ARCHIVES OF HELLENIC MEDICINE: ISSN 11-05-3992

ORIGINAL PAPER
ΕΡΕΥΝΗΤΙΚΗ ΕΡΓΑΣΙΑ

Differences between patients initiating insulin and exenatide in clinical practice in Greece (the CHOICE study)

ARCHIVES OF HELLENIC MEDICINE 2012, 29(3):336–344
ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2012, 29(3):336–344

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Διαφορές κατά την κλινική πράξη μεταξύ ασθενών ως προς την έναρξη χορήγησης ινσουλίνης και εξενατίδης στην Ελλάδα (η μελέτη CHOICE)

Περίληψη στο τέλος του άρθρου

OBJECTIVE **Exenatide BID, in head-to-head Phase III clinical trials with insulin, provided similar glycemic control in patients whose diabetes mellitus (DM) was uncontrolled by oral antidiabetic medications (OADs). A variety of criteria appeared to influence the critical decision to move towards an injectable DM therapy. CHOICE is a multinational, prospective, non-interventional, observational study designed to assess the time to change to injectable glucose-lowering therapy (exenatide or insulin) among adults with type 2 DM, and the factors associated with the choice. This paper describes baseline data from Greek patients in the study.** METHOD **In the course of routine clinical care, the demographic/clinical characteristics and healthcare resource use of patients initiating injectable antidiabetic therapy were analyzed, using univariate tests to quantify differences between cohorts on either exenatide or insulin.** RESULTS **Of 807 eligible patients (52.5% men, mean age 63±11 years), 318 (39.4%) initiated exenatide and 489 (60.6%) insulin, according to protocol-defined criteria. Patients initiating exenatide were younger than those initiating insulin (59±10 vs 65±11 years, p<0.0001), with a higher proportion of women than men (54.4% vs 42.9%, p<0.01), a higher mean body mass index (BMI; 34.4±7 vs 28.7±5 kg/m^2; p<0.0001) and waist circumference (112±15 vs 99±14 cm; p<0.0001). They also had lower mean levels of glycated hemoglobin (HbA_{1c}) in the 3 months prior to initiation of injectable therapy (8.4±1.5% vs 9.3±1.9%, p<0.0001), and lower mean blood levels of low-density lipoprotein cholesterol, creatinine and both fasting and random glucose and less often had microalbuminuria. In addition, those initiating exenatide reported a shorter mean duration of DM (9±6 vs 12±8 years, p<0.001) with fewer macrovascular (21.4% vs 28.2%, p<0.05) or microvascular (10.4% vs 17.2%, p<0.01) complications. Of all the participants 45 (5.6%) reported ≥1 episode of hypoglycemia in the 3 months prior to initiation of injectable therapy, 15 (4.7%) initiating exenatide and 30 (6.1%) initiating insulin. More patients initiating exenatide had been given dietary and exercise advice (77.7% vs 68.9%, p<0.05). At the time of initiation of injectable therapy, 32% of patients initiated with insulin and 10% of those initiated with exenatide did not report taking any OAD therapy.** CONCLUSIONS **Patients initiating exenatide rather than insulin as injectable therapy for DM in Greece were on average younger and more obese, with lower HbA_{1c}, a shorter duration of DM, and fewer macro- and microvascular comorbitities, while more had received diet and exercise instructions. The percentage of patients in the insulin group reporting no OAD use at the time of initiation of injectable therapy was 3 fold that in the exenatide group.**

Key words

Exenatide
Greece
Insulin
Treatment initiation
Type 2 diabetes mellitus

Submitted 30.9.2011
Accepted 8.10.2011

Well-designed observational studies are essential to enhancing the evidence upon which the management of type 2 diabetes mellitus (DM) is based.[1] While randomized controlled trials are the gold standard for assessing the efficacy and safety of therapy, observational studies can provide complementary evaluation of patterns of treat-

The CHOICE study was funded by Eli Lilly and Co.

ment use, effectiveness, and safety in clinical practice.[1,2]

Exenatide BID, the first approved glucagon-like peptide-1 receptor (GLP-1) agonist, was launched in Europe in 2007 (US in 2005) for use in patients with type 2 DM with insufficient glycemic control on maximal doses of oral antidiabetic (OAD) agents. In head-to-head Phase III clinical trials, exenatide and insulin (glargine and biphasic insulin aspart), administered randomly, provided similar glycemic control in patients whose DM was not controlled by OADs. Exenatide treatment was associated with weight loss, while the patients randomized to insulin typically gained weight.[3–5] Metabolic improvements achieved with exenatide were demonstrated to have been maintained in a subset of patients for over 3 years.[6]

Clinical practice patterns of exenatide usage across Europe have not been evaluated. It is therefore unclear which patients requiring injectable glucose-lowering therapy are initiated on exenatide in routine practice, or how, when and why exenatide-based treatment is intensified, and the extent of the clinical response observed in patients taking exenatide has not been adequately assessed. Primary care databases, the principal source of retrospective observational data available to researchers, are of limited use in this regard because exenatide –being a newly approved injectable therapy– is commonly (although not exclusively) initiated in the secondary care setting.

