Recent Developments in GLP-1RA therapy: A Review of The Latest Evidence of Efficacy and Safety and Differences Within The Class

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Introduction

As of 2021, nine percent of the global population is now affected by type 2 diabetes mellitus (T2DM). In the United Kingdom, 20% of National Health Service in-patients suffer from diabetes as a co-morbidity, whilst 10% of healthcare expenditure is linked to diabetes. Failed attempts to reduce the diabetes epidemic are due to an inability to halt rising levels of obesity and sedentary lifestyle. This has led to the development of an abundance of therapeutic agents to control hyperglycaemia and in the United States there are now twelve different classes of glucose-lowering medication.

The glucagon-like peptide 1 (GLP-1) receptor agonists (RAs) act in a glucose-dependent manner by enhancing insulin secretion and reducing production of glucagon. GLP-1RAs are peptides which are resistant to dipeptidyl peptidase and provide supra-physiological stimulation of the GLP-1 receptor. They also retard gastric emptying and increase satiety; these effects in tandem lead to weight loss in a substantial proportional of people with T2DM.

Exenatide was the first GLP-1RA to be launched and was based on the exendin-4 molecule (isolated from Gila Monster lizard saliva) and is administered by twice daily subcutaneous injection at meal-times due to its short half-life (1). Subsequent GLP-1RAs were longer acting, once daily (OD) preparations (liraglutide and lixisenatide) administered without regard to meals (2,3). Then in 2011 the European Medicines Agency (EMA) issued authorisation for the first long-acting GLP-1RA, a once-weekly (QW) version of exenatide. (4).

Currently the most widely prescribed GLP-1RA is liraglutide, however, the convenience of less frequent dosing has led to an expansion of new prescriptions of the once-weekly GLP-1RAs (5). Unfortunately, exenatide extended release (ER) is manufactured as microspheres suspended in a vehicle of medium chain triglycerides, which requires vigorous shaking (> 15 seconds) prior to injection (6). Injection-site swelling is also a prevalent issue due to the slow clearance of the co-formulated polymer, which does not resolve itself until several weeks following injection. As a result, exenatide ER is less frequently prescribed and this review will focus on dulaglutide and semaglutide.

Dulaglutide was launched in 2014 and is a polypeptide analogue of human GLP-1 covalently linked to the Fc arms of human immunoglobulin G4 (7). This structure reduces immunogenicity and is soluble allowing for simple administration of a clear solution. Dulaglutide is administered in four doses (0.75mg, 1.5mg, 3.0mg & 4.5mg QW) and the lower two doses have no need for up-titration. More recently, the long-acting GLP-1RA semaglutide was approved (2018) (8). This molecule is 94% homologous with human GLP-1, differing by only two amino acids. There is an 18-carbon fatty di-acid chain attached to amino acid 26 of the molecule which provides strong binding to albumin and facilitates prolonged activity. A benefit of the long-acting GLP-1RA semaglutide is its administration as a clear 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 with the option for further up-titration to 1.0mg QW.

Glucose-lowering

The dulaglutide phase 3 clinical trial programme was known as AWARD (Assessment of Weekly AdministRation of LY2189265 [dulaglutide] in Diabetes) and assessed its glucose lowering efficacy versus commonly prescribed second-line therapies. The spectrum of patients with T2DM was broad, extending from treatment-naïve to those needing insulin, and the primary end-point in each trial (AWARD 1-6) was change in HbA1c (9, 10, 11, 12, 13, 14). The primary endpoint was assessed at 26 weeks in AWARD 1 and 3-6 and at 52 weeks in AWARD 2 (versus insulin glargine U100). Doses of 0.75mg and 1.5mg QW dulaglutide were assessed and all studies had extended periods of observation (4-78 weeks) allowing for the collection of additional safety data. Both doses of dulaglutide achieved statistically superior glucose lowering to the following active comparators: metformin; sitagliptin; exenatide and insulin glargine U100. The higher dose of dulaglutide was also non-inferior to liraglutide 1.8mg OD. From a baseline HbA1c of 59.6-69.4mmol/mol (7.6–8.5%), the reductions in HbA1c were 7.8-17.4mmol/mol (0.71-1.59%) for dulaglutide 0.75mg QW and 8.5-17.9mmol/mol (0.78-1.64%) for dulaglutide 1.5mg QW. Post-launch, the dose of dulaglutide for glucose lowering was increased following the AWARD 11 trial (15). This assessed the efficacy of dulaglutide 3.0mg and 4.5mg QW versus dulaglutide 1.5mg QW and reported additional glucose lowering of 1.9mmol/mol (0.17%) and 3.7mmol/mol (0.34%) respectively, which were both statistically significant after 36 weeks treatment.

Phase 3 clinical trials of semaglutide were named SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 diabetes) and included 8,416 people with T2DM (SUSTAIN 1-5) (16, 17, 18, 19, 20). Semaglutide was assessed in people across the spectrum of T2DM, from treatment-naïve, through combinations with oral glucose lowering agents and insulin. All were randomised controlled trials (RCTs) and assessed HbA1c lowering over 30 – 56 weeks versus placebo, sitagliptin, exenatide ER and insulin glargine U100. The fall in HbA1c was significantly greater for both doses of semaglutide versus comparator and ranged from 13.2-16.0 mmol/mol (1.2-1.5%) for 0.5mg QW and 16.8-20.2mmol/mol (1.6-1.9%) for semaglutide 1.0mg QW. An application to the FDA for a 2.0mg QW dosing of semaglutide for glucose lowering was refused in March 2021 but resubmission is anticipated (21).

