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REVIEW

The combination of insulin and GLP-1 analogues in the treatment of type 2 diabetes

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ABSTRACT

GLP-1 analogues have been proven to be effective in the treatment of type 2 diabetes mellitus. They stimulate insulin production and secretion, and suppress glucagon secretion, depending on the blood glucose level. They also have an effect on the brain, enhancing satiety, and on the gut, where they delay gastric emptying. Theoretically, in type 2 diabetes mellitus patients, the combination of a GLP-1 analogue with insulin seems attractive, because of the weight loss perceived in users of GLP-1 analogues in contrast to the weight gain seen in most patients starting insulin therapy, leading to even more insulin resistance. There are only a few randomised controlled trials which have studied this combination and several uncontrolled studies, which will be reviewed here.

KEYWORDS

GLP-1 analogue, review, diabetes mellitus, insulin, combination

INTRODUCTION

GLP-1 analogues have been proven to be effective in the treatment of type 2 diabetes mellitus.[1] They stimulate insulin production and secretion, and suppress glucagon secretion, depending on the blood glucose level. They also have an effect on the brain, enhancing satiety, and on the gut, where they delay gastric emptying. In Europe, these drugs are being reimbursed for use in patients with a body mass index (BMI) of 35 kg/m^2 or higher, in combination with a sulphonylurea or metformin or a thiazolidinedione, or in triple therapy, in combination with metformin and a sulphonylurea, or with metformin and a thiazolidinedione. Before starting the GLP-1 analogue, it is mandatory that the combination of metformin and a sulphonylurea has been proven ineffective in the maximum tolerable dose. The combination of a GLP-1 analogue and insulin is not reimbursed in the Netherlands, although the combination of insulin glargine and exenatide has been approved by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). In practice, this leads to frustration in patients who have type 2 diabetes mellitus, use insulin and are obese, and would like to use a GLP-1 analogue in combination with insulin, or even substitute insulin for a GLP-1 analogue, because they hope to lose weight when using these drugs and reduce their insulin dose. The question is whether the combination of insulin and GLP-1 analogues is effective and does have an effect on weight, and whether this combination leads to other side effects than use of a GLP-1 analogue alone.

Recently, several studies were published concerning the use of GLP-1 analogues and insulin in type 2 diabetes. There are only three randomised controlled trials and several retrospective case series. We will discuss them here.

EFFECT OF GLP-1 ANALOGUES

GLP-1 or glucagon-like peptide 1 is an incretin secreted from enteroglucagon-producing cells in the lower gut. It is a gastrointestinal hormone that regulates insulin and glucagon secretion in response to ingested nutrients. GLP-1 stimulates insulin production and secretion, and suppresses glucagon secretion, both in a glucose-dependent manner. Furthermore, it has an effect on the brain, enhancing satiety, and on the gut, where it delays gastric emptying. GLP-1 analogues mimic the endogenous GLP-1. They were shown to normalise blood glucose

concentrations in the fasting state in patients with poorly controlled type 2 diabetes with secondary failure after sulphonylurea treatment by elevating insulin and reducing glucagon concentrations.[2] Furthermore, after glucose levels had normalised, insulin levels decreased and glucagon levels increased despite ongoing infusion of the GLP-1 analogue.

