Options for intensification of basal insulin in type 2 diabetes: Premeal insulin or short-acting GLP-1 receptor agonists?

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Abstract

Type 2 diabetes is an evolutive disease with a progressive defect of beta-cell insulin secretion. This characteristic points to a need for treatment that takes into account such a natural history. When oral antidiabetic drugs fail to achieve the patient’s target HbA1c level, basal insulin treatment is usually initiated and titrated in association with oral drugs to manage fasting hyperglycaemia. Over a period of time, it is enough to simply achieve the HbA1c target. However, when even a good fasting blood glucose level is no longer sufficient to control overall glycaemia, then prandial treatment must be combined with the titrated basal insulin to deal with the postprandial hyperglycaemia responsible for the elevation of HbA1c.

Of the different therapeutic options now available for this, rapid-acting insulins and GLP-1 receptor agonists (RAs) can be used. Rapid-acting insulins can be added either at each meal, achieving full insulin supplementation with a basal-bolus regimen, or at the main meal only as a “basal-plus” regimen. Compared with the full basal-bolus, the basal-plus strategy is associated with fewer injections, yet provides similar efficacy in terms of HbA1c improvement, but with less weight gain and lower hypoglycaemic risk. As for GLP-1 RAs, numerous studies, and especially those using short-acting GLP-1 RAs, have demonstrated more pronounced effects on postprandial hyperglycaemia, good complementary effects with basal insulin, and significant improvement of HbA1c with no weight gain and a low risk of hypoglycaemia. Similarly, direct and indirect comparisons of the use of rapid-acting insulins and GLP-1 RAs to intensify basal insulin have shown comparable efficacy in terms of HbA1c control, but with less weight gain and fewer hypoglycaemic episodes with GLP-1 RAs.

Keywords: GLP-1 receptor agonists; Postprandial hyperglycaemia; Basal insulin; Premeal insulin

1. Introduction

When oral antidiabetic drugs (OADs) become insufficient to achieve glycaemic goals in type 2 diabetes (T2D), adding basal insulin is the unanimously recommended strategy for improving glucose control [1]. However, the progressive decline of β-cell function in T2D and the inability of basal insulin to control postprandial glucose spikes mean that this regimen will inexorably need to be intensified over time to counteract the deterioration of glucose control. When HbA1c remains over target levels despite adequate, structured titration of basal insulin to control fasting plasma glucose (FPG), the next therapeutic step needs to address postprandial plasma glucose (PPG) excursions [2]. This may be achieved by intensifying insulin therapy, usually with the addition of one injection of rapid-acting insulin analogue before the meal inducing the highest postprandial glucose spike (“basal-plus”) or three injections of rapid-acting insulin analogue before each meal (“basal-bolus”) or, in some selected patients, the less flexible use of premixed formulations of intermediate- and rapid-acting insulin in fixed ratios [1]. Nevertheless, although intensifying insulin therapy generally provides a significant decrease in HbA1c, this happens at the cost of hypoglycaemia, weight gain and, in some patients, difficulty with, or a reluctance and/or unwillingness to manage, a multidose insulin regimen.

However, the recent updated American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement on the management of hyperglycaemia in T2D now presents the option of adding a glucagon-like peptide-1 receptor agonist (GLP-1 RA) for T2D patients whose diabetes remains uncontrolled despite a combination of basal insulin and OADs [1]. The rationale for such an option is justified by physiological and pharmacological considerations, and is now strengthened by a growing amount of robust clinical data [3-8]. Furthermore, it should be emphasized that such a combination is now also approved by health authorities.
Table 1
Key efficacy and safety parameters in the intensification of basal insulin treatments with rapid-acting insulin

