

INITIATE (INITiate Insulin by Aggressive Titration and Education). A randomized study to compare initiation of insulin combination therapy in type 2 diabetic patients individually and in groups

Received for publication 6 November 2006 and accepted in revised form 13 March 2007.

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Short title: Initiation of insulin in groups

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ABSTRACT

Background. Insulin is often postponed for years because initiation is time-consuming.

Objectives. To compare initiation of insulin individually (IND) and in groups (GROUP) with respect to change in HbA_{1c} and several other parameters in type 2 diabetic patients.

Design: A randomized (1:1), multi-center two-arm parallel design study with a recruiting period of up to 14 weeks and a 24-week treatment period. 121 insulin-naïve type 2 diabetic patients with an HbA_{1c} of 7.0-12.0 % were randomized to initiate bedtime insulin glargine either in groups of 4-8 or individually using the same personnel and education program. The patients visited the treatment center before, at the time of insulin initiation and at 6, 12 and 24 weeks. Patients self-adjusted the insulin dose to achieve a fasting plasma glucose of 4.0-5.5 mmol/l.

Results. At 24 weeks, HbA_{1c} had decreased from 8.7±0.2 to 6.9±0.1% in IND and from 8.8±0.2 to 6.8±0.1% in GROUP (NS). Insulin doses averaged 62±5 IU and 56±5 IU at 24 weeks (NS), respectively. The frequency of hypoglycemia was similar. The total time (visits and phone calls) spent in initiating insulin in GROUP (2.2±0.1 hrs) was 48% less than in IND (4.2±0.2 hrs). Diabetes treatment satisfaction improved significantly in both groups.

Conclusions. Similar glyceic control and treatment satisfaction can be achieved by initiating insulin in groups and individually. Starting insulin in groups takes half as much time as individual initiation.

INTRODUCTION

Despite new guidelines with strict glycemic targets, a recent survey of 157 000 type 2 diabetic patients indicated that over two thirds have HbA_{1c} concentrations above 6.5% (1). In the 2005 guidelines by IDF, insulin therapy is recommended when HbA_{1c} exceeds 7.5% despite other therapies (2). This is because large trials have shown that it is feasible to achieve an HbA_{1c} target of 7.0% using insulin combination therapy regimens (3-6). However, reluctance to initiate insulin is still common, in part because lack of time and resources. There is thus a need for innovative strategies to facilitate transition to insulin therapy.

Simple addition of basal insulin to existing oral agents is an attractive way to start insulin therapy as it involves only one injection of insulin, which dose can be adjusted based on measurement of fasting glucose (FPG) (4,7-9). In studies where an HbA_{1c} of ~7.0% was achieved, the insulin dose was aggressively titrated by daily measurement of FPG and frequent self-adjustment of insulin dose (4,6,9). Recent comparison of titration algorithms in 4961 patients with type 2 diabetes showed that a simple subject-administered titration conferred significantly improved glycemic control with a low incidence of severe hypoglycemia compared with physician-managed titration (10).

Historically, insulin therapy has been started individually in patients with type 2 diabetes. Considering limited resources the large numbers of patients and that patients with type 2 diabetes by definition 'survive without insulin', it would seem worthwhile to establish whether insulin can be started in groups. The present study was designed to test in a randomized fashion in poorly controlled insulin-naive patients with type 2 diabetes whether this is the case.

SUBJECTS AND METHODS

Study design

This was a multi-center, open, randomized, parallel-group study to compare initiation of insulin in groups vs. individually in insulin-naive type 2 diabetic patients who were poorly controlled on oral hypoglycemic agents.

The study consisted of a 3 to 14-week run-in phase and a 24-week treatment phase. It was performed in Finland, Sweden, U.K. and the Netherlands in accordance with the Declaration of Helsinki and good clinical practice (GCP) as described by Note for Guidance CPMP/ICH/135/95. Approval by institutional ethics committees was obtained for each site. All patients provided written informed consent prior to study entry. The study design was investigator-initiated (H.Y.). sanofi-aventis provided funding and helped in conducting the study according to GCP guidelines (S.L.) but did not participate in data-analysis, interpretation of the data or writing the manuscript.

