Non-Alcoholic Fatty Liver Disease
An Update in Management and Treatment Guidelines

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Disclosures

- Speaker Bureau for Intercept Pharmaceuticals
- Investigator in Research Protocols for Merck Sharp and Dohme (MSD) and Pfizer Inc.

Definition

Defining Nonalcoholic Fatty Liver Disease

- Definition of NAFLD excludes significant alcohol use
- Significant alcohol use
  - >21 standard drinks on average per week in men
  - >14 standard drinks on average per week in women
  - Standard drink = ~14 grams of pure alcohol

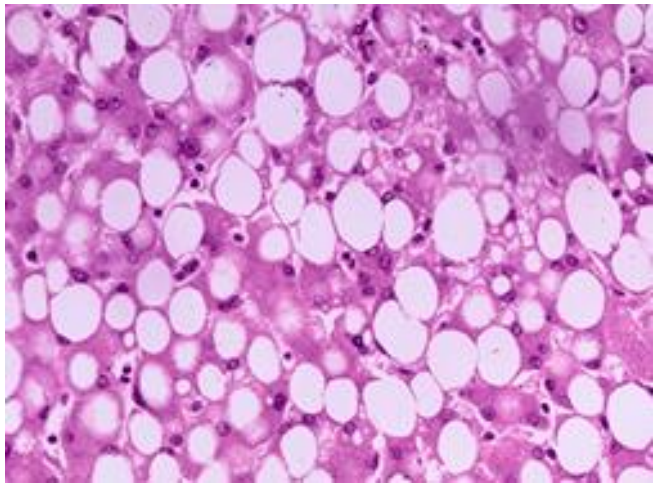
Examples of "standard drinks"
12 ounces of 5% alcohol beer
8 ounces of 7% alcohol malt liquor
5 ounces of table wine
1.5 ounces of distilled spirits (40% alcohol)

Chalasani N, et al. Hepatology 2018;67:328-357
Sanyal AJ, et al. Hepatology 2011;54:344-353

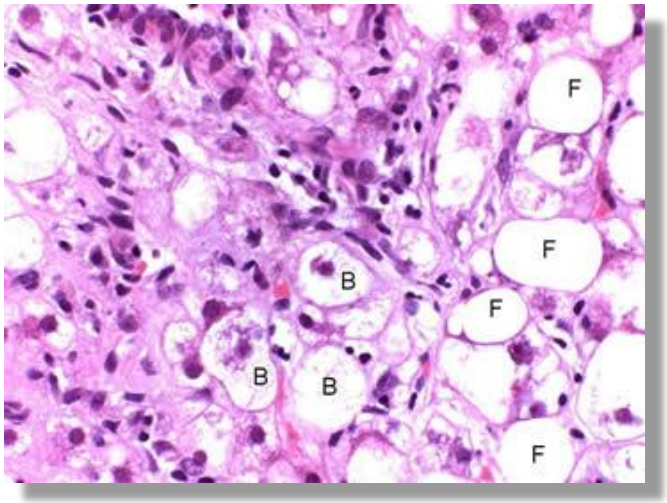
NAFL vs NASH: Histologic Criteria

- NAFL:
  - Hepatic Steatosis
  - No evidence of Hepatocellular Injury (ballooning)
  - No evidence of Fibrosis

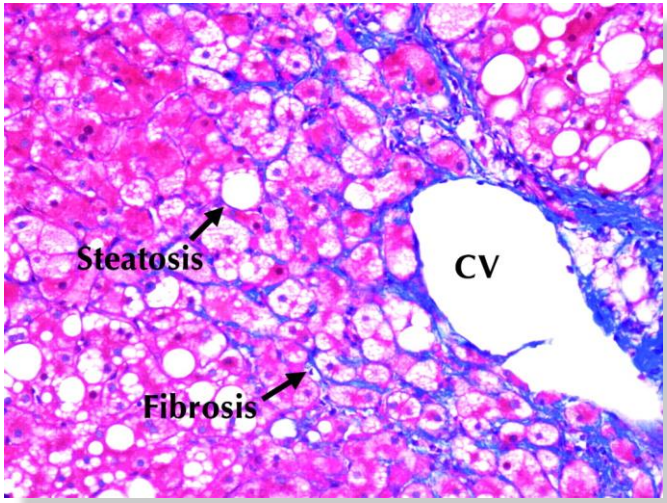
- NASH:
  - Hepatic Steatosis
  - Inflammation
  - Evidence of Hepatocellular Injury (ballooning)
  - Presence or Absence of Fibrosis