CHOICE is a European ongoing, longitudinal (24 month) prospective, observational cohort study designed to assess the time to a significant change in treatment, and to document clinical and patient-reported outcomes and common adverse events among patients who initiate their first injectable glucose-lowering therapy with either exenatide or insulin. It is being conducted in Denmark, Belgium, France, Germany, Greece and Sweden. Exenatide BID and insulin were the only injectable forms of antiglycemic treatment available when this study commenced.

A pre-planned interim study analysis was conducted to describe the characteristics of patients with type 2 DM at the time of their initiation of injectable treatment (i.e., exenatide BID or insulin). This paper reports the baseline characteristics of the patients in Greece enrolled in the CHOICE study, with an analysis of the factors associated with initiation of an injectable treatment regime.

MATERIAL AND METHOD

Study design and patient characteristics

CHOICE is a prospective, multinational, non-interventional observational study (www.clinicaltrials.gov identifier NCT00635492).

Eligible for inclusion in the study were adults aged ≥18 years initiating their first injectable glucose-lowering therapy with insulin or exenatide BID for the treatment of type 2 DM in routine clinical practice. At study entry the patients could be taking any other OADs, but were not concurrently participating in any other study to investigate any drug or procedure, and they had sufficient understanding of the Greek language to be able to complete the questionnaires. The patients were invited to participate following a clinical decision to initiate a form of injectable therapy for DM. All patients gave written informed consent for the use of their data. Appropriate ethical review board approval was obtained for the research.

The CHOICE study plans for assessment of the patients at study visits during their routine medical appointments at the time of initiation of injectable therapy (baseline, reported here) and at approximately 3, 6, 12, 18 and 24 months thereafter, according to their routine care needs. Interim analyses are planned at baseline, and at 6 and 12 months, with the final analysis at 24 months.

Data collected

At baseline (initiation of injectable therapy), data were collected from each patient on: demographic characteristics; clinical characteristics (current status and medical history), including glycated hemoglobin (HbA_{1c}) level at initiation and over the previous 2 years) and other relevant variables; retrospectively recalled incidence of self-reported hypoglycemic episodes over the preceding 3 months, and gastrointestinal symptoms over the preceding 4 weeks; previous and ongoing DM treatment and care; concomitant medications; patient reported measures of health status and functioning.

Analysis

Sample size justification

The CHOICE study recruited 2,295 patients across the 6 participating countries, with a ratio of approximately 60% of patients recruited at initiation of insulin therapy and 40% at initiation of exenatide therapy. In Greece, it was planned for 800 patients to be enrolled, roughly 500 in the insulin cohort and 300 in the exenatide cohort. The sample size calculation was based on the estimation of the median time to significant treatment change, and the width of the corresponding confidence interval (CI) and was calculated by means of Monte-Carlo simulation, assuming patient drop-out rates of 10–15% per year and a median time to significant treatment change of 9.0 months for the exenatide cohort and 8.6 months for the insulin cohort.[7] The insulin cohort was designed to be larger than the exenatide cohort because of the greater variability in the former (linked to use of different insulin regimes), which necessitated a larger population in order to achieve similar precision for the estimation of time to treatment change (i.e., 95% CIs of 3 months width around the median within countries and cohorts).

Statistical analysis

All patients eligible at baseline were included in the analyses. Baseline patient data were reported using descriptive statistics and 95% CI where appropriate. For continuous variables, mean, standard deviation (SD), median, minimum, maximum, and quartiles were calculated. Absolute numbers and percentages (including missing values) were used for categorical variables. Overall analyses and per country analyses were performed.

To investigate factors associated with injectable treatment regimes, univariate analyses were first performed to compare the baseline patient characteristics between the two cohorts (both for the overall population and per country). Continuous variables were analysed using the t-test, analysis of variance (ANOVA) or, where necessary, the corresponding non-parametric alternatives (e.g., Wilcoxon signed rank test). Categorical variables were analysed using the Chi-square test, Fisher's exact test and trend test.

A multivariate model was built to explore the factors associated with the injectable treatment regime. For this analysis, variables found to have statistically significant differences between cohorts ($p<0.10$) at the univariate level were explored: The percentage of missing values for each variable was displayed, correlation between variables was checked and when two variables were highly correlated that with less missing values was included in the model. Missing values were not imputed. Forward and backward selection processes using $p=0.1$ as the threshold were used.

Lastly, to further describe imbalances between cohorts, baseline data were used to derive propensity scores from logistic regression utilising the same approach as the multivariate model. Propensity scores were derived by imputing missing values, and by excluding missing values. The results derived from the approaches showed no differences.

