Review

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Report on the AASLD/EASL joint workshop on clinical trial endpoints in NAFLD☆

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Summary

Non-alcoholic fatty liver disease (NAFLD) is a global public health concern. Its natural history, the development of non-alcoholic steatohepatitis (NASH) and fibrosis, is highly variable, prone to endogenous (*e.g.*, genetics, microbiota) and exogenous (*e.g.*, nutrition, alcohol, physical activity) disease modifiers, and can fluctuate over time. The complexity of its pathophysiology is reflected by the multitude of pharmacological targets in development. NASH clinical trials have provided valuable insight that is applicable to future trial design. Endpoints for NASH have evolved over the past decade and will continue to be refined. Currently accepted endpoints for conditional approval include resolution of NASH without worsening of fibrosis and/or improvement in fibrosis without worsening of NASH by standardized evaluation of paired liver histology. In pediatric NASH, practical obstacles, pubertal hormonal changes, and stringent safety requirements mandate adaptations in trial design. In adult patients with NASH-related cirrhosis, decrease in portal pressure as well as clinical events (*e.g.* decompensation, hepatocellular carcinoma, transplantation, death) are more prevalent and thereby are viable primary endpoints for clinical trials. Consideration of the natural fluctuation of disease, the clinical implication of the chosen primary endpoint, and factors that may affect placebo response will facilitate an accurate determination of efficacy of emerging therapeutics for NASH. *Conclusion:* The June 2018 American Association for the Study of Liver Diseases and European Association for the Study of the Liver joint workshop on NAFLD endpoints summarized important findings from ongoing and completed trials, defined the scientific evidence supporting distinct endpoints, and provided guidance for future trial design.

Keywords: Outcomes; Pediatric; Fibrosis; Biomarker; Pharmacotherapy.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of disease that ranges from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) with progressive fibrosis.[1–5] Table 1 outlines currently accepted definitions and staging of NASH. Hepatic fibrosis, which may progress to cirrhosis and end-stage liver disease,[4] is strongly associated with NASH. There is also collinearity between the presence of NASH and the features and severity of individual components of the metabolic syndrome.[6–8] The presence of NAFLD is an independent risk factor for the development of cardiovascular diseases.[9]

No drugs have been approved for the treatment of NASH.[10] Approval of drugs in the United States is contingent on demonstration of clinically meaningful benefit or improvement in a surrogate endpoint that is considered generally accepted by the Food and Drug Administration. Similar standards are also required by the European Medicines Agency. Because demonstration of a clinically meaningful benefit may take several years, a conditional approval system was established in both the United States and Europe that is contingent on the use of "reasonably accepted" surrogates. A key challenge in the use of such surrogate endpoints is their definition and generation of the evidence to support their efficacy and safety. The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) held a joint NAFLD Endpoints Conference on June 29-30, 2018, in Alexandra, Virginia, to review the scientific foundations of clinical trials for NASH, gaps in knowledge and trial endpoints, with the primary objectives of providing direction to the field and refining clinical trial design and implementation. This report highlights essential observations and consensus opinions.

Epidemiology

From 2005 to 2010, the global prevalence of NAFLD increased from 15% to 25% and is projected to increase further by 2030, with a higher proportion of patients affected by advanced disease.[11,12] The prevalence and severity of NAFLD varies by geographic region and ethnicity, with highest prevalence in the Middle East (31.79%), South America (30.45%), and Asia (27.37%), followed by North America (24.13%) and Europe (23.71%), and lowest prevalence in Africa (13.48%).[2]

There are many potential explanations for the variations in NAFLD prevalence and severity across

Table 1. Currently accepted scoring systems to grade and stage NASH in clinical trials.

	FLIP steatosis, activity, and fibrosis score			National Institute of Diabetes and Digestive and Kidney Diseases NAS		
Histological feature	**Score range and components**	**Category definition**		**Score range and components**	**Category definition**	
Steatosis	0–3	0	<5%	0–3	0	<5%
		1	5–33%		1	5–33%
		2	34–66%		2	34–66%
		3	>66%		3	>66%
	SAF steatosis score (S): 0–3					
Hepatocyte ballooning	0–2	0	None	0–2	0	None
		1	Clusters of hepatocytes with rounded shape and pale cytoplasm		1	Few
		2	Same as grade 1 with enlarged hepatocytes (>×2 normal size)		2	Many
Inflammation	0–2	0	None	0–3	0	None
		1	<2 foci per ×20 field		1	1–2 foci per ×20 field
		2	>2 foci per ×20 field		2	2–4 foci per ×20 field
					3	>4 foci per ×20 field
	SAF activity score (A) = ballooning + inflammation: 0–4			**NAS total = steatosis + ballooning + inflammation: 0–8**		
Fibrosis	0–4	0	No fibrosis	0–4	0	No fibrosis
		1a	Zone 3 mild perisinusoidal		1a	Zone 3 mild perisinusoidal
		1b	Zone 3 moderate perisinusoidal		1b	Zone 3 moderate perisinusoidal
		1c	Periportal/portal		1c	Periportal/portal
		2	Zone 3 plus portal/periportal		2	Zone 3 plus portal/periportal
		3	Bridging		3	Bridging
		4	Cirrhosis		4	Cirrhosis
	Fibrosis score: 0–4			**Fibrosis score: 0–4**		

