



Exenatide twice daily versus insulin glargine for the treatment of type 2 diabetes in Poland — subgroup data from a randomised multinational trial GWAA

Porównanie skuteczności eksenatydu i glarginy w leczeniu cukrzycy typu 2 — obserwacje polskiej grupy badania klinicznego GWAA

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Abstract

Introduction: We explored the safety and efficacy of exenatide BID *v.* insulin glargine in a subgroup of Polish patients with type 2 diabetes sub-optimally controlled with metformin plus a sulfonylurea, participating in a 26-week randomised, controlled open-label trial.

Material and methods: In Poland, 80 patients (HbA_{1c} 7–10%, BMI 25–45 kg/m²) were randomised to exenatide 10 µg BID (n = 40) or insulin glargine once daily (n = 40). We present exploratory analyses on HbA_{1c}, glucose profiles, body weight, hypoglycaemia and adverse events (AEs).

Results: Mean (SD) baseline HbA_{1c} was 7.9% (0.86) for exenatide and 7.8% (1.02) for insulin glargine. At Week 26, LS mean (SEM) HbA_{1c} decreased in both groups (exenatide –0.72% [0.12]; glargine –0.64% [0.12]), as did fasting glucose. Postprandial glucose excursions after breakfast and dinner were smaller in patients treated with exenatide. LS mean (SEM) body weight decreased by –1.9 (0.48) kg with exenatide and increased by 1.6 (0.48) kg with glargine (group difference [95% CI]: –3.5 kg [–4.9 to –2.2]). Hypoglycaemia was low in both groups; nocturnal hypoglycaemia was reported for three *v.* seven patients (three *v.* 24 episodes) in the exenatide and glargine groups, respectively. Adverse events were more common with exenatide (nausea n = 22 *v.* n = 1, vomiting n = 5 *v.* n = 0, headache n = 8 *v.* n = 2).

Conclusion: This exploratory analysis confirms that findings from the global study apply to patients treated with exenatide BID and glargine in Poland, showing that exenatide BID was as effective as insulin glargine. Data suggested that changes in HbA_{1c} were similar, with fasting glucose changes greater in the glargine group and postprandial changes greater in the exenatide BID group. Exenatide BID was associated with weight reduction, less nocturnal hypoglycaemia, but more gastrointestinal events compared to glargine.

(*Endokrynol Pol* 2013; 64 (5): 375–382)

Key words: type 2 diabetes mellitus, GLP-1 agonist, exenatide, insulin glargine

Streszczenie

Wstęp: Ocena bezpieczeństwa i efektów leczenia analogiem GLP-1 (eksenatyd) i długodziałającym analogiem insuliny (glargina) pacjentów z cukrzycą typu 2, nieskutecznie leczonych doustną terapią skojarzoną, biorących udział w polskiej grupie 26-tygodniowego, wieloośrodkowego, otwartego, randomizowanego badania klinicznego GWAA.

Materiał i metody: 80 pacjentów z cukrzycą typu 2 skojarzoną z otyłością (BMI 25–45 kg/m²), nieskutecznie (7% < HbA_{1c} < 10%) leczonych doustną terapią skojarzoną (metformina + pochodna sulfonilomocznika) zostało zrandomizowanych do dwóch grup leczenia interwencyjnego. Pierwsza otrzymywała eksenatyd 20 µg/dobę, a druga glarginę w jednej dawce na dobę. Analizie porównawczej poddano masę ciała, BMI, HbA_{1c}, dobowy profil glikemii i działania niepożądane.

Wyniki: Średnie stężenie HbA_{1c} było 7,9% (0,86) i 7,8% (1,02) w odpowiednich grupach. W 26 tygodniu leczenia uzyskano redukcję HbA_{1c} w obu grupach (eksenatyd –0,72% [0,12]; glargina –0,64% [0,12]). Poposiłkowa glikemia, po śniadaniu i kolacji, była niższa u pacjentów leczonych eksenatydem. Masa ciała w tej grupie uległa redukcji 1,9 (0,48) kg, natomiast wzrosła 1,6 (0,48) kg u pacjentów leczonych insuliną (różnica: –3,5 kg [95% CI –4,9; –2,2]). Nocne hipoglikemie zostały zgłoszone przez 3 pacjentów w porównaniu do 7 (3 *v.* 24 epizody) odpowiednio w grupie leczonej eksenatydem i glarginą. Objawy uboczne występowały częściej w grupie leczonej eksenatydem (nudności n = 22 *v.* n = 1, wymioty n = 5 *v.* 0, bóle głowy n = 8 *v.* n = 2) w porównaniu z grupą leczoną glarginą.

