Early Insulin Glargine Initiation in Iranian People With Uncontrolled Type 2 Diabetes: Glycemic Control, and Adverse Events

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Received: 10 Jun. 2017; Accepted: 18 Dec. 2017

Abstract- To explore glycemic control, and adverse events of Iranian people with uncontrolled type 2 diabetes after initiation of long-acting basal insulin, glargine. People with uncontrolled type 2 diabetes that was on at least two oral anti-diabetic drugs (OAD) were enrolled in this observational prospective study. Insulin glargine was prescribed by physicians in the course of routine clinical practice. Patients were followed for 24 weeks. Insulin doses were titrated to reach fasting blood sugar (FBS) target between 90 mg/dl and 130 mg/dl. HbA1c and adverse events were recorded at baseline, week 12, and week 24. Form a total of 292 participants, 243 patients completed the study. HbA1c, FBS, postprandial glucose, total cholesterol, triglycerides, and low-density lipoprotein cholesterol, but not body mass index decreased during the study. The proportion of poorly controlled patients (HbA1C>9%) decreased from 172 (58.9%) to 39(13.4%), and 21(7.2%) during follow up. Controlled glycemia (HbA1C<7%) was detected in 7(2.4%), 48 (16.4%) and 56 (19.2%) of patients at baseline, week 12 and week 24. Hypoglycemia was reported in 5.1% and 3.4% of the participants in the week at 12 and 24, respectively. Patients felt more satisfied with their blood glucose control, timing and choices of meals, and hypo/hyperglycemic experiences. Insulin glargine initiation in people with uncontrolled type 2 diabetes on 2 OADs is associated with significant improvement in metabolic control. Insulin glargine has good safety profile and well tolerated by the patients.

Acta Med Iran 2018;56(4):249-254.

Keywords: Long-acting insulin; Adverse effects; Hyperglycemia; Hypoglycemia

Introduction

The total prevalence of diabetes in the world will increase from 415 million in 2015 to 642 million in 2040 (1). This increase is in part due to high prevalence of obesity which increased from 13.6% in 1999 to 19.6% in 2005 and 22.3% in 2007 (2), sedentary life (40%; adult population 2007) (3), low fruit and vegetable consumption (4) and hypertension (26,6%; adult population 2007) (5) The estimated annual cost per diabetic patient was 2.7 times higher respectively than that of non-diabetic subjects. For the Iranian population, the direct and indirect costs of diabetes were estimated to be $537 m and $140 million, respectively in 2004-05, of which $356 m of direct costs and $80 million of indirect costs were estimated to be attributable to diabetes. Approximately 18% of Iranian diabetic subjects had at least one known microvascular or macrovascular complication (6). Several studies have shown that tight glycemic control could reduce these complications (7-10). Nevertheless, a high proportion of patients remain poorly controlled (11,12). Mirzazadeh *et al*., showed that about 57% of Iranian diabetic subjects had a fasting plasma glucose level equal or greater than 130 mg/dL (13).

Insulin therapy in type 2 diabetes is generally reserved for patients unresponsive to diet, exercise, and oral antidiabetic agents (OADs). After 5-10 years of

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clinically recognized type 2 diabetes, a majority of patients will need insulin administration as a part of their therapeutic regimen to maintain target glycemic control (14,15). American Diabetes Association and European Association for the Study of Diabetes recommended the early addition of insulin therapy in patients who do not reach glycemic goals (16). Early insulin therapy is known to diminish the deleterious process of lipotoxicity directly or indirectly (17). Insulin exerts an inhibitory effect on oxidative stress caused by sustained hyperglycemia and glucose variability in non-insulin treated type 2 diabetes (18). Many patients and physicians, however, are reluctant to initiate insulin therapy for a variety of reasons, including concerns regarding the risks of hypoglycemia, needle phobia, a fear of weight gain and the perceived complexity of insulin regimens (19,20). Insulin glargine (LANTUS, Sanofi-Aventis, Paris, France), a long-acting basal insulin analog providing relatively peak-free insulin levels and a 24-h duration of action following once-daily administration, has facilitated several barriers and disadvantages associated with conventional insulin therapies to be overcome (21). In people with type 2 diabetes, insulin glargine is associated with a lower risk of hypoglycemic events vs. NPH insulin (22-26), with at least equivalent glycemic control (27-30) and less weight gain. In this open-label observational study, we explored the efficacy and safety of early insulin therapy in type 2 diabetic subjects who were on OADs and failed to reach the recommended metabolic targets.