The SUSTAIN 7 trial was a direct comparison of semaglutide with dulaglutide (22). Patients with T2DM and suboptimal glycaemic control on metformin were randomised to dulaglutide 0.75mg or 1.5mg QW versus semaglutide 0.5mg or 1.0mg QW. The mean BMI was 33.1–33.7 kg/m^2 and diabetes duration 7.0–7.7 years. The mean baseline HbA1c was 66.1–67.2 mmol/mol (8.2-8.3%) and fell significantly in all treatment cohorts after forty weeks. Comparison of the low and high doses of each drug showed a significant advantage for semaglutide over dulaglutide (semaglutide 0.5mg QW 16.5 mmol/mol (1.5%) versus dulaglutide 0.75mg QW 12.1 mol/mol (1.1%) and semaglutide 1.0mg QW 19.4 mmol/mol (1.8%) versus dulaglutide 1.5mg 14.9 mmol/mol [1.4%]).

Weight

Dulaglutide 1.5mg QW and exenatide exhibited similar effects on body weight in AWARD-1 but patients receiving the 0.75mg QW dose experienced a small weight gain compared with exenatide (9). In the AWARD-3 monotherapy study, there was similar weight loss with dulaglutide 1.5mg QW compared with metformin but significantly less with the lower 0.75mg QW dose (11). In AWARD-5 weight loss was significantly greater for both dulaglutide doses compared with sitagliptin 100mg OD (13) and in the two head-to-head comparisons with insulin glargine U100 (AWARD-2 and AWARD-4) there was a significant weight advantage for dulaglutide (10, 12). In AWARD-6, patients taking dulaglutide 1.5mg QW showed significantly less weight loss versus liraglutide 1.8mg OD (14). In the AWARD-11 trial, the higher doses of dulaglutide led to increased weight loss compared with 1.5mg QW (0.9 Kg for 3.0mg QW and 1.6Kg for 4.5mg QW) (15).

Reduction in weight was a secondary endpoint in the SUSTAIN programme and weight loss with semaglutide 0.5mg QW and 1.0mg QW was significantly better than placebo, sitagliptin and insulin glargine U100 (22). Semaglutide 0.5mg QW was associated with 3.5 - 4.6 Kg weight loss, equivalent to 3.7 – 4.8% reduction of baseline body mass. The 1.0 mg QW semaglutide dose achieved reductions of 4.5 - 6.5 Kg (4.7 – 7.0% baseline body mass). Significant weight loss was also seen when semaglutide was added to basal insulin therapy. Finally, in the head-to-head comparison of semaglutide versus dulaglutide, weight loss data showed highly significant findings for the comparison of the two doses of semaglutide versus dulaglutide, with reductions of 4.6 and 6.5kg (semaglutide 0.5mg and 1.0mg QW) versus 2.3 and 3.0kg (dulaglutide 0.75mg and 1.5mg QW) respectively (22).

The clear advantage of semaglutide over dulaglutide in weight loss has led to the former being assessed in high dose as an anti-obesity agent (24). The Semaglutide Treatment Effect in People with obesity (STEP) programme is made up of five studies of overweight individuals (mean BMI 35.7 - 38.5 Kg/m2). STEP 1 assessed the efficacy and safety of subcutaneous semaglutide 2.4mg QW versus placebo in 1,961 adults treated for 68 weeks (25). The trial met both co-primary endpoints with a statistically significant body weight reduction with semaglutide 2.4mg QW compared to placebo. Semaglutide-treated subjects achieved a mean weight loss of 14.9%, (from baseline body weight of 105.3 kg) compared to a 2.4% weight loss with placebo; 86.4% achieved weight loss > 5% compared to 31.5% with placebo. The most common adverse events (AEs) among people treated with high dose semaglutide were gastrointestinal (GI) and these were typically transient and mild or moderate in severity. STEP 2 assessed semaglutide 2·4mg QW versus 1·0mg QW and placebo in 1,210 overweight or obese adults with type 2 diabetes again treated for 68 weeks (26). Estimated change in mean bodyweight was –9·6% with semaglutide 2·4mg QW versus –3·4% with placebo. 68.8% of subjects on semaglutide 2·4mg lost >5% of body weight compared with 28·5% on placebo (p<0·0001). AEs were more frequent with semaglutide 2·4mg QW and 1·0mg QW compared with placebo (being 87.6%, 81.8% and 76·9% respectively).

