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REVIEW

Comparative Effectiveness of Long-Acting GLP-1 Receptor Agonists in Type 2 Diabetes: A Short Review on the Emerging Data

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Abstract: Glucagon-like peptide-1 (GLP-1) receptor agonists have been available as glucose-lowering therapies for people with type 2 diabetes since 2006, when twice-daily exenatide was licenced. Since then, advances in peptide chemistry and delivery have allowed for once-daily and more recently once-weekly (QW) delivery of peptides in this class and there are currently three QW "long-acting" GLP-1 receptor agonists available in clinical practice. This short review describes the therapeutic landscape that is occupied by the modern type 2 diabetes glucose-lowering therapies with a particular focus on long-acting GLP-1 receptor agonists. The efficacy and side-effect profiles of the available QW GLP-1 receptor agonists are discussed, focusing on head-to-head clinical trial comparisons. There is also an appraisal of the cardiovascular outcome trials, for which there has been an assessment of each of the QW GLP-1 receptor agonists, leading to clinical conclusions regarding their comparative effectiveness.

Keywords: GLP-1, type 2 diabetes, cardiovascular trial

Introduction

The incidence of type 2 diabetes mellitus (T2D) continues to rise and it is estimated that 9% of the global adult population are affected by this condition. In the United Kingdom, 10% of healthcare spend is attributable to diabetes and in the most recent audit of National Health Service hospitals, 20% of in-patients have diabetes as a co-morbidity. Attempts to reduce the burden of the "diabetes epidemic" by prevention have been universally unsuccessful, due to failure to reverse rising levels of obesity and sedentary lifestyle. This has led to a proliferation of pharmacologic therapies for hyperglycaemia and in the United States, there are now ten different classes of glucose-lowering medication.

Two of these drug classes, initially launched in the mid-2000s, impact on the incretin system. They stimulate the glucagon-like peptide 1 (GLP-1) receptor, which enhances insulin secretion and reduces the production of glucagon, both in a glucose-dependent manner. The dipeptidyl peptase-4 (DPP-4) inhibitors are oral agents, which enhance endogenous GLP-1 activity by reducing its degradation by the widely distributed enzyme DPP-4. Their mechanism of action means that they do not cause hypoglycaemia nor lead to weight gain. They have also been shown to be safe in large studies examining their potential to increase cardiovascular (CV) disease (a mandatory regulatory requirement for new glucose-lowering therapies).

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The second class of incretin agents are the GLP-1 receptor agonists (GLP-1RAs). These are injectable peptides which are resistant to DPP-4 degradation, providing supra-physiological stimulation of the GLP-1 receptor. GLP-1RAs also slow gastric emptying and, probably via an effect on the brain, increase satiety; both of these effects lead to weight loss in a substantial proportion of patients. They are, however, less well tolerated than DPP-4 inhibitors, with gastro-intestinal side-effects of nausea, vomiting and diarrhoea being common following initiation (although these diminish over time in most subjects).

The first GLP-1RA to be marketed (exenatide [Byetta®]) was based on the exendin-4 molecule (isolated from the saliva of the Gila Monster lizard) and had to be administered twice daily with meals due to its short half-life.[1] Subsequently launched GLP-1RAs were once-daily preparations (liraglutide [Victoza®] and lixisenatide [Lyxumia®]) which could be administered without regard to meal times;[2,3] in 2011 the European Medicines Agency issued marketing authorisation for a once-weekly (QW) version of exenatide [Bydureon®], the first long-acting GLP-1RA.[4]

Exenatide extended release (ER) contains the exendin-4 molecule interlinked with microspheres of poly-(D, L-lactide-co-glycolide) polymers, degradable material that had previously been used in absorbable sutures. The absorption of exenatide involves an initial phase of release for 48 hrs, then continued diffusion of exenatide for fourteen days; finally, there is release mediated by erosion for up to seven weeks. These pharmacokinetic features facilitate a continual release of drug without significant peaks and troughs in plasma concentration and allow for once weekly (QW) administration. Exenatide ER is prescribed as a powder and this needs to be suspended in aqueous solution immediately prior to injection; this has led to the development of various devices to aid suspension, some of which have involved vigorous shaking. There is also an issue of injection-site swelling due to the slow clearance of polymer, which can still be felt four weeks post-injection. Exenatide ER is administered as a single dose of 2mg QW with no need for slow up-titration.

