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Northern California Society for Clinical Gastroenterology

Future Therapies for NASH

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December 8, 2018

Disclosures

- Advisor, Gilead: “NASH Models of Care”
- Investigator, NASH clinical trials:
  - BMS
  - Conatus
  - Genfit
  - Gilead
  - Intercept

Present & Future Therapies for NASH

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Clinical Case

- You are seeing your now-60 year-old Asian male patient with prediabetes, dyslipidemia, hypertension and overweight in follow up. He has lost 3% of his body weight – about 5 pounds. His ALT is down to 54 but his AST is 44.
- He has also had a FibroScan which showed a CAP score of 330 dB/m and a liver stiffness measurement of 14 kPa. According to your clinic's FibroScan protocol this is consistent with cirrhosis.

Case

- You refer the patient for liver biopsy to clarify his fibrosis stage and receive this report:
- Ballooning: 2 points *(few ballooned cells per 20x field)*
- Inflammation: 1 point *(2-4 foci per 20x field)*
- Steatosis: 1 point *(5-33% of liver biopsy)*
- Fibrosis: stage 3 with several areas of bridging fibrosis and residual whispy pericentral and perisinusoidal fibrosis.

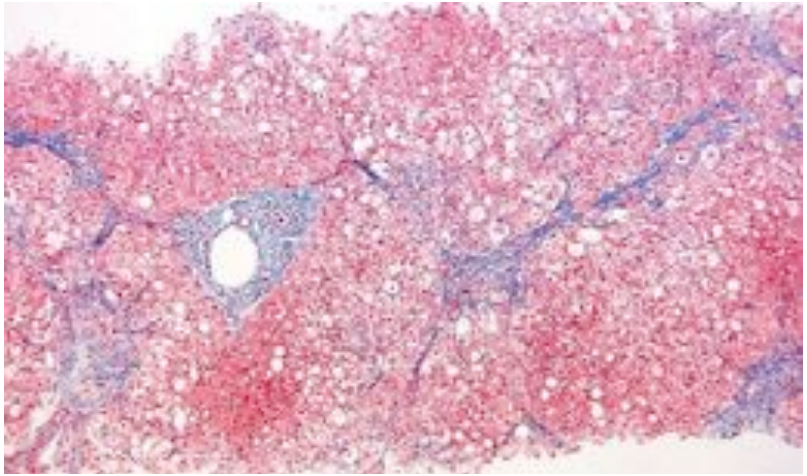

Image credit to David Kleiner: https://handouts.uscap.org/AN2017/2017_CM10_klein_0601.pdf

Case

- The patient is interested in knowing what can be done to treat disease and prevent or reverse fibrosis.

- What will you tell this patient about his disease?
- What effective treatments are available right now?
- What effective treatments will be available in the future?

What will you tell this patient about his disease?

- NAFLD associated with increased risk of
  - Diabetes, OR 2.73 *(Sung, Diabetes Care 2012)*
  - Cardiovascular disease, RR 1.85 *(**2018 AASLD abstract #1713**)*
  - Chronic kidney disease, HR 1.22 *(**2018 AASLD abstract #1698**)**
  - Cirrhosis, 0.7%/10.8% NAFLD/NASH *(Soderberg, Hepatology 2010)*
  - HCC, <0.1%/10% NAFLD/NRC *(Yatsuji, J Gastroenterol Hepatol 2009)*
  - Liver-related mortality, MRR 1.41/42.30 F1/F4 *(Dulai, Hepatology 2017)*
  - All-cause mortality, MRR 1.58/6.40 F1/F4 *(Dulai, Hepatology 2017)*

MRR = mortality rate ratio

Will Treating NASH Be Effective?

Estimating the Impact of Hypothetical Treatment for Patients with Advanced Non-Alcoholic Steatohepatitis (NASH) on Clinical Outcomes

- Anticipating moving from lifestyle changes to pharmacotherapy
- Markov models to compare SOC to pharmacotherapy
- Included 7 age cohorts and 10 disease-severity cohorts
- Prevalence and disease progression determined by lit review
- Modelled for 10-100% treatment of each cohort, F3 only
- Assumed 2 years fibrosis regression followed by lifetime stability

Younossi, 2018 AASLD Abstract #1724

Will Treating NASH Be Effective?

- Treat 10%, progression reduced 50%, lifetime horizon:
  - 21k LT and 88k LRM avoided; 661k QALYs gained
- Treat 50%, progression reduced 50%, lifetime horizon:
  - 104k LT and 438k LRM avoided; 3.3M QALYs gained
- Highest treatment impact estimated in age cohorts between 30-69

LT = liver transplantation, LRM = liver-related mortality, QALY = quality-adjusted life year

Younossi, 2018 AASLD Abstract #1724

Will Treating NASH Be Effective?

Age Group	NASH Cohort Size	Liver Transplants Averted	Liver Related Deaths Averted	Cardio-vascular Deaths Averted	DCC-Person-Years Averted	HCC Person-Years Averted	Lifetime Discounted QALYs Gained
18-29	134,338	-8,775	-23,341	-2,749	-21,813	-7,680	193,308
30-39	276,640	-13,742	-38,951	-4,974	-38,491	-13,129	314,426
40-49	1,016,100	-34,235	-110,460	-15,572	-119,960	-38,500	865,201
50-59	1,971,855	-33,226	-151,740	-24,370	-190,139	-55,562	1,151,285
60-69	1,815,150	-11,975	-86,924	-15,484	-120,233	-33,849	618,351
70-79	1,008,900	-2,034	-24,422	-4,555	-34,319	-10,286	156,278
80+	428,610	-133	-2,214	-402	-2,772	-1,075	11,146
Total	6,651,593	-104,120	-438,052	-68,106	-527,727	-160,081	3,309,995

Younossi, 2018 AASLD Abstract #1724 – **SOC vs. 50% of cohort receiving treatment**

What effective treatments are available now?

