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REVIEW ARTICLE

The efficacy and safety of liraglutide

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Abstract *Aim of the review* To systematically analyze the efficacy and safety of liraglutide for the treatment of diabetes mellitus in comparison to other mono- and combination therapies. *Method* PubMed (any date) and EMBASE (all years) search was conducted with liraglutide as a search term. Phase III clinical trials retrieved by the two databases and resources posted in Drug@FDA website were evaluated with regard to outcomes of efficacy and safety. *Results* Eight Phase III clinical studies compared the efficacy and safety of liraglutide to other monotherapies or combinations. Liraglutide as monotherapy in doses of 0.9 mg or above showed a significantly superior reduction in HbA1C compared to monotherapies with glimepiride or glyburide. When liraglutide was used as add-on therapy to glimepiride in doses of 1.2 mg or above, the reduction of HbA1C was greater than that in the combination therapy of glimepiride and rosiglitazone. However, liraglutide as add-on therapy to metformin failed to show benefit over combination of metformin and glimepiride. Triple therapy of using liraglutide in addition to metformin plus either glimepiride or rosiglitazone resulted in additional benefit in HbA1C reduction. Most common adverse events were gastrointestinal disturbance such as nausea, vomit, diarrhea, and constipation. During the eight clinical studies, six cases of pancreatitis and five cases of cancer were reported in liraglutide arm, whereas there was one case of each of pancreatitis in exenatide and glimepiride arms, respectively, and one case of cancer in metformin plus sitagliptin arm. *Conclusion* Liraglutide is a new therapeutic option to improve glycemic control in patients with type 2 diabetes. However, the present lack of evidence of durability of efficacy and long-term safety appear to limit its utility in the general treatment of type 2 diabetes at this time.

Keywords Adverse events · Diabetes mellitus · HbA1C · Liraglutide · Safety · Type 2 diabetes

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Impact of findings on practice

- Reduction in HbA1C under the influence of liraglutide takes place over the first 8–12 weeks of treatment, there is no further reduction thereafter.
- Most common adverse events associated with the use of liraglutide are gastrointestinal disorders such as nausea, vomiting, and diarrhoea.
- Since liraglutide is associated with the incidence of pancreatitis, clinicians should use caution for patients with family history of pancreatitis and discontinue treatment if pancreatitis is suspected or confirmed.

Introduction

Liraglutide is a long-acting glucagon-like peptide-1 (GLP-1) analogue with 97% amino acid homology to human endogenous GLP-1 and longer half-life, which makes it suitable for once daily subcutaneous injection [1–5]. Although physiological function of GLP-1 is not clearly understood, it suppresses glucagon secretion, stimulates insulin synthesis and release, and delays gastric emptying [6, 7]. However, potential of GLP-1 for the treatment of type 2 diabetes has been limited since GLP-1 is rapidly

degraded by dipeptidyl peptidase-4 (DPP-4). Liraglutide is a fragment of the naturally occurring human GLP-1 having two modifications: (1) lysine at position 34 replaced by arginine, and (2) addition of palmitic acid to the lysine at position 26. Liraglutide precursor is produced by recombinant DNA technology using *Saccharomyces cerevisiae*, and the precursor is attached with fatty acid (palmitic acid) afterward [8]. This fatty acid enhances protein binding of the drug to serum albumin, protecting it from enzymatic degradation by DPP-4 and rapid excretion by glomerular filtration which, in turn, prolongs half life of the drug [9–11]. Clinical trials of liraglutide were performed by Liraglutide Effects and Action in Diabetes (LEAD) program for the treatment of patients with type 2 diabetes. Liraglutide was approved by the US Food and Drug Administration (FDA) in January 2010 and became available as once daily subcutaneous injection instead of twice daily administration of exenatide which is the first drug in this class.

There have been several reviews published with a general scope such as pharmacology, pharmacokinetics, pharmacodynamics, and drug interactions of liraglutide [12–16]. In this paper, we performed a systematic analysis of the literature with particular attention to the efficacy and safety of the liraglutide in order to provide unbiased drug information for healthcare professionals, researchers, and policy makers.

Aims of the review

The aim of this review was to systematically analyze the efficacy and safety of liraglutide for the treatment of type 2 diabetes as monotherapy and as add-on therapy to other various regimens.

Method

A PubMed (any date) and EMBASE (all years) search was conducted on April 15, 2011 with liraglutide as a search term. Limits for Pubmed search were randomized controlled trial and English in the title/abstract field. Limits for EMBASE search were randomized controlled trial, article, English, and physiology and endocrinology area. Identified studies were divided into relevant studies and others, with relevant studies being Phase III clinical trials for the treatment of type 2 diabetes assessing therapeutic efficacy and safety of liraglutide with sufficient sample size ($n > 300$). The relevant clinical studies were analyzed with regard to study design and outcomes of efficacy and safety. A flow chart of the article retrieval process is shown in Fig. 1. Resources such as printed labeling, chemistry review, pharmacology review, clinical pharmacology and biopharmaceutics review, and medical review posted in Drug@FDA website were also used.

