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Current and Future Therapeutic Regimens for Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

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Abstract

Nonalcoholic fatty liver disease (NAFLD) and its progressive form non-alcoholic steatohepatitis (NASH), are rapidly becoming among the top causes of cirrhosis, hepatocellular carcinoma, and indications for liver transplantation. Other than lifestyle modification through diet and exercise, there are currently no other approved treatments for NASH/ NAFLD. Although weight loss can be

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effective, it is difficult to achieve and sustain. In contrast, bariatric surgery can improve metabolic conditions associated with NAFLD, and has been shown to improve liver histology. To have approved regimens for the treatment of NASH/NAFLD, several issues must be addressed. First, all stakeholders must agree on the most appropriate clinical trial endpoints for NASH. Currently, resolution of NASH (without worsening fibrosis) or reduction of fibrosis stage (without worsening NASH) are the accepted endpoints by the regulatory authorities. It is important to recognize the prognostic implication of histologic features of NASH. In this context, although histologic NASH has been associated with advanced fibrosis, it is not an independent predictor of long-term mortality. In contrast, there are significant data to suggest that fibrosis stage is the only robust and independent predictor of liver-related mortality. In addition to the primary endpoints, several important secondary endpoints, including noninvasive biomarkers, long-term outcomes, and patient-reported outcomes must be considered. In 2018, a few phase 3 clinical trials for the treatment of NASH have been initiated. Additionally, a number of phase 2a and 2b clinical trials targeting different pathogenic pathways in NASH are in the pipeline of emerging therapies.

Conclusion: Over the next 5 years, some of these regimens are expected to provide potential new treatment options for patients with NASH/NAFLD.

Nonalcoholic fatty liver disease (NAFLD) is rapidly being recognized as the leading cause of chronic liver disease worldwide.[1–3] Over the past two decades, there is substantial evidence to suggest that NAFLD is highly prevalent throughout the world and represents a spectrum of diseases, some of which can progress to cirrhosis and hepatocellular carcinoma.[2–5] The majority of subjects with NAFLD are asymptomatic and are diagnosed incidentally. Although all subtypes of NAFLD increase the risk for cardiovascular events and mortality, non-alcoholic steatohepatitis (NASH) is the main diagnostic subtype of NAFLD that predisposes patients to cirrhosis and liver-related complications.[1–3]

As of 2018 there are no approved drug treatments for NAFLD or NASH.[6] Nevertheless, a large number of emerging therapies are being evaluated in clinical trials. As our understanding of the basic pathogenesis of the progressive form of NAFLD (NASH) increases, it is almost certain that new treatment targets will be considered and new treatment regimens will be developed for NASH patients at risk of progressive hepatic fibrosis and its associated clinical outcomes.[1–8]

In the quest to find an effective and safe treatment for the progressive form of NAFLD or NASH, several priorities and challenges must be recognized. First, since NASH is the potentially progressive form of NAFLD, it should be the target of new therapeutic regimens. Furthermore, the severity of hepatic fibrosis (i.e., fibrosis stage) predicts liver-related mortality in NAFLD and therefore, the development of treatment regimens for patients with significant hepatic fibrosis must be prioritized.[7–10] In addition to the appropriate endpoints, it is important to consider the placebo effect on the histology of NASH patients who are treated in randomized controlled trials. In fact, this placebo effect has been shown to be substantial.[11] Additionally, spontaneous regression of NASH and even NASH-related fibrosis has been observed, potentially related to the lifestyle modifications and behavioral changes of these subjects during the clinical trial.[11] An example of this phenomenon was observed in the National Institute of Diabetes and Digestive and Kidney Diseases sponsored

Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis (PIVENS) trial, in which placebo-treated subjects experienced significant weight loss.[11] In fact, the interaction with weight loss during a clinical trial can be an important confounder when evaluating the histologic response of patients with NASH.[12]

In this context, an important challenge in the field of NASH therapeutics is to develop a consensus on how to accurately assess treatment response. There is an ongoing debate as to which endpoint truly represents the best surrogate for the "hard" outcomes (liver-related morbidity and mortality) in NAFLD/ NASH. Although still debated, improvement of stage of fibrosis may be the best endpoint to use in clinical trials of NASH. Although resolution of histologic NASH does correlate with the improvement of fibrosis, it may be flawed by the variability inherent in its histologic assessment. In addition to the clinical endpoints, inclusion of validated patient-reported out-comes in therapeutic trials of NASH will be important.[9,13]

In this review, we summarize the current and future treatment modalities that were presented in a recent trend conference on NASH sponsored by the American Association for the Study of Liver Disease (AASLD).