Patients

Male or female patients aged ≥ 18 years of age with type 2 diabetes treated with a stable dose (any dose) of sulfonylurea and metformin (≥ 1.5 grams) or either drug alone for at least 6 months were recruited. Further inclusion criteria included a body mass index < 45 kg/m², HbA_{1c} between 7.0 and 12 %, willingness and ability to inject insulin and perform self-monitoring of blood glucose and to share some health information (glycemic control and body weight) with other members. Main exclusion criteria were as in (9).

Study protocol and treatment

Screening visit at -14 to -3 weeks (individual)

Informed consent was obtained and the inclusion and exclusion criteria were reviewed. After a history and physical examination, a fasting blood sample was

taken for measurement of HbA_{1c} (central measurement), FPG, sodium, potassium, creatinine, ALT and blood counts. Body weight and height were measured. Other tests included ECG, urine analysis, and a pregnancy test. A retinal examination was scheduled if not performed within the last 12 months. Oral anti-diabetic drugs were continued unchanged. The importance of dietary and lifestyle approaches were reinforced.

After visit 1, eligible patients were randomized to either an individual or a group education program. Randomization was performed centrally using the method minimization of differences (11) of the following variables (relative weight is given in parentheses): age (1x); gender (0.5x); body mass index (1.5x); HbA_{1c} (1.5x), duration of diabetes (0.5x); previous oral agents (1x); history of macrovascular disease (0.5x) and education (1x).

Pre-initiation visit at – 2 weeks (group or individual)

The group size was 4 to 8. The same nurse led group and individual sessions. After screening visit, education was entirely taken care of by the nurse. The participants received counseling on pathogenesis and treatment (especially insulin treatment) of type 2 diabetes. All educational materials for each visit were similar in all centers. The participants were taught and asked to perform self-monitoring of FPG every morning, and to send glucoses to the treatment center using a modem before the next visit. In the U.K., the patients sent glucose values recorded on a diary card to the study center by mail.

Initiation of insulin visit at 0-weeks (group or individual)

At this visit, participants were taught how to inject insulin, use the insulin pen (OptiSet, Aventis Pharma, Germany), and self-adjust insulin dose. Symptoms and signs of hypoglycemia were discussed. Treatment satisfaction was assessed by asking the

patients to fill in a DTSQ form (12). The participants were told to inject 10 IU s.c. of insulin glargine (Lantus®, sanofi-aventis, Germany) daily at bedtime and to measure their FPG every morning. The patients were asked to increase the dose of insulin glargine by 2-4 IU when FPG exceeded 5.5 mmol/l for 3 consecutive days. The target FPG was 4.0-5.5 mmol/l. If FPGs were <4.0 mmol/l and symptomatic hypoglycemia occurred without an identifiable reason, the patients were asked to decrease the insulin dose by 2 IU/day. Participants were also asked to record glucose values and insulin doses daily in a diary to facilitate self-adjustment. They recorded symptoms of hypoglycemia and glucose values in the diary. At this and all subsequent visits, body weight and blood pressure were recorded. A blood sample was taken for measurement of serum lipids and HbA_{1c}.

Phone calls at weeks 1, 2, 4, 8, 16 and 20

The patients sent FPGs using a modem or by mail prior to calling the study center. During the call, the study nurse reviewed glucose measurements received at a website (www.prowellness.com), encouraged self-adjustment of insulin dose, and asked for possible adverse events, hypoglycemia and for changes in medication.

6-week visit (group or individual)

The patients examined their FPGs which had been sent via modem to the treatment center and discussed self-adjustment of insulin dose. Body weight and vital signs were recorded, and a blood sample for local measurement of HbA_{1c} was obtained. Effects of insulin therapy on body weight, and importance of healthy lifestyle (diet, exercise) were discussed. Adverse events were recorded.

12-week visit (group or individual)

As the 6-week visit. In addition, the importance of HbA_{1c} measurement, and causes for a variation of insulin

requirements in type 2 diabetes were discussed.