FLIP, fatty liver inhibition of progression; SAF, Steatosis, Activity, and Fibrosis score.

different geographic regions and ethnicities.[1,2] Although there is clearly a heritable component, NAFLD is a complex disease in which disease severity is influenced by environmental and behavioral factors (*e.g.*, diet, physical activity, socioeconomic influences). The best characterized genetic determinants of disease severity are genes encoding patatin-like phospholipase domain-containing 3 (*PNPLA3*) rs738409 c.444C>G (p.I148M) and transmembrane 6 superfamily member 2 (*TM6SF2*) rs58542926 c.449C>T (p.E167K), which have been strongly associated with the severity of steatosis, NASH, and fibrosis/cirrhosis.[13,14] More recently, the rs641738 variant in the gene membrane bound 0-acyltransferase domain containing 1 (*MBOAT1*) and the rs72613567 variant in the hydroxysteroid 17-beta dehydrogenase 13 (*HSD17B13*) gene have also been linked to NAFLD.[15,16]

There are substantial differences in the distribution of these genetic polymorphisms across ethnic groups. Potential heterogeneity across continents has substantial implications for clinical trial design and drug development for NASH, as the effect of genes on responsiveness to placebo as well as pharmacotherapies is unknown. In pivotal trials, the effect of geographical genetic diversity may be de-risked through regional stratification or by performing separate trials in different territories.

NAFLD natural history and subtypes

There is considerable fluidity between disease states in NAFLD, whereby NASH and even fibrosis can progress, regress, or remain stable over time. These outcomes can be strongly impacted by lifestyle factors such as nutrition, physical activity, and alcohol use.[17,18] Although the prevalence of NAFLD is high, a small proportion of those affected will develop progressive liver disease or experience liver-related death. The transition from NAFL to NASH is highly dynamic and bidirectional, and neither the frequency of oscillation nor the amplitude of consequent injury are fully characterized.[3,4] Furthermore, the median rates of fibrosis progression and characteristics of subpopulations with rapid or slow progression are not well established (Fig. 1). The situation is compounded by sampling error on biopsy, interobserver/intraobserver variability in the reading, and apparent spontaneous improvement in fibrosis. Thus, histological fibrosis improvement by one stage has been reported in about 20% (15% to 35%) of patients with placebo.[4] In a study with subsequent biopsies, patients with initial fibrosis improvement on placebo after 1 year were highly likely (80%) to worsen between year 1 and year 2.[19] With advanced fibrosis (stage F3-F4), outcomes become more predictable, as exemplified by a dramatic increase in the risk

Abbreviations: AASLD, American Association for the Study of Liver Diseases; CI, confidence interval; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; MELD, Model for End-Stage Liver Disease; NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD activity score; and NASH, non-alcoholic steatohepatitis.

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of progression to "hard outcomes" (i.e., decompensation of liver disease, liver transplantation, death). Preventing progression, or inducing regression, of advanced fibrosis is therefore a clear priority. Advanced fibrosis, especially established cirrhosis, is less prone to spontaneous regression than earlier stages of fibrosis. Pharmacological induction of fibrosis regression may be a particularly exacting endpoint in the later stages of disease.

Comorbidities

Patients with NAFLD often have concomitant extrahepatic diseases such as obesity, insulin resistance, type 2 diabetes, metabolic syndrome, and cardiovascular diseases. The presence of such comorbidities may influence treatment response. For example, patients with diabetes may have a more robust response to pioglitazone and have a less pronounced placebo response.[20]

Thus, comorbidities such as type 2 diabetes are potentially worthy of consideration in clinical trial design, depending on the drug's mechanism of action. Currently, there is insufficient evidence to incorporate aspects of metabolic comorbidities into trial endpoints. Because of the increased frequency of cardiovascular events in patients with NASH, there is a clear consensus that a drug meant to treat NASH should not increase cardiovascular risk. In general, drugs to treat NASH should either be neutral in their effect on metabolic comorbidities, or, preferably, confer a beneficial effect. Limited data suggest that decreased NAFLD activity score (NAS) is associated with an improved cardiovascular risk profile.[21] It is recommended that a careful assessment of the impact of therapy on cardiometabolic risk factors be included as secondary endpoints in both phase 2 and phase 3 trials.

Relevance of alcohol as a potential cofactor in NAFLD progression

A potentially important factor not adequately addressed within the design of current clinical trials is the impact of the quantity, duration, and pattern of alcohol use on disease progression or spontaneous improvement in NASH. Alcohol consumption in excess of 20/30 g for women/men daily excludes subjects from clinical trials; however, these arbitrary thresholds are based on levels above which the risk of cirrhosis is higher and have not been specifically shown to modify NASH.[22] Furthermore, alcohol can worsen hepatic injury even when coexisting with other liver diseases including NAFLD.[17] Presently, the assessment of alcohol consumption is usually confined to screening at trial entry, with neither biomarkers (*e.g.*, urinary ethyl glucuronide, phosphatidylethanol) nor standardized psychological tests for at-risk drinking routinely used in clinical practice or trials. The need to assess alcohol intake more accurately is underrecognized; therefore, better assessment could identify and control for an important confounder.