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change from baseline in HbA1c (%)</th>
<th>Change from baseline in PPG (mmol/L)</th>
<th>Change from baseline in PPG (mmol/L)</th>
<th>Change from baseline in body weight (kg)</th>
<th>Hypoglycaemia (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal-bolus</td>
<td>-0.3 to -2.1</td>
<td>-2.9</td>
<td>0.6 to 4.5</td>
<td>Symptomatic: 11 to 89</td>
<td></td>
</tr>
<tr>
<td>Premix</td>
<td>vs Basal-plus: -0.03 to -0.2</td>
<td></td>
<td></td>
<td>Severe: 1 to 2</td>
<td></td>
</tr>
<tr>
<td>Basal-plus</td>
<td>-0.4 to -1.1</td>
<td>-0.8</td>
<td>0.5 to 1.8</td>
<td>Symptomatic: 46 to 52</td>
<td></td>
</tr>
<tr>
<td>Insulin glargine:</td>
<td>-0.05 to -0.3</td>
<td></td>
<td></td>
<td>Severe: 0 to 2</td>
<td></td>
</tr>
<tr>
<td>Basal-plus</td>
<td></td>
<td></td>
<td></td>
<td>Nocturnal: 11 to 22</td>
<td></td>
</tr>
</tbody>
</table>

PPG: postprandial plasma glucose; FPG: fasting plasma glucose

2. Intensification of basal insulin with rapid-acting insulins (RAIs)

Treatment intensification with RAIs can be administered as either a “basal-plus” regimen (basal insulin plus one RAI injection at the main meal) or “basal-bolus” regimen (basal insulin plus an injection of RAI before each meal). Basal-bolus treatment is the more physiological approach, while basal-plus was developed to provide a simplified dosing regimen. Key efficacy and safety parameters for intensification of basal insulin with rapid acting insulins are developed below and summarized in Table 1.

2.1. Basal-bolus treatment

Thirteen studies have reported on the efficacy of basal-bolus treatment for T2D [9-21]. Study durations ranged from 16 weeks to 1 year, and the majority of patients were obese at enrolment with an HbA1c > 8%. For all these studies, the mean changes from baseline in HbA1c and body weight ranged from -0.3% to -2.1% and from 0.6 kg to 4.5 kg, respectively. Dailey et al. [22] reported a significant reduction from baseline in PPG with a basal-bolus regimen in a pooled analysis of five clinical trials (baseline: 183 mg/dL; endpoint: 152 mg/dL), while self-monitored plasma glucose (SMPG) was reduced vs a comparator agent in seven basal-bolus reports [10-12,18-21].

One 18-month open-label study examined the most effective way to initiate RAI therapy by comparing administration of thrice daily (TD) insulin glulisine from treatment onset with a progressive increase in the number of insulin glulisine injections [21]. During a 6-month optimization period, insulin glulisine was administered as a single injection while insulin glulisine was titrated according to PPG. At 18 months, optimal glycaemic control (HbA1c < 7%) was not achieved in any of the study groups. However, a progressive increase in insulin glulisine did result in significantly smaller weight increases [21], suggesting that this approach may be appropriate for patients who are overweight or obese, as it may attenuate weight gain compared with basal-bolus treatment.

Yet another, 32-week, study showed that stepwise prandial insulin intensification provided glycaemic control that was non-inferior to a full basal-bolus regimen with a significantly lower hypoglycaemia risk and better patient satisfaction [12].

2.2. Basal-plus treatment

This strategy for treatment intensification is based on three arguments: prandial glycaemia is part of HbA1c; prandial glucose excursions are not the same after each meal of the day; and correction of the highest prandial glucose excursion will have an impact on the rest of the glycaemia, especially preprandial episodes, so avoiding the need to cover every meal of the day with RAI [23].

Eight studies examined the efficacy of basal-plus regimens for the treatment of T2D [21,22,24-29]; five of them had no control arm [22,25-27,29], but are included for completeness. Study durations ranged from 12 weeks to 1 year and the majority of patients were overweight at enrolment, with HbA1c levels > 7.5%. Mean changes from baseline in HbA1c, PPG and body weight ranged from -0.4% to -1.1%, -0.8 mmol/L to -3.9 mmol/L and 0.5 kg to 1.8 kg, respectively.

In a 6-month, phase-IV, controlled study that compared insulin glargine with insulin glargine plus insulin glulisine, a basal-plus regimen significantly improved glycaemic control, albeit with a non-significant increase in body weight [27]. Two meta-analyses confirmed these data, and demonstrated that basal-plus treatment resulted in non-significant or small weight increases and was associated with a low prevalence of hypoglycaemias [25,30].