RESULTS

Data were analysed for a total of 807 patients enrolled in Greece, who initiated injectable glucose-lowering therapy between April 2008 and June 2009. Of the 48 participating investigators, 47 (98%) were secondary care physicians [18 board-certified endocrinologists (38.2%), 21 board-certified internal medicine specialists (44.7%) and 7 specialist diabetologists (14.9%)], and 1 (2%) was a primary care physician. Among the participating investigators, 18 (38.3%) were working in the National Health System, while 20 (42.6%) were in private practice and 9 (19.1%) were practicing in both settings. The majority of participating investigators (46; 97.9%) were practicing in an urban setting.

Of the participants in Greece, 318 (39.4%) patients initiated exenatide BID (the exenatide group) and 489 (60.6%) insulin. More than half (56.9%) of the 489 patients initiating insulin took basal only insulin, 32.5% mixtures, 6.3% a basal-bolus regime, and 1% took short-acting only (3.3% other or missing); most received insulin analogs (88.5%) while the rest were given human insulins (10.4%), with only one patient taking both. For the purpose of cohort comparisons, these patients initiating various starter insulin regimens were considered together (the insulin group).

Most patients initiating exenatide (89.6%) were administered a daily dose of 10 μg, while a daily dose of 20 μg was given to 10.4% of patients. With a single exception, the patients received an injection twice daily.

Demographic characteristics

The patients had a mean age of 63±11 years, body weight of 85±20 kg, body mass index (BMI) of 30.9±6.4 kg/m^2 and a mean level of HbA_{1c} (previous 3 months) of 9.0%±1.8%. Their mean duration of diagnosed DM was 11±7 years. Univariate analyses revealed statistically significant differences between the exenatide group and the insulin group (tab. 1). The exenatide group patients were on average significantly younger than the insulin group patients (mean age 59±10 vs 65±11 years; $p<0.0001$), with a higher proportion of women (54.4% vs 42.9%, respectively, $p<0.01$). The exenatide group had significantly higher mean body weight (95.1±21.2 kg vs 78.9±15.1 kg; $p<0.0001$), BMI (34.4±7 vs 28.7±5 kg/m^2; $p<0.0001$) and waist circumference (112±15 vs 99±14 cm; $p<0.0001$) than the insulin group (tab. 1). The two groups also differed significantly in educational level and occupational status when all sub-categories were taken into account (tab. 1).

Diabetes and glucose control

The exenatide group had a significantly shorter mean duration of diagnosed DM than the insulin group (9±6 vs 12±8 years; $p<0.0001$). Exenatide group patients had a lower mean level of HbA_{1c} prior to initiation of injectable therapy (8.4±1.5% vs 9.3±1.9%, $p<0.0001$, the most recent value within past the 3 months). Overall, 6.3% of patients (51/807) initiated injectable therapy despite having an HbA_{1c} measurement of <7% in the past 3 months (9.7% for exenatide and 4.1% for insulin). The exenatide group also had significantly lower mean fasting and random blood glucose levels, and lower blood levels of low-density lipoprotein cholesterol and creatinine than the insulin group, and more often had microalbuminuria (tab. 1). In total, 31.7% of the insulin group and 9.7% of the exenatide group did not report OAD at initiation of injectable therapy, and 4.7% (n=15) of the exenatide and 6.1% (n=30) of the insulin group reported experiencing at least one hypoglycemic episode in the 3 months prior to initiation. Few patients reported severe (4 and 9, respectively, for

Table 1. Baseline characteristics of patients (n=807) initiated on exenatide or insulin.