When individuals with identical histological severity at baseline are followed prospectively, those with modest alcohol consumption had either greater steatosis or less improvement in steatosis over time, whereas there were no differences in inflammation, ballooning, or fibrosis.[23] This does not exclude the possibility that small amounts of alcohol consumption may be a treatment outcome modifier. An Alcohol Timeline Followback assessment currently represents a "best practice" in tracking alcohol consumption but requires specific training of personnel.[24] It may be considered particularly useful in the context of long-term trials to evaluate its potential for affecting trial outcomes.

Placebo response: A critical determinant of trial success

Ultimately, the margin of efficacy of an investigational compound above that of placebo determines an intervention's success. Unlike hepatitis C virus infection, in which the placebo response in a clinical trial is negligible, the placebo response in NASH trials is highly variable across studies. In recently reported NASH studies, placebo histological responses have ranged from 9%-40%.[25–29] (This effect has been further quantified in a recent meta-analysis, incorporating 1,463 placebo-arm patients across 39 randomized control trials.[30] In this meta-analysis, 25% (95% confidence interval [CI] 21%-29%) exhibited a 2-point NAS improvement, with more than one-third of patients exhibiting an improvement of more than 1 point in at least one NAS component (steatosis, ballooning, or inflammation). In addition, 21% (95% CI 16%-26%) exhibited at least a one-stage fibrosis improvement.[30]

Factors contributing to the placebo response can be broadly categorized into "patient related" or "study design related." A frequently underestimated patient-related factor is the "Hawthorne effect," whereby the knowledge that one is being observed, or simply participating in a clinical trial, alters behavior.[30,32] This phenomenon is especially relevant to conditions such as NAFLD, in which lifestyle change can significantly affect the underlying disease.[31]

The significant effect of lifestyle on NAFLD clinical trial outcomes can render it difficult to ascertain whether results are attributable to medication or lifestyle modification. Lifestyle changes that produce even modest results (for example, sustained weight loss of no more than 5% of initial body weight can reduce steatosis,[7] liver enzymes,[31] and metabolic parameters, and is sometimes used as secondary endpoints in NAFLD clinical trials). In addition, dietary composition itself (*e.g.*, Mediter-

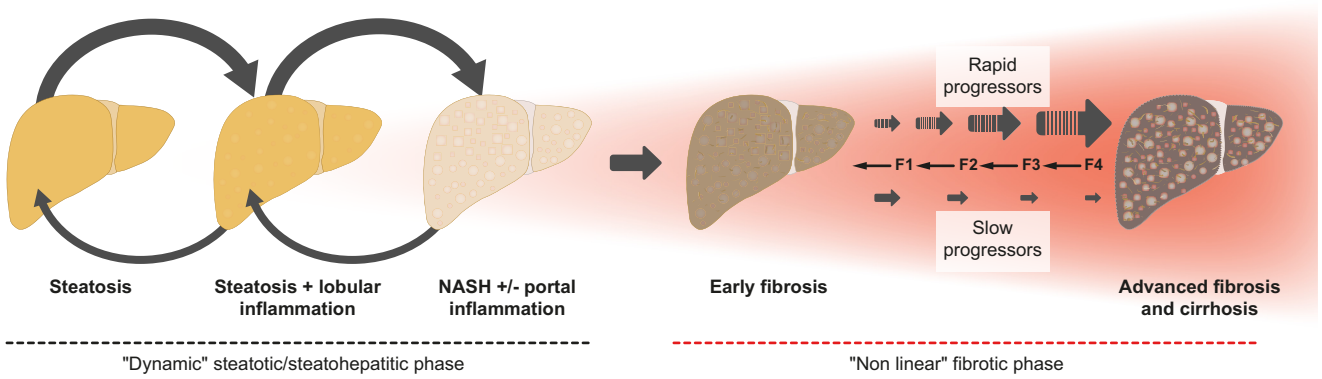

Fig. 1. The dynamic natural history of NAFLD. Current thinking based on longitudinal cohort studies and dual-biopsy cohorts is that the natural history of NAFLD is highly dynamic. The degree of steatohepatitis and therefore transition between NAFL and NASH is characterized by periods of waxing and waning. Similarly, fibrosis may progress or regress, and while most patients exhibit only slow progression, up to 20% of patients may be more rapid progressors. Risk of morbidity and mortality increases with fibrosis stage.

ranean versus Western-style diet) is a factor affecting hepatic outcomes, regardless of weight loss.[19] Fibrosis is less susceptible to minor changes in weight or dietary composition, but regresses in patients achieving sustainably greater than 10% weight loss.[31] Thus, data capture is recommended for diet (caloric intake, composition, and as discussed previously, alcohol consumption), physical activity, and anthropometric measures (*e.g.*, weight, body mass index, waist circumference, visceral adipose tissue, abdominal fat). Data analysis of such factors can identify potential confounding effects, an imbalance between arms, and facilitate comparisons across trials.[32] Various techniques including mobile applications that assist in self-monitoring physical activity and/or calorie intake could be considered to more accurately quantify the extent to which each individual participating in a clinical trial adopts lifestyle recommendations.[33] Data tracking and capture holds the potential to clarify which factors influence disease progression and to determine whether health measures detected in study participants are attributable to lifestyle factors or medication.[32] Consideration should also be given to altering study design to incorporate a lead-in phase, before baseline biopsy is conducted and active intervention commenced, to mitigate against the impact of lifestyle modification and/or to determine whether both arms are similarly impacted.

