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Therapies In Non-Alcoholic Steatohepatitis (Nash)

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Abstract

The hallmark of non-alcoholic fatty liver disease (NAFLD) is excessive fatty accumulation in the hepatocytes, which may be an isolated event (non-alcoholic fatty liver, NAFL) or accompanied by evidence of inflammation and cell injury with or without fibrosis (non-alcoholic steatohepatitis, NASH). NASH, the more aggressive form of NAFLD, may progress to cirrhosis and hepatocellular carcinoma. Because it has been estimated that NASH will overtake hepatitis C virus infection as the leading cause of liver transplantation in the US in the coming decade, and there are no current FDA-approved therapies for this disease, the need to find appropriate therapeutic targets is now more urgent than ever before. Diet and other life-style modifications have always been difficult to maintain and this approach alone has not slowed the rising tide of the disease. While the results of traditional therapies such as vitamin E and pioglitazone have been significant for steatosis and inflammation, they have had no effect on fibrosis, which is the strongest indicator of mortality in this condition. However, the understanding of the pathogenesis and progression of NASH has evolved and several promising novel therapies to target and possibly reverse fibrosis are being evaluated, making the future outlook of NASH therapy more optimistic.

Keywords

Nonalcoholic fatty liver disease (NAFLD); Nonalcoholic steatohepatitis (NASH); ROS (reactive oxygen species); Peroxisome proliferator-activator receptor (PPAR) agonists; Farnesoid X receptor (FXR); Glucagon-like peptide (GLP-1) agonist

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the Western hemisphere and a leading cause of liver-related morbidity and mortality worldwide.[1] An estimated 30% of Americans may be affected by this disease.[2,3] NAFLD represents a clinico-pathological spectrum of disease that primarily manifests as excessive accumulation of fat in the hepatocyte (steatosis). It is considered to be the hepatic manifestation of the metabolic syndrome, whose other pathologies include obesity, insulin

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resistance, hypertension and hyperlipidemia. NAFLD is broadly categorized into 2 phenotypes, namely: non-alcoholic fatty liver (NAFL) which is marked by isolated steatosis, while the more aggressive subtype, non-alcoholic steatohepatitis (NASH), is characterized by cell injury, inflammatory cell infiltration and hepatocyte ballooning that may further progress to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). [4,5] NASH is expected surpass hepatitis C virus infection as the leading etiology of end-stage liver disease requiring liver transplantation in the next 5 to 15 years.[6] NASH is also currently the leading etiology driving the burden of hepatocellular carcinoma.[7]

Despite the significant burden to the public health system, there are no FDA-approved drugs that are specifically tailored for this condition. Therefore, the need for effective treatment that manages the complex pathophysiologic processes of NASH, can no longer be ignored.[8] Several novel medications targeting different stages and molecular events in the disease process are currently in the pipeline, while other previously known off-label treatments are still used. In this paper, we will review the pathophysiology and therapeutic approaches of this condition.

Pathophysiological rationale for treatment

The pathophysiology and clinical significance of the various molecular disturbances in NASH are both complex and multifactorial. However, the metabolic imbalance leading to excessive fatty accumulation in the liver appears to occur from 3 major sources: 1) increased dietary fat delivery to the liver from the gut, either due to increased intake or a dysregulated gut physiology and microbiome; 2) increased influx of free fatty acids from the non-esterified pool (mainly from white adipose tissue); and 3) increased *de novo* hepatic lipogenesis from excess carbohydrates (and or hyperinsulinemia from adipose tissue insulin resistance).[9,10] When these processes cannot be offset by a compensatory increase in very low density lipoprotein (VLDL) secretion from the liver or use in other metabolic pathways, there is a net deposition of triglycerides and free fatty acids in hepatocytes.[11]

While triglyceride accumulation is believed to be relatively benign, hepatocyte lipotoxicity is thought to be chiefly caused by free fatty acids and their metabolites. These changes within the liver place extra metabolic stress on the mitochondria and endoplasmic reticulum and produce a cascade of stress-induced responses including release of reactive oxygen species (ROS) and recruitment of immune cells and other cell injury mediators. These lead to further cell injury culminating in further inflammation, programmed cell death (apoptosis) and fibrotic remodeling via collagen deposition from activated stellate cells.[12,13] Alterations in gut microbiota may also lead to bacterial (product) translocation, especially the highly immune-reactive gram negative cell wall component called lipopolysaccharide (LPS), into the systemic circulation, further worsening the inflammatory process by activating macrophages and Kuppfer cells.[14] (see fig. 1)

Because of the complexity of the different potential pathways involved in the pathogenesis of NASH, treatment may have to target several key elements in the process of cellular and molecular events to achieve meaningful results. Obviously, depending on the individual

patient and the extent of disease activity, more than just one treatment modality may be needed to be effective.

