Future Watch: Evolving Trends in the Management of Nonalcoholic Steatohepatitis

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Nonalcoholic steatohepatitis (NASH) has emerged as the leading etiology of chronic liver disease in the United States and is a growing problem in virtually all parts of the world. It is not only associated with increased liver-related morbidity and mortality but also increased cardiovascular- and cancer-related outcomes and mortality.^{1,2} The cancer-related risks not only pertain to hepatocellular cancer (HCC) but also to a variety of nonhematologic cancers as well. Moreover, a large proportion of HCC associated with NASH occurs in the absence of cirrhosis.³ These factors underscore the need to develop effective preventive and therapeutic strategies against NASH.

Heterogeneity of NAFLD and Its Implications for Diagnostic Assessment and Therapeutics

It is common to consider all nonalcoholic fatty liver disease (NAFLD) and NASH as one disorder, but there is strong evidence that this traditional view of the condition is incorrect. Both hepatic steatosis and steatohepatitis can develop via a multitude of molecular pathways. Steatosis can occur from an imbalance between lipid influx and synthesis on one hand and its turnover and export on the other. A variety of disorders of lipid metabolism can result in NAFLD. Also, a diverse array of drugs, such as diltiazem, tamoxifen, and amiodarone, can cause the full histological spectrum of NAFLD. Both high-fat and high-carbohydrate diets can lead to NAFLD.^{4,5} The risk of liver injury and progressive disease depends on the activation of cell injury, inflammatory, and fibrosis pathways on one hand and tissue

repair mechanisms on the other. These are not only affected by the breakdown of metabolic homeostasis in the liver but by a systemic activation of the innate immune system, changes in gut microbiota, and the genetic predisposition of an individual subject. A number of genetic polymorphisms, eg, the PNPLA3 and TM6SF2 have been linked to NASH and advanced disease. The interactions between these genetic factors with other obesity- or diabetes-related genes are largely unknown. The influence of varying degrees of alcohol consumption below the thresholds for alcoholic liver disease is also uncertain. At a molecular level, these numerous variables lead to a multitude of variations in pathway activation which can result in a common histological phenotype, ie, fatty liver or steatohepatitis. A major challenge for the future will be to understand the specific pathways involved in a given subject and tailor therapeutics to their needs.

Current Approaches to the Evaluation of NAFLD

NAFLD affects about 30% of the adult population and 10% of the pediatric population in North America.^{6,7} A subset of these individuals develops liver-related outcomes. The current standard of care involves a liver biopsy to identify the presence of steatohepatitis and the stage of fibrosis to determine the risk of progression to cirrhosis, the principal pathologic outcome of the disease which is related to clinically meaningful outcomes such as death, ascites, encephalopathy, and variceal hemorrhage. There are, however, several limitations of this approach. Liver biopsies are invasive, associated with some discomfort and occasionally severe

Abbreviations: HCC, hepatocellular cancer; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

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morbidity and even mortality. This has limited the willingness of patients and primary care physicians to refer subjects who are relatively asymptomatic to start with this procedure. There is also variability in the expression of the disease from one section of the liver to the next even when taken from the same liver biopsy core. The problem is further compounded by both intra- and interobserver variability in reading the histological findings, even in expert hands.⁸ Importantly, traditional histological techniques provide no clue about the molecular basis for the disease or the specific pathways involved in an individual person. Finally, the medical manpower to perform and interpret liver biopsies in a third of the population does not exist. There is therefore an urgent need to develop better methods to identify those at risk.

Futuristic Trends in the Evaluation of NAFLD

There is already growing interest in identifying the presence of steatohepatitis via a variety of noninvasive methods and algorithms. These are being combined with noninvasive assessment of hepatic fibrosis, particularly the presence of advanced fibrosis (ie, bridging fibrosis or cirrhosis). The APRI, FIB4, and NAFLD fibrosis scores all identify the presence of advanced fibrosis in NASH with areas under the receiver operating characteristic curve (AUROCs) of approximately 0.8 and have all been shown to predict liver-related outcomes.^{9,10} Transient elastography using ultrasound or MR technology can also identify those with advanced fibrosis.¹¹⁻¹³ Modifications of these technologies to diagnose steatosis, steatohepatitis, and to separate those with none from those with stage 1 or higher fibrosis will allow further refinements in the noninvasive assessment of NAFLD. These are providing proof of concept that the risk of a liver-related outcome in those with the disease can be ascertained noninvasively. However, the accuracy of these approaches for specific clinically meaningful diagnostic questions remains suboptimal and need continued refinement.

