Patients with type 2 diabetes inadequately controlled on premixed insulin: effect of initiating insulin glargine plus oral antidiabetic agents on glycaemic control in daily practice*

H. Hammer, A. Klinge

SUMMARY

Aim: Premixed insulin regimens are commonly used for type 2 diabetes mellitus (T2DM) patients. However, there is limited information regarding next-step therapy options in cases where premixed insulin does not provide adequate glycaemic control. This 12-week observational study of everyday clinical practice evaluated the efficacy and safety of insulin glargine (glargine) plus oral antidiabetic drugs (OADs) in T2DM patients previously treated with premixed insulin. Methods: Type 2 diabetes mellitus patients taking premixed insulin were identified from German clinics and were eligible to switch to glargine plus OADs at the physicians’ discretion, as part of routine clinical practice. The study design and conduct was in accordance with German regulations. Fasting blood glucose (FBG), 2-h postprandial blood glucose (PPBG) and glycosylated haemoglobin (HbA1c) were measured at the start and after a 12-week observation period. Results: A total of 5045 patients were followed-up and received glargine plus OADs. FBG [start to end-point: 9.9 ± 2.7 to 6.9 ± 1.5 mmol/l (178 ± 48 to 124 ± 26 mg/dl); p ≤ 0.001], 2-h PPBG [10.8 ± 2.8 to 7.8 ± 1.5 mmol/l (195 ± 50 to 140 ± 27 mg/dl)] and HbA1c (8.3 ± 1.2 to 7.2 ± 0.8%; p ≤ 0.001) improved significantly from start to end-point, respectively. A total of 48.9%, 38.4% and 73.9% of patients had FBG < 6.7 mmol/l (< 120 mg/dl), 2-h PPBG < 7.2 mmol/l (< 130 mg/dl) or HbA1c < 7.5%, respectively, after 12 weeks. Significant reductions in body weight were observed between the start and end of the observation period. A total of 71 adverse events were reported by 38 patients. Hypoglycaemia was the most common event (n = 16). Conclusions: This observational study shows that, in T2DM patients inadequately controlled with premixed insulin, switching therapy to glargine plus OADs is associated with significant improvements in FBG and HbA1c, and is well tolerated in everyday clinical practice. Further intensification of insulin therapy, perhaps by adding one or more injections of prandial insulin, would help provide further improvements in glycaemic control in these patients.

Introduction

It is estimated that more than 40% of patients with type 2 diabetes mellitus (T2DM) worldwide use premixed insulin as part of their therapeutic regimen (1). Premixed insulin usually contains a rapid-acting insulin and an intermediate-acting insulin to mimic endogenous insulin secretion patterns and should be taken twice daily, normally before breakfast and dinner (2). While the newer premixed insulin analogues may confer greater improvements in glycaemic control compared with regular human insulin or neutral protamine Hagedorn (NPH) insulin (3), for many patients, premixed insulin alone is insufficient to maintain adequate glycaemic control and is associated with significant day-to-day variability (2).

Optimising fasting blood glucose (FBG) with premixed insulin may, therefore, increase the risk of hypoglycaemia and may not provide sufficient flexibility for patients to achieve optimal glycaemic control (4). The LAPTOP study has demonstrated that, for insulin-naïve patients, a regimen composed of
once-daily insulin glargine (LANTUS®; sanofi-aventis, Frankfurt, Germany) plus oral antidiabetic drugs (OADs) is associated with better glycaemic control and reduced risk of hypoglycaemia compared with premixed insulin (4). Despite this, there is limited information regarding therapeutic options for patients for whom premixed insulin provides inadequate glycaemic control or whom frequently experience episodes of hypoglycaemia.

The aim of this observational study was to evaluate the efficacy and safety of insulin glargine with concomitant OADs in everyday clinical practice when used by patients with T2DM who were previously treated with premixed insulin.

Methods

Study design

This 12-week study was an open-label, non-interventional, multicentre (n = 1791), observational study of patients with T2DM in Germany and based in everyday clinical practice.

This type of study is regulated by the German Drug Law [Arzneimittelgesetz (AMG)] section 67 (6) and is primarily intended to gather knowledge about the safety and efficacy of marketed drugs in daily practice. As part of the sponsor’s obligations, the National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundersvereinigungen) was notified of the implementation of this observational study. Owing to the non-interventional nature of this observational study, no ethical approval or informed patient consent was obtained, in accordance with local regulations (AMG), and participation was voluntary. Participating general practitioners (GPs) were asked to document their everyday experience in treating patients with insulin glargine in combination with OADs and received a small compensation for the documentation of each patient, which is common practice for this type of study. All changes in therapy, which were recorded as part of this observational study, were at the discretion of the physician and the patient.

