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

Treatment Targets and Therapeutic Regimens for Non-alcoholic Fatty Liver Disease (NAFLD) and Non-alcoholic Steatohepatitis (NASH): A Summary of AALSD Trend Conference in NASH

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Conflict of Interest

Abstract

NASH 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 no other approved treatment 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. One of the important issues in NASH research is what endpoints are most appropriate for clinical trials. There is significant data to suggest that stage of fibrosis is the only robust and independent predictor of liver-related mortality. Although histologic NASH has been associated with advanced stage of fibrosis, it is not an independent predictor of long term mortality. Nevertheless, currently, resolution of NASH (without worsening fibrosis) or reduction of fibrosis (without worsening NASH) are the accepted endpoints by the regulatory bodies. There are a number of important secondary endpoints, including wet or dry non-invasive biomarkers, long term outcomes and patient reported outcomes. In 2017, there are a few phase 3 clinical trials for treatment of NASH. Additionally, a number of phase 2a and 2b clinical trials targeting different pathogenic pathways in NASH. Over the next 5 years, some of these regimens are expected to provide treatment options for subjects with NASH.

Introduction

NAFLD is rapidly being recognized as the leading cause of chronic liver disease, worldwide. [1-3] Over the past 2 decades, there is substantial evidence to suggest that NAFLD is highly prevalent throughout the world and represents a spectrum of diseases some of which are associated with the development of cirrhosis and hepatocellular carcinoma (HCC). [2-5] The majority of subjects with NAFLD are asymptomatic and are diagnosed incidentally. In 2017, there are no approved drug treatments for NAFLD and NASH. [6] Nevertheless, a large number of regimens 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 that will be considered to treat subjects who are at risk of progressive liver disease. [1-6]

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, NASH represents the potentially progressive form of NAFLD and as such, it should be the target of treatment. Furthermore, stage of fibrosis predicts mortality in NAFLD and therefore NAFLD and NASH patients with significant fibrosis must be the priority for development of treatment regimens. [7,8] Nevertheless, as we design clinical trials for these patients, it is important to also remember that the "placebo effect" plays a larger role in the clinical trials of NASH as compared to other liver diseases (9). Although still controversial, the spontaneous regression of NASH and even NASH-related fibrosis has been observed which may be related to the life style modifications and behavioral changes that can occur just by becoming a research subject. An example of this phenomenon was observed in the NIDDK-sponsored PIVENS trial of vitamin E versus pioglitazone versus placebo, where placebo-treated subjects experienced significant weight loss.

[9] In fact, the interaction between weight loss and histologic response can be an important confounder, as was recently observed in the clinical trial of liraglutide for NASH. (9)

Another central challenge in the field of NASH therapeutics is how to accurately assess treatment response. There is ongoing debate as to what endpoint truly represent the best surrogate for hard outcomes such as liver-related mortality. Additionally, inclusion of validated patient reported outcomes in therapeutic trials of NASH have only recently being considered. (10)

Historically, the therapeutic trials primarily focused on steatohepatitis and its improvement by NAFLD Activity Score (NAS). In fact, improvement of NAS score and its resolution of NASH were considered the most important endpoints. Although NAS scoring does provide valuable quantifiable scoring to assess histologic changes in NASH, there are problems with the individual histologic components of NAS. Furthermore, inter-observer variability of histologic components such as ballooning degeneration (a key pathologic feature of NASH) has been problematic. [11-15] Additionally, ballooning degeneration is an independent predictor of liver-related mortality. [14,15] Recently, there has been greater enthusiasm for selecting improvement in hepatic fibrosis stage as the most consequential endpoint in NASH. This has been based on the rationale that improvement in fibrosis may be a better surrogate endpoint for survival and may correlate with actual clinical outcomes such as prevention of cirrhosis or regression of advanced fibrosis. [16-19]

In addition to histology, other important endpoints include measurement of hepatic venous pressure gradient (HVPG) in NASH subjects with cirrhosis. This endpoint selection is based on the data suggesting that HVPG values above a certain threshold are associated with reduced

survival [20] Given the long natural history of NASH and presence of comorbidities in this population, studies designed to show improvement in survival will be difficult and not feasible.