The placebo response can also be significantly affected by study design. Primarily, this relates to trial entry criteria, particularly the histological severity threshold for enrollment, and the stringency of the efficacy endpoint adopted. Most studies specify a minimum NASH grade and fibrosis stage for trial entry. Past trials provide valuable lessons demonstrating that the permissiveness of inclusion criteria can influence trial outcomes, largely by increasing the placebo response rate. In GOLDEN-505, participants with a NAS of at least 4 had a less-pronounced placebo response rate (PRR) than those with a lower NAS (25% PRR with entry NAS = 3 versus 9% PRR with entry NAS ≥4).[26] Therefore, adopting a more stringent endpoint definition for NASH resolution reduces the placebo response rate.[5]

Although less clearly defined in the literature, this may also hold true for fibrosis-related endpoints, in which a spontaneous improvement in fibrosis by one stage is more likely to occur (10% at year 1, 17% at year 2) than an improvement by two stages in the placebo group (3% at year 1, 3% at year 2).[26]

Preclinical tools for the identification of promising targetable pathways in NAFLD

Extensive research efforts have identified multiple disease-promoting pathways that could be targeted by novel or repurposed drugs. The level of preclinical evidence required to move into clinical development is heavily debated. To this end, several innovative *in vitro* models (*e.g.*, liver slices, biochips, organoids) as well as *in vivo* rodent models (*e.g.*, genetic, chemical, dietary) have been developed. A core challenge is that none of the current models fully recapitulate all aspects of human disease. Distinct facets of human NAFLD can, however, be reproduced in mouse models, including steatosis, inflammation, and fibrosis. There is consensus that no single perfect model provides optimal insight into the efficacy of interventions across all mechanisms of action. The rational use of models that best reflect the pathogenic aspect targeted by a new compound is the most appropriate approach.

One of the emerging insights from published phase 2 trials is the inconsistent translatability of preclinical efficacy to human disease. Much of this may be due to the complexity of human NAFLD, in which there is heterogeneity in the dominant mechanism in a given individual that is influenced by external factors. In other cases, muted or lack of efficacy could be attributed to insufficient preclinical data justifying progression to phase 2 trials. To the extent possible, robust preclinical data is essential to justify advancement into human trials,

as our primary responsibility is the wellbeing of our patients. The following principles might help predict the clinical relevance of emerging signals from preclinical models:

- Efficacy signals should be consistent across more than one experimental model. Ideally, efficacy should be recapitulated in different labs and conditions (*e.g.*, differing microbiota, mouse strains, handling);
- The experimental model should properly reflect the pathogenic mechanism that is targeted by a drug, and this specific mechanism of action should be relevant to human disease;
- The pharmacological intervention should also be tested in "regression models" (*e.g.*, switching mice from a pathogenic diet to normal chow to induce disease regression), without delaying disease regression/resolution; and
- The timing of intervention in mice and humans in the context of the disease should be similar, with a comparable organ dose exposure and target engagement of the drug, conducted in preclinical studies that are properly randomized and appropriately powered to detect differences in efficacy.

Proposed standards for clinical trials and data capture

Current phase 3 trials will provide important preliminary evidence to begin stratifying NASH patients with respect to natural history and treatment response. The ability to subcategorize NASH patients will refine future study design and identify those patients best suited to different treatment approaches. Additional phenotyping tools and validated biomarkers are urgently needed to further segment and stratify the NASH population in clinical trials. These challenges are being addressed by large-scale international academia-industry collaborations such as the Noninvasive Biomarkers of Metabolic Liver Disease consortium of the Foundation for the National Institutes of Health in the United States[34] and the Liver Investigation: Testing Marker Utility in Steatohepatitis consortium in Europe.[35] As such, genetic markers, alterations of gut microbiota (dysbiosis), metabolism (lipid markers, bile acids, gut metabolites), and collagen turnover as well as imaging techniques may help to better sub-phenotype patients. Thus, trials provide an opportunity to gather evidence to support a personalized medicine approach to NASH patients. In phase 3 trials, ethnic or genetic differences can be captured, and single nucleotide polymorphism chips or sequencing techniques can be used to seek subtypes of disease more or less likely to respond to therapy or at varying risk of drug side effects.[5] However, therapeutic trials were not designed *a priori* to assess the role of such factors; therefore, associations would require independent validation in further studies.

Reporting results from clinical trials on NAFLD

Inconsistent reporting from phase 2 clinical trials limits the ability to compare results between studies and to objectively evaluate the safety and efficacy of novel therapeutic approaches. Adherence to standard rules for reporting results from NAFLD clinical trials would provide additional transparency and facilitate understanding of a compound's efficacy in this population. A strong consensus view was that reporting results from NAFLD clinical trials should follow International Committee of Medical Journal Editors rules and specifically should:

- Include a detailed description of baseline patient characteristics, including not only demographics and liver disease status, but also comorbidities (*e.g.*, obesity, metabolic syndrome, type 2 diabetes, cardiovascular disease, depression), quantitative assessments of alcohol consumption, and concomitant medications;[22]
- Report efficacy data related to all of primary and secondary endpoints applied to the study, by absolute changes with *P* values for every efficacy-related finding reported, not just percent changes;
- Report absolute numbers and proportion of patients who improved, remained stable, or worsened on treatment and on placebo;
- Report on the concordance or discordance between different diagnostic modalities and biomarkers in relation to the study endpoint (for example, simultaneously report noninvasive fibrosis assessment alongside histological fibrosis staging);
- Avoid phrases like "clinically meaningful change," unless supportive clinical outcome data from the study cohort are being reported; and
- Report detailed safety data (adverse events, drug-induced liver injury, liver-related events, liver transplant, cardiovascular events, death), specifically including biochemical effects on insulin resistance/glycemic control and circulating lipid profiles.

