GLP-1 receptor agonist and basal insulin co-therapy in type 2 diabetes: Clinical evidence and practicalities of use

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Article points

1. The combination of a basal insulin and a glucagon-like peptide-1 (GLP-1) receptor agonist (RA) can result in improved glycaemic control and no weight gain or weight loss, and with potential advantages in terms of hypoglycaemia risk.
2. While there may be gastrointestinal side effects with GLP-1 RAs, these are generally transient and can be reduced through slow titration and dietary adjustments.
3. New GLP-1 RA and basal insulin products, such as once-daily fixed-ratio combinations, may potentially lead to further improvements in efficacy, tolerability and convenience.

Key words

- Basal insulin
- Combination therapy
- GLP-1 receptor agonists

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Many people with type 2 diabetes in the UK are not reaching glycaemic treatment targets. A treatment regimen combining a basal insulin and a glucagon-like peptide-1 (GLP-1) receptor agonist (RA) can result in improved glycaemic control and may encourage weight loss and provide potential advantages in terms of reducing hypoglycaemia risk. There may be transient gastrointestinal side effects with GLP-1 RAs; however, these can be reduced using slow titration and through dietary adjustments. New GLP-1 RA and basal insulin products, such as once-daily fixed-ratio combinations, may potentially lead to further improvements in efficacy, tolerability and convenience of their co-use.

Owing to the progressive nature of the condition, many people with type 2 diabetes will eventually require insulin therapy; however, insulin initiation is often substantially delayed in UK clinical practice (Blak et al, 2012a; Khunti et al, 2013). In those people who have started basal insulin therapy, many are not achieving adequate glycaemic control (Dale et al, 2010; Blak et al, 2012a; Blak et al, 2012b). Despite elevated HbA_{1c} levels, intensification of basal insulin therapy with meal-time or pre-mixed insulins appears infrequent (Blak et al, 2012b). Combining basal insulin and glucagon-like peptide-1 (GLP-1) receptor agonist (RA) therapies is a treatment approach that may help overcome the inertia with basal insulin initiation alone or insulin intensification. This article reviews the potential benefits of this treatment combination in people with type 2 diabetes and addresses the practicalities of implementing such an approach in primary care.

Brief overview of GLP-1 RAs

GLP-1 RAs improve glycaemic control by stimulating insulin secretion and inhibiting glucagon secretion in response to elevated glucose levels, such as post-meal hyperglycaemia (Baggio and Drucker, 2007). As a result of this glucose-dependent mechanism of action, rates of hypoglycaemia are very low with GLP-1 RA treatment, except when combined with sulphonylurea or insulin treatment (Nauck et al, 2009; Marre et al, 2009). Treatment with GLP-1 RA therapy is also generally associated with clinically significant weight loss, the extent of which varies with each agent (Vilsbøll et al, 2012). The most common side effect with GLP-1 RA therapy is transient gastrointestinal (GI) adverse events, although these usually subside within 12 weeks of treatment (MacConell et al, 2012) and with practical meal adjustments (Hicks et al, 2014).

There are currently five GLP-1 RAs available for use in the UK: exenatide once weekly (Bydureon®), exenatide twice daily (Byetta®), liraglutide (Victoza®), lixisenatide (Lyxumia®) and – the most recent addition – dulaglutide once weekly (Trulicity®). An overview of these agents is presented in *Table 1*.

Rationale for combining GLP-1 RAs and basal insulin

While the licences of some of the GLP-1 RAs may have been updated only relatively recently to include combination with basal insulin therapy, the concept is not new to the UK. In audits of both exenatide (2007) and liraglutide (2009) by the Association of British Clinical Diabetologists, the combination

Table 1. Overview of GLP-1 RAs (electronic Medicines Compendium, 2014a; 2014b; 2015a; 2015b; 2015c; 2015d; 2015e).

