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Follow the Yellow Brick Road: The Pathway for NAFLD and NASH Drug Development in Early Phase Clinical Trials

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The current market for type 2 diabetes mellitus (T2DM) medications is saturated with a plethora of choices of therapeutic agents, many of which have very favorable safety profiles. It has been proposed that the combination of this crowded and competitive landscape along with the increased burden of thorough cardiovascular risk assessment required since 2008, have stifled innovation in the development of new anti-diabetic medications. In stark contrast, there are currently no medications on the market for the specific treatment of non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH).

NAFLD is a common disorder that is closely associated with other metabolic derangements including obesity, insulin resistance, T2DM, and dyslipidemia. The incidence of NAFLD is estimated between 10% - 30% of children and adults in the general population [1,2].Moreover, the prevalence of NAFLD among obese and T2DM patients is estimated at 70% and 75% respectively [3].

While the etiology of this metabolic disorder still remains unknown, excessive dietary fructose consumption has been implicated in the development of NAFLD. The overconsumption of fructose and initial metabolism of this substrate by fructokinase (or ketohexokinase) is not rate limited which may lead to liver damage through fructose-induced depletion of hepatic ATP. Additionally, hepatic metabolism of fructose favors lipogenesis as opposed to convergence with glycolytic pathways [4]. Fructose in the liver can be metabolized through pathways that generate glycerol, which is an essential component for the formation of triacylglycerols, and can also be a source of citrate within the cell, a key stimulator of fatty acid synthesis [4]. Further, fructose metabolism may be implicated in derangements known to have causal relationships with metabolic disturbances. These derangements include stimulation of inflammatory pathways, oxidative stress, hepatic lipid peroxidation, and hyperuricemia [4]. The dietary transition of increased fructose consumption that began in the 1970s and continues to present may be pathogenically linked with the coincidental epidemic prevalence of metabolic disturbances such as obesity, diabetes, and nonalcoholic fatty liver. This is concordant with the first naming and description of NASH in 1980 [5].

Non-alcoholic fatty liver, or simple hepatosteatosis, is relatively asymptomatic and in some cases benign [6]. At present, there are no predictive markers for which patients will develop advanced states of this disease, and the progression of which may be quite protracted. However, it is estimated that approximately 20% of individuals with NAFLD will develop NASH [7]. NASH is a serious health threat that, as a result of prolonged steatosis, is distinguished by lobular inflammation, hepatocellular ballooning, and fibrosis. In advanced stages of NASH, fibrosis may progress to hepatocellular carcinoma with or without cirrhosis [6]. NASH is also rapidly eclipsing all other causes of liver transplantation.

One of the primary obstacles to developing NAFLD/NASH specific therapies has been the absence of a clear pathway for approval. Therefore, in order to promote drug development in this area, the Food and Drug Administration (FDA) and American Association for the Study of Liver Disease (AASLD) recently published their views on a pathway to diagnose and treat liver diseases such as NAFLD and NASH [8].

In a recent article in Hepatology, Sanyal and colleagues comprehensively detailed the suggestions brought forth during a joint FDA-AASLD workshop describing the challenges and opportunities for NAFLD therapeutic development [8]. Both organizations recognize that the lengthy process in which fatty liver disease may progress into NASH or the worsening of NASH to cirrhosis can be a major obstacle in a clinical trial setting as all-cause morbidity or mortality, considered traditional clinical endpoints, could result in studies enduring several years before drug efficacy is observed. Therefore, opting for realistic outcomes for early phase studies, rather than complications associated with liver-related mortality, the joint workshop suggested pharmacological agents that render a clinically beneficial effect of a surrogate endpoint would be an acceptable treatment outcome. These surrogate endpoint markers may include the reversal of steatohepatitis without the development of advanced fibrosis [8].

In a clinical setting, liver fat is measured directly by obtaining biopsy tissue and performing histological assessments, or through a non-invasive imaging tool such as magnetic resonance spectroscopy or ultrasonography approaches. Implementation of these may have limitations in early phase clinical explorations. Early phase clinical research is, however, well positioned to be strategically leveraged for signals of efficacy with more practical, specialized assessments. For instance, factors influencing lipid accumulation within the liver such as the measurement of de novo lipogenesis (DNL) would have a

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meaningful clinical impact with regards to assessing the efficacy of an investigational product.

While early studies proposed that NAFLD was simply associated with adipose tissue insulin resistance, resulting in excess fatty acid lipolysis and the liver absorbing the brunt as an ectopic lipid storage site [9,10]. More recent evidence suggests that in addition to the impact of adipose tissue dysregulation, the liver also actively participates in the disorder through upregulation of DNL [11]. For example, DNL is increased 3-fold in individuals with a fatty liver compared to age- and BMI-matched controls [12]. DNL can be experimentally induced by the administration of fructose as a challenge agent. Then, DNL rates can then be determined by sophisticated stable-isotope labeled tracer studies, which examine the rate of labeled VLDL-triacylglycerol palmitate derived from the administration of deuterated water [12-14] or ^{13}C-acetate [15,16]. As such, DNL measurement has been harnessed as an in vivo biomarker of efficacy for interventions of hepatic steatosis.

In addition to measuring DNL, fatty acid oxidation measurements may be important complementary assays used during clinical studies. Lipid oxidation can be simply tracked by evaluating ketone levels, a byproduct of beta-oxidation or via indirect calorimetry. Indirect calorimetry measures oxygen consumption and carbon dioxide production through gas exchange and this refined technique can detect subtle changes in fuel utilization, such as increased fatty acid oxidation rates or decreased whole-body DNL, which would be beneficial indicators of improved metabolism influencing liver fat accumulation.

Therefore, with respect to treating NAFLD and preventing progression to NASH, many opportunities exist for pharmacological development in this area. Large markets created by unmet needs encouraged by the recently proposed pathway to approval are promoting innovation in this therapeutic indication. Although the recent FDA-AASLD publication did acknowledge the challenges associated with the development of diagnostic and pharmacological treatment of NASH, unfortunately full consensus on a pathway was not achieved. Nonetheless, findings from their session did suggest key endpoint and surrogate markers for early phase clinical research trials and that these outcome measures would be considered under the FDA's Accelerated Approval Pathway [8]. In summary, NAFLD and NASH affect a large portion of the population; yet predicting who will progress to advance stages of chronic liver disease still remains a challenge. Therapeutic agents designed to reduce lipid accumulation within the liver are critical for treating these metabolic disorders and surrogate endpoints such as reducing hepatic steatosis are being considered as potential outcome measures of drug efficacy in early phase research.

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