Endpoints

Currently accepted endpoints for conditional approval in precirrhotic NASH include resolution of NASH without worsening of fibrosis and/or improvement in fibrosis without worsening of NASH.[36,37] Table 2 outlines currently accepted endpoints across the NASH spectrum according to the phase of development. The utility of variations such as improvement of NASH (and how this might be defined) requires further study. It is notable that endpoints must be considered in the context of the mechanism of action of a given drug. For drugs with a predominantly metabolic or anti-inflammatory mechanism of action, there

is an expectation of an improvement in steatosis and hepatocyte injury (i.e., ballooning and inflammation). However, a purely antifibrotic agent might be expected to demonstrate an antifibrotic effect that may be independent of improvements in steatosis or disease activity, but should not adversely affect disease activity.

Currently, an improvement in fibrosis by one stage is considered an acceptable endpoint. However, as more evidence accumulates, this may need to be revised given that improvement by one stage is variable, and response in the placebo group ranges from 14% to 44% in the three largest phase 2 studies. A more rigorous standard such as an improvement in fibrosis by at least 2 stages would increase specificity and minimize the unpredictability of the placebo response. However, if implemented, a smaller proportion of subjects would be likely to achieve the primary endpoint, which could potentially increase sample-size requirements and trial duration.

Key clinical outcomes

Liver-related mortality is most pronounced in those with NASH and advanced fibrosis, a minority of NAFLD patients. The largest long-term cohort study to date found the leading causes of death in precirrhotic NAFLD patients to be cardiovascular disease (38%) and extrahepatic malignancy (19%), with liver-related deaths (including those attributed to hepatocellular carcinoma [HCC]) representing 9% of cases.[38] More recent data provide further granularity to this observation, reporting clinically relevant outcomes in NAFLD patients with advanced fibrosis (stage 3) and compensated cirrhosis (Child-Pugh A5 or A6).[39] It is not surprising that in this study, the annual incidence of cardiovascular disease was higher in precirrhotic NAFLD patients and lowest in patients with decompensating cirrhosis (0.9/year [0.5–1.8] versus 0.2 [95% CI 0.03–0.6]).[39] Conversely, the annual incidence of liver-related death, transplantation, or HCC were greatest in those with cirrhosis (0.5 [0.2–1.2] versus 11.1 [8.3–14.8]; 0.2 [0.02–0.9] versus 4.7 [3.0–7.5], respectively).[39,40] Although there is a link between cardiovascular disease and NASH, and evidence that NASH resolution is associated with atherogenic lipid profiles, there are currently no data indicating that reversing NASH impacts cardiovascular outcomes.[21] Liver-related outcomes including death, transplantation (surrogate Model End-Stage Liver Disease [MELD] score >15), decompensation (ascites, variceal hemorrhage, hepatic encephalopathy), and HCC and are also highly enriched in those with advanced fibrosis, although HCC can occur across the NAFLD spectrum.[1,4,8–10]

There remain considerable challenges in substratification of those with compensated cirrhosis, to identify strata for decompensation that represent a clinically meaningful outcome. Specifically, the presence of portal hypertension[12] (≥6 mmHg hepatic venous pressure gradient [HVPG]), particularly higher HVPG (>10 mmHg), is a key predictor of cirrhosis decompensation.[40] Each 1-mmHg increase in HVPG above 10 mmHg is associated with an 11% increase in risk of hepatic decompensation. HVPG less than 10 mmHg implies a 90% probability that no clinical decompensation will occur over a median 4-year follow-up.[41] Threshold values may be different in a strictly NASH population and will be further informed by emerging data from clinical trials. Results from the first treatment trial in NASH cirrhosis suggested that this may not be as reliable in the setting of NASH, as some patients had portal hypertensive complications at HVPG less than 10 mmHg. Once hepatic decompensation occurs, MELD may be a better predictor of mortality than HVPG.[42] MELD score greater than 10 can also identify those with increased risk of decompensation and may be used as enrichment tools; however, emerging data suggest that these cutoffs may be less reliable in NASH cirrhosis.[43] It is also unclear whether all decompensating events have similar implications in this population. A growing consensus suggests that the development of ascites has a greater effect on prognosis than variceal hemorrhage alone.[43] The biology of clinical decompensation in those with previously compensated cirrhosis is not fully understood. Therefore, it remains to be determined whether treatment of the underlying steatohepatitis as opposed to the fibrosis will prevent clinical decompensation. These possibilities are currently under active investigation. Additionally, several biological processes are involved once cirrhosis develops, and it remains unclear whether NASH therapies will favorably affect these, particularly in the setting of hepatic decompensation. It is anticipated that further subsegmentation of patients with cirrhosis and clarification of endpoints is needed to stimulate therapeutic development for this population.

