ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2023 December 28; 29(48): 6168-6238

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 29 Number 48 December 28, 2023

World Journal of Gastroenterology

Weekly Volume 29 Number 48 December 28, 2023

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Takaaki Arigami, MD, PhD, Senior Lecturer, Gastroenterology Center, Kagoshima University Hospital, 8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan. arigami@m.kufm.kagoshima-u.ac.jp

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (*WJG*, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The *WJG* is now abstracted and indexed in Science Citation Index Expanded (SCIE), MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJG* as 4.3; Quartile category: Q2. The *WJG*'s CiteScore for 2021 is 8.3.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

PUBLICATION DATE
December 28, 2023

PUBLISHING PARTNER
Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute, Fudan University
Biliary Tract Disease Institute, Fudan University

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

POLICY OF CO-AUTHORS
https://www.wjgnet.com/bpg/GerInfo/310

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

PUBLISHING PARTNER's OFFICIAL WEBSITE
https://www.shca.org.cn
https://www.zs-hospital.sh.cn

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2023 December 28; 29(48): 6235-6238

DOI: 10.3748/wjg.v29.i48.6235

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LETTER TO THE EDITOR

Potential therapeutic targets for nonalcoholic fatty liver disease: Glucagon-like peptide 1

Yue-Hua Yin, Li-Xuan Sang, Bing Chang

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Gatselis NK, Greece; Marchesini G, Italy; Virovic-Jukic L, Croatia; Ji G, China

Received: October 7, 2023
Peer-review started: October 7, 2023
First decision: October 23, 2023
Revised: November 8, 2023
Accepted: December 6, 2023
Article in press: December 6, 2023
Published online: December 28, 2023

Yue-Hua Yin, Bing Chang, Department of Gastroenterology, The First Affiliated Hospital of China Medical University, Shenyang 110001, Liaoning Province, China

Li-Xuan Sang, Department of Gastroenterology, Shengjing Hospital of China Medical University, Shenyang 110022, Liaoning Province, China

Corresponding author: Bing Chang, Chief Physician, Postdoc, Professor, Department of Gastroenterology, The First Affiliated Hospital of China Medical University, No. 155 Nanjing North Street, Shenyang 110001, Liaoning Province, China. cb000216@163.com

Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most rapidly growing contributor to liver mortality and morbidity. Hepatocellular injury in nonalcoholic steatohepatitis (NASH) is caused by an increase in metabolic substrates (glucose, fructose, and fatty acids), leading fatty acids to participate in pathways that cause cellular injury and a poor response to injury. The pathogenesis of this disease is largely associated with obesity, type 2 diabetes, and increasing age. To date, there are no Food and Drug Administration-approved treatments for NAFLD/NASH or its associated fibrosis. Since one of the pathogenic drivers of NASH is insulin resistance, therapies approved for the treatment of type 2 diabetes are being evaluated in patients with NASH. Currently, the glucagon-like peptide-1 receptor agonist (GLP-1RA) semaglutide is a safe, well-studied therapeutic for NAFLD/NASH patients. Existing research demonstrates that semaglutide can increase the resolution of NASH but not improve fibrosis. However, improving the fibrosis of NAFLD is the only way to improve the long-term prognosis of NAFLD. Given the complex pathophysiology of NASH, combining therapies with complementary mechanisms may be beneficial. Researchers have conducted trials of semaglutide in combination with antifibrotic drugs. However, the results have not fully met expectations, and it cannot be ruled out that the reason is the short trial time. We should continue to pay increasing attention to GLP-1RAs.

Key Words: Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Antidiabetic drugs; Glucagon-like peptide 1; Semaglutide

Core Tip: Semaglutide is effective and safe for nonalcoholic fatty liver disease (NAFLD) but does not improve fibrosis. The treatment of NAFLD requires further combinations of drugs with different and complementary mechanisms of action.

Citation: Yin YH, Sang LX, Chang B. Potential therapeutic targets for nonalcoholic fatty liver disease: Glucagon-like peptide 1. *World J Gastroenterol* 2023; 29(48): 6235-6238
URL: https://www.wjgnet.com/1007-9327/full/v29/i48/6235.htm
DOI: https://dx.doi.org/10.3748/wjg.v29.i48.6235

TO THE EDITOR

We read with great interest the work by Zhu *et al*[1], who further validated that semaglutide can improve the resolution of nonalcoholic steatohepatitis (NASH) but not fibrosis by summarizing the histological results of semaglutide in the treatment of nonalcoholic fatty liver disease[1,2].

