DDNEWS

SPECIAL REPORT

Liver Disease

THE PHANTOM MENACE

In NASH, researchers battle a largely invisible threat

BY RANDALL C WILLIS

MARGARET HATED visiting her doctor because his response was always the same: improve your diet and get more exercise.

She'd been hearing this for decades. She knew she was overweight, but she never felt like anything was wrong.

Margaret was about to learn, however, that the blood work from her last visit had flagged some anomalies in her liver enzymes.

She might feel okay, but her doctor had a nagging suspicion that her liver was feeling otherwise, that Margaret's lifestyle had caught up with her. He suspected that fat was building in her liver in a condition known as non-alcoholic fatty liver disease, or NAFLD.

CREDIT: ICON PLC

Non-alcoholic fatty liver disease is defined by the presence of fat vesicles in hepatocytes that are not due to classical triggers of steatosis, such as excessive alcohol consumption, and there is a growing consensus that there are a multitude of mechanisms by which the disease can evolve.

UNSEEN FOE

As its name would imply, NAFLD is defined by the presence of fat vesicles in hepatocytes that are not due to classical triggers of steatosis, such as excessive alcohol consumption. As such, explained Antwerp University Hospital's Sven Francque and Luisa Vonghia in a recent review, NAFLD has typically been a diagnosis of exclusion; *i.e.*, if it isn't anything else, it must be NAFLD.

But fat deposition is just one component, and can be accompanied by chronic low-grade inflammation.

"When lobular inflammation and ballooning of hepatocytes … are both present, the diagnosis of non-alcoholic steatohepatitis (NASH) can be established," the authors continued.

Tissue fibrosis is also common in NASH, and when severe enough (F4), is described as cirrhosis, which itself can progress to hepatocellular carcinoma (HCC).

This is not to suggest, however, that the evolution of NAFLD into NASH and onward is linear. Rather, there is a growing consensus that there are a multitude of mechanisms by which the disease can evolve.

In their review of the evolution of NASH to HCC, Ozlem Kutlu and colleagues from Turkey's Sabanci University explained what they described as the multiparallel hit theory.

"This theory suggests that NASH is the consequence of numerous conditions acting in parallel, including genetic variations, abnormal lipid metabolism, oxidative and/or endoplasmic reticulum stress, mitochondrial dysfunction, altered immune responses, and imbalance in gut microbiota," they wrote. "According to this theory, hepatic inflammation is the first cause of fibrosis progression in NASH rather than steatosis."

Before reaching these more advanced stages, however, NAFLD and NASH can go largely unrecognized by patients and clinicians, as the conditions are largely asymptomatic. Alternatively, symptoms can be complicated or encompassed within other related pathologies that are common comorbidities, such as obesity, insulin resistance and metabolic syndrome.

"The biology of the disease is very complex, and we're really at our infancy in understanding the biology," says Rob Myers, vice president, fibrosis clinical research lead at Gilead Sciences, adding that the patient population is quite heterogeneous.

"You have patients who have diabetes and some don't," he explains. "You have obese patients, and some patients with NASH are lean. And in some patients, there are known genetic polymorphisms that are associated with NASH, and in others, you don't find those polymorphisms."

This heterogeneity, he continues, can create challenges when evaluating potential therapies.

"For example, a drug targeting one mechanism of action may not be relevant to the entire population of patients with NASH," he adds, which is part of the reason Gilead has focused its clinical development programs on combination therapy.

The diverse etiology of NASH has led Dawie Wessels, chief medical officer at AES, a PPD business, to speculate on some future day when NASH is seen less as a single pathology than as multiple diseases with the same outcome.

"We're going to end up in a few years with four different diseases, or we're going to step back and say that what we said is NASH is actually different types of diseases with the same effect on the liver," he says.

Given these challenges, the learning curve has been steep.

"I've been working in the cardiometabolic field for about 40 years, and NASH was never discussed until about 10 years ago," offers Martin Benson, senior director and global lead for Cardiometabolic Drug Development Services at ICON.

"If you go back to clinicaltrials.gov and you search for NASH and NAFLD, in 2000, there was about one trial starting each year," he says. "Now, there are about 30 trials starting every year—or more, even."