Wnioski: Eksenatyd był równie efektywny jak glargina w zakresie wyrównania gospodarki węglowodanowej w badanych grupach pacjentów z cukrzycą typu 2. Terapia eksenatydem skuteczniej obniżała glikemię poposiłkową, zaś insulinoterapia zapewniała niższe glikemie na czczo. Przewagą leczenia eksenatydem była redukcja masy ciała oraz mniej epizodów hipoglikemii, jednak przy większej częstotliwości objawów ubocznych ze strony przewodu pokarmowego. (*Endokrynol Pol* 2013; 64 (5): 375–382)

Słowa kluczowe: cukrzyca typu 2, agonista GLP-1, eksenatyd, insulina glargina

This study was sponsored by Eli Lilly and Company and Amylin Pharmaceuticals LLC.



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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, progressive disease, comprising one of the biggest unsolved problems of healthcare systems worldwide. Its progressive vascular complications, associated with an acceleration of atherosclerosis, are the main cause of the increased mortality of patients with T2DM [1–3]. Multifactorial therapeutic approaches play a vital role in preventing and blocking the macro- and microvascular diabetic complications. A more individualised therapeutic approach is often needed, using drugs with different mechanisms of action depending on the individual stage of diabetes [4].

It has been suggested that incretin hormones are an essential component of normal glucose homeostasis; they enhance glucose-dependent insulin secretion after meals [5, 6]. The incretins, of which glucagon-like-peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) appear the most important in humans, are released from the intestines following food intake. The incretin effect describes the observation that oral glucose induces a greater insulin response compared to an equivalent intravenous challenge. The incretin response accounts for approximately 70% of the total insulin secreted following the administration of oral glucose [7]. Their mechanism of action is to increase insulin secretion, decrease glucagon release, reduce food intake, and slow gastric emptying, which makes GLP-1 based therapies appropriate for treatment of T2DM. They have been associated with improvement in postprandial and, to a lesser extent, fasting glucose levels. In addition, they have been associated with weight loss and may help to preserve β -cell function, both major problems in T2DM patients [8–11]. The outcomes of initial clinical trials with GLP-1 analogues or GLP-1 receptor activation as well as with inhibitors of dipeptidyl peptidase-4, the enzyme responsible for proteolysis of incretins, in T2DM patients were very promising [12–14]. In recent years, incretin-based therapy has attracted interest as a novel therapeutic alternative for patients with T2DM [15, 16].

To date, no clinical data has been reported for exenatide twice daily (*bis in die*, BID) treatment in patients from Poland. Therefore, we explored the safety and efficacy of exenatide BID *v.* the long-acting insulin analogue glargine in a cohort of Polish patients participating in the global clinical trial reported by Heine et al. [17]. This randomised, multicentre, controlled, open-label trial compared exenatide BID *v.* insulin glargine in patients with T2DM sub-optimally controlled with metformin and a sulfonylurea.

Material and methods

Data source and overall study protocol

Data from a 26-week, multicentre, comparator-controlled, open-label, randomised, two-arm clinical trial was used for this analysis [17]. Following a four-week screening period, patients with T2DM sub-optimally controlled with metformin and a sulfonylurea were randomly assigned at baseline (1:1) to one of two injectable medications: exenatide BID (initial dose 5 μ g BID for four weeks, subsequently increased to 10 μ g BID; subcutaneously injected 15 minutes before morning and evening meals); or insulin glargine (injected subcutaneously once daily at bedtime, initial dose 10 IU per day). A fixed-dose algorithm was used to adjust the insulin glargine dose [17]. Patients self-titrated the dose in 2-IU increments every three days based on fasting blood glucose concentrations to achieve a target concentration of < 5.6 mmol/L (< 100 mg/dL). The study was conducted in accordance with the principles described in the Declaration of Helsinki. All study participants gave informed written consent before participation. The overall clinical study protocol was approved by the Ethics Committees within each country; for Poland, this was the Ethical Review Board of the Medical University of Lublin.

The primary objective of the overall study was to test the hypothesis that glycaemic control, as measured by change in HbA_{1c}, achieved with exenatide BID is non-inferior to that of insulin glargine. A further description of the study design has been published elsewhere [17].