Variable	Exenatide (n=318)	Starter insulin (n=489)	p value*	Total (n=807)	Missing data
Male, n (%)	145 (45.6)	279 (57.1)	0.001	424 (52.5)	
Age, years (SD)	59 (10.0)	65 (11.0)	<0.0001	63 (11.0)	0%
Weight, kg (SD)	95.1 (21.2)	78.9 (15.1)	<0.0001	85.3 (19.5)	0.2%
BMI, kg/m^2 (SD)	34.4 (6.8)	28.7 (4.9)	<0.0001	30.9 (6.4)	1.0%
Waist circumference, cm (SD)	111.8 (14.5)	99.1 (13.5)	<0.0001	104.3 (15.3)	23.3%
Blood pressure, mmHg (SD)					
Systolic	136.5 (17.1)	136.8 (18.2)	0.987	136.7 (17.8)	0.5%
Diastolic	81.2 (10)	80.0 (9.8)	0.146	80.5 (9.9)	0.5%
Plasma lipids, mmol/L (SD)**					
Total cholesterol	4.96 (1.06)	5.11 (1.10)	0.064	5.05 (1.09)	10.4%
LDL cholesterol	2.96 (1.00)	3.15 (0.99)	0.006	3.07 (1.00)	13.1%
HDL cholesterol	1.15 (0.29)	1.18 (0.32)	0.108	1.17 (0.31)	14.4%
Triglycerides	2.09 (1.12)	1.96 (0.99)	0.270	2.01 (1.05)	10.7%
Creatinine, mmol/L (SD)**	83.0 (24.9)	95.3 (47.8)	<0.0001	90.4 (40.7)	11.3%
Microalbuminuria present, n (%)	38 (11.9)	90 (18.4)	0.045	128 (15.9)	40.2%
Smoking status, n (%)					1.3%
Ever smoked	141 (44.3)	209 (42.7)	0.604	350 (43.4)	
Current smoker	55 (17.3)	94 (19.2)	0.346	149 (18.5)	
Employment, n (%)			<0.0001†		0.4%
Working full/part time	125 (39.3)	138 (27.0)	–	257 (31.8)	
Retired	98 (30.8)	226 (46.2)	–	324 (40.1)	
Unemployed and other	95 (29.9)	131 (26.8)	–	226 (28.0)	
Education, n (%)			0.028†		0.4%
No formal	27 (8.5)	40 (8.2)	–	67 (8.3)	
Minimum mandatory	141 (44.3)	264 (54.0)	–	405 (50.2)	
Further education	71 (22.3)	82 (16.8)	–	153 (19.0)	
University	43 (13.5)	48 (9.8)	–	91 (11.3)	
Unknown or missing	36 (11.3)	55 (11.2)	–	91 (11.3)	
Co-morbid illness, n (%)	242 (76.1)	353 (72.2)			
Patients with at least one co-morbidity					
Hypertension	196 (61.6)	292 (59.7)	–	488 (60.5)	
Hyperlipidemia	186 (58.5)	241 (49.3)	–	427 (52.9)	
Concomitant therapy, n (%)					
Any	274 (86.2)	421 (86.1)	0.704	695 (86.1)	
Lipid-lowering	194 (61.0)	297 (60.7)	0.880	491 (60.8)	
Cardiovascular	221 (69.5)	347 (71.0)	0.608	568 (70.4)	
Antiplatelet	141 (44.3)	265 (54.2)	0.006	406 (50.3)	
Weight-lowering	26 (8.2)	8 (1.6)	<0.0001	34 (4.2)	
Time since diabetes diagnosis, years (SD)	9 (6.0)	12 (8.0)	<0.0001	11 (7.0)	0.5%
HbA_{1c}, most recent in previous 3 months, % (SD)	8.41 (1.51)	9.34 (1.87)	<0.0001	8.97 (1.79)	2.4%

HbA_{1c}: Glycated hemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; NS: Non-significant; OAD: Oral antidiabetic agents; SD: Standard deviation; continuous data are expressed as mean (SD)

*Wilcoxon test used for continuous data. Chi-squared or Fisher's exact tests used for categorical data; †Comparisons under "employment" and "education" take into account all subcategories under these headings; ** Reported within the last 6 months prior to T1 (initiation)

Table 1. (continued) Baseline characteristics of patients (n=807) initiated on exenatide or insulin.

Variable	Exenatide (n=318)	Starter insulin (n=489)	p value*	Total (n=807)	Missing data
HbA_{1c} <7%, n (%)	31 (9.7)	20 (4.1)	–	51 (6.3)	2.4%
Random blood glucose, mmol/L (SD)	10.4 (2.9)	12.3 (4.1)	<0.0001	11.5 (3.8)	18.3%
No of OADs used at the time of initiation of injectable, n (%)					
0	31 (9.7)	155 (31.7)	–	186 (23.0)	
1	144 (45.3)	177 (36.2)	–	321 (39.8)	
2	134 (42.1)	149 (30.5)	–	283 (35.1)	
3	9 (2.8)	8 (1.6)	–	17 (2.1)	
Diet and exercise counselling, n (%)	247 (77.7)	337 (68.9)	0.031	584 (72.4)	12.8%
Diabetes complications, n (%)					
≥1 macrovascular complication	68 (21.4)	138 (28.2)	0.030	206 (25.5)	
≥1 microvascular complication	33 (10.4)	84 (17.2)	0.007	117 (14.5)	

HbA_{1c}: Glycated hemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; NS: Non-significant; OAD: Oral antidiabetic agents; SD: Standard deviation; continuous data are expressed as mean (SD)
*Wilcoxon test used for continuous data. Chi-squared or Fisher's exact tests used for categorical data; †Comparisons under "employment" and "education" take into account all subcategories under these headings; ** Reported within the last 6 months prior to T1 (initiation)

the exenatide and insulin groups) or night-time episodes (4 and 13, respectively).

Significantly fewer in the exenatide group reported one or more macrovascular complications (21.4% vs 28.2%, p<0.05) or microvascular complications (10.4 vs 17.2%, p<0.01), compared with the insulin group. More patients in the exenatide group had been given dietary and exercise advice in the past (77.7% vs 68.9%, p<0.05).