In one pooled study without a control arm in which patients who initiated basal insulin (titrated according to a protocol-defined blood glucose in two out of four pooled studies), Owens et al. [28] demonstrated that basal-plus with insulin glulisine resulted in significant improvements from baseline at week 24 in HbA1c and PPG, regardless of T2D duration. These data suggest that the basal-plus is an effective regimen.
even in patients who may have advanced disease and poor β-cell function, such as elderly individuals.

In another 24-week study, a single daily injection of insulin glulisine titrated at the investigator’s discretion on top of basal insulin (≥ 3 months of treatment at baseline; dose adjusted according to target FPG) provided effective glycemic control irrespective of whether it was given at breakfast or at the main meal. However, more patients achieved an HbA1c ≤ 7% at week 24 in the main-meal group (52.2%) compared with the breakfast group (36.5%) [31]. Moreover, yet another study comparing titrated insulin glargine plus 0-1 insulin glulisine injections (basal-plus) with titrated insulin glargine plus 0-3 insulin glulisine injections (basal-bolus) for 60 weeks found that the reduction in HbA1c with basal-plus was statistically non-inferior to that with basal-bolus. Although body weight increased progressively in all groups, at week 60, weight increases were significantly lower in the basal-plus group [29].

Taken altogether, these data demonstrate that basal-plus regimens can provide glycemic control comparable to basal-bolus regimens, but with a flexibility of dosing that, alongside the smaller number of injections and smaller weight increases, may improve compliance [32].

3. Intensification of basal insulin with GLP-1 RAs

Combining basal insulin with a GLP-1 RA has a logical and compelling rationale, as these therapies have complementary properties [3]. On the one hand, basal insulin primarily targets FPG control by inhibiting hepatic glucose production overnight, but induces fat storage and weight gain. On the other hand, GLP-1 RAs: i) display glucose-dependent insulin-enhancing and glucagon-suppressing effects that provide additional lowering of PPG without increasing the risk of hypoglycemic events, so totally preserving this counterregulatory response to hypoglycemia; and ii) delay gastric-emptying and promote satiety, which may contribute to the reduction of insulin-induced weight gain and insulin dose requirements. In addition, a theoretical benefit of such an association is that exogenous insulin may give β cells a “rest” and reduce glucotoxicity, enabling greater recovery of the endogenous prandial insulin response, a major target of GLP-1 RAs. Furthermore, incretin-stimulated insulin secretion is more physiological than exogenous meal-time insulin administration, as insulin is secreted via the portal system. Indeed, recent data suggest that the combination of insulin and GLP-1 in T2D is more effective than either insulin or GLP-1 alone for improving endothelial dysfunction, inflammation and oxidative stress [33].

In recent years, numerous observational and interventional studies have demonstrated the benefits of combining basal insulin and GLP-1 RAs in T2D (irrespective of the sequence of their introduction) [3-8]. In a systematic review and meta-analysis of 15 randomized controlled trials, the combination of basal insulin and a GLP-1 RA was shown to significantly improve glycemic control compared with other antidiabetic treatments, along with no increases in either weight loss or hypoglycemia; there was even a decrease in hypoglycemia risk compared with basal-bolus therapy [34]. Of the GLP-1 RAs, short-acting ones such as exenatide and lixisenatide may represent more logical and suitable options after failure of a basal insulin regimen because of their more pronounced effects on PPG through their preferential action on gastric motility [35]; in contrast, long-acting GLP-1 RAs, administered once daily (liraglutide) or once weekly (exenatide QW, albiglutide, dulaglutide, semaglutide), preferentially target FPG. Table 2 summarizes the design of seven randomized controlled studies evaluating the addition of a short-acting GLP-1 RA in T2D patients who were uncontrolled despite basal insulin. Their main findings are summarized below and in Table 3.