What effective treatments are available now?

What effective treatments are available now?

1. Antioxidant; improved NASH in PIVENS trial vs. placebo (43% vs. 19%); did not reduce fibrosis *(Sanyal, N Engl J Med 2010)*
2. GLP-1 agonist; improved NASH vs. placebo in small RCT (39% vs. 9%); did not reduce fibrosis *(Armstrong, Lancet 2016)*
3. Resolved NASH in 85% of subjects and reduced fibrosis in 33.8% after 1 year *(Labreuche, Gastroenterology 2015)*
4. PPAR-γ agonist; may cause weight gain; improved NASH and fibrosis in meta-analysis *(Boettcher, Aliment Pharmacol Ther 2012)*
5. Macronutrient; improved liver fat and enzymes in meta-analysis; did not reduce fibrosis *(Yan, Medicine 2018)*

? ? ? ? ?

A. Pioglitazone (Actos)

B. Liraglutide (Victoza)

C. Vitamin E (α-tocopherol)

D. PUFA (Fish Oil)

E. Weight loss (surgery)

What effective treatments are available now?

Managing Hepatic Steatosis with Omega-3 in NAFLD Patients

- 172 subjects with ultrasound-confirmed hepatic steatosis
- 3g/d proprietary EPA/DHA formula vs. olive oil pills (placebo) + AHA dietary guidance
- Labs at baseline, 12 weeks and end of study (24 weeks)
- Primary outcome = MR-PDFF and Omega-3 Index (validated tool that measures omega-3 incorporation into liver)

Tobin, 2018 AASLD Abstract #2348B

What effective treatments are available now?

Managing Hepatic Steatosis with Omega-3 in NAFLD Patients

- Change in Omega-3 Index from baseline to weeks 12 & 24
  - Intervention group: 4.8% → 8.7% → 8.0%
  - Placebo group: 4.9% → 5.8% → 5.3% ($p<0.0001$ for comparison at week 24)
- Reduction in hepatic fat fraction by MR-PDFF (n=120) in intervention group was not significantly greater than for placebo
  - In post-hoc sub group analysis of those with highest hepatic fat index, *reduction in hepatic fat fraction became significantly greater than with placebo*

Tobin, 2018 AASLD Abstract #2348B

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What effective treatments are available now?

A Lifestyle Intervention in Patients with Type 2 Diabetes Aimed to Improve Glycemic Control Also Reduces Hepatic Stiffness

- Non-randomized intervention study of 81 patients
- Endocrinology-based lifestyle intervention program
- 4-days included visits with physician, diabetes nurse and dietician
- Liver stiffness, labs measured at baseline and 3 months
- F/U data available for 73 patients – age 58.4 years, 62.5% male