24-week visit (group or individual, end of study)

As the 6-week visit. In addition, a blood sample for measurement of fasting serum lipids, HbA_{1c} (central measurement), FPG, sodium, potassium, creatinine, ALT, and blood counts was obtained. The participants were asked to fill in DTSQs and DTSQc forms (13).

Analytical procedures

HbA_{1c} was measured by high pressure liquid chromatography using the fully automated Glycosylated Hemoglobin Analyzer System (BioRad, CA) traceable to the DCCTI reference method, with a reference range of 4.0 to 6.0%. Lipids, electrolytes, S-ALT, blood counts and creatinine concentrations, pregnancy tests and urine analyses were performed using methods in local laboratories.

Statistical analyses

The primary endpoint was difference in HbA_{1c} between the education programs. The educational programs were defined equally successful if HbA_{1c} at the end of the study differed by less than 0.5 %. In a previous study where insulin regimen consisted of basal insulin (glargine or NPH) combined with metformin (9), the HbA_{1c} at the end of the study averaged 7.19±0.91 % (mean±SD). Assuming a common standard deviation of 0.91 % and an equivalence region of (-0.5 %, 0.5 %), equivalence between the two education programs can be demonstrated with 53 patients per group at the 0.05 level of significance and 80 % power. The goal was to recruit at least 120 patients to allow for drop-outs.

Secondary objectives included comparison of the two educational methods with respect to: Time spent by a nurse on education, physician's time, number and duration of phone calls; Change in the concentrations of serum HDL and LDL cholesterol, and

serum triglycerides; Change in body weight and blood pressure; Change in FPG; Insulin dose at study end; Change in subject's treatment satisfaction; Incidence of hypoglycemic episodes, defined as in (9), during the study.

All statistical analyses were performed on an intent-to-treat basis, defined as randomized patients who received at least one injection of insulin. Statistical testing was performed at a two-sided significance level of $\alpha=0.05$. The primary endpoint was evaluated by using an analysis of covariance (ANCOVA) model with HbA_{1c} change from baseline to the end of the study as a response variable. The method of education and center were included as fixed effects, and the baseline value of HbA_{1c} as a covariate in the ANCOVA model. A similar ANCOVA model was used for LDL and HDL cholesterol (log-transformed), triglycerides (log-transformed), body weight, blood pressure and fasting glucose concentration. The change in subject's treatment satisfaction was compared between the groups using Mann-Whitney U-test. The proportion of patients with hypoglycemic events and the number of events were compared using Cochran-Mantel-Haenszel test stratified by center. All statistical analyses were performed by 4Pharma Ltd (Kista, Sweden).

RESULTS

Patient characteristics

128 patients were eligible at randomization visit. 7 patients dropped out during the recruitment phase while waiting for start of insulin therapy (metastasis of papillary thyroid carcinoma, retinal neovascularisation, unwillingness to continue n=2, group formation took too long n=1, other n=2). A total of 121 patients started insulin therapy and comprised the intention to treat population. 5 dropped out from the IND education arm (poor

compliance n=2, hypoglycemia n=1, protocol violation n=1, new adverse event n=1). No patients dropped out from the GROUP education arm. The mean group size was 5.3 persons. 95.6% and 90.3% of the scheduled visits were attended in the IND and the GROUP education arms (NS). Baseline demographic and clinical characteristics were similar between the treatment groups (**Table 1**).

Glycemic control

HbA_{1c} decreased from 8.65±0.18% at 0 weeks to 6.89±0.14% at 24 weeks in the IND (p<0.001), and from 8.79±0.20% to 6.81±0.12% in the GROUP education arm (p<0.001) with no difference between the two arms (**Fig. 1**).

FPG averaged 9.0±0.1, 7.1±0.1 and 6.3±0.1 mmol/l in IND and 8.7±0.1, 6.9±0.1 and 6.4±0.1 mmol/l in GROUP during weeks 0-7, 8-15 and 16-23. The cumulative percent of patients achieving target (weekly mean fasting plasma glucose within the target range 4.0-5.5 mmol/l) was 47% by week 12 and 66% by study end in the GROUP arm. The corresponding fractions were 41% and 70% in the IND arm (NS between educational arms).