Diet and Physical Activity

The first line of management in NASH involves lifestyle modifications, mainly sustained weight loss (through a calorie-restricted diet) and increased physical activity (exercise).[15,16] While a modest weight loss of about 3% may reduce hepatic steatosis, up to 10% or more is needed to reduce inflammation and for the regression of fibrosis in NASH patients.[17-19]

Even in well-organized settings, only a few patients achieve and sustain a 10% weight loss.[20] A more detailed review of lifestyle measures employed in NASH therapy is not the purpose of this review, but may be obtained elsewhere.[21]

Based of the difficulties in applying lifestyle-changing measures alone, the need to combine them with pharmacotherapy will probably remain the norm in NASH management in the foreseeable future.

Pharmaco-therapeutic Options in NASH

1) PPAR agonists

Peroxisome proliferator-activator receptors (PPARs) are a group of nuclear receptors that are expressed in the liver, adipose tissue, heart, skeletal muscle and kidney and transcriptionally regulate multiple metabolic processes including B-oxidation, lipid transport and gluconeogenesis.[22] There are 3 PPAR receptors (α, β/δ and γ) which differ by tissue distribution but target the same DNA segment.[23]

PPARα agonists, such as fibrates, are extensively used in the treatment of hypertriglyceridemia but have been shown to have no significant benefit in NAFLD, probably because of the receptor's extensive distribution in organs outside the liver.[24] PPARδ, because of its presence in macrophages, has the additional effect of decreasing macrophage and Kupffer cell activation and increasing fatty acid oxidation.[25] Although a PPARβ/δ agonist (GW501516), was highly promising in initial trials, the drug may have been withdrawn due to safety concerns.[26]

The dual PPARα/δ agonist, elafibranor may be effective not only in improving both hepatic and peripheral insulin sensitivity in abdominally obese individuals in a liver-targeted fashion, but was also shown to resolve NASH in a phase IIb, randomized double-blind placebo controlled trial (GOLDEN-505).[27] This was a multicenter, international study with NASH patients (without cirrhosis) who were randomly assigned to 3 different groups: elafibranor 80 mg/day (n = 93), elafibranor 120 mg/day (n = 91), or placebo (n = 92) for a total of 52 weeks. The primary outcome (resolution of NASH without worsening fibrosis) was not obtained when the elafibranor groups were compared to placebo in the initial analysis. However, when a modified definition was used in a post-hoc analysis, the primary outcome was obtained in patients taking elafibranor 120 mg/day compared to placebo (19% versus 12%; P = .045). In addition, the resolution of NASH was significantly higher in patients with an NAFLD activity score (NAS) ≥4 (n = 234) who took elafibranor 120

mg/day compared to placebo, both with the initial protocol definition (20% versus 11%; P = .018) and the modified criteria (19% versus 9%; P = .013). Interestingly, there was regression in the stage of fibrosis in the patients in whom NASH resolved with elafibranor 120 mg, compared to those in whom it did not (P < .001). Other metabolic parameters including liver enzymes and lipid profile were also improved in the 120mg/day group.[28,29] A phase III trial (NCT02704403) is currently in the recruitment phase.

PPARγ agonists have been extensively used in diabetes as insulin sensitizers in the form of Thiazolidinediones (TZDs). They have also been shown to be effective in the treatment of NASH.[30-32] In the PIVENS trial, pioglitazone was evaluated with vitamin E and placebo with improvement in NASH histology as a primary end-point. Although there was a trend towards improvement in NASH histology with pioglitazone compared to placebo (34% versus 19%; P=0.04), this did not reach the study's goal (P=0.025). On the other hand, a significant reduction in the serum alanine and aspartate aminotransferase (ALT and AST) as well as in hepatic steatosis and lobular inflammation were obtained compared to placebo (P<0.001),(P<0.001) and (P=0.004) respectively. However, in this particular trial, there was no significant improvement in fibrosis with pioglitazone compared to placebo (P=0.12). Furthermore, the known side effect of weight gain (which also occurred in the PIVENS study) and risk of congestive heart failure may limit its use in the treatment of NASH.[32,33]

A dual PPARα/γ agonist, saroglitazar, which has been approved to treat diabetic dyslipidemia in India has also been shown to result in a significant decrease in ALT levels in subjects with NAFLD and biopsy-proven NASH.[34,35] Further clinical studies are needed in this drug to confirm this initial success.