Patients and study conduct

Patients with T2DM and who were treated with regular human or analogue premixed insulin (most frequently prescribed ratios: 25/75 and 30/70) with or without OADs, were eligible for inclusion in this observational study of everyday clinical practice. The decision to use a therapy regimen including insulin glargine with or without OADs was at the discretion of the physicians and patients, and depended mainly on subjective parameters, as reported by the physician, including: lack of efficacy of premixed insulin, patient wanting a more flexible lifestyle, ability to give up between-meal snacks, frequent occurrence of hypoglycaemia with previous therapy, insufficient mixtures of insulin suspensions available and lack of tolerability with previous therapy. Exclusion criteria were according to the indications and contra-indications (i.e. patients hypersensitive to insulin glargine or any of the excipients) given in the prescribing information and summary of product characteristics for insulin glargine.

At the start of the observation, patients were given insulin glargine to be administered once daily via subcutaneous injection; dosing decisions were at the discretion of the physician, although, when switching from twice-daily NPH insulin, a reduction in the daily dose of insulin by 20–30% is recommended, followed by adjustment of the daily dose (5). Concomitant OAD therapy (dosage, type and changes where necessary) was at the discretion of the physician. All patients in the insulin glargine + OAD set received OADs during the observational study. After the initial visit (week 0; start of observation), subsequent visits were scheduled at weeks 2, 6 and 12 (end of observation).

The case report form specified that up to a maximum of nine blood glucose (BG) values [FBG, 1-h postprandial blood glucose (PPBG) and 2-h PPBG morning, mid-day and evening] should be documented at the start of the observation period and at each follow-up examination. Self-monitored blood glucose (SMBG) was performed using the patients’ own BG meter. Physicians gave all patients training to ensure they could perform SMBG correctly and accurately. Optimum titration of the insulin dose was to the target FBG value of ≤ 5.5 mmol/l (≤ 100 mg/dl) and was measured by the subject via SMBG. An FBG in the range of 5.0–6.7 mmol/l (90–120 mg/dl) and 2-h PPBG in the range of 7.2–8.9 mmol/l (130–160 mg/dl) were considered clinically important to show improvements in glycaemic control with insulin glargine after 12 weeks therapy.

Glycosylated haemoglobin (HbA1c) measurements were made at the start and at the end of the observational period using HbA1c measurement systems that were aligned with the original Diabetes Control and Complications Trial method (AlcNowTM, Metrika Inc., Sunnyvale, CA, USA or DCA® 2000+ analyzer, Bayer Diagnostics, Eckhart, IN, USA). Owing to the relatively short duration of the observation period, the therapeutic target at week 12 for HbA1c was set at < 7.5%, which was considered clinically important to show improvements in glycaemic control with insulin glargine.

Adverse events (AEs), which included episodes of hypoglycaemia, and adverse drug reactions (ADRs)
were reported by the patients either at each visit or as and when they occurred. All events were recorded by the physician. Patients and physicians were not requested to provide details of episodes of hypoglycaemia, such as symptomatic/non-symptomatic or BG levels. At the end of the observation period, physicians were asked to complete a 5-item questionnaire to investigate how they rated aspects of therapy with insulin glargine (BG control, safety, weight management, patients’ quality of life and demand on physician time). Each item was rated as very good, good, satisfactory or unsatisfactory. Physicians were also asked to note whether therapy with insulin glargine was to be continued. If therapy with insulin glargine was to be discontinued, reasons for discontinuation were to be given.

Data validation
Dual data entry was performed for some variables (case report form number, patient number, sex and date of birth) to ensure correct identification of patients and prevent duplicate patient entry. Validation methods were used to ensure all data were within plausible ranges (any extreme values were followed up) and in the correct order (e.g. the date listed for the first visit was earlier than the date listed for the last visit; incorrect dates were corrected using the original case report form).