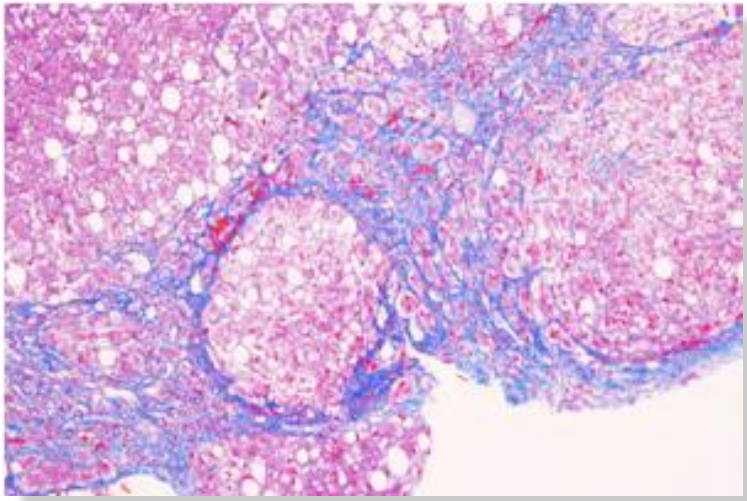
Fatty Liver



NASH – Fat + Ballooning + inflammation



Zone 3 pericellular and central vein fibrosis



Cirrhosis

Pathogenesis of NAFLD

Pathogenesis of NAFLD

- **Excessive importation of FFA from adipose tissue**
  - **Over feeding**
  - **Obesity**

- **Diminished hepatic export of FFA**
  - **Accumulation of hepatocyte lipids leading to oxidative hepatocyte damage**

Pathogenesis of NAFLD

- **Metabolic Factors**
- **Inflammatory Pathways**
- **Fibrosis**
- **Microbiome**
- **Genetic Factors**

Pathogenesis of NASH: Metabolic Factors

- **Insulin Resistance**:
  - Peripheral lipolysis
  - Increased uptake of fatty acids
  - Activation of TRβ
  - ACC activation with increase in acetyl-Co A levels
  - Increased FFA and triglyceride synthesis

Pathogenesis of NASH: Metabolic Factors

Insulin resistance leads to attenuation of:

- **Peroxisome Proliferator-Activated Receptors**
  - **PPAR-α** reduces triglyceride levels
  - **PPAR-γ** causes insulin sensitization and enhances glucose metabolism
  - **PPAR-β/δ** enhances fatty acids metabolism
- **Farnesoid X nuclear receptor**: binds to lipophilic bile acids
  - promotes insulin sensitivity
  - decreases hepatic gluconeogenesis
  - Increases activity of SHP leading to attenuation of SREPβ-1

Pathogenesis of NASH: Metabolic Factors

Insulin Resistance leads to attenuation of:

- Glucose-dependent insulinotropic polypeptide (**GIP**)
  - Stimulates insulin secretion from pancreatic beta-cells
  - Found in intestinal cells

- Glucagon-like peptide-1 (**GLP-1**)
  - Potentiates insulin secretion after meal ingestion
  - Important role in glucose homeostasis
  - Reduces hepatic fat content
  - Found in cells of small intestine

Pathogenesis of NASH: Metabolic Factors

Insulin Resistance leads to attenuation of:

Adiponectin

- Secreted exclusively by adipose tissue
- Enhances both **lipid clearance** from plasma and **beta-oxidation of fatty acids** in muscle
- Anti-inflammatory effects: **suppressing TNF**
- **FGF21 increases Adiponectin levels**

Pathogenesis of NASH: Metabolic Factors

- Increased **cholesterol levels**
  - Lipotoxic trigger
  - Sensitizes hepatocytes to TNF alpha and F (murine models)
  - Depletion of **mitochondrial glutathione** and loss of mitochondrial integrity