Study population

For the overall trial, 551 patients had been randomised at 82 sites in 13 countries [17]. Of these, 80 patients, 40 in each treatment group, had been enrolled in Poland between June 2003 and April 2004. Table I summarises the main inclusion and exclusion criteria.

Assessments

HbA_{1c} was measured at screening, randomisation (baseline, week 0), and at Weeks 12 and 26. Blood chemistries were assessed at screening and at Weeks 12 and 26. A central laboratory performed all HbA_{1c} measurements, fasting serum glucose (FSG), and other laboratory tests. Seven-point, self-monitored blood glucose (SMBG) profiles were performed at screening and at Weeks 4, 8, 12, 18, and 26. Measurements were taken before the three main meals, two hours after the start of each meal, and during the night (3:00 a.m.).

Adverse events (AEs) were assessed at each visit. Symptomatic hypoglycaemia was defined as a blood glucose measurement below 3.4 mmol/L (< 60 mg/dL) or hypoglycaemia accompanied by typical clinical symp-

Table I. Summary of main inclusion and exclusion criteria**Tabela I. Kryteria włączenia i wyłączenia**

Inclusion criteria
Type 2 diabetes (WHO classification)
30–75 years of age, inclusive
Stable, optimal doses of metformin and SU for at least three months prior to screening
HbA _{1c} ranging from 7.0% to 10.0% at the time of screening
Body mass index ranging from 25 kg/m ² to 45 kg/m ²
A history of stable body weight ($\leq 10\%$ variation for ≥ 3 months before screening)
Exclusion criteria
Participation in an interventional medical, surgical, or pharmaceutical study within 30 days before screening
More than three episodes of severe hypoglycaemia within six months before screening
Therapy for a malignant disease other than basal-cell or squamous-cell skin cancer
Cardiac disease that was class III or IV according to the New York Heart Association criteria
Serum creatinine concentration $> 135 \mu\text{mol/L}$ ($> 1.5 \text{ mg/dL}$) for men or greater than $110 \mu\text{mol/L}$ ($> 1.2 \text{ mg/dL}$) for women; or obvious clinical signs or symptoms of liver disease
Long-term (> 2 weeks) systemic glucocorticoid therapy or such therapy within two weeks immediately before screening
Using any prescription drug to promote weight loss within three months before screening
Treatment for > 2 consecutive weeks with insulin within three months before screening, with thiazolidinediones within four months before screening, with alpha-glucosidase inhibitors within three months before screening, or with meglitinides within three months before screening

SU — sulfonylurea; WHO — World Health Organisation

toms. Severe hypoglycaemia was defined as an episode with symptoms consistent with hypoglycaemia in which the patient required the assistance of another person and which was associated with either a blood glucose concentration $< 2.8 \text{ mmol/L}$ (50 mg/dL) or prompt recovery after oral carbohydrate, glucagon, or intravenous glucose.

Statistical analysis

All statistical analyses were done post-hoc on the subgroup of Polish patients who participated in the international clinical trial. Baseline characteristics, dose information, and AE data were analysed descriptively; means and standard deviations (SD) are presented for continuous variables. To explore the changes from baseline in HbA_{1c}, an exploratory analysis of covariance (ANCOVA) model was performed, with treatment and baseline HbA_{1c} as covariates, applying the last-observation-carried-forward (LOCF) approach. Results were presented as least-square (LS) means and standard error of the mean (SEM) for each group; and the corresponding 95% confidence interval (CI) for the treatment group difference was reported. Similar exploratory models were calculated for other continuous variables including body weight and hypoglycaemia rate. Self-monitoring blood glucose profiles were explored with the same analytical approach used for HbA_{1c}. To explore categorical data, Fisher's exact tests were calculated as appropriate. However, no confirmatory conclusions can be drawn.

All results were presented for the intention-to-treat (ITT) population. The ITT population included all patients who took at least one dose of study drug and had at least one post-baseline measurement of the respective dependant variable. All calculations and analyses were performed using SAS software (SAS Institute, Inc., Cary, NC, USA).

Results

Patient characteristics

Of 551 patients randomised for the overall trial, 80 patients (14.5%, 40 per treatment group) had been enrolled in Poland and are reported here. Of these, 76 patients completed the study; three patients were withdrawn due to protocol violations (one patient in the exenatide BID group, two patients in the insulin glargine group), and one patient was withdrawn in the exenatide BID group based on patient decision. No patient discontinued due to AEs.

