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Mini Review

NASH Drug Development: Seeing the Light at the End of the Tunnel?

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Abstract

Nonalcoholic steatohepatitis (NASH) is a chronic liver disease affecting a large population worldwide. No clinically approved drugs are available. In this minireview, we discuss the heterogeneous nature of NASH and lack of consensus in outcome measures among clinical trials. We summarize NASH therapeutic targets and candidate drugs. We compare the efficacy of 33 published clinical trials that evaluated noninvasive biomarkers and liver biopsy. Currently, phase II trial results of fibroblast growth factor 21 (FGF21) and phase III trial results of resmetirom and pioglitazone are encouraging.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) describes a collection of steatotic liver conditions. Nonalcoholic steatohepatitis (NASH), first coined by Ludwig *et al*.[1] in 1980 is the inflammatory subtype of NAFLD involving liver steatosis, inflammation, and hepatocyte ballooning often along with fibrosis.[2] Even though NASH has become a global epidemic,[3] it receives much less attention from the public, healthcare professionals, and policymakers than other metabolic diseases such as diabetes and cancer. Recent consensus and recommendations from a Delphi study may raise public awareness of the disease and provide a solid foundation for a comprehensive public health response to NAFLD.[4] Nevertheless, there is no approved drug for NASH treatment in the clinic. Considerable efforts have been vested in NASH drug development; the arduous road continues.

Heterogeneous nature of NASH

Approximately 25% of the world population develops NAFLD, and 20% progress to NASH (Fig. 1). NASH is a heterogeneous disease, and its phenotypic manifestation likely reflects the interactions of different primary drivers and coexisting disease modifiers. Environmental factors such as diet and microbiota, genetic determinants such as PNPLA3 and TM6SF2 mutations as well as epigenetic modifications such as methylation and acetylation can all contribute to NASH. Comorbidities, e.g., type 2 diabetes, dyslipidemia, and gout may exacerbate the disease and thus should be evaluated in NASH patients. Other types of liver conditions such as autoimmune hepatitis, HBV/HCV infection, and Wilson's disease differ from NASH and should be excluded from NASH clinical trials. Unfortunately, present trial recruitment is mainly based on histologic grading and staging, and the response rates to investigational agents are often low.[5]

Clinical trials

Currently, 1282 NASH-related trials are registered at the ClinicalTrials.gov website (https://clinicaltrials.gov), 537 are drug intervention trials including 289 phase II trials, 75 phase III trials, and 67 phase IV trials. Of all registered trials, 68 (5.6%) have published results in peer-reviewed journals (Supplementary Table 1). This percentage is significantly lower than those of type 2 diabetes (18%) and obesity trials (89%). The vast majority (94%) of NASH trials are in the adult population (Supplementary Table 1), and most involve Caucasians (66%) followed by Hispanics (43%), Asians (22%), and Africans (21%).

Trials using surrogate biomarkers or histological outcome endpoints can lead to regulatory agency conditional or full approval of drugs. Some investigators argue whether a biopsy-based evaluation is an appropriate efficacy endpoint because imprecise histological staging may disproportionally impact the active arm relative to the placebo. Many clinicians and investigators do consider liver biopsy and histological evaluation as the reference standard for NASH. Thirty-three of 68 trials (49%) have histological outcome measures (Supplementary Table 1). Thirty-nine trials evaluate drug effects on noncirrhotic NASH (F1-F3), four trials are on cirrhotic NASH (F4) and four trials include both (F1–F4). Of three known histological assessment systems, the National Institute of Diabetes and Digestive and Kidney Diseases NASH Clinical Research Network (commonly referred to as CRN) system, the Steatosis-Activity-Fibrosis system, and the Goodman classification, the CRN system have been unanimously adopted in all 33 publications. Frequently used noninvasive measures (Supplementary Table 1) include biometric markers (body weight, body mass index, and hepatic fat), liver function markers (alanine aminotransferase, aspartate