The second long-acting GLP-1RA launched in 2014 was albiglutide (Eperzan®), closely followed by dulaglutide (Trulicity®).[5,6] Unlike exenatide, both of these GLP-1RAs are analogues of the human GLP-1 molecule rather than exendin-4. Albiglutide is made up of multiple copies of a modified human glucagon-like peptide (amino acids 7–36) coupled to recombinant human albumin. After subcutaneous administration it appears to be absorbed via the lymphatic circulation with a maximum plasma concentration achieved around four days and with steady state after 4–5 weeks QW administration. Unfortunately, the administration of this medication is also complicated involving two periods of mixing separated by a 15–30 min wait, depending on the dose (30–50mg).

Dulaglutide is a recombinant DNA-produced polypeptide analogue of human GLP-1 (amino acids 7–37) which is covalently linked to each Fc arm of human immunoglobulin G4 (IgG4). This structure improves solubility and reduces immunogenicity, whilst also lowering renal clearance. As a result of the solubility, no shaking or mixing is required and the administration is very simple. Dulaglutide is administered in two doses (0.75mg and 1.5mg QW) without the need for up-titration.

The most recently lunched long-acting GLP-1RA (2018) is semaglutide (Ozempic®).[7] This molecule differs from human GLP-1 by two amino acids (94% homology), one of which protects against DPP4 degradation. There is an 18 carbon fatty diacid chain attached via a spacer to the lysine amino acid at position 26 of the molecule, which provides strong binding to albumin, facilitating the prolongation of action. Semaglutide is delivered as a clear, colourless solution which does not require resuspension. It is initiated at a dose of 0.25mg QW titrated after one month to a maintenance dose of 0.5mg or, with further up-titration, 1.0mg QW.

As mentioned earlier, all new glucose-lowering therapies are subjected to cardiovascular outcome trials (CVOTs) and, as per the FDA mandate, the long-acting GLP-1RAs have been assessed against placebo. The CVOT for exenatide ER confirmed non-inferiority (i.e. cardiovascular safety) but did not show superiority for the primary end-point, which was a composite of major cardiovascular events (CV death, non-fatal myocardial infarction or non-fatal stroke, termed 3-P MACE).[8] In contrast, the long-acting GLP-1 analogues (albiglutide, dulaglutide & semaglutide) have not only been found to be safe but have also demonstrated CV benefit over placebo.[9–11] It is quite possible that this represents differences in the trial designs and, indeed, meta-analyses suggest no significant differences between medications in this class.[12] However, the CVOT of lixisenatide, which is also exendin-4 based did not show CV superiority whilst the LEADER trial of liraglutide, a molecule closely analogous to semaglutide was positive.[13,14]

Unlike most classes of glucose-lowering therapies, some head-to-head comparisons of long-acting GLP-1RAs have been published, allowing some direct comparison of

effectiveness. The SUSTAIN 3 trial compared the safety and efficacy of semaglutide 1.0mg QW with exenatide ER 2.0mg QW in a Phase 3a, open-label, randomised clinical trial.[15] 813 subjects with T2D already taking oral glucose-lowering medications were randomised to active comparator therapy for 56 weeks with the primary end-point being change from baseline HbA1c.

The mean HbA1c (baseline 8.3% [67.7 mmol/mol]) fell by 1.5% (16.8mmol/mol) in subjects receiving semaglutide and by 0.9% (10.0 mmol/mol) with exenatide ER (estimated treatment difference [ETD] −0.62% [95% CI −0.80, −0.44] [−6.78 mmol/mol (95% CI −8.70, −4.86)]). This was statistically significant for both non-inferiority and superiority, in favour of semaglutide, and more patients receiving semaglutide (67%) achieved an HbA1c <7.0% (<53 mmol/mol) versus 40% of those taking exenatide ER. The baseline bodyweight (mean of 95.8 kg) was lowered by 5.6 kg (semaglutide) and 1.9 kg (exenatide ER) respectively, giving an ETD −3.78 kg [95% CI −4.58, −2.98] which was highly significant. The treatments both had similar safety profiles although gastrointestinal adverse events were more common with semaglutide (41.8%) than with exenatide ER (33.3%). Injection-site reactions were more frequently reported with exenatide ER (22.0%) than with semaglutide (1.2%).