Patient characteristics at baseline are presented in Table II; there were no notable differences between treatment groups. Patient age ranged between 41 and 75 years, and 56% were female.

In the Polish patient population, the mean final insulin glargine dose at week 26 was 16.6 U (median 14, range 10–34 IU/day). Also the majority of exenatide patients in the Polish subset ($n = 30$ of 38 at Week 26) achieved the target dose of $20 \mu\text{g/d}$.

Table II. Baseline characteristics of the study population**Tabela II. Charakterystyka badanej populacji**

Characteristic	Exenatide BID N = 40	Insulin glargine N = 40
Age (years)	60 ± 9	60 ± 9
Sex, female/male (n)	24/16	21/19
Weight [kg]	84.6 ± 15.86	86.7 ± 17.47
BMI [kg/m ²]	32.0 ± 4.41	32.1 ± 5.23
Fasting serum glucose [mmol/L]	9.7 ± 0.35	9.5 ± 0.35
HbA _{1c} (%)	7.9 ± 0.86	7.8 ± 1.02
Duration of diabetes (years)	9.15 ± 4.87	7.65 ± 5.41
Systolic blood pressure [mm Hg]	138 ± 14.2	143 ± 15.7
Diastolic blood pressure [mm Hg]	80 ± 7.2	84 ± 5.8

Data is for the intent-to-treat population. Values for continuous variables are expressed as means ± SD. BID — twice daily; BMI — body mass index; SD — standard deviation

Glycaemic control: HbA_{1c} and FSG

Least-square mean HbA_{1c} decreased from baseline to Week 26 in both treatment groups (Fig. 1). In the exenatide BID group, LS mean (SEM) changes in HbA_{1c} were -0.72% (0.12) at Week 26. In the insulin glargine group, the corresponding change was -0.64% (0.12). This translated into an estimated treatment group difference of -0.07% (LS mean group difference exenatide BID minus insulin glargine, based on exploratory ANCOVA: -0.07% (0.17) [95% CI: -0.41 to 0.26]).

At Week 26, 42% of patients on exenatide and 38% of patients on insulin glargine had achieved the HbA_{1c} target of ≤ 7%. Fasting serum glucose concentrations decreased in both treatment groups from baseline to Week 26. Least-square mean (SEM) FSG concentrations decreased by -0.56 (0.40) mmol/L in patients treated with exenatide BID and by -1.43 (0.39) mmol/L in patients treated with insulin glargine; starting from baseline concentrations of 9.67 (0.35) mmol/L and 9.47 (0.35) mmol/L, respectively. For the change in FSG, the LS mean treatment group difference [95% CI] derived from the exploratory ANCOVA model (exenatide minus insulin glargine) was 0.87 [-0.24 to 1.98] mmol/L.

Body weight

Patients on exenatide BID progressively lost body weight, while patients on insulin glargine gained weight (Fig. 2). Baseline mean (SD) body weights were 84.6 (15.86) kg and 86.7 (17.47) kg in the exenatide BID and the insulin glargine group, respectively. LS mean (SEM) weight decreased by -1.9 (0.48) kg on exenatide BID compared to a weight gain of 1.6 (0.48) kg on insulin glargine. At Week 26, the treatment group difference had reached

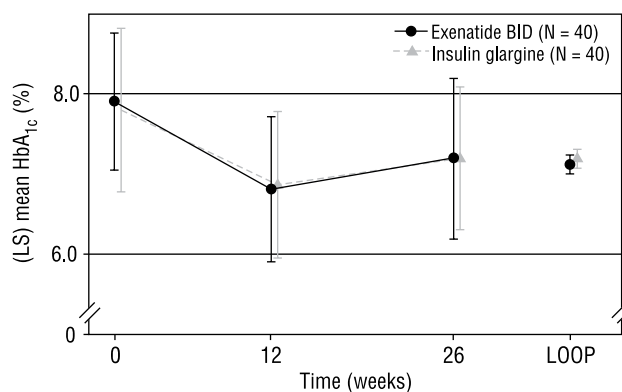


Figure 1. (LS) Mean HbA_{1c} (%) at each visit and at end-point, intent-to-treat population. Presented are mean and standard deviation for the values at each visit (0, 12, and 26 weeks); LS mean and standard error for the value at end-point (LOCF from exploratory analysis of covariance analysis). BID — twice daily; LOCF — last observations carried forward; LS — least-square