	Dulaglutide (Trulicity®)	Exenatide once weekly (Bydureon®)	Exenatide twice daily (Byetta®)	Liraglutide (Victoza®)	Lixisenatide (Lyxumia®)
Dose frequency and timing	Once weekly – any time of day, independent of meals	Once weekly – any time of day, independent of meals	Twice daily – any time within an hour before the morning and evening meal (or the two main meals of the day, approximately 6 hours or more apart)	Once daily – any time of day, independent of meals	Once daily – any time within an hour before any meal of the day
Dosage	Monotherapy: 0.75 mg Add-on therapy: 1.5 mg	2 mg	Initial: 5 µg Maximum: 10 µg	Initial: 0.6 mg Maximum: 1.8 mg	Initial: 10 µg Maximum: 20 µg
Licensed combinations with oral antidiabetes agents	With oral glucose-lowering products	With metformin, a sulphonylurea or pioglitazone With metformin + a sulphonylurea or pioglitazone	With metformin, a sulphonylurea or pioglitazone With metformin + a sulphonylurea or pioglitazone	With oral glucose-lowering products	With oral glucose-lowering products
Licensed insulin combinations	With insulin ± oral glucose-lowering products	None	With basal insulin ± metformin and/or pioglitazone	With basal insulin ± oral glucose-lowering products	With basal insulin ± oral glucose-lowering products
Hypoglycaemia-related dosing precautions when combined with other diabetes medications	With sulphonylurea: Consider dose reduction of sulphonylurea With insulin: Consider dose reduction of insulin	With sulphonylurea: Consider dose reduction of sulphonylurea	With sulphonylurea: Consider dose reduction of sulphonylurea With insulin: Insulin dose should be evaluated	With sulphonylurea: Consider dose reduction of sulphonylurea With basal insulin: Consider dose reduction of basal insulin	With sulphonylurea: Consider dose reduction of sulphonylurea With basal insulin: Consider dose reduction of basal insulin
Very common adverse events (≥1/10)	Hypoglycaemia (with prandial insulin, metformin* or metformin plus glimepiride), nausea, diarrhoea, vomiting* and abdominal pain*	Hypoglycaemia (with sulphonylurea), nausea, vomiting, diarrhoea, constipation and injection site pruritus	Hypoglycaemia (with sulphonylurea and/or metformin), nausea, vomiting and diarrhoea	Nausea and diarrhoea	Hypoglycaemia (with sulphonylurea and/or basal insulin), headache, nausea, vomiting and diarrhoea
Indicated use in people with renal impairment	Mild or moderate impairment: No dose adjustment required Severe impairment (eGFR <30 mL/min/1.73 m²) or worse: Not recommended on account of very limited therapeutic experience	Mild impairment (CrCl, 50–80 mL/min): No dose adjustment required Moderate impairment (CrCl, 30–50 mL/min) or worse: Not recommended on account of very limited therapeutic experience	Mild impairment (CrCl, 50–80 mL/min): No dose adjustment required Moderate impairment (CrCl, 30–50 mL/min): Dose escalation from 5 µg to 10 µg should proceed conservatively Severe impairment (CrCl <30 mL/min) or worse: Not recommended	Mild or moderate impairment (CrCl, 60–90 or 30–59 mL/min, respectively): No dose adjustment required Severe impairment (CrCl <30 mL/min) or worse: Not recommended as there is a lack of therapeutic experience	Mild impairment (CrCl, 50–80 mL/min): No dose adjustment required Moderate impairment (CrCl, 30–50 mL/min): Use with caution on account of limited therapeutic experience Severe impairment (CrCl <30 mL/min) or worse: Not recommended as there is a lack of therapeutic experience

*Very common for 1.5-mg dose; common (≥1/100 but <1/10) for 0.75-mg dose.
CrCl=creatinine clearance; eGFR=estimated glomerular filtration rate; GLP-1=glucagon-like peptide-1; RA=receptor agonist.

was extensively used off-licence in secondary care, with this being reported in almost 40% of people treated with a GLP-1 RA (Ryder and Thong, 2012). The most recent clinical guidelines for management of type 2 diabetes from NICE (2009) and SIGN (2010) do not include recommendations for this combination; the NICE guideline, which, at the time of writing, is undergoing an update, recommended further studies. However, in 2012, the American Diabetes Association and the European Association for the Study of Diabetes released a joint position statement recommending GLP-1 RA and basal insulin combination therapy for people not meeting glycaemic targets on dual

Box 1. A case study with basal insulin as an add-on to glucagon-like peptide-1 receptor agonist therapy.

Joseph is a 69-year-old man who was diagnosed with type 2 diabetes 5 years ago after developing a leg ulcer following an accident. His HbA_{1c} is 67 mmol/mol (8.3%) and he has an estimated glomerular filtration rate >60 mL/min. He has a BMI of 33 kg/m^2 and he leads an active lifestyle with a busy social life, going for many meals out with friends and playing darts twice weekly.