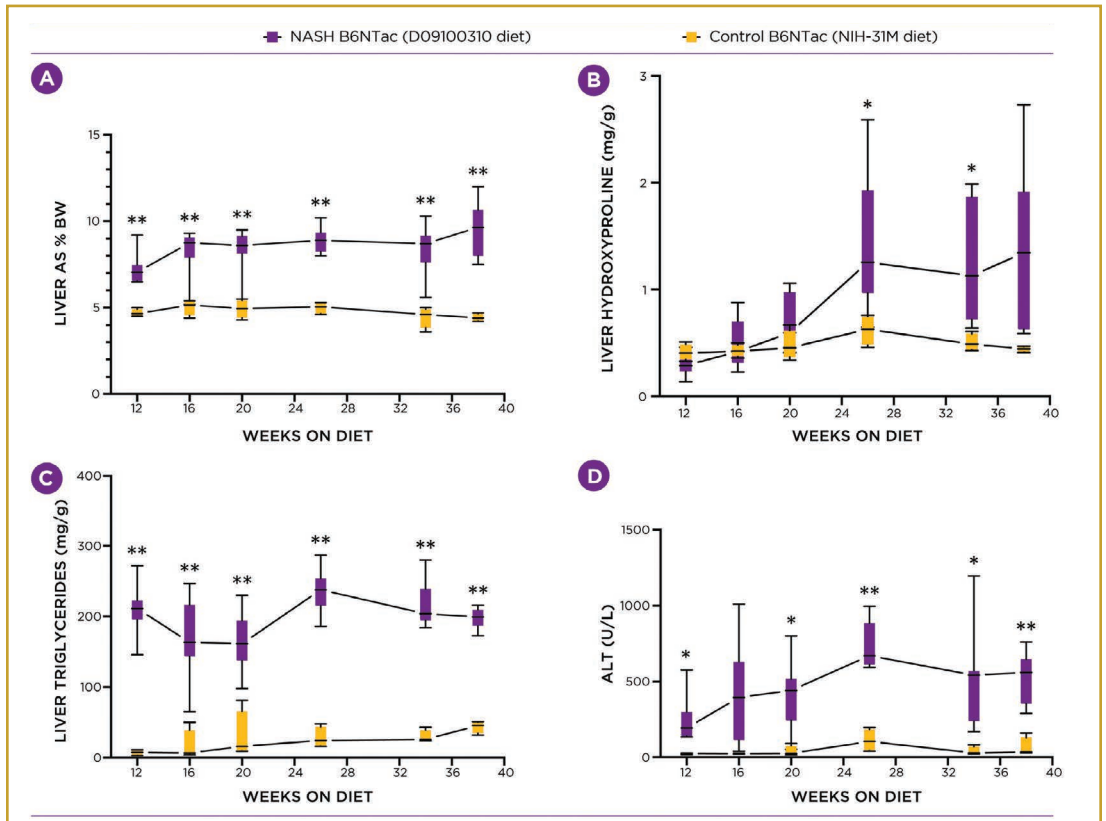
"Clearly, people were aware that patients who were obese and type 2 diabetic, in particular, were prone to having fatty livers," Benson explains. "But it went unexplored because the focus at that time was on treatments for lowering plasma glucose."

In the last 10 to 15 years, he notes, regulatory authorities in both dyslipidemia and diabetes have started to insist on cardiovascular outcomes trials for new anti-diabetic and anti-dyslipidemic drugs, which has ramped up the scale of clinical trials and therefore the costs of development for the pharma industry.

The result, he opines, has been a move toward the relative greenfield area of NAFLD and NASH, a market likely to expand.

"The prevalence of NAFLD is about 30 percent of the population in the Western world, about 24 percent globally," Benson says. "And it is growing because of growing urbanization, changing diets, and reduction in exercise, generally in the population globally."

"The subcomponent that is NASH, where the disease has progressed further, is about 3 to 4 percent in the United States," he adds. "But because so few patients are diagnosed—about 98 percent of patients aren't diagnosed—it is very difficult to get an accurate handle on that."



Comparison between C57BL/6NTac mice placed on D09100310 diet (NASH B6NTac) or kept on chow diet (Control B6NTac) from 5 weeks of age. A) Liver weight as a percentage of total body weight. B) Liver hydroxyproline content. C) Liver triglycerides. D) Serum alanine aminotransferase levels (ALT). For each time point, n=8 for NASH B6NTac and n=4 for Control B6NTac. Different individual animals were used for each time point (i.e. data is not longitudinal by animal). * and ** indicate statistical significance between NASH and control animals. Two-way ANOVA with multiple comparisons, with p-value<0.05* or p-value<0.01** Data provided by an anonymous pharmaceutical company.