A recent Cochrane review discussed the effects of GLP-1 analogues in patients with type 2 diabetes.[1] Studies had to be randomised controlled trials of a minimum duration of eight weeks. Comparisons that were included were GLP-1 analogue as a third-line agent *vs* placebo or another antihyperglycaemic agent, GLP-1 analogue as a second-line agent *vs* placebo or another antihyperglycaemic agent, or GLP-1 analogue *vs* another GLP-1 analogue. In total, 17 randomised controlled trials with relevant data on 6899 participants were included. Conclusions were that GLP-1 analogues significantly improve glycaemic control when added to dual treatment with oral antihyperglycaemic drugs, and can be an alternative to starting insulin. There was an improvement of 1% in HbA1c, and in the percentage of patients reaching the target HbA1c. The majority of clinical trials reported a significantly larger reduction of body weight compared with placebo. Most commonly reported adverse events were nausea, vomiting and diarrhoea, but these complaints were mainly present during the initial weeks of treatment. Hypoglycaemia was more often seen in patients on exenatide and concomitant sulphonylurea and on 1.8 mg liraglutide than on placebo. Beta cell function improved with GLP-1 analogues, as was estimated by a variety of measures such as HOMA-B, HOMA2-%B, proinsulin-to-insulin ratio or proinsulin-to-C-peptide ratio. Exenatide in its once weekly formulation and liraglutide were superior to insulin glargine with regards to HbA1c improvement, weight loss, and hypoglycaemia incidence. There were no trials available comparing GLP-1 analogues with neutral protamine Hagedorn (NPH) insulin. The authors said that there were concerns regarding side effects as pancreatitis and renal failure with exenatide, and pancreatitis and thyroid carcinoma with liraglutide, but the studies were not long enough to prove or dispute these concerns.

The effect of GLP-1 analogues on weight loss was reviewed in another paper.[3] Vilsboll *et al.* included 25 trials of adult patients with or without type 2 diabetes, with a BMI of 25 kg/m^2 or more. Patients used exenatide twice daily (bid) or once weekly or liraglutide once daily. Controls were placebo, no intervention, or blood glucose lowering drugs (including another GLP-1 analogue). The duration of the trial had to be at least 20 weeks. All trials reported weight loss, more in the GLP-1 analogue group than in the control group. A random effects meta-analysis was performed including 3395 participants randomly assigned to GLP-1 analogue and 3016 to the control group. Overall change in body weight was expressed in a weighted mean difference between the GLP-1 analogue and the control group and amounted to -2.9 kg (95% CI -3.59 to -2.22). Weight loss occurred in participants with and participants without diabetes. There was no difference between liraglutide and exenatide. Also, there was a reduction in systolic and diastolic blood pressure and total cholesterol in participants treated with a GLP-1 analogue. Again, the most frequent adverse events were nausea, vomiting, and diarrhoea.

COMBINATION WITH INSULIN: RATIONALE

The start of insulin therapy generally leads to an increase in body weight. Several mechanisms underlie this effect. First of all, there will be reduction of glucosuria, hence the number of calories wasted by this is reduced. Secondly, insulin has been reported to increase appetite, and thirdly, patients need to take extra amounts of carbohydrates when hypoglycaemia occurs. This weight gain leads to further insulin resistance, and ultimately leads to a new equilibrium in which a higher dose of insulin is required for adequate glucose control. As a consequence, in daily clinical practice many patients with type 2 diabetes need a large amount of insulin to control their diabetes. In this situation, very low calorie diets have been tried with short-term success, but limited data are available about their long-term effects.[4] By addition of a GLP-1 analogue to existing insulin therapy, patients may benefit from the combined effects on endogenous insulin secretion, on reduction of increased appetite, and on slowing of gastric emptying. Taken together, on theoretical grounds, it could be expected that there would be a reduction of caloric intake, less pronounced postprandial blood glucose increase, and possibly also a lower need for exogenous insulin.[5]

PROSPECTIVE STUDIES

Unfortunately, there are only a few randomised controlled clinical trials in patients with type 2 diabetes mellitus, in whom a GLP-1 analogue was added to existing insulin therapy. A first short-term, small-scale, randomised controlled clinical trial was performed by Kolterman *et al.*[6] This was a proof-of-concept study for the study later published by Buse *et al.*[7] They showed a reduction in postprandial glycaemic excursion when adding exenatide bid in 24 participants, of whom only six were using insulin.