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Abbreviations: FGF21, fibroblast growth factor 21; NASH, nonalcoholic steatohepatitis.
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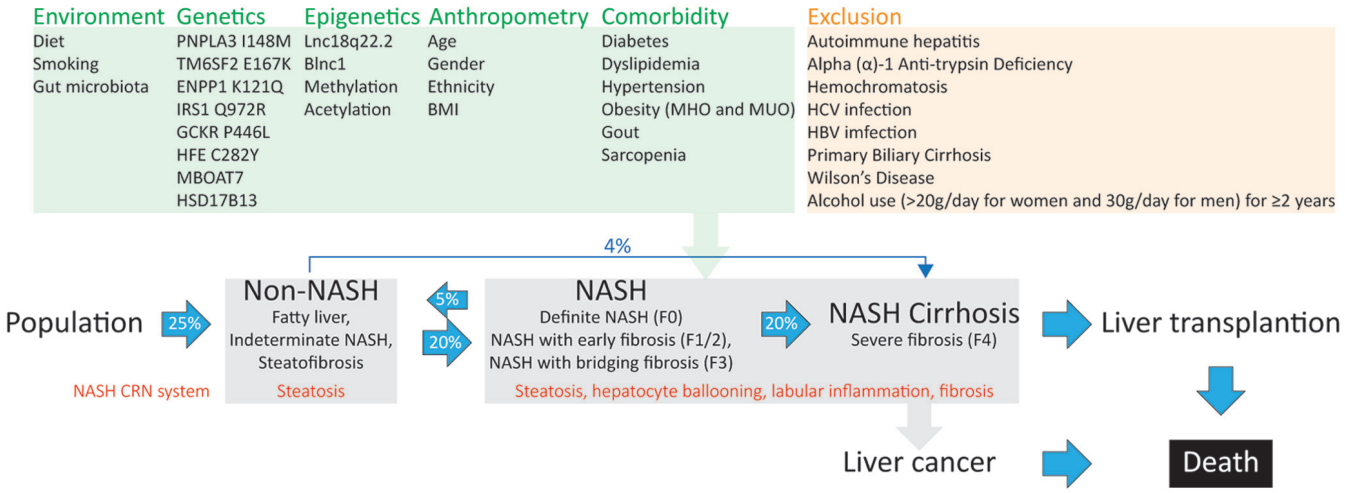

Fig. 1. Heterogeneity of nonalcoholic fatty liver disease. Disease progression from fatty liver to cirrhosis is illustrated. Possible major anthropometric, environmental, genetic, and epigenetic factors are listed. Important comorbidities associated with nonalcoholic steatohepatitis (NASH) are shown. Other types of liver disease that should be excluded from NASH are suggested. PNPLA3 I148M, patatin-like phospholipase domain containing three amino acids 148 I to M mutation; TM6SF2 E167K, transmembrane 6 superfamily member two amino acid 167 E to K mutation; ENPP1 K121Q, ectonucleotide pyrophosphatase one amino acid 121 K to Q mutation; IRS1 Q972R, insulin receptor substrate one amino acid 972 Q to R mutation; GCKR P446L, glucokinase regulator amino acid 446 P to L mutation; HFE C282Y, homeostatic iron regulator amino acid 282 C to Y mutation; MBOAT7, membrane bound O-acyltransferase domain containing 7; HSD17B13, hydroxysteroid 17-beta dehydrogenase 13; Lnc18q22.2, liver cell viability associated long noncoding RNA; Blnc1, brown fat long noncoding RNA 1; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity.

aminotransferase, and gamma-glutamyl transferase), lipid markers (plasma cholesterol, triacylglycerol, high-density lipid cholesterol, and low-density lipid cholesterol), glycemic markers (fasting plasma glucose, insulin, homeostatic model assessment for insulin resistance and glycated hemoglobin). However, common sets of noninvasive clinical measures for steatosis, inflammation, and fibrosis remain to be established, and biomarkers for hepatocyte ballooning are absent.

Therapeutic drugs and targets

Approximately 216 drugs are being or have been evaluated for the treatment of NASH (Fig. 2 and Table 1). Most drugs target metabolic pathways; some aim at inflammation or fibrosis. The vast majority (>80%) are small-molecule drugs. Biological drugs include fibroblast growth factor 21 (FGF21), FGF19, glucagon-like peptide 1 (GLP-1), glucagon, glucose-dependent insulinotropic polypeptide (GIP or gastric inhibitory polypeptide), or a combination thereof (Fig. 2).