Materials and Methods

Eligible participants were people with type 2 diabetes, with diabetes duration less than 5 years, on 2 OADs, and with inadequate glycemic control (HbA1C >7%). Pregnant and breastfeeding mothers, patients younger than 18 years, subjects with severe dysglycemia (HbA1C >10%) or co-morbidities, hospitalized or severely ill patients and those previously treated with insulin in out-patient settings were excluded. Insulin glargine was prescribed by physicians in the course of routine clinical practice as single daily injection. Titration and dose adjustments were done by the physicians. The target glycemic control was defined as FBS <130 and >90 mg/dl. Changing the dose of OADs was at the discretion of the physicians. Hypoglycemic events in relation to daily activities and need to hospitalization were recorded. Patients were weighted, and their HbA1c and lipid panel were determined at baseline, week 12 and week 24. This study was conducted in accordance with the principles of the 18th World Medical Assembly (Helsinki, 1964) and the applicable amendments. Ethics Committee of Iran University of Medical sciences reviewed and approved the study protocol. All patients gave written informed consent and received complementary Glucose meter and educational classes. Data were analyzed and handled anonymously. Data quality control and verifications were performed with on-site audits and patient contacts based on standard protocol.

Statistical analyses

Main endpoints were percentage of patients with HbA1c<7% at week 12 and week 24, HbA1c changes from baseline, hypoglycemic events. Mean standard deviation and frequencies with 95% confidence interval are reported when appropriate. For the changes in HbA1C in addition to *t*-test and analysis of Variance, general regression model was used. Statistical analyses were conducted with SPSS Software version 19.

Results

Two hundred and ninety-two type 2 diabetic patients (175 females) were enrolled for this nation-wide multi-center study. Twenty-two endocrinologists all over the country enrolled the study. The study started November 2009 and the last patient last visit was performed in May 2011. Characteristics of the participants at baseline are summarized in table 1. Patients aged 51.8 ± 10.3 years and they were typically urban dwellers (91%) and obese (70%). Biguanides were the most common OAD used in 255 patients (87.3%) followed by sulphonylureas in 227 (77.7%). Thiazolidines were used in 38, alpha-glucosidase inhibitors in 17, and glinides in 5 subjects. Biguanides were continued in 238 (81.5%) and sulphonylureas in 159 (54.5%) patients after initiation of insulin glargine. The effectiveness of basal insulin initiation on metabolic variables is presented in table 2. HbA1c, FBG and 2 hour PPG levels as well as total cholesterol, LDL, and triglycerides but not BMI and blood pressure decreased significantly during the study (P<0.001 for the trends). The mean decrease in HbA1c was 1.8% (±1.4). , and the mean decrease in FBG was 92.3 ± 78.8 mg/dl. Reductions in 2-h PPBG levels were also observed over the 24-week observation period, the mean decrease in 2-h PPBG was 111.9 ± 106.2 mg/dl. The differences were significant from the baseline to the week 12 for the HbA1c, FBG and 2 hour PPG levels as well as total cholesterol and triglycerides. From week 12 to week -24, the only significant variable which

deceased further was HbA1c (*P*=0.002 for Sidak test). At baseline, 172 (58.9%) of patients had HbA1c ≥9; this figure reduced to 39(13.4%) at week 12 and 21(7.2%) at week 24. Good glycemic control (HbA1C<7%) was detected in 7(2.4%), 48 (16.4%) and 56 (19.2%) of patients consequently at baseline, week 12 and week.