CREDIT: TACONIC BIOSCIENCES

LIVER DAMAGE. Within weeks of starting a NASH-inducing diet, the liver demonstrates consistent signs of damage, including elevated levels of metabolic markers.

Getting those patients diagnosed has proven challenging.

DIAGNOSTIC DILEMMA

As suggested earlier, the asymptomatic nature of NAFLD—and to a lesser extent, NASH—helps explain why so many patients likely remain undiagnosed, particularly in the seeming absence of other risk factors, such as obesity or family history. Adding to this is the fact that definitive diagnosis relies on liver biopsy, a procedure that many see as more risk than benefit.

"We did a survey earlier this year of more than 12,000 U.S. physicians: family practitioners, endocrinologists and GI specialists," explains Wessels. "We just wanted to find out what is their awareness of these guidelines on treating patients with fatty liver and NAFLD and NASH."

"The number one reason why family practitioners don't refer patients for a liver biopsy is because it doesn't change the treatment outcomes," he continues. "There is absolutely no medications for it, so they asked why would you put anyone through a liver biopsy if by the end, you're going to tell them there's no treatment?"

As well, the limitations of biopsy are well understood.

"It is a pretty flawed test itself because basically what you do is take 1/50,000th of a liver and then you base the diagnosis on that," Wessels says. Moving the needle even slightly in the same patient could change the diagnosis, making false negatives and positives problematic.

In response to this challenge, he continues, the FDA is encouraging groups like the Liver Forum as well as LITMUS in Europe to establish some non-invasive biomarker and diagnostic imaging data (see sidebar "Imaging NASH" on page 20).

Beyond sampling variability, notes Gilead's Myers, there is also significant concern about variability in the skills of different histologists and hepatologists to diagnose NASH, or even in how consistently a single pathologist reads the histology of multiple samples.

To improve this consistency, Gilead recently partnered with PathAI, an imaging company looking to reduce variability using machine learning and artificial intelligence.

In November, the companies described their efforts to compare the staging and character of liver disease by the PathAI platform and by experienced pathologists using liver biopsy samples from patients who participated in Gilead's Phase 3 STELLAR clinical trial. They noted that results produced by the machine learning system were highly consistent with those of the independent pathologists, and perhaps more importantly, that the computational determination of fibrosis severity correlated highly via the NASH Clinical Research Network and Ishak staging systems.

In a separate analysis, they also demonstrated that the machine learning models were predictive of disease progression, illustrated fibrosis heterogeneity, and correlated with non-invasive biomarkers being examined concurrently.

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Rob Myers, vice president, fibrosis clinical research lead at Gilead Sciences

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According to Myers, Gilead has been very happy with the results so far, and is also looking to incorporate the platform in their analysis of the ongoing ATLAS clinical trial.

At the same time, he presses, Gilead continues to pursue non-invasive biomarker assays that might one day be accepted as clinical trial endpoints.

To that end, in late October, the company announced its collaboration with Glympse Bio, a company that combined synthetic biomarkers with machine learning to stage diseases such as NASH and to monitor progression and response to treatment.

At the Liver Meeting in November, Glympse presented preclinical results of its Glympse Liver Test (GLT) to monitor NASH in a rat model. The GLT platform not only effectively staged fibrosis level two or more (F2+) and detected disease progression as early as four weeks, but it was also more accurate than two other protein measurements in F2+ identification.

Furthermore, GLT was able to identify treatment-related fibrosis improvement within one week of treatment initiation.

"NAFLD fibrosis score, AST-to-platelet ratio index (APRI), FIB-4 index, BARD, CA index, ELF and FibroTest have also been proposed as indices to predict advanced fibrosis in NAFLD patients," offered Naoki Tanaka and colleagues at Shinshu University in a recent review. "ELF and FibroTest use direct markers of collagen synthesis and degradation, but such measurements are uncommon in clinical situations."

"In contrast, NAFLD fibrosis score, APRI and FIB-4 exploit the biochemical test components of age, AST, ALT, glucose, BMI, platelets and albumin, all of which are routinely obtained in clinical practice," they noted. "However, the scores of these indices tend to be increased in the elderly, and it is also unclear whether changes in AST, ALT and BMI are correlated with the degree of actual fibrosis."

