NASH: How to Conquer this Global Health Crisis

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5 Challenges and Best Practices of NASH Clinical Research

By Claudia Filozof

Tens of millions of adults worldwide are unaware they have a silent, progressive disease called Non-Alcoholic Steatohepatitis (NASH). It is damaging their livers and can lead to severe disease states such as cirrhosis, liver carcinoma, liver failure and even death. By the time symptoms emerge, the disease has typically progressed too far for reversal. And while its prevalence is estimated at a staggering 5 percent of adults globally, NASH diagnosis rates are unknown because they are so low.

Currently, there is no approved therapy for NASH, but due to the increasing prevalence and health burden, regulatory authorities are motivated to help. Accelerated/conditional approvals with surrogate endpoints, registration with just one study and flexibility for adaptive design are all being supported.

The size and severity of this global health threat could result in approval of multiple therapies of potentially blockbuster size. As a result, dozens of pharmaceutical companies are scrambling for even a sliver of this massive potential market.

NAFLD vs NASH

Non-alcoholic fatty liver disease (NAFLD) covers a spectrum of liver injuries that begins with the presence of excess fat in the liver (steatosis). This condition is a possible precursor to a more serious condition (NASH) with inflammation and liver cell damage that can then lead to fibrosis (scarring) and cirrhosis. An estimated +30 percent of the general population and 60 percent of obese subjects are affected with NAFLD and approximately 12 to 40 percent of NAFLD patients will progress to the more dangerous stage of NASH. NASH has a high likelihood of advancing to cirrhosis, hepatocellular carcinoma, liver failure and even death. Both simple steatosis and NASH are associated with an increased risk of metabolic complications (e.g., Type 2 Diabetes and Dyslipidemia) and cardiovascular disease.

NASH is the leading cause of chronic liver disease and recently (2016) surpassed the hepatitis C virus as the leading cause for adults on liver transplant lists.1 NASH is growing in parallel with the obesity epidemic. The disease progresses more rapidly in those with diabetes, increasing with age and obesity. Risk factors include obesity and insulin resistance, but in some cases neither is present.

NASH Diagnosis

The lack of symptoms in early stages of the disease often allow it to progress unnoticed. Although astute doctors can diagnose NAFLD with imaging, a diagnosis of NASH can only be confirmed with a liver biopsy. Due to the invasive nature, pain and possible complications resulting from a biopsy, diagnosis has historically been limited.

If a biopsy is collected, three histological characteristics are required for a NASH diagnosis: steatosis (presence of fat greater than 5 percent), liver cell ballooning and inflammation. The diagnosis of NASH and its distinction from NAFLD carry important implications due to the increased risk of progression to cirrhosis and hepatocellular carcinoma. Early identification of individuals who will progress to NASH and cirrhosis remains a challenge.

Limitations of Alternate Diagnostic Methods

Due to the challenges associated with obtaining a liver biopsy, researchers continue to seek alternative noninvasive diagnostics; however, current noninvasive methods have limitations – including low sensitivity. Examples of noninvasive alternatives and their limitations are outlined below:

- **Liver aminotransferases:** More than 60 percent of patients with NAFLD have liver aminotransferases (i.e., enzymes associated with liver damage) within normal reference ranges, even at late stages of the disease.
- **Ultrasound:** While ultrasound is an easy and inexpensive method to diagnose fatty liver, it is not sensitive enough to detect small amounts of fat.
- **Magnetic resonance imaging (MRI):** MRI has good sensitivity to detect liver fat, but it is expensive and therefore used for clinical research purposes only.

Further research to develop a noninvasive alternative is ongoing. New ultrasound-based technology can assess liver stiffness, an indirect marker of fibrosis. Multiple serum markers of inflammation or liver fibrosis have also been studied as potential diagnostic tools, but none are validated for NASH diagnosis.

Grading and Staging Severity of NAFLD and NASH

Two scores are used to provide objectivity, assess severity, select patients for study enrollment and evaluate changes during clinical trials.