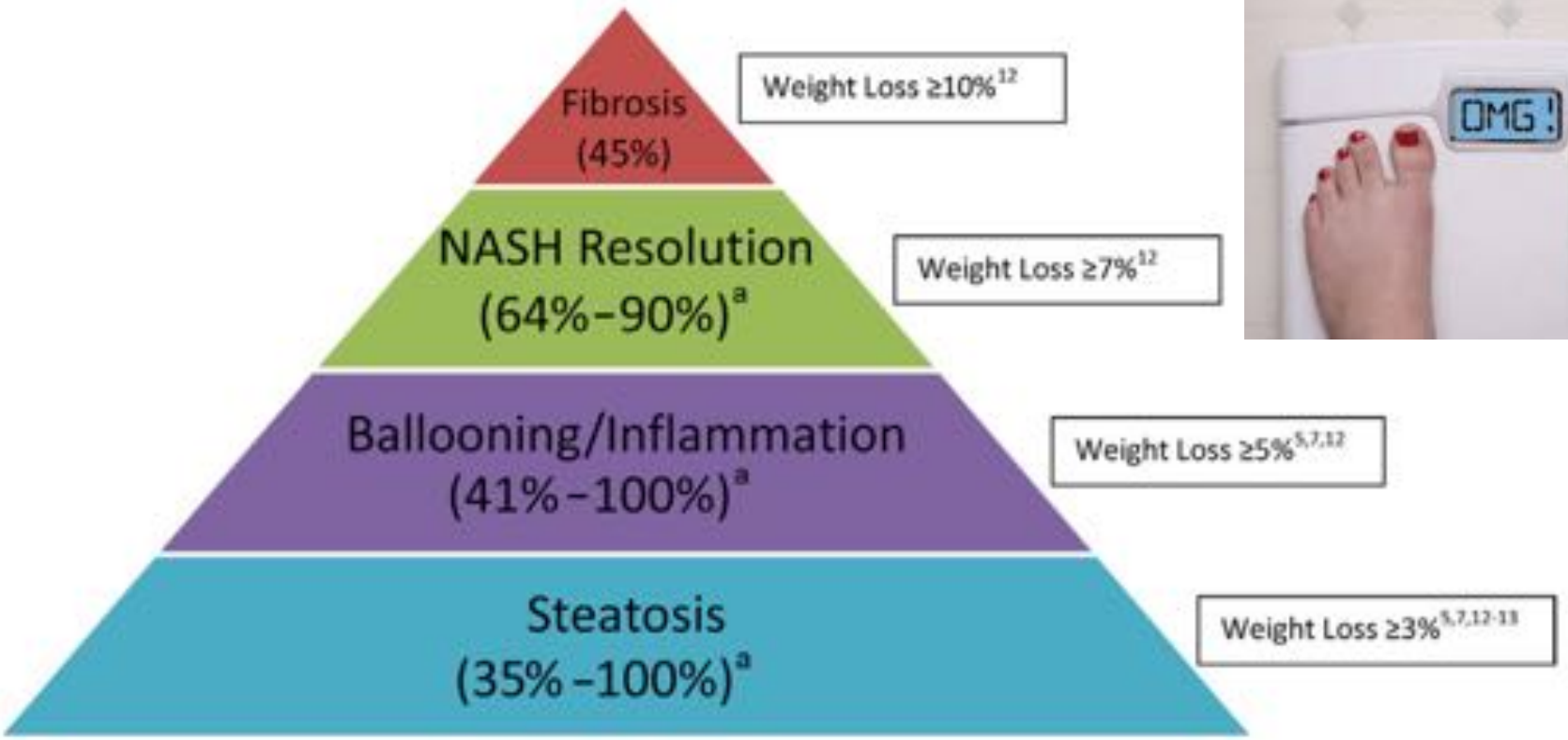
Bjorkstrom, 2018 AASLD Abstract #1753

What effective treatments are available now?

	Baseline	3 months	p-value
BMI	31.6 kg/m^2	30.8 kg/m^2	p<0.001
HbA1c	8.8 mg/dL	8.2 mg/dL	p<0.001
Δ ALT	-3.1 U/L		p=0.2
Liver Stiffness Measurement	8.3 kPa	6.7 kPa	p=0.02

Bjorkstrom, 2018 AASLD Abstract #1753

What effective treatments are available now?



Hannah, Clin Liver Dis 2016

What effective treatments are available now?

Intragastric Balloon in Compensated Nash (non alcoholic steato hepatitis) Cirrhotics – an Observational study

- Prospective observational study, 46 patients, 3/16 – 1/18
- 46 adults with NASH-related cirrhosis age 18-65, BMI >30
- Data recorded at 1, 3 and 6 months post-IGB placement
- Mean f/u 5.27 ±1.52 months; *baseline data not provided*

Sarin, 2018 AASLD Abstract #1715

What effective treatments are available now?

	1 month	3 months	6 months
Δ Body Weight	-6.46 kg	-13.09 kg	-18.12 kg
Δ Body Weight %	-6.5%	-13.2%	-18.2%
Δ Liver Stiffness	-4.66 kPa	-7.70 kPa	-12 kPa
Δ ALT	-7.69 IU/L	-7.72 IU/L	-12.63 IU/L
Δ CTP score	-0.75	-0.90	-1.3
Δ BMI	-2.31 kg/m^2	-4.68 kg/m^2	-6.54 kg/m^2
Δ HVPG	--	--	-7.0 mmHg

Sarin, 2018 AASLD Abstract #1715

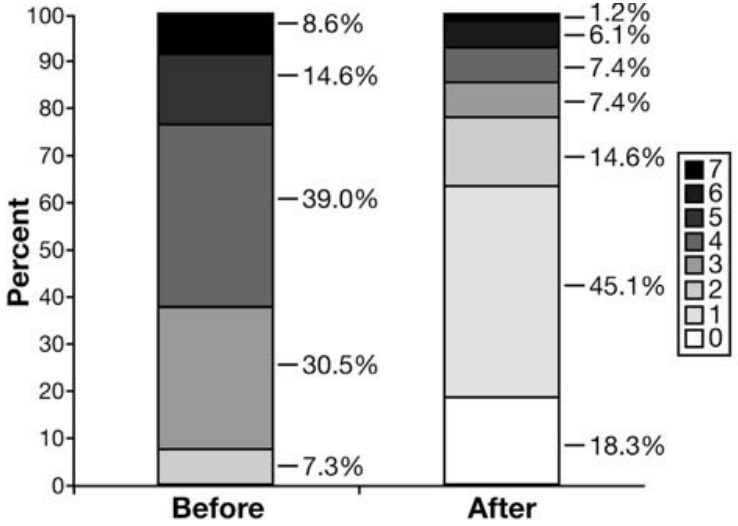
What effective treatments are available now?