- **Visceral fat** correlates with **interleukin-6 levels and TNF alfa**

Pathogenesis of NASH: Inflammatory Pathways

- **Lipid peroxidation** and **free oxygen radical species** deplete **antioxidant enzymes** leading to regulatory T-cell apoptosis and hepatic inflammation

Activation of:

- **Apoptosis signal-regulating kinase** (**ASK1**):
  - Increases inflammatory cytokines
  - Up-regulates genes involved in fibrosis
  - Promotes apoptosis and cellular proliferation

- **Caspase 2**
  - activation leads to cellular apoptosis

Pathogenesis of NASH: Fibrosis

- **Galectin-3**
  - Promotes fibrosis by collagen deposition and apoptosis

- **C-C chemokine receptor types 2 (CCR2) / 5 (CCR5)**
  - Promotes fibrogenesis
  - Monocyte/macrophage recruitment and tissue infiltration
  - Hepatic stellate cell activation

Pathogenesis of NASH: Microbiome

- Diets high in saturated fat and fructose alter **microflora**
- This results in **dysbiosis** with increased intestinal barrier permeability (diminished tight junctions and adherens junction proteins), bacterial translocation and activation of hepatic receptor induced **inflammation (iNOS expression, CYP2E1)**
- Involved in **endotoxin production (enterocyte apoptosis)**

Hepatology 2021;73:2180-2195

Pathogenesis of NASH: Genetic Factors

- Patatin-like phospholipase domain-containing gene (PNPLA-I148M)

- High prevalence in Hispanics
- In the presence of high sugar diet
  - Up regulation of ceramide metabolism (antagonizes insulin action)
  - ER stress/oxidative stress (p-JNK levels)
  - Activation of immune system: TNF, IL-6, STAT 1, Jak-STAT3
  - Microbial dysbiosis, intestinal barrier disruption, translocation of microbial products leading to activation of toll-like receptors
  - Activation of Hepatic Stellate Cells and collagen transcript levels
- Small interfering RNA-lipid nanoparticles can be used to silence PNPLA-3 expression and prevent NASH related fibrosis

Banini et al. Hepatology 2021;73:1290-1306

Fibrosis is a strong predictor of prognosis

- 20% of patients with NAFLD will develop NASH
- 11% of patients with fibrosis will develop cirrhosis in about 15 years
- 31% of patients with cirrhosis develop decompensation over 8 years
- 7% of patients with cirrhosis can develop HCC in over 6.5 years
- Hispanic patients with steatosis have about 54% higher risk of fibrosis

Torres DM, et al. Clin Gastroenterol Hepatol. 2012,10(8):837-858.

Factors Associated with Fibrosis

- Framingham Heart Study:
  - Fibrosis is positively associated with obesity, metabolic syndrome, type 2 diabetes, hypertension, low HDL

  Long et al. Hepatology, Vol.73, No.2, 2021

- NHANES 2017-2018 Data:
  - Fibrosis is positively associated with HbA1c, waist circumference, systolic blood pressure and total cholesterol
  - Men with normal waist circumference have low chances of developing fibrosis even with hepatic steatosis

Any antifibrotic therapy is unlikely to be effective if glucose and body weight are not controlled

Fibrosis is a strong predictor of prognosis

- 1135 pts with compensated cirrhosis who had failed to simtuzumab (anti-Lysyl Oxidase-Like 2-inh. crosslinking of collagen fibers) and selonsertib (ACC inhibitor) trials
- Baseline and 48 week parameters:
  - Histologic scores (NASH CRN and Ishak)
  - Hepatic collagen and alfa-SMA expression (morphometry)
  - VCTE
  - Serum NITs: ELF, NAFLS Fibrosis Score, FIB-4
- Risk of events lower in patients:
  - Improvement in Ishak fibrosis score
- Risk of events higher in patients:
  - Increases in hepatic collagen, alfa-SMA, NFS and liver stiffness