Even with their limitations, these aggregate biomarker scores and imaging modalities are increasingly being examined as part of clinical trials analyses.

"In our ATLAS study, we've shown that we can recruit cohort of patients just based on non-invasive tests," offers Myers. "Not only can they predict fibrosis, but they are also prognostic. The higher the score on ELF or liver stiffness, the higher the risk of developing liver-related complications or a non-cirrhotic patient progressing to cirrhosis."

"We think that supports the concept that these can be used as endpoints," he explains. "In other words, if you can reduce their values with your therapies, then that should be associated with a reduced risk of disease progression."

Wessels concurs, suggesting "the combination of the FibroScan and the ELF test has about 87-percent correlation with the liver biopsy."

In November, Echosens announced development of the FAST score, which combines biophysical measurements of liver stiffness and fat content with circulating AST biomarkers to identify individuals at-risk for fibrotic NASH.

"The FAST score was derived from a prospective, multi-center study with 350 patients undergoing a liver biopsy and then validated in seven external cohorts with 1,026 patients," explained University of Birmingham's Phil Newsome in the announcement. "FAST score provides an efficient way to non-invasively identify at-risk patients with progressive NASH that merit consideration for further treatment."

As suggested earlier, however, even if we get better at monitoring the signs of NAFLD and NASH, the multidimensional aspects of the disease are just starting to be teased apart. And without a clear understanding of the underlying pathological processes, developing and targeting therapeutic approaches will be challenging.

PLUMBING PATHOLOGY

"What it looks like is that there are four different stages of NASH and four different pathways that cause it," says Wessels. "First, you have your insulin resistance, which is a big part of it. Then you have your fat deposits in the liver. Then you have the inflammatory side of it and the fibrotic side of it."

"Companies like Intercept focus on the fibrotic side of it, which is more the end stage of the disease, whereas the diabetes companies are looking at their compounds now that actually reduce the insulin resistance part of it," he explains. "And then there are the few companies that are looking at the fat deposits pathway, and then finally the inflammatory pathway, as well."

Central to any effort to understand NAFLD and NASH will be model systems, whether *in vitro* or *in vivo*, and although efforts continue to improve existing models or develop new systems, there are questions as to the value of the models to this point.

"It is obvious that a non-human species will never be identical to humans," stated Arun Sanyal and colleagues at Virginia Commonwealth University School of Medicine in a 2018 review. "However, animal models should mimic human disease with respect to its development by diet-induced obesity, the most common risk factor for the disease in humans."

"Importantly, the dietary composition should broadly resemble human diets in terms of their macronutrient composition and not contain unnatural toxins, such as very high levels of cholesterol or di-ethylnitrosamine," the authors continued.

They opined that models should also recapitulate metabolic and inflammatory characteristics such as dyslipidemia and increases in cytokines, as well as hepatic characteristics such as steatosis, lobular inflammation, hepatocellular ballooning and fibrosis.

Myers questions how well we have reached these benchmarks.

"In an animal model, we generally only modulate one or two aspects of the physiology; for example, feeding mice a high-fat diet or a high-cholesterol, high-sugar diet," he says. "The human situation is not as straightforward."

He offers the example of Gilead's ASK-1 inhibitor selonsertib, for which the company had positive data in multiple animal models of NASH and fibrosis, but which did not achieve its primary endpoint in the Phase 3 STELLAR-3 study.

While acknowledging that no optimal animal model exists at the moment, Janell Richardson, field applications scientist for Taconic Biosciences, is quick to emphasize that the key to selecting the right model is understanding the exact question you hope to answer.

"I think every model is useful," she says. "You don't necessarily want to throw something away."

She categorizes NASH models into three flavors: dietary, genetic and chemical.

On the dietary side, she offers examples such as high-fat diets or the special formulation of diet produced for Taconic by Research Diets. She contrasts these from what she describes as negative diets, those that include nutritional deficiencies that can, for example, lead to fibrotic phenotypes. An example would be the methionine-cholesterol deficiency or MCD diet.

The impacts of these diets can be enhanced when combined with genetic models such as the ob/ob or leptin-receptor deficient mouse.