For precirrhotic NASH, regulatory surrogates include NASH resolution, a decrease in disease activity (which is not yet clearly defined), or a reduction in fibrosis stage. Furthermore, a "likely" surrogate such as progression to cirrhosis (or regression from cirrhosis) represents a "generally accepted" surrogate for these clinically meaningful outcomes (Table 2). Extrahepatic outcomes include cardiovascular disease and extrahepatic malignancy; however, these are unlikely to be viable outcomes in the context of current NASH clinical trials.[9]

Definition of disease worsening

The concept of "worsening of NASH" was discussed at the conference; however, consensus was not reached on its precise definition. An increase in steatosis alone has not been associated with worsening fibrosis in short-term stud-

Table 2. Suggested endpoints for NASH trials across the development spectrum.

	Precirrhotic NASH	Cirrhotic NASH	Pediatric NASH
Early phase development	ALT, AST Hepatic fat (MRI-PDFF) Note: Consider mechanism of action of drug when choosing	Safety Hepatic impairment studies Proof of mechanism studies; endpoints will depend on mechanism of action	No clear recommendation
Phase 2b	NASH resolution without worsening of fibrosis or at least one stage reduction in fibrosis At least a 2-point reduction in NAFLD NAS: At least a 1-point reduction in either lobular inflammation or hepatocellular ballooning AND no worsening of fibrosis stage	Increase of MELD score from <12 to ≥15 At least a 1-point improvement in fibrosis with no worsening of NASH Reduction in HVPG of ≥2 mmHg	No clear recommendation
Phase 3	NASH resolution* with no worsening of fibrosis AND/OR At least a 1-point improvement in fibrosis with no worsening of NASH	MELD progression from <12 to ≥15 Fibrosis reduction by at least one stage without worsening of NASH Hepatic decompensation events – Ascites – Variceal hemorrhage – Encephalopathy Sepsis All-cause mortality Liver transplant† Hospitalization rates	No clear recommendation
Phase 4	Confirmatory clinical benefit trials Composite of: – Histological progression to cirrhosis – All-cause mortality – Liver transplant† – Hepatic decompensation events – Increase of MELD score from below 12 to ≥15		No clear recommendation

Enrollment of minors into clinical trials that involve greater than minimal risk requires the demonstration of potential direct benefit to the subject as a result of the drug intervention, which can be derived from adult studies, preclinical, and in some instances mechanistic rationale. Pediatric patients should be studied after there is sufficient information about dosing, safety, and efficacy in adults to inform the risk/benefit analysis.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; MRI-PDFF, magnetic resonance imaging–derived proton density fat fraction.

* Disappearance of ballooning and disappearance or persistence of minimal, lobular inflammation that do not qualify for the diagnosis of NASH.

† It is recognized that liver transplantation is dependent on a large number of factors unrelated to the liver disease such as financial status, behavioral problems, social support, compliance, comorbidity profile, and severity, as well as the region where a person lives. It is the position of the academic community that meeting severity of liver disease criteria for consideration for transplant rather than liver transplantation should be the criteria rather than the number of liver transplantations themselves. The authors diverge from the FDA on this point. In their most recent guidance, the FDA does not encourage reversal of cirrhosis as an endpoint at this time though notes that this could be discussed on an individual basis.

ies[1,4,10,26,38,39] and is not considered to reflect worsening steatohepatitis. Recent studies indicate that increased ballooning and inflammation, especially portal inflammation, are likely associated with increasing fibrosis. Increasing composite disease activity scores over time has also been related to worsening fibrosis. It must be noted that the methodology of the retrospective data on which these paradigms are based is controversial, and data from pivotal trials will help resolve this issue more confidently.

Because NASH is histologically dynamic, it is important to have consensus over what constitutes worsening of the disease, as opposed to the waxing and waning of disease. From a regulatory point of view, a 1-point increase in fibrosis stage represents worsening fibrosis. However, it is recognized that the current fibrosis stages do not describe the continuum of fibrosis accurately, because their ordinal nature introduces error at the boundaries of stages. Furthermore, the dynamic range of fibrosis is nonlinear and so varies, with a one-stage progression from stage F0-F1 versus stage F3-F4. It also captures both fibrosis distribution and quantity leading to internal discrepancies. Thus, an individual with stage 2 fibrosis may have less extracellular matrix deposition than another with stage 1 fibrosis. Fibrosis quantity also does not increase linearly, and a major step up is seen with progression from stage 2 to stage 3 fibrosis. This has major implications for the validation of biomarkers that measure fibrosis quantity rather than distribution. Of note, some trials have already introduced automated quantification of collagen deposition staining from biopsies, but are not yet able to link this parameter to the fibrosis staging based on the evaluation of an expert pathologist.[26]

Disease stability

Prevention of disease progression (maintaining disease stability) should be reported in clinical trials, particularly for less-advanced disease stages, in patients at risk of progression. The endpoint for fibrosis is currently focused on fibrosis regres-

sion. However clinical outcomes are linked to progression to cirrhosis. Therefore, disease stability (i.e., nonprogression to cirrhosis) may also be considered as an endpoint, but has not yet been accepted by regulatory agencies as an endpoint.[4]