Sanyal A et al. Abst 90. Hepatology, Volume 72, Number 1 (Suppl), 2020

Management of NAFLD

Goals of Treatment

- Management of metabolic comorbidities
- Pharmacologic treatments aimed at improving liver disease
  - Patients with biopsy proven NASH and fibrosis

Chalasani N, et al. Hepatology 2018;67:328-357

Division of Hepatology and Nutrition at the FDA

Drugs used for treatment of NASH:

- For NASH with moderate or bridging fibrosis (F2 and F3):
  - Resolution of steatohepatitis and no worsening of liver fibrosis
  - Improvement in liver fibrosis greater than or equal to one stage and no worsening of steatohepatitis
  - Resolution of both steatohepatitis and improvement in fibrosis

Hepatology, Vol.73, No.5, 2021

Clinical Trial Endpoints

- Histologic improvement: liver biopsies required
- Serologic parameters:
  - ALT (10 u/L reduction associated with histologic resolution of NASH, >17 U/L reduction predicted histologic response)
  - FIB-4
  - NFS
  - ELF: hyaluronic acid, procollagen III amino terminal peptide, tissue inhibitory of matrix metalloproteinase
- Radiological parameters:
  - VCTE
  - MRI-PDFF (>5% absolute reduction associated with improvement in steatosis, >30% relative reduction associated with improvement in NAFLD activity score without fibrosis worsening)
- Combination of modalities

Treatment

- Weight loss
- Lifestyle interventions
- Insulin Sensitizers
- Vitamin E
- GLP 1 agonists
- Ursodeoxycholic acid and Omega 3 fatty acids
- Bariatric Surgery/Endoscopic Interventions
- Novel Medications

Insulin Sensitizers-AASLD Guidance

1. Metformin may improve serum aminotransferases
2. Improves insulin resistance
3. No significant improvement in liver histology

Not recommended for treatment of NASH

Marchesini G, et al. Lancet 2001;358:893-894
Nair S, et al. Aliment Pharmacol Ther 2004;20:23-28
Bugianesi E, et al. Am J Gastroenterol 2005;100:1082-1090

PPARγ agonist (thiazolidinedione)– AASLD Guidance

1. In biopsy proven NASH, Pioglitazone improves histology in patients with and without diabetes
2. Risks and benefits should be discussed with each patient
3. Should not be used to treat NAFLD without biopsy proven NASH

Chalasani N, et al. Hepatology 2018;67:328-357

GLP-1 Agonists – AASLD Guidance

1. Stimulate glucose dependent insulin release
2. Associated with weight loss
3. Liraglutide (LEAN Study) has shown improvement of NASH and decreasing rate of disease progression

It is premature to consider GLP-1 agonists to treat NAFLD with NASH

Semaglutide associated with weight loss, normalization of LFT's and decrease in hepatic fat content

Chalasani N, et al. Hepatology 2018;67:328-357
Armstrong MJ et al. Lancet 2016:13:679-90
O'Neil PM et al.Lancet 2018;392:637-649

Vitamin E – AASLD Guidance

1. Vitamin E (*rrr* α-tocopherol) 800 IU/day improves liver histology in nondiabetic with biopsy proven NASH
2. Risk and benefits should be discussed with each patient
3. Vitamin E is not recommended to treat NAFLD without biopsy proven NASH

Chalasani N, et al. Hepatology 2018;67:328-357

Ursodeoxycholic Acid and Omega-3 Fatty Acids – AASLD Guidance

1. Ursodeoxycholic acid is not recommended for the treatment of NAFLD or NASH

2. Omega-3 fatty acids should not be used as a specific treatment of NAFLD or NASH, but may be used to treat hypertriglyceridemia in patients with NAFLD

Chalasani N, et al. Hepatology 2018;67:328-357

Bariatric Surgery – AASLD Guidance

1. Bariatric surgery can be considered in otherwise eligible obese individuals with NAFLD or NASH
2. Bariatric surgery is not yet an established option to specifically treat NASH
3. Type, safety and efficacy of bariatric surgery in otherwise eligible patients with cirrhosis is not established