Three randomised controlled trials have subsequently been reported. The study by Arnolds *et al.* was a single-centre, randomised, open-label, active comparator-controlled study

with a three-arm parallel group design.[8] They studied 48 subjects with type 2 diabetes treated with insulin glargine and metformin. These subjects were randomised to receive additional exenatide 5 µg bid for the first two weeks, and 10 µg bid for the second two weeks, or sitagliptin 100 mg once daily, or no additional drug. After four weeks, a standardised breakfast meal challenge was performed. The addition of exenatide or sitagliptin led to a significantly smaller unadjusted 6-hour postprandial blood glucose excursion (17% reduction for exenatide, and 20% for sitagliptin), and lowered HbA1c. Baseline HbA1c was 8.1 ± 0.7% overall, 7.9% in the sitagliptin and control group, and 8.4% in the exenatide group, and dropped for exenatide by -1.8 ± 0.7, and for sitagliptin by -1.5 ± 0.7 *vs* -1.2 ± 0.5% points in the control group. The decrease of HbA1c in the exenatide group was significantly larger than in the control group. Addition of exenatide led, however, to the highest number of adverse events (47 *vs* 12 and 10 in the sitagliptin and control group respectively), mostly gastrointestinal (56%), and one subject stopped the study because of loss of appetite. There was no difference in hypoglycaemia rates, which were low. Body weight decreased in the exenatide group (-0.9 ± 1.7 kg) and was stable in the sitagliptin (0.1 ± 1.6 kg) and the control group (0.4 ± 1.5 kg). As was discussed by the authors in their article, the number of patients was relatively small, and the mean duration of diabetes was only six years. Also, in addition to the between-group difference in baseline HbA1c, the duration of the study was too short to see the full effect on HbA1c, and the open-label design represents a limitation.

The study by Buse *et al.* was a parallel, randomised, placebo-controlled trial, blocked and stratified by HbA1c level at site.[7] The trial was performed in 59 centres in five countries in 261 participants with type 2 diabetes who used insulin glargine alone or in combination with metformin or pioglitazone, or both. Participants were randomised to exenatide 10 µg bid (138 participants) or placebo injections (123 participants). The trial lasted 30 weeks. HbA1c level decreased by 1.74% in the exenatide group and 1.04% in the placebo group (between-group difference -0.69%, p<0.001). The proportion of participants reaching the target HbA1c of 7.0% or less was 60% in the exenatide group and 35% in the placebo group (between-group difference 25%, p<0.001), and the target HbA1c of 6.5% or less was 40% in the exenatide group and 12% in the placebo group (between-group difference 28%, p<0.001). The authors did not observe a reduction in insulin dose, not even in the exenatide group. The insulin dose increased by 13 units per day in the exenatide group and 20 units per day in the placebo group (between-group difference -6.5, p=0.030). There was no difference in fasting plasma glucose levels between the two groups. Body weight decreased by -1.8 kg in the exenatide group, and increased by 1.0 kg in the placebo group (between-group difference -2.7 kg, p<0.001). There was no effect on serum lipid measurements, but there was a significant decrease in systolic and diastolic blood pressure, which was only observed in the exenatide group (the between-group difference in systolic blood pressure was 4.4 mmHg and in diastolic blood pressure 3.4 mmHg, both in favour of the exenatide group). The rate of hypoglycaemia was similar in the two groups. In total 26 participants in the exenatide group and 22 in the placebo group withdrew; 13 participants in the exenatide group and one in the placebo group withdrew because of adverse events. Nausea, diarrhoea, vomiting, headache and constipation occurred more in the exenatide group than in the placebo group. Baseline characteristics differed with regards to gender (more females in the exenatide group, 49 *vs* 36%), and prestudy oral antihyperglycaemic agents used (more participants on metformin alone in the placebo group (75 *vs* 66%), and more participants on metformin plus pioglitazone in the exenatide group (17 *vs* 7%)), and HbA1c levels (8.35 in the exenatide group *vs* 8.53% in the placebo group). After adjustment for these variables, none affected the primary outcomes.

In a post-hoc analysis of 137 exenatide and 122 placebo participants of this study, it was investigated whether baseline HbA1c, baseline body weight, and diabetes duration had an effect on the outcome of glycaemic control and weight loss.[9] Exploratory subgroup analyses revealed that users of exenatide had greater HbA1c reductions compared with optimised insulin glargine alone, irrespective of baseline HbA1c (p<0.001). Also, greater HbA1c reductions were seen in the exenatide users with longer diabetes duration (9-15 and >15 years) and those with lower BMI (BMI <30 and 30-36 kg/m^2) (p<0.01). Irrespective of baseline HbA1c or BMI, exenatide users lost more weight than those on placebo (p<0.05). Exenatide users with longer diabetes duration (>15 years) lost the most weight (p<0.001).

