Leveraging Clinical Pharmacology to Optimize Drug Development for Nonalcoholic Steatohepatitis (NASH) and Cholestatic Liver Diseases

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About the Issue Brief

The following summarizes challenges impeding the development of therapies for NASH and cholestatic liver disease and recommends goals for basic research and clinical study. Academicians and biopharmaceutical developers can adopt these goals to expedite the availability of novel therapies. The following challenges and recommendations synthesize the discussion of a broad coalition of liver disease experts convened by the Duke-Margolis Center for Health Policy and the U.S. Food and Drug Administration (FDA).

About the Duke-Margolis Center for Health Policy

The Robert J. Margolis, MD, Center for Health Policy at Duke University is an academic research center and policy laboratory addressing pressing issues in health policy. The Center's mission is to improve health and the value of health care through practical, innovative, and evidence-based policy solutions. To learn more, visit healthpolicy.duke.edu.

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Nonalcoholic steatohepatitis (NASH) is a clinically significant histologic subtype of nonalcoholic fatty liver disease (NAFLD) increasing in prevalence alongside the global obesity epidemic.[1] NASH can necessitate liver transplants and drives significant liver-related mortality.[1] Unfortunately, there are no drugs approved for the treatment of NASH and several late-stage clinical trial failures underscore the significant scientific barriers impeding drug development for NASH and related liver diseases.[2,3,4]

The U.S. Food and Drug Administration (FDA) and its collaborators are committed to increasing the availability of effective therapies for NASH and cholestatic liver disease. FDA supports drug development by publishing guidances, engaging sponsors throughout the investigational new drug (IND) process, encouraging data sharing among stakeholders, and guiding biomarker qualification. The Critical Path Institute and consortiums such as NIMBLE and LITMUS are also advancing solutions, including the use of models to understand drug effects and disease progression, as well as the development of qualified biomarkers.

In December 2019, the Duke-Margolis Center for Health Policy and the FDA convened liver disease experts to discuss how researchers can leverage clinical pharmacology to expedite drug development for NASH and cholestatic liver diseases. To advance therapeutic development, researchers, biopharmaceutical developers, and trialists can adopt the research and development priorities discussed at the meeting and outlined below.

Understanding the Challenges Impacting Therapeutic Development

Multiple NASH Phenotypes Result in Substantial Variation in Treatment Response and Patient Outcomes

NASH phenotypes vary widely among clinical trial participants on the basis of individual patient characteristics and differences in disease progression and can lead to varied clinical responses, trial endpoints, and patient outcomes. Predicting how target engagement may translate into therapeutic efficacy during early clinical development is therefore complicated. However, selecting the right target for the right phenotype is key to successful drug development.

Designing effective trials and enrolling the appropriate patients is challenging without knowing which targets result in therapeutic efficacy among varied NASH patients. To date, several investigational therapies have shown only narrow margins of efficacy compared to placebo, even among highly phenotyped cohorts. Approving such drugs for the broader NASH patient population might result in reduced efficacy owning to phenotypic heterogeneity. As such, developers must be able to effectively identify and enroll the appropriate trial participants to generate targeted therapeutics.

Chronic Liver Disease Dynamically Alters Pharmacokinetics and Pharmacodynamics

Some variation in therapeutic response occurs specifically because NASH and other cholestatic liver diseases dynamically alter the pharmacokinetics (PK) and pharmacodynamics (PD) of investigational therapies. When investigational therapies target molecules or pathways within the liver that themselves change as a result of disease progression, both therapeutic efficacy and potential risk to the patient can change over time. This effect may be especially relevant for

therapies intended for long-term use. As patients' livers heal, the PK properties of their therapies may change and require altered dosing.

NASH also impacts investigators' ability to infer intrahepatic drug exposure based on plasma drug concentrations. NASH alters liver transport proteins that may change the relationship between liver and plasma drug concentrations.[5] For example, the change in plasma concentrations of obeticholic acid in patients with NASH stratified by fibrosis stage did not correlate well with the change in intrahepatic concentrations.[6] Thus, determining when to alter doses and by how much depends on additional clinical research and further complicates drug development.

Histologic Diagnosis, Disease Staging, and Biomarker Development Impede Trials

Dependence on liver biopsies is another major challenge to development. Liver biopsies are burdensome and invasive but remain the most accurate method to diagnosis and stage NASH. Without efficient diagnosis and staging, clinical trial design, endpoint selection, and patient enrollment suffer. Liver biopsies are also subject to sampling variability as well as intra- and inter-observer variability. Each tissue sample depends on the precise biopsy location. The resulting proportions of fatty, inflamed, or fibrotic tissue and the intensity of each classification vary accordingly. Furthermore, the pathologists examining biopsies introduce additional variability that diminishes the reliability of the resulting measurements. As a result, more reliable and less invasive methods to diagnose and stage disease are needed.

Less-invasive biomarkers that accurately characterize disease and enable appropriate patient screening and trial enrollment can facilitate therapeutic development. Unfortunately, developing biomarkers for NASH is especially challenging. Biomarkers that indicate even dramatic reductions in liver fat or other measures of NASH may not translate to meaningful changes in clinical endpoints. This poor predictive value results from the impact of multiple pathways on disease progression. Furthermore, a single biomarker is unlikely to represent a surrogate for the total spectrum of NASH and a combination of soluble, imaging, and functional markers may ultimately prove most useful.

Expert-Recommended Goals for Preclinical Research and Clinical Trials

First, further research characterizing the molecular pathophysiology and progression of NASH and cholestatic liver disease is necessary to advance therapeutic development. Developing and validating non-invasive biomarkers depends on additional basic research. Without this research, investigators will continue to face challenges delineating liver disease phenotypes and anticipating and addressing PK and PD changes resulting from variations in disease progression and hepatic impairment. Developing biomarkers suitable for comparing therapeutic effects among different disease phenotypes and investigational therapies will be essential to future development.

Second, expanded and earlier completion of hepatic impairment studies can facilitate patient selection, patient safety, and PK data collection that benefits later-stage development. Ensuring the safety of investigational therapies depends, in part, on understanding how compensatory mechanisms impact a diverse patient population and how investigational therapies may

dynamically alter PK and PD effects. Hepatic impairment studies conducted early during clinical development can provide investigators with PK data to inform safer patient enrollment, especially in the context of potentially asymptomatic progression toward hepatic impairment in patients enrolled in longer-term phase II and III studies.

Third, advancing approaches such as physiologically based pharmacokinetic modeling and quantitative systems pharmacology can guide dose-selection throughout phase II and III and improve overall clinical trial designs. Effective translational science depends on understanding the PK and PD of investigational therapies and fully characterizing their pharmacological targets. Improved modeling can facilitate dose selection studies, especially when two investigational therapies are studied in combination, as is likely to become common in the context of liver disease.

Next Steps

Clinical pharmacology tools and methods can enhance drug development by improving diagnosis and staging, and by contributing to modeling that characterizes hepatic impairment and dose-response relationships. Stakeholders must work collaboratively to elucidate the complex pathology of NASH and cholestatic liver disease and public private partnerships can accelerate the pace of innovation. Addressing the obstacles discussed can advance biomarker development and pharmacological modeling, resulting in safer, more efficient clinical trials and new therapeutic options.

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