Table 1. Baseline characteristics of the participants

		n=292
Age (years)		51.8 (±10.3)
Duration of diabetes (months)		44.9 (±17.6)
BMI(Kg/m$^{2)}$		27.8 (±4.8)
Gender (Female)		175 (60%)
Obesity (BMI≥30)		205 (70%)
Location	**Urban**	267 (91%)
	Rural	25 (9%)
Education status	**No formal education**	45 (15%)
	Primary	111 (38%)
	Secondary	88 (30%)
	Higher	48 (17%)
Micro-vascular complications		67 (30%)
Macro-vascular complications		37(13%)

Percentages (%) or standard deviations (SD) are presented in the parentheses

Table 2. Baseline, week 12, and week 24 data for effectiveness of basal insulin initiation

	Baseline	Week 12	Mean difference from baseline	Week 24	Mean difference from week 12	Patients with 3-valid readings	*P*
HbA1c (%)	9.2 (±1.4)	7.9 (±1.1)	1.42	7.5 (±1)	0.38	243	0.001
BMI(kg/m^2)	27.9 (±4.7)	27.8 (±4.4)		28.1 (±4.4)		238	NS
FBS(mg/dl)	220.7 (±69.5)	139.4 (±35)	81.96	130.3 (±36.3)	10.02	241	0.001
PPG(mg/dl)	295.4 (±92.7)	194.8 (±51.3)	108.48	182.9 (±46.6)	12.47	234	0.001
Triglycerides(mg/dl)	199.6 (±108.4)	170.2 (±82.3)	35.52	162.6 (±60.1)	9.17	197	0.001
Cholesterol(mg/dl)	187.9 (±48.1)	175.1 (±36.7)	18.1	167.9 (±31.1)	7	181	0.001
LDL(mg/dl)	109.8 (±38.9)	97.9 (±30)	8.03	94.3 (±23.5)	8.84	162	0.001
HDL(mg/dl)	44.7 (±11.2)	44.5 (±9.2)		44.3 (±9.2)		152	NS
SBP(mmHg)	125.5 (±15.3)	124.3 (±13.4)		124 (±12.7)		225	NS
DBP(mmHg)	79.1 (±10.8)	79.2 (±7.2)		79.6 (±6.9)		206	NS

Data are mean and standard deviations in parentheses.
Glycated hemoglobin, HbA1C; Body mass index , BMI; Fasting Blood Sugar, FBS; Post-prandial Glucose, PPG; High-Density Lipoprotein, HDL; Low-Density Lipoprotein, LDL; Systolic Blood Pressure, SBP; Diastolic Blood Pressure, DBP
General linear models for multiple measurements were designed
NS indicates no significant difference

The mean initial starting dose of insulin was 12.1 (8.2) IU/day. This increased to 20.2 (9.1) U/day at week 24 (Figure 1). The clinical hypoglycemia was reported in 15 cases (5.1%) during the first 12 weeks (9 subjects ≤2 and others 3 to 5 events); and 10 cases (3.4%) between the week 12 and 24 (9 subjects≤ 2 and a patient 4 events). The most frequently reported hypoglycemic symptom was tremor and weakness. The reported rate of all hypoglycemic episodes was less than 5%. No major and or nocturnal hypoglycemia was reported during the entire period of the study.

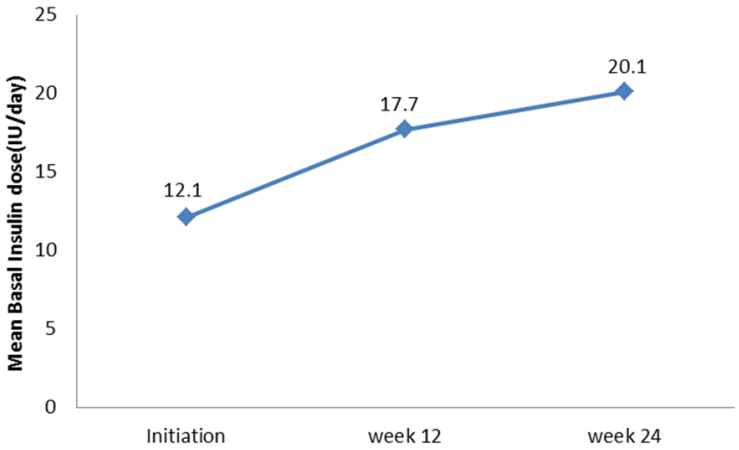

Figure 1. Mean Basal Insulin glargine dose (IU/day) at initiation, week 12 and week 24