"What we typically tend to hear from customers is that this model can be very valuable, but it is extremely technically challenging to work with," Richardson says. "The fact that leptin receptor deficiency tends to be a highly proinflammatory background and NASH itself is a proinflammatory disorder, some can argue that they muddy the waters, so to speak. Others say that it is still translatable."

Effectively recapitulating many NASH pathological features is the STAM mouse model, chemically induced with streptozocin, a bacterial toxin that eliminates pancreatic beta cells, inducing insulin deficiency.

Earlier this year, Jordi Gracia-Sancho and colleagues at Barcelona's CIBEREHD combined a high-fat diet and chemical induction in rats to produce the Barcelona NASH or BarNa model, which not only recapitulated many of the pathological and biochemical characteristics of both advanced (10 weeks) and cirrhotic NASH (24 weeks), but also activated many of the same genes dysregulated in human NASH.

"Interestingly, the NASH-CH BarNa [24 weeks] model shared more pathways with human NASH than with human steatosis," the authors noted, "and on the contrary, the NASH BarNa [10 weeks] model seemed to be more coincident with the dysregulated pathways in patients with steatosis."

BUSY BODIES: Some of the lead therapeutics being tested in NAFLD and NASH.

COMPANY	CANDIDATE	MODE OF ACTION	PHASE
89bio	BIO80-100	Glycopegylated FGF21 analogue	1
Akero Therapeutics	AKR-001	Fc-FGF21 fusion protein	2
Can-Fite	Namodenoson	A3 adenosine receptor agonist	2
CohBar	CB4211	MOTS-c analogue	1
Cyclerion	Praliciguat	Soluble guanylate cyclase agonist	Pre
Enanta	EDP-305	FXR agonist	2
Enyo Pharma	EYP001	FXR agonist	2
Galmed Pharmaceuticals	Aramchol	SCD1 inhibitor	3/4
Genfit	Elafibranor	PPARα/δ agonist	3
Gilead	Cilofexor	FXR agonist	2
	Firsocostat	ACC inhibitor	2
	Selonsertib	ASK-1 inhibitor	3
Hepagene Therapeutics	HPG1860	FXR agonist	1
Intercept Pharma	Obeticholic acid	FXR agonist	3
Ionis Pharma	AKCEA-ANGPTL3-LRx	ANGPTL3 antisense	2
Madrigal Pharmaceuticals	Resmetirom	Thyroid hormone receptor agonist	3
NGM Bio	Aldafermin	FGF19 analogue	2
Northsea Therapeutics	Icosabutate	Eicosapentaenoic acid derivative	2
Novo Nordisk	Semaglutide	GLP-1 analogue	2
Pliant Therapeutics	PLN-1474	Integrin αvβ1 inhibitor	1
Terns Pharmaceuticals	TERN-101	FXR agonist	1
	TERN-201	Semicarbazide-sensitive amine oxidase inhibitor	1
Thera Technologies	Tesamorelin F8	Growth-hormone-releasing hormone	2
Zydus Cadila	Saroglitazar	PPARα/δ agonist	2/3

(SOURCES: RESPECTIVE WEB SITES. FRANCQUE AND VONGHIA ADVANCES IN THERAPY. 2019;36:1052-1074. CLINICALTRIALS.GOV)

"Transcriptomic analysis of liver tissues using next-generation sequencing reinforces the similarity of the BarNa model with the human disease," the authors expounded. "Pathway enrichment analysis illustrated that BarNa animals shared a relevant number of central pathways involved in NASH pathophysiology, including classical features of the disease (metabolism-related, inflammatory, and diabetes pathways) and characteristics of cirrhotic livers (extracellular matrix and cancer-related pathways)."

Of course, rodents are not the only available model systems, and again, depending on the questions you are asking, might not be the ideal model, according to Richardson.

"Certainly, rodents are leveraged to be able to ask those questions," she says, "but understanding that the multivariable pathogenesis can apply to things that tend to be more translatable at the pig or non-human primate level should certainly be appreciated."

Richardson is less convinced, however, that 3D cell cultures and microtissues can recapitulate the complex interplay of variables that occur within the liver during NAFLD and NASH development, including balances between paracrine and endocrine systems, and links to glandular, muscular and nervous systems.

"How do you recapitulate those things on a chip, let alone the interplay between, for example, the liver, the gallbladder, adipose tissue, muscle tissue?" she asks.

InSphero hopes to answer that specific question with its 3D Insight Human Liver Disease platform in collaborations with Akero Therapeutics and Cyclerion Therapeutics.