Population subsets and statistical analysis
All patients who met the inclusion/exclusion criteria were included in the full data set. Five analysis sets were identified for the purpose of this observational study:
• Total population: all patients who were enrolled in this observational study.
• Full data set: patients with T2DM who were previously treated with premixed insulin, with or without OADs prior to the start of observation. Patients in the full data set were treated with insulin glargine with or without OADs during the observation period.
• Prior premixed insulin – OAD set: all patients who were treated with premixed insulin without OADs prior to the observational study. Patients in the prior premixed insulin – OAD group were treated with or without OADs during the observation period.
• Prior premixed insulin + OAD set: all patients who were treated with premixed insulin with OADs prior to the observational study. Patients in the prior premixed insulin + OAD group were treated with or without OADs during the observation period.
• Insulin glargine + OAD set: all patients who were treated with insulin glargine plus OADs during the observational period. Prior to the study, patients in the insulin glargine + OAD set were treated with premixed insulin with or without OADs.

Descriptive statistics are presented. The Wilcoxon signed rank test was used to evaluate changes in FBG, HbA1c and body weight between the start and end of observation. Data are presented as means with standard deviation. Statistical analyses were performed using SPSS for Windows (version 11.01; SPSS Inc., Chicago, IL).

Results
Population characteristics at the start of observation
The official start of the observation period was February 2004 and the last available follow up was December 2004. A total of 6560 patients from 1791 centres (general medicine, 56.0%; internal medicine, 27.9%; GP, 13.9%; other/no data available, 2.2%) were included in the analysis of this surveillance study with insulin glargine (safety analysis set). A total of 49.7% were male and 49.7% were female (no data were available for 0.6% of the patients). Median age was 63.2 and 66.3 years, and median body mass index (BMI) was 28.4 and 29.0 kg/m² for males and females, respectively. Characteristics of the subsets of patients at the start of observation are summarised in Table 1.

Of the 6560 patients that comprised the full data set, 252 patients did not meet the criteria for data analysis (for 244 patients, the previous therapy was not premixed insulin; two patients did not have T2DM; six patients did not meet either criterion). The remaining 6308 T2DM patients were switched from premixed insulin to insulin glargine as part of their clinical management. These patients, thus, comprised the full data set. Of these, a total of 3098 patients were treated with premixed insulin without OADs (prior premixed insulin – OADs) and 3210 patients were treated with premixed insulin plus OADs (prior premixed insulin + OADs), prior to the start of the observation period. A total of 3045 patients were treated with premixed insulin (with or without OADs) prior to the start of the observation period and switched therapy to insulin glargine plus OADs (insulin glargine + OAD set).

At the start of observation, a total of 62.6% of patients in the full data set had experienced one, or more, secondary complications associated with diabetes (Table 1); 45.5%, 34.5%, 22.9% and 6.6% had microalbuminuria, neuropathy, retinopathy or macroalbuminuria, respectively.

In the full data set, the most common reasons given by physicians and patients for switching from premixed insulin to insulin glargine included: lack
of efficacy of premixed insulin (68.8%), patient wanting a more flexible lifestyle (55.6%), ability to give up between meal snacks (37.1%) and frequent occurrence of hypoglycaemia (23.5%). Of those citing frequent occurrence of hypoglycaemia (n = 1306), the mean number of episodes per person in the 3 months preceding the observation period was 5.0 ± 4.2 (median: 4.0).

Less frequent reasons cited for switching from premixed insulin to insulin glargine included insufficient mixtures of insulin suspensions available (13.7%) and lack of tolerability with previous therapy (13.3%).

### Efficacy

Glycaemic control improved significantly in patients within each subset, with significant improvements in FBG (Figure 1A) and HbA1c (Figure 1B).

In the full data set, the mean decrease in FBG was 3.0 ± 2.6 mmol/l (54.7 ± 46.3 mg/dl) and the median decrease was 2.7 mmol/l [48 mg/dl; interquartile range: −4.2 to −1.5 mmol/l (−75.0 to −27.0 mg/dl)]. As a result, of those patients who provided FBG measurements at the end of the observation (5998 of 6308), 2643 (44.1%) met the therapeutic target for FBG [5.0–6.7 mmol/l].