1. **NAFLD Activity Score (NAS)** is an un-weighted composite of the degree of steatosis (0 to 3 points), inflammation (0 to 3 points) and ballooning (0 to 2 points). The total score ranges from 0 to 8. Patients who have a very low NAS score tend to be in early stages of the disease.
2. **Fibrosis Staging**, as the name implies, is a measure used to categorize the stages of fibrosis, which are the main predictor of mortality in patients with NASH. The staging score ranges from 0 to 4, starting with delicate periportal-only fibrosis (stage 1), increasing to dense perisinusoidal, portal, and periportal fibrosis (stage 2), bridging fibrosis (stage 3), and cirrhosis (stage 4).

Five Challenges of NASH Clinical Research

Awareness of the specific challenges facing NASH clinical studies can help research organizations improve their success. Below, we've outlined five key challenges, as well as best practices for managing these challenges.

1. **Very low rate of confirmed NASH diagnoses**

   Despite high prevalence, one of the greatest challenges of NASH research is enrolling patients with confirmed diagnoses. Some data suggest only 25 percent of U.S. hepatologists follow guidelines for when to request a liver biopsy. In addition to the limited number of patients with biopsy-confirmed NASH, several current clinical trials aim to enroll patients with NASH and some degree of fibrosis.

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Overcoming this challenge requires multiple approaches. Predictive analysis can be used to pre-identify patients who are at the disease stage needed for a clinical trial. This requires using clinical and genetic data as well as modeling the latest knowledge of the disease's progression. Maintaining relationships with prospective and previous investigators is vitally important for trial readiness. This requires regular follow-up with investigators, sharing, and gathering information to stay updated about the feasibility of starting new trials. It is recommended to not only maintain relationships with hepatologists, but also investigators from prior diabetes, obesity and lipid trials. These physicians can be involved as investigators or as referrers to the principal investigator. In the latter case, the referring physician sends patients with a high risk of NASH to the principal investigator who can evaluate and request a liver biopsy in the context of the clinical trial.

2. **Long natural history of the disease**

   NAFLD has a long natural history and it often does not develop into cirrhosis or produce outcomes for more than 20 years. In order to demonstrate a new drug's impact on clinical outcomes (i.e., improvement in an endpoint such as presence of cirrhosis) trial durations are long and expensive. Knowledge of the disease's natural history is critical for intelligent design of clinical trials.

   An effective strategy to reduce time and cost is to target patients for clinical trials who will have clinical outcomes (progression to cirrhosis or cirrhosis decompensation symptoms, variceal hemorrhages, etc.) in a reasonable time frame. The recommendation is to enroll confirmed NASH patients with a NAS score of 4 or higher and a fibrosis stage of 2 or 3. These patients have advanced in the disease to where an outcome can occur and therefore demonstrate the impact of the investigational drug in reducing outcomes.

3. **Different genotypes and phenotypes impact progression rate and possibility of spontaneous regression**

   Certain genotypes and phenotypes can cause faster progression of NASH. The PNPLA3 genetic mutation, for example, causes faster progression of the disease. Older patients and patients with diabetes can progress faster relative to young non-diabetics. NAS has also been reported as a predictor of disease progression.

   Knowledge of faster progressing pheno- and genotypes can be used early in the development program to enrich patient selection. In some cases there may be a need to stratify by these factors. Patients in very early stages of the disease can have a spontaneous regression (i.e., improvement); this is less likely in late stages. Regression is more likely to occur early in the disease (i.e., NAS score of 1, 2 or 3) and in those without fibrosis. Thus, enrolling patients with a NAS score of 4 or higher and with fibrosis will minimize this risk and facilitate data interpretation. All these factors must also be considered when making patient enrollment decisions.

4. **Limitations of the liver biopsy**

- **Reluctance of patients to have two liver biopsies within 12 to 18 months.**
  Increased education and awareness are needed to convince both patients and investigators about the importance of liver biopsies for developing new treatments for this disease.

- **Variability of biopsy sampling**
  Liver biopsies are obtained with a needle through the abdomen by different investigators at different sites. It is important to limit the sampling variability that can occur due to varying techniques. For instance, a 16-gauge needle is recommended. Some hepatologists use a needle that is too small and as such, do not get a sufficient sample. To limit sampling variation, it is important to educate investigators about the specific protocol to be used in sample collection.