Hypoglycaemia

The number of symptomatic hypoglycemia averaged 3.5 and 3.1 episodes/pt year in the IND and GROUP arms (NS). The % of patients experiencing symptomatic hypoglycemia was 44 and 40 %, respectively (NS). Of symptomatic hypoglycemia 13% and 10% were nocturnal in the IND and GROUP arms (NS). There were no severe hypoglycemia. The number of fasting hypoglycemia, defined as an FPG <2.5, 3.2 and 4.0 mmol/l averaged 0.73, 3.6 and 19.5 episodes/pt year in the IND and 0.53, 4.4 and 20.1 episodes/pt year in GROUP arm (NS). The % of patients with FPG <2.5, 3.2 and 4.0 mmol/l averaged 13, 33 and 60 % in the IND and 12, 38 and 66% in the GROUP arm (NS) (**Fig. 1**).

Insulin dose

Insulin doses were similarly titrated by both study arms. At 24 weeks the insulin doses averaged 62±5 and 56±5 IU/day (NS) (0.64±0.05 and 0.60±0.05 IU/kg·day, NS) in the IND and GROUP arms.

Body weight

Mean weight gain during 24 weeks was significantly lower in IND (2.2±0.4 kg) than the GROUP (3.7±0.6 kg, p<0.02) arm.

Lipids, blood pressure and liver enzymes

There were no within education arm differences in serum triglycerides, HDL or LDL cholesterol. Serum triglycerides decreased from 2.4±0.2 to 1.7±0.1 mmol/l (p<0.001 for 24 vs 0 weeks) in the IND and from 2.1±0.1 mmol/l to 1.8±0.1 mmol/l (p<0.001 for 24 vs. 0 weeks) in the GROUP arm (NS). Serum HDL cholesterol averaged 1.26±0.05 vs. 1.27±0.04 mmol/l (NS) in IND and 1.28±0.05 vs. 1.34±0.05 mmol/l (p<0.05 for 24 vs. 0 weeks) in the GROUP arm at 0 vs. 24 weeks (NS). Serum LDL cholesterol remained unchanged and averaged 2.78±0.10 vs. 2.77±0.10 mmol/l in IND and 2.58±0.12 vs. 2.71±0.11 mmol/l in the GROUP arm at 0 vs 24 weeks (NS).

Systolic (IND 140±2 vs. 142±3 mmHg, GROUP 140±2 vs. 142±3 mmHg, 0 vs. 24 weeks) and diastolic (IND 83±1 vs. 82±1 mmHg, GROUP 85±1 vs. 83±1 mmHg, 0 vs. 24 weeks) blood pressures remained unchanged.

Serum ALT decreased highly significantly in both the IND and the GROUP education arms (**Fig. 1**).

Treatment satisfaction and time spent on patient education.

Total treatment satisfaction outcome improved significantly and similarly in both education arms (**Fig. 1**). There were no significant differences between the groups in responses to the individual questions of the DTSQ (data not shown).

The total time (scheduled and extra) over 24 weeks spent in starting insulin was 48% lower in the GROUP than the IND education arm (**Fig. 2**). There was no correlation between class-time or total time and the HbA_{1c} achieved or the change in HbA_{1c} or the percent decrease in HbA_{1c} (data not shown) within the educational arms.

Adverse events

The incidence of adverse events considered not to be related to treatment was similar: 31 patients (49%) in IND and 28 patients (48%) in the GROUP arm reported at least one adverse event. Most common were infections and musculoskeletal disorders with no differences between the arms. There was one side effect considered to be related to treatment: one injection site reaction in the IND arm. Four patients (GROUP n=1, IND n=3) had serious adverse events during the course of the study. All serious adverse events recovered without sequelae.