Selection of Endpoints in Clinical Trials of NASH

Until recently, therapeutic trials of NASH have primarily focused on improvement in steatohepatitis as defined by the NAFLD Activity Score (NAS).[14] In addition to the improvement of NAS, resolution of histologic evidence for steatohepatitis is also considered an important primary endpoint in most clinical trials for patients with NASH.[15] Although NAS scoring does provide valuable quantifiable scores to assess the individual histologic components of NASH, the grading is still subjective.[16] The interobserver variability of histologic components of NAS such as ballooning degeneration (a key pathologic feature of NASH) has been problematic.[14,17] Additionally, ballooning degeneration as an individual pathologic feature is not an independent predictor of liver-related mortality.[14,17] In this context, the endpoint should be a surrogate of the hard outcome of liver-related mortality. As noted previously, there is now increasing evidence that stage of fibrosis is the best predictor of mortality and may serve as the best surrogate for clinically relevant outcomes in NASH.[8,18]

In addition to histology, other important endpoints in NASH subjects with cirrhosis include measurement of the hepatic venous pressure gradient. The selection of this endpoint is based on the data suggesting that hepatic venous pressure gradient values above a certain threshold are associated with reduced survival in patients with cirrhosis.[19] Although improvement in survival is always desirable, given the long natural history of NASH and presence of comorbidities in this population, studies designed to capture this endpoint will be difficult to design and will not be feasible to perform.

Although there is little doubt about the value of histologic assessments in NASH, liver biopsy is invasive and not easily accepted by patients. Furthermore, repeat biopsies to assess

worsening or improvement of liver injury and histologic fibrosis in clinical practice is not feasible. Therefore, a flurry of efforts to develop and validate noninvasive modalities to assess the stage of fibrosis in NASH and to document its progression and regression has ensued. Challenges surrounding the ability to noninvasively define these therapeutic endpoints must be overcome to truly advance the therapeutic field of NAFLD and NASH.

Finally, it is important not only to include clinical endpoints that best predict mortality but also to include patient-reported outcomes that are the best surrogates of patient experience. In this context, the use of a disease-specific validated instrument such as the chronic liver disease questionnaire (CLDQ)-NAFLD-NASH in the clinical trials of NASH will be important.[13]

Data Regarding Weight Loss and Exercise in NAFLD

Lifestyle modification that includes weight loss and structured exercise remains the cornerstone of treatment for patients with NAFLD and NASH.[20] In this context, weight loss has been associated with a reduction in liver fat and improvement in aminotransferase levels.[6] The amount of weight loss is a determinant of histologic improvements in liver injury and fibrosis. Although small reductions (3%−5% body weight loss) can reduce hepatic steatosis and the associated metabolic parameters, greater weight reduction (at least 7%) is required to improve or resolve steatohepatitis.[21,22]

In the context of mild to moderate obesity, weight loss can be achieved by dietary interventions that restrict calorie intake.[21] However, it should be noted that long-term sustained weight loss can only be experienced by 3%−6% of subjects.[6,21] Although the benefit of different diets may vary according to the underlying metabolic abnormalities, the Mediterranean diet has been demonstrated to have a beneficial role in reducing all-cause mortality, cardiovascular diseases, cancer, obesity, and type 2 diabetes.[22] However, the efficacy of these different diets in patients with NASH has not been formally assessed. Nevertheless, dietary macronutrient composition generally seems to have a lesser role than caloric restriction in reducing liver fat in patients with NAFLD.[21,22]