Although there is little doubt about the value of histologic gold standard in NASH and its related fibrosis, liver biopsy is invasive and not easily accepted by patients. Furthermore, repeat biopsies to assess worsening or improvement of liver disease in NAFLD is not feasible. This has led to a flurry of efforts to develop and validate non-invasive modalities to assess the stage of fibrosis and document its progression and regression. These endpoint challenges must be overcome to 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 disease specific validated instrument such as CLDQ-NAFLD-NASH in the clinical trials of NASH will be important. [21]

In this manuscript, we will review the current and future treatments that are being developed for NASH.

Weight Loss and Exercise in NAFLD

Currently, there are no approved pharmacological treatments for NAFLD or its inflammatory form, NASH. Ideally, any therapy should not only reduce steatosis, liver injury and adverse liver-related outcomes, but also alter the systemic metabolic milieu that results in cardiovascular, diabetes and cancer outcomes. Life style modification including weight loss and structured exercise still offers the only holistic treatment for NAFLD, and remains the cornerstone of therapy. [21]

Weight loss is the best predictor of reduction in liver fat and improvement in aminotransferases. [22] 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 steatosis and the associated metabolic parameters, the larger weight reduction (≥10%) is required to observe improvement or resolution of steatohepatitis. [23]

In mild to moderate obesity, weight loss can be achieved by dietary interventions that restrict calorie intake. [24] However, it should be noted that long term sustained weight loss can be experienced by only 3-6% of subjects. 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. [25] However, in general, dietary macronutrient composition seems to have a lesser role than caloric restriction to reduce liver fat. [24]

In addition to diet, physical activity plays an important role in the development of NAFLD. In fact, one study showed that half of NAFLD patients are inactive, and a third of these patients do not perform any physical exercise. [26] Based on recent data, the efficacy of exercise *per se* for the reduction of hepatic fat has now been recognized. Therefore, exercise is now routinely recommended for the management of NAFLD. [22] In addition to improvement in hepatic steatosis, exercise has been shown to improve liver enzymes, and ameliorate insulin resistance. [22] In this context, it can be anticipated that exercise may improve liver inflammation and 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 NAFLD and its resolution over a mean five years of follow up. [27]

Several recent studies have attempted to address issues related to the optimal dose (type, intensity and amount) of exercise for a hepatic benefit. Some reports have suggested no difference in the amount of change in liver fat reduction by aerobic exercise dose or intensity. In contrast, it was only the act of exercising which was most important. [28-30] Another report found that the reduction of liver fat by aerobic exercise regimens occurred without a clinically significant weight loss suggesting that exercise alone is an independent factor in reducing liver fat. [29] As such, current recommendation suggests that resistance training should complement, not replace, aerobic exercise which allows the recommendation to be in accordance with the exercise guidance for cardiovascular disease risk modification as well. [29,30]

Diet and exercise should remain the first line of therapy for NASH. However, more clinical research is needed to better understand the interaction between weight loss and exercise in improving NAFLD/NASH and liver-related outcomes.

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 receive medical treatment.[31] 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 placebo controlled trials. [32-36]

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 liver and muscle. [32,33] One such drug, Pioglitazone has been shown to improve histological NASH in terms of steatosis, inflammation, hepatocyte ballooning, NAS score and resolution of NASH; however, the beneficial effects are not sustained when the drugs are discontinued as ALT values return to baseline and NASH reappears (34,36] Further, the long-term safety and efficacy of pioglitazone in subjects with NASH has not been established. Nevertheless, for diabetic biopsy-proven NASH patients, pioglitazone can provide a viable treatment option. [31]

Vitamin E is an antioxidant which prevents liver injury by blocking intrinsic apoptotic pathways and by protecting against mitochondrial toxicity. [37] Data from PIVEN 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. [34] However, there are some concerns that long term use of vitamin E may be associated with increased incidence of hemorrhagic stroke, and increased risk of prostate cancer. [38] Nevertheless, AASLD Guideline suggested that in non-diabetic biopsy-proven NASH patients, vitamin E may be considered. [31] It important to note that the beneficial impact of vitamin E or pioglitazome on hepatic fibrosis, the primary predictor of all-cause mortality and liver-related mortality, has not been established. Also, vitamin E is not recommended in NASH patients with diabetes, NAFLD without a liver biopsy, NASH cirrhosis or crytogenic cirrhosis. [31]