Started on metformin at diagnosis, he could not tolerate the side effects and was subsequently switched to treatment with modified-release metformin, eventually tolerating 2 g daily. One year after diagnosis, Joseph's HbA_{1c} had dropped to 60 mmol/mol (7.7%). Following NICE recommendations for people with an HbA_{1c} ≥47 mmol/mol (≥6.5%), gliclazide 80 mg twice daily was added to his regimen. However, he began to get dizzy spells at night and found he had to eat extra snacks before bed to prevent them. He had gained 3 kg in weight and his home blood glucose tests were 4–7 mmol/L before breakfast, 6–12 mmol/L before lunch and 4–11 mmol/L before bed. His post-meal tests could reach 15 mmol/L, particularly after meals out.

Joseph discontinued the gliclazide owing to his hypoglycaemia. He was also having trouble sleeping and was diagnosed with mild sleep apnoea. Joseph and his care team discussed his options (sodium–glucose cotransporter 2 inhibitors were not available at the time):

- Pioglitazone – these were not felt suitable owing to potential side effects.
- Insulin – Joseph expressed concern that it may affect his regular driving.
- A dipeptidyl peptidase-4 (DPP-4) inhibitor – this was opted for and worked initially but was discontinued when his HbA_{1c} had started to increase again.

After discontinuation of the DPP-4 inhibitor, Joseph and his care team chose to add in glucagon-like peptide-1 (GLP-1) receptor agonist (RA) therapy, as recommended by NICE (2009) for use in people with a BMI >30 kg/m^2 and "psychological or medical problems associated with high body weight," such as sleep apnoea.

Joseph was started on liraglutide once a day based on his home blood glucose monitoring results. He reported that the new regimen made him feel full and deterred him from snacking. His HbA_{1c} and weight improved and he reported that he generally felt well.

He began to notice that his overnight home blood glucose had risen to 10–14 mmol/L on waking. His HbA_{1c} was back up to 64 mmol/mol (8%) but his BMI had reduced to 29 kg/m^2. NICE (2009) recommendations advise to continue GLP-1 RA therapy beyond 6 months only if HbA_{1c} has dropped by a percentage point and there had been a decrease of at least 3% of initial body weight. Joseph's care team were pleased with his weight loss and wellbeing and decided to continue treating him with GLP-1 RA therapy, but with the addition of 10 units of insulin detemir at bedtime.

Since the addition of basal insulin to his regimen, Joseph finds that his overnight blood glucose test results have improved

therapy with either metformin and a GLP-1 RA or metformin and basal insulin (Inzucchi et al, 2012). This was reinforced in the recent update of this statement (Inzucchi et al, 2015).

Combining a basal insulin with a GLP-1 RA provides people with the complementary actions of the two products, as shown in a recently published systematic review and meta-analysis, which found that use of the combination in type 2 diabetes can help achieve adequate glycaemic control with no increased risk of hypoglycaemia or weight gain (Eng et al, 2014). While both classes of drug are effective at lowering blood glucose levels, basal insulin primarily acts on fasting plasma glucose (FPG), while short-acting GLP-1 RAs target postprandial glucose (PPG) and long-acting GLP-1 RAs have effects on both FPG and PPG (Drucker et al, 2008). It has been shown that fasting hyperglycaemia has the most impact on HbA_{1c} when diabetes is poorly controlled while postprandial hyperglycaemia is the major contributor in people nearing HbA_{1c} goals (Monnier et al, 2003). Additionally, insulin therapy often results in weight gain and an increased risk of hypoglycaemic events, while treatment with GLP-1 RAs can be associated with weight loss without increased risk of hypoglycaemia (Inzucchi et al, 2015).

Evidence to support the combination of basal insulin and GLP-1 RA therapy

There are two approaches to using a GLP-1 RA in combination with a basal insulin; adding a basal insulin to existing GLP-1 RA therapy or adding a GLP-1 RA to basal insulin therapy, both of which have been studied in phase III trials.

Adding a basal insulin to GLP-1 RA therapy

Two studies have demonstrated that adding basal insulin to GLP-1 RA therapy significantly reduces HbA_{1c} and with a low rate of hypoglycaemia (0.29 and 0.57 events per patient-year for liraglutide in combination with insulin detemir and insulin degludec, respectively; DeVries et al, 2012; Aroda et al, 2014). In this sequence, there was either no change in mean body weight or a small increase. *Box 1* presents a case illustrating the rationale for the addition of a basal insulin to the treatment regimen of a person with sub-optimally controlled type 2 diabetes who is already taking a GLP-1 RA.