Endpoints for cirrhotic trials

Patients with cirrhosis require different endpoints and are the most likely to develop hard outcomes (*e.g.*, decompensation, progression to MELD ≥15, liver transplantation, death). Both improvement in histologic fibrosis stage and HVPG have been the primary endpoints of trials focused on NASH cirrhosis. Each has limitations, and the impact of reaching these endpoints on clinical outcomes will have to be proven. For example, improvements in fibrosis stage may reflect either true regression or sampling bias, and changes in HVPG may be reflective of a true reduction in hepatic resistance, operator error, or other confounders. Although the changes in HVPG may be related to inconsistent technique, this is unlikely in phase 2b trials in which each HVPG measurement was quality-checked. HVPG is affected by both changes in fibrosis as well as dynamic changes in sinusoidal resistance. These are not captured with enough granularity to allow dissection of the causes of improvement in HVPG in the placebo arm. Furthermore, while the implications of worsening HVPG are well established, the implications of improvement in HVPG are linked to the mechanism of reduction (for example, transjugular intrahepatic portosystemic shunt and several drugs reduce HVPG) but not survival. Studies are needed to demonstrate that improvement in HVPG due to reduced fibrotic remodeling of the liver translates into improved clinical outcomes. As such, the most recent FDA guidance on clinical trials in NASH cirrhosis does not discuss HVPG as an endpoint in this context. There is an unmet need to develop and qualify noninvasive tools to assess the progression toward mortality or liver-related outcomes in those with cirrhosis due to NASH, and to establish that improvement in such markers predicts disease stability or improvement. Such tests could include markers of disease activity, fibrosis, fibrogenesis, or quantitative liver function.

Pediatric considerations

The study of pediatric disease is critical for understanding the natural history of NAFLD across the age spectrum. The prevalence of pediatric NAFLD is high due to the global obesity epidemic, and affects an estimated 10% of children.[44] Typically, pediatric medical intervention is considered for those aged approximately 12-14 years. A large proportion of children with NAFLD go on to have the disease in adulthood.[44,45]

Risk factors associated with pediatric NAFLD include obesity, male gender, adolescence, family concordance, and certain metabolic syndrome comorbidities.[44,45] There is a pediatric subtype of histologic features found in about a third of children; this subtype generally demonstrates more pronounced hepatic steatosis, increased portal predominance of inflammation and fibrosis, minimal or no lobular inflammation, little or no cellular ballooning, and lack of perisinusoidal fibrosis.[44,45] There are multiple knowledge gaps in the realm of pediatric NAFLD/NASH (*e.g.*, natural history, disease phenotypes, optimal treatment approaches). Further, histological subtypes (zonality of steatosis and fibrosis) in childhood may influence the development of steatohepatitis or more progressive fibrosis later in life.[44,45]

Conducting clinical research in pediatric patients with NAFLD has unique obstacles, including practical considerations (*e.g.*, inability/unwillingness to swallow pills, fear, dosing uncertainty), safety concerns (*e.g.*, study-related biopsy procedures, drug toxicity), and uncertainties about the benefits of clinical endpoints (*e.g.*, mortality) in pediatric patients (Fig. 2). The multiple knowledge gaps also present challenges to study design. The uncertainties in rates of progression to liver disease that is likely to lead to clinically meaningful outcomes is currently a major barrier to drug development for those children particularly at risk of developing advanced liver disease.

Clinical barriers in pediatric NASH

The potential benefits of treatment must be weighed against the risks of drug exposure to many who are not at risk of progression in this vulnerable population. Data captured in pediatric studies should therefore be analyzed to seek subpopulations at risk of liver-related outcomes, so that high-risk patients can be prioritized and low-risk patients can avoid unnecessary exposure to drugs with potential toxicity. Until there is broad consensus on this subject, pediatric development plans should focus on children at highest risk of liver-related outcomes (bridging fibrosis or cirrhosis). For drugs with an established safety and tolerability profile, one may also consider children with NASH and lower stages of fibrosis with the understanding that it may take many years to demonstrate reduced progression to cirrhosis, the current generally accepted surrogate endpoint for full approval.

In long-term pediatric studies, transition through puberty involves substantial biological, hormonal, and behavioral changes that can affect metabolic status. Furthermore, issues of adherence and experimentation with alcohol or other drugs can affect trial outcomes, and study design and implementation should account for such issues.

As two major multicenter randomized controlled trials have been completed by the National

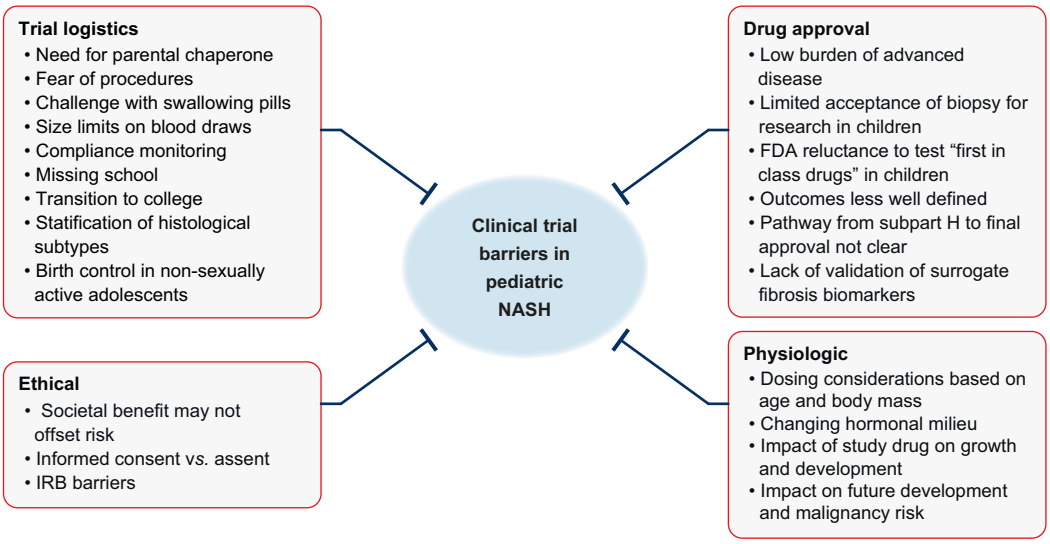

Fig. 2. Potential barriers in drug development for children with NASH. These include logistical barriers such as the fear of procedures, ethical barriers, regulatory barriers, and physiological barriers. Specific examples of each type of barrier are provided. IRB, internal review board; NASH, non-alcoholic steatohepatitis.