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

All patients with NAFLD require treatment of associated metabolic risk factors, such as obesity, diabetes, hypertension, dyslipidemia and obstructive sleep apnea. In fact, preliminary data suggest that there is an added benefit to the liver when the associated co-morbidities are treated. [40-42] Statins are safe to use in NAFLD population and in addition to the beneficial effect on dyslipidemia, they improve insulin resistance, liver function and reduce the risk of HCC. [43, 44] In a small pilot study, rosuvastatin monotherapy was found to ameliorate biopsy proven NASH within 12 months. [42]

Investigations over the last two decades have led to a better understanding of the natural history, epidemiology and pathophysiology of this disease. However, despite having tested a large number of agents, no single agent or combination of agents stands out as a therapy with proven

efficacy. Until the results of the ongoing randomized, double-blind, placebo-controlled trials investigating multiple therapeutic options become available, effective preventive and therapeutic strategies and a multidisciplinary approach using lifestyle modifications and optimizing metabolic risk factors is the best option for now,

The Current Surgical Options for Treatment of Obesity in Subjects with NASH

Another option which has shown some promise for treatment of NAFLD/NASH is bariatric surgery. Bariatric surgery has been shown to induce long-term weight loss and decrease overall long-term mortality particularly from diabetes, heart disease, and cancer. [45,46] In a study with more than 10 years of follow-up, weight change in control subjects was less than 2%, whereas the weight losses from baseline were 25%, 16% and 14 % in patients who underwent gastric by-pass, vertical banded gastroplasty and gastric banding, respectively. [46] In addition, bariatric surgery prevents cardiovascular events, as demonstrated by the lower occurrence of cardiovascular events in individuals treated with bariatric surgery than in control individuals. [47] Two non-blinded, randomized, controlled trials showed that patients treated with bariatric surgery achieved glycemic control more frequently than those with medical therapy alone. [48,49] In addition, diabetes remission occurred in most surgical patients but not in any of those treated with medical-therapy. [48]

In addition, there is a decrease in the amount of fat after bariatric surgery regardless of the type of contemporary surgical procedure which is an important piece of the surgery since fat is associated with increased insulin resistance and insulin resistance is independently associated with severe steatosis and predicts its persistence one year after surgery. [50,51] In fact, patients

with a refractory insulin resistance profile after surgery have a probability of having severe steatosis twice as high as those patients who improved their insulin resistance. [51]

However, preliminary studies have reported that there was resolution of NASH in approximately 85%–90% of patients who underwent gastric banding or bypass surgeries. [52] A recent prospective study analyzing sequential liver biopsies from one hundred and nine patients with biopsy-proven NASH showed disappearance of NASH in approximately 85% of the patients one year later- though NASH resolved in a greater proportion of patients with mild disease (94%) than from those with moderate or severe disease (70%) at baseline. [53] Bariatric surgery significantly reduced all the histological components of NASH including fibrosis that was improved in about 30% of cases. [53] An area that needs further exploration given the outcomes achieved with surgery, is to determine whether bariatric surgery is effective for severely obese patients who are candidates for liver transplantation. [54]

The NIH conference consensus on bariatric surgery recommends that surgery should be considered for individuals with a BMI above 40 who strongly desire weight loss, and may also be considered for patients with a BMI between 35 and 40 who suffer from high-risk comorbidities though nonsurgical treatments should be attempted prior to considering bariatric surgery. In addition, only motivated persons should be carefully selected by a multidisciplinary team with medical, surgical, psychiatric, and nutritional expertise. Therefore, scientific societies and experts after taking into account these criteria along with the expected risk of perioperative morbidity/mortality, may consider bariatric surgery as a therapeutic option to only a limited number of NAFLD/NASH patients. [55]