Co-morbidity and concomitant medications

The exenatide group reported statistically less micro- and macrovascular complications than the insulin group (p=0.007 and 0.030, respectively). At least, one co-morbidity was reported by 76.1% of patients in the exenatide group at entry in the study compared with 72.2% in the insulin group. Among the co-morbidities a diagnosis of hypertension was reported for 61.6% vs 59.7% of patients in the exenatide or insulin groups, respectively, and a diagnosis of hyperlipidemia by 58.5% vs 49.3%, respectively. No differences were found in the mean blood pressure between groups at baseline, and for the whole study population the readings were 136.7±17.8 mmHg (systolic) and 80.5±9.9 mmHg (diastolic). Overall, 86.1% of patients were using at least one concomitant, non-diabetic medication (mainly cardiovascular, lipid-lowering and antiplatelet agents) at initiation of injectable therapy. The exenatide group had a lower rate of use of antiplatelet agents than the insulin group (p=0.006), but there was no difference regarding the use of lipid-lowering and cardiovascular agents between the 2 groups (tab. 1). Patients in the exenatide group were more likely to have used weight-lowering medications than those in the insulin group [8.2% (n=26) vs 1.6% (n=8); p<0.0001]. Of the total cohort, 72% reported receiving metformin (MET) during the 12 months prior to initiating injectable therapy, while some patients reported use of sulfonylurea (SU; 66%), thiazolidinediones (TZDs; 16%), dipeptidyl peptidase IV (DPP-4) inhibitors (11%), TZD+MET (5%), glinides (3%), combination of MET and glibenclamide (3%), and acarbose (<1%). During these preceding 12 months, 214 (27%) patients reported taking one OAD, 343 patients (43%) reported taking two, 164 (20%) three, and 8 patients (1%) taking four, although it is unclear whether they were used in combination or consecutively. The remaining 78 patients (10%) had taken no OAD therapy in the past 12 months (30 patients in the exenatide and 48 in the insulin group). Approximately 14% (n=45) of the exenatide and 24% (n=115) of the insulin group had stopped one or more OADs within the 4 weeks prior to initiation of injectable therapy while a very small percentage (2% and 1%, respectively) had started an OAD during that period. Of the 160 patients stopping OADs, 62% stopped an SU [44% in the exenatide group (20/45) vs 69% in the insulin group (79/115)], 35% stopped MET [31% in the exenatide group (14/45) vs 37% in the insulin group (42/115)], 20% stopped TZDs [18% in the exenatide group (8/45) vs 21% in the insulin group (24/115)], and 17% stopped a DPP-4 [22% in the exenatide group (10/45) vs 15% in the insulin group (17/115)]. At the time of initiation of injectable therapy 186 (23%) patients did not report current use of

Table 2. Baseline variables that were statistically significantly associated with treatment choice: Insulin or exenatide (n=807) (logistic regression using forward selection based on p<0.10).

Variable	OR	95% CI	p value
Body mass index			
1 kg/m^2 change	1.225	1.179–1.274	<0.0001
5 kg/m^2 change	2.764	2.276–3.356	<0.0001
Most recent HbA_{1c}: 1% change	0.624	0.549–0.709	<0.0001
Age			
1 year change	0.969	0.951–0.987	<0.0001
5 years change	0.854	0.777–0.937	0.0009
10 years change	0.729	0.604–0.879	0.0009
Microvascular diagnoses (yes versus no)	0.411	0.225–0.751	0.0012
EQ-5D index value			
1 unit change	3.419	1.674–6.983	0.0021
0.1 unit change	1.131	1.053–0.215	0.0007
Gastrointestinal symptoms in the last 4 weeks prior to T1 (yes versus no)	3.580	1.456–8.803	0.0027
Duration of diabetes (years)			
1 year change	0.962	0.933–0.991	0.0121
5 years change	0.823	0.707–0.957	0.0116
10 years change	0.677	0.500–0.916	0.0116
DHP: Dis-inhibited eating	1.056	1.001–1.114	0.0461

CI: Confidence interval; HbA_{1c}: Glycated hemoglobin; LDL: Low-density lipoprotein; EQ-5D: Standardised questionnaire, self-completed instrument for measuring health outcomes and a single index value for health status; OR: Odds ratio, exenatide vs insulin

Note: Only a few patients presented gastrointestinal symptoms within the 4 weeks before initiation of injectable treatment but a higher percentage of patients presented those symptoms in exenatide cohort. The large confidence interval is due to the low number of patients

any OAD therapy [31 (10%) in the exenatide and 155 (32%) in the insulin group]; 321 (40%) were taking one OAD (45% exenatide, 36% insulin), 283 (35%) were taking two OADs (42% exenatide, 31% insulin), and 17 patients (2%) were taking three OADs (3% exenatide, 2% insulin). The most common monotherapy taken four weeks after initiation of exenatide or insulin was MET (35% and 28%, respectively) followed by SU (4% and 5%). Common dual-OAD therapy included MET+SU (37% and 26%), MET+TZD (2% both), and SU+TZD (1% both). Patients taking three OADs at the point of initiation of injectable therapy were mostly taking MET, SU and TZD (2% and 1%).