Major therapeutic targets include lipid metabolic enzymes acetyl-CoA carboxylase (ACC)[6] and fatty acid synthase (FASN),[7] which affect liver steatosis; farnesoid X receptor (FXR)[8] which interferes with bile acid signaling; nuclear receptors peroxisome proliferator-activated receptor (PPAR),[9] and thyroid hormone receptor beta (THRb)[10] as well as anti-diabetic-peptide receptors GLP-1 receptor (GLP1R),[11] glucagon receptor (GCGR)[12] and GIP receptor (GIPR),[13] which alter glucose and lipid metabolism; FGF21 and FGF19 receptors, which have pleiotropic effects on liver steatosis, inflammation and fibrosis;[14] chemokine (C-C motif) ligand 2 and 5 (CCL2/5)[15] and amine oxidase copper containing 3 (AOC3),[16] which influence inflammation; lysyl oxidase-like 2 (LOXL2),[17] which involves in fibrosis; and caspases, which are key players in apoptosis (Fig. 2). Despite hundreds of potential drugs and a plethora of targets, there is no clear winner.

Seeking alpha

Although no consensus on noninvasive measures for NASH has been reached, histological evaluations of steatosis, inflammation, hepatocyte morphology, and fibrosis are well accepted. We have appraised treatment efficacy in the 33 trials with histological outcome measures (Supplementary Table 1, trials labeled in red) from seven perspectives, i.e. effects on liver steatosis, hepatocyte ballooning, inflammation, fibrosis (F1-F3), cirrhosis (F4), treatment duration, and safety (treatment-emergent adverse events). The first five parameters are NASH-specific and the last two are important clinical considerations for all medications.

FGF21 (NCT03976401), FGF19 (NCT03912532), obeticholic acid (NCT01265498, T02548351), pioglitazone (NCT00994682, NCT00063622, NCT00062764, CT00227110), semaglutide (NCT02970942), and resmetirom (NCT02912260) had significant effects on NASH patients (Table 2). It seems that FGF21 was the most efficacious, followed by resmetirom, pioglitazone, FGF19, semaglutide, and obeticholic acid (Table 2 and Fig. 3). FGF21 had a greater antifibrosis activity and shorter treatment duration than other drugs.

Obeticholic acid improved steatosis, ballooning, inflammation, and fibrosis but had significant side effects, i.e. pruritus (aka itching).[18,19] The FXR agonist cilofexor[20,21] and EDP-305[22] treatment were also associated with pruritus. It is unclear whether the itching side effect is obeticholic acid-specific or associated with bile acid metabolism in general. Compared with other PPAR agonists lanifibranor, rosiglitazone,and elafibranor, pioglitazone had a greater effect on steatosis, hepatocyte ballooning, inflammation, and fibrosis.[23–26] Glitazones for type 2 diabetes therapy have been linked to serious side effects such as fluid retention, congestive heart failure, weight gain, bone loss, and increased risk of bladder cancer.[27–29] Interestingly, pioglitazone had a safe profile in all four trials (NCT00994682, NCT00063622, NCT00062764, CT00227110). Side effects of longer treatment duration remain unclear. GLP-1 analog semaglutide[30] and exenatide[31] reduced liver steatosis, ballooning, and inflammation, but not fibrosis. It is noteworthy that obeticholic acid and pioglitazone data are from phase III trials and other drug results are from phase II trials. Resmetirom was effective in a phase