Liver Transplantation in Subjects with NASH

Liver transplantation (LT) is another treatment option for NAFLD/NASH. In fact, 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. [56,57] Currently, the survival rates post LT for patients with NASH are 1-year 87.6%, 3-year 82.2% and 5-year 76.7% which are comparable to other indications. [58] However, NAFLD after LT can either recur in patients transplanted for NASH or it can develop *de novo* in patients transplanted for non-NASH indications.[59] While the risk of steatosis is time dependent and approaches 100% at 5-years after LT in patients who were transplanted for NASH, the risk of developing NASH is ~10-30%, and the risk of developing advanced fibrosis is low (5% at 5 years and 10% at 10 years).(3,5) In multivariate analysis, the variables associated with post-LT recurrence of NAFLD have been found to be hypertriglyceridemia post-LT, and a high BMI pre-and post-LT.[59]

Survival after LT is excellent, with the most common cause of death for NAFLD and cryptogenic cirrhosis being cardiovascular disease (CVD) rather than recurrent liver disease.[60] An important exception to the generally low risk of progressive fibrosis following LT for NASH is hypopituitarism, which is frequently associated with rapid recurrence of NASH with advanced fibrosis and graft loss and is commonly associated with hepatopulmonary syndrome. [61] However, recurrence of NASH and hepatopulmonary syndrome has been reported to be responsive to growth hormone supplementation in patients with hypopituitarism. [61]

Follow up care for patients who have undergone LT presents several challenges. There is a strong rationale for adopting a minimalist approach to maintenance 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 metabolic syndrome. Corticosteroids should be avoided beyond the early (first 6 month) postoperative period. [58]

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, has greatly reduced the need for liver biopsy. [62] Weight gain is nearly ubiquitous following liver transplantation and, as obesity and the components of the metabolic syndrome are important predictors of posttransplant outcomes, management of weight, the key determinant of posttransplant metabolic syndrome is a cornerstone of optimizing outcomes. [63,64] The role of bariatric surgery at the time of or after liver transplantation is evolving but increasingly appears to be of potential utility in selected patients. [54]

In summary, bariatric surgery appears to reduce fibrosis and the necroinflammatory processes altering NASH disease progression thus preventing the development of cirrhosis and its complications. [54] However, due to the strict criteria for the selection of candidates for bariatric surgery, the benefits of surgery may be limited. On the other hand, recipients who undergo liver transplantation do very well but present pretransplant and posttransplant challenges. Optimal approaches to pre- and perioperative management (including bariatric surgery),

immunosuppression, nutritional, psychological and pharmacotherapeutic means of minimizing the frequency and impact of NASH in liver transplant recipients are evolving rapidly but as of this writing are not fully approved for general use.

Emerging Therapy for NASH: Non-Antifibrotics

As the pathogenesis of NAFLD/NASH continues to unfold, multiple pathways (insulin resistance, lipotoxicity, oxidative stress, altered immune/cytokine/mitochondrial functioning, and apoptosis) are being implicated in the development of therapies for NASH. Therefore, the investigative therapeutic modalities are targeting many of these pathways and are currently in various stages of development with most studies being conducted with single modality therapy (3 are in phase 3, 18 are in phase 2a and 2 b development, Table 1). However, it is expected that combination therapy will soon be targeted. The following will highlight the current therapies which are in development and directed towards improving steatosis, inflammation, and liver cell injury.

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: decreases hepatic steatosis, increases insulin sensitivity, decreases inflammation, decreases fibrosis and dyslipidemia. 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 and a decrease in the NAS score of ≥ 2 points for those on OCA compared to the placebo group. Although there were some evidence of worsening dyslipidemia, co-administration of statins led to the improvement of lipid profile. [65,66]

Another agent in phase 3 clinical trial is Elafibranor which is a dual receptor peroxisome proliferator activated alpha/delta (PPAR α/□□) agonist Elafibranor was studied in the GOLDEN Study 2b trial and was also compared to a placebo. Patients who received elafibranor (120 mg/d for 1 year) were found there was no fibrosis worsening in both the intention to treat patients and in those with moderate or severe NASH as well as being well tolerated and improving patients' cardiometabolic risk profile. However, patients did experience an increase in creatinine level that resolved when the medication was stopped. [36]