Rycina 1. Zmiany HbA_{1c} podczas poszczególnych wizyt w obu grupach badanych

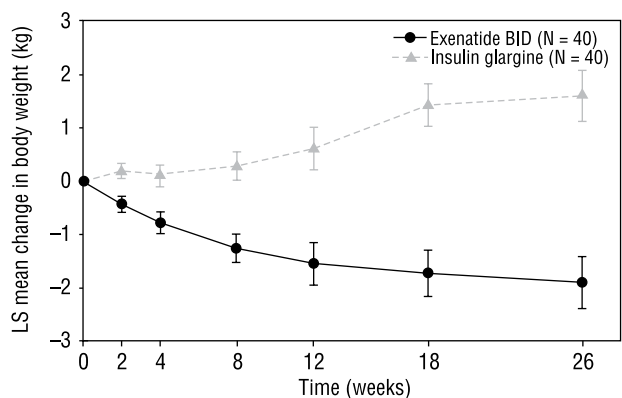


Figure 2. LS mean change of body weight at each visit, intent-to-treat population. Error bars indicate standard error of the mean. BID — twice daily; LS — least-square; wks — weeks

Rycina 2. Zmiany masy ciała podczas poszczególnych wizyt w obu grupach badanych

-3.5 kg (LS mean group difference exenatide BID minus insulin glargine, based on exploratory ANCOVA: -3.5 (0.68) kg [95% CI: -4.9 to -2.2 kg], $p < 0.001$).

SMBG profiles

Average SMBG profiles at baseline and Week 26 are shown in Figure 3. In the exenatide BID group, the primary change was in postprandial glucose excursions, whereas in the insulin glargine group, the primary change was a reduction in fasting glucose concentrations. In the exploratory ANCOVA analysis, LS mean (SEM) glucose excursions associated with exenatide BID decreased by 2.3 (0.28) mmol/L after breakfast and by 1.6 (0.24) mmol/L after dinner, compared to 0.3 (0.29)

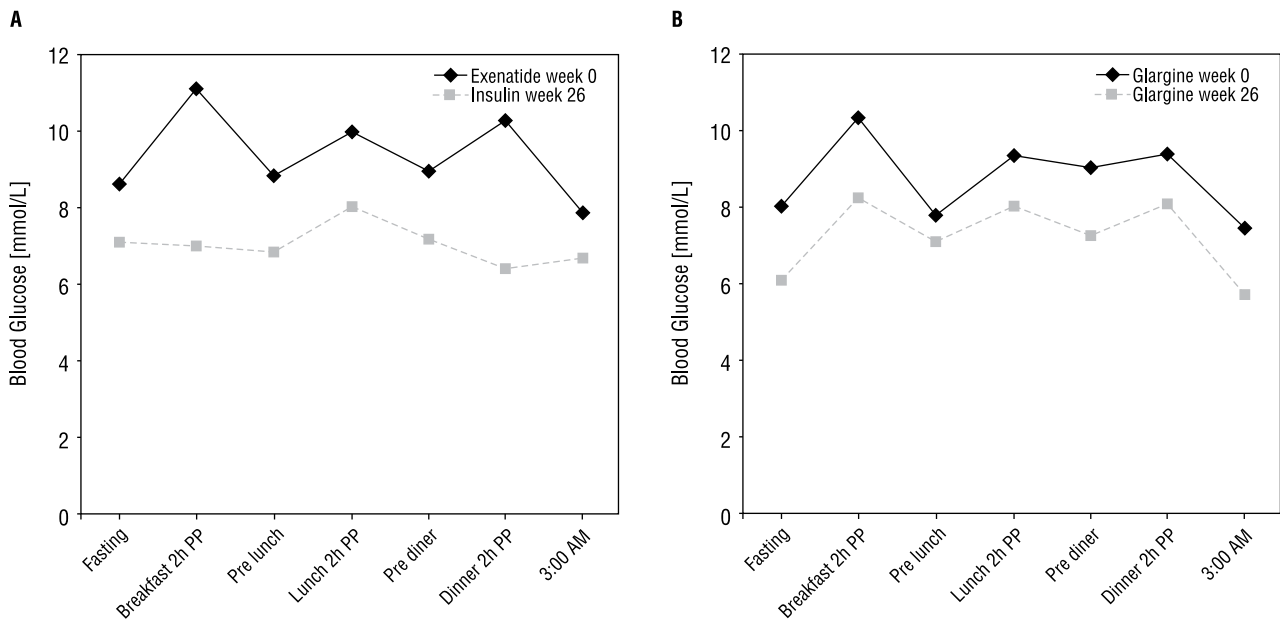


Figure 3. Mean seven-point SMBG profiles at baseline and Week 26 in both treatment groups, intent-to-treat population. PP — postprandial; SMBG — self-monitoring blood glucose