STEP 3 compared the effects of semaglutide 2.4mg QW with placebo for weight management in adults with overweight or obesity, as an adjunct to a low-calorie diet for 8 weeks and intensive behavioural therapy (made up of thirty counselling visits) (27). 611 participants were followed for 68 weeks with the same co-primary outcomes as in STEP 1 and STEP 2. The estimated mean body weight change from baseline was –16.0% for semaglutide vs –5.7% for placebo (P<0.001). 86.6% of semaglutide participants lost >5% baseline body weight versus 47.6% who received placebo (P<0.001). Treatment discontinuation due to GI side-effects occurred in 3.4% of semaglutide participants compared with 0% placebo. STEP 4 reported on 803 participants who received 20 weeks treatment with subcutaneous semaglutide, escalated to 2.4mg QW who were then randomised to continued drug versus placebo (both with continued lifestyle intervention) for a further 48 weeks (28). The recruits who continued to receive semaglutide had a further mean weight loss of 7.9% over the second period of the trial whereas those who switched to placebo gained a mean of 6.9%, giving a difference of 14.8% in favour of semaglutide. This indicates that maintenance of semaglutide is necessary to continue weight reduction and avoid weight regain. As a result of the STEP programme data, the FDA has recently approved once weekly semaglutide for weight loss; a licence for this indication has not yet been granted in the European Union.

The SELECT study commenced in 2018 and is a randomised, double-blind, placebo-controlled trial to determine the impact of semaglutide 2.4mg QW on cardiovascular outcomes in overweight or obese participants with cardiovascular disease who do not have diabetes (29). The primary endpoint is a composite of the major adverse cardiovascular events (MACE), cardiovascular death, nonfatal MI or nonfatal stroke (3-component MACE). The study is due to enrol around 17,500 participants with estimated completion in 2023 and is the first cardiovascular outcome trial (CVOT) in obesity powered to detect superiority of a therapeutic intervention (30).

Blood Pressure and pulse

GLP-1RAs are known to raise pulse rate and to reduce blood pressure (BP) although they are not approved as blood pressure lowering therapies (31, 32). Dulaglutide was assessed in a study using ambulatory BP and pulse monitoring over a twenty-six-week period (33). 755 subjects with T2DM received either dulaglutide 0.75mg QW, dulaglutide 1.5mg QW or placebo and were subjected to three 24-hour periods of ambulatory monitoring. After 26 weeks, the placebo-corrected systolic BP fell by 1.7mmHg (dulaglutide 0.75mg QW) and 2.7 mmHg (1.5mg QW). Placebo-corrected increases in diastolic BP of 0.2mmHg and 0.5mmHg respectively were observed. Heart rate increases of 1.3 beats per minute (BPM) and 3.5 BPM were seen at 26 weeks for the 0.75mg and 1.5mg dulaglutide doses.

In the SUSTAIN phase 3 programme, therapy with semaglutide 0.5mg QW was associated with a fall in systolic blood pressure (SBP) of 2.4-5.1 mm Hg whilst the 1.0mg QW dose led to a fall of 2.7-6.3 mm Hg (23). This effect was significantly greater than that seen with comparators except for placebo in SUSTAIN 1 (16) and dulaglutide in SUSTAIN 7 (22). Diastolic blood pressure was also lowered although to a lesser extent, and generally not significantly different from comparators (apart from SUSTAIN 7 where semaglutide achieved a larger reduction than dulaglutide [22]).

Across the programme, semaglutide caused an increase in pulse rate of 1–4 BPM. In SUSTAIN 7 semaglutide 1.0mg QW showed a greater increase in heart rate than dulaglutide 1.5mg QW (4.0 *versus* 2.4 BPM) (23).

Cardiovascular Outcome Trials (CVOTs)

CVOTs were mandated by the Food and Drug Administration (FDA) in the United States in 2008 for new glucose lowering medicines (34). This followed on from a controversy as to whether rosiglitazone, a thiazolidinedione, caused an increase in myocardial infarction in people with T2DM (who are already at a significantly increased risk) (35). Both dulaglutide and semaglutide have been examined in placebo controlled CVOTs.

The 'Researching CV Events with a Weekly INcretin in Diabetes' (REWIND) study was the CVOT for dulaglutide and it recruited 9,901 people with T2DM, HbA1c < 9.5% (90mmol/mol) and an estimated glomerular filtration (eGFR) rate $\geq$ 15mL/min (36). The mean age of participants was 66 years, 55% were male and 69% did not have known cardiovascular disease. Participants were given dulaglutide 1.5mg QW or placebo on top of standard of care. The primary endpoint was the 3-component MACE (as above). 'Standard of care' is mandated by the FDA and requires optimal management of hypertension, LDL-cholesterol and use of anti-platelet therapies in diabetes CVOTs, as well as aiming for equivalent glucose lowering in each of the trial arms (34). In 12% of dulaglutide participants, the primary endpoint was observed, versus 13% placebo, and resulted in a hazard ratio (HR) of 0.88 with confidence intervals (CI) between 0.79 and 0.99. Hence, the statistically significant superiority of dulaglutide was demonstrated (P=0.026). The REWIND trial had the longest median follow-up and lowest placebo event rate of the diabetes CVOTs. This was because only a minority of trial participants (31%) had prior cardiovascular disease (defined as previous MI, ischaemic stroke, revascularisation, unstable angina with ECG changes or myocardial ischaemia on imaging or stress test). It is of note that the HR (0.87, CI 0.74-1.02) was identical in both the primary and secondary prevention cohorts, showing that the overall outcome was not driven by the results from high-risk subjects. This was in contrast to results from the LEADER CVOT trial for liraglutide, which appeared to show little benefit in lower risk participants (37).