- 109 French patients underwent WLS 1994-2013
  - Biliointestinal bypass, gastric band, gastric bypass & sleeve
  - 82 had f/u bx at 1 year (2 of other 27 died of complications)
- Patients with WLS had improvements in:
  - ALT, 52 vs. 25, $p<0.0001$
  - Inflammation (any stage), 98.8% vs. 39%, $p<0.0001$
  - Ballooning (any stage), 98.8% vs. 19.5%, $p<0.0001$
  - Fibrosis (F2-4), 59.3% vs. 38.3%, $p<0.0001$

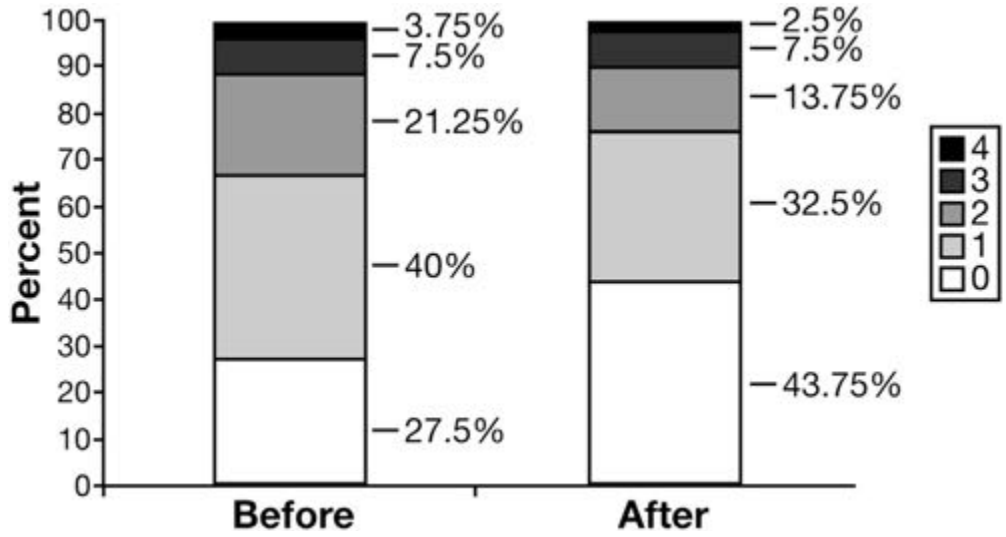
Labreuche, Gastroenterology 2015

What effective treatments are available now?

NAS before and after surgery (n=0.03, p<0.0001)



Fibrosis stage before and after surgery (n=82, p<0.003)



NASH resolution in 85%, ≥1 stage fibrosis reduction in 33.8%

Labreuche, Gastroenterology 2015

What effective treatments are available now?

Weight Loss Surgery Significantly Reduces the Risk of Liver-Related Morbidity in Obese Adults with Nonalcoholic Fatty Liver Disease: A Long-Term Cohort Study*

- Retrospective study of adults with BMI ≥35 kg/m^2 with liver biopsy at Kaiser in Northern California 2000-2015
- 310 subjects had WLS ≤90 days from biopsy (92% REYGB) and 1,039 did not (medical weight loss)
- Median f/u was 7.5 years

Sharpton, 2018 AASLD Abstract #1747

What effective treatments are available now?

	WLS	MWL	p-value
Median BMI*	40.9	38.2	
Female*	84.2%	66.5%	p<0.001
Diabetes*	44.8%	36.1%	p=0.01
Steatohepatitis*	31%	40.6%	p=0.01
F3-4*	13.9%	34.3%	p<0.001
5-year liver-related morbidity**	0.3%	2.4%	p<0.001

*measured at the time of initial liver biopsy

**liver-related morbidity defined as ascites, variceal hemorrhage, hepatic encephalopathy, hepatocellular carcinoma or hepatorenal syndrome

Sharpton, 2018 AASLD Abstract #1747

What effective treatments are available now?

- F3-4 but not steatohepatitis was independently associated with liver-related morbidity
  - HR 2.9 (2.0-4.2, p<0.001)
- WLS was independently associated with liver-related morbidity
  - HR 0.55 (0.33-0.93, p=0.02)
- MV model adjusted for age, sex, ethnicity, BMI, DM, NASH *and advanced fibrosis*

Sharpton, 2018 AASLD Abstract #1747

What effective treatments are available now?

- Model developed to assess 3 weight loss strategies: no treatment, intensive lifestyle intervention and laparoscopic Roux-en Y gastric bypass
- Model based on knowledge of disease progression and potential for reversibility
- Data collected on QOL at different stages of disease
- Probabilities of disease progression with and without intervention documented.

Klebanoff, Hepatology 2017

What effective treatments are available now?

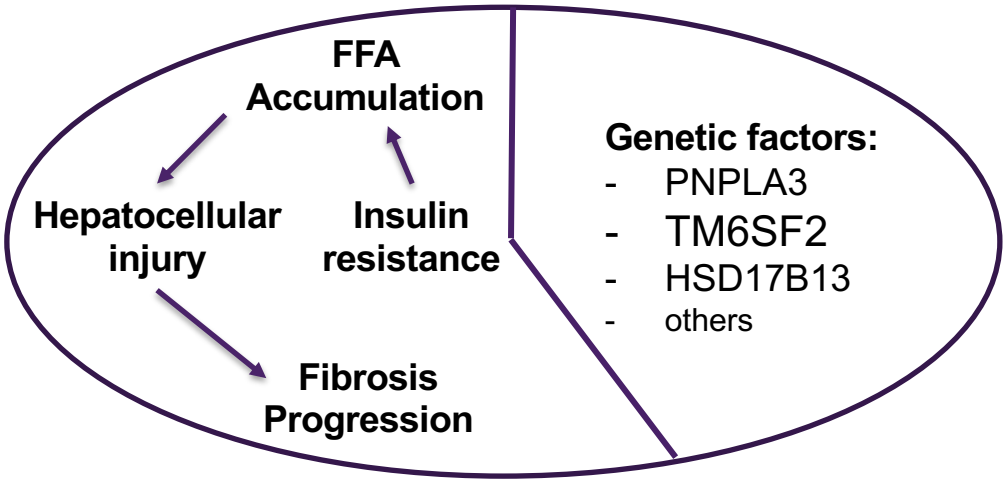
Disease	Surgical Strategy	ICER ($/QALY)
Overweight	F3 only	$30,484
	All	$1,136,760
Mild Obesity	F3 only	$18,309
	All	$48,836
Moderate Obesity	F3 only	$13,869
	All	$24,949
Severe Obesity	F3 only	$12,439
	All	$19,222

ICER = incremental cost effectiveness ratio

In this model WLS was cost-effective in all obese patients but showed the greatest benefit in those with stage 3 fibrosis.