2) FXR-bile acid axis

The bile acid intracellular receptor, farnesoid X receptor (FXR), negatively regulates bile acid synthesis and decreases hepatic gluconeogenesis, lipogenesis and steatosis.[36,37] Obeticholic acid, or OCA, is a synthetic bile acid derivative and FXR agonist that was recently studied in biopsy-proven NASH patients without cirrhosis in the FLINT trial (a multicenter, randomized, double-blind, placebo controlled study). In this study, 283 patients were randomly assigned to receive either a daily dose of 25mg OCA (n=141) or placebo (n=142) for 72 weeks. The findings showed a significant histological improvement in the OCA group (45% versus 21% of control; P=0.0002) as well as an improved fibrosis score (35% versus 19% of controls; p=0.004). The development of the adverse effect, pruritus, was noted in OCA-treated patients (23%) leading to discontinuation of the medication in some cases and raising questions about drug tolerability. Even though it is reversible, there was also worsening of the lipid profile in subjects treated with OCA, which may require closer monitoring for possible cardiovascular consequences.[38] Otherwise, thus far, OCA appears to be highly promising for the treatment of NASH and its upcoming phase III trial (NCT02548351), with more ambitious end-points (including mortality and liver-related morbidity), will hopefully confirm efficacy of this treatment in these patients.

FGF-19 is a hormone that is transcriptionally regulated via FXR activation in response to the postprandial influx of bile acids in the terminal ileum. FGF-19 then binds to the FGFR4/β-klotho receptor complex on the hepatocyte cell membrane, thus suppressing

gluconeogenesis while promoting glycogen synthesis.[39,40] It has been suggested that FGFR4 activation could have a cancer-promoting effect on hepatocytes. Thus non-tumorigenic variants have been developed with some success in initial studies.[41,42] NGM-282 is considered to be one non-cancer-promoting agent and it is currently in a phase II trial (NCT02443116) to evaluate its effect in NASH patients over a 12-week treatment period.There are ongoing studies evaluating other FXR-modulating, as well as bile acid-sequestrating agents, in either animal testing phases or in preliminary clinical trials (see fig. 1).

3) Lipid-altering agents

Stearoyl-CoA desaturase (SCD) is an enzyme that catalyzes the rate-limiting step in the synthesis of monounsaturated fatty acids such as oleic acid.[43] Located in the endoplasmic reticulum, animal studies have shown that a deficiency (or inhibition) of the SCD-1 isoform is associated with decreased liver steatosis as well as improved insulin sensitivity.[44-46] Obese subjects with NASH appear to have greater stearoyl-CoA desaturase 1 activity (SCD1, $p < 0.002$) than those with a normal liver, which is also reflected at the level of gene expression.[47]

Aramchol, an SCD-1 inhibitor, is a cholic acid-arachidic acid conjugate that was evaluated in a double-blind, placebo-controlled trial of 60 patients with biopsy-proven NAFLD (only 6 had NASH) who were randomized assigned to daily 100mg or 300mg Aramchol versus placebo (n=20 per group). The drug was associated with reduced hepatic fat content when administered as a 300mg/day regimen versus placebo for 3 months.[48] Aramchol is currently being evaluated in a multicenter phase IIb trial to determine its effectiveness in NASH patients.