To date, there are no Food and Drug Administration-approved treatments for nonalcoholic fatty liver disease (NAFLD)/NASH or its associated fibrosis. Fibrosis or cirrhosis has been recognized in recent guidelines as the main diagnostic and therapeutic target to halt the progression of NASH to end-stage liver disease, change the natural history of the disease, and improve the long-term prognosis of patients with NASH[3,4].

Because insulin resistance is a shared characteristic of type 2 diabetes and obesity and is a key pathogenic driver of NASH[5], pharmacologically, antidiabetic drugs with weight loss effects should be effective against NASH. Therefore, most of the antidiabetic drugs used to treat NASH focus on peroxisome proliferator-activated receptor (PPAR) agonists, glucagon-like peptide-1 receptor agonists (GLP-1RAs), or sodium-glucose transporter 2 (SGLT2) inhibitors[6,7]. Pioglitazone can improve fibrosis in NASH[7]. However, its harmful adverse effects limit its use, and its long-term benefits are not obvious, thus reducing enthusiasm for its use[8,9]. Currently, SGLT-2 is and GLP-1 RAs are gaining more attention in the treatment of NAFLD/NASH metabolic dysfunction-associated fatty liver disease.

GLP-1 RAs may represent the most promising treatment option for improving hepatic steatosis and liver enzyme levels (serum aspartate transaminase, alanine transaminase and gamma-glutamyl transferase) in patients with NAFLD[10]. As a GLP-1 RA, semaglutide appears to be more prominent in the treatment of NASH[11]. Semaglutide activates the hepatic PPAR-α, thereby reducing apolipoprotein C production and breaking down fats and triglycerides in plasma, delaying gastric emptying, prolonging satiety, and reducing waist circumference[3]. Moreover, semaglutide increases insulin production and secretion and decreases glucagon secretion[3]. Current studies have demonstrated that semaglutide is effective in reducing hepatic steatosis and inflammation but not fibrosis[2,5]. The complex pathophysiology of the disease and the multiple often redundant "escape" treatment pathways strongly suggest that combinations of therapies with different but complementary mechanisms of action are considered the best way to improve efficiency, slow disease progression, and even reverse NASH[7].

Alkhouri *et al*[12] conducted a phase 2 clinical trial to validate the potential value of combination therapy[7]. The results of this experiment showed that GLP-1 RA in combination with antifibrotic drug therapy [cilofexor (nonsteroidal FXR agonist)/firsocostat (carboxylase inhibitor)] demonstrates greater improvement in hepatic steatosis, liver biochemistry, and noninvasive fibrosis measured by the magnetic resonance imaging-estimated proton density fat fraction, despite similar weight loss (7%-10%) compared to semaglutide monotherapy[12-15]. The role of GLP-1 RAs is undeniable, and combinations of GLP-1 RAs and other incretin receptor agonists have been developed with good results [16]. Cotadutide, a GLP-1R/GcgR agonist, significantly improves glucose tolerance and decreases C3M plasma levels and P4NP7S circulating levels compared to liraglutide and obeticholic acid in biological experiments[17]. Tirzepatide, a dual agonist of GLP-1 and glucose-dependent insulinotropic polypeptide receptors, has associated therapeutic effects and can induce significant weight loss, improve glycaemic control, and improve plasma lipids in trials related to the treatment of obesity and diabetes[16,18]. In addition, the new drugs lanifibranor (a pan-PPAR agonist) and Aramchol (a partial inhibitor of hepatic stearoyl-CoA desaturase) have performed well as an antifibrotic therapy for NASH, but it is unclear whether there is an unintended effect when combined with GLP-1 RAs[7,19].

Although GLP-RA monotherapy does not perform well as an antifibrotic therapy, it is undeniable that its associated combinations have a role in NASH. In addition, GLP-1RAs have outstanding performance in fat loss, weight loss, and improvement of insulin resistance and have a potential protective effect against the complications of NASH. Thus, we should pay closer attention to GLP-1RAs.