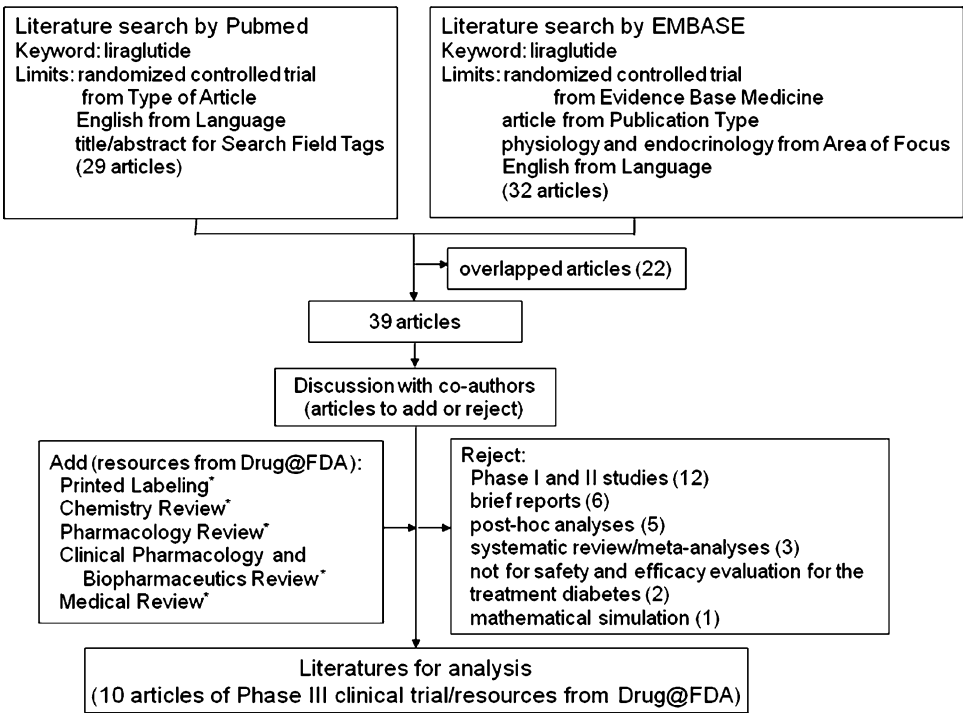

Fig. 1 Flow chart of literature search process and analysis of the data for liraglutide (*posted in Drug@FDA website)

Results

Twenty-nine articles and thirty-two articles were identified by a PubMed and EMBASE search, respectively, with search term and limits described above (Fig. 1). Overlapped articles, Phase I/II clinical studies, brief reports, post hoc studies, systematic review/meta-analyses, and mathematical simulation were rejected, resulting in twelve clinical studies. Two studies were also rejected because one study assessed the efficacy of liraglutide for the treatment of obesity in individuals without type 2 diabetes and the other study assessed only calcitonin response to the treatment with liraglutide. The resulting ten Phase III clinical studies assessed the therapeutic efficacy and safety of liraglutide in the treatment of patients with type 2 diabetes (Table 1) [17–26]. Two of the ten studies were 1- and 2-year extension study results of their original 26-week and 1-year studies, respectively [18, 23].

The primary endpoint in all ten studies was the mean change in hemoglobin A1C (HbA1C) from baseline to the end of the study. Secondary endpoints overlapped considerably and included the proportion of target achievers (defined by HbA1C <7.0% or ≤6.5% at the end of the study), mean changes in fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and body weight. Beta-cell function, safety, and tolerability were also included in the secondary endpoints. The efficacy and safety of liraglutide as monotherapy and add-on therapy are described below and summarized in Tables 2, 3, and 4. Although assessment of beta-cell function was intriguing and challenging, the data is excluded in this review because clinical significance of the assessment is uncertain at present [27].

Liraglutide as monotherapy

Garber et al. compared liraglutide monotherapy to glimepiride monotherapy [17, 18]. Enrollees were type 2 diabetes patients with mean baseline HbA1C and FPG of 8.2% and 9.5 mmol/L (171 mg/dL), respectively. Thirty-six percent of the enrollees had been treated with diet and exercise only, and the rest had been treated with a single oral antidiabetic drug.