A 38-week trial of adding liraglutide to metformin followed by a randomised, open-label investigation of further intensification with systematically titrated basal insulin detemir was performed by De Vries *et al.*[10] This study was performed in 202 office- or hospital-based sites in Belgium, Canada, France, Germany, Italy, the Netherlands, Spain, the UK and the US between March 2009 and April 2010. The trial comprised a 12-week run-in period during which liraglutide was started and uptitrated to 1.8 mg, followed by a 26-week, randomised, two-armed, parallel-group period for participants not achieving an HbA1c <7.0%. Sulphonylurea use was discontinued before the study and metformin was continued. Participants were randomised to receive insulin detemir (randomised treatment group) added to metformin and liraglutide, or continued metformin and liraglutide (randomised

control group). Participants who had achieved an HbA1c <7.0% were the observational group. A total of 988 participants entered the 12-week run-in period, 987 were exposed to liraglutide, 168 withdrew during the run-in period, of whom 92 due to adverse events (76 gastrointestinal). Therefore, 821 participants entered the 26-week randomisation period, of whom 498 entered the observational group, and 323 were randomised, 162 receiving insulin and 161 not. In total, of these 821, 80 participants withdrew, of whom 19 due to adverse events (evenly distributed among the groups). Participants reaching the target had a shorter diabetes duration, lower HbA1c and fasting plasma glucose levels (FPG), and more had been treated with metformin only before enrolment. HbA1c was reduced by 1.3% in the observational group and by 0.6% in the randomised groups. Body weight decreased by 3.5-4.4 kg, FPG by 1.0-2.0 mmol/l. Nausea was the most frequently reported adverse event in the run-in period, but there was also one case of acute pancreatitis, and one subject was diagnosed with papillary thyroid carcinoma. In the randomised groups, adding insulin detemir reduced HbA1c by a further 0.51% *vs* an increase of 0.02% in the placebo group (p<0.0001). Mean FPG decreased by 2.1 mmol/l in the detemir group *vs* 0.4 mmol/l in the placebo group. The detemir group lost 0.16 kg body weight *vs* 0.95 kg in the placebo group (p=0.03). HbA1c <7% was achieved by 17 *vs* 43% (p<0.0001), and ≤6.5% by 6 *vs* 18% (p=0.0016) in the placebo and detemir group respectively. The composite endpoint (HbA1c <7% and no weight gain and no hypoglycaemia) was reached by 21% in the detemir and 9% in the control group. There were not many hypoglycaemic events and no major hypoglycaemia. No significant changes in blood pressure and lipids were found, except for a larger reduction in free fatty acids in the detemir group (-0.11 *vs* -0.003 mmol/l, p=0.002). More adverse events and increased lipase were found in the detemir group, but without signs or symptoms. HbA1c reduction was 1.1% overall in the observational group, FPG decreased by 2.1 mmol/l, and weight by 4.8 kg. Adverse events were found in 81% of the observational group, 49 serious of which 45 were considered unlikely to be caused by the study drug, and without obvious pattern. No major and 9.0% minor hypoglycaemia occurred. The authors mention that perhaps more participants might have reached the target HbA1c level if the run-in period had lasted longer or with a lower FPG target for insulin titration. Furthermore, the study used the highest liraglutide dose; maybe there would have been less withdrawals if it had been allowed to return to the 1.2 mg dose. Also, there was no active comparator or masked placebo.

Until now, there are no studies in which addition of exenatide or liraglutide to basal insulin has been compared with another comparator. In one study (Clinicaltrials NCT00960661), addition of exenatide bid to existing treatment with insulin glargine and metformin is compared with addition of thrice-daily insulin lispro. The results of this study are expected in the Spring of 2013. To evaluate the differences between GLP-1 analogues and other possible treatments, we really need long-term comparative studies between active treatment modalities. It can be doubted whether studies, in which the addition of a GLP-1 analogue *vs* placebo is studied (as in NCT01617434) really will advance our knowledge about the benefits of combined insulin/GLP-1 analogue treatment compared with existing therapies.