FOOTNOTES

Author contributions: Yin YH, Sang LX and Chang B wrote this letter.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Country/Territory of origin: China

ORCID number: Yue-Hua Yin 0009-0002-8560-9984; Li-Xuan Sang 0000-0002-4562-0022; Bing Chang 0000-0003-1965-5827.

S-Editor: Qu XL
L-Editor: A
P-Editor: Qu XL

REFERENCES

1 **Zhu K**, Kakkar R, Chahal D, Yoshida EM, Hussaini T. Efficacy and safety of semaglutide in non-alcoholic fatty liver disease. *World J Gastroenterol* 2023; **29**: 5327-5338 [PMID: 37899788 DOI: 10.3748/wjg.v29.i37.5327]
2 **Stower H**. Therapy for NASH. *Nat Med* 2021; **27**: 21 [PMID: 33442011 DOI: 10.1038/s41591-020-01219-z]
3 **Ahmed NR**, Kulkarni VV, Pokhrel S, Akram H, Abdelgadir A, Chatterjee A, Khan S. Comparing the Efficacy and Safety of Obeticholic Acid and Semaglutide in Patients With Non-Alcoholic Fatty Liver Disease: A Systematic Review. *Cureus* 2022; **14**: e24829 [PMID: 35693370 DOI: 10.7759/cureus.24829]
4 **Majzoub AM**, Nayfeh T, Barnard A, Munaganuru N, Dave S, Singh S, Murad MH, Loomba R. Systematic review with network meta-analysis: comparative efficacy of pharmacologic therapies for fibrosis improvement and resolution of NASH. *Aliment Pharmacol Ther* 2021; **54**: 880-889 [PMID: 34435378 DOI: 10.1111/apt.16583]
5 **Newsome PN**, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, Sanyal AJ, Sejling AS, Harrison SA; NN9931-4296 Investigators. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. *N Engl J Med* 2021; **384**: 1113-1124 [PMID: 33185364 DOI: 10.1056/NEJMoa2028395]
6 **Mantovani A**, Byrne CD, Targher G. Efficacy of peroxisome proliferator-activated receptor agonists, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors for treatment of non-alcoholic fatty liver disease: a systematic review. *Lancet Gastroenterol Hepatol* 2022; **7**: 367-378 [PMID: 35030323 DOI: 10.1016/S2468-1253(21)00261-2]
7 **Fraile JM**, Palliyil S, Barelle C, Porter AJ, Kovaleva M. Non-Alcoholic Steatohepatitis (NASH) - A Review of a Crowded Clinical Landscape, Driven by a Complex Disease. *Drug Des Devel Ther* 2021; **15**: 3997-4009 [PMID: 34588764 DOI: 10.2147/DDDT.S315724]
8 **Musso G**, Cassader M, Paschetta E, Gambino R. Thiazolidinediones and Advanced Liver Fibrosis in Nonalcoholic Steatohepatitis: A Meta-analysis. *JAMA Intern Med* 2017; **177**: 633-640 [PMID: 28241279 DOI: 10.1001/jamainternmed.2016.9607]
9 **Armstrong MJ**, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, Hazlehurst JM, Guo K; LEAN trial team, Abouda G, Aldersley MA, Stocken D, Gough SC, Tomlinson JW, Brown RM, Hübscher SG, Newsome PN. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet* 2016; **387**: 679-690 [PMID: 26608256 DOI: 10.1016/S0140-6736(15)00803-X]
10 **Kongmalai T**, Srinonprasert V, Anothaisintawee T, Kongmalai P, McKay G, Attia J, Thakkinstian A. New anti-diabetic agents for the treatment of non-alcoholic fatty liver disease: a systematic review and network meta-analysis of randomized controlled trials. *Front Endocrinol (Lausanne)* 2023; **14**: 1182037 [PMID: 37441498 DOI: 10.3389/fendo.2023.1182037]
11 **Gu Y**, Sun L, Zhang W, Kong T, Zhou R, He Y, Deng C, Yang L, Kong J, Chen Y, Shi J, Hu Y. Comparative efficacy of 5 sodium-glucose cotransporter protein-2 (SGLT-2) inhibitor and 4 glucagon-like peptide-1 (GLP-1) receptor agonist drugs in non-alcoholic fatty liver disease: A GRADE-assessed systematic review and network meta-analysis of randomized controlled trials. *Front Pharmacol* 2023; **14**: 1102792 [PMID: 36992825 DOI: 10.3389/fphar.2023.1102792]