DISCUSSION

The present study is to our knowledge the first attempt to compare in a randomized fashion, initiation of insulin therapy by adding basal insulin to existing oral agents individually and in groups. We found that both education methods were equally effective with respect to improvement of glycemic control. There were also no differences in the time course of titration of the insulin doses or in symptomatic or biochemical hypoglycemia, or in treatment satisfaction. Individual initiation took twice as much nurse educator's time as initiation of insulin in groups. Weight gain was slightly greater when insulin was started in groups as compared to individually.

We chose to start insulin therapy by adding basal insulin to existing oral agents, which mostly consisted of sulfonylureas combined with metformin. This regimen compared to other options such as use of insulin mixtures or multiple insulin injection regimens requires only one measurement of fasting

glucose and one injection of insulin, and is associated with less weight gain and hypoglycemia than multiple insulin injection regimens (5-8). Recommending only one fasting measurement for adjusting a single injection of insulin also facilitates interpretation of glucose values received by modem (9). One center did not use the modem but nevertheless managed to achieve good glycemic control in both education arms. We found use of the modem very helpful as it allows immediate visualization of whether the FPG target has been reached. The modem also allowed accurate assessment of fasting hypoglycemia but on the other hand symptomatic hypoglycemia is underestimated unless patients are strongly encouraged to record hypoglycemia also on a card. In keeping with this, we found almost twice the rate of confirmed hypoglycemia (episodes of FPG < 4.0 mmol/l per patient per year) than e.g. in the treat to target study but less symptomatic hypoglycemia (4). This could possibly be due to use of the modem which allows accurate recording of all measured glucoses.

The HbA_{1c} achieved at the end of 24 weeks in the GROUP education arm (6.71%) is to our knowledge the best glycemic control achieved in any insulin treatment study in established type 2 diabetes (4-6,9,14-15). Compared to other studies, this cannot be attributed to differences in baseline BMI, glycemic control, duration of diabetes, lack of weight gain during insulin therapy, or choice of oral agents. We attribute the success to use of adequate titration of insulin doses and to not discontinuing the sulfonylurea. In the large 'Treat to Target study' where basal insulin was added to sulfonylurea and metformin combination therapy (4), FPG was higher than in the LANMET study, where only metformin was used, yet HbA_{1c} was lower. Our patients were just as obese as those in the study of Riddle et al (4) but used 55-62 IU of insulin while the insulin doses in the latter study were 42-47 IU.

Body weight increased by 3.7 kg in the GROUP arm which was 1.5 kg more than in the IND arm. We have previously shown that for every 1% decrease in HbA_{1c}, body weight increases by 2 kg (16). This increase reflects the net effects of reduction in calories lost in the urine and of changes in energy expenditure due to an increase in fat free mass which accompanies weight gain, and a decrease in the energy consumed for glucose production (16). Since HbA_{1c} decreased by 2% in both arms, one would have predicted a 4 kg weight gain in both arms but this was only observed in the GROUP arm. The difference in weight gain between the two educational arms suggests that the patients may have received more dietary advice during the individual education sessions than in the group.

Treatment satisfaction improved similarly in both educational arms. While this implies that patients were equally satisfied with both educational methods, it is not possible to determine why treatment satisfaction improved. We have previously shown that treatment satisfaction improved with combination therapy compared to use of continued oral agents (7) suggesting that improved glycemic control rather than simply participating in a study improves general well-being. Of note, treatment satisfaction was similar although participation in the group arm took required more time of the patient than individual education.

In conclusion, starting insulin in type 2 diabetes in groups gives as good glycemic control as individual initiation. Group and individual education also appear similar with respect to hypoglycemia, lipid changes, and insulin doses. Body weight increased more in the group education than in the individual education arm. Given years of delay in initiating insulin and the growing number of patients needing intensified treatment, we recommend initiation of insulin therapy using the simple principles of the present study in groups rather than individually because this saves considerable

amount of time and resources. Although not everybody will be eligible for this method of education, we believe a substantial proportion is.

Acknowledgements

This study was investigator-initiated and supported by sanofi-aventis.