Statins are HMG-CoA reductase inhibitors that are extensively used in both primary and secondary prevention of cardiovascular disease due to their effective plasma lipid-lowering abilities.[49] Dyslipidemia is a common feature of both the metabolic syndrome and NAFLD, placing patients at increased risk of cardiovascular events.[50,51] Moreover, NAFLD alone is an independent risk factor for cardiovascular disease. However, statins have been found to be underused for this condition, even though they are considered to be generally safe at moderate doses in patients with chronic liver disease.[52,53] In fact, even though there are only a few studies on the use of statins in NASH, in a cohort of 1201 Europeans who underwent liver biopsy for suspected NASH, these agents were found to provide protection from steatosis ($p=0.004$), steatohepatitis ($p<0.001$), and stage F2-F4 fibrosis ($p=0.017$).[54] A small, prospective but uncontrolled study also showed resolution of NASH in 19/20 patients with a 10mg/day dose of rosuvastatin for 12 months.[55]

4) Incretin-based Therapies

Glucagon-like peptide 1 (GLP-1) is a hormone that belongs to the incretin group of proteins that is secreted in the distal ileum and proximal colon by L cells.[56] Besides stimulating the pancreas to cause beta cell proliferation and enhance insulin biosynthesis, GLP-1 also interacts with receptors in other parts of the GI tract and in the lung, kidney and CNS. Thus, GLP-1 has several metabolic functions including delayed gastric emptying, appetite

suppression, enhanced liver glucose uptake and peripheral insulin sensitivity, as well as glucose-dependent insulin secretion while inhibiting the release of glucagon from α-cells.[57,58] GLP-1 undergoes rapid degradation by the dipeptidyl peptidase 4 (DPP-4) enzyme; therefore, these medications are made to resist this immediate cleavage by DDP-4.[56]

While GLP-1 receptor agonists such as exenatide and liraglutide have mainly been approved for diabetes mellitus type 2, a meta-analysis of several studies has shown significant results in patients with NASH. These beneficial effects include decreased serum ALT levels, as well as an improvement in hepatic fat content and fibrosis. The associated weight loss with these medications make them potentially attractive for use in patients with NASH and the metabolic syndrome.[59-61]

The LEAN study evaluated the safety and efficacy of liraglutide in NASH in 52 patients randomized to receive either 1.8mg/day of liraglutide or placebo for 48 weeks (n=26 in each group). The study found that 39% of patients in the liraglutide group met the primary end-point (resolution of NASH without worsening of fibrosis) compared to 9% in the placebo group (p=0.019). While fibrosis only progressed in 9% of patients in the liraglutide group, it occurred in 36% (p=0.019) of the placebo group. [62] This makes liraglutide one of the most attractive potential therapies available for NASH.

Dipeptidyl peptidase 4 (DPP-4) inhibitors, such as sitagliptin and vildapliptin, act on the enzyme DPP-4, which is known to rapidly degrade GLP-1. Thus, these medications are expected to prolong the action of GLP-1. Thus far, results in sitagliptin have been mixed for liver enzyme levels, fat content and the measurement of fibrosis and there is no convincing consensus on the effectiveness of this group of medications in NASH at this time.[35,63-66] Further studies are needed to fully confirm their clinical efficacy.

5) Agents targeting inflammation, cell injury or death (apoptosis) and oxidative stress

At present vitamin E is considered to be a first line pharmacological treatment in the management of NASH especially when diet and other lifestyle changes are insufficient. Vitamin E, with its known antioxidant effects, was initially shown to be effective in NASH in a successful pilot study.[67] This was followed by the PIVENS trial comparing non-diabetic, biopsy-proven NASH patients who received 800 IU/day of vitamin E (800mg/day; n=84) to patients receiving pioglitazone (30mg/day; n=80) and placebo (n=83). This study showed that vitamin E was better than placebo in reducing ALT levels (P<0.001), liver steatosis (P0.005) and inflammation (P=0.02) and also showed that vitamin E effectively promoted resolution of NASH (43 % versus 19% in placebo; P=0.001). However, there was no improvement in the liver fibrosis score (P=0.24).[32] Similar findings were recorded in the TONIC trial, which was performed in children and adolescents.[68]

Although vitamin E was not specifically studied in diabetic NASH patients, indirect evidence from pooled data from the PIVENS trial and the placebo arm of the FLINT trial who received vitamin E supports the efficacy of vitamin E in diabetics as well. In that analysis, whatever the status of diabetes, the histological features of the liver were markedly higher in patients receiving vitamin E than in those who did not receive the medication.[69]

