Perspective

Glucagon-like Receptor 1 Agonists in the Treatment of Type 2 Diabetes

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During the last decades, there has been a huge increase in the prevalence of type 2 diabetes mellitus (T2DM), mostly due to the Western lifestyle [1,2]. T2DM and its vascular complications increase patient morbidity, hospitalisations and healthcare costs [3,4]. Thus, it is beyond doubt that we need medication which can confer some improvement in the underlying pathophysiological factors leading to T2DM and its complications.

Glucagon-like peptide 1 receptor agonists (GLP-1RAs) are a class of antidiabetic agents, which was introduced in the 21st century. They successfully target not only blood glucose control but also obesity in patients with T2DM [5,6]. Currently, exenatide, liraglutide, lixisenatide, albiglutide and dulaglutide are already on the market [5,7]. The newest agent is semaglutide [5–7].

All GLP-1RAs are used subcutaneously. Albiglutide, dulaglutide and semaglutide show a long action and are administered once weekly [6,8–11]. Liraglutide is used once daily. Exenatide exists in two preparations: a quick acting used twice per day, and a long-acting used once per week [6,8–11]. An oral form of semaglutide is currently under development [6,8–11].

GLP-1 RAs mainly act by activating the GLP-1 receptors in pancreatic beta cells to stimulate glucose-dependent insulin secretion. Additionally, they reduce appetite and delay gastric emptying, eventually leading to reduced food intake [6,8–10]. They can be used either as monotherapy or an add-on therapy to other antidiabetic agents, including insulin, in T2DM [11–13]. GLP-1RAs have very recently been recommended as the second antidiabetic agent after metformin in patients with established atherosclerotic cardiovascular disease and chronic kidney disease [14]. However, they should not be used together with dipeptidyl peptidase-4 inhibitors [10–13]. As regards type 1 diabetes mellitus, they have been studied but they are not currently approved [9,11,13].

The advantages of GLP-1RAs include: (a) efficacy (reduction of glycated haemoglobin 0.6–1.9% in a period of 24–30 weeks); (b) absence of hypoglycaemias; (c) weight reduction; (d) reduction of appetite; (e) reduction of fatty liver infiltration. These actions are significant and clinically meaningful (see Table 1) [5,10,11–13,15,16].

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Table 1. Major efficacy results of trials with GLP-1RAs.

GLP-1RAs	Dose	Trial	HbA1c reduction	Weight loss
Liraglutide	0.6–1.8 mg/once daily	LEAD-6	1.48% in 26 weeks	0.2–2.8 kg
Exanatide	5–10 μg/twice daily	DURATION-5	1.5% in 30 weeks	1.1–2.9 kg
	2 mg/once weekly	DURATION-5	1.9% in 30 weeks	1.3–2.3 kg
Albiglutide	30–50 mg/once weekly	HARMONY-7	0.78% in 32 weeks	0.4–1.1 kg
Dulaglutide	1.5 mg/once weekly	AWARD-6	1.42% in 26 weeks	0.9–3.4 kg
Lixisenatide	10–20 μg/once daily	GetGoal-X	0.79% in 24 weeks	0.3–2.8 kg

Regarding their combination with other antidiabetic agents, there are interesting results from some trials. In a study including patients treated with a GLP-1RA together with a sodium glucose transporter 2 inhibitor (SGLT2), the mean reduction of glucose was 2.2 mmol/L (39.6 mg/dL) ($p < 0.0004$) after 6 months [17]. This therapeutic combination achieved not only adequate glycaemic control, but also weight loss (2.1 kg; $p < 0.00003$) and decrease of blood pressure [17]. In addition, 34.3% of patients achieved Hb1Ac levels <7% and weight loss >5%, without hypoglycaemias [17]. These results are also supported by another real-world observational study in with patients receiving a GLP-1RA in combination with metformin and a SGLT-2 inhibitor [18].