Subcutaneous semaglutide was evaluated in the SUSTAIN 6 trial (38), which was designed as a non-inferiority (safety) study, to be followed by a larger superiority study following drug approval. SUSTAIN 6 was, therefore, much smaller and shorter than REWIND. Subjects were allocated to semaglutide 0.5mg and 1.0mg QW or volume-matched placebo, in addition to cardiovascular standard of care. SUSTAIN 6 enrolled 3,297 people with T2DM at high CV risk and was both event and time-driven, patients having two years exposure to trial product. High CV risk was defined by two categories; age ≥50 years and an established CV disease (cerebrovascular disease, coronary heart disease, chronic kidney disease (stage 3 or higher), peripheral vascular disease or chronic heart failure of New York Heart Association classes II–III), or age >60 years and one or more CV risk factors. The primary outcome was, once again, the 3-component MACE, which occurred in 6.6% people receiving semaglutide versus 8.9% placebo (HR 0.74 (95% CI [CI] 0.58 – 0.95). This 26% reduction in HR for the primary endpoint demonstrated statistically significant CV safety for semaglutide (P<0.001); a test for superiority was also significant (P<0.02) although this was not pre-specified (because it was completely unexpected). For reasons outlined below, the follow-on superiority CVOT of subcutaneous semaglutide was never undertaken.

Both dulaglutide and semaglutide have demonstrated CV safety and superiority over placebo in CVOTs, albeit with differing levels of trial evidence. Both are now recommended as second-line therapy for glucose lowering after metformin in people with T2DM and atherosclerotic CVD (ASCVD) or even as first-line, prior to metformin, in some cardiology guidelines (39, 40).

Possible Neuroprotection

Analysis of the individual parts of the 3-component MACE in both REWIND and SUSTAIN 6 show that non-fatal stroke was significantly reduced in these GLP-1RAs. In REWIND, dulaglutide 1.5mg QW reduced the HR by 24% (HR 0.76; CI 0.61-0.95, P=0.017)) and in SUSTAIN 6 the HR was 0.61 (CI 0.38-0.99, P=0.04) (36, 38).

An exploratory analysis further examined stroke outcomes in REWIND (41). In the trial, strokes were categorised into three sub-groups: fatal or non-fatal, ischaemic, haemorrhagic, or undetermined. The modified Rankin scale was used to determine stroke severity. During the median follow-up of 5·4 years, 3·2% of 4,949 participants assigned to dulaglutide (N=158) and 4·1% of 4,952 placebo participants (N=205) suffered from a stroke (HR 0·76, CI 0·62–0·94; P=0·010). Dulaglutide reduced the incidence of ischaemic stroke (HR 0·75, CI 0·59–0·94, P=0·012) but did not impact the risk of haemorrhagic stroke (HR 1·05, CI 0·55–1·99; P=0·89). Dulaglutide was also found to reduce the composite of non-fatal stroke or all-cause death (HR 0·88, CI 0·79–0·98; P=0·017) and disabling stroke (HR 0·74, CI 0·56–0·99; P=0·042). Treatment assignment did not affect the degree of disability post-stroke. The authors interpretation was that long-term use of dulaglutide may reduce clinically relevant ischaemic stroke in people with T2DM but did not affect stroke severity.

Another exploratory analysis of REWIND focussed on cognitive impairment. In the study, both the Montreal Cognitive Assessment (MoCA) and Digit Symbol Substitution Test (DSST) were used to assess cognitive function (42). The exploratory primary cognitive outcome was first occurrence of a follow-up score on MoCA or DSST that was 1·5 standard deviations or more below the baseline mean score in the participant's country. Baseline and follow-up scores were available for 8,828 trial participants of whom 4,456 received dulaglutide and 4,372 placebos. In dulaglutide participants, the cognitive outcome occurred in 4·05 per 100 patient-years versus 4·35 per 100 patient-years in participants receiving placebo (HR 0·93, CI 0·85–1·02; P=0·11). After a *post hoc* adjustment for individual standardised baseline scores, the HR for substantive cognitive impairment was reduced by 14% in those assigned dulaglutide (HR 0·86, CI 0·79–0·95; P=0·0018) suggesting that long-term therapy might reduce cognitive impairment in people with T2DM.

A *post hoc* analysis on pooled data from three CVOTs including two using semaglutide was performed to examine dementia-related AEs (43). 15,820 patients with median follow-up of 3.6 years were included in this analysis and AEs were identified using Standardised MedDRA (version 21.1) query for 'dementia' narrow search terms. Across the three CVOTs, 15 GLP-1 RA-treated patients and 32 placebo-treated patients were identified with development of dementia, giving a significant estimated HR of 0.47 (CI 0.25-0.86) in favour of the GLP-1 RA treatment. A placebo controlled RCT of semaglutide in people with early Alzheimer's disease (EVOKE) is due to begin recruitment in 2021 (44).