The SUSTAIN 7 trial compared once-weekly semaglutide with dulaglutide in people with sub-optimally controlled T2D.[16] This open-label, parallel-group, phase 3b trial recruited patients aged 18 years or older who were on metformin monotherapy with an HbA1c between 7.0–10.5% (53.0–91.0 mmol/mol). Patients were randomised to receive semaglutide 0.5 mg QW, dulaglutide 0.75 mg QW, semaglutide 1.0 mg QW or dulaglutide 1.5 mg QW. The primary endpoint of SUSTAIN 7 was change in HbA1c from baseline; a secondary endpoint considered the change in bodyweight after 40 weeks treatment exposure. The trial was powered for HbA1c non-inferiority (set at a margin of 0.4%, [4.4mmol/mol]) and for bodyweight superiority.

A total of 1201 patients were randomised with similar numbers of participants (~300) in each of the four study arms and approximately 6% of patients withdrew from the study (43 receiving semaglutide and 29 receiving dulaglutide). The mean HbA1c was reduced by 1.5% (16.4 mmol/mol) with 0.5 mg semaglutide compared with 1.1% (12.1mmol/mol) with 0.75mg dulaglutide and this difference was statistically significant, in favour of semaglutide. Similarly, comparison of the higher doses of the two agents showed a significantly better reduction in HbA1c for semaglutide (ETD −0.41% [4.5mmol/mol]; p<0.0001). For the secondary end-point of bodyweight, this was reduced by 4.6–6.5 Kg for the two doses of semaglutide compared with 2.3–3.0 Kg with dulaglutide; comparisons of the respective doses were highly significant, both favouring semaglutide.

As expected, gastrointestinal adverse events were frequently reported and occurred in, 43–44% of subjects receiving semaglutide compared with 33–48% with the two doses of dulaglutide. These side-effects were also the most common reason for discontinuing treatment in the trial.

Albiglutide has not been directly compared with either semaglutide or dulaglutide but was assessed versus once-daily liraglutide in the HARMONY 7 trial.[17] Comparison with liraglutide is of interest since this agent was also in a head-to-head comparison with once-weekly exenatide ER in the DURATION-6 trial, where liraglutide was seen to be superior to exenatide ER in terms of HbA1c lowering.[18] HARMONY 7 was a 32-week, open-label, phase 3 trial which recruited 841 adults with suboptimally controlled T2D and BMI 20–45 kg/m^2. Subjects were randomised to receive albiglutide 30 mg QW titrated to 50 mg at week 6, or liraglutide titrated to 1.8 mg OD over a two week period.[17] The primary endpoint was change in HbA1c from baseline for both albiglutide versus liraglutide, with a 95% CI upper margin of 0.3% to show non-inferiority. 422 subjects were allocated to the albiglutide group and 419 to liraglutide and the change in HbA1c at week 32 was −0.78% (8.6mmol/mol) in the albiglutide group and −0.99% (10.9mmol/mol) in the liraglutide group. The treatment difference was 0.21% with confidence intervals (0.08–0.34%) extending beyond 0.3% and so non-inferiority was not demonstrated, i.e. liraglutide showed superior glucose lowering to albiglutide. More patients given albiglutide experienced injection-site reactions compared to subjects who received liraglutide (12.9% vs 5.4%), whereas the opposite was seen for gastrointestinal adverse events, which occurred in 49.0% of patients in the liraglutide group versus 35.9% in the albiglutide group; both of these between-group differences were statistically significant.