### Table 1 Characteristics of patients who were included in this observational study

| Factor | Full data set (n = 6308) | Prior premixed insulin – OADs (n = 3098) | Prior premixed insulin + OADs (n = 3210) | Insulin glargine + OAD set (n = 5045) |
|--------|--------------------------|----------------------------------------|---------------------------------------|-------------------------------------|
|        | n  | %     | n  | %     | n  | %     | n  | %     |
| Duration of diabetes (years)* | 5144 (8.6 ± 6.1) | 2497 (8.6 ± 6.3) | 2647 (8.7 ± 6.0) | 4143 (8.7 ± 5.9) |
| Secondary disorders† | | | | | |
| Patients with disorders | 3950 (62.6) | 1890 (61.0) | 2060 (64.2) | 3191 (63.3) |
| Micro-albuminuria | 2871 (45.5) | 1383 (44.6) | 1488 (46.4) | 2317 (45.9) |
| Macro-albuminuria | 419 (6.6) | 221 (7.1) | 198 (6.2) | 333 (6.6) |
| Retinopathy | 1442 (22.9) | 665 (21.5) | 777 (24.2) | 1160 (23.0) |
| Neuropathy | 2174 (34.5) | 1041 (33.6) | 1133 (35.3) | 1767 (35.0) |
| Prior insulin therapy‡ | | | | | |
| 10/90 only | 26 (0.4) | 9 (0.3) | 17 (0.5) | 20 (0.4) |
| 15/85 only | 30 (0.5) | 13 (0.4) | 17 (0.5) | 20 (0.4) |
| 20/80 only | 141 (2.2) | 74 (2.4) | 67 (2.1) | 102 (2.0) |
| 25/75 only | 1167 (18.5) | 579 (18.7) | 588 (18.3) | 961 (19.1) |
| 30/70 only | 4381 (69.5) | 2132 (68.8) | 2249 (70.1) | 3509 (69.6) |
| 40/60 only | 72 (1.1) | 35 (1.1) | 37 (1.2) | 45 (0.9) |
| 50/50 only | 315 (5.0) | 163 (5.3) | 152 (4.7) | 250 (5.0) |
| Other | 34 (0.5) | 11 (0.4) | 23 (0.7) | 27 (0.5) |
| More than one formulation | 142 (2.3) | 82 (2.7) | 60 (1.9) | 111 (2.2) |
| Insulin dose*,†,‡,§ | | | | | |
| 25/75 (U/day) | 1193 (35.3 ± 15.5) | 595 (36.6 ± 14.9) | 978 (35.4 ± 15.5) | |
| 30/70 (U/day) | 4317 (35.2 ± 14.8) | 2109 (35.8 ± 14.9) | 3464 (35.3 ± 14.7) | |
| Prior OAD therapy‡ | | | | | |
| Patients taking OADs | 3210 (50.9) | n/a | n/a | 3080 (61.1) |
| Glimepiride | 847 (13.4) | n/a | n/a | 811 (16.1) |
| Glibenclamide | 593 (9.4) | n/a | n/a | 559 (11.1) |
| Metformin | 2192 (34.8) | n/a | n/a | 2117 (42.0) |
| Other OAD¶ | 160 (2.5) | n/a | n/a | 155 (3.1) |
| Concomitant OAD therapy | | | | | |
| Patients taking OADs | 5045 (80.0) | 1965 (63.4) | 5045 (100.0) | |

As some patients had incomplete data, the numbers of patients with valid data for each characteristic are given. Reasons for missing data were not collected. Results are n and per cent except *mean ± SD. †Patients can be in more than one subcategory. ‡Premixed insulin formulation previously used (soluble/proteminated insulin). §Mean daily dose of premixed insulin prior to the start of the observation period. ¶Includes acarbose (full data set, n = 61), repaglinide (34), pioglitazone (21), nateglinide (17), rosiglitazone (13) or another OAD (17). Full data set = all patients who fulfilled the inclusion criteria; prior premixed insulin – OAD = all patients who were treated with premixed insulin without OADs prior to the observational study; prior premixed insulin + OAD = all patients who were treated with premixed insulin plus OADs prior to the observational study. Insulin glargine + OAD set = all patients who were treated with insulin glargine plus OADs during the observational period. OADs, oral antidiabetic agents.
and a further 272 (4.5%) patients had FBG < 5.0 mmol/l (< 90 mg/dl) (Table 2). The mean decrease in HbA1c was 1.1 ± 1.0%, with a median of −1.0% (interquartile range: −1.50 to −0.50%). Thus, of 6179 (of 6308) patients for whom HbA1c was measured at the end of the observation, 4593 (74.3%) had HbA1c < 7.5% (Table 2).
Improvements in FBG and HbA1c and the proportions of patients who achieved the target FBG or HbA1c were similar in each of the subsets, including the insulin glargine + OAD set.