Announced in October, the Akero project will see the company examine the effects of its FGF21 analogue candidate AKR-001 on liver metabolism, hepatocyte apoptosis pathways and NASH-induced fibrosis, among other impacts. The goal is to provide metabolic context for any anti-inflammatory or anti-fibrotic impacts arising from their ongoing Phase 2a clinical trial.

In preclinical studies, meanwhile, Cyclerion used both InSphero's microtissues and various mouse models to examine the metabolic and transcriptional impacts of its soluble guanylate cyclase stimulator praliciguat vs. NASH and fibrotic liver disease.

As Cyclerion's Katherine Hall and colleagues published in August, the *in-vitro* experiments allowed them to see that the drug impacted hepatic stellate cells and myofibroblasts rather than hepatocytes, and to identify the mechanisms by which sGC stimulation exerted its anti-inflammatory effects.

Concerns about model translatability is one of the main reasons why Gilead announced its collaboration with insitro, back in April. The effort will apply insitro's machine-learning expertise to Gilead's clinical, preclinical and genetic data sets to derive *in-vitro* model systems that it hopes will more accurately reflect the human situation.

A couple of months later, Gilead then entered a collaboration with Renown Institute of Health Innovation, who will sequence and analyze DNA from 15,000 individuals living with NASH or NAFLD, as well as 40,000 control subjects. The data will then be analyzed alongside electronic health records.

"We're excited about that collaboration because in this Renown health system, there is a very large population of very well-phenotyped patients," Myers explains. "They have a very complete electronic medical record, and they have access to these patients to collect genetic samples."

"We're hoping that by looking at a well-phenotyped population who have a high likelihood of NASH and advanced fibrosis, we can use the genetics to identify polymorphisms associated with the disease, and again, use that in our efforts to identify rational drug targets for future development."

Despite open questions about disease diagnosis and progression, despite concerns about preclinical translatability and recapitulation of human NASH, and even in the face of clinical trial recruitment challenges, a quick survey of the last couple of years of *DDNews* would suggest that no one is waiting for ideal conditions to develop new treatments (see table "Busy bodies" on page 18).

EXPANDING PIPELINES

To date, Gilead has focused its efforts on three targets: ASK-1, farnesoid X receptor (FXR) and acetyl CoA carboxylase (ACC).

"We have shown, based on preclinical work and even by analyzing

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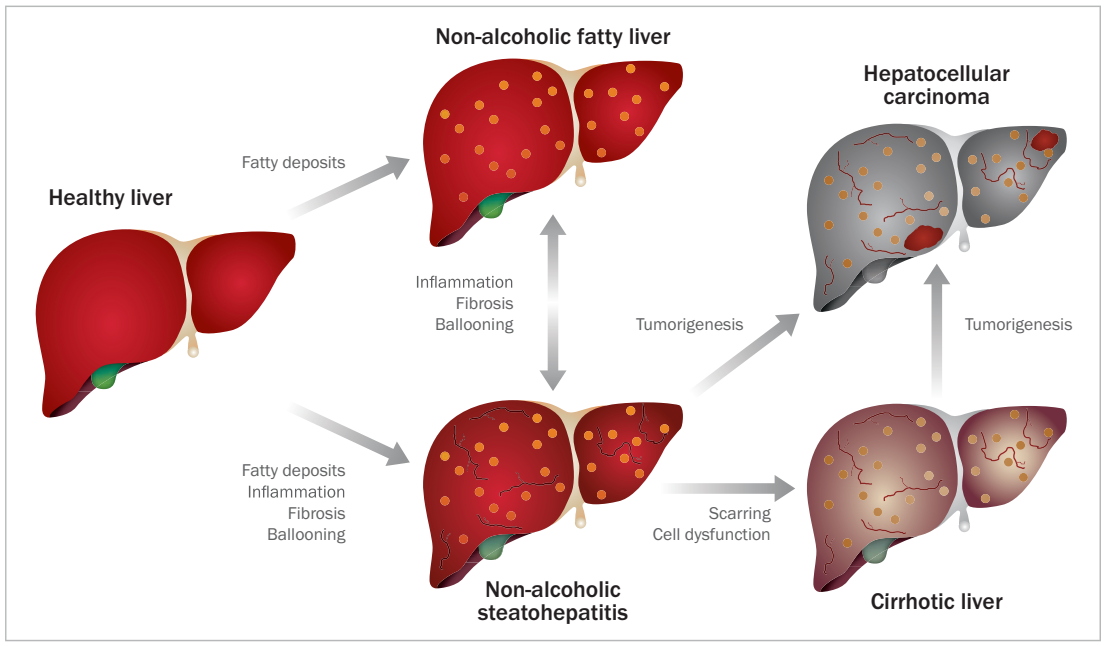

NO SINGLE PATH. The development of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis —and their possible progression to cirrhosis and hepatocellular carcinoma—results from a complex interplay of multiple insults.