Klebanoff, Hepatology 2017

What effective treatments will be available in the future?



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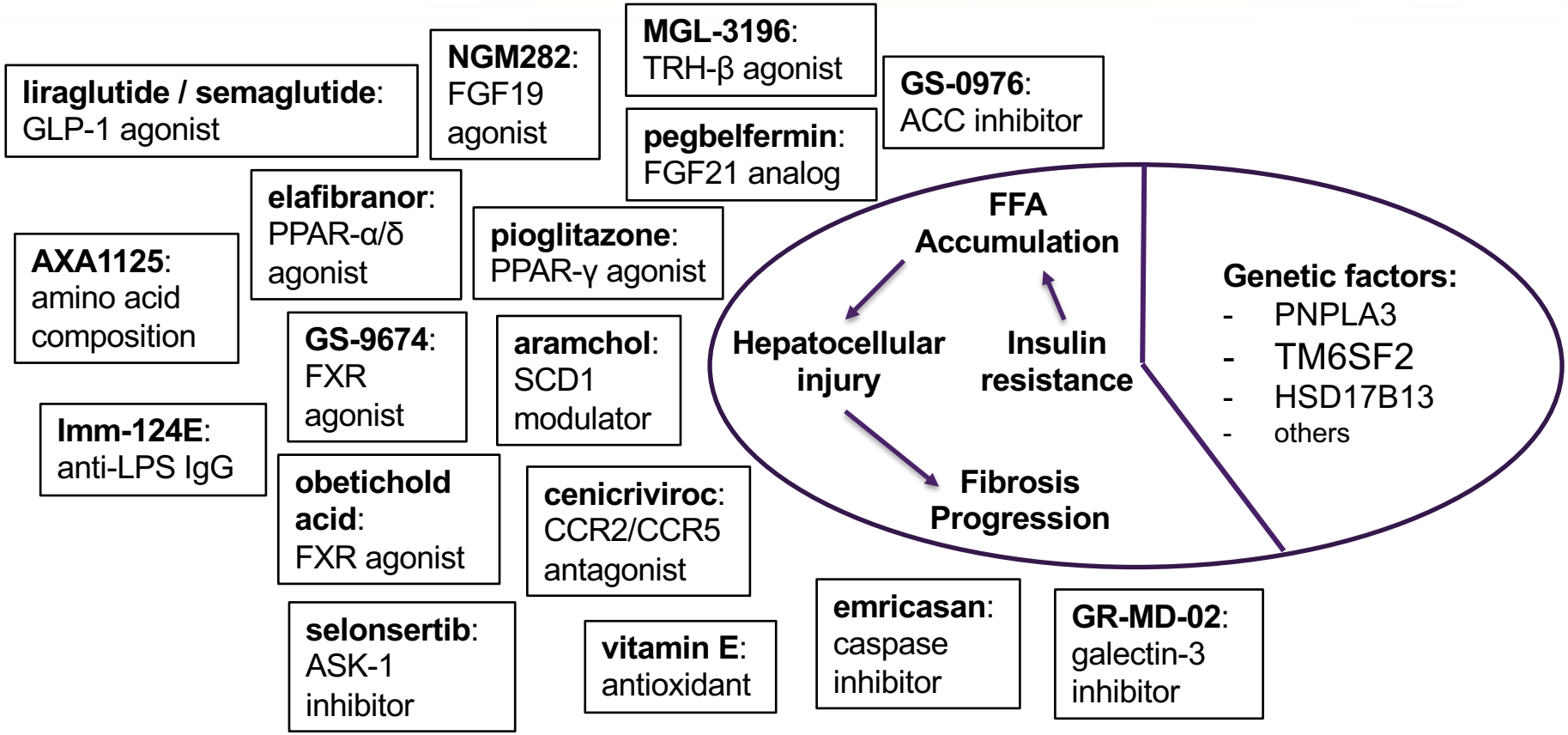