UNCONTROLLED STUDIES/ OBSERVATIONS

Several uncontrolled, nonrandomised, mostly retrospective reports derived from clinical practice have been published.[11-19] Data of these studies are summarised in *table 1*. Most studies reported a decrease in HbA1c, weight, and insulin dose upon addition of GLP-1 to insulin therapy. There are several problems with these studies. First, participation was voluntary so there is a risk of selection bias. No strict protocols as in randomised studies are followed and diabetes treatment changes were individually tailored. Glycaemic improvements in the ABCD study were possibly attenuated by concurrent reductions in other hypoglycaemic agents such as insulin.[16] Not all data were always available on all patients, possibly leading to bias. Larger reductions in HbA1c and weight could possibly be due to the additional start or intensification of lifestyle interventions. There were no control groups, and all studies were observational.

The ABCD trial was analysed again with patients on whom baseline diabetes treatment details and three-month HbA1c and/or weight data were available.[20] These patients were grouped as: Group 1 (non-insulin users, n=2427), Group 2 (insulin continued, n=927), and Group 3 (insulin stopped, n=319). The authors found that at three months, the mean HbA1c reduction for Group 1 was 0.90 ± 1.57% (p<0.001), for Group 2 0.51 ± 1.51% (p<0.001), and for Group 3 0.00 ± 1.91% (p=0.968), and weight loss was -4.1 ± 4.6 kg, -4.6 ± 5.0 kg and -6.6 ± 5.2 kg (all p<0.001). Among insulin-treated patients, increasing insulin dose reduction led to less HbA1c reduction, but more weight reduction.

GLP1 ANALOGUES IN TYPE 1 DIABETES

We identified a few studies which assessed the effects of GLP-1 analogue treatment in type 1 diabetes. The rationale is that the effect of GLP-1 on glucagon, appetite

Table 1. *Summary of nonrandomised, mostly uncontrolled and retrospective studies*[11-19]