Significant reductions in HbA1C and FPG were achieved with liraglutide compared to comparator regimen (Table 2). Proportion of target achievers was dose-dependent and significantly increased in liraglutide arms, with over 50% being achieved by liraglutide 1.8 mg once daily injection. Reduction in HbA1C was more significant in drug-naive participants. Participants switched from an oral antidiabetic drug to liraglutide showed less reduction of HbA1C than did those previously treated with only diet and exercise. HbA1C generally declined over the first 8–12 weeks of treatment. However, further reduction was not found in all treatment arms. In fact, in liraglutide 1.2 mg arm, the value was slightly but significantly ($P = 0.0071$) increased, indicating a rebound phenomenon. Changes in FPG and body weight were also dose-dependent and significant in liraglutide arms compared to glimepiride arm. Two-year extension study result was also in consistent with one-year study.

Seino et al. [19] compared liraglutide monotherapy to glyburide monotherapy in Japan. Glyburide dose was 2.5 mg once a day, but allowed to reduce to 1.875 or 1.25 mg by study protocol. Mean baseline values of HbA1C and FPG of the enrollees were 8.9% and 11.3 mmol/L (203 mg/dL), respectively. Proportion of participants previously treated with a single oral antidiabetic drug was 82%, and the rest were drug-naive.

Significant reduction in HbA1C was achieved with liraglutide compared to glyburide. Changes in FPG, PPG, and body weight were also significantly in favor of liraglutide over glimepiride. Proportion of target achievers in liraglutide arm was significantly higher than that in glyburide arm ($P < 0.0001$). However, in subpopulation of drug-naive participants, there was no significant difference between liraglutide and glyburide arms in terms of HbA1C reduction (−1.8% vs. −1.6%, P value not reported).

Liraglutide as add-on therapy

Marre et al. [20] compared add-on therapy of liraglutide to glimepiride versus glimepiride monotherapy and glimepiride plus rosiglitazone combination therapy. Seventy percent of the participants had been previously treated with combination therapy using oral antidiabetic drugs and the rest had been on monotherapy.

In overall population, the reduction in HbA1C in liraglutide arms was significant compared to glimepiride monotherapy arm (Table 3). However, it was not significant at the low dose of liraglutide compared to glimepiride plus rosiglitazone arm. The extent of HbA1C reduction was greater in the subpopulation of the patients previously on monotherapy compared to those previously on combination therapy. Proportion of target achievers and mean changes in FPG and PPG were significantly greater in all three liraglutide arms versus glimepiride monotherapy arm.

Nauck et al. [21] compared add-on therapy of liraglutide to metformin versus metformin monotherapy and metformin plus glimepiride combination therapy. In overall population, significant reductions in HbA1C were achieved with all doses of liraglutide compared to metformin monotherapy. However, the addition of liraglutide to metformin failed to show superiority over metformin plus glimepiride. Change in body weight was the only parameter which was in favor of the add-on therapy of liraglutide over metformin plus glimepiride.

Table 1 Summary of study designs for the eight Phase III clinical studies of liraglutide for the treatment of type 2 diabetes mellitus

	Garber [17, 18]	Seino [19]	Liraglutide as monotherapy			Liraglutide as add-on therapy		
			Marre [20]	Nauck [21]	Pratley [22, 23]	Buse [24]	Zinman [25]	Russell-Jones [26]
Subjects (*n*)	745	411	1,041	1,091	665	464	533	581
Sites	126 in US, Mexico	75 in Japan	116 mostly in Europe	170 mostly in Europe	158 in US, Canada, Europe	132 in US, Europe	96 in US, Canada	107 mostly in Europe
Design	db, ac, pg	db, ac, pg	db, ac, pg	db, ac, pg	OL, ac, pg	OL, ac, pg	db, ac, pg	db/OL[a], ac, pg
Duration (weeks)	52 (104)[b]	24	26	26	26 (52)[b]	26	26	26
Background treatment	None	None	Glim 2–4 mg	M 1 g BID	M[c]	M and/or SU[c]	M 1 g BID + R 4 mg BID	M 1 g BID + Glim 2–4 mg qd
Treatment regimen	Glim 8 mg, L 1.2 mg, L 1.8 mg	Glyb 2.5 mg, L 0.9 mg	L pbo + R pbo, L pbo + R 4 mg, L 0.6 mg + R pbo, L 1.2 mg + R pbo, L 1.8 mg + R pbo	L pbo + Glim pbo, L pbo + Glim 4 mg, L 0.6 mg + Glim pbo, L 1.2 mg + Glim pbo, L 1.8 mg + Glim pbo	S 100 mg, L 1.2 mg, L 1.8 mg	E 10 μg BID, L 1.8 mg	L pbo, L 1.2 mg, L 1.8 mg	IG[d], L 1.8 mg
Primary endpoint	Mean change in HbA1C from baseline to the end of the study							
Secondary endpoints	Target achievers[e] ΔFPG, ΔPPG, ΔBW Beta-cell function Blood pressure Glucagon QOL Safety	Target achievers[e] ΔFPG, ΔPPG, ΔBW Lipids profile CV biomarkers Safety	Target achievers[e] ΔFPG, ΔPPG, ΔBW Beta-cell function Blood pressure Safety	Target achievers[e] ΔFPG, ΔPPG, ΔBW Beta-cell function Safety	Target achievers[e] ΔFPG, ΔPPG, ΔBW Beta-cell function CV biomarkers Lipid profile Safety	Target achievers[e] ΔFPG, ΔPPG, ΔBW Beta-cell function Blood pressure Lipid profile Glucagon Safety	Target achievers[e] ΔFPG, ΔPPG, ΔBW Beta-cell function Lipid profile Safety	Target achievers[e] ΔFPG, ΔPPG, ΔBW Beta-cell function Waist circumference Safety