Even though no significant major adverse events have been reported with vitamin E in the above mentioned studies, prolonged use of this medication, especially at higher doses, may influence mortality. Although the effect on all-cause mortality was not supported by subsequent studies on the subject, [70,71] some studies have linked long-term use of vitamin E to increased risks of prostate cancer and hemorrhagic stroke.[72,73] Therefore, these potential risks need to be considered in relation to the extent of disease activity (NASH) and the patient's health when deciding on treatment. A dose of 400 IU daily could be a solution in certain circumstances.[74]

Tumour necrosis factor (TNF)α signaling stands at the crossroads of the major pathways mediating hepatocyte cell injury and caspase-regulated programmed cell death (apoptosis) in NASH.[75,76] Emricasan is a pan-caspase inhibitor that was initially studied in patients with chronic liver diseases of diverse etiologies, and was found to lower ALT levels, in particular in patients with hepatitis C and with NASH.[77] The efficacy of Emricasan is being evaluated in a phase IIb trial (ENCORE-NF; NCT02686762) in patients with NASH and fibrosis.

Pentoxifylline (PTX) is a methylxanthine derivative that has an inhibitory effect on phosphodiesterase as well as on TNFα, and could therefore modulate the functions of other inflammatory cytokines.[78,79] Although it was previously used in a subset of patients with alcoholic hepatitis, the improved survival reported in these patients is currently in serious question.[80,81] Nevertheless, significant histologic improvement was found with PTX in patients with biopsy-proven NASH (400mg three times daily for a year), based on an NAS of ≥2 in 38.5% (n=26) of the treatment group compared to 13.8% (n=29) with placebo (P=0.036). Although fibrosis decreased in more patients in the PTX group (35%) than in the placebo group (15%), this was not statistically significant. Another study suggests that the mechanism of PTX may be due, at least in part, to a reduction in lipid peroxidation, through this agents oxygen radical scavenging properties and glutathione-replenishing ability.[82-84] Larger, robust studies are needed to confirm the efficacy of PTX in the treatment of NASH.

During liver injury, hepatocytes and other liver cell types release inflammatory chemokines such as CCL2 (MCP1) and CCL5 (RANTES) that help recruit macrophages and other inflammatory cells to the site.[85,86] CCL2 and CCL5 act via their respective receptors, CCR2 and CCR5, located on a host of inflammatory cell types to elicit migration. Interestingly, CCL2 and CCL5 are two of 17 up-regulated genes in NASH patients.[87] Cenicriviroc is a CCR2/CCR5 antagonist and the results of a phase IIb trial (CENTAUR) with this drug are awaited in NASH patients.

Other agents that may affect inflammation, cell injury or apoptosis as well immune related factors are currently in ongoing clinical trials. For example, GS-4997, an inhibitor of apoptosis signal-regulating kinase 1 (ASK1), a MAP3 kinase that may play a role in hepatic steatosis and fibrosis is being studied for this indication.[35]

6) Gut and Microbiome related therapies

Disturbed gut-liver barrier integrity has been reported to be essential in the pathogenesis of NAFLD and NASH since bacteria and their products (especially lipopolysaccharide or LPS) can escape into the systemic circulation causing a massive inflammatory response from the

liver.[88] Thus, any therapies that prevent this bacterial or LPS 'translocation' to the systemic circulation and liver are of interest.

IMM-124e is an IgG-enhanced bovine-derived colostrum with favorable results in preliminary clinical studies including improved glycemic control, insulin resistance and lipid profile.[89] Further studies are ongoing.

Orlistat is an FDA-approved lipase inhibitor to treat obesity whose action is located in the gut to reduce dietary fat absorption (8626884). Although it seems to improve liver enzyme levels and liver content, its efficacy in NASH has not yet been clearly evaluated.[90]

Other agents targeting the microbiome include a macrolide antibiotic, solithromycin, which is currently in a phase II trial (NCT02510599).

7) Antifibrotic Therapies

Recent work has shown the stage of liver fibrosis to be the strongest predictor of mortality in patients with NAFLD. Hence, there is great interest in developing appropriate therapeutics to target various elements in fibrogenesis.[91]

Simtuzumab is a monoclonal antibody targeting lysyl oxidase-like 2 (LOXL2), which is a key matrix enzyme in collagen formation and highly expressed in the liver.[92] The drug is currently being studied in a phase II trial in both cirrhotic and non-cirrhotic subjects with NASH (NCT01672866).