Adding a GLP-1 RA to basal insulin therapy

The addition of a GLP-1 RA to basal insulin therapy can significantly improve HbA_{1c} levels

without increasing the risk of hypoglycaemia, and the addition of a GLP-1 RA to basal insulin is also commonly associated with clinically significant weight loss (Buse et al, 2011; Riddle et al, 2013a; Riddle et al, 2013b; Ahmann et al, 2014; Mathieu et al, 2014; Rosenstock et al, 2014a). See *Box 2* for an example of how a GLP-1 RA may be added to basal insulin therapy.

Why is this combination particularly relevant in primary care?

Owing to the improvements in glycaemic control with a low risk of hypoglycaemia when adding a basal insulin to existing GLP-1 RA therapy (DeVries et al, 2012; Aroda et al, 2014), this approach presents primary care clinicians with a potentially attractive option for appropriate people with diabetes. Additionally, while intensifying basal insulin treatment by adding in a prandial or pre-mixed insulin often requires referral to secondary care, which may lead to increased costs and delays due to longer waiting times (Cuddihy et al, 2011), we feel that the addition of a GLP-1 RA to basal insulin is more suitable for a primary care setting.

Furthermore, intensification of basal insulin with a GLP-1 RA may be more acceptable to people with diabetes than the addition of prandial insulin injections owing to the more favourable weight profile and reduced likelihood of hypoglycaemic events with the GLP-1 RA (Mathieu et al, 2014; Rosenstock et al, 2014a). Basal insulin intensification with a GLP-1 RA has also been shown to be associated with reduced hospitalisation rates and lower all-cause costs compared with intensification using prandial insulin, in a US setting (Dalal et al, 2015).

Practical tips for using the combination

Adjusting prior medication doses

To reduce the risk of hypoglycaemia when adding a GLP-1 RA to basal insulin, a reduction in basal insulin dose should be considered (*Table 1*). In clinical studies, protocols have generally specified a reduction of around 20–25% of the prior dose in people with HbA_{1c} <69 mmol/mol (<8.5%) at initiation (Viswanathan et al, 2007; Buse et al, 2011). In addition – again, owing to the risk of hypoglycaemia – for people treated with a GLP-1 RA or basal insulin in combination with a sulphonylurea, withdrawal, or at least a dose reduction, of the sulphonylurea should be considered prior to intensifying therapy with a basal insulin or GLP-1 RA (see *Table 1*).

Timing of injections

Injections should be administered as recommended in each product's prescribing information, with regards to timing and frequency. Basal insulin and GLP-1 RA injections can be administered at the

Box 2. A case study with a glucagon-like peptide-1 receptor agonist as an add-on to basal insulin therapy.

Judy is a 54-year-old woman with type 2 diabetes. Her mean HbA_{1c} is 67 mmol/mol (8.3%) and her estimated glomerular filtration rate is 82 mL/min. At diagnosis 7 years ago, she was morbidly obese and her BMI is currently 44 kg/m^2. She has never smoked and infrequently drinks alcohol. In addition to her diabetes medication, she takes lisinopril and amlodipine for hypertension and atorvastatin for dyslipidaemia. Her father also has type 2 diabetes and has had two myocardial infarctions. Judy feels she eats a healthy diet but admits to evening snacking and taking little exercise. She has a sedentary part-time job at the post office. Her two grown-up children have also had weight problems.

Prior to treatment, Judy's HbA_{1c} was 84 mmol/mol (9.8%). She was initially treated with metformin 500 mg daily, uptitrated to 2 g daily with no gastrointestinal side effects. Following NICE (2009) recommendations for people with an HbA_{1c} >48 mmol/mol (>6.5%), gliclazide was added to treatment; however, Judy stopped taking this medication as it made her hungry and she had heard it caused weight gain.

She was later treated with a DPP-4 inhibitor but did not achieve the 5.5 mmol/mol (0.5%) HbA_{1c} reduction that NICE (2009) advises for continuation with the therapy. Pioglitazone was considered but was not prescribed owing to risk of fluid retention and further weight gain. Dapagliflozin was prescribed; however, this was discontinued after Judy experienced thrush.

Presenting with thirst and polyuria, and with an HbA_{1c} of approximately 75 mmol/mol (9%), Judy was started on pre-mixed insulin. She continued with metformin and began therapy with Humulin® M3 at 14 units before breakfast and 10 units before her evening meal. Her care team encouraged her to increase her insulin dose with its support.