Each study had a similar inclusion and exclusion criteria. All trials were randomized, active-controlled, multi-center, parallel group trials, and assessed change in HbA1C as primary endpoint

ac Active-controlled, *BID* two times a day, *ΔBW* mean change in body weight, *CV* cardiovascular, *db* double-blind, *E* exenatide, *ΔFPG* mean change in fasting plasma glucose, *Glim* glimepiride, *Glyb* glyburide, *ΔHbA1C* mean change in HbA1C, *IG* insulin glargine, *L* liraglutide, *M* metformin, *OL* open label, *pbo* placebo, *pg* parrellel-group, *ΔPPG* mean change in postprandial plasma glucose, *qd* once a day, *QOL* quality of life, *R* rosiglitazone, *S* sitagliptin, *SU* = sulfonylurea

[a] Patients were provided with open-labelled insulin glargine

[b] Duration including extension study which is published later

[c] Doses of metformin and/or sulfonylurea were not reported

[d] Dose of insulin glargine was titrated twice weekly by patients, aiming for a target value of FPG ≤5.5 mmol/L (99 mg/dL)

[e] Percent of patients achieving target HbA1C recommended by American Diabetes Association (<7.0%), International Diabetes Federation (≤6.5%), or American Association of Clinical Endocrinologists (≤6.5%)

Table 2 Results of the two Phase III clinical studies of liraglutide as monotherapy for the treatment of type 2 diabetes mellitus

	ΔHbA1C (%)	Target achievers[a] (<7.0%) (%)	Target achievers[a] (≤6.5%) (%)	ΔFPG (mmol/L)	ΔPPG (mmol/L)	ΔBW (kg)	PPG_AUC$_{0-3}$ (mmol/L × h)
Garber [17]							
Glim 8 mg ($n = 248$)	−0.51	27.8	16.2	−0.29	−1.36	1.12	–
L 1.2 mg ($n = 251$)	−0.84**	42.8***	28.0**	−0.84*	-1.71^{NS}	−2.05****	–
L 1.8 mg ($n = 246$)	−1.14****	50.9****	37.6***	−1.42****	−2.08**	−2.45****	–
2-year extension of Garber [18]							
Glim 8 mg	−0.3	23.2	15.4	0.11	−1.38	0.95	–
L 1.2 mg	−0.6**	36.9**	25.0*	−0.52*	-1.52^{NS}	−1.89****	–
L 1.8 mg	−0.9****	44.4***	29.9***	−0.88***	−2.06*	−2.70****	–
Seino [19]							
Glyb 2.5 mg ($n = 139$)	−1.28	30.8	10.8	−2.86	–	1.17	37.3
L 0.9 mg ($n = 272$)	−1.93****	49.0****	27.8****	−3.68****	–	−1.14****	32.1****

* $P < 0.05$ versus active control; ** $P < 0.01$ versus active control; *** $P < 0.001$ versus active control; **** $P < 0.0001$ versus active control; *NS* not significant

[a] Percent of patients achieving target HbA1C recommended by American Diabetes Association (<7.0%), International Diabetes Federation (≤6.5%), or American Association of Clinical Endocrinologists (≤6.5%)

ΔBW mean change in body weight, *ΔFPG* mean change in fasting plasma glucose, *Glim* glimepiride, *Glyb* glyburide, *ΔHbA1C* mean change in HbA1C, *L* liraglutide, *ΔPPG* mean change in postprandial plasma glucose, *PPG_AUC$_{0-3}$* mean area under the curve of postprandial plasma glucose from the beginning to 3 h after breakfast

Pratley and colleagues likewise compared add-on therapy of liraglutide to metformin versus metformin plus sitagliptin [22, 23]. Significantly more participants achieved the target HbA1C with the add-on therapy than with metformin plus sitagliptin, while the change in PPG was not reported because data was highly variable. Changes in FPG and body weight were also significantly in favor of the add-on therapy. There was no significant difference of lipid profile between the add-on therapy and metformin plus sitagliptin in all test items except slightly lower total cholesterol in liraglutide 1.8 mg arm (*P* value: 0.03).