In the full data set, reductions in both fasting preprandial BG and 2-h PPBG levels were observed over the 12-week observation period (Table 3) and the majority of patients reached target 2-h PPBG levels of 7.2–8.9 mmol/l (130–160 mg/dl) (Table 3). Similar reductions in both fasting preprandial and PPBG levels were observed in patients who were treated with premixed insulin + OADs or premixed insulin – OADs prior to the observation period (Table 3). In the insulin glargine + OAD set, fasting preprandial and 2-h PPBG levels decreased by 2.9 mmol/l (52 mg/dl) and 3.1 mmol/l (55 mg/dl), respectively (Table 3). A total of 81.6% of patients in the insulin glargine + OAD set achieved the target 2-h PPBG level of 7.2–8.9 mmol/l (130–160 mg/dl).

Body weight
In the full data set, significant reductions in body weight were observed between the start and end of the observation period (–1.5 ± 3.3 kg; p ≤ 0.001; median change in body weight: –1.0 kg; interquartile range: –3 to 0 kg) (Table 3). Reductions in body weight were of a similar magnitude and were statistically significant in the other subsets of the study population.

Insulin dose and oral antidiabetic therapy
In the full data set, the mean daily dose of insulin increased by 4 U between week 0 (22.1 ± 10.6 U) and week 12 (26.3 ± 11.6 U). A similarly low increase in the daily insulin dose was seen in patients in the other subsets of the total population.

In the insulin glargine + OAD group, there were no changes in the frequency of patients taking each OAD between the start and end of the observation; metformin (54.8% vs. 58.2% for start vs. end of observation) glimepiride (40.5% vs. 44.5%) and glibenclamide (10.9% vs. 9.8%) were used most frequently. The proportion of patients taking other OADs was 4.4% and 5.2% at the start and end of observation, respectively.

Safety
All patients (n = 6560) were included in the full data set. A total of 71 AEs were reported in 38 patients; of these, 33 events (17 patients) were classified as serious AEs. Hypoglycaemia was the most commonly reported AE (16 events), followed by hyperhydrosis (three events).

A total of 30 events in 14 patients were classified as ADRs; hypoglycaemia was the most commonly reported ADR (13 events), followed by hyperhydrosis (three events), over the 12-week observation period. Two patients died during the course of the observation period; one was due to acute kidney failure, which was not considered related to the treatment regimen, but no indication was available for the second, thus it was not possible to determine whether it was related to treatment or not.

Table 2 Proportion of patients who achieved clinically relevant fasting blood glucose levels [5.0–6.7 mmol/l (90–120 mg/dl)] or HbA1c (< 7.5%) at week 12

|                         | Full data set (n = 6308) | Prior premixed insulin – OADs (n = 3098) | Prior premixed insulin + OADs (n = 3210) | Insulin glargine + OAD set (n = 5045) |
|-------------------------|-------------------------|-----------------------------------------|-----------------------------------------|-------------------------------------|
| **FBG**                 |                         |                                         |                                         |                                     |
| Number of patients with FBG measurement | 5998 | 2930 | 3068 | 4815 |
| < 5.0 mmol/l (< 90 mg/dl) | 272 | 4.5 | 128 | 4.4 | 144 | 4.7 | 214 | 4.4 |
| 5.0–6.7 mmol/l (90–120 mg/dl) | 2643 | 44.1 | 1335 | 45.6 | 1308 | 42.6 | 2139 | 44.4 |
| Total < 6.7 mmol/l (< 120 mg/dl) | 2915 | 48.6 | 1463 | 49.9 | 1452 | 47.3 | 2353 | 48.9 |
| **HbA1c**               |                         |                                         |                                         |                                     |
| Number of patients with HbA1c measurement | 6179 | 3033 | 3146 | 4965 |
| < 7.5%                  | 4593 | 74.3 | 2277 | 75.1 | 2316 | 73.6 | 3670 | 73.9 |

As some patients had incomplete data, the number of patients with valid data for each characteristic are given. Results are n and per cent of patients who provided valid data for that characteristic. Reasons for missing data were not collected. Full data set = all patients who fulfilled the inclusion criteria; prior premixed insulin – OAD = all patients who were treated with premixed insulin without OADs prior to the observational study; prior premixed insulin + OAD = all patients who were treated with premixed insulin plus OADs prior to the observational study. Insulin glargine + OAD set = all patients who were treated with insulin glargine plus OADs during the observational period. OAD, oral antidiabetic agent; FBG, fasting blood glucose; HbA1c, glycosylated haemoglobin.

