Current and Future Therapeutic Regimens for Non-alcoholic Fatty Liver Disease (NAFLD) and Non-alcoholic Steatohepatitis (NASH)

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List of Abbreviations:

NASH- non alcoholic steatohepatitis

NAFLD- nonalcoholic fatty liver disease

HCC- hepatocellular carcinoma

NIDDK- National Institute of Diabetes and Digestive and Kidney Diseases

PIVENS- Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis

NAS- NAFLD Activity Score

HVPG- hepatic venous pressure gradient

CLDQ- chronic liver disease questionnaire

AASLD- American Association for the Study of Liver Disease

ALT- alanine aminotransferase

GLP-1- glucagon-like peptid-1

HDL- high density lipids

BMI- body mass index

LT-liver transplant

FXR- farnesoid X receptor

FLINT- Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment

OCA- obeticholic acid

REGENERATE- Randomized Global Phase 3 Study to Evaluate the Impact on NASH With Fibrosis of Obeticholic Acid Treatment

PPAR α/ δ- peroxisome proliferator activated alpha/delta agonist

LEAN- liragtytide semaglutide

ACC- acyl co-A carboxylase

ASK-1- apoptosis signal-regulating kinase 1

Abstract

NASH/NAFLD is rapidly becoming one of top causes of cirrhosis, hepatocellular carcinoma and indication for liver transplantation. Except for life style modification through diet and exercise, there are currently no other approved treatments for NASH/NAFLD. Although weight loss can be effective, it is hard to achieve and sustain. In contrast, bariatric surgery can improve metabolic conditions associated with NAFLD and has been shown to improve liver histology. In order to have approved regimens for treatment of NASH/NAFLD, a number of issues that 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 stage of fibrosis, it is not an independent predictor of long term mortality. In contrast, there is significant data to suggest that stage of fibrosis is the only robust and independent predictor of liver-related mortality. In addition to the primary endpoints, a number of important secondary endpoints, including non-invasive biomarkers, long term outcomes, and patient reported outcomes, must be considered. In 2017, a few phase 3 clinical trials for treatment of NASH are in progress. Additionally, a number of phase 2a and 2b clinical trials targeting different pathogenic pathways in NASH enriches 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.

Background:

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 (HCC). [2-5] The majority of subjects with NAFLD are asymptomatic and are diagnosed incidentally. Although all subtypes of NAFLD increase the risk for the cardiovascular events and mortality, NASH is the main diagnostic subtype of NAFLD which predisposes patients to cirrhosis and liver-related complications [1-3].

In 2017, there are no approved drug treatments for NAFLD and 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 increases, almost certainly, there will be new treatment targets considered and new treatment regimens to 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, a number of priorities and challenges must be recognized. First, as noted previously, NASH represents the potentially progressive form of NAFLD and as such, it should be the target of treatment. Furthermore, the severity of hepatic fibrosis (i.e. fibrosis stage) predicts liver-related mortality in NAFLD and therefore, patients with significant hepatic fibrosis must be the cohort for whom development of treatment regimens is prioritized. [7-10] In addition to the appropriate endpoints, it is important to consider the placebo effect on the histology of NASH patients 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 life style 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 (NIDDK) sponsored Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis (PIVENS) trial, where 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 ongoing debate as to what 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 represent the best endpoint that can be used in the 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 outcomes in therapeutic trials of NASH will be important. [9,13]

This manuscript is the summary of 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 End Points in the 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 score, resolution of histologic evidence for NASH is also considered an important primary endpoint in most clinical trials for patients with NASH. [15] In this context, it is important to recognize that although NAS scoring does provide valuable quantifiable scores to assess the individual histologic components of NASH, the grading is still subjective. [16] The inter-observer 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 hepatic venous pressure gradient (HVPG). The selection of this endpoint is based on the data suggesting that HVPG values above a certain threshold is 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 carry out.

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 non-invasive modalities to assess the stage of fibrosis in NASH and to document its progression and regression has ensued. Challenges surrounding the

ability to non-invasively 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 important 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 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

Life style modification including 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 aminotransferases. [6] The amount of weight lost is a determinant of histologic improvements in liver injury and fibrosis. Though small reductions (3–5% body weight loss) can reduce hepatic steatosis and the associated metabolic parameters, the larger weight reduction (at least 7%) is required to observe improvement or resolution of 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 to reduce liver fat in patients with NAFLD. [21,22]

In addition to diet, physical activity plays an important role in the development of NAFLD. [23,26] In this context, about half of NAFLD patients are inactive, and a third of these patients do not perform 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. [27, 28] In addition to improvement in hepatic steatosis, exercise has also been shown to improve liver enzymes and ameliorate insulin resistance. [24] In this context, it can be anticipated that 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 five years of follow up. [29]

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 a clinically significant weight loss, suggesting that exercise alone is an independent factor of reducing liver fat. [25] 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. [25,26]