Discussion

This was the first study performed to assess the use of insulin glargine in a real-life setting in patients with type 2 diabetes in Iran. The efficacy and safety of insulin glargine for patients with sub-optimally controlled T2DM while on OAD regimen were evaluated. We highlighted additional benefits of early treatment with insulin glargine in terms of efficacy and safety. Addition of insulin glargine to the OADs reduced HbA1c and fasting and postprandial blood glucose levels and improved lipid profile in patients with T2DM who were poorly controlled prior to the observation period. The results are in line with the data from previous international studies (22,24,28). No evidence of significant change in BMI or major/nocturnal hypoglycemic experiences were reported.

This study addresses the trends to use of insulin earlier in the course of diabetes to prevent long-term complications of dysglycemia (31). The rationale for the early use of insulin includes increased insulin gene expression, improved insulin synthesis, rest to beta cells, and cell regeneration over time (17). Glargine is an insulin analog with no significant plasma peak after sub-dermal injections (32). Its effect starts 1 hour after injection and lasts at least 24 hours in adults (33). The duration of action is shorter in children and use in pregnancy is not approved (34). It was first employed in Type 1 diabetes with the promising result and then in type 2 diabetes (24,35). Comparing NPH and glargine, ki-Jarvinen *et al*., reported improved glycemic control after additional use of either of the insulin types in patients on OAD and inadequate glycemic control (27). They showed that with similar insulin dosage and weight gain, subjects receiving combination therapy with glargine compared to NPH had less hypoglycemic events. It is known that same doses of glargine, and human insulin have equal effects on glucose disposal rate (36). These findings were confirmed later in large samples of diabetic patients with inadequate glycemic control on OADs (28).

Glargine improves vasodilation and reduces long-term micro and macrovascular complications of diabetes (37) similar to human insulin (38) with comparably less hypoglycemic events (24,33,39-41). Nevertheless, the finding of this study concerning no significant clinical hypoglycemia is unique and may be biased with the impression and expression of the symptoms in Iranian patients as well as the target glycemic control. Of note in this study, insulin glargine dosing (with a mean daily dose of 20 IU after 24 weeks) was actually lower than in previous clinical studies where the mean daily dose ranged from 23 to 47 IU (22,26,27). A recent clinical trial in line with our findings demonstrated how glycemic control targets could be achieved with a low insulin dose in patients at an early stage of type 2 diabetes (28).

The majorities of our patients were ≤60-year-old and were overweight. High blood glucose levels reported at the start of the study reflected the patients' poor glycemic control on OADs and indicated the need for a change in their current treatment regimens. At the end of study approximately 65% of patients met the target HbA1c level of ≤7.5% after 24 weeks of treatment, indicating the role of insulin glargine in achieving glycemic targets in clinical practice. Further intensification of therapy, perhaps by adding one or more bolus short-acting insulin injections, would help improve glycemic control (27). We believe the improvements observed in the present study provide a foundation on which further therapies should be added.

The interpretation of our results should be concerned with the nature of the observational study. First, since a comparator group was not included, it is likely that some of the improvements observed may be related to a study effect rather than the pure therapeutic effect of insulin. Unfortunately, as this study was uncontrolled, it is not possible to precisely delineate the relationship between the study effect and the regimen used. Second, due to self-documentation of the outcomes and wide follow-up visit intervals, high proportion of lost participants and missing data occurred, and the adherence to the treatment habits was uncertain.

Insulin glargine initiation in people with uncontrolled type 2 diabetes was associated with significant improvement in metabolic control. Insulin glargine had a good safety profile and was well tolerated by the patients.

Acknowledgements

The authors acknowledge all patients and physicians participated in this study. This project was sponsored by Sanofi-Iran.

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