Buse et al. [24] compared add-on therapies of liraglutide and exenatide in patients on maximally tolerated doses of metformin, sulfonylurea, or both. Doses of background therapy were not reported in the article. Addition of liraglutide resulted in significant benefit over the addition of exenatide in primary endpoint. However, the change in PPG was in favor of exenatide after breakfast and dinner (mean value was not reported). Treatment differences of PPG after breakfast and dinner were 1.33 mmol/L (95% CI 0.80–1.86, $P < 0.0001$ versus exenatide arm) and 1.01 mmol/L (95% CI 0.44–1.57, $P = 0.0005$ versus exenatide arm), respectively. As far as body weight reduction, there was no difference between liraglutide and exenatide arms. Treatment differences of total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were not significant between the two arms, while triglyceride was slightly in favor of liraglutide arm (*P* value: 0.049).

Zinman et al. [25] compared the triple therapy (addition of liraglutide to metformin plus rosiglitazone) versus metformin plus rosiglitazone. Majority of the participants had been previously treated with combination therapy using oral antidiabetic drugs (82–84%).

Significant reductions in HbA1C were achieved with the triple therapy compared to the combination therapy. Proportion of target achievers, mean changes in FPG, PPG, and body weight were significantly greater in the triple therapy arms compared to the combination therapy arm. Low-density lipoprotein and triglyceride values were slightly in favor of the triple therapy with liraglutide 1.2 mg ($P < 0.05$), but this advantage was not found in the triple therapy arm with liraglutide 1.8 mg.

Russell-Jones et al. [26] compared the triple therapy (addition of liraglutide to metformin plus glimepiride) versus metformin plus glimepiride combination therapy and another triple therapy (addition of insulin glargine to metformin plus glimepiride). Metformin dose was fixed to 2,000 mg, but glimepiride dose was allowed to reduce from 4 to 2 mg based on researcher's discretion. Dose of insulin glargine was titrated, aiming for a target value of FPG ≤ 5.5 mmol/L (99 mg/dL).

Significant reductions in HbA1C was achieved with the triple therapy with liraglutide compared to both combination therapy and the other triple therapy with insulin glargine. Proportion of target achievers was not reported. Although the triple therapy with liraglutide showed significant reduction in FPG and PPG compared to

Table 3 Results of the six Phase III clinical studies of liraglutide as add-on therapy for the treatment of type 2 diabetes mellitus