3.1. Results of randomized controlled studies of exenatide after basal insulin

In a study by Shao et al. [36], 60 obese patients with non-alcoholic fatty liver disease and newly diagnosed with diabetes were randomized to receive exenatide twice daily or insulin aspart thrice daily in addition to insulin glargine for 12 weeks: at the end of the intervention, FPG, PPG and HbA1c were all significantly decreased in both groups, whereas body weight and waist circumference significantly decreased in the exenatide group, but increased in the intensive insulin group (P < 0.001). Also, levels of hepatic enzymes in the exenatide group were significantly lower than in the intensive insulin group (P < 0.001). Furthermore, the reversal rate of fatty liver was significantly higher in the exenatide group (93.3%) than in the intensive insulin group (66.7%; P < 0.01).

With the aim of comparing twice-daily exenatide injections vs placebo on HbA1c levels in T2D patients treated by basal insulin, Buse et al. [37] conducted a randomized controlled trial of 261 adults with T2D and HbA1c levels of 7.1-10.5%; all were using insulin glargine alone or in combination with metformin and/or pioglitazone and assigned to exenatide 10 µg or placebo twice daily for 30 weeks. At week 30, HbA1c levels decreased by 1.74% with exenatide and by 1.04% with placebo (between-group difference: -0.69%; 95% CI: -0.93 to -0.46%; P < 0.001), and the difference was primarily due to a greater reduction in PPG with exenatide. Weight decreased by 1.8 kg with exenatide and increased by 1.0 kg with placebo (between-group difference: -2.7 kg, 95% CI: -3.7 to -1.7 kg). Average increases in insulin dosages with exenatide and placebo were 13 U/d and 20 U/d, respectively. The estimated rate of minor hypoglycemia was similar between groups. On exploratory post-hoc analysis, these results were confirmed irrespective of baseline HbA1c, diabetes duration and body mass index [38], and regardless of the extent of insulin titration [39]. As expected, gastrointestinal side-effects were more frequent with exenatide vs placebo (nausea: 41% vs 8%; diarrhoea: 18% vs 8%; vomiting: 18% vs 4%; and constipation: 10% vs 2%, respectively).

In an open-label, multicentre, randomized non-inferiority trial (4B Study), Diamant et al. [40] compared exenatide twice daily (10–20 µg/d) and mealtime insulin lispro thrice daily (titrated to a premeal glucose level of 5.6–6.0 mmol/L) in 637 T2D patients whose glycemic control remained poor with
metformin and insulin glargine, despite a 12-week period of up-titration. At week 30, HbA1c reduction with exenatide was non-inferior to the reduction observed with insulin lispro \([-1.13\% \text{ vs } -1.10\%]\), respectively; treatment differences: \(-0.04 (95\% \text{ CI: } -0.18 \text{ to } 0.11)\) in per-protocol and \(-0.03 (95\% \text{ CI: } -0.16 \text{ to } 0.11)\) in intention-to-treat populations]. Exenatide was associated with significantly lower FPG (6.5 mmol/L \text{ vs } 7.2 \text{ mmol/L; } P = 0.002) and weight (-2.5 kg \text{ vs } +2.1 kg; \(P < 0.001\)) vs basal-bolus therapy. Incidence of minor diurnal hypoglycemia was lower with exenatide than with lispro (30% \text{ vs } 41%) whereas no difference was seen for nocturnal hypoglycemia (25% \text{ vs } 27%). Two exenatide and seven lispro recipients displayed at least one major hypoglycemic episode. Exenatide resulted in more gastrointestinal adverse events than lispro. Nevertheless, more patients reported treatment satisfaction and better quality of life with exenatide than with lispro, despite the larger proportion of patients experiencing adverse events with exenatide.

3.2. Results of randomized controlled studies of lixisenatide after basal insulin

GetGoal-L was a randomized controlled trial conducted to compare the efficacy and safety of adding lixisenatide 20 μg once daily \text{ vs } placebo to previous basal insulin therapy administered alone or together with metformin in 495 patients with uncontrolled T2D [41]. The basal insulin dose remained unchanged throughout the study except when necessary to limit hypoglycaemia. At week 24, the placebo-corrected change of HbA1c from baseline with lixisenatide was \(-0.4% (P = 0.0002)\). In addition, lixisenatide significantly reduced 2-h plasma glucose levels after a standardized breakfast (placebo-corrected: \(-3.8 \text{ mmol/L; } P < 0.0001\)) and body weight (placebo corrected: \(-1.3 \text{ kg; } P < 0.0001\)) and insulin daily doses (placebo corrected: \(-3.7 \text{ U/d; } P = 0.012\)). Symptomatic hypoglycaemia was reported by 28% of patients treated with lixisenatide and 22% of patients taking a placebo (severe hypoglycaemia: 1.2% \text{ vs } 0%, respectively).