There are small studies in Parkinson's Disease (PD) suggesting that exenatide may improve motor impairment and a two-year placebo-controlled RCT of exenatide ER (EXENATIDE-PD3) is currently recruiting patients (45, 46, 47). In-keeping with this, are studies suggesting that semaglutide may have a neuroprotective effect in animal models of PD. Zhang et al examined the neuroprotective effects of semaglutide in the MPTP mouse model and showed reduced motor impairment and changes consistent with protection of dopaminergic neurons (48). A clinical trial testing semaglutide in PD patients is planned (49).

Possible Renoprotection

In common with other diabetes CVOTs the REWIND trial investigators examined other efficacy and safety outcomes apart from the primary cardiovascular endpoints. An exploratory analysis of REWIND was simultaneously published with the main study to assess the effect of dulaglutide on the renal component of the composite microvascular outcome (50). This was defined as the first occurrence of new macroalbuminuria (UACR >33.9 mg/mmol [>300 mg/g]), a sustained decline in eGFR of 30% or more from baseline, or chronic renal replacement therapy. At baseline, 791 (7.9%) subjects had macroalbuminuria and mean eGFR was 76.9 mL/min/1.73 m^2. During follow-up, the renal composite outcome occurred in 848 (17.1%) participants in the dulaglutide group and in 970 (19.6%) placebo participants (HR 0.85, CI 0.77–0.93; P=0.0004). The major driver was new onset macroalbuminuria (HR 0.77, CI 0.68–0.87; P<0.0001), with HRs of 0.89 (CI 0.78–1.01; P=0.066) for sustained decline in eGFR of 30% or more and 0.75 (CI 0.39–1.44; P=0.39) for chronic renal replacement therapy.

Although the HR for a sustained decline in eGFR of 30% was non-significant, the favourable trend led the authors to perform a series of sensitivity analyses. These showed that dulaglutide was associated with a significantly reduced incidence of a sustained eGFR decline of 40% or more (HR 0·70, CI 0·57–0·85) and 50% or more (HR 0·56, CI 0·41–0·76) (50). These results are also supportive of the findings from the AWARD-7 trial (51). This was a 26-week study comparing dulaglutide 0.75mg and 1.5mg QW with insulin glargine U100 in participants with T2DM and moderate or severe CKD. The trial reported comparable glycaemic control, however, participants receiving dulaglutide experienced greater weight loss and less hypoglycaemia than those receiving insulin glargine. Additionally, eGFR decline was mitigated and albuminuria was reduced: these benefits were most evident when the UACR exceeded 3.39 mg/mmol (30 mg/g).

In SUSTAIN 6, renal microvascular outcomes were pre-specified secondary outcomes and there was a significant reduction of the composite renal endpoint (HR 0.64; CI 0.46–0.88; P=0.005) (38). This success was driven by a fall in new cases of persistent macroalbuminuria (2.5% versus 4.9%) whereas trial participants who experienced a doubling of serum creatinine and/or needed continuous renal replacement therapy was a small number and similar between groups. This improvement in renal composite outcome driven by reductions in albuminuria rather than 'hard' clinical renal endpoints is not unusual and has been seen with liraglutide and lixisenatide (as well as with linagliptin, a DPP4-inhibitor) (37, 52, 53). To settle the question definitively regarding reno-protection, a placebo-controlled trial of semaglutide with primary renal endpoints is currently ongoing and expected to

report in 2024 (54). The primary endpoint for this study is time to first occurrence of a composite of persistent eGFR decline of greater than or equal to 50% from baseline, ESKD (eGFR <15 mL/min/1.73 m^2, dialysis or transplantation), death from kidney disease or death from cardiovascular disease.

Possible Hepatoprotection

A *post hoc* analysis of 1,499 participants from AWARD-1, AWARD-5, AWARD-8 and AWARD-9 evaluated the effect of dulaglutide 1.5mg QW on liver and metabolic parameters in people with T2DM and in a subgroup with possible non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) (9, 5, 55, 56, 57). Thresholds of alanine aminotransferase (ALT) ≥30 IU/l in men and ≥19 IU/l in women were used to determine the NAFLD/NASH subgroup. In the overall population at 6 months, dulaglutide significantly reduced ALT, aspartate transaminase (AST) and γ-glutamyl transpeptidase (γGT) levels versus placebo. In the subgroup with presumed NAFLD/NASH, more pronounced reductions in ALT were observed with dulaglutide versus placebo (–8.8 IU/L vs –6.7 IU/L) whereas there was no significant difference between groups when the baseline ALT was in the normal range.

The impact of dulaglutide on liver fat was subsequently assessed in an open-label, parallel-group RCT (58). Sixty-four adults with T2DM and MRI-derived proton density fat fraction-assessed liver fat content (LFC) ≥6.0% at baseline, were randomly assigned to receive dulaglutide QW for 24 weeks or usual care. Dulaglutide resulted in a control-corrected absolute change in LFC of −3.5% (CI −6.6, −0.4; P= 0.025) and relative change of −26.4% (−44.2, −8.6; P= 0.004). Dulaglutide-treated participants also showed a significant reduction in γGT levels. The authors suggested that dulaglutide could be considered for early treatment of NAFLD in people with T2DM.