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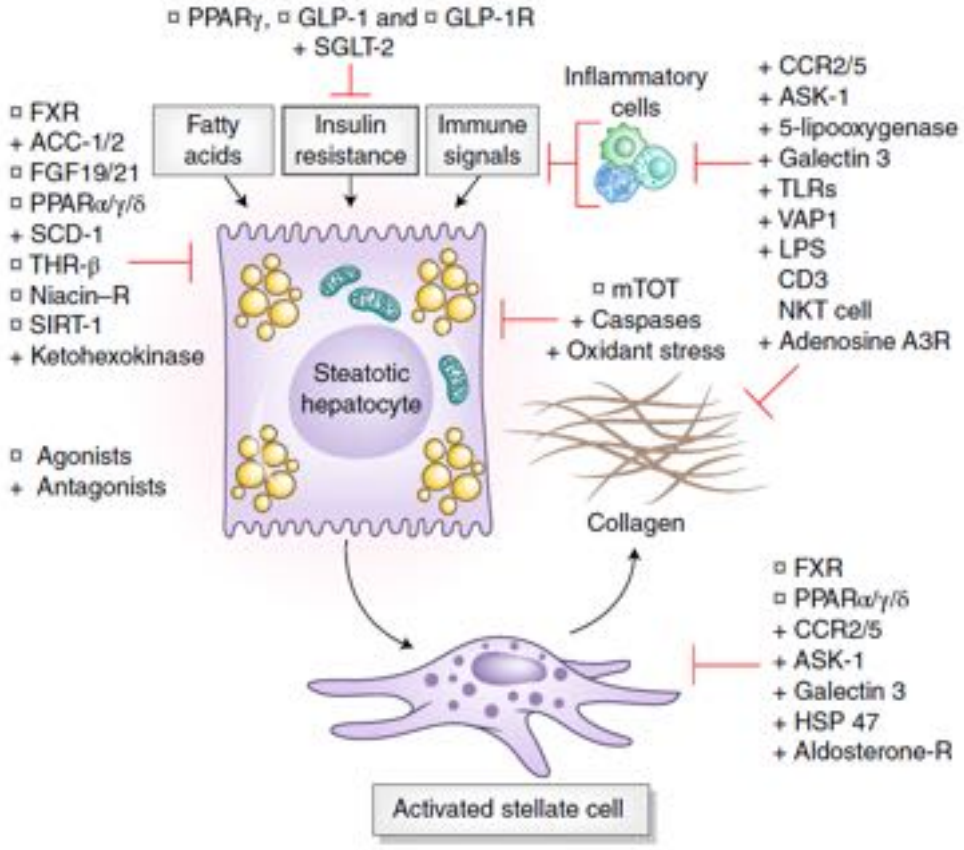
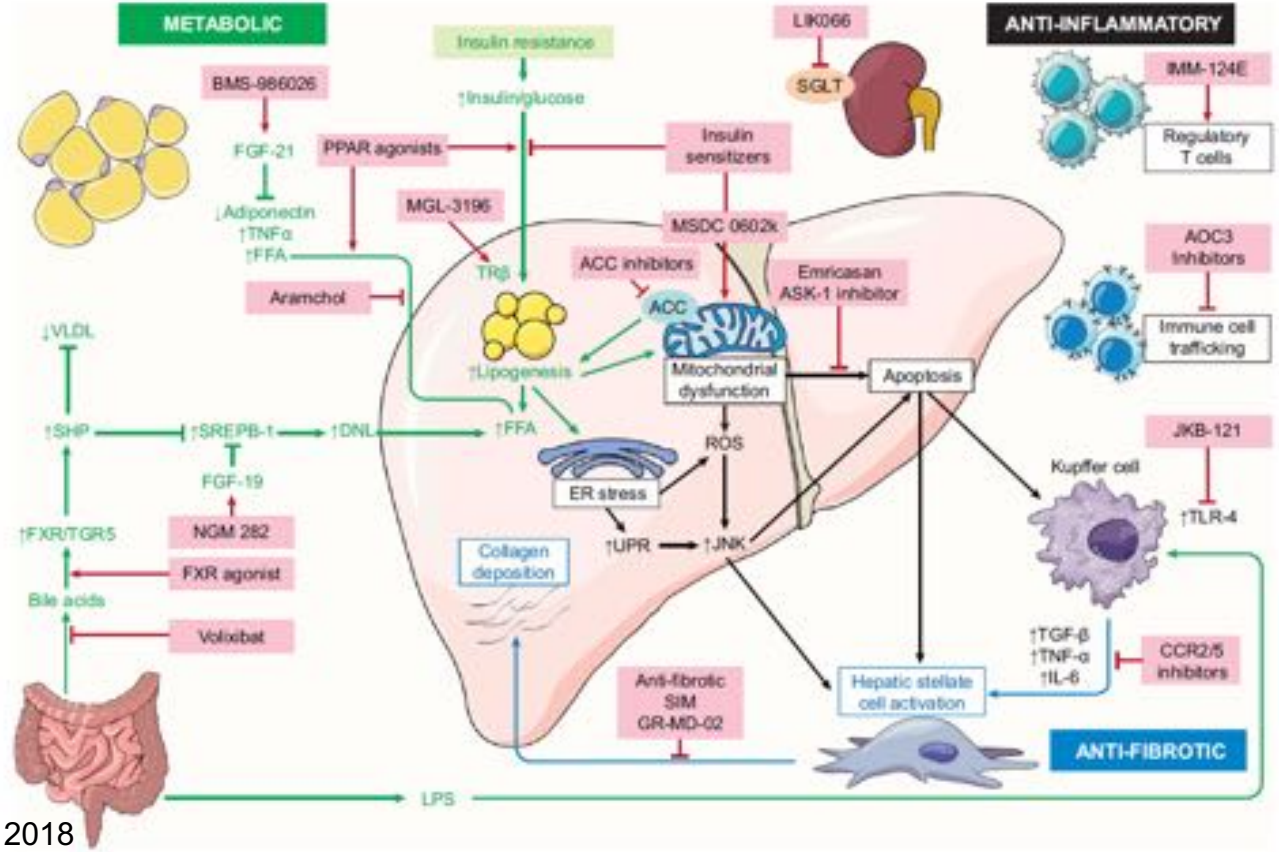


Friedman, Nat Med 2018

What effective treatments will be available in the future?