Rycina 3. Siedmiopunktowy profil glikemii na początku badania i w 26. tygodniu, w grupach badanych

mmol/L and 0.2 (0.24) mmol/L with insulin glargine (exploratory $p < 0.001$ for both meals). The responses after lunch in both treatment groups were similar.

Adverse events

Treatment-emergent AEs that occurred in $\geq 5\%$ of patients are shown in Table III. Gastrointestinal events were more common in the exenatide BID group than in the insulin glargine group. No patients withdrew because of nausea or other gastrointestinal symptoms. All other AEs occurred only once.

Hypoglycaemia

Overall, 17 patients (42.5%) in the exenatide BID group and 14 patients (35.0%) in the insulin glargine group reported at least one hypoglycaemic episode. Hypoglycaemia rates were low in both groups with 0.1 events/patient/30 days (Table IV). Few patients in the exenatide BID group experienced nocturnal hypoglycaemic events — three patients reported one episode each, compared to seven patients reporting 24 episodes in the insulin glargine group, although this was not statistically significantly different.

Discussion

A post-hoc pooled analysis found that both treatments, patients treated with exenatide BID and starter insulins, experienced improvement in fasting glucose concentrations. Although changes in LS mean fasting

Table III. Adverse events reported in $\geq 5\%$ of patients

Tabela III. Zdarzenia niepożądane występujące u $\geq 5\%$ pacjentów

Preferred term	Exenatide BID (N = 40)		Insulin glargine (N = 40)	
	n (%)	n events	n (%)	n events
Nausea	17 (43%)	22	1 (3%)	1
Headache	4 (10%)	8	2 (5%)	2
Vomiting	4 (10%)	5	0 (0%)	0
Nasopharyngitis	4 (10%)	4	2 (5%)	2
Upper abdominal pain	3 (8%)	3	0 (0%)	0
Hypertension	2 (5%)	2	0 (0%)	0
Respiratory tract infection	2 (5%)	2	0 (0%)	0

BID — twice daily

glucose concentrations from baseline at 26 weeks in the insulin treatment group were statistically different from the exenatide BID treatment group in favour of the insulin group, these differences were not observed in the subgroup treated for one year. At 52 weeks, the LS mean fasting glucose concentrations were -1.9 mmol/L and -2.0 mmol/L for patients treated with insulin and exenatide BID, respectively [18].

Based on SMBG profiles, patients treated with exenatide BID had smaller postprandial glucose excursions, especially after morning and evening meals,

Table IV. Hypoglycaemia rates (events/patient/30 days)

Tabela IV. Częstość występowania hipoglikemii (epizod hipoglikemii/pacjent/30 dni)

	Exenatide BID (N = 40)		Insulin glargine (N = 40)		Group difference (exenatide minus insulin glargine) [95% CI] p-value
	LS mean	SEM	LS mean	SEM	
Overall	0.11	0.08	0.10	0.08	[-0.22; 0.22], p = 0.995
Nocturnal	0.00	0.05	0.10	0.05	[-0.25; 0.05], p = 0.175

CI — confidence interval; LS — Least-square, SEM — standard error of the mean

whereas insulin glargine appeared to predominantly affect fasting glucose concentrations. This pattern is consistent with the timing of dosing and exenatide's mode of action.

According to an analysis of epidemiological studies by Ceriello et al., postprandial hyperglycaemia is associated with a higher risk of cardiovascular disease and an increase in overall mortality [19]. Glucagon-like-peptide-1 receptor agonists and other therapies shown to be effective in reducing postprandial glucose excursions may therefore potentially improve this cardiovascular risk factor [17, 19-24].