Factors associated with the injectable treatment regime

A multivariate logistic regression analysis model including all the baseline variables showing statistically significant difference between groups (p<0.10) at the univariate level, identified 8 variables that were associated with an increased likelihood of the patient receiving exenatide (forward selection), specifically: Higher BMI, lower HbA_{1c}, lower age, less microvascular complications, high (EQ-5D) index value, presence of gastrointestinal symptoms in the last 4 weeks, shorter duration of DM, and higher diabetes health profile (DHP). While the data entered into the multivariate analysis model can help to improve the understanding of the factors most strongly associated with the choice of injectable therapy, it is possible that several other variables that were not captured –such as clinical guidelines and patient preference– may be at least as clinically relevant.

Adjustment of the baseline characteristics through a propensity scoring approach underlined the differences between treatment groups: selecting an equal number of patients from the two groups by matching based on their propensity score a match of 42% of the patients (338 patients, 169 per treatment group), largely under-representing the upper tail of the exenatide distribution and the lower tail of the insulin distribution (fig. 1).

DISCUSSION

From preliminary analysis of the characteristics at recruitment of the CHOICE study cohort in Greece, differences could be identified between patients with DM whom physicians initiated on exenatide and those initiated on starter insulin in routine clinical practice. Overall, the patients initiated

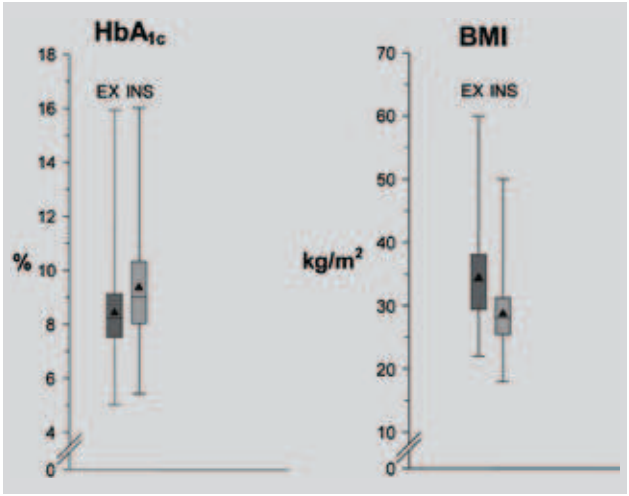

Figure 1. Level of glycated hemoglobin (HbA_{1c}: most recent during the past 3 months) and body mass index (BMI) among patients in Greece with type 2 diabetes mellitus at the initiation of injectable therapy with exenatide (EX) or insulin (INS). Box plots show mean (triangle), median (line), 25% and 75% quartiles (box) and minimum/maximum values (whiskers).

on exenatide were characterized by younger age, greater body weight, BMI and waist circumference, lower blood level of LDL cholesterol, shorter time since the diagnosis of DM, and better glycemic control. Exenatide patients also had a lower frequency of microvascular and macrovascular complications, a finding that might reflect their younger mean age and duration of DM. In general, BMI, HbA_{1c} and age were highly significant factors associated with injectable treatment differentiation ($p<0.0001$).

The risk of treatment-induced hypoglycemia is an important consideration during treatment selection,[3–5] especially in patients with HbA_{1c} close to or within target levels, and a recently published statement on type 2 DM management specifies exenatide as an option when hypoglycemia is a particularly important consideration.[8] The frequency of recent hypoglycemia in the CHOICE Greek cohort was very small in both groups (i.e., 4.7% of the exenatide and 6.1% of the insulin group). The higher mean weight at recruitment of patients in the exenatide group is consistent with findings of its favorable effect on body weight and the ADA/EASD consensus statement on treatment options for these patients.[3–5,8]

Mean HbA_{1c} level at initiation of injectable therapy exceeded the recommended target level of <7%[8] in both groups. Indeed, the HbA_{1c} of the study patients over the 2 years prior to initiation of injectable therapy was on average above optimum (data not shown). In the 3 months prior to injectable initiation the mean HbA_{1c} was 9.3% in the insulin group and 8.4% in the exenatide group. Although this finding may reflect different disease progression in the two groups prior to the initiation of either exenatide or insulin, missing pre-baseline HbA_{1c} records for many patients make interpretation of this phenomenon difficult. These findings are consistent with previous observational evidence that insulin initiation is very often delayed for years despite poor glycemic control on OADs.[7,9–11]