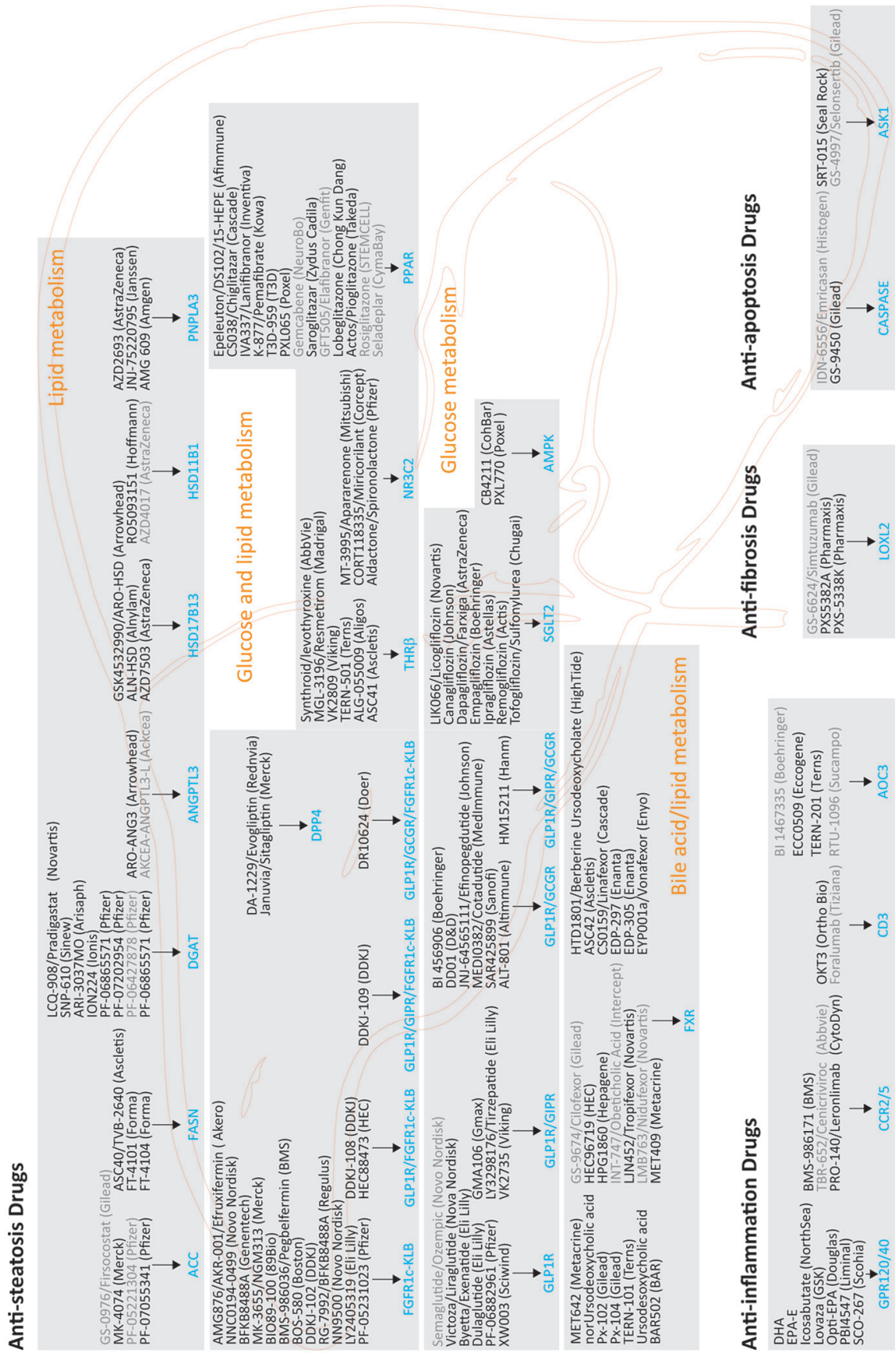

Fig. 2. Major targets and drugs in NASH. Names and producers of drugs are listed. Drugs in gray letters failed in clinical trials. Drugs are classified as antisteatosis, anti-inflammatory, antifibrosis, and anti-apoptotic agents. ACC, acetyl-CoA carboxylase; FASN, fatty acid synthase; DGAT, diacylglycerol O-acyltransferase; ANGPTL3, angiopoietin-like 3; HSD17B13, hydroxysteroid 17-beta dehydrogenase 13; HSD11B1, hydroxysteroid 11-beta dehydrogenase 1; PNPLA3, patatin-like phospholipase domain containing 3; CCR2/5, chemokine (C-C motif) ligand 2 and 5; AOC3, amine oxidase copper containing 3; FXR, farnesoid x receptor; SGLT2, sodium-glucose cotransporter-2; AMPK, adenosine 5′ monophosphate-activated protein kinase; FFAR1/4, free fatty acid receptor 1/4; ASK1, apoptotic signal-regulating kinase 1; LOXL2, lysyl oxidase-like 2; THRb, thyroid hormone receptor beta; NR3C2, nuclear receptor subfamily 3 group C member 2; PPAR, peroxisome proliferator-activated receptor; FGFR, fibroblast growth factor receptor; KLB, beta klotho; GLP1R, glucagon-like peptide 1 receptor; DPP4, dipeptidyl peptidase-4; GIPR, glucose-dependent insulinotropic polypeptide receptor; GCGR, glucagon receptor.