Chalasani N, et al. Hepatology 2018;67:328-357

Novel Medications
AASLD 2020 Abstract Submissions

NASH Treatments Under Phase 2 or 3 Investigation

- Insulin Resistance and/or lipid metabolism:
  - PPARγ: Pioglitazone (Actos)
  - GLP1: Liraglutide (Victoza), Semaglutide (Ozempic)
  - SGLT: Empagliflozin (Jardiance), licogliflozin, canagliflozin (Invokana)
  - DPP4: Sitagliptin (Januvia)
  - ACC: GS0976 (Firsocostat), PF05221304
  - SCD1: Aramchol
  - ASBT: Volixibat

NASH Treatments Under Phase 2 or 3 Investigation

- Lipotoxicity and Oxidative Stress
  - PPAR$\alpha\delta$: Elafibranor
  - PPAR$\alpha\gamma$: Saroglitazar
  - Pan-PPAR: Lanifibranor
  - FGF19: NGM282 (Adalfermin)
  - FGF21: Pegbelfermin, Efruxifermin
  - FXR: OCA, Cilofexor, Tropifexor, Nidufexor
  - MPC: MSDC 0602K (second generation thiazolidinedione)
  - TGR5: INT 767/777
  - THRβ: Resmetirom/VK2809

NASH Treatments Under Phase 2 or 3 Investigation

- Inflammation and immune activation:
- CCR2/5: Cenicriviroc
- P2X7R: SGM-1019
- TLR4: JKB-121/122

NASH Treatments Under Phase 2 or 3 Investigation

- Cell Death (apoptosis and necrosis):
  - ASK1: Selonsertib
  - Caspase: Emricasan

NASH Treatments Under Phase 2 or 3 Investigation

- Fibrogenesis and collagen turnover:
  - Galectin: GR MD 02
  - LOXL2: Simtuzumab

Regenerate trial: 18-month interim efficacy analysis FXR Agonist: Lipotoxicity/Oxidative stress

- 2730 pts with NASH (F1-3):
  - Obeticholic acid 10 mg, 25 mg or placebo
  - Significant Fibrosis improvement (>1 stage with no worsening of NASH): 18% for 10 mg, 23% for 25 mg, 12% for placebo)
  - No statistical difference for NASH resolution
  - At present liver biopsies are under revision per request of FDA

Younossi Z et al. Lancet. 2019 Dec 14;394(10215):2184-2196

ALDAFERMIN Clinical Trial

FGF 19 analog (NGM282): Metabolic/Lipotoxicity/Oxidative Stress

- Aldafermin 24 weeks vs placebo (once daily subcutaneous injection)
- 78 patients with biopsy-proven NASH with NAS≥4, F2 or F3 fibrosis and absolute liver fat content (LFC) ≥8%.
- MRI-PDFF and liver biopsies at baseline (BL) and W24
- Aldafermin produced greater reductions in fibrogenesis biomarker Pro-C3 in F3 patients than in F2 patients
- Compared with placebo, aldafermin had greater effect in improving fibrosis in patients with NASH and advanced fibrosis (F3)
- These data support further studies of aldafermin in patients with NASH and advanced fibrosis

Francque S et al. Abst LP9. Hepatology, Volume 72 1(Suppl),2020

Efruxifermin (EFX): Balanced Phase 2a Study
FGF21 analogue: Metabolic/Lipotoxicity Stress

- 80 pts with biopsy proven NASH F1-3
- EFX 28 mg, 50 mg, 70 mg, placebo
- Endpoint: absolute change in liver fat measured by MRI-PDFF
- After 16 weeks of treatment:
  - 48% $\geq$ 1-STAGE fibrosis improvement with no worsening of NASH
  - 48% NASH resolution with no worsening of fibrosis
  - 28% $\geq$ 2 stage fibrosis improvement
  - Significant reductions in serum triglycerides and weight and increase in HDL
  - Robust decrease in C-peptide (less insulin secretion)
  - Safe and generally well tolerated

Harrison S et al. Abst 8. Hepatology, Volume 72, Number 1(SUPPL), 2020

Namodenoson (CF101) Phase 2 Trial
A3 Adenosine Receptor (A3AR) Agonist
Oxidative/Inflammatory Stress

