalence rates, is the fact that the actual available patient pool is much lower than anticipated. This is reflected in low average enrolment rates currently observed. There are many reasons for this, including lack of broad awareness, largely asymptomatic population, and highly invasive diagnostic assessments. NASH will remain a hidden pandemic until accurate and robust non-invasive methods become available to perform population screening, diagnostic assessment and therapy response evaluation.

Non-alcoholic Fatty Liver Disease: Definition and Clinical Picture

Non-alcoholic fatty liver disease (NAFLD) is now being recognised as the link to metabolic syndrome and obesity. NAFLD is defined by the excessive accumulation of fat (steatosis) in the liver (>5 % by histological evaluation). A subgroup of NAFLD patients has NASH with hepatic injury and inflammation, which is virtually indistinguishable histologically from alcoholic steatohepatitis (ASH). Therefore, the exclusion of any other chronic liver aetiology (e.g. viral, alcohol, drugs, autoimmune) is essential for the diagnosis of NASH. The presence of lobular inflammation and hepatocellular ballooning dramatically increases the risk of developing cirrhosis, liver failure and hepatocellular carcinoma. The presence of hepatic fibrosis is not part of the definition of NASH, but is the strongest indicator for disease progression (mean annual rate of progression: 9 %). NASH has now been identified as one of the leading causes of cirrhosis in adults, and liver transplantation in the US.

NASH is widely considered the liver component of "metabolic syndrome", characterised as type II diabetes, insulin resistance, central obesity, hyperlipidaemia, and hypertension (Figure 1). Individuals with NASH are usually asymptomatic. At the present time, scoring systems and imaging approaches are not robust enough prospectively to allow screening/diagnosis, prediction of progression and therapy response assessment. Liver biopsy is invasive and has a significant risk for sampling errors and inconsistent quantitative reading, but remains presently the gold standard for the diagnosis of NASH and the assessment of therapy responses. FDA and EMA are requesting that ongoing Phase III NASH trials have a staging liver biopsy at inclusion and a biomarker assessment with a second liver biopsy after one to two years of treatment. Final efficacy needs to be demonstrated by the outcome assessment with a reduction in the progression rate to end-stage liver disease (e.g. cirrhosis).

Figure 1: Obesity and the metabolic syndrome.
Fatty liver disease, as either steatosis or steatohepatitis, is representing the hepatic link. NASH is now a major contributor to clinically relevant and progressing end-stage liver disease with cirrhosis.

Presently, patients with predicted NAFLD are advised to consider lifestyle changes, as modest weight reduction causes liver histology improvement.

NASH Diagnosis in Clinical Practice:

Reviewing the electronic medical records for 160 million people in the US from January 2015 to January 2016 using the NASH ICD-9 codes 571.8 and 571.9, suggests that approximately 750 thousand patients present with NASH and require medical utility (Figure 2). This represents around 67 % of all recorded diagnoses of chronic liver disease and cirrhosis. It is of further interest that only 27 % of these patients are being seen by a hepatologist or gastroenterologist. Therefore, while NASH has been recognised as a significant medical problem in the academic sense, but has not yet been widely targeted by the medical community as a relevant disease to diagnose and manage.

Clinical Trials in NASH Patients:

Between 2012 and 2016, ten multi-centre industry-sponsored trials have been completed involving NASH patients. The range of the average enrolment varies between 0.11 and 0.60 patients/site/month (p/s/m) with a mean of 0.31 ± 0.15 p/s/m and median of 0.29 p/s/m (Figure 3). Overall, the average enrolment rate is much lower than the prevalence data for obesity, NAFLD and NASH would predict. The increased awareness of NASH in recent years has not changed the recruitment rate. The presently ongoing Phase IIB and III trials are hindered

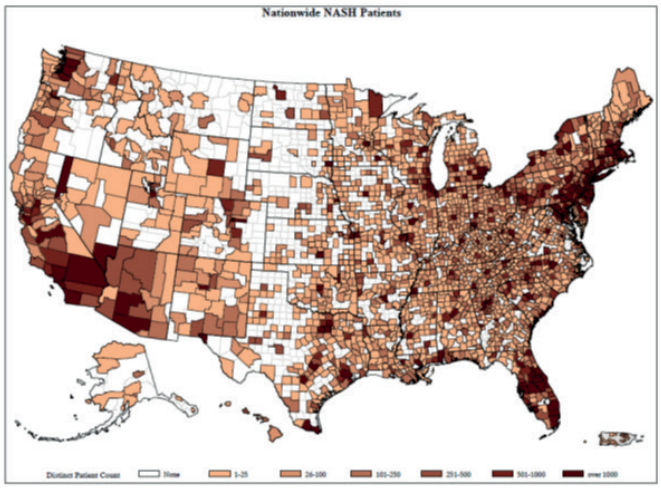

Figure 2: Electronic medical records in the US for NASH ICD9 code. The graph shows the distribution of NASH claims across the US (Source: DarkMatter Incorporation; data from January 2015 to January 2016)

by much lower than expected enrolment rates due to the diagnosis criteria and the requirement for liver biopsies in an often asymptomatic patient. Several agents are in later-stage development (e.g. GFT505, obeticholic acid, simtuzumab) and need to show an improvement in NASH histology plus long-term outcome to prove efficacy.

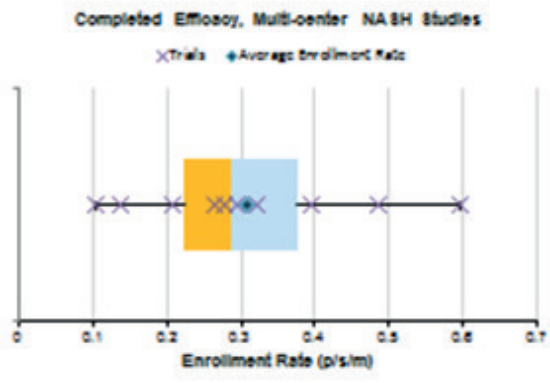

Figure 3: Average enrolment rates in multicentre NASH trials (time period 2012-2016 and n=10).
The average recruitment is around one patient per site and quarter. The data are generated from clinicaltrials.gov (August 2016)

Future Development of NASH Treatments:
The worldwide obesity rates indicate that our changing lifestyles are contributing factors to increased health problems, including liver diseases. NASH is now a growing major global public health problem; a pandemic. The presence of NASH is often asymptomatic and the diagnosis is often delayed until cirrhotic liver changes occur and become clinically visible.

Liver biopsy remains presently the gold standard for diagnosis and staging of NASH. The acceptance of repeat liver biopsies in a mainly asymptomatic population is associated with a significant negative impact on the recruitment rates in NASH trials. The acceptance of clinical trials by NASH patients will be much higher when robust and accurate non-invasive clinical assessments are available and accepted by the medical and regulatory communities. This also will have the beneficial effect of significantly increasing the available NASH pool for large clinical trials.

Furthermore, the development of non-invasive assessments to diagnosis and stage NASH will be essential to fully evaluate disease prevalence and its impact on the health system.

NASH is a hidden pandemic which cannot be assessed widely due to the lack of non-invasive, robust and accurate diagnosis and staging modalities. The future development of treatments for this hidden disease will depend on the development of the non-invasive markers broadly accepted by the medical and regulatory communities to manage NASH.

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