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REVIEW

Clinical Effectiveness of Liraglutide in Type 2 Diabetes Treatment in the Real-World Setting: A Systematic Literature Review

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ABSTRACT

Introduction: In clinical trials, liraglutide has proven to be an effective drug for the treatment of type 2 diabetes mellitus (T2DM). The real-world effectiveness of liraglutide has been investigated in numerous studies. The aim of this systematic literature review is to collate evidence on the real-world clinical effectiveness of liraglutide.

Methods: A review of publications from Medline, EMBASE, the Cochrane Library, and conference proceedings was conducted to identify observational studies that assessed the clinical effectiveness of liraglutide in real-world clinical practice. This review was conducted according to the National Institute of Health and Care Excellence (NICE) guidance. No language or time limits were applied, except to the conference proceedings (2013–2015). Endpoints for data extraction were decided a priori. Study quality appraisal was done for full-text journal articles.

Results: Of 124 publications included in the review, 43 were full-text articles. Liraglutide significantly reduces glycated hemoglobin (HbA1c) within 6 months of initiating treatment (mean change in HbA1c from baseline: −0.9% to −2.2%; HbA1c <7.0%: 29.5–65.0%). The NICE composite endpoint (HbA1c reduction ≥1% and weight reduction ≥3%) was met in 16.9–47.0% of patients with liraglutide treatment. Liraglutide therapy led to a mean change in absolute weight from baseline of −1.3 to −8.65 kg. Liraglutide treatment was well tolerated in patients with T2DM. The rate of occurrence of hypoglycemia with liraglutide monotherapy was ≤0.8%. Hypoglycemia was more common in patients taking antidiabetic medications (0.0–15.2%) together with liraglutide. The

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beneficial glycemic and weight effect of liraglutide therapy in patients with T2DM was maintained for at least 12 months.

Conclusion: Evidence from observational studies reflecting real-world clinical practice demonstrates that liraglutide therapy improves glycemic control with a low risk of hypoglycemia, and is associated with significant weight loss in patients with T2DM. These observations are consistent with clinical trial findings.

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Keywords: Effectiveness; HbA1c; Hypoglycemia; Liraglutide; Literature review; Real-world evidence; Safety; Type 2 diabetes; Weight

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by increased blood glucose levels, i.e., hyperglycemia, which over time can cause microvascular and macrovascular complications [1]. The main goal of T2DM treatment is to achieve and maintain patients' individual target blood glucose levels, thus reducing the occurrence of complications [2].

There are several guidelines for the management of T2DM including those developed by the International Diabetes Federation (IDF) [3], the American Diabetes Association (ADA) [4], the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) [5], and the National Institute of Health and Care Excellence (NICE) from the UK [6]. The treatment recommendations are generally consistent but with some differences. For example, the ADA and the European Association for the Study of Diabetes (EASD) suggest a treatment algorithm for patients with T2DM [7] which suggests that patients with T2DM should initially be offered education in lifestyle changes, with advice to lose weight by changing dietary habits and increasing physical activity. If a patient's blood glucose level is not decreased to, and maintained at, the individualized target glycated hemoglobin (HbA1c) levels [7], it is recommended that medical treatment with anti-diabetic drugs be initiated. Over the years, glucagon-like peptide (GLP-1) receptor agonists (RAs) have become integral as second- or third-line therapies in many treatment guidelines, such as the ADA/EASD, the AACE, and the IDF [3–7].

GLP-1 RAs are one among many treatment options available for patients with T2DM. GLP-1 RAs mimic the effects of endogenous GLP-1, which regulates plasma glucose levels by stimulating the secretion and biosynthesis of insulin and by inhibiting the secretion of glucagon and by delaying the gastric emptying of food and reducing food intake [8, 9]. Based on this mechanism of action, GLP-1 RA has effects on controlling glucose level and reducing body weight. Liraglutide was the second GLP-1 RA that was approved for the treatment of T2DM by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) in 2009 and 2010, respectively. Currently, liraglutide is the most used GLP-1 RA worldwide [10]. The efficacy and safety of liraglutide mono- and combination therapy have been evaluated in the Liraglutide Effect and Action in Diabetes (LEAD) clinical program which consisted of six clinical trials [11–16], and recently a clinical trial comparing liraglutide head-to-head with lixisenatide was finalized [17]. There exist a number of different clinical trials on the efficacy of liraglutide, among others comparative trials vs. albiglutide

[18], dulaglutide [19], exenatide [20], sitagliptin [21, 22], switching to GLP-1 RA from sitagliptin [23] and with other oral antidiabetic drugs (OADs; dipeptidyl peptidase-4 inhibitors [DPP-4i], sulfonylurea [SU], glinide, metformin [MET], α-glucosidase inhibitor, or thiazolidinedione [TZD]) [24]. Furthermore, one Japanese trial assessed liraglutide in combination with insulin [25]. Results from all these trials consistently showed that patients treated with liraglutide had significantly improved glycemic control (with a high proportion of patients reaching HBA1c <7.0% at the end of the trial) and achieved substantial reductions in absolute body weight. Importantly, these beneficial effects of liraglutide occurred with a low risk of hypoglycemia, and the drug was well tolerated in patients with T2DM [11–25].

Established as a drug with robust clinical efficacy and safety profile in controlled settings, the clinical effectiveness and safety of liraglutide for the treatment of patients with T2DM have also been investigated in observational studies reflecting real-life clinical practice. We performed a systematic literature review to evaluate the effectiveness of liraglutide for the treatment of patients with T2DM in real-world clinical practice. The goal of the review is to provide a succinct overview of the evidence on the clinical effectiveness of liraglutide which could help guide clinical decision making and assist clinicians in deciding how different therapies fit into the current treatment algorithm, and help inform current and future treatment guidelines for the management of patients with T2DM.