Galectin-3 is a protein expressed predominantly in immune cells that recognizes and binds to galactose residues. Galectin-3 is an essential protein in liver fibrogenesis and thus a good target of the inhibitor, GR-MD-02. This drug is currently in two phase II clinical trials in NASH patients with fibrosis/cirrhosis (NCT02462967).

Summary

In the absence of any existing FDA-approved medications for the treatment of NAFLD/NASH, the mainstay of management continues to be dietary and other lifestyle changes tailored to the individual patient. Since the acceptable threshold for weight loss needed to resolve NASH and for the regression of fibrosis (more than 10% of body weight) is difficult to obtain even in highly motivated individuals, pharmacotherapies are urgently needed.

Numerous medications have been added to the pipeline of novel therapies, increasing the promise of successful treatment of NASH in the future. In the meantime, first line drugs such as vitamin E and pioglitazone continue to serve their purpose in carefully selected patients, with or without diabetes.

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Key Points

1. NASH is the more aggressive subtype of NAFLD and may replace hepatitis C as the leading cause of liver transplantation by 2020
2. The presence of fibrosis is the strongest predictor of mortality in patients with this disease.
3. Beside life-style changes, there are no FDA-approved medications for patients with NASH
4. Common medications that have showed good results in reducing disease activity are vitamin E and pioglitazone, but these have no consistently reliable effect on fibrosis
5. There are multiple other promising drugs targeting fibrosis and other elements involved in the pathogenesis of NASH that are currently in various stages of clinicial study

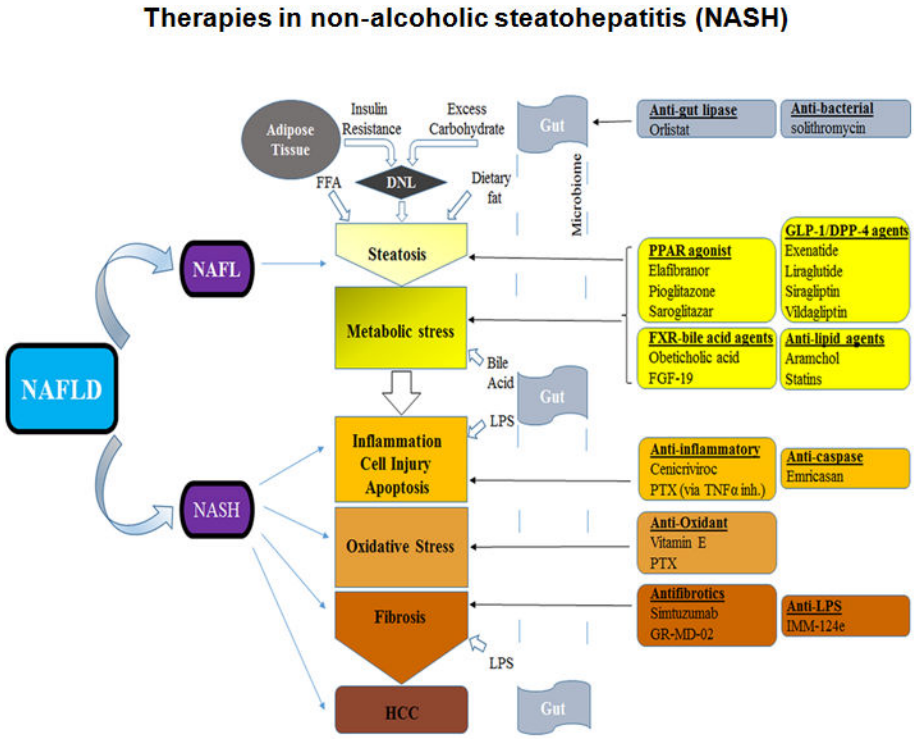

Fig 1. Pathologic processes in NAFLD and potential therapeutic targets

An illustration of the complex processes involved in NASH development and the expected site(s) of action of medications currently being used off-label or under investigation. DNL, de novo lipogenesis; FFA, free fatty acid; NAFL(D), non-alcoholic fatty liver (disease); NASH, non-alcoholic steatohepatitis; TNFα inh., tumor necrosis factor inhibition; PTX, pentoxifylline; HCC, hepatocellular carcinoma; black single-line arrows point to the expected site of action of the medications (but does not indicate the specific stimulatory or inhibitory process involved).