In addition to diet, physical activity plays an important role in the development of NAFLD.[23,24] In this context, about half of NAFLD patients are inactive, and one third of these patients do not engage in any physical exercise.[23] Based on the recent data, there has been increasing recognition of the efficacy of exercise *per se* in reducing hepatic fat. Therefore, exercise is now routinely recommended for the management of NAFLD.[25,26] In addition to improvement in hepatic steatosis, exercise has also been shown to improve liver enzymes and ameliorate insulin resistance.[27] In this context, exercise may improve liver inflammation and liver cell injury in patients with NAFLD. In fact, a recent study of 169,347 men and women with repeat measures of liver fat (quantified with ultrasound) and physical activity demonstrated a strong association between exercise and changes in NAFLD over a mean 5 years of follow-up.[28]

Although exercise is generally beneficial, the optimal dose of exercise may have relevance for subjects with NAFLD and NASH. Several recent studies have attempted to address the

issues of optimal exercise dose (type, intensity, and amount) for subjects with NAFLD. Some reports have suggested that there are no differences in the amount of liver fat reduction by aerobic exercise dose or intensity. In this context, only the act of exercising seems to be important.[24–29] Additionally, another study has suggested that the reduction of liver fat by aerobic exercise occurred without clinically significant weight loss, suggesting that exercise alone is an independent factor of reducing liver fat.[29] In this context, the current recommendations suggest that resistance training should complement aerobic exercise. In fact, this recommendation is also consistent with the exercise guidance for cardiovascular disease risk modification.[24,29]

In summary, diet and exercise should remain the first line recommendations for patients with NASH. However, more clinical research is needed to better understand the magnitude of improvement in clinical and histologic outcomes and to determine the interaction between weight loss and exercise in subjects with NASH/NAFLD.

Current Medical Treatment for Patients With NASH

The AASLD guidelines recommend that only biopsy-proven NASH should be considered for medical treatment.[25,26] Several drugs have been tested but none have been approved to treat NASH.[30–37]

In this context, glitazones are a class of drugs that have been used to treat NASH. Glitazones up-regulate adiponectin, an adipokine with anti-steatogenic and insulin-sensitizing properties, which increase the synthesis and uptake of fatty acids by adipocytes, rather than their uptake by organs such as the liver and muscle.[33,34] One such drug, pioglitazone, has been shown to improve histological NASH in terms of steatosis, inflammation, and hepatocyte ballooning as well as NAS activity score, resolution of NASH and improving fibrosis.[37,38] However, these beneficial effects are not sustained, with an increase in serum alanine aminotransferase values and reappearance of NASH after the medication is discontinued. Also, there are additional concerns related to the weight gain that accompanies the use of pioglitazone.[37]

The most recent version of AASLD Guidance document for NAFLD suggests that since it appears that pioglitazone improves liver histology for patients with and without type 2 diabetes mellitus, it may be a viable option for treatment, but only after the risks and benefits for patients have been reviewed. In addition, before starting treatment of a diabetic patient, a liver biopsy should be considered to document histologically proven NASH.[26]

Vitamin E is an antioxidant that prevents liver injury by blocking intrinsic apoptotic pathways and protecting against oxidative stress.[33] Data from the PIVENS trial show that vitamin E can improve histological NASH in terms of steatosis, inflammation, ballooning, NAS, and resolution of NASH at a dose of 800 IU/day.[11] How-ever, there are some concerns that long-term use of vitamin E may be associated with increased incidence of hemorrhagic stroke and an increased risk of prostate cancer.[33] Nevertheless, the AASLD Guidance document suggest that vitamin E may be used daily at a dose of 800 IU/day in nondiabetic adults with biopsy-proven NASH. However, at this time the AASLD Guidance

document does not recommend the use of vitamin E as a treatment for NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis.[26] The beneficial impact of vitamin E or pioglitazome on all-cause mortality and liver-related mortality has not been established.