LIVER

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our clinical samples, that all three of these targets are relevant in NASH, particularly in patients with advanced fibrosis," says Myers. "We showed in animal models of NASH and fibrosis that all three of them had beneficial effects in terms of steatosis, inflammation, fibrosis."

As mentioned earlier, the company suffered something of a setback in the development of its ASK-1 inhibitor selonsertib when the compound failed to achieve its primary endpoint in Phase 3 clinical trials, but as Myers suggests, the company is taking what it can from the study.

As they tease apart the data, he says they are learning a lot about the natural history of the disease, NASH biomarkers and the utility of liver biopsies.

The setback, however, hones the company's focus on their FXR agonist celifexor and ACC inhibitor firsocostat.

"We did Phase 2 studies of those drugs in monotherapy and showed that in patients with NASH and fibrosis, they improved steatosis in the liver, improved liver biochemistry, and also non-invasive tests of fibrosis," Myers continues.

"Based on those positive Phase 2 data, we decided to initiate the ATLAS study, which is testing those drugs alone or in combination in patients who have F3/F4 fibrosis for 48 weeks."

Although the ATLAS results have yet to come in, Gilead (and many others) see combination therapy as the key to controlling and ideally reversing NASH.

"The first [reason] is due to the complexity of the biology of NASH," Myers explains. "We think that you'll need to affect multiple aspects of the pathophysiology to really achieve the benefits that we're looking for."

"Two is about the heterogeneity of patients," he presses. "One patient may be likely to respond to one medication mechanism, whereas another patient may be more likely to respond to another."

"Ultimately, we want to increase the proportion of patients who respond, but also the depth of that response," he notes. "Rather than just regressing fibrosis by one stage, if we can regress the patient's fibrosis from F4 or cirrhosis down F2 or F1, we think ultimately the patient's outcomes will be better."

There is also the increasing recognition of the importance of the comorbidities associated with NASH, which Myers suggests may be a hepatic manifestation of insulin resistance.

"That's one of the reasons why we're very excited about our collaboration with Novo Nordisk, which has a long-standing history in developing therapies for metabolic diseases, particularly diabetes," he says.

In April, the two companies announced that they would explore synergies between Gilead's ACC and FXR compounds with Novo's GLP-1 receptor agonist semaglutide.

Other glycemic control drugs that are being or have been tested in NAFLD and NASH include metformin, sitagliptin, empagliflozin and dapagliflozin.

FORMA Therapeutics, meanwhile, is trying to tackle NAFLD and NASH at its earliest stages, targeting *de-novo* lipogenesis (DNL).

"From our perspective, DNL is one of our first hits; there is no question in our minds," explains Patrick Kelly, chief medical officer of FORMA. "The other hits that it takes are downstream. If you can reduce the fuel that's starting that fire, [patients] can benefit in the long run."

Key to quelling that fire, FORMA believes, is inhibiting fatty acid synthase (FASN), the enzyme that catalyzes the final step in DNL.

FORMA has two candidates: the systemic FASN inhibitor FT-4101 and a more liver-targeted version FT-8225.

At the Liver Meeting in November, FORMA presented results of the Phase 1 study of FT-4101, demonstrating that in healthy subjects, the inhibitor reduced hepatic DNL in a dose-dependent manner without any of the side effects that have been seen with ACC inhibitors.

"DNL occurs in many places, not just the liver," Kelly explains. "That's what the ACC inhibitors have learned, that it comes with a cost."

This was the rationale behind FT-8225, which would hopefully avoid extra-hepatic side effects.

"The liver-targeted approach assumes the liver is the target organ," offers Patricia Schroeder, FORMA's FASN project lead, "which is something we are able to investigate with the franchise: one that is systemic, that can interact all over, as well as one that's just focused on the liver."