- 60 pts with NFLD and serum ALT > 60 IU/mL
- Namodenoson 12.5 mg bid, 25 mg bid or placebo
- Significant decrease in ALT and MRI PDFF
- Increase in adiponectin
- Significant decrease in body weight and FIB-4
- Consistent dose dependent decrease in body weight
- Well tolerated, no significant side effects or hepatotoxicity

Safadi R et al. Abst LO1. Hepatology, Volume 72 1(Suppl),2020

Native Phase 2b Trial with Lanifibranor in Non-cirrhotic NASH pan-PPAR agonist: Metabolic/Lipotoxicity Stress

- Lanifibranor
  - well-balanced agonist of all 3 PPAR isotypes
  - Increases HDL-cholesterol and adiponectin
  - Decreases insulin resistance and triglycerides (TG)
- 247 pts treated for 24 weeks
  - 103 T2DM/144 non diabetics
  - 82% F2-3
  - Reduction in fasting glycemia starting at week 4 and HbA1c starting at week 14
  - Median HDL-c increase was > 8%
  - Median TG decrease was > 20% from week 4 onwards
  - Major improvement in fibrosis and in NASH resolution in both groups when compared to placebo

Anstee Q. Abst. LP36. Hepatology, Volume 72 1(Suppl),2020

ATLAS Study Phase 2 Clinical Trial
Combination of Pathways

- 48 week trial in F3/F4, compensated cirrhosis
- Individual and combination regimens of:
  - Cilofexor (30 mg): non steroidal FXR agonist
    - Increases FGF19 and decreases bile acid synthesis, lipogenesis, and gluconeogenesis
  - Firsocostat (20 mg): allosteric inhibitor of acetyl coA carboxylase
    - Inhibits rate limiting step in de novo lipogenesis
  - Selonsertib (18 mg): inhibitor of ASK1 (apoptosis signal regulating kinase)
    - Inhibits inflammation and apoptosis

ATLAS Study Phase 2 Clinical Trial

- Results:
  - Firsocostat + Cilofexor:
    - Improvement in non-invasive markers of fibrosis (from F3-F4 to $\leq$ F2)
    - Improvement in hepatic steatosis (MRI-PDFF)
    - Highest rate of fibrosis regression: machine learning approach (ML approach)-automated and quantitative assessment of NASH

ATLAS Study Phase 2 Clinical Trial

- Side effects:
  - Pruritus 20-29%
  - Increase in VLDL
  - Decrease in HDL

Loomba R et al. Hepatology, Volume 73, Issue 2.Feb 2021.625-643

COMBINATION THERAPIES INCLUDING SEMAGLUTIDE (GLP-1 receptor agonist), CILOFEXOR (Farnesoid X receptor agonist), AND FIRSOCOSTAT (ACC inhibitor) IN Non-Cirrhotic PATIENTS WITH NASH Phase 2 Trial

- 108 non-cirrhotic patients with NASH (F2-F3 on biopsy, or MRI-PDFF ≥10% and liver stiffness by transient elastography [LS by TE] ≥7 kPa)
- sema (n=21), sema+CILO 30 mg (n=22), sema+CILO 100 mg (n=22), sema+FIR 20 mg (n=22), or sema+CILO 30 mg+FIR 20 mg (n=21) for 24 weeks (W24). CILO and FIR were taken once daily and sema subcutaneously once weekly (dose escalated from 0.24 mg to 2.4 mg weekly over 16 weeks)
- Significant improvements in hepatic steatosis (MRI-PDFF) and ALT in combination arms vs semaglutide alone
- Liver stiffness and ELF declined in all groups but no difference between groups
- Well tolerated, minimal GI effects