The finding that the patients initiated on exenatide in the Greek CHOICE cohort had lower HbA_{1c} levels than those initiated on insulin is consistent with both US observational data[12] and data from the other countries in the CHOICE study.[13] It is also in line with the American Diabetes Association and the European Association for the Study of Diabetes (ADA/EASD) consensus statement that identifies exenatide as an option for patients with glycemic control close to target levels.[8] Clinical data, however, support use of exenatide at various ranges of HbA_{1c}.[14–16]

In the Greek study cohort, diagnosis of hypertension was reported for 61.6% and 59.7%, respectively of patients in the exenatide and insulin groups and a diagnosis of hyperlipidemia for 58.5% and 49.3%, respectively. Statistical differences in the rates of micro- and macrovascular complications between groups have also been found by Fabunmi et al who reported that patients initiated on exenatide had significantly lower rates of macrovascular and microvascular complications than those initiated on insulin.[12] Overall, the mean blood pressure values among the Greek CHOICE patients at baseline would classify the population at low risk according to the target of 130/80 mmHg of the International Diabetes Federation (IDF)[17] and a Taskforce of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD),[18] or the target of 140/90 mmHg recently recommended by the European Society of Hypertension.[19] Even if blood pressure values had been found elevated, hypertension is unlikely to be a determinant of treatment choice independently of HbA_{1c} and weight. Insulin-initiating patients were older and with a lower weight and had significantly higher blood creatinine levels than exenatide patients. Renal complications, as complications, might have contributed to the initiation of insulin.

The CHOICE study has several limitations. Although the study was designed to recruit a representative sample of patients, the degree to which the data can be generalized is unclear. The CHOICE population appears similar to that of the observational INSTIGATE study,[7] in terms of such variables as mean age, BMI and duration of DM among participants, although INSTIGATE patients had a higher mean HbA_{1c} at the initiation of insulin therapy (9.6% vs 9.2% in CHOICE). All these findings have to be interpreted in the context of an observational setting.

In conclusion, in Greece, healthcare providers added injectable therapy, either exenatide or insulin, to a variety of oral therapy for patients with DM generally in accordance with recently published guidelines and consensus algorithms. Within the CHOICE study cohort of patients, those in the group initiating exenatide were younger, more obese, and had a lower HbA_{1c} than those in the group initiating insulin. Exenatide was favoured when weight gain was a particular concern and when HbA_{1c} was modestly raised. The insulin group had a higher percentage of patients who had received no OADs at the time of initiation of injectable therapy, and a higher percentage of patients who did not start OADs, than those in the exenatide group.

These data suggest that in Greece the patient profile contributed to the prescribing choice of an injectable glucose-lowering therapy regime for patients with type 2 DM.

ACKNOWLEDGEMENTS

The authors are much thankful to Drs Sourmeli Sotiria, Arampatzi Kalliopi and Liakou Aikaterini for diligent assistance to the study.

The Greek CHOICE study team: Adamidis Sotiris, Alexandridis Theodoros, Angelopoulos Nicholas, Anthimidis Georgios, Avramidis Iakovos, Boniakos Anastasios, Duntas Leonidas, Georgas Georgios, Giannakopoulos Petros, Grypaiou Christodoula, Ierapetritis Ioannis, Ioannidis George, Kazakos Kyriakos, Kiouras Stergios, Kofopoulos Savvas, Korakovouni Areti, Koureta Panagiota, Kravvariti Maria, Kyriakopoulos Konstantinos, Makriyannis Dimitrios, Maleza Avgi, Maras Perikles, Melidonis Andreas, Michalopoulos Athanasios, Milopoulos Christos, Mouslech Jadalla, Nikolaou Evgenia, Oikonomidou Christina, Pagkalos Emmanouil, Papantoniou Stefanos, Pappas Angelos, Pappas Stavros, Pavlopoulos Vasileios, Piaditis Georgios, Pigkas Georgios, Polizoulis Georgios, Rampaouni Athina, Sampanis Christos, Simelidis Dimitrios, Somali Maria, Soulis Konstantinos, Spanou Eleftheria, Spina Giovanna, Tentolouris Nikolaos, Theodorakis Michael, Tzotzas Themistoklis, Vlachogiannis Nikolaos and Vryonidou Andromachi / Phenekos Konstantinos.