Liraglutide, a long-acting glucagon-like peptide 1 (GLP-1) agonist, is secreted after eating. GLP-1 is secreted by the L cells of the small bowel and proximal colon, and stimulates insulin secretion by the pancreatic beta cells, decreases hepatic glucose production, increases satiety by delaying gastric emptying, and has cardioprotective effects.[12] GLP-1 has a half-life of less than 2 minutes, whereas liraglutide, the synthetic analogue, has a half-life that allows a single daily administration.[39] In a phase 2 trial, liraglutide 1.8 mg subcutaneous injection administered once daily resulted in resolution of NASH while improving key metabolic risk factors (weight, body mass index, glucose level, and high-density lipoprotein cholesterol) with minimal side effects (mainly gastrointestinal, such as diarrhea).[12] Phase 3 trials are awaited to confirm these preliminary data.

A large proportion of patients with NAFLD have underlying metabolic risk factors which will require medical treatment. In fact, preliminary data suggest that there may be an added liver-related benefit when the associated comorbidities are treated.[37–41] For instance, statins are safe to use in the NAFLD population and can provide the beneficial effects of treating dyslipidemia, improving insulin resistance, and reducing the risk of hepatocellular carcinoma.[40–42] Additionally, ezetimibe also appears to be safe and potentially beneficial in patients with NAFLD.[39,43]

In summary, despite the initial assessment of a large number of agents, no single agent or combination has proven efficacy for subjects with NASH. Until the results of the ongoing randomized, double-blind, placebo-controlled trials become available, lifestyle modifications and optimizing metabolic risk factors are the best medical treatment option for patients with NASH.

Current Surgical Options for Treatment of Obesity in Subjects With NASH

As noted previously, sustained weight loss can be beneficial for NAFLD. In this context, bariatric surgery can induce long-term weight loss and decrease long-term mortality related to diabetes, heart disease, and cancer.[44,45] In a study with more than 10 years of follow-up, weight loss of 25%, 16%, and 14% was noted in patients who underwent gastric bypass, vertical-banded gastroplasty, and gastric banding, respectively.[45] In addition, bariatric surgery can prevent cardiovascular events[46] and improve type 2 diabetes.[47,48]

Regardless of the type of bariatric surgical procedure performed, a decrease in adiposity is seen after bariatric surgery. This is an important factor to consider because increased adiposity is associated with increased insulin resistance, which is independently associated with hepatic steatosis. In fact, persistence of insulin resistance is an independent predictor of presence of NAFLD, one year after surgery and significantly increases the probability of having severe steatosis compared with those patients whose insulin resistance improved after their surgery.[49,50]

Preliminary studies have also reported a resolution of NASH in approximately 85%−90% of patients who undergo bariatric surgery.[51] A recent prospective study analyzing sequential liver biopsies from a final cohort of 82 patients with biopsy-proven NASH showed the disappearance of NASH in approximately 85% of the patients 1 year later, though NASH resolved in a greater proportion of patients with baseline mild disease (94%) than in those with baseline moderate or severe disease (70%).[52] Specifically, bariatric surgery significantly reduced all the histological components of NASH, including hepatic fibrosis.[52]

Despite these data, NASH is currently not an indication for bariatric surgery. In fact, patients with NASH must have other qualifying conditions as delineated by the National Institutes of Health consensus conference to be able to undergo weight loss surgery.[53] It is possible that this recommendation will be changed in the future, because weight reduction surgery appears to effectively address metabolic conditions, which can lead to a reversal of NASH.

Liver Transplantation in Subjects With NASH

Liver transplantation (LT) is the standard treatment option for NASH and advanced liver disease. Currently, cirrhosis due to NASH is now the second most common indication for liver transplantation in the United States, and patients who undergo transplantation for NASH have similar survival as those who receive transplants for other etiologies.[54–57] In fact, the 1-, 3-, and 5-year survival rates after LT for patients with NASH are 87.6%, 82.2%, and 76.7%, respectively, which are comparable to rates for other indications.[57] However, NASH after LT can either recur or can develop *de novo* in patients who have undergone transplantation.[58] Although the risk of steatosis is time-dependent and approaches 100% at 5 years after LT in NASH patients, the risk of developing histologic NASH is approximately 10%−30%, whereas the risk of developing advanced fibrosis is low (5% at 5 years and 10% at 10 years).[2,5,7] In multivariate analyses, the post-LT recurrence of NAFLD has been found to be associated with hypertriglyceridemia and high body mass index post-LT.[59]