Finally, another phase 3 clinical trial assesses the Safety and Efficacy of Selonsertib in Subjects with NASH and Advanced fibrosis (STELLAR). STELLAR 3 are 48 week trials of Selonsertib whose primary endpoint is a ≥ 1 point decrease in fibrosis stage without worsening of NASH ballooning or inflammation. The five-year outcome of the study is the reduction in progression to cirrhosis (STELLAR-3) and hepatic decompensation, HCC, transplant, death (STELLAR-3 and -4). [67]

A number of phase 2 clinical trials are assessing the potential efficacy in subjects with NASH. In this context, another GLP-1 analogue, Liragtytide Semaglutide (LEAN), is being assessed for improving insulin sensitivity and NAFLD. [68] Another trials in NASH focuses on an ACC inhibitor which is a rate limiting step in the de-novo lipogenesis. A small pilot study has shown that ACC inhibitor may improve steatosis, inflammation and fibrosis leading to a decrease in liver stiffness. [69]

However, it is not anticipated that all of these drugs will ultimately achieve FDA approval, but our armamentarium of therapeutic options for NASH is likely to expand significantly in the coming years.

Emerging Therapies for NASH: Antifibrotics

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 death in patients with NASH. [14,70,71] However, a key challenge limiting progress in the testing of anti-fibrotic drugs is the lack of approved noninvasive endpoints that correlates well with long-term clinical outcomes, a key requirement for FDA approval of any agents for this disease.

Currently, all ongoing Phase 2B or Phase 3 clinical trials of anti-fibrotic drugs require liver biopsy to quantify fibrosis before and after treatment. This requirement imposes limitations on 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 cannot 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 been elusive 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. The current targeted pathways include abnormalities in fatty acid homeostasis, insulin resistance, inflammation, mitochondrial dysfunction, and direct antifibrotic therapies. Among antifibrotic therapies, those already under evaluation in clinical trials include FXR agonists, PPAR agonists, and combinations of antagonists to the CCR2/CCR5 chemokine receptors, galectin antagonists, an inhibitor of apoptosis signal-regulating kinase 1 (ASK1) and an siRNA target in stellate cells that reduces expression of heat shock protein. [77]

There are also many more compounds that are 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.

CONCLUSION

NAFLD is known as the metabolic syndrome of the liver and is a comprehensive term used to cover a spectrum of chronic liver diseases which range from simple fatty liver disease to cirrhosis, hepatocellular carcinoma, liver transplantation, and premature death. NAFLD currently affects over 25% of the worldwide adult population but is increasing parallel to the increasing rates of obesity especially within the adolescent population where the Hispanic youth and adults are disproportionately affected.

Despite the encompassing nature of NAFLD, its full pathogenic mechanisms are still elusive but current research is ongoing in the areas abnormalities in mitochondria and endoplasmic reticulum, white adipose tissue, and the gut microbiome to determine their roles in the pathogenesis of NASH. As such, there are also ongoing issues in correctly diagnosing NAFLD. Although, liver biopsy is considered the "gold" standard, it is an invasive procedure which requires a trained hepatopathologists to correctly interpret the results. Serum markers, radiographic tests and non-invasive biomarkers are all being investigated to supplement or replace reliance on liver biopsy. Choosing the most accurate and reliable diagnostic method is especially important in on-going clinical trials investigating new therapeutic agents.

Currently, the only available treatment for NAFLD/NASH is diet and exercise. However, there are emerging therapies for NASH which include non- antifibrotic as well as antifibrotic regimens. It is plausible that subject with NASH and fibrosis will be the target of regimens containing one or combination of different drugs targeting pathogenic pathways in NASH. Thus, there is still much work to be done in order to combat this disease, but with the increased awareness of the associated prevalence and outcomes, we are developing a more thorough understanding of the disease and how best to treat it.

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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 FGF21 analogue
JKB-121 (Nakmefene hydrochloride)	TLR-4 agonist
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	mTOT 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