	ΔHbA1C (%)	Target achievers[a] (<7.0%) (%)	Target achievers[a] (≤6.5%) (%)	ΔFPG (mmol/L)	ΔPPG (mmol/L)	ΔBW (kg)	ΔWaist circumference (cm)
Marre [20]							
G 2–4 mg ($n = 114$)	0.23	8	4	1.01	−0.4	−0.1	–
Glim 2–4 mg + R 4 mg ($n = 232$)	−0.44	22	10	−0.88	−1.8	2.1	–
Glim 2–4 mg + L 0.6 mg ($n = 233$)	−0.60****,^{NS}	24****,^{NS}	13**,^{NS}	−0.72****,^{NS}	−0.6****,^{NS}	0.7*,$^{\$\$\$\$}$	–
Glim 2–4 mg + L 1.2 mg ($n = 228$)	−1.08****,$^{\$\$\$\$}$	35****,$^{\$\$\$\$}$	22****,$^{\$\$\$\$}$	−1.57****,$^{\$\$}$	−2.5****,$^{\$\$}$	0.3$^{NS,\$\$\$\$}$	–
Glim 2–4 mg + L 1.8 mg ($n = 234$)	−1.13****,$^{\$\$\$\$}$	42****,$^{\$\$\$\$}$	21****,$^{\$\$\$\$}$	−1.59****,$^{\$\$}$	−2.7****,$^{\$\$}$	−0.2$^{NS,\$\$\$\$}$	–
Nauck [21]							
M 2 g ($n = 122$)	0.09	10.8	4.2	0.4	−0.6	−1.5	–
M 2 g + G 4 mg ($n = 244$)	−0.98	36.3	22.2	−1.3	−2.5	1.0	–
M 2 g + L 0.6 mg ($n = 242$)	−0.69*,^{NS}	28.0*,^{NS}	11.3*,^{NS}	−1.1***,^{NS}	−1.7***,^{NS}	−1.8 $^{ns,\$\$\$\$}$	–
M 2 g + L 1.2 mg ($n = 241$)	−0.97*,^{NS}	35.3*,^{NS}	19.8*,^{NS}	−1.6****,^{NS}	−2.3***,^{NS}	−2.6**,$^{\$\$\$\$}$	–
M 2 g + L 1.8 mg ($n = 242$)	−1.00*,^{NS}	42.4*,^{NS}	24.6*,^{NS}	−1.7****,^{NS}	−2.6***,^{NS}	−2.8**,$^{\$\$\$\$}$	–
Pratley [22]							
M[c] + S 100 mg ($n = 219$)	−0.90	22.0	11.3	−0.83	NR	−0.96	–
M[c] + L 1.2 mg ($n = 225$)	−1.24$^{\$\$\$\$}$	43.7$^{\$\$\$\$}$	21.2$^{\$\$}$	−1.87$^{\$\$\$\$}$	NR	−2.86$^{\$\$\$\$}$	–
M[c] + L 1.8 mg ($n = 221$)	−1.50$^{\$\$\$\$}$	55.0$^{\$\$\$\$}$	35.1$^{\$\$\$\$}$	−2.14$^{\$\$\$\$}$	NR	−3.38$^{\$\$\$\$}$	–
1-year extension of Pratley [23]							
M[c] + S 100 mg	−0.88	27.1	16.8	−0.59	NR	−1.16	–
M[c] + L 1.2 mg	−1.29$^{\$\$\$\$}$	50.3$^{\$\$\$\$}$	24.3^{NS}	−1.71$^{\$\$\$\$}$	NR	−2.78$^{\$\$\$\$}$	–
M[c] + L 1.8 mg	−1.51$^{\$\$\$\$}$	63.3$^{\$\$\$\$}$	40.4$^{\$\$\$\$}$	−2.04$^{\$\$\$\$}$	NR	−3.68$^{\$\$\$\$}$	–
Buse [24]							
M/SU[b] + E 10 μg BID ($n = 231$)	0.79	43	21	−0.60	NR	−2.87	–
M/SU[b] + L 1.8 mg ($n = 233$)	−1.12$^{\$\$\$\$}$	54$^{\$\$}$	35$^{\$\$\$\$}$	−1.61$^{\$\$\$\$}$	NR	−3.24^{NS}	–
Zinman [25]							
M 2 g + R 8 mg ($n = 177$)	−0.5	28.1	14.4	−0.4	−0.8	0.6	–
M 2 g + R 8 mg +L 1.2 mg ($n = 178$)	−1.5$^{\$\$\$\$}$	57.5$^{\$\$\$}$	36.2$^{\$\$\$}$	−2.2$^{\$\$\$\$}$	−2.6$^{\$\$\$}$	−1.0$^{\$\$\$\$}$	–
M 2 g + R 8 mg +L 1.8 mg ($n = 178$)	−1.5$^{\$\$\$\$}$	53.7$^{\$\$\$}$	37.3$^{\$\$\$}$	−2.4$^{\$\$\$\$}$	−2.7$^{\$\$\$}$	−2.0$^{\$\$\$\$}$	–
Russell-Jones [26]							
M 2 g + Glim 2–4 mg ($n = 115$)	−0.24	NR	NR	0.53	−0.03	−0.42	−0.62
M 2 g + Glim 2–4 mg +IG ($n = 234$)	−1.09$^{\$\$\$\$}$	NR	NR	−1.79	−1.61	1.6	0.89

Table 3 continued

	ΔHbA1C (%)	Target achievers[a] (<7.0%) (%)	Target achievers[a] (≤6.5%) (%)	ΔFPG (mmol/L)	ΔPPG (mmol/L)	ΔBW (kg)	ΔWaist circumference (cm)
M 2 g + Glim 2–4 mg + L 1.8 mg ($n = 232$)	$-1.33^{\$\$\$\$,\#\#}$	NR	NR	$-1.55^{\$\$\$\$,\P}$	$-1.81^{\$\$\$\$,\P}$	$-1.8^{\$\$\$\$,\#\#\#\#}$	$-1.50^{NS,\#\#\#\#}$

ΔBW mean change in body weight, *ΔFPG* mean change in fasting plasma glucose, *Glim* glimepiride, *ΔHbA1C* mean change in HbA1C, *IG* insulin glargine, *L* liraglutide, *M* metformin, *NR* data not reported, *ΔPPG* mean change in postprandial plasma glucose, *R* rosiglitazone, *S* sitagliptin, *SU* sulfonylurea