Post-LT care for patients with NASH can present several challenges. There is a strong rationale for adopting a minimalist approach to maintenance of immunosuppression for patients with a history of NASH. The lowest effective doses of calcineurin inhibitors, mammalian target of rapamycin inhibitors, and antimetabolites are recommended. Corticosteroids can cause and exacerbate features of the metabolic syndrome and should be avoided beyond the early (i.e., first 6 months) postoperative period.[57,60]

In addition, there are no definitive data regarding the optimal time to biopsy recipients who were transplanted for NASH or cryptogenic cirrhosis. A significant portion of patients with NASH can have normal liver enzymes. The emergence and availability of transient elastography (TE) and magnetic resonance elastography (MRE) may reduce the need for liver biopsy.[61] Weight gain is nearly ubiquitous after LT. Because obesity and the components of the metabolic syndrome are important predictors of posttransplantation outcomes, weight management is a cornerstone of optimizing outcomes and a deterrent to post-LT metabolic syndrome.[62,63]

In summary, NASH patients who undergo LT do very well. Nevertheless, these patients do present pre-and posttransplantation challenges. Optimal approaches to pre-and perioperative management (including bar-iatric surgery) and immunosuppression are evolving rap-idly, and effective nutritional, psychological, and pharmacotherapeutic agents are being developed, but none have been fully accepted.

Emerging Therapy for NASH: Nonantifibrotic and Antifibrotic Regimens

As new information about the pathogenesis of NAFLD/NASH continues to unfold, multiple pathogenic pathways (insulin resistance, lipotoxicity, oxidative stress, altered immune/cytokine/mitochondrial functioning, and apoptosis) are being implicated in the development of NASH and its progression.[64] Therefore, new therapeutic modalities are being developed to target many of these pathways. These treatment regimens are currently in various stages of development, with most of the current studies conducted with a single treatment modality. However, it is expected that combination therapy of multiple drugs to treat NASH will soon follow. The following will highlight the current treatment regimens in clinical trials directed toward improving hepatic steatosis, inflammation, liver cell injury, and fibrosis.

One of the drugs that has progressed to phase 3 development for NASH is obeticholic acid (OCA), which is a farnesoid X receptor (FXR) agonist whose potential actions include decreasing hepatic steatosis, inflammation, and fibrosis while increasing insulin sensitivity. In the Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment (FLINT) phase 2 trial, in which OCA was compared with a placebo, there was no worsening of fibrosis, and the NAS decreased by ≥2 points in patients who were receiving OCA. Although there was some evidence of worsening dyslipidemia, coadministration of statins led to improvement of participants' low-density lipoprotein profiles to at or below baseline levels.[65]

A phase 3 clinical trial of OCA in patients who had NASH without cirrhosis (stage 2 and 3) is ongoing (Randomized Global Phase 3 Study to Evaluate the Impact on NASH with Fibrosis of Obeticholic Acid Treatment [REGENERATE; https://clinicaltrials.gov/ct2/show/NCT02548351]). The primary endpoint of the study is either improvement of fibrosis without worsening NASH or resolution of NASH without worsening fibrosis. A number of secondary endpoints and long-term outcomes are being monitored for assessment of both efficacy and safety.

Another agent in phase 3 clinical trials is elafibranor, a dual receptor peroxisome proliferator activated alpha/ delta (PPARα/δ) agonist. Elafibranor was studied in the GOLDEN Study 2b Trial, and its effects were compared to that of a placebo.[35] Despite some methodological limitations of the GOLDEN trial, elafibranor, 120 mg/day for a year, seemed to induce resolution of NASH without fibrosis worsening. Elafibranor was also well tolerated and improved patients' cardiometabolic risk profile. However, patients did experience an increase in their creatinine level that resolved when the medication was stopped.[35] The ongoing phase 3 clinical trial of elafibranor (RESOLVE-IT) has identified the primary endpoint for the study as resolution of NASH without worsening of fibrosis. The study is also following long-term outcomes such as all-cause mortality, cirrhosis, and liver-related clinical outcomes.