Konerman, J Hepatol 2018

What effective treatments will be available in the future?

Agent	Mechanism	Phase	Insulin Resistance	FFA Accumulation	Inflammation & Injury	Apoptosis & Cell Death	Collagen Formation
Cenicriviroc	CCR2/5 inhibitor	**3**					
Elafibranor	PPARα/δ agonist	**3**					
Obeticholic Acid	FXR agonist	**3**					
Selonsertib	ASK-1 inhibitor	**3**					
Aramchol	SCD-1 inhibitor	**2**					
Emricasan	Caspase inhibitor	**2**					
GR-MD-02	Galectin-3 inhibitor	**2**					
IMM-124E	Anti-LPS IG	**2**					
MGL-3196	THR-β agonist	**2**					
NGM-282	FGF19 analogue	**2**					
Pegbelfermin	FGF21 analogue	**2**					
GS-0976	ACC-1 inhibitor	**2**					
Semaglutide	GLP-1 analog	**2**					
AXA-1125	AA Composition	**1**					

What effective treatments will be available in the future?

What effective treatments will be available in the future?

NGM282 Rapidly Improves NAFLD Activity Score (NAS) and Fibrosis in 12 Weeks in Patients with Biopsy-Confirmed Nonalcoholic Steatohepatitis (NASH): Results of a Phase 2 Multi-Center Dose Finding Study

- FGF-19 analogue previously tested at 3mg/6mg now at 1mg/3mg
- 38 subjects with NASH, NAS ≥4 (1/component) with stage 1-3 on biopsy and MR-PDFF ≥ 8%within 3 months of screening.
- Primary endpoint was reduction in MR-PDFF by ≥5%

Harrison, 2018 AASLD Abstract #104

What effective treatments will be available in the future?

	NGM282 3mg (n=19)	NGM282 1mg (n=19)
MR-PDFF	-11.2%	-10.9%
ALT	-53 U/l	-68 U/L
≥1 stage fibrosis improvement	42%	26%
≥2 point decrease in NAS	63%	63%
Resolution of NASH	11%	16%

Harrison, 2018 AASLD Abstract #104

What effective treatments will be available in the future?

AXA1125, a Novel Composition of Amino Acids Reprograms the Multifactorial Pathophysiology in NAFLD

- Novel ‘Defined Amino Acid Composition’ (DAAC) with multiple targets in metabolic dysregulation in NASH and effect on insulin resistance, inflammation and fibrosis
- 12-week open label pilot study of 24 subjects with DM2 and NAFLD

Newsome, 2018 AASLD Abstract #105

What effective treatments will be available in the future?

- In humans, over the 12-week study:
  - MR-PDFF decreased by 21%
  - HOMA-IR decreased by 36%
  - Adiponectin increased by 63%
  - ALT, CRP, MCP1 and CK18 all decreased by 30-40% and ProC3 by 28%
- Individual AXA1123 components did not achieve the same histologic response on simultaneously tested mice as the complete DAAC.

Newsome, 2018 AASLD Abstract #105

What effective treatments will be available in the future?

Imm-124E Improves Metabolic Endotoxemia and Markers of Liver Injury in Nonalcoholic Steatohepatitis

- Compound derived from bovine colostrum and enriched with anti-LPS immunoglobulins
- Multicenter phase 2A prospective DB-PC-RCT of 133 patients over 24 weeks (600 mg po TID = 43, 1200 TID = 46, placebo = 44)
- Endpoints: safety, decrease in LPS, AST & ALT and MR-PDFF

Abdelmalek, 2018 AASLD Abstract #108

What effective treatments will be available in the future?

- Drug was well-tolerated vs. placebo
- No anti-LPS antibodies detected
- Only 1200 mg group met any endpoints
- Only those with ALT >50 met endpoint of ALT decrease >30%
- There was no significant change in MR-PDFF or HOMA-IR
- Drug deemed safe and a potential candidate for further evaluiation

Abdelmalek, 2018 AASLD Abstract #108

What effective treatments will be available in the future?

One-Year Results of the Global Phase 2b Randomized Placebo-Controlled Arrest Trial of Aramchol, a Stearoyl CoA Desaturase Inhibitor, in Patients with NASH

- Oral fatty acid / bile acid conjugate that down regulates stearoyl CoA 1, thus slowing the rate-limiting step in the biosynthesis of monounsaturated fatty acids.
- Multicenter trial of 247 diabetic / prediabetic patients over 1 year, 2:2:1 400 mg vs. 600 mg vs. placebo (n=101/98/48)