Study & author	Data source	Cases	Controls	Study duration	Comparison	Results	Weight	Insulin dose	Adverse events
Observational, retrospective Viswanathan 2007 [11]	Medical records (outpatient clinic)	Group A: 38 patients who took EXE regularly	Group B: 14 patients who discontinued EXE due to insurance, personal or economic reasons	Mean follow-up 26 weeks	Group A vs Group B	Group A: mean HbA1c ↓ by 0.6±0.2% (p=.007) In Group A, but not Group B, ↓ of TC by 8.5±3.3% (p=.03), TG by 26±7.6% (p=.01), SBP by 9.2±3.3 mmHg (p=.02), hsCRP by 34±14.3% (p=.05)	Mean body weight ↓ by 6.46±0.8 kg (p<.001) in Group A and ↑by 2.4±0.6 kg in Group B (p<.001)	Insulin dosage requirement ↓for rapid-acting and mixed insulins (p<.02)	Not reported
Observational, retrospective Sheffield 2008 [12]	Electronic medical records (outpatient clinic)	EXE added to insulin, n=124 (out of 134)	None	1 year follow-up	Before and after start of EXE	↓ in HbA1c of 0.87% after a year (p<.001)	Mean weight ↓ 5.2 kg (p<.001)	45% stop of pre-meal insulin (p<.001) 9 U ↓mean pre-meal insulin doses (p=.0066), ↓ in median number of daily insulin injections from 2 to 1 (p=.0053) 59% discontinuation of SU (p=.0088)	14 patients (10%) experienced (mostly mild) hypoglycaemia, 48 patients (36%) discontinued EXE due to AE mostly gastrointestinal
Observational, retrospective Yoon 2009 [13]	Medical records	EXE added to insulin, n=188 (out of 268) Excluded: 38 discontinued EXE < 2 mo, 30 lost to follow-up, 12 no evaluable data	None	Up to 27 mo	Before and after start of EXE	Mean change in HbA1c -0.54 to -0.66 % (p<0.001 to p=0.020). Slight rise after 18 mo	Mean weight ↓2.4-6.2 kg (p<0.001, p<0.01). Slight rise after 18 mo. Positive correlation between weight loss and decrease in insulin TDD	-18.0 U/day at 0-6 mo, and -14.8 U/day at 6-12 mo (p<0.001), mainly prandial doses 11 patients stopped insulin	26 discontinued due to AE, mainly gastrointestinal; hypoglycaemia in 4.0% Two serious AEs: acute renal failure not attributed to EXE, and pancreatitis
Prospective audit of clinical protocol use of EXE in people with type 2 DM, obesity and progressive weight gain on insulin therapy Nayak 2010 [14]	Outpatient clinic	EXE added to insulin, n=174, n=160 analysed	None	6-12 mo, n=160 completed 6 mo, n=57 completed 12 mo	Before and after start of EXE	No change in HbA1c, SBP fell from 141 ± 19 to 136 ±22 mm Hg at 6 mo	Weight ↓ 10.7± 5.7 kg at 6 mo, and 12.8±7.5 kg at 12 mo	Insulin TDD ↓ from 144±90 to 51±55 U/day at 6 mo, and 55±53 U/day at 12 mo. 25% came off insulin at 3 mo	14 (8%) discontinued EXE because of intolerable gastrointestinal AE, in others AE mainly gastrointestinal. One patient died after 6 mo due to cardiac events
Observational, retrospective Lane 2011 [15]	Chart review, outpatient clinic	LIRA 1.2 or 1.8 mg daily, added to high-dose insulin ± metformin, n=15 2 patients used EXE before the study (was discontinued)	None	12 weeks	Before and after start of LIRA	HbA1c ↓1.4 ± 0.7% (p=0.0001)	Weight ↓ 5.1 ±3.9 kg (p=0.0001), range -12.2 to +0.36 kg.	↓ of insulin TDD by 28% (range -100 to +30 U/day, mean change in insulin TDD -53±35 U/day, p=0.0001)	No severe episodes of hypoglycaemia

Study & author	Data source	Cases	Controls	Study duration	Comparison	Results	Weight	Insulin dose	Adverse events
Nationwide EXE audit Thong 2011 (ABCD) [16]	4857 patients from 126 centres across the United Kingdom	Total n=1921 (n = 1257 insulin at baseline with EXE, and n = 664 insulin started after EXE initiation)	n=2936 not on insulin during EXE	1 year, median follow-up 31 weeks	HbA1c, weight: insulin at baseline with EXE vs not on insulin during EXE, AE and treatment satisfaction: all patients with EXE and insulin vs EXE wo. Insulin	Mean HbA1c ↓ after 6 mo: 0.51 ± 0.06% vs 0.94 ± 0.04%, difference p<0.001 HbA1c ↓ of ≥1%: 34.2% versus 49.0%, p<0.001	Mean weight ↓ 5.8±0.2 kg versus 5.5±0.1 kg, difference ns	Insulin TDD reduced by 42±2 U/day 209 (16.6%) came off insulin, 32.1% off SU, 54.3% off TZD	More insulin-treated patients discontinued EXE (31 vs 14%, p<0.001), had gastrointestinal AE (28 vs 25%, p=0.008), hypoglycaemia (9 vs 6%, p<0.001), and treatment dissatisfaction (21 vs 6%). Treatment dissatisfaction associated with start of insulin during EXE therapy, and with more injections per day
Observational, retrospective Levin 2012 [17]	National US insurance claims database (the Integrated Health Care Information Services Impact database)	At least one prescription claim each for insulin GLA and EXE 3 groups: n=141, EXE followed by GLA (EXE+); n=281, GLA followed by EXE (GLA+); n=31, GLA and EXE initiated together (GLA+EXE)	None	1 year	EXE+ versus GLA+ and GLA+EXE versus GLA+	HbA1c: GLA+EXE: -1.2% EXE+ -0.9% GLA+ -0.4%, all p<0.01 HbA1c ↓ in GLA+EXE and EXE+ sign. higher than in GLA+ HbA1c <7% at 1 year: GLA+ 28.1%, EXE+ 31.2%, GLA+EXE 48.3%, higher in GLA+EXE than GLA+ (p=0.0196)	No data available	No data available	No significant rise in number of hypoglycaemic events No data on AE
Observational, retrospective Levin 2012 [18]	US chart review	n=44: GLA added after EXE (EXE/GL) n=121: EXE added after GLA (GL/EXE)	None	24 mo	EXE/GL vs GL/EXE	HbA1c ↓ pooled -0.7% (p<0.001) 33% achieved HbA1c ≤7.0%.	Weight unchanged in EXE/GL, ↓in GL/EXE (-2.5±6.7 kg, p=0.001)		Hypoglycaemia frequency similar in both treatment groups. No data on adverse events
Observational, retrospective Lind 2012 [19]	Medical records (outpatient clinic)	n=61 analysed Use of insulin (multiple injections 52%, basal only 34%, premixed 12%), combined with metformin (68.9%) or SU (1.6%) 40 patients started on LIRA, 21 on EXE	None	Average follow-up time 7 mo	Before and after start of LIRA or EXE	Mean HbA1c ↓ 1.0% (p<0.001) Treatment satisfaction higher than with previous regimen (DTSQ)	Weight ↓ by a mean of 7.1 kg (p<0.001)	Insulin therapy discontinued in 5 patients, insulin doses on average ↓ by a mean of 38.6 U	4 of 65 discontinued GLP-1 analogue use because of AE (2 nausea, one fatal MI, one acute sepsis affecting the liver) One severe hypoglycaemic event, number of symptomatic hypoglycaemias low and less than with previous regimen (DTSQ)