* $P < 0.05$ versus monotherapy; ** $P < 0.01$ versus monotherapy; *** $P < 0.001$ versus monotherapy; **** $P < 0.0001$ versus monotherapy; $^{\$\$}$ $P < 0.01$ versus combination therapy; $^{\$\$\$}$ $P < 0.001$ versus combination therapy; $^{\$\$\$\$}$ $P < 0.0001$ versus combination therapy; $^{\#\#}$ $P < 0.01$ versus triple therapy; $^{\#\#\#\#}$ $P < 0.0001$ versus triple therapy; *ns* not significant versus monotherapy; *NS* not significant versus combination therapy; ¶ not significant versus triple therapy

[a] Percent of patients achieving target HbA1C recommended by American Diabetes Association (<7.0%), International Diabetes Federation (≤6.5%), or American Association of Clinical Endocrinologists (≤6.5%)

[b] Doses of metformin and/or sulfonylurea were not reported

combination therapy, there was no difference from the other triple therapy with insulin glargine.

Safety and tolerance

In the eight studies involving 5,531 participants, discontinuation due to adverse events ranged from 2 to 12% in liraglutide arms versus 2–13% in various comparator arms. The most frequent adverse events of liraglutide were gastrointestinal disorders such as nausea and diarrhea (Table 4). The incidences were highest in the first 4 weeks and then declined with time. Nausea was most common in all studies and proportional to dose of liraglutide except at 0.9 mg dose performed by Seino et al. in Japan, indicating ethnic difference in the incidence of adverse events. The average incidence of nausea was 25% at a daily dose of 1.8 mg while it was less than 10% in comparator arms using non-GLP-1 analogues. In a study performed by Buse et al. [24] the incidence in patients exposed to exenatide was 28% as well, indicating that nausea is a typical adverse event of GLP-1 analogues.

Out of 3,456 patients exposed to liraglutide during the eight Phase III clinical studies [17, 19–22, 24–26], 7.0% withdrew from the study due to adverse events while 4.3% withdrew from the study out of 2075 patients who were exposed to comparator drugs. Six cases of pancreatitis were reported in the liraglutide arms of the eight studies, whereas two cases were reported in non-liraglutide arms (one case each in exenatide and glimepiride arm, risk ratio: 1.80, 95% CI 0.36–8.92). Five cases of cancer were reported in patients exposed to liraglutide, compared to one case in non-liraglutide arms (risk ratio: 3.00, 95% CI 0.35–25.68). The reported cancers were two cases of pancreas adenocarcinoma and one case of each of lung adenocarcinoma, thyroid neoplasm, epiglottic carcinoma in liraglutide arm [22, 24]. One case of renal carcinoma was also reported in patients exposed to sitagliptin [22]. However, there was no cancer case reported in patients exposed to comparator drugs, which do not act on GLP-1 pathway. There were three deaths (one each by gastroenteritis, pancreatitis, and pancreas carcinoma) reported among participants exposed to liraglutide, compared to one death by cardiac arrest in patients exposed to comparator drugs.

The incidence of antibodies to liraglutide ranged from 4 to 13% in three studies [20, 25, 26]. The incidence did not cause any significant effects on HbA1C level. The most common adverse events among antibody-positive patients were infections [28].

Discussion

Diabetes is one of the most common risk factors for death worldwide [29, 30]. As such, the primary goal of diabetes

Table 4 Rates of withdrawal and adverse events reported in the eight Phase III clinical studies of liraglutide (%)

	Exposure to liraglutide				
	No exposure	0.6 mg	0.9 mg[a]	1.2 mg	1.8 mg
Withdrawal rate[b]	4.3	3.4	3.7	7.5*	8.3*
Serious adverse events[c]	4.5	3.0	4.9	4.4	4.0
Hypoglycemia[b]	17.1	4.0	17.5	7.6	12.4
Nausea[e]	7.0	11.2	4.5	20.5**	25.1**
Diarrhea[d]	5.2	9.9	6.3	9.8*	13.5**
Vomiting[d]	3.1	–	–	7.9**	9.3**
Constipation[d]	3.5		5.6	6.5**	7.0**
Headache[d]	7.6	–	–	10.1*	9.0
Nasopharyngitis[d]	8.4	–	19.8	8.0	9.1
Metabolism and nutrition disorders[d]	10.9	–	–	12.6	12.6

Compiled from the data reported in the articles published in scientific journals

* $P < 0.05$ compared to no exposure; ** $P < 0.01$ compared to no exposure

[a] Phase III clinical trials of liraglutide at daily dose of 0.9 mg was performed only by Seino et al. [19]

[b] Compiled from data reported in all of the eight Phase III clinical studies

[c] Compiled from data reported in all of the eight Phase III clinical studies except Nauck's study because it was not reported

[d] Compiled from data reported in the relevant articles because some articles did not provide the incidence

treatment is prevention of complications that often lead to death or disability. Although successful prevention of complications requires multiple strategies, tight control of HbA1C by oral antidiabetic drugs has been mainstay to reduce the risk of complications. American Diabetes Association (ADA) recommends an HbA1C goal of less than 7%, and International Diabetes Federation (IDF) and American Association of Clinical Endocrinologists (AACE) recommend less than or equal to 6.5% [31–33].