Despite targeting a single metabolic point, however, Schroeder is first to acknowledge that whatever drug took the lead, it would be part of a combination approach.

"Fibrosis doesn't reverse quickly, if at all," adds Kelly. "It takes time. I think that's part of the frustration—even in the setting of combination therapy, you have these long trials that the companies and the patients have to be willing to invest in."

"Who's going to be clever enough to figure out the best combination for everyone?" he continues. "I think it's going to be multiple combinations, which is great."

As the clinical space fills up with new candidates, pressures will increase to recruit more patients to run bigger trials.

"The average site recruits 0.25 patients per month per site," Wessels suggests. "So basically, every four months, they find one patient. That is way too small for all of the compounds that are coming through, so we really have to figure that out."

Ironically, the solution to that problem will likely come in the form of the first therapeutic that crosses the regulatory finish line.

"We're at that borderline within the NASH area, where the ultimate proof that beneficial effects can be gained by treating NASH will ultimately depend on the approval of some of the drugs that are close to approval now," adds ICON's Benson.

"I was around in the field before the statins were approved, and there was massive debate about whether there was any proof that lowering cholesterol could reduce atherosclerosis and thereby reduce myocardial infarction and stokes," he recounts. "When the statins came along, they were sufficiently potent at reducing LDL cholesterol in particular, that essentially the ultimate proof came from the clinical trials with those drugs."

The hope is that at least one of the lead NASH drugs will prove just as enticing and ultimately, pierce the silence. ■

EDITCONNECT: E121935

Imaging NASH

ALTHOUGH IT REMAINS THE GOLD STANDARD for diagnosing NASH, liver biopsy has its risks, and at least in the current absence of treatments beyond lifestyle changes, there is significant reluctance to inflict such a test on patients.

Because of this, says Martin Benson, senior director and global lead for Cardiometabolic Drug Development Services at ICON, the field is actively seeking to develop non-invasive biomarker- and imaging-based tests that could conceivably supersede liver biopsy, expanding patient populations by facilitating diagnosis.

"In the imaging field, we've got a number of different modalities," Benson offers, the simplest and most widely accessible being ultrasound.

"Straightforward ultrasound can detect big differences in the amount of fat," he says, although he acknowledges sensitivity issues as ultrasound would require the liver to have about 20 to 30 percent fat.

"Just to put that into perspective, expert pathologists will be scoring [biopsy] sections on the basis of something like 5 to 10 percent fat," he explains, adding that it also can't tell clinicians anything about the degree of liver fibrosis.

To facilitate fibrosis detection, Echosens has developed FibroScan, a modified ultrasound system that sends vibrations through the abdominal wall and into the liver.

Much like a seismograph monitors vibration through the ground, FibroScan monitors the rate at which the shockwave passes through the tissues to determine its stiffness or degree of fibrosis. The faster it travels, the stiffer the tissue.

"It has its limitations in that the more obese the patient is, the instrument loses accuracy," Benson cautions, and most NASH patients will be obese.

FibroScan has also been augmented with a technology called Controlled Attenuation Parameter, or CAP, that allows clinicians to not only measure fibrosis but also steatosis, Benson explains, which he says was heavily promoted at the recent Liver Meeting in Boston, led by AASLD.

Moving further up the scale are diagnostic platforms centered on magnetic resonance imaging (MRI).

"In most studies that we run these days, MRI proton density fat fraction, or PDFF, is used to measure steatosis," Benson offers.

Because fat is measured throughout the entire liver, he notes, the technique is potentially a vast improvement over liver biopsy, which looks at a small fragment that may or may not be representative of the entire liver.

Even though the modality is expensive and can't be transported, unlike the bedside FibroScan, MRI PDFF is seeing increasing interest.

Another MRI-based imaging modality is magnetic resonance elastography, or MRE.

"Like the FibroScan, it has a little paddle that sits on the surface and vibrates, sending shockwaves through the liver," states Benson. "The MRI detects those shockwaves and can translate that into the stiffness of the liver."

"It is less affected by the obesity of the patient and is more accurate than FibroScan," he says, "but it is more expensive because it needs a magnetic resonance imaging machine."

Although each imaging modality has its drawbacks, Benson is confident that their relative safety and improving accuracy relative to liver biopsy will soon give regulators and payors reason to more readily accept these diagnostic tests for drug approval. ■