EXE=exenatide; LIRA=liraglutide; GLA=glargine; SU=sulphonylureas; mo=months; vs=versus; AE=adverse events; wo.=without; ↓=decrease; ↑=increase; TC=total cholesterol; TG=triglycerides; SBP=systolic blood pressure; DTSQ=Diabetes Treatment Satisfaction Questionnaire; TDD=total daily dose; ns=not significant; TZD=thiazolidines; DM=diabetes; MI=myocardial infarction.

and the GI system may assist in achieving more stable control and reduction of body weight. A study by Raman *et al.* analysed the response to a mixed meal after a single dose of exenatide 1.25 or 2.5 µg in combination with insulin or insulin alone in eight subjects with type 1 diabetes.[21] The insulin dose was reduced by 20% in those receiving exenatide. The authors observed reduced postprandial hyperglycaemia (p<0.0001), and a lower delta plasma glucose area under the curve in the early postprandial period (1.25 µg *vs* insulin alone: p<0.008, 2.5 µg: p<0.007). Gastric emptying was delayed but the authors do not mention how much delay they found. There was no difference in glucagon concentration between the groups. Another study reported that liraglutide added to insulin therapy in 14 patients with type 1 diabetes during one week reduced mean fasting and mean weekly glucose concentrations (p<0.01), and reduced glycaemic excursions, while lowering the basal and bolus insulin dose.[22] Prior to starting liraglutide 0.6 mg, glucose control was intensified until stable doses of insulin were reached. The insulin dose was decreased by 25% for basal insulin and 33% for bolus insulin at the onset of liraglutide therapy. Six patients discontinued liraglutide after one week, because they were not able to continue continuous glucose monitoring due to the costs. In eight patients liraglutide was continued for 24 weeks and increased to 1.2 and 1.8 mg daily after one and two weeks respectively. The effects remained, HbA1c decreased from 6.5% to 6.1% (p=0.02), and they also lost body weight (-4.5 ± 1.5 kg, p=0.02). Patients reported a reduction in appetite and food intake following liraglutide. This was not a double-blind, placebo-controlled study. A short-term study (4 weeks) reported that treatment with liraglutide in type 1 diabetic patients reduced the insulin dose with improved or unaltered glycaemic control.[23] Ten C-peptide positive and 10 C-peptide negative patients were treated with liraglutide plus insulin for four weeks, and ten C-peptide negative patients served as a control group and were treated with insulin monotherapy. Insulin dose decreased more in C-peptide positive patients. Total area under the curve of glucagon after a mixed meal test followed by exercise decreased significantly (p=0.002) in liraglutide-treated patients. Once more, adverse events were mainly gastrointestinal. Almost all liraglutide-treated patients lost weight, -2.8±0.3 kg in C-peptide positive and -1.8 ± 0.6 kg in C-peptide negative patients. In one retrospective study, it is foreseen that patients with type 1 diabetes on treatment with either continuous subcutaneous insulin infusion (CSII) or multiple (four or more) injections of insulin per day on continuous glucose monitoring system (CGMS) will be included. These patients were treated with liraglutide in addition to insulin. Data are not yet available (NCT01299012).