One of the main factors that differentiates exenatide BID from insulin — reduction in body weight — was also observed in this country-specific patient cohort from Poland; mean weight decreased by -1.9 kg in the exenatide BID group and increased by 1.6 kg in the insulin glargine group. Weight control is one of the important considerations in the treatment of patients with T2DM, according to the American Diabetes Association and the Polish Diabetes Association [24, 25]. Overweight and obesity are independent cardiovascular risk factors, and body weight reduction should be an integral component of treatment [26, 27]. The majority of oral glucose-lowering drugs used in T2DM, as well as insulin, result in weight gain or are at most weight-neutral [28]. Glucagon-like-peptide-1 receptor agonists have consistently been demonstrated to have unique effects on reducing body weight [20, 27-30]. In the UK Prospective Diabetes Study, the significant advantage of metformin over other oral antidiabetes medications in overweight and obese patients has been clearly shown [31]. Exenatide has been shown to reduce body weight in animals as well as in humans [32-35]. Exenatide reduced food intake in rodents following either central or peripheral administration. Exenatide has been shown to inhibit the

kinetics and secretory functions of the gastrointestinal tract, especially gastric emptying, which may result in a reduction of caloric intake and a progressive body weight reduction in rodents [34, 35] and humans [36]. This potential anorectic effect of exenatide and GLP-1 is assumed to be caused by an activation of peripheral visceral nerve fibre endings located in the stomach wall, regulating the rate of stomach emptying [37, 38]. But in addition, GLP-1 also acts centrally on the hypothalamic satiety centre, particularly on neurons of the arcuate nucleus in rats [39]. Currently, there is disagreement as to whether the central effect is or is not independent of the activation of peripheral visceral nerve fibres' endings in the stomach wall [38, 40]. Consistent with the weight reduction observed in animal studies, exenatide BID treatment among patients with T2DM has been associated with a delay in gastric emptying [40].

Use of exenatide BID may be more convenient for patients than treatment with insulin which requires more attention and trained personnel [41]. The difficulty of monitoring and changing the doses of insulin is eliminated with the use of exenatide BID which does not require dose titration beyond the first month of treatment and the need for routine SMBG surveillance is reduced in those patients who do not receive concomitant sulfonylurea [42].

Hypoglycaemia is a common and typical AE of drugs stimulating insulin secretion, such as sulfonylureas. The incidence of hypoglycaemic events increases according to the intensity of therapy administered to achieve adequate glycaemic control [43]. In this Polish cohort, hypoglycaemia rates were low (0.1 events/patient/30 days) in both groups; nocturnal hypoglycaemia was reported for three patients on exenatide BID *v.* seven patients on insulin glargine (three *v.* 24 episodes). In previous studies, hypoglycaemic episodes (usually mild) were noted primarily when exenatide was given in combination with a sulfonylurea, whereas they were less common when exenatide was combined with metformin [44]. This finding may be connected to the mode of action of these drugs. The potential insulinotropic effect of exenatide is glucose-dependent [45]. In contrast, sulfonylureas increase insulin secretion independently of glucose concentration, thereby resulting in a higher potential incidence of hypoglycaemia [44]. The possible interaction between molecular actions of GLP-1 and glucose-lowering drugs such as sulfonylureas should be emphasised. Sulfonylureas can reduce the interaction between GLP-1 and glucose concentration, mainly by blocking of the K channel of adenosine triphosphate in b-cells, resulting in a persistent stimulation of insulin secretion [45-47].

The data is not entirely up-to-date (2004/2005) and these factors are potential limitations. The low patient number precludes any confirmatory conclusions.

Conclusions

This exploratory subgroup analysis confirms that findings from the global study apply to patients treated with exenatide BID and glargine in Poland, showing that exenatide BID was as effective as insulin glargine. For this cohort of patients with T2DM inadequately controlled by metformin and sulfonylurea combination treatment, the data suggests that the changes in HbA1c were certainly similar, but decreases in fasting glucose were greater in the insulin glargine group and postprandial excursions were fewer in patients treated with exenatide BID. As previously seen in several large international trials, exenatide BID was associated with body weight reduction, a low incidence of nocturnal hypoglycaemia, but frequent occurrence of mild to moderate gastrointestinal events.

Acknowledgments

The authors express their appreciation to the following Polish investigators who participated in this study: K. Cypriak (Lodz), T. Kasperska-Czyzyk (Warsaw), A. Kozłowski (Mielec), K. Janik (Czestochowa), E. Jarosz-Skokowska (Lublin), K. Markiewicz (Warsaw), M. Polaszewska-Muszynska (Bydgoszcz), E. Semetkowska-Jurkiewicz (Gdansk), A. Stankiewicz (Krakow).

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