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

The Current Medical Treatment for Patients with NASH

The American Association for the Study of Liver Disease (AASLD) guidelines recommend that only biopsy-proven NASH should be considered for medical treatment. [27,28] There have been several drugs tested for the treatment of NAFLD but are not yet recommended due to discordant results and/or lack of therapeutic benefit in randomized controlled trials. [30-37]

In this context, glitazones are a class of drugs that have been used to treat NASH. Glitazones upregulate adiponectin, an adipokine with anti-steatogenic and insulin-sensitizing properties, which increase the synthesis and uptake of the fatty acids by the adipocytes, rather than being taken-up 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, hepatocyte ballooning, NAS score and resolution of NASH as well as improving fibrosis as noted in a recent meta-analysis. [37,38] However, the beneficial effects are not sustained when the drugs are discontinued as alanine aminotransferase (ALT) values return to baseline and NASH reappears.

Additional concern is also 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 review of the risks and benefits for patients. In addition, prior to starting treatment of a diabetic patient, a liver biopsy should be considered to document histologically-proven NASH. [28]

Vitamin E is an antioxidant which prevents liver injury by blocking intrinsic apoptotic pathways and by protecting against oxidative stress. [33] Data from the PIVENS trial showed that vitamin E can improve histological NASH in terms of steatosis, inflammation, ballooning, NAS score, and resolution of NASH at a dose of 800 IU/day. [11] However, 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, AASLD Guidelines 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 AASLD does not recommend the use of Vitamin E as treatment for NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis. [28] It important to note that the beneficial impact of vitamin E or pioglitazome on all-cause mortality and liver-related mortality, has not been established.

Liraglutide, a long acting GLP-1 (glucagon-like peptid-1) agonist, is secreted after eating. GLP-1 is secreted by the L cells of the small bowel and proximal colon which 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, while, liraglutide, the synthetic analogue, has a half-life that allows a single daily administration. [39] In a phase II 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 (BMI), glucose level, and high density lipids (HDL) cholesterol] with minimum of side effects (mainly gastro-intestinal, such as diarrhea). [12] Phase III trials are awaited to confirm these preliminary data.

It is important to remember that a large proportion of patients with NAFLD require treatment of their metabolic risk factors. In fact, preliminary data suggest that there may be an added benefit to the liver when the associated co-morbidities are treated. [37-41] For instance, statins are safe to use in NAFLD population and can provide the beneficial effect of treating dyslipidemia, improving insulin resistance and reducing the risk of HCC. [40,41,42] Additionally, Ezetimibe and rosuvastatin also appear 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.

The 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 % were noted in patients who underwent gastric by-pass, vertical banded gastroplasty, and gastric banding; respectively. [45] In addition, bariatric surgery can prevent cardiovascular events [46] and improve type 2 diabetes [47,48]

It is important to note that, regardless of the type of bariatric surgical procedure performed, a decrease in adiposity is seen after bariatric surgery. This is an important factor to take into account as 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 increase the probability of having severe steatosis compared to 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 gastric banding or bypass surgeries. [51] A recent prospective study analyzing sequential liver biopsies from a final cohort of eighty two patients with biopsy-proven NASH showed the disappearance of NASH in approximately 85% of the patients one year later-though NASH resolved in a greater proportion of patients with baseline mild disease (94%) than from 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 institute of

health consensus conference to be able to undergo weight loss surgery. [53] It is possible that this recommendation be changed since weight reduction surgery appears to effectively address metabolic conditions 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, with patients transplanted for NASH having similar survival as those transplanted for other etiologies. [54-57] In fact, the 1 year, 3 year, and 5 year survival rates post LT for patients with NASH are: 87.6%, 82.2%, and 5-year 76.7%, respectively, rates comparable to other indications. [57] However, NASH after LT can either recur or can develop *de novo* in transplanted patients. [58] While 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 ~10-30%, while the risk of developing advanced fibrosis is low (5% at 5 years and 10% at 10 years). [2, 5, 7] In multivariate analysis, post-LT recurrence of NAFLD has been found to be associated with hypertriglyceridemia, and high BMI post-LT. [59]

Post-transplant care for LT recipients 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. Lowest necessary 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 (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 may reduce the need for liver biopsy. [61] Weight gain is nearly ubiquitous following liver transplantation. Since obesity and the components of the metabolic syndrome are important predictors of posttransplant outcomes, management of weight, is a cornerstone of optimizing outcomes, and a deterrent to posttransplant metabolic syndrome, [62,63]

In summary, NASH patients who undergo liver transplantation do very well. Nevertheless, these patients do present pre-transplant and post-transplant challenges. Optimal approaches to pre- and perioperative management (including bariatric surgery), immunosuppression, nutritional, psychological and pharmacotherapeutic agents are evolving rapidly but have not been fully accepted.