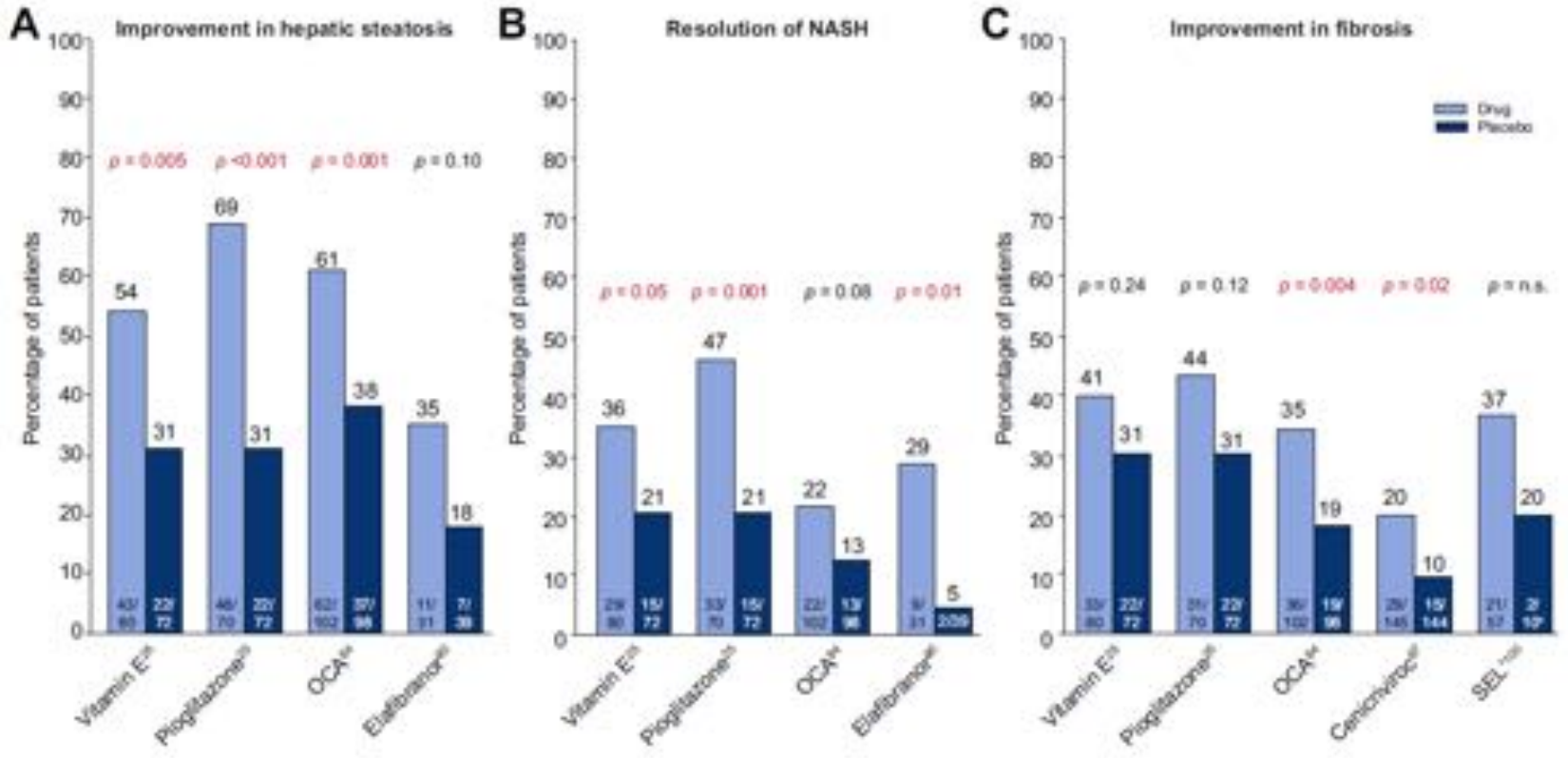
Ratziu, 2018 AASLD Abstract #LB-5

What effective treatments will be available in the future?

- ≥5% decrease in liver fat by MR spectroscopy:
  - 47% on 600 mg, 37% on 400 mg and 24% on placebo ($p<0.028$ for 600 vs. PLB)
- NASH resolution without worsening of fibrosis
  - 16.7% on 600 mg vs. 5.0% on placebo (OR 4.74 [0.99-22.66], p=0.051)
- ≥1 stage fibrosis improvement without worsening of NASH
  - 29.5% on 600 mg vs. 17.5% on placebo (p=0.21)
- Progression to cirrhosis in:
  - 1.3% on 600 mg, 7.5% on 400 mg and 7.5% on placebo

Ratziu, 2018 AASLD Abstract #LB-5

What effective treatments will be available in the future?



Konerman, J Hepatol 2018

What effective treatments will be available in the future?

Quantifying the Placebo Effect on Liver Fat Using Magnetic Resonance Imaging-Proton Density Fat Fraction in NAFLD Clinical Trials

- Secondary analysis of 4 phase 2 clinical trials
- MR-PDFF and ALT at 12,16 and 24 weeks
- Endpoints: steatosis reduction ≥30%, ALT reduction ≥50%
- 112 subjects, 50 years old, baseline MR-PDFF 18.5% and ALT 72.7 U/L
- Placebo met steatosis endpoint in 27.8%, ALT endpoint in 11.5%
- MRI-PDFF reduction was predicted by duration of placebo treatment

Chaudhry, 2018 AASLD Abstract #107

Summary

- Models of NASH treatment – and trials of WLS – promise immense public health benefit, if successful.
- Lifestyle modification and weight loss will always have a central role in the treatment of NASH.
- While newer agents appear to improve steatosis, inflammation and fibrosis, most favor just one these pathways of NASH pathogenesis.
- A combination approach is likely to characterize future treatment of NASH, using at least 1 drug with predominantly metabolic effects and 1 drug with predominantly anti-inflammatory or anti-fibrotic effects.