Considering semaglutide liver data, analysis of ALT and high-sensitivity C-reactive protein (hsCRP) from SUSTAIN 6 and a 52-week weight management trial (semaglutide 0.05-0.4 mg/day) was undertaken (59). In weight management trial participants, 52% presented with elevated baseline ALT (defined as above) and end-of-treatment ALT reductions were seen in 6-21% (P<0.05 for doses≥0.2 mg/day)) and hsCRP reductions 25-43% vs placebo (P < 0.05 for 0.2 and 0.4 mg/day). Normalisation of elevated ALT occurred in 25-46% of weight management trial subjects versus 18% on placebo. Elevated baseline ALT was present in 41% of SUSTAIN 6 subjects. In these subjects, no significant ALT reduction was noted for semaglutide 0.5mg QW whereas a significant 9% reduction vs placebo was seen for semaglutide 1.0 mg QW (P = 0.0024). Treatment ratios for changes in ALT and hsCRP were, however, not statistically significant after adjustment for weight change.

Newsome et al conducted a 72-week, double-blind trial in people with biopsy-confirmed NASH and stage F1-3 liver fibrosis who were randomised to various doses of subcutaneous semaglutide OD or placebo (60). The primary endpoint was resolution of NASH with no worsening of fibrosis and 320 people (230 with F2 or F3 fibrosis) were included. The percentage of subjects who satisfied the primary endpoint was 36-59% of the semaglutide-treated patients and 17% placebo; this was significant (P<0.001) for semaglutide 0.4mg OD versus placebo. A confirmatory secondary endpoint of improvement of at least one fibrosis stage occurred in 43% of semaglutide 0.4mg OD patients and 33% of placebo (P = 0.48). The authors concluded that treatment with semaglutide resulted in a significantly higher percentage of patients with NASH resolution than placebo, however, without an improvement of fibrosis stage.

Safety

The AEs seen with dulaglutide and semaglutide are mainly GI (nausea, vomiting & diarrhoea), as expected with this class of glucose lowering therapies (61, 62, 63). In the SUSTAIN 7 direct comparison,

GI AEs were reported in 43-44% of subjects receiving 0.5mg and 1.0mg QW semaglutide compared with 33-48% for 0.75mg and 1.5mg doses of dulaglutide (22). In AWARD-11, the higher doses of dulaglutide (3.0 & 4.5mh QW) had more GI AEs than the 1.5mg QW comparator (15). GI AEs can lead to patient drop-out in clinical trials and poor adherence with GLP-1RA therapies in the real world. This can be partially addressed by a slow escalation of dose, smaller portion sizes, advising people to stop eating if they feel nauseated and the avoidance of spicey or fatty meals.

The initial concerns regarding an increased risk of thyroid C-cell malignancy and pancreatic pathology (pancreatitis and pancreatic cancer) have not been substantiated for the GLP-1RA class. There is no clinically significant increase in risk of benign or malignant neoplasia with dulaglutide or semaglutide. Rates of non-malignant gall bladder pathology are low with both drugs (62, 63).

An unexpected safety signal from SUSTAIN 6 was an increase in diabetic retinopathy (DR) events (38). DR endpoints were reported for more people randomised to semaglutide (50 subjects (3.0%)) than to placebo (29 subjects (1.8%), p=0.02). Visbol et al. subsequently conducted a detailed evaluation of DR data from the SUSTAIN clinical trial programme (64). No difference in DR AEs was found comparing semaglutide with comparator in the SUSTAIN 1-5 (and Japanese regulatory) trials. During these studies it was noted that patients were excluded from recruitment if they were suffering with DR requiring active medical treatment and HbA1c limits were set at 86-91mmol/mol (10.0-10.5%), neither of which applied to SUSTAIN 6. They also reported that the impact of semaglutide on DR events could be a result of the speed and degree of HbA1c reduction during the first 16 weeks of the trial (65). Furthermore, the DR AEs were seen in individuals with pre-existing DR, high HbA1c at baseline and who were already receiving insulin. It is of interest that in REWIND there was a 24% (albeit non-significant) increase in DR events with dulaglutide, the latter in a trial with an upper HbA1c inclusion limitation of 81mmol/mol (9.5%) (36).

The EMA have requested a RCT to generate further evidence regarding DR and semaglutide. This trial (named FOCUS) is recruiting people with T2DM and an Early Treatment Diabetic Retinopathy Study (ETDRS) level of 10-75; evaluations are by fundus photography and assessed by a central reading centre (66). The primary endpoint of this placebo-controlled trial is presence of at least 3 steps ETDRS subject level progression. The study completion date is estimated to be 2025.

Oral GLP-1RAs

An orally available preparation of semaglutide was approved in 2019 as a co-formulation with 300mg Sodium N-(8-[2-hydroxybenzoyl] Amino) Caprylate (SNAC) (67). SNAC is a small fatty acid derivative which causes a local increase in pH in the stomach leading to higher solubility and protection of the semaglutide peptide from proteolytic degradation (68). It also enhances the transcellular absorption of semaglutide. The effect of SNAC is strictly time-, molecular size- and concentration-dependent and is fully reversible. It is rapidly cleared with no accumulation and has previously been co-formulated with other drugs such as heparin and vitamin B12 to increase their absorption and so is considered to be safe (69, 70).