While presently used antidiabetic drugs have been shown to reduce the risk of complications, achievement of blood sugar control continues to be a worldwide health problem. Multiple studies have shown that large proportions of patients with diabetes fail to achieve the recommended HbA1C goals [34–36]. Hence, newer antidiabetic agents are needed to expand therapeutic options.

Liraglutide is a new GLP-1 receptor agonist with longer half-life (13 h) compared to that of exenatide (1–3 h), the first drug in the class of the GLP-1 analogues. The extended half-life enables liraglutide to be used once daily and, therefore, is expected to increase patient adherence [37].

Liraglutide was studied as monotherapy and as add-on therapy to existing oral antidiabetic drugs in six studies sponsored by LEAD program. Two additional Phase III studies [19, 22] were also included in this systematic review.

When used as monotherapy, liraglutide appeared beneficial over glimepiride and glyburide in terms of primary and various secondary endpoints. However, since liraglutide needs subcutaneous injection, patient adherence may be a problematic issue. Concern on carcinogenicity of the drug also needs to be addressed. In rats and mice, liraglutide caused thyroid C-cell tumors [38, 39]. This finding was added as a black box warning to prescribing information of liraglutide.

When used as add-on therapy to other oral antidiabetic agents, liraglutide appeared to result in some benefits over monotherapy in terms of the primary and secondary endpoints. However, the addition of liraglutide to metformin failed to show superiority over metformin plus glimepiride not only in the primary end point but in all secondary endpoints except body weight [21]. Therefore, add-on therapy of liraglutide to other oral antidiabetic agent may be useful option for patients with type 2 diabetes whose major concerns are overweight and/or hypoglycemia associated with antidiabetic agents. Unfortunately, so far, benefit of add-on therapy of liraglutide was not evaluated in comparison to widely used combination therapies such as metformin plus pioglitazone (both of which are insulin sensitizers) and glimepiride plus DPP-4 inhibitor.

When used as triple therapy, liraglutide resulted in additional improvement over the combination therapy of metformin plus rosiglitazone or metformin plus glimepiride in terms of the primary and most secondary endpoints [25, 26]. Comparison between triple therapy using liraglutide (metformin plus glimepiride plus liraglutide) and triple therapy using insulin glargine (metformin plus glimepiride plus insulin glargine) resulted in favor of liraglutide in the primary endpoint. However, in terms of reductions in FPG and PPG, the difference was not

significant. Further research is warranted in this regard to delineate any benefit of using triple therapy with liraglutide over other triple therapy combinations with insulin.

Liraglutide is classified by the FDA as pregnancy category C [28]. Liraglutide has been shown to cause teratogenecity and growth retardation in rats at clinically relevant exposures. Therefore, liraglutide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Liraglutide was secreted into the milk of lactating rats at concentrations of approximately 50% of maternal plasma concentrations, but it is not known whether the drug is excreted in human milk. Therefore, nursing mothers are recommended to avoid the use of liraglutide. Dose adjustment is not proposed for patients with renal or hepatic impairment. However, since clinical studies did not enroll subjects with these impairment, clinicians should use caution when using liraglutide for patients with renal or hepatic impairment [40].

The average wholesale price of liraglutide (Victoza®) is $144.48 per pre-filled pen, which is a month-supply if used 0.6 mg once daily [41]. If used 1.8 mg once daily, three pre-filled pens are needed for a month-supply, which accounts for $433.44 monthly. Considering unestablished place of therapy by ADA and AACE and drug cost, the use of liraglutide may be recommended only for patients who have overweight or hypoglycemia problems associated with conventional therapy.

Strength of this review is that all the published Phase III clinical trials are compiled and systematically analyzed with particular attention to efficacy and safety of liraglutide. However, the fact that the clinical trials were sponsored by manufacturer and small-sized trials were not included may be limitations of this review.

Conclusion

Liraglutide is a new therapeutic option as monotherapy or add-on therapy to improve glycemic control in patients with type 2 diabetes. However, because of the present lack of evidence with regard to durability of efficacy and long-term safety, clinicians are encouraged to utilize regimens with more appreciable and longstanding evidence of benefit.

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