Judy gradually increased her insulin to 48 units in the morning and 50 units in the evening. Over time, her weight has increased by 5 kg. She considers there to be little room for improvement in her diet but is attending appointments with the dietitian. Her mobility is becoming increasingly limited with complaints of aches and pains, which are not thought to be related to her statin therapy.

Judy's insulin has been changed to Humulin® I 40 units twice daily and she began treatment with the glucagon-like peptide-1 receptor agonist lixisenatide. Her care team plans to reduce her insulin dose as home monitoring and HbA_{1c} levels improve.

"Further developments in basal insulins and glucagon-like peptide-1 receptor agonists may also impact the way the combination is used in future."

same time and in the same general area of the body; however, we strongly recommend that they are not administered at the same injection site. Depending on which product is used, dosing may or may not be independent of meal-times (see *Table 1* for GLP-1 dose timing), which should be factored into decisions about the chosen regimen.

Reducing GI side effects

With exenatide twice daily, liraglutide and lixisenatide, in order to reduce the risk of GI side effects following addition of the GLP-1 RA to basal insulin, treatment should be initiated at a reduced dose of the GLP-1 RA (see *Table 1*) and then gradually increased to the recommended dose (electronic Medicines Compendium [eMC], 2014a; 2014b; 2015c; 2015e). Additionally, in our experience, avoiding large or high-fat meals after injection can also help reduce nausea, especially early in treatment.

The future of combination therapy

Two once-daily, single-injection products that combine a GLP-1 RA and basal insulin at a fixed ratio have been developed. IDegLira (Xultophy®), which has a ratio of 1 unit of insulin degludec to 0.036 mg of liraglutide, is now available in the UK (eMC, 2014c). LixiLan, which combines insulin glargine and lixisenatide), is in phase III trials at the time of writing (ClinicalTrials.gov, 2015a; 2015b; Rosenstock et al, 2014b).

IDegLira is administered once daily at any time (preferably at the same time of the day) based on dose steps, with each step consisting of 1 unit of insulin and 0.036 mg of liraglutide. The recommended starting dose is 10 dose steps (10 units of insulin degludec and 0.36 mg of liraglutide) if added to oral antidiabetes therapy, or 16 dose steps if people were previously receiving a basal insulin (eMC, 2014c).

The dose is adjusted using a dial on the injection pen and is based on fasting self-measured blood glucose readings. We recommend increasing or decreasing the dose by two steps twice a week, with the aim of achieving individualised glycaemic targets, to a maximum of 50 dose steps (50 units insulin degludec and 1.8 mg of liraglutide).

Four phase III studies of IDegLira have been completed, two of which have been published in full (Buse et al, 2014; Gough et al, 2014). When added to oral antidiabetes therapy, these two studies have found reductions in HbA_{1c} (mean reduction of 21 mmol/mol [1.9%] in both trials) with IDegLira that were non-inferior to (Gough et al, 2014), or significantly greater than (Buse et al, 2014), that with insulin degludec, and that were significantly greater than that with liraglutide (Gough et al, 2014). Gough et al (2014) also reported that fewer participants in the IDegLira group reported gastrointestinal adverse events than in the liraglutide group (nausea, 8.8% versus 19.7%), which was probably attributable to the slower titration of the liraglutide component in IDegLira. The studies also found that IDegLira was weight neutral (reduction of 0.5 kg) when used in insulin-naïve people (Gough et al, 2014) and resulted in weight loss (reduction of 2.7 kg) in those previously treated with a basal insulin (Buse et al, 2014).

Further developments in basal insulins and GLP-1 RAs may also impact the way the combination is used in future.

Conclusions

The combination of a GLP-1 RA and a basal insulin is an efficacious treatment for people with type 2 diabetes. Co-use of these offers complementary effects on glycaemic control with potential advantages in terms of hypoglycaemia risk. The combination is also beneficial in terms of body weight, resulting in weight loss with the addition of a GLP-1 RA to basal insulin.

When initiating the combination, minor adjustments in prior treatment regimen can help reduce the risk of hypoglycaemia. While GI side effects are possible in the early stages of GLP-1 RA treatment, there are a number of ways to help minimise these effects, and these should be discussed with individuals.

Furthermore, once-daily, single-injection combinations of a basal insulin and a GLP-1 RA have been developed, with one of these already having been launched in the UK. ■

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"The combination of a glucagon-like peptide-1 receptor agonist and a basal insulin is an efficacious treatment for people with type 2 diabetes. Co-use of these offers complementary effects on glycaemic control with potential adavanatges in terms of hypoglycaemia risk."