For optimal effect, the semaglutide/SNAC co-formulation must be taken in the fasting state with no food or drink (other than a small volume of water [<120mL]) for 30 minutes – this includes avoidance of other oral medications for this period. Even with these restrictions, the absorption of semaglutide is low (~1%) and has significant day-to-day variation and so once-daily dosing is recommended. Once absorbed, the long half-life of semaglutide smoothes out the differences in daily drug exposure and allows for high levels of efficacy. This has been confirmed in the Peptide InnOvatioN for Early diabetes tReatment (PIONEER) programme of phase 3 clinical trials (71). PIONEER assessed oral semaglutide across the spectrum of T2DM, from people who were treatment naïve (PIONEER 1) through to those

treated with insulin (PIONEER 8) (72, 73). In patients with sub-optimal HbA1c treated with oral glucose lowering therapies (metformin, sulphonylureas, TZD and SGLT2-inhibitors), oral semaglutide has been compared with empagliflozin 25mg OD (PIONEER 2), sitagliptin 100mg OD (PIONEER 3 & 7) and liraglutide 1.8mg OD (PIONEER 4) (74, 75, 76, 77). The primary endpoint in all but one of these trials (PIONEER 7) was change in HbA1c at the end of twenty-six weeks exposure to trial product.

The baseline characteristics of people recruited to PIONEER 1-4 and 8 were baseline age 55-61 years, diabetes duration 3.5-15 years, BMI 31-33 Kg/m2 and HbA1c 64-67mmo/mol (8.0-8.3%) (69). The higher maintenance dose of oral semaglutide (14mg OD) demonstrated a superior reduction in HbA1c versus all comparators (placebo, empagliflozin, sitagliptin and insulin). In the three trials that included the lower maintenance dose of 7mg OD, oral sitagliptin was statistically superior to placebo and sitagliptin 100mg OD. In all five of these PIONEER trials, both doses of oral semaglutide achieved significantly higher proportions of subjects achieving a HbA1c <53mmol/mol (<7.0%) versus comparator. The reductions in HbA1c seen with oral semaglutide were 13-15mmmol/mol (1.2-1.4%) for the 14mg OD dose.

Considering the secondary endpoint of change in body weight, in the same studies oral semaglutide 14mg OD achieved statistically superior weight loss compared to placebo, semaglutide, liraglutide and insulin. The mean weight loss seen after 26 weeks was 3.4-4.4 Kg for oral semaglutide 14mg OD and only empagliflozin 25mg OD achieved a similar weight reduction. Across the PIONEER trial programme, the AEs were largely GI in nature, as expected with the GLP-1RA class. There were no unexpected AEs and rates of hypoglycaemia were low and similar to comparators (including placebo).

PIONEER 6 was the CVOT for oral semaglutide (79). Key inclusion criteria were T2DM and increased cardiovascular risk defined as; age $\geq$50 years and clinical evidence of CV disease or moderate CKD or age $\geq$60 years and CV risk factors only. 3,183 people were recruited and randomised 1:1 to oral semaglutide escalated to the 14mg OD dose or matched placebo, on top of CV standard of care. The primary composite endpoint was the 3-component MACE and it is important to note that PIONEER 6 was purely event-driven, with the aim to complete as soon as possible after 122 first MACEs had occurred. The mean age at baseline was approximately 66 years and 68.4% of participants were male. The mean body weight was 90.9Kg and HbA1c 66mmol/mol 8.2%). They had a mean duration of T2DM of almost 15 years and the majority (85%) had established CV disease and/or moderate CKD.

PIONEER 6 completed after only 83 weeks, at which point there had been 61 MACE events in the semaglutide group and 76 in placebo, giving a HR of 0.79 (CI 0.57-1.11) which confirmed non-inferiority (CV safety) (P<0.0001) (80). Since the confidence intervals crossed unity, CV superiority was not confirmed (P=0.1749), however, there were encouraging reductions in both CV death (HR 0.49, CI 0.27-0.92) and total mortality (HR 0.51, CI 0.31-0.84) both in favour of oral semaglutide. Importantly there was no signal for increased DR events, patients with proliferative retinopathy or maculopathy requiring treatment having been excluded from the trial.

The reason for the short duration of PIONEER 6 was that, as was the case for SUSTAIN 6, it was designed as a pre-licence study to demonstrate CV safety with a larger superiority study to follow. The original trial of injectable semaglutide 'A Heart Disease Study of Semaglutide in Patients with Type 2 Diabetes (SOUL)' had been postponed in 2018 after the FDA agreed that only one CVOT was needed, implying a view was that the CV effects of the semaglutide molecule would be the same irrespective of its mode of delivery. Hence, the SOUL trial which commenced in 2019 is comparing oral semaglutide with placebo in 9,462 people with T2DM and established CVD or CKD on top of CV standard of care (81). It had a twenty month recruitment period (which was unaffected by the Covid-19 pandemic) and

is event-driven, aiming for 1,225 3-component MACEs. The anticipated trial duration is five years and so results should be available in 2024.