The GetGoal-L Asia trial had the same design and involved 311 Asian T2D patients who were insufficiently controlled by basal insulin therapy administered either alone or with or without sulphonylureas [42]. At week 24, the placebo-corrected change of HbA1c from baseline with lixisenatide was \(-0.88% (P < 0.0001)\). Lixisenatide also significantly improved 2-h PPG and glucose excursions, average 7-point self-monitored blood glucose levels and FPG. Symptomatic hypoglycaemia was more frequent with lixisenatide (42.9%) \text{ vs } placebo (23.6%), but was similar between groups not taking sulphonylureas (32.6% \text{ vs } 28.3%, respectively). No severe hypoglycaemia was reported. The greater benefits found in GetGoal-L Asia than in GetGoal-L may be explained by the fact that incretin-based therapies might be more effective in Asian T2D patients due to pathophysiological considerations, such as more pronounced insulin and GLP-1 deficiencies in such patients.

<table>
<thead>
<tr>
<th>Background treatment in study groups</th>
<th>Interventions in study groups</th>
<th>Duration of interventions (weeks)</th>
<th>Subjects (n)</th>
<th>Mean age (years)</th>
<th>Mean baseline weight (kg)</th>
<th>Mean diabetes duration (years)</th>
<th>Mean baseline HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal insulin ± SU</td>
<td>LIXI QD vs PBO</td>
<td>24</td>
<td>311</td>
<td>58.3</td>
<td>65.8</td>
<td>13.9</td>
<td>8.5</td>
</tr>
<tr>
<td>Basal insulin ± MET</td>
<td>LIXI QD vs PBO</td>
<td>24</td>
<td>495</td>
<td>57</td>
<td>87.7</td>
<td>12.5</td>
<td>8.4</td>
</tr>
<tr>
<td>Basal insulin ± thiazolidinedione</td>
<td>LIXI QD vs PBO</td>
<td>12-24 (after 12-week glargine titration)</td>
<td>446</td>
<td>56</td>
<td>87</td>
<td>9.2</td>
<td>7.6</td>
</tr>
<tr>
<td>Basal insulin ± thiazolidinedione</td>
<td>LIXI QD vs PBO</td>
<td>12-24 (after 12-week glargine titration)</td>
<td>510</td>
<td>59.4</td>
<td>90.2</td>
<td>11.5</td>
<td>7.6</td>
</tr>
<tr>
<td>Basal insulin ± thiazolidinedione</td>
<td>LIXI QD vs glulisine QD or TD</td>
<td>26 (after 12-week glargine titration)</td>
<td>894</td>
<td>60</td>
<td>89</td>
<td>12</td>
<td>8.5</td>
</tr>
</tbody>
</table>

MET: metformin; PIO: pioglitazone; EXE: exenatide; BD: twice daily; PBO: placebo; SU: sulphonylurea; LIXI: lixisenatide; QD: once daily; TD: thrice daily