- **Variability in sample interpretation**
  Sample interpretation is another area where variability can occur due to multiple readers. An inherent amount of variability exists, even with good protocols. Intersubject variability can be as high as 25 percent. Slides of liver cell biopsies obtained from multiple sites throughout the world need to be interpreted by a pathologist. Different pathologists with varying levels of NASH expertise introduce variability into the results. One way to manage this is by using an expert central reader, a unique pathologist with NASH expertise.

- **Cost and risk of sample transportation in a global trial**
  Obtaining biopsies from sites across the world and safely transporting these samples to a central location for reading can also present challenges. The timeliness and controlled conditions needed to preserve the sample must be managed and can be costly. Also, multiple handoffs during shipping present risk for loss or damage to samples. Digital imaging technology is one way to avoid these issues. After the biopsy sample is prepared at the central lab, the slides can be processed, scanned into a digital image and sent to the central reader. Thus limiting cost and avoiding risk associated with transport of samples.

5. **Late-stage referrals to hepatologists**

   Endocrinologists and diabetologists who follow most NASH patients often refer them to hepatologists too late. The main reasons for late referrals are lack of symptoms, liver enzyme test results within normal ranges, and low sensitivity of the ultrasound. This issue requires long-term education to raise the awareness of specialists who are likely to encounter patients with signs of NAFLD and NASH. Some useful algorithms, based on routine assessments, may also facilitate the identification of patients at high risk for NASH.

Opportunities for NASH Research

The challenges presented by the very low number of diagnoses, combined with a high unmet need, enable accelerated regulatory initiatives to be applied on a global basis to accelerate development of investigational drugs.

1. **Accelerated/conditional approvals**

   Accelerated approval is a regulatory pathway of drugs for serious unmet medical needs. By using an appropriate, surrogate clinical endpoint the sponsor can seek an accelerated or conditional marketing approval for a new drug. With liver research, normally a clinical endpoint would have to show that a drug improves the progression of cirrhosis, or the number of patients experiencing complications associated with cirrhosis or liver transplantation, or even overall mortality.

   For NASH, two surrogate endpoints are being utilized – resolution of NASH by histology (i.e., disappearance of ballooning, with no or mild inflammation) is one of them. Since fibrosis is a predictor of mortality in patients with NASH, resolution of NASH should be associated with no worsening of fibrosis. In addition, improvement in liver fibrosis by at least one stage is also accepted as a surrogate marker likely to be associated with an improvement in outcomes. To date, these types of surrogate clinical endpoints are being suggested as acceptable endpoints for an accelerated or conditional marketing approval. Following an accelerated/conditional approval, a post-approval confirmatory clinical study using clinical outcomes is required to achieve a full marketing approval. As of early 2017, there have been no accelerated/conditional approvals for any drug in NASH, although several companies are conducting clinical studies toward this goal.

2. **Adaptive trial design**

   Adaptive trial designs are being increasingly evaluated as a way to optimize the time to development without compromising the data's quality. An adaptive design provides the opportunity for prospectively planned modifications to one or more specified aspects of a study design (i.e., making adjustments at the end of each stage) and may allow for minimizing the overall number of patients required in the development program. It may further allow the same subjects to move from one phase to another and thus reduce the need to find additional subjects for treatment trials who will be willing to accept multiple biopsies.

Industry-wide Collaboration Needed

To overcome the growing momentum of the NASH health crisis requires industry-wide collaboration from participants. This will take a combined effort including: higher awareness and education among the medical community and patients, higher rates of diagnosis, improved noninvasive diagnostics, multiple approved therapies and the continued support of regulatory authorities.

Joint efforts of the scientific community, health authorities and pharma companies have resulted in two current registrational trials and many Phase 2b trials. The first approved therapies are expected within the next few years; however, many more will be needed to achieve a multi-targeted therapeutic approach and to reverse the growth of this substantial healthcare burden.

Major opportunities await those who accept the challenge.

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Sources

1. Findings presented at the American College of Gastroenterology, October 2016.

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