Another drug that has been advanced to phase 3 clinical trial is selonsertib (SEL). SEL is an inhibitor of apoptosis signal-regulating kinase-1 (ASK-1), the use of which leads to improvement of inflammation and fibrosis in animal models of NASH. A recent phase 2 clinical trial assessed the safety and efficacy of selonsertib with or without simtuzumab in subjects with NASH stage 2 or 3 fibrosis.[66] The primary endpoint of the study was improvement of fibrosis without worsening of NASH. A number of other secondary endpoints were assessed. The study suggested significant histologic improvement as well as improvements in a number of secondary endpoints.[66] However, based on recent data documenting its lack of efficacy, simtuzumab was considered to have a placebo effect. Based on these data, a phase 3 clinical trial has been initiated and is currently enrolling subjects with NASH and advanced fibrosis (STELLAR-3 and −4). The trial consists of a 48-week trial of selonsertib in subjects with stage 3 and 4 NASH; the primary endpoint is a ≥1-point decrease in fibrosis stage without worsening of NASH ballooning or inflammation. The study's 5-year outcome is the reduction in progression to cirrhosis (STELLAR-3) and hepatic decompensation, hepatocellular carcinoma, transplantation, or death (STELLAR-3 and 24).[67]

In addition to these phase 3 clinical trials, a number of early phase trials are underway (Table 1). These include a phase 2 clinical trial using the GLP-1 analogue semaglutide which has shown promising results.[12] Additionally, another trial for treatment of NASH focuses on an inhibitor of acyl co-A carboxylase (ACC), a rate-limiting step in *de novo* lipogenesis. In a very small open label study, an ACC inhibitor showed reduction in alanine aminotransferase, elastometry and MRI PDFF quantification of liver fat.[68]

Despite the great enthusiasm and activity in the field of NASH therapeutics, there is no treatment for NASH that has been approved by the United States Food and Drug Administration. Nevertheless, it is almost certain that our armamentarium of therapeutic options for NASH is likely to expand in the near future.

There are also drugs in development designed to disrupt fibrosis development in patients with NASH. This is an area of significant therapeutic need, because fibrosis is the strongest predictor of mortality in patients with NASH.[18,69]

Currently, all ongoing phase 2B or phase 3 clinical trials of antifibrotic drugs require liver biopsy to quantify fibrosis before and after treatment. As noted previously, this requirement imposes limitations on the clinical trial design, including the invasive nature of biopsy, which limits access to tissues at intermediate time points during a trial. Moreover, although biopsy is highly informative, the NASH fibrosis staging system may not universally and precisely predict outcomes, although the use of quantitative assessment of fibrosis by morphometry may improve its predictive performance in NASH.[70]

Moreover, even when cirrhosis is established, collagen continues to accumulate, yet standard pathologic scoring systems are not able to detect this increase, whereas morphometric assessment of collagen may be more accurate.[71] Whereas determinants of fibrosis progression have been well validated for hepatitis C virus, a similar predictive model for NASH has not been validated.[72–74] This is probably due to the multifactorial nature of

NASH and lack of identical contributions from different pathogenic drivers in all patients who present with histologic and clinical NASH phenotype.[72–74]

As a result of the complexity and multifactorial nature for underlying NASH, there is an unusually broad effort to focus on many targets, alone or in combination. Antifibrotic therapies, in addition to those discussed previously (FXR agonists, PPAR agonists, and inhibitor of ASK1), include combinations of antagonists such as CCR2/CCR5 chemokine receptors, galectin antagonists, and a small interfering RNA target in stellate cells that reduces expression of heat shock protein.[76] The use of cenicriviroc, a CCR2/CCR5 chemokine receptor blocker, aims to mediate interactions driving inflammation and fibrosis. In a 2-year phase 2b multinational, randomized, double-blind placebo-controlled study for the treatment of NASH in 289 adults using cenicriviroc, year 1 results have demonstrated improvement in fibrosis without worsening of NASH for subjects who received cenicriviroc. The safety profile was also encouraging; the only drug-related treatment emergent adverse events with a grade of >2 and a frequency of >2% were fatigue (2.8%) and diarrhea (2.1%).[77] A Phase 3, A multicenter, randomized, double-blind, placebo-controlled study of cenicriviroc for the treatment of fibrosis in NASH (AURORA) is currently underway. The primary outcome is improvement of fibrosis without worsening NASH. There are a number of other secondary outcomes.[77]