The view of the FDA has also further legitimised *post hoc* analyses that pool data from the SUSTAIN 6 and PIONEER 6 CVOTs (which had identical inclusion criteria and hence populations with very similar baseline characteristics) (82, 83). These suggest that semaglutide has a beneficial impact on the MACE outcome across a continuum of baseline CV risk, similar to that reported with deulaglutide in the REWIND study.

Small molecule GLP-1RAs – the future?

Until very recently it seemed implausible that the complex interactions between the GLP-1 peptide and the extracellular domain of its receptor could be achieved by small non-peptide molecules (84). However, at least three such GLP-1RAs are now in development (TT-OAD2, LY3502790 and PF-06882961) and one of these has reported data from a four-week Phase 1 study during the scientific sessions of the American Diabetes Association in June 2020 (85). Danuglipron (PF-06882961) was assessed in three doses (15, 70 and 120mg OD) and reduced HbA1c by 10-13mmol/mol (0.9-1.2%) versus 4mmol/mol (0.4%) for placebo (86). The 70mg and 120mg doses reduced body weight by 4.0 kg and -7.9 kg respectively compared to -1.9 kg change with placebo. Of note, the pharmacokinetic profiles of danuglipron in the fasting and fed states were comparable, implying absorption in the small intestine rather than the stomach. This potentially enables a less restrictive dosing regimen that is required for oral semaglutide. Danuglipron was well-tolerated with AEs consistent with the GLP-1RA class.

Considering the short half-life of danuglipron (4.3-61 hours) there are likely to be attempts to create a modified-release formulation. This may also be necessary to replicate the CV benefits which are most pronounced in the currently long-acting (QW) GLP-1RAs. Pfizer has now initiated Phase 2 studies in T2DM as well as a Phase 2 study in obesity (87, 88, 89).

Conclusions

GLP-1RAs have been available as a glucose lowering therapy in T2DM for almost 15 years and have evolved from a twice daily pre-meal subcutaneous treatment into QW injections and, more recently, an oral OD option. In countries with full access, weekly GLP-1RAs are now the most common option when GLP-1RAs are initiated, with dulaglutide and semaglutide being the market-leaders. Hence, they are the focus of this review of recent developments. Both medicines deliver potent glucose lowering along with the secondary benefits of weight loss and blood pressure lowering. Reduction of body weight is more potent with high dose semaglutide, for which data from the STEP phase 3 clinical trial programme have recently been published. Neither agent is likely to be promoted as an antihypertensive option.

The cardiovascular safety and benefits of both dulaglutide and semaglutide have been examined, with superiority over placebo and CV standard of care confirmed for dulaglutide and results for semaglutide from the SOUL study awaited. All of the initial safety concerns for the GLP-1RA class (especially pancreatitis and pancreatic cancer) have been resolved, with no safety signals for dulaglutide and semaglutide. AEs for both drugs are GI (nausea, vomiting and diarrhoea), as expected from the GLP-1RA class, although there is the query regarding an increase in diabetic retinopathy AEs. A significant increase was seen in the SUSTAIN 6 trial of semaglutide although a non-significant signal for worsening of retinopathy was also seen for dulaglutide (and liraglutide). We feel that this represents the well-known phenomenon of worsening of diabetic retinopathy seen with rapid improvement in glycaemia on the background of significant retinopathy (especially with co-existing insulin treatment). This

concern is being addressed by the on-going FOCUS trial of semaglutide in patients with diabetic retinopathy, which has a composite primary retinopathy endpoint.

Going beyond glucose lowering, weight reduction and cardiovascular protection, there are other potential benefits of the GLP-1RA class. *Post hoc* analyses suggest reno protection for both dulaglutide and semaglutide and these are being formally examined for the latter in the FLOW trial, which has a composite primary renal endpoint. There is also major interest in the possibility that these agents may have brain and liver benefits. Preliminary data suggest that GLP-1RAs prevent not only stroke but also other neuro-degenerative conditions such as Alzheimer's disease and Parkinson's disease. Controlled clinical trials are on-going, as well as an additional cognitive assessment included in the SOUL CVOT of oral semaglutide. The potential for GLP-1RA therapy to treat liver pathologies such as NASH and NAFLD, which are often seen as a co-morbidity of T2DM, have also been addressed in clinical trials. Promising results will continue to be explored in people with diabetes and possibly those with pre-diabetes.

The recent licence of an oral GLP-1RA has the potential to increase access to this class of drug which has proven cardiovascular protection for people with type 2 diabetes. There is a presumption that low levels of GLP-1RA prescribing to people who would have satisfied the inclusion criteria for diabetes CVOTs was due to a reluctance to initiate injectable therapies in primary care. The phase 3 clinical trials suggest that oral semaglutide has high efficacy in terms of glucose lowering and weight reduction, however, the restrictions in terms of fasting dosing and subsequent avoidance of food, drink and other medications for 30 minutes post-administration may impact on efficacy (although this was not an issue for trial participants). Perhaps the small molecule GLP-1RA drugs beginning to be assessed in phase 2 clinical trials will address this issue going forwards….

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