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of basal-bolus). In fact, they were add-ons to insulin glargine QD as basal-plus) or before each meal (glulisine TD as rapid-acting insulin analogue before the main meal (glulisine TD, 0.10 mg/kg U/d). Once-daily prandial GLP-1 RA (lixisenatide 20 µg) with a twice daily basal insulin (insulin glargine U/d). GetGoal-Duo 2 was a randomized controlled trial to compare once-daily prandial GLP-1 RA (lixisenatide 20 µg) with a rapid-acting insulin analogue before the main meal (glulisine QD as basal-plus) or before each meal (glulisine TD as basal-bolus). In fact, they were add-ons to insulin glargine with or without metformin in 894 T2D patients who were previously treated with basal insulin and up to three OADs, yet whose glycaemic control remained poor (HbA1c 7–9%) despite a 12-week period of glargine titration [44]. At week 26, lixisenatide QD was non-inferior to glulisine QD and glulisine TD in reducing HbA1c (-0.6 ± 0.1% vs -0.6 ± 0.1% and -0.8 ± 0.1%, respectively), and statistically superior to both in reducing 2-h PPG after a standardized breakfast (placebo corrected: -3.2 mmol/L; P < 0.0001) and had a favourable effect on body weight (placebo corrected: -0.89 kg; P = 0.0012). Symptomatic hypoglycaemic events were more common with lixisenatide.

Presented during the 75th ADA Scientific Sessions, GetGoal-Duo 2 was a randomized controlled trial to compare once-daily prandial GLP-1 RA (lixisenatide 20 µg) with a rapid-acting insulin analogue before the main meal (glulisine QD as basal-plus) or before each meal (glulisine TD as basal-bolus). In fact, they were add-ons to insulin glargine

| Buse et al. (2011) | -1.74% (EXE) vs -1.04% (PBO), Δ -0.69% (95% CI -1.03 to -0.36, p < 0.001) | -1.8 kg (EXE) vs +1 kg (PBO), Δ -2.7 kg (95% CI -3.7 to -1.7, p < 0.001) | Minor hypoglycaemia (% patients): 25% (EXE) vs 29% (PBO)Minimal nocturnal hypoglycaemia (% patients): 17% (EXE) vs 26% (PBO) Major hypoglycaemia (% patients): 0% (EXE) vs 1% (PBO) |
| Seino et al. (2012) (GetGoal-L Asia) | -0.77% (LIXI) vs +0.11% (PBO), Δ -0.88% (95% CI -1.2 to -0.56, p < 0.0001) | -0.38 kg (LIXI) vs +0.06 kg (PBO) (95% CI -0.95 to +0.061, p = 0.09) | Symptomatic hypoglycaemia (% patients): 42.9% (LIXI) vs 23.6% (PBO)Symptomatic hypoglycaemia (% patients not receiving SU): 32.6% (LIXI) vs 28.3% (PBO) |
| Riddle et al. (2013) (GetGoal-L) | -0.7% (LIXI) vs -0.4% (PBO), Δ -0.3% (95% CI -0.6 to -0.2, p = 0.0002) | -1.8 kg (LIXI) vs -0.5 kg (PBO), Δ -1.3 kg (95% CI -1.8 to -0.7, p < 0.0001) | Symptomatic hypoglycaemia (% patients): 23.7% (LIXI) vs 21.6% (PBO)Severe hypoglycaemia (% patients): 1.2% (LIXI) vs 0% (PBO) |
| Riddle et al. (2013) (GetGoal-Duo 1) | -0.7% (LIXI) vs -0.4% (PBO), Δ -0.3% (95% CI -0.5 to -0.2, p < 0.0001) | +0.3 kg (LIXI) vs +1.2 kg (PBO), Δ -0.9 kg (95% CI -1.4 to -0.4, p = 0.0012) | Symptomatic hypoglycaemia (% patients): 39.9% (LIXI) vs 16.1% (PBO) |
| Diamant et al. (2014) (4B) | -1.13% (EXE) vs -1.10% (LIS TD), Δ -0.04% (95% CI -0.18 to +0.11, ns) | -2.5 kg (EXE) vs +2.1 kg (LIS TD), Δ -4.6 kg (95% CI -5.2 to -3.9, p < 0.001) | Minor hypoglycaemia (% patients): 41% (EXE) vs 30% (LIS TD)Nocturnal hypoglycaemia (% patients): 25% (EXE) vs 27% (LIS TD)Major hypoglycaemia (number of patients): 2 (EXE) vs 7 (LIS TD) |
| Shao et al. (2014) | -1.42% (EXE) vs -1.31% (INS TD), ns | -7.7 kg (EXE) vs +3.3 kg (INS TD), p < 0.001 | Symptomatic hypoglycaemia (% patients): 0% (EXE) vs 10% (INS TD) |
| Rosenstock et al. (2015) (GetGoal-Duo 2) | -0.65% (LIXI) vs -0.58% (GLU QD) vs -0.84% (GLU TD), Δ -0.05% (95% CI -0.17 to +0.06) vs GLU QD, Δ +0.21% (95% CI 0.10 to 0.33) vs GLU TD | -0.7 kg (LIXI) vs +0.9 kg (GLU QD) vs +1.3 kg (GLU TD), Δ -1.7 kg (95% CI -2.3 to -1.1, p < 0.0001) vs GLU QD, Δ -0.2 kg (95% CI -2.6 to -1.4, p < 0.0001) vs GLU TD | Symptomatic hypoglycaemia (% patients): 32.9% (LIXI) vs 38.9% (GLU QD) vs 44.9% (GLU TD) |