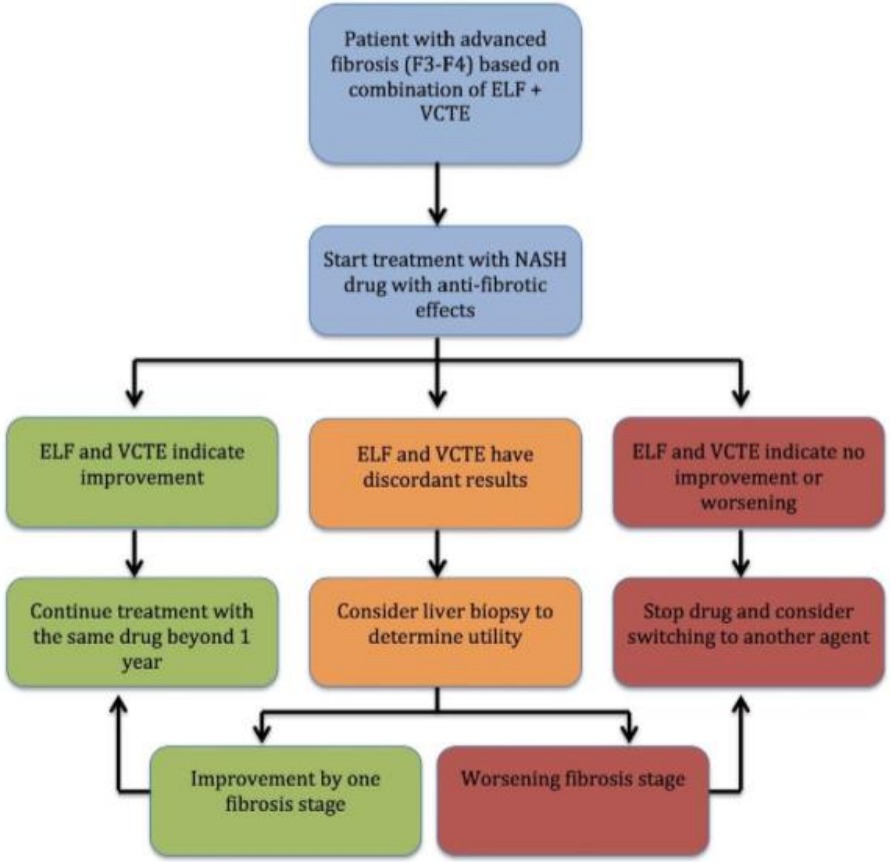
Alkhouri N et al. Abst L02. Hepatology. Volume 72, Number 1 (SUPPL),2020

Regimens in Phase 3 Clinical Trials

- Elafibranor (PPAR) did not meet the endpoint of NASH resolution (RESOLVE-IT)
- Selonsertib (ASK-1) did not meet fibrosis endpoint in patients with cirrhosis (Stellar 4) or bridging fibrosis (Stellar 3) (Nat Rev Gastroenterol Hepatol 17, 260, 2020)
- Cenicriviroc (CCR2/CCR5) met only fibrosis improvement in Phase 2 CENTAUR, phase 3 AURORA is on going (Hepatology, Vol.67, No.5, 2018)
- Resmetirom (THR agonist) 2 pt reduction in NAS, 40% reduction in ALT relative to placebo (Lancet Vol 394, 10213: 2012-2024, 2019)
- Aramchol (inhibits stearoyl CoA desaturase modulator) reduced FA synthesis and improves insulin resistance (ARREST): fibrosis improvement and significant decrease in LFT's (Hepatology,AASLD Meeting 2019)
- MSDC-0602K (second generation thiazolidinedione) (binds MPC and modulates entry of pyruvate into mitochondria) improves insulin resistance (EMMINENCE trial) significant decrease in NFS but not in fibrosis (Hepatology, LO1, AASLD Liver meeting 2019)

Proposed algorithm to determine treatment response to fibrotic NASH medications

- Start with a combination of highly accurate NITs
- Reassess in 1 year or longer
- You may add, stop or switch if no improvement
- You can assess periodically as these tests are east to do



Alkhouri, Lawitz and Noureddin; Hep Comm 2019

Conclusions

- Prevalence of NASH amongst the US population is approximately 5% to 6% and is expected to increase markedly by 2030, driven by the increase in its risks factors, obesity, and diabetes
- Fibrosis is a predictor of mortality and the development of end-stage-liver disease
- For some patients with advanced fibrosis (F3), progression to cirrhosis can be as rapid as 2.5 years
- Effective therapies that can halt or reverse fibrosis progression are urgently needed
- Ultimate goal of therapy is to prevent the development of end stage liver disease and its complications
- Medication therapy must be accompanied by lifestyle modifications