Conflicts of interest

H.Y. has acted as a consultant or speaker for Amylin, Astra-Zeneca, Aventis, Lilly, Merck, MSD, Pfizer and sanofi-aventis and received grant support for investigator-initiated trials from Astra-Zeneca, Aventis, Lilly, Novartis and Roche. M.J.D. has acted as consultant and speaker for Novartis, Novo Nordisk, sanofi-aventis and Eli Lilly, and has received grants in support of investigator and internal trials from Servier, Novartis, Novo Nordisk, Pfizer and sanofi-aventis. S.L.(M.D., Ph.D.) is an employee of sanofi-aventis.

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Table 1. Baseline demographics and characteristics of the study groups (intention-to-treat groups).

Characteristic	IND	GROUP
Patients (n)	63	58
Sex (male/female; %)	65/35	59/41
Age (years)	58±1	58±1
Weight (kg)	93.8±2.6	90.1±2.8
Body mass index (kg/m ²)	31.5±0.7	31.2±0.9
Duration of diabetes (years)	8±1	7±1
HbA _{1c} (%)	8.65±0.18	8.79±0.20
Complications/other conditions		
Hypertension	55%	50%
Macrovascular disease	14%	16%
Microvascular disease	47%	55%
Oral agents before insulin		
Sulfonylurea and metformin	84%	79%
Metformin only	10%	10%
Sulfonylurea only	6%	10%
Education		
Elementary school	41%	43%
Vocational education	44%	48%
Academic	14%	9%

Data are shown as mean ± SE.

Fig. 1. HbA_{1c}, serum ALT activities, total diabetes treatment satisfaction score, and the % of patients with FPGs < 4.0 mmol/l in the IND and GROUP arms at baseline (0 weeks) and after 24 weeks of treatment. The FPGs < 4.0 mmol/l at 24 weeks denote the % of patients during the entire 24 week period.

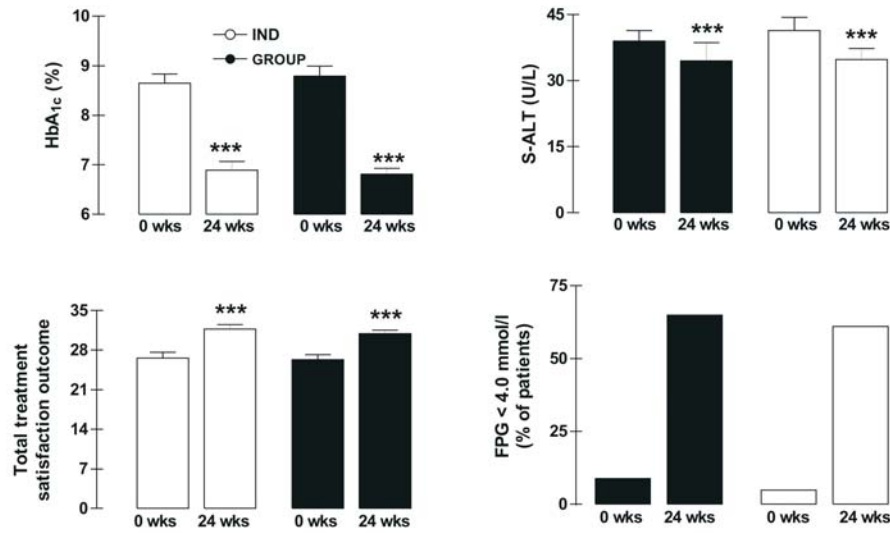


Fig 2. Total time spent to initiate insulin during the study. The total (scheduled in class or over the phone and extra) time for the GROUP arm was 2.3 ± 0.1 hours (n=58): 1.6 ± 0.1 hours for scheduled visits nad 0.59 ± 0.03 hours for scheduled phone calls, 0.73 ± 0.24 hours for extra visits (n=10) and 0.17 ± 0.05 hours for phone calls (n=11). The corresponding times in the IND arm were: 4.4 ± 0.2 (n=63), 3.6 ± 0.2 , 0.59 ± 0.03 , 0.59 ± 0.2 (n=14), 0.14 ± 0.03 hours (n=11).

