Clinics and Research in Hepatology and Gastroenterology (2017) 41, 284—295

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

ORIGINAL ARTICLE

Efficacy and safety of glucagon-like peptide-1 receptor agonists in non-alcoholic fatty liver disease: A systematic review and meta-analysis

Yajie Dong[a,1], Qingguo Lv[a,1], Sheyu Li[a,1], Yuan Wu[a], Ling Li[b], Juan Li[a], Fang Zhang[a], Xin Sun[b], Nanwei Tong[a,*]

[a] *Department of Endocrinology and Metabolism, West China Hospital of Sichuan University, No. 37 Guoxue Road, Chengdu, Sichuan 610041, China*
[b] *Chinese Evidence-Based Medicine Center, West China Hospital of Sichuan University, Chengdu, Sichuan, China*

Available online 5 January 2017

Summary
Background and objective: New drugs are urgently needed for the treatment of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). The aim of this meta-analysis was to evaluate the efficacy and safety of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in NAFLD/NASH.
Methods: We searched the MEDLINE, Embase, and Cochrane Library Central to identify randomized controlled trials (RCTs) and observational studies that compared GLP-1RAs with a control treatment or baseline values with respect to efficacy and safety in patients with NAFLD/NASH. Mean differences (MDs) with 95% confidence intervals (CIs) and odds ratios (ORs) were pooled using a random-effect model.
Results: Six studies were eligible and included. Among the 329 NAFLD/NASH patients included in these studies, 277 patients had type 2 diabetes (T2D). GLP-1RA treatment produced significant reductions relative to baseline in liver histology scores for steatosis (MD, 0.80; 95% CI, 0.49 to 1.11), lobular inflammation (MD, 0.22; 95% CI, 0.00 to 0.45), hepatocellular ballooning (MD, 0.41; 95% CI, 0.15 to 0.67) and fibrosis (MD, 0.35; 95% CI, 0.00 to 0.70). Compared with

Abbreviations: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; GLP-1RAs, glucagon-like peptide-1 receptor agonists; RCT, randomized controlled trial; MD, mean difference; CI, confidence interval; OR, odds ratio; T2D, type 2 diabetes; GGT, gamma-glutamyl transpeptidase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SD, standard deviation.

* Corresponding author.
E-mail address: buddyjun@hotmail.com (N. Tong).

[1] Yajie Dong, Qingguo Lv, and Sheyu Li contributed equally to this work and share first authorship.

http://dx.doi.org/10.1016/j.clinre.2016.11.009

placebo and positive agents, GLP-1RAs significantly reduced gamma-glutamyl transpeptidase (GGT) levels (MD, 13.8 U/L; 95% CI, 7.4 to 20.3; $P < 0.001$). The reported major adverse events associated with GLP-1RA treatment included mild to moderate gastrointestinal discomfort that resolved within a few weeks.

Conclusions: Our study suggests that in NASH patients, particularly patients with diabetes, GLP-1RAs may improve liver histology and reduce aminotransferase levels from baseline. Benefits of GLP-1RAs are considered to outweigh the risks in NAFLD/NASH patients with or without diabetes.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of conditions of macrovesicular hepatic steatosis unrelated to alcohol consumption [1]. Non-alcoholic steatohepatitis (NASH) is considered the progressive form of NAFLD, characterized by steatosis with hepatocyte ballooning degeneration, lobular inflammation, and perivenular, perisinusoidal collagen deposition [2]. The prevalence of NAFLD ranges from 20 to 40% worldwide [3,4], with approximately 9 to 20% of NASH patients progressing to cirrhosis, one-third of whom will die from various complications, including liver failure and hepatocellular carcinoma, or will require liver transplantation [5,6]. Despite its increased prevalence in recent years, the true prevalence of NAFLD/NASH remains underestimated [1,7].

As a non-communicable chronic disease, the occurrence and progression of NAFLD/NASH are closely related to various metabolic disorders, particularly obesity and diabetes, which are associated with excess risks of arteriosclerotic cardiovascular disease. High body mass index and diabetes are essential pathophysiological factors in NAFLD/NASH [8,9] and represent two independent predictors of fibrotic progression in NAFLD [10].

The glucagon-like peptide-1 receptor agonist (GLP-1RA) liraglutide, which has significant effects on glycemic control [11] and weight loss [12,13], is licensed for type 2 diabetes (T2D) treatment and weight management in overweight and obese adults in the presence of metabolic disorders. A review suggests that the GLP-1RA lixisenatide reduces alanine aminotransferase (ALT) levels in obese or overweight patients with T2D [14]. Moreover, recent studies have shown that GLP-1RAs have direct effects on hepatocytes because they suppress de novo lipogenesis and nutrient-induced hepatic pro-inflammatory responses in mouse models [15,16].

However, the effects of GLP-1RAs on NAFLD/NASH remain unknown [1]. We conducted this systematic review to evaluate the efficacy and safety of GLP-1RAs in patients with NAFLD/NASH.

Methods

This systematic review and meta-analysis was conducted in accordance with the PRISMA guidelines [17].

Literature search

Two authors (Y.W. and L.L.) independently conducted literature searches of the MEDLINE (January 1966 to February 2016) and Embase (January 1974 to February 2016) databases and the Cochrane Central Register of Controlled Trials in the Cochrane Library (Issue 1, January 2016). Search terms included medical subject headings and keywords that were related to NAFLD/NASH and GLP-1RAs (see Supplemental digital content 1, which illustrates search strategies).

Inclusion criteria

The inclusion criteria were as follows: (a) population: patients with a definitive diagnosis of NAFLD or NASH established by liver biopsy or imaging; (b) intervention: an examination of GLP-1RA treatment; (c) control: placebo, other active agents or no control; (d) outcomes: mean change from baseline scores for liver histology (including steatosis [0—3], hepatocellular ballooning [0—2], lobular inflammation [0—2], and fibrosis [0—4]) [18], the rate of improvement of liver histology, or effects on the levels of aminotransferases (including ALT, aspartate aminotransferase [AST], and gamma-glutamyl transpeptidase [GGT]); and (e) study design: a randomized controlled trial (RCT) or an observational study. Studies with quantitative data for liver histology and aminotransferase levels were eligible and included in the meta-analysis.

Data extraction

Two authors (Y.W. and L.L.) independently extracted data regarding the following characteristics of the included studies: first author, publication year, study design, sample size, patient characteristics, intervention strategy (regimen, dosage, route, and duration), control (placebo or other), change in liver histology, change in aminotransferase levels, and other outcome data. Extracted data were entered into a standardized Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington, USA) file and were verified by another author (J.L.). Any disagreements were resolved by discussion and consensus.