Once disease develops, from a patient-centered perspective, the key diagnostic questions are: (1) is NAFLD present, (2) what is the risk of a liver, cardiovascular, or cancer outcome, (3) which molecular pathways are driving this risk, and (4) can therapeutics be tailored to the specific pathways involved while minimizing the risk of toxicity. We foresee the use of high-throughput technologies combined with powerful computing algorithm development to include genetics, diet, lifestyle, clinical and routine laboratory data, along with gene expression and metabolic profiling to answer these questions. The development of such methodologies is a burning priority in the field.

Current Treatment of NAFLD

There is currently no approved therapy for NASH. The US multisociety practice guideline recommends the use of

vitamin E (800 IU/day of RRR- α -tocopherol) for nondiabetic noncirrhotic subjects with NASH. Vitamin E improves histology in about 43% of such subjects compared to 19% of those receiving placebo.¹⁴ However, almost two-thirds of subjects do not respond, and there remain questions about the long-term safety of such doses of vitamin E. Similarly, while pioglitazone has been shown to improve liver histology in phase 2b trials,¹⁵ its use is associated with progressive weight gain, increased fracture risk, and fluid retention. The potential risks of bladder carcinoma also limit the long-term utility of this agent.

Future Treatment of NASH

From a societal perspective, the key time for preventive interventions is in childhood. There is a critical need to increase awareness in those who provide pediatric care and link approaches to wellness enhancement by early society-wide adoption of better diet and lifestyle choices, including physical activity. The actualization of this concept crosses the boundaries of medicine into agriculture, economics, social trends, and politics, making this a complex and difficult process. This should not however deter doing the right thing, and it is hoped that health care providers will partner with other stakeholders to ensure the health and well-being of future generations.

In the meantime, several agents are entering phase 2b and pivotal phase trials for NASH. Some such agents target the steatohepatic component and early-stage disease. Obeticholic acid is a farnesoid-X-receptor agonist. It has been shown to improve all of the individual histological components of NASH, including hepatic fibrosis.¹⁶ It also causes some weight loss but the histological improvement is independent of the weight loss. It is, however, associated with increased pruritus and also a modest increase in LDL-cholesterol by 5–10 mg/dL. The clinical relevance of the latter finding remains to be determined. Another compound that is nearing completion of a phase 2b trial is the GFT-505 molecule, which is a PPAR- α agonist. It has relatively liver-specific effects and has not been previously associated with the adverse event profile of PPAR- γ agonists. There are numerous other agents that are currently in early-phase development (see ClinicalTrials.gov for a list).

Another approach is to take those with advanced fibrosis and focus on the fibrosis. The rationale for this approach is that this may prevent hepatic decompensation and liver-related outcomes, including death. It may also buy time for other approaches directed at the steatohepatitis itself to work. There is currently a multinational phase 2b/3 trial of a monoclonal antibody to lysyl-oxidase that is ongoing. A phase 1 trial of a Galectin-antibody has also been completed without evidence of toxicity. Numerous other fibrosis targets

are currently also being evaluated in early-phase trials (see ClinicalTrials.gov for a list of such agents).

Ultimately, it is hoped that a diverse array of agents which are safe and attack a variety of molecular targets will be available for the treatment of NASH. Improvement in non-invasive and molecular pathology methods will allow identification of the molecular targets relevant for a given individual and permit treatment to be tailored to the indi-

vidual. Although much work remains to be done, there is considerable optimism and excitement, which provides hope that this vision of personalized medicine will be actualized to control this modern epidemic.

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