12 **Alkhouri N**, Herring R, Kabler H, Kayali Z, Hassanein T, Kohli A, Huss RS, Zhu Y, Billin AN, Damgaard LH, Buchholtz K, Kjær MS, Balendran C, Myers RP, Loomba R, Noureddin M. Safety and efficacy of combination therapy with semaglutide, cilofexor and firsocostat in patients with non-alcoholic steatohepatitis: A randomised, open-label phase II trial. *J Hepatol* 2022; **77**: 607-618 [PMID: 35439567 DOI: 10.1016/j.jhep.2022.04.003]
13 **Younis IR**, Kirby BJ, Billin AN, Xiao D, Song Q, Watkins TR, Othman AA. Pharmacokinetics, pharmacodynamics, safety and tolerability of cilofexor, a novel nonsteroidal Farnesoid X receptor agonist, in healthy volunteers. *Clin Transl Sci* 2023; **16**: 536-547 [PMID: 36573450 DOI: 10.1111/cts.13469]
14 **Loomba R**, Kayali Z, Noureddin M, Ruane P, Lawitz EJ, Bennett M, Wang L, Harting E, Tarrant JM, McColgan BJ, Chung C, Ray AS, Subramanian GM, Myers RP, Middleton MS, Lai M, Charlton M, Harrison SA. GS-0976 Reduces Hepatic Steatosis and Fibrosis Markers in Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology* 2018; **155**: 1463-1473.e6 [PMID: 30059671 DOI: 10.1053/j.gastro.2018.07.027]
15 **Targher G**, Mantovani A, Byrne CD. Mechanisms and possible hepatoprotective effects of glucagon-like peptide-1 receptor agonists and other incretin receptor agonists in non-alcoholic fatty liver disease. *Lancet Gastroenterol Hepatol* 2023; **8**: 179-191 [PMID: 36620987 DOI: 10.1016/S2468-1253(22)00338-7]
16 **Boland ML**, Laker RC, Mather K, Nawrocki A, Oldham S, Boland BB, Lewis H, Conway J, Naylor J, Guionaud S, Feigh M, Veidal SS, Lantier L, McGuinness OP, Grimsby J, Rondinone CM, Jermutus L, Larsen MR, Trevaskis JL, Rhodes CJ. Resolution of NASH and hepatic fibrosis by the GLP-1R/GcgR dual-agonist Cotadutide *via* modulating mitochondrial function and lipogenesis. *Nat Metab* 2020; **2**: 413-431 [PMID: 32478287 DOI: 10.1038/s42255-020-0209-6]
17 **Valenzuela-Vallejo L**, Guatibonza-García V, Mantzoros CS. Recent guidelines for Non-Alcoholic Fatty Liver disease (NAFLD)/ Fatty Liver Disease (FLD): Are they already outdated and in need of supplementation? *Metabolism* 2022; **136**: 155248 [PMID: 35803320 DOI: 10.1016/j.metabol.2022.155248]
18 **Francque SM**, Bedossa P, Ratziu V, Anstee QM, Bugianesi E, Sanyal AJ, Loomba R, Harrison SA, Balabanska R, Mateva L, Lanthier N, Alkhouri N, Moreno C, Schattenberg JM, Stefanova-Petrova D, Vonghia L, Rouzier R, Guillaume M, Hodge A, Romero-Gómez M, Huot-

Marchand P, Baudin M, Richard MP, Abitbol JL, Broqua P, Junien JL, Abdelmalek MF; NATIVE Study Group. A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH. *N Engl J Med* 2021; **385**: 1547-1558 [PMID: 34670042 DOI: 10.1056/NEJMoa2036205]

19 **Ratziu V**, de Guevara L, Safadi R, Poordad F, Fuster F, Flores-Figueroa J, Arrese M, Fracanzani AL, Ben Bashat D, Lackner K, Gorfine T, Kadosh S, Oren R, Halperin M, Hayardeny L, Loomba R, Friedman S; ARREST investigator study group, Sanyal AJ. Aramchol in patients with nonalcoholic steatohepatitis: a randomized, double-blind, placebo-controlled phase 2b trial. *Nat Med* 2021; **27**: 1825-1835 [PMID: 34621052 DOI: 10.1038/s41591-021-01495-3]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com