Table 1. Additional targets and drugs

Drug	Target	Company
Cysteamine	/	Raptor Pharma
FIA586	/	Novartis
LY3849891	/	Eli Lilly
MG-1	/	/
NC101 (undefined)	/	/
NRL972 (cholyl lysyl fluorescein)	/	Norgine
TRO19622 (Olesoxime)	/	Hoffmann-La Roche
XZP-5610	/	Xuanzhu Biotech
XZP-6019	/	Xuanzhu Biotech
ZSP0678	/	Raynovent
TEV-45478	/	*Teva Pharma*
FM101	A3AR	Future Medicine
Namodenoson	A3AR	Can-Fite BioPharma
PBF-1650	A3AR	Palobiopharma
Aceon (Perindopril)	*ACE*	/
CF102	ADORA3	Can-Fite BioPharma
WY-8678 (Guanabenz acetate)	ADRA2A	Pfizer
Cozaar (Losartan)	AGTR	Organon
Nitazoxanide	Antiparasitic	Genfit
LPCN 1144 (testosterone)	AR	Lipocine
SHP626 (Volixibat)	*ASBT*	*Shire*
BLD-0409 (Cudetaxestat)	ATX	Blade Therapeutics
PLN-1474	avb1	Pilant
IDL2965	avb3	Indalo
Dasatinib (Sprycel)	BCR-ABL	BMS
CP-945598	CB1R	STEMCELL Technologies
JNJ-2463 (Nimacimab)	CB1R	Bird Rock Bio
Proglumide	CCKA/BR	AdvaCare Pharma
CM-101	CCL24	Chemomab
RYI-018	CNR1	Bird Rock Bio
SNP-630	CYP450	Sinew Pharma
Singulair (Montelukast)	CYSLTR	Merck
MN-001 (Tipelukast)	CYSLTR/PDE/5-LOX	MediciNova
DUR-928	Epigenetic	Durect
Estradiol	ER	/
NGM282 (Aldafermin)	*FGFR4-KLB*	*NGM*
GB1211	Galectin-3	Galecto Biotech
GR-MD-02 (Belapectin)	*Galectin-3*	*Galectin Therapeutics*
NGM395	GFRAL	NGM
Tesamorelin (GHRH)	GH	Theratechnologies
LUM-201 (Ibutamoren)	GHSR	Lumos Pharma
Crestor (Rosuvastatin)	*HMGCR*	*Astra Zeneca*
BMS-986263	HSP47	BMS

(continued)