EXE: exenatide; LIXI: lixisenatide; PBO: placebo; MET: metformin; LIS: lispro; INS: insulin; GLU: glulisine; BD: twice daily; QD: once daily; TD: thrice daily
4. Summary and future perspectives

According to these encouraging results, adding a short-acting, prandial GLP-1 RA to the treatment of T2D patients still uncontrolled despite basal insulin and OADs now represents a promising strategy, and could constitute a worthwhile alternative to insulin intensification with basal-plus and basal-bolus regimens. Indirect comparisons derived from five randomized trials show that lixisenatide offers a safe and effective therapeutic alternative to enhanced basal insulin treatments, improving glucose control without weight gain and with less risk of hypoglycaemia than a once-daily meal-time rapid-acting insulin [45]. Although direct comparisons are as yet limited, the available data suggest that adding a prandial GLP-1 RA results in a similar or greater reduction of HbA1c, weight loss instead of weight gain and a lower risk of hypoglycaemic episodes compared with the addition of once-daily up to thrice-daily meal-time rapid-acting insulin analogues [36,40,44].

This emerging strategy is becoming a more attractive – albeit more expensive – alternative in T2D patients insufficiently controlled with basal insulin when clinicians wish primarily to limit weight gain (or even induce weight loss) or reduce the risk of hypoglycaemia, or when patients are not able or not willing to deal with the complexities of multitdose insulin regimens. Moreover, adding a GLP-1 RA to insulin may also be of value, as it can reduce basal insulin dose requirements, thereby reducing hypoglycaemia risk and facilitating weight management. In patients starting a GLP-1 RA in combination with basal insulin, some authors recommend an empirical 20% decrease in basal insulin doses in those with HbA1c < 8%, as in the study by Buse et al. [37], with evaluation of the patient’s responses over time to allow further insulin dose adjustments. In addition, the effect of GLP-1 RA on α-cell function would explain why this therapeutic option would be of value even in late-stage T2D. Also, although insulin injections are generally perceived as worrisome by T2D patients, the subcutaneous route of GLP-1 RA administration does not appear to affect patient satisfaction [46]. In fact, a fixed-ratio formulation combining insulin glargine with lixisenatide (LixiLan) in a simple pen device is currently in development and has already shown promising results [47]. Finally, while gastrointestinal adverse events are common with GLP-1 RAs especially during initiation and titration, their combination with basal insulin is not expected to augment the expected side-effects.

Nevertheless, long-term controlled studies are still needed to further examine the potential clinical benefits and cost-effectiveness of such a combination, even though a low rate of hypoglycaemia may well reduce the economic burden. Also, in future, short-acting GLP-1 RAs will have to be compared with long-acting GLP-1 RAs for those indications, although once-weekly albiglutide has already been shown to be a simpler therapeutic option than thrice-daily lispro for enhancing basal insulin glargine therapy, resulting in comparable HbA1c reductions with weight loss and lower hypoglycaemia risk [48]. The durability of the combination of GLP-1 RAs to intensify basal insulin and control PPG will also need to be assessed, given that short-acting GLP-1RAs act mainly via gastric-emptying delay whereas long-acting GLP-1 RAs work mainly through insulin secretion stimulation.

Disclosure of interest

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