The similar levels of difference in HbA1c reduction for both exenatide ER (DURATION-6) and albiglutide (HARMONY 7) compared to liraglutide are consistent with an indirect comparison of the two studies using a Bucher analysis.[19] This showed a treatment difference of 0.0% in mean change in HbA1c from baseline, and that albiglutide 50 mg was non-inferior to exenatide 2.0 mg QW at the non-inferiority margin of 0.3%. The effect of different agents on

Table 1 Effect of Treatment on HbA1c and Body Weight

Study	Drug	Dose	Frequency	HbA1c Reduction Mean (SE)	Body Weight Change Mean (SE/SD)
SUSTAIN 3[15]	Exenatide ER Semaglutide	2 mg 1 mg	Weekly Weekly	−0.9 (0.06) % **−1.5 (0.06) %**	−1.9 (0.29) kg **−5.6 (0.29) kg**
SUSTAIN 7 (low dose)[16]	Dulaglutide Semaglutide	0.75 mg 0.5 mg	Weekly Weekly	−1.1 (0.05) % **−1.5 (0.06) %**	−2.3 (0.27) kg **−4.6 (0.28) kg**
SUSTAIN 7 (high dose)[16]	Dulaglutide Semaglutide	1.5 mg 1.0 mg	Weekly Weekly	−1.4 (0.06) % **−1.8 (0.06) %**	−3.0 (0.27) kg **−6.5 (0.28) kg**
HARMONY 7[17]	Albiglutide Liraglutide	50 mg 1.8 mg	Weekly Daily	−0.78% **−0.98%**	−0.6 (3.12) kg **−2.2 (4.15) kg**
DURATION 6[18]	Exenatide ER Liraglutide	2 mg 1.8 mg	Weekly Daily	−1.28 (0.05) % **−1.48% (0.05) %**	−2.68 (0.18) kg **−3.57 (0.18) kg**

Note: Results in bold type represent significant benefit ($p < 0.05$) in outcome over the comparator drug.

HbA1c and body weight in the various studies reported here are summarised in Table 1.

Current licencing for GLP 1RAs recommends their use to improve glycaemic control alongside other glucose-lowering medications including insulin. The 2018 joint ADA/EASD guidelines for the management of hyperglycaemia in patients with type 2 diabetes promote the use of GLP 1 RAs or SGLT2i as second-line therapy in those with Atherosclerotic cardiovascular disease (ASCVD), heart failure or renal impairment.[20] The decision on which agent to recommend will largely be dictated by individual factors such as co-morbidity and renal function. However, there is interest in the use of GLP 1 RAs and SGLT2i in combination. Although evidence is scarce on the use of this combination, The DURATION 8 study demonstrated that the combination of Exenatide ER and Dapagliflozin resulted in greater improvements in glycaemic control, weight and systolic blood pressure than when either drug used alone.[21] Similarly, the addition of Dulaglutide in patients already treated with SGLT2i and uncontrolled Diabetes produced additional reductions in HbA1c and greater weight loss versus placebo.[22] It is speculated than the addition of a GLP 1 RA may reduce the higher glucagon levels seen with SGLT2i therapy.

Conclusions

In terms of HbA1c and weight, it appears that semaglutide is the most efficacious of the currently available long-acting GLP-1RAs. Regarding side-effects, which are predominantly gastro-intestinal, these appear to be a class effect but with some relationship to glucose-lowering potency (more with semaglutide, less with albiglutide). Increased diabetic retinopathy (DR) events seen with semaglutide in SUSTAIN 6 are thought to be related to rapid reduction in glucose levels in subjects with poor glycaemic control and existing retinopathy.[11,23,24] It is of note that a non-significant increase in DR events was also seen in the CVOTs for both liraglutide and dulaglutide[10,14] consistent with an impact of potent glucose-lowering. Other aspects will also impact on clinical decision-making, for example, the injection preparation (problematic for exenatide ER and albiglutide) as well as the design of administration device, which may favour dulaglutide. These tend to be reflected in quality of life assessments.[25] Finally, there is the issue of cost, which will obviously vary in different health care systems. Where the prices of the long-acting GLP-1RAs are equivalent, then health technology analyses are largely driven by HbA1c and weight and reflect differences in efficacy.[26]

End note

Albiglutide was globally withdrawn for commercial reasons in July 2018. However, the CVOT for albiglutide was subsequently published and demonstrated superiority and so it has been suggested that another pharmaceutical company may relaunch this product in the future and so it has been included in this review.

Disclosure

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