Table 1. *(continued)*

Drug	Target	Company
GM-60106	HTR2A	JD Bioscience
Elobixibat	*IBAT*	*Albireo*
HPN-01	IKK	Hepanova
CC-90001	JNK	Celgene
PF-06835919	KHK	Pfizer
Metreleptin	LEPR	Amylin Pharma
IMM-124E	*LPS*	*Immuron*
Oltipraz (Dithiolethiones)	LXRa	PharmaKing
BMS-963272	MGAT2	BMS
Metformin	mGPD	/
LB-P6	Microbiome	LISCure Biosciences
RG-125 (AZD4076)	*miR-103/107*	*Regulus*
MSDC-0602K	MPC	Cirius Therapeutics
IdB 1016 (Siliphos)	NF-κB	Indena
GRI0621	NK cell	GRI Bio
DFV890	NLPR3	Novartis
SGM-1019	*P2X7R*	*Second Genome*
CER209	P2Y13R	Abionyx
ZSP1601	PDE	Raynovent
ASP9831	*PDE4*	*Astellas Pharma*
CRV-431 (Rencofilstat)	PPI	Hepion Pharma
Rifampicin	*PXR*	/
Denosumab	RANKL	Amgen
TB-840	RORa	Therasid Bioscience
Hydroxytyrosol	ROS	/
IDDF2019-ABS-0026 (Metadoxine)	*ROS*	*Micro Labs*
Vitamin E	ROS	/
AGN-242266	RXR	Abbvie
Aramchol	SCD1	Galmed
BI 685509	sGC	Boehringer Ingelheim
Idebex (Idebenone)	Shc	ABCO Lab
NS-0200	SIRT1/AMPK	NuSirt Biopharma
Amlexanox	TBK1/IKKε	/
ZED1227	TG2	Zedira
Pradaxa (Dabigatran)	Thrombin	Boehringer Ingelheim
JKB-122	*TLR4*	*TaiwanJ Pharma*
Trental (Pentoxifylline)	*TNFα*	/
Vitamin D	*VDR*	/
Uloric (Febuxostat)	XDH	Takeda

/, unknown. Italic font indicates drugs that failed clinically.

II trial[32] and positive phase III results have recently been announced by Madrigal (https://www.madrigalpharma.com/).

FGF21 phase II trial results are encouraging. AKERO-001 (an FGF21 analog) had excellent effectiveness on liver steatosis, ballooning, inflammation, and fibrosis with a short duration and mild adverse drug reactions.[33] It was also effective in patients with cirrhosis (https://ir.akerotx.com/news-releases/news-release-details/akero-announces-pos-

Table 2. Outcomes of major clinical trials

Trial	Phase	Drug	Steatosis (Score)	Ballooning (Score)	Inflammation (Score)	Fibrosis F1-F3 (Score)	Cirrhosis (Score)	Tx Duration (Score)	Safety (Score)	Total score
NCT03976401	II	FGF21	17/17 (1)	13/14 (0.93)	13/14 (0.93)	10/13 (0.77)	7/12 (0.58)	12 (1)	No increase (1)	6.21
NCT03912532	II	FGF19	34/43 (0.79)	21/43 (0.49)	0/43 (0)	7/43 (0.16)	ND (0)	24 (0.8)	Grade 1 (0.8)	3.04
NCT01265498	III	Obeticholic acid	62/102 (0.61)	47/102 (0.46)	54/102 (0.53)	36/102 (0.35)	ND (0)	72 (0.4)	Grade 3 (0.4)	2.75
NCT02548351	III		127/308 (0.41)	108/308 (0.35)	136/308 (0.44)	84/308 (0.27)	ND (0)	72 (0.4)	Grade 3 (0.4)	2.27
										2.51
NCT00994682	IV	Pioglitazone	35/50 (0.70)	25/50 (0.50)	25/50 (0.50)	20/50 (0.40)	NC (0)	72 (0.4)	No increase (1)	3.10
NCT00063622	III		55/80 (0.69)	35/80 (0.44)	48/60 (0.6)	35/80 (0.44)	ND (0)	96 (0.2)	Weight gain (0.8)	3.17
NCT00062764	II		6/18 (0.33)	6/18 (0.33)	6/18 (0.33)	6/18 (0.33)	ND (0)	48 (0.6)	Weight gain (0.8)	2.72
NCT00227110	IV		17/26 (0.65)	14/26 (0.54)	17/26 (0.65)	12/26 (0.46)	ND (0)	24 (0.8)	No increase (1)	4.10
										3.27
NCT02970942	II	Semaglutide	33/56 (0.59)	33/56 (0.59)	33/56 (0.59)	0/56 (0)	ND (0)	72 (0.4)	Grade 2 (0.6)	2.77
NCT02912260	II	Resmetirom	41/73 (0.60)	41/73 (0.60)	41/73 (0.60)	21/73 (0.29)	ND (0)	12 (1)	Grade 2 (0.6)	3.69

Steatosis, ballooning, inflammation, fibrosis and cirrhosis score: number of responders/total number of patients; Treatment duration score: weeks 1–12=score 1, 13–24=score 0.8, 25–48=score 0.6, 49–72=score 0.4, > 72=score 0.2; no effect=score 0; Safety (TEAE) score: no increase in TEAE over placebo=score 1, increase in Grade 1=score 0.8, Grade 2=score 0.6, Grade 3=score 0.4, Grade 4=score 0.2, Grade 5=score 0, no result=score 0; Average score in case of having multiple trials. N, no change; ND, not determined.