There are many more compounds undergoing evaluation in animal models to reverse existing fibrosis. Should any one of these prove effective in a clinical trial, it will likely have a catalyzing effect on the field. An exciting observation from antiviral trials has been the recognition that cure of hepatitis C virus or suppression of hepatitis B virus can often reverse cirrhosis, which was unimaginable decades ago.[76] Uncovering and exploiting mechanisms by which the liver innately degrades scar tissue in these diseases could yield new therapeutic approaches that could transform the outlook for patients with chronic fibrosing liver disease, including NASH.

Conclusions

Despite many advances in understanding the epidemiology of NAFLD and NASH, currently, the only available treatment for NAFLD/NASH is weight loss. One of the important challenges in the field of NASH is the lack of a reliable and noninvasive endpoint for NASH that can accurately serve as a surrogate for the hard outcome of mortality. In this context, there is still much debate about the appropriate endpoints for clinical trials of NASH. Although histologic assessment is currently the most widely used modality, it is a suboptimal and invasive approach. Nevertheless, resolution of NASH and/or improvement of fibrosis have been the currently accepted endpoints.

In this context, there are emerging therapies for NASH that include non-antifibrotic as well as antifibrotic regimens. Most recent clinical trials have focused on NASH and fibrosis as the most appropriate candidates for these regimens. Although most clinical trials have focused on monotherapy, the combination of different drugs targeting different pathogenic pathways in NASH may be more appropriate. There is much enthusiasm and interest in this area of liver disease, and a potential effective treatment is on the horizon.

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Abbreviations:

AASLD	American Association for the Study of Liver Disease
ACC	acyl co-A carboxylase
ASK-1	apoptosis signal-regulating kinase-1
FLINT	Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment
FXR	farnesoid X receptor

GLP-1	glucagon-like peptide 1
LT	liver transplantation
MRE	Magnetic Resonance Elastography
NAFLD	nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	nonalcoholic steatohepatitis
OCA	obeticholic acid
PIVENS	Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis
PPARα/δ	peroxisome proliferator activated receptor alpha/delta
REGENERATE	Randomized Global Phase 3 Study to Evaluate the Impact on NASH With Fibrosis of Obeticholic Acid Treatment
TE	transient elastography

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TABLE 1.

Non-antifibrotic Drugs in Early Development and Their Potential Site of Action

Drug	Potential Action Site
NGM282	Recombinant FGF-19 agonist
BMS-986036	Pegylated FGF-21 analogue
JKB-121 (nalmefene hydrochloride)	TLR-4 antagonist
Aramchol	Synthetic fatty acid/bile acid conjugate
Volixibat	ASBT inhibitor
MGL-3196	Thyroid hormone receptor-β agonist
GS-0976	ACC inhibitor
LMB763	FXR agonist
LJN45	FXR agonist
Emricasan	Oral caspase inhibitor
Saroglitazar	PPAR α/γ agonist
IVA337	Pan PPAR agonist
MSDC 0602K	mTOR modulating insulin sensitizer
Semaglutide	GLP-1 analogue
Liraglutide	GLP-1 analogue
Combination GS-0976 and GS-9674	ACC inhibitor/FXR agonist
IMM-124E- Hyperimmune bovine colostrum	Induction of regulatory T cells
Bl-1467335	VAP-1/AOC3 inhibitor

ASBT: apical sodiumbile acid transporter, mTOR: mechanistic/mammalian target of rapamycin, VAP-1/AOC3: vascular adhesion protein 1/amine oxidase, copper containing 3, FGF: Fibroblast growth factor