Effect of Glucagon-like Peptide-1 Receptor Agonists on Lipid Profiles Among Type 2 Diabetes: A Systematic Review and Network Meta-analysis

Feng Sun, PhD*,[1,2]; Shanshan Wu, MPH[1,*]; Jing Wang, MSc[1]; Shuxia Guo, MPH[2]; Sanbao Chai, PhD[3]; Zhirong Yang, MPH[1,4]; Lishi Li, MSc[1,5]; Yuan Zhang, MPH[1]; Linong Ji, PhD[6]; and Siyan Zhan, PhD[1]

[1]Department of Epidemiology and Biostatistics, School of Public Health, Peking University Health Science Center, Beijing, China; [2]Department of Preventive Medicine, College of Medicine, Shihezi University, Shihezi, China; [3]Department of Physiology, Capital Medical University, Beijing, China; [4]Shantou-Oxford Clinical Research Unit, Shantou University Medical College, Guangdong, China; [5]Department of Statistics, Graduate School of Arts and Sciences, Columbia University, New York, New York; and [6]Department of Endocrinology and Metabolism, People's Hospital, Peking University, Beijing, China

ABSTRACT

Purpose: The goal of this study was to assess the effect of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on lipid profiles in patients with type 2 diabetes.

Methods: The MEDLINE, Embase, Cochrane Library, and ClinicalTrials.gov databases were searched from inception through October 31, 2013. Randomized controlled trials with available data were selected if they compared GLP-1 RAs with placebo and traditional antidiabetic drugs with a duration ≥8 weeks. The weighted mean difference for changes in lipid profiles was estimated by using the random effects model, and a network meta-analysis was performed to supplement direct comparisons.

Findings: Thirty-five trials with 13 treatments were included in the analysis. GLP-1 RAs decreased HDL-C with a range of –0.06 mmol/L (95% CI, –0.11 to –0.01) to –0.13 mmol/L (95% CI, –0.17 to –0.10) compared with thiazolidinediones, whereas thiazolidinediones were associated with a significant increase in HDL-C compared with placebo (0.09 mmol/L [95% CI, 0.06 to 0.12]). A significant reduction in LDL-C was detected for all GLP-1 RAs versus placebo (range, –0.08 to –0.16 mmol/L), insulin (range, –0.10 to –0.19 mmol/L), and thiazolidinediones (range, –0.16 to –0.24 mmol/L). Exenatide, liraglutide 1.8 mg once daily, and taspoglutide decreased total cholesterol with a range of –0.16 mmol/L (95% CI, –0.26 to –0.06) to –0.27 mmol/L (95% CI, –0.41 to –0.12) versus placebo and thiazolidinediones (range, –0.26 to –0.37 mmol/L). The decreased effect was more evident in exenatide long-acting release and liraglutide 1.8 mg once daily. A significant reduction in triglyceride levels was observed with liraglutide 1.8 mg once daily (–0.30 mmol/L [95% CI, –0.49 to –0.11]) and taspoglutide 20 mg once weekly (–0.17 mmol/L [95% CI, –0.31 to –0.01]) versus placebo.

Implications: GLP-1 RAs were associated with modest reductions in LDL-C, total cholesterol, and triglycerides but no significant improvement in HDL-C. Further evidence is needed to determine if improvements in lipid profiles might translate into reductions in cardiovascular outcomes. (*Clin Ther.* 2015;37:225–241)

Key words: GLP-1 receptor agonists, lipid profiles, network meta-analysis, type 2 diabetes.

INTRODUCTION

An increasing number of patients with type 2 diabetes mellitus (T2DM) are being treated with glucagon-like peptide-1 receptor agonists (GLP-1 RAs).[1,2] As a new class of antidiabetic agents based on incretin therapy, GLP-1 RAs can stimulate insulin secretion, improve

Accepted for publication November 11, 2014.
http://dx.doi.org/10.1016/j.clinthera.2014.11.008
0149-2918/$ - see front matter

*These authors contributed equally to this work.

insulin resistance, and slow gastrointestinal motility.[3–5] Exenatide* and liraglutide,† the two earliest GLP-1 RAs, were approved by the US Food and Drug Administration in 2005 and 2010, respectively.[6,7] Albiglutide‡ and lixisenatide§ were approved by the European Medicines Agency in 2013. Taspoglutide is currently in Phase III clinical trials.