METHODS

This systematic literature review was conducted in accordance with the NICE guidance to obtain relevant information using a consistent, reproducible, and transparent methodology [26]. According to this guidance, this process involves the development of a study protocol (see supplementary file 1), parallel review of retrieved publications by two independent researchers for the selection of relevant publications, followed by a full-evidence data extraction and quality assessment of study methodology, results, and implication of results to routine T2DM clinical practice.

Search Strategy

To collect evidence on the effectiveness of liraglutide, different databases were selected. These included Medline (1979–2016) and EMBASE (1974–2016; searched simultaneously via ProQuest), Cochrane (1992–2016; Cochrane Database of Systematic Reviews [CDSR]; Database of Abstracts of Reviews of Effects [DARE]; Cochrane Methodology Register [CMR]; Health Technology Assessments Database [HTA]; and The National Health Services [NHS] Economic Evaluation Database [EED]), health technology assessment websites, and conference proceedings (International Society for Pharmacoeconomics and Outcomes Research [ISPOR], ADA, EASD, World Diabetes Congress-IDF [WDC-IDF]).

The search terms included both free-text and Emtree/MeSH terms of indication, clinical effectiveness, comparative effectiveness, generic and brand name of liraglutide, and were designed to meet the requirements outlined in NICE guidelines for the methods of technology appraisal [26]. Complex search strings, combining extensive lists of search terms for indication and topic, were used to search the databases through ProQuest. For other databases, less complex search strings

were used as the search engines provided fewer options. In all databases, no language or time limits were applied to ensure that no relevant publications were missed. The annual meeting abstracts were only searched for the last 3 years (up until 2015), because it was assumed that after 3 years these would have been published as full publications in a peer-reviewed journal. The search terms that were applied per database are provided in the study protocol (see supplementary file 1).

The database searches were executed on October 13, 2015 and an updated search in ProQuest was conducted on January 7, 2016.

Eligibility Criteria

After all the searches were performed, the results were screened (based on title and abstract followed by full-text review) in parallel by two independent researchers after the removal of duplicate publications. If the researchers could not reach agreement on the selection of a relevant publication, a third independent researcher was consulted to decide eligibility of the publication for the review. The inclusion and exclusion criteria for the screening and selection process are provided in Table 1.

Data Extraction and Assessment of Study Quality

The data extraction of selected studies was performed by one researcher (AO). A second researcher performed a thorough quality check to assure all relevant data were extracted to the correct parameter (WX). Endpoints for data extraction were decided a priori. These primarily included effectiveness (glucose control and weight) and if the studies identified in the literature search reported safety endpoints (hypoglycemia, adverse events [AEs], serious AEs) related to liraglutide treatment for patients with T2DM, then these were also included. No statistical analyses were performed.

Following data extraction, a critical appraisal of the quality of selected studies was performed by a single researcher (AO), and reviewed by a second researcher (WX). This quality assessment was completed for all selected observational studies that were published in full text based on the recommendations of the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in healthcare [27]. The quality of full-text publications was subjectively evaluated based on several criteria including completeness of reporting, study population and design, sample size, sampling procedure, study follow-up duration, treatment setting, patient inclusion and exclusion criteria and patient enrollment and study completion rates. In addition to this, quality appraisal was further informed by assessing potential sources of confounding and biases (e.g., patient baseline characteristics, misclassification, selection bias, reporting bias, etc.) which are known to be prominent in observation studies. The limitations described in the individual articles from the authors' perspective were also used to guide the quality appraisal. The quality assessment of abstracts was not performed as study details were not adequately reported.

Data Reporting

The results section focuses mainly on the findings from full-text journal publications identified in the systematic literature review. These findings are supplemented with supportive evidence from the conference abstracts. This approach for presentation was chosen because full-text publications are peer

Table 1 Study eligibility criteria

Item	Inclusion criteria	Exclusion criteria
Population	Patients with T2DM	Type 1 diabetes mellitus
		Gestational diabetes
		Other diseases
Intervention	Treatment regimens including liraglutide	Insulin therapy
		NIADs
Comparator	Treatment regimens including NIADs	Insulin therapy
	TZD (e.g., pioglitazone)	
	DPP-4i (e.g., sitagliptin or saxagliptin)	
	SGLT2 inhibitor (e.g., dapagliflozin or canagliflozin)	
	GLP-1 RA (e.g., exenatide, albiglutide, or dulaglutide)	
	MET	
	SU	
	Other OADs	
Outcomes	Clinical effectiveness and safety of liraglutide	Studies not reporting the clinical effectiveness/safety of either liraglutide compared to other NIADs
	Comparative effectiveness and safety of liraglutide compared to other NIADs	
Study design	Chart review	RCT
	Medical record analysis	Case-reports
	Database analysis	Letters to editor
	Expert panel studies	
	Prospective follow-up studies	
	Post-marketing surveillance studies	
Location	All	None
Language	All	None

DPP-4i dipeptidyl peptidase-4 inhibitor, *GLP* glucagon-like peptide, *MET* metformin, *NIAD* non-insulin antidiabetic drug, *OAD* oral antidiabetic drug, *RA* receptor agonist, *RCT* randomized controlled trials, *SGLT2* sodium-glucose cotransporter type-2, *SU* sulfonylurea, *T2DM* type 2 diabetes mellitus, *TZD* thiazolidinedione

reviewed and considered to be of higher quality than abstracts from annual conference proceedings as complete methodological details and results are reported in full-text articles.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of

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