Institute of Diabetes and Digestive and Kidney Diseases NASH Clinical Research Network using prespecified histologic endpoints as either primary or secondary outcomes, there is less insistence on histology as a primary endpoint. Given the focus on safety, including the risk of liver biopsy, the use of surrogates for histology are more easily accepted as trial endpoints compared with adult patients. Although these trials principally demonstrated the feasibility of liver histology as a surrogate endpoint in pediatric trials, validating surrogate markers for NAFLD progression in children would increase acceptance of clinical research to academic centers and families, and would further reduce the study-related risks. Although less well-validated surrogates could be accepted as trial endpoints (*e.g.*, alanine aminotransferase, magnetic resonance imaging–derived proton density fat fraction) to minimize procedure-associated risks for children/adolescents, histology-based trials revealed a remarkable discordance between changes in alanine aminotransferase or other surrogates for severity of NAFLD with histology features, arguing for histology-based studies to demonstrate noninferiority and utility in pediatric studies.

In summary, our understanding of the natural course of NAFLD and the selection of subjects for clinical trials has advanced, although subsegmenting the population based on underlying disease biology and rates of progression remains a major gap. Improved understanding of interfering comorbidities and disease modifiers as well as rapid advances in technology (*e.g.*, imaging techniques, microbiota, genetic analyses) support the expectation that a more granular stratification of patients with NAFLD will be feasible in the foreseeable future. Similarly, despite a large amount of data on molecular mechanisms of disease development and progression, there is a need to identify key targets that will improve the disease in most individuals. Endpoints in clinical trials regarding liver disease progression need to reflect the aspects of pathogenesis that are targeted by an intervention, while simultaneously monitoring concomitant cardiovascular and metabolic diseases as well as ensuring safety. It is essential that these are reported transparently when trial results are published. The choices of endpoints are likely to be further refined to reflect emerging data on the course of the disease and those that link specific surrogates to clinically meaningful outcomes.

Conflict of interest

Dr. Rinella consults and advises for Intercept; she consults for Gilead, Genfit, Enanta, Bristol-Myers Squibb, Novartis, NGM, Immuron, CymaBay, Merck, Viking, Gelesis, Metacrine, Allergan, Thetis, 3vBio, Madrigal, and Fractyl. Dr. Tacke consults, advises, and received grants from Allergan, Inventiva, and Galapagos; he consults and advises Bayer, Boehringer Ingelheim, and Intercept; he received grants from Bristol-Myers Squibb. Dr. Anstee consults, is on the speakers' bureau, has active research collaborations, and received grants from Allergan/Tobira; he consults, is on the speakers' bureau, and has active research collaborations with Genfit SA; he consults, has active research collaborations, and received grants from Novartis and Pfizer; he consults and is on the speakers' bureau for Abbott and Gilead; He consults and has active research collaborations with Eli Lilly, HistoIndex, Intercept, and Novo Nordisk; he has active research collaborations and received grants from AbbVie, AstraZeneca, GlaxoSmithKline, and

Glympse Bio; he consults for Acuitas, Blade, BNN Cardio, Cirius, CymaBay, EcoR1, E3Bio, Galmed, Grunthal, Indalo, Imperial Innovations, Inventiva, IQVIA, Janssen, Kenes, Madrigal, MedImmune, Metacrine, NewGene, NGM, North Sea, Poxel, ProSciento, Raptor, Servier, and Viking; he is on the speakers' bureau for Bristol-Myers Squibb, Clinical Care Options, Falk, Fishawack, Integritas, and MedScape; he has active research collaborations with Antaros, Boehringer Ingelheim, Ellegaard, Exalenz, iXscient, Nordic, One Way Liver Genomics, Perspectum, Sanofi-Aventis, SomaLogic, and Takeda; he received grants from Vertex; he received royalties from Elsevier. Dr. Sanyal consults and received grants from Conatus, Gilead, Echosens-Sandhill, malinckrodt, Salix, Novartis, Galectin, and Sequana; he consults and owns stock in GenFit, Hemoshear, Durect, and Indalo; he consults for Immuron, Intercept, Pfizer, Boehringer Ingelheim, Nimbus, Lilly, Novo Nordisk, Fractyl, Allergan, Chemomab, Affimmune, Teva, Aredlyx, Terns, ENYO, Birdrock, Albireo, Sanofi, Takeda, Janssen, Zydus, BASF, AMRA, Perspectum, Owl, Poxel, Servier, Second Genome, General Electric, and 89 Bio; he received grants from Bristol-Myers Squibb; he received royalties from Elsevier and Uptodate; he owns stock in Exhalenz, Akarna, and Tiziana.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

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