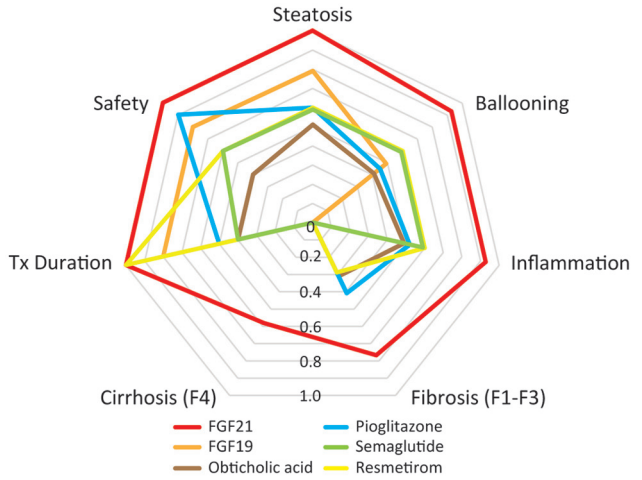

Fig. 3. Efficacy of various treatments. Efficacy is evaluated from perspectives of steatosis, hepatocyte ballooning, lobular inflammation, fibrosis, cirrhosis, treatment duration, and safety (treatment-emergent adverse events). Steatosis, ballooning, inflammation, fibrosis, and cirrhosis score: responders/patients; duration score: weeks 1–12=1, 13–24=0.8, 25–48=0.6, 49–72=0.4, >72=0.2; no effect=0; safety score: no increase in TEAE over placebo=1, increase in Grade 1=0.8, Grade 2=0.6, Grade 3=0.4, Grade 4=0.2, Grade 5=0, no result=0; average score in case of having multiple trials.

itive-histological-improvements-cirrhotic). Among patients with PNPLA3I148M mutation, 8/18 (44% I/M carriers) and 5/9 (56% M/M carriers) achieved a ≥ 4-point improvement in NAS and 10/18 (56% I/M carriers) and 7/9 (78% M/M carriers) had a ≥ 1 stage improvement in fibrosis (kyale@akerotx.com). FGF19, a close relative, was less effective than FGF21, possibly owing to a significant elevation of total plasma cholesterol and low-density lipid cholesterol.[34] Therefore, the FGF21 analog appears to be a strong therapeutic candidate for NASH.

There may still be room for improvement of FGF21 analogs. Pegbelfermin and BIO89-100 are FGF21 peptides stabilized by polyethylene glycol modification, whereas AKERO-001 is stabilized by FGF21-IgG1 Fc fusion. FGF21-Fc fusion protein seems to be more stable and thus more effective than PEG-modified ones. However, AKERO-001 is expressed in prokaryotic cells, and our experiment suggests that eukaryotic-expressed FGF21-Fc is significantly more stable and consequently more efficacious than the prokaryotic-expressed proteins. In addition, multitarget fusion peptides are emerging; for example, GLP1-FGF21 (DDKJ Biomedicals, HEC Pharm), GLP1-GCG-FGF21 (Doer Biologics), and GLP1-GIP-FGF21 (DDKJ Biomedicals). Preclinical evidence indicated that dual targeting molecule GLP1-FGF21 was more effective than FGF21 alone.[35] GLP1-GIP combination has been reported to reduce GLP-1-caused gastrointestinal problems,[36] therefore, the combination of GLP1-GIP-FGF21 may have a significant effect on both glucose and lipid metabolism while minimizing gastrointestinal discomfort. Are we seeing the light at the end of the tunnel? One should cautiously wait for the outcome of the FGF21 Phase III clinical trial.

Funding

None to declare.

Conflict of interest

YQC holds shares of DDKJ Biomedicals.

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