SIDE EFFECTS

The most commonly reported adverse events in all studies were nausea, vomiting and diarrhoea, and in most studies these complaints were mainly present during the initial weeks of treatment. In the study by de Vries *et al.*, nausea was the most frequently reported adverse event in the run-in period, but there was also one case of acute pancreatitis, and one subject was diagnosed with papillary thyroid carcinoma.[10] Ryder *et al.* described the main results of the ABCD nationwide exenatide audit in an earlier article.[24] They mentioned four cases of pancreatitis, of which, after scrutiny, one could be related to the use of exenatide, and the other three had alternate causes. Furthermore, 14 cases of acute renal failure were reported, six as a result of nausea, vomiting or diarrhoea resulting in dehydration. Two had an underlying renal impairment or nephropathy, in one there was a probable other cause, and one could not be clarified by the contributor. In four cases there was no reported alternative cause other than the use of exenatide. There were 13 cases of allergy reported, of which five anaphylactic-like reactions. In a review on the safety and efficacy of once-weekly GLP-1 analogues, Madsbad *et al.* found that gastrointestinal side effects seem to be less with the exenatide once weekly formulation than with exenatide bid, and less with liraglutide than with exenatide bid, probably related to peak concentrations of the drug.[25] On the other hand, antibodies seem to be most frequent with exenatide once weekly. In studies in rodents, C-cell hyperplasia was found during administration of liraglutide and exenatide, but in humans there are as yet no data indicating an association between treatment with GLP-1 analogues and C-cell cancer. Also, cases of pancreatitis have been published, but in most cases patients had other factors predisposing to pancreatitis, and the risk of pancreatitis does not seem to be higher in GLP-1 analogue users than in patients with diabetes mellitus who are treated with other drugs.[25]

CONCLUSION

There is limited approval for the combination of use of insulin and GLP-1 analogues. The FDA and EMA approved the addition of exenatide to existing insulin glargine treatment, either alone or in combination with metformin and/or pioglitazone, while also the addition of insulin detemir to existing liraglutide therapy has been approved. However, these combinations are not reimbursed in the Netherlands. Also, the addition of a GLP-1 analogue to existing multiple insulin injection regimens has not yet been approved. There is a limited amount of evidence, but all studies available show a decline in HbA1c and in

body weight, perhaps less in the insulin users than in the non-insulin users, but at the same time a decline in insulin dose, except for the study by Buse *et al*.[7] The ABCD study showed more side effects in the insulin group.[16] Side effects are mainly gastrointestinal, and no new side effects were encountered in the group of patients using a combination of a GLP-1 analogue with insulin, compared with users of GLP-1 analogue monotherapy or a GLP-1 analogue in combination with other oral blood glucose lowering drugs. One has to be aware, however, that the number of patients treated is limited, and study duration was never longer than one year. Pancreatitis occurred in some studies, but remained rare. There was also one patient who was diagnosed with a small thyroid cancer.

Adding GLP-1 analogues to insulin has the benefit of reducing HbA1c as well as weight, while we know that the major problem with uptitrating insulin is weight gain.

Further randomised trials will be needed to confirm what was found in these (mostly observational) studies.

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