ΠΕΡΙΛΗΨΗ

Διαφορές κατά την κλινική πράξη μεταξύ ασθενών ως προς την έναρξη χορήγησης ινσουλίνης και εξενατίδης στην Ελλάδα (η μελέτη CHOICE)

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Αρχεία Ελληνικής Ιατρικής 2012, 29(3):336–344

ΣΚΟΠΟΣ Η εξενατίδη, χορηγούμενη δύο φορές ημερησίως σε κλινικές μελέτες φάσης III σε σύγκριση με ινσουλίνη, οδήγησε σε παρόμοιο γλυκαιμικό έλεγχο ασθενών με σακχαρώδη διαβήτη τύπου 2 (ΣΔ2) που δεν ρυθμίζονταν με από του στόματος αντιδιαβητικά φάρμακα (OADs). Εν τούτοις, ποικίλα κριτήρια φάνηκε να επηρεάζουν την κρίσιμη απόφαση για έναρξη ενέσιμης θεραπείας, καθώς και για την επιλογή αυτής. Η μελέτη CHOICE αποτελεί προοπτική, πολυκεντρική, μη παρεμβατική μελέτη παρατήρησης, με στόχο την εκτίμηση του χρόνου προς τη σημαντική μεταβολή της ενέσιμης αγωγής μεταξύ ασθενών με ΣΔ2, που αρχίζουν για πρώτη φορά ενέσιμη αντιδιαβητική αγωγή (εξενατίδη ή ινσουλίνη). **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ** Τα κλινικά και τα δημογραφικά χαρακτηριστικά των ασθενών κατά την έναρξη της ενέσιμης θεραπείας αναλύθηκαν με τη χρήση μονομεταβλητών δοκιμασιών μεταξύ ομάδων. **ΑΠΟΤΕΛΕΣΜΑΤΑ** Από 807 ασθενείς που πληρούσαν τα κριτήρια εισαγωγής (52,5% άνδρες, ηλικίας [ΜΟ±SD] 62,7±10,8 έτη), σύμφωνα με το πρωτόκολλο της μελέτης, 318 (39,4%) τέθηκαν σε εξενατίδη και 489 (60,6%) σε ινσουλίνη. Οι πρώτοι ήταν κατά μέσον όρο νεότεροι (59±10 έναντι 65±11 έτη, p<0,001), με υψηλότερο το ποσοστό των γυναικών (54,4% έναντι 42,9% ανδρών, p<0,01), με υψηλότερο δείκτη μάζας σώματος (ΔΜΣ: 34,4±7 έναντι 28,7±5 kg/m^2) και περιφέρεια μέσης (112±15 έναντι 99±14 cm), ενώ είχαν χαμηλότερα μέσα επίπεδα γλυκοζυλιωμένης αιμοσφαιρίνης (HbA_{1c}) κατά το τρίμηνο χρονικό διάστημα πριν από την έναρξη της ενέσιμης θεραπείας (8,4±1,5% έναντι 9,3±1,9%, p<0,001), καθώς και χαμηλότερα μέσα επίπεδα LDL-χοληστερόλης, κρεατινίνης ορού, μικρολευκωματινουρίας και γλυκόζης αίματος σε νηστεία και σε τυχαία μέτρηση. Επίσης, ανέφεραν βραχύτερη διάρκεια παρουσίας του διαβήτη (9±6 έναντι 12±8 έτη, p<0,001) και σπανιότερα μακρο-αγγειακές (21,4% έναντι 28,2%, p<0,05) ή μικρο-αγγειακές (10,4% έναντι 17,2%, p<0,01) επιπλοκές έναντι των ασθενών που άρχιζαν ινσουλίνη. Συνολικά, 45 συμμετέχοντες (5,6%) εμφάνισαν ≥1 επεισόδιο υπογλυκαιμίας κατά το τρίμηνο πριν από την έναρξη της αγωγής, 15 (4,7%) στην ομάδα εξενατίδης και 30 (6,1%) στην ομάδα ινσουλίνης. Οι περισσότεροι από τους πρώτους ασθενείς έλαβαν οδηγίες για άσκηση και κατάλληλη δίαιτα (77,7% έναντι 68,9%, p<0,05). Κατά την έναρξη της θεραπείας, 32% των ασθενών στην ομάδα της ινσουλίνης δεν ελάμβανε κάποιο υπογλυκαιμικό φάρμακο από το στόμα (αντίστοιχα, 10% για την ομάδα εξενατίδης). **ΣΥΜΠΕΡΑΣΜΑΤΑ** Οι Έλληνες ασθενείς που άρχισαν θεραπεία με εξενατίδη ήταν νεότεροι, περισσότερο παχύσαρκοι, με χαμηλότερο επίπεδο HbA_{1c}, βραχύτερη διάρκεια του διαβήτη, λιγότερες μακρο- και μικρο-αγγειακές επιπλοκές και είχαν λάβει πιο λεπτομερείς οδηγίες για κατάλληλη δίαιτα και άσκηση σε σύγκριση με όσους άρχισαν ινσουλίνη, ενώ τριπλάσιο ποσοστό ασθενών που άρχισαν ινσουλίνη δεν ελάμβανε κάποιο από του στόματος υπογλυκαιμικό φάρμακο σε σύγκριση με τους ασθενείς που άρχιζαν εξενατίδη.

Λέξεις ευρετηρίου: Ελλάδα, Έναρξη αγωγής, Εξενατίδη, Ινσουλίνη, Σακχαρώδης διαβήτης τύπου 2

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