Given the insulin-resistant state and metabolic disturbances among patients with T2DM, dyslipidemia is a common comorbidity.[8] The typical lipid profile in T2DM patients usually includes decreased HDL-C and elevated LDL-C, triglycerides (TG), and total cholesterol (TC). The combination of a poorly controlled lipid profile and blood glucose level plays an important role in the pathogenesis of atherosclerosis; this combination greatly increases the risk of cardiovascular complications such as heart failure, myocardial infarction, and stroke, as well as total mortality.[8–12] According to the Quebec Cardiovascular Study, the combination of diabetes, elevated small dense LDL-C, and elevated apolipoprotein B synergistically confers a 20-fold increased risk for cardiovascular events.[12] Treatment guidelines recommend aggressive management of lipid profiles; such treatment is believed to be associated with a comprehensive risk reduction in cardiovascular disease.[9–11] Therefore, in addition to adequate glycemic control, it is critical for T2DM patients to better manage these cardiovascular risk factors (including HDL-C, LDL-C, TC, and TG) to achieve favorable cardiovascular safety profiles. Interestingly, several clinical trials for GLP-1 RAs have shown an improvement in lipid profiles, although the mechanisms are not clearly understood. Similar results were indicated in a meta-analysis of the LEAD-6 (Liraglutide Effect and Action in Diabetes) trials for liraglutide.[13] However, these studies were all evaluations of head-to-head comparisons of various GLP-1 RAs versus placebo or active comparator drugs, and most of them only evaluated exenatide and liraglutide. Thus far, few studies included all kinds of GLP-1 RAs simultaneously to assess if there are differences in lipid profiles between any two of them. In addition, no study evaluated the impact of different dosages on lipid profiles within each GLP-1 RA.

The goal of the present study was to summarize the current evidence of GLP-1 RAs on lipid profiles in patients with T2DM. An additional network meta-analysis was conducted to assess the robustness of the pairwise meta-analysis, supplement missing evidence of head-to-head comparisons by combining both direct and indirect evidence, and rank treatments in the evidence network.

MATERIALS AND METHODS

Search Strategy

The MEDLINE, Embase, and Cochrane Library databases were searched from inception to October 31, 2013. The following search strategy for Ovid-MEDLINE was adapted for other databases: (1) exp glucagon-like peptide-1 agonists/; (2) (glucagon like peptide* or GLP-1).tw.; (3) (exenatide or liraglutide).tw.; (4) randomized controlled trial.pt.; (5) (randomized or randomised).tw.; and (6) (1 or 2 or 3) and (4 or 5). In addition, completed but unpublished trials were identified from the ClinicalTrials.gov website by using a similar search strategy. The bibliographies of published systematic reviews[13,14] were also searched.

Study Selection

Only randomized controlled trials with available data on lipid profiles in which GLP-1 RAs were compared with placebo, active antidiabetic drugs, or other kinds of GLP-1 RAs in patients with T2DM were included in the analysis. The duration of trials was at least 8 weeks. Any ongoing or completed studies but with no results on the ClinicalTrials.gov website were excluded from the analysis. The eligibility of studies for inclusion criteria was assessed independently by 4 reviewers (S.S.W., Z.R.Y., Y.Z., and S.B.C.) in duplicate.

Clinical Dosage of GLP-1 RAs

Only dose arms that are likely to be used in routine clinical practice were included in the analysis. Trials or arms using nonstandard dosages, especially those from dose-ranging studies, were excluded. The standard exenatide regimens are 5 μg BID (EX5BID), 10 μg BID (EX10BID), and 2 mg once weekly (EXELAR).

*Trademark: Byetta® (Eli Lilly & Co, Indianapolis, Indiana).
†Trademark: Victoz® (Novo Nordisk Inc, Plainsboro, New Jersey).
‡Trademark: Eperzan® (GlaxoSmithKline, Research Triangle Park, North Carolina).
§Trademark: Lyxumia® (Sanofi US, Bridgewater, New Jersey).