Emerging Therapy for NASH: Non-Antifibrotic and Antifibrotic Regimens

As 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 (Table 1). 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 towards 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 a decrease of hepatic steatosis, inflammation, and fibrosis ~~and dyslipidemia~~ while increasing insulin sensitivity. In the Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment (FLINT) phase 2 trial where OCA was compared to a placebo, investigators found no worsening of fibrosis as well as a decrease in the NAS score of ≥ 2 points for those on OCA. Although there was some evidence of worsening dyslipidemia, co-administration of statins led to the improvement of the participant's low density profile (LDL) lipid profile to at or below baseline levels. [65]

A phase 3 clinical trial of OCA in non-cirrhotic patients with NASH (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 trial is elafibranor, a dual receptor peroxisome proliferator activated alpha/delta (PPAR α/ δ) agonist. Elafibranor was studied in the GOLDEN Study 2b

trial, and its effects were compared to a placebo. [35] Despite some methodological limitations of the GOLDEN trial, elafibranor, 120 mg/d for a year, induced resolution of NASH without fibrosis worsening in the ITT population. The effect seemed to be stronger in patients with more advanced NASH activity. 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 end point 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.

A 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 the recent data documenting the lack of efficacy of Simtuzumab, Simtuzumab was considered to have a placebo effect. Based on these data, a phase 3 clinical trial is being initiated and enrolling subjects with NASH and advanced fibrosis (STELLAR-3 and -4). The trial consists of a 48-week trial of Selonsertib in subjects with NASH stage 3 and 4. The primary endpoint is a ≥ 1 point decrease in fibrosis stage without worsening of NASH ballooning or inflammation. The study's five-year outcome is the reduction in progression to cirrhosis (STELLAR-3) and hepatic decompensation, HCC, transplant, or death (STELLAR-3 and -4). [67]

Another phase 2 clinical trial is investigating the improvement in insulin sensitivity and NAFLD using the GLP-1 analogue, ~~liragtytide~~ semaglutide. [68] Additionally, another trial for treatment of NASH focuses on an acyl co-A carboxylase (ACC) inhibitor, which is a rate limiting step in the *de novo* lipogenesis. In a very small open label study, an ACC inhibitor showed reduction in ALT, elastometry and MRI PDFF quantification of liver fat [69]

Despite the great enthusiasm and activity in the field of NASH therapeutics, there is no currently FDA approved treatment for NASH. 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 since fibrosis is the strongest predictor of mortality in patients with NASH. [18,70,71]

Currently, all ongoing Phase 2B or Phase 3 clinical trials of anti-fibrotic 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 the trial. Moreover, while biopsy is highly informative, 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. [72]

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. [73] While genetic determinants of fibrosis progression have been well validated in HCV, a similar fibrosis risk score has not been widely

validated in NASH. [74-76] 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. [74-76]

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. Among antifibrotic therapies, in addition to those previously discussed [FXR agonists, PPAR agonists, and inhibitor of apoptosis signal-regulating kinase 1 (ASK1)], are combinations of antagonists which include: CCR2/CCR5 chemokine receptors, galectin antagonists, and a siRNA target in stellate cells that reduces expression of heat shock protein. [78]. Cenicriviroc (CVC), a CCR2/CCR5 chemokine receptor blocker, aims to mediate interactions driving inflammation and fibrosis. In a two year Phase 2b multinational, randomized, double-blind placebo-controlled study for the treatment of NASH in 289 adults using CVC, year one results have demonstrated improvement in fibrosis without worsening of NASH for subjects who received CVC. The safety profile was also found to be encouraging as the only drug-related treatment emergent adverse events with a grade >2 and having greater than 2% frequency were fatigue (2.8%) and diarrhea (2.1%). (79)

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 HCV or suppression of HBV can often reverse cirrhosis, something unimaginable decades ago. [78] Uncovering and exploiting mechanisms by which the liver innately degrades scar in these diseases could yield new therapeutic approaches that could transform the outlook for patients with chronic fibrosing liver disease, including NASH.

CONCLUSIONS

Despite a great deal of 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 non-invasive endpoint for NASH that can accurately serve as a surrogate for the hard outcome of mortality. In this context, there is still a great deal of debate about the appropriate endpoints for clinical trials of NASH. Although histologic assessment is currently the most widely used modality, it is suboptimal and invasive. Nevertheless, resolution of NASH and/or improvement of fibrosis have been the currently accepted endpoints.

In this context, there are emerging therapies for NASH which 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, combination of different drugs targeting different pathogenic pathways in NASH, may be most appropriate. There is a great deal of enthusiasm and interest in this area of liver disease with potential effective treatment on the horizon.

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Table 1: Non- Antifibrotic Drugs in Development and their Potential Site of Action

Drug Name	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/ɣ 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
BI-1467335	VAP-1/AOC3 inhibitor