The main adverse effects of GLP-1RAs are gastrointestinal: nausea, vomiting, diarrhoea and abdominal complaints (see Table 2) [19]. However, these are mostly self-limited over time [19]. Another adverse effect is injection-site reactions [19]. Moreover, there are indications that incretin-based therapies may cause pancreatic diseases. Nevertheless, according to real-world evidence, the risk of pancreatic disease associated with add-on GLP-1RAs to metformin therapy appears to be no higher than that associated with other antidiabetic agents [20].

Table 2. Safety and tolerability of GLP-1RAs.

GLP-1RAs	Dose	Trial	Major hypoglycemia	Minor hypoglycemia	Gastrointestinal adverse effects (nausea/vomiting/ diarrhoea)	Withdrawal due to adverse effects
Liraglutide	0.6–1.8 mg/once daily	LEAD-6	0%	2%	25% (Nausea)	6%
Exanatide	5–10 μg/twice daily	DURATION-5	0%	0%	35%/9%/4%	5%
	2 mg/once weekly	DURATION-5	0%	0%	14%/5%/9%	5%
Albiglutide	50 mg/once weekly	HARMONY-2	0%	0%	9%/3%/13%	13%
Dulaglutide	1.5 mg/once weekly	AWARD-6	0%	9%	20%/7%/12%	6%
Lixisenatide	10–20 μg/once daily	GetGoal-M	0%	2%	22%/9%/10%	7%

Obviously, the need for injection may discourage some patients, but this can easily be overcome with patient education [16,19]. Moreover, the new pens and (especially) the once-weekly injection of some compounds render them more user friendly [11,16,19]. Another consideration is administration and ease of use. For example, albiglutide needs reconstruction before injection, making its use difficult for some patients, including those with visual or dexterity issues [11,16,19].

The most important challenge for GLP-1RAs is, as indeed for all antidiabetic agents, the potential cardioprotective actions [21,22]. In this context, GLP-1RAs have demonstrated: (a) slight improvements in arterial pressure, lipid parameters and inflammation in humans; (b) improvements in heart failure and myocardial infarction in the experimental setting [21–24].

Of particular relevance, GLP-1RAs exhibit important differences in their cardiovascular effects in

large clinical trials. Indeed, liraglutide and semaglutide significantly reduce the risk of major adverse cardiac events [25,26]. By contrast, once-weekly exenatide and lixisenatide have shown a neutral cardiovascular effect: safety but no benefit [27,28]. These differences need to be appreciated in clinical practice, especially when prescribing antidiabetic treatment to patients with known cardiovascular morbidity [29,30].

Importantly, in the most recent cardiovascular outcomes trial [31], once-weekly albiglutide reduced the primary cardiovascular endpoint by 22%, exhibiting superiority compared with placebo (p = 0.0006). This trial further enhances the importance of GLP-1RAs, especially in patients with established cardiovascular disease [31,32].

Furthermore, there is recent evidence that that GLP-1RAs may improve the natural history of diabetic complications. A pharmacovigilance meta-analysis has demonstrated that reduced incidence of retinopathy with GLP-1RAs, as compared to other antidiabetic agents [33]. Importantly, GLP-1RAs appear to exert an additional protective role in the kidneys. According to real-world evidence, their use in patients with low estimated glomerular filtration rate (eGFR) was related to less pronounced reduction in eGFR (−0.80 *vs.* −1.03 mL/min/1.73 m^2, p = 0.0005), as compared with other therapies, while HbA1c was significantly reduced as well [34].

Finally, it is now being increasingly appreciated that GLP-1RAs can be excellently be combined with basal insulin [32]. In this more modern combination, GLP-1RAs target post-prandial hyperglycaemia, while basal insulin targets fasting glucose. Nowadays, fixed GLP-1RAs+basal insulin combinations used as a single daily injection in the same pen are available to increase patient compliance [32].

In conclusion, GLP-1RAs are antidiabetic agents with many advantages [5,8,14,35]. Their beneficial actions are increasingly being appreciated in the treatment of T2DM.

CONFLICTS OF INTEREST

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AUTHORS' CONTRIBUTIONS

N.P. conceived the perspective. T.P. wrote the first draft. N.P. edited and finalised the manuscript.

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