2014 Insulin glargine in everyday clinical practice
ª2007 The Authors
Journal compilation ª2007 Blackwell Publishing Ltd Int J Clin Pract, December 2007, 61, 12, 2009–2018
Table 3 Preprandial and 2-h postprandial blood glucose and body weight at the start and at the end of the 12-week observation period

| Factor | Full data set (n = 6308) | Prior premixed insulin – OADs (n = 3098) | Prior premixed insulin + OADs (n = 3210) | Insulin glargine + OAD set (n = 5045) |
|--------|--------------------------|-----------------------------------------|-----------------------------------------|---------------------------------------|
|        | n | Mean ± SD               | n | Mean ± SD               | n | Mean ± SD               | n | Mean ± SD               |
| **Prandial blood glucose** |               |                                    |                                         |                                         |
| Start [mmol/l (mg/dl)] | 2870 | 9.7 ± 2.6 (174 ± 46) | 1409 | 9.6 ± 2.4 (173 ± 44) | 1461 | 9.7 ± 2.7 (175 ± 48) | 2265 | 9.6 ± 2.5 (173 ± 45) |
| End [mmol/l (mg/dl)] | 2366 | 6.8 ± 1.3 (122 ± 23) | 1144 | 6.7 ± 1.2 (121 ± 22) | 1222 | 6.8 ± 1.3 (122 ± 24) | 1896 | 6.8 ± 1.3 (122 ± 23) |
| **2-h postprandial** |               |                                    |                                         |                                         |
| Start [mmol/l (mg/dl)] | 2870 | 10.8 ± 2.8 (195 ± 50) | 1409 | 10.8 ± 2.8 (195 ± 50) | 1461 | 10.9 ± 2.8 (196 ± 50) | 2265 | 10.9 ± 2.8 (196 ± 50) |
| End [mmol/l (mg/dl)] | 2366 | 7.8 ± 1.5 (140 ± 27) | 1144 | 7.8 ± 1.4 (140 ± 25) | 1222 | 7.8 ± 1.6 (140 ± 29) | 1896 | 7.8 ± 1.6 (141 ± 28) |
| **Proportion of patients reaching postprandial therapeutic target** |               |                                    |                                         |                                         |
| Number of patients with valid data | 2183 | 1075 | 1108 | 1719 |
| < 7.2 mmol/l (< 130 mg/dl)* | 839 | 38.4 | 440 | 39.7 | 639 | 37.2 |
| 7.2–8.9 mmol/l (130–160 mg/dl)* | 966 | 44.3 | 473 | 42.7 | 763 | 44.4 |
| Total < 8.9 mmol/l (< 160 mg/dl)* | 1805 | 82.7 | 913 | 82.4 | 1402 | 81.6 |
| **Body weight** |               |                                    |                                         |                                         |
| Start (kg) | 6175 | 84.8 ± 14.4 | 3030 | 84.0 ± 14.2 | 3145 | 85.6 ± 14.6 | 4958 | 85.2 ± 14.4 |
| End (kg) | 6175 | 83.3 ± 14.1 | 3030 | 82.5 ± 14.0 | 3145 | 84.0 ± 14.2 | 4958 | 83.6 ± 14.1 |
| Change | –1.5 ± 3.3† | –1.5 ± 3.3† | –1.6 ± 3.3† | –1.5 ± 3.2† |

As some patients had incomplete data, the numbers of patients with valid data for each characteristic are given. Results are means ± SD; *n, per cent; †p ≤ 0.001 for within-group change in body weight from start of observation. Full data set = all patients who fulfilled the inclusion criteria; prior premixed insulin – OAD = all patients who were treated with premixed insulin without OADs prior to the observational study; Prior premixed insulin + OAD = all patients who were treated with premixed insulin plus OADs prior to the observational study. Insulin glargine + OAD set = all patients who were treated with insulin glargine plus OADs during the observational period. SD, standard deviation; OAD, oral antidiabetic agents.

Physician assessment of insulin glargine therapy

In the full data set, physicians consistently rated insulin glargine therapy as very good or good for the rated aspects of therapy (Table 4) – quality of life (94.1%), BG control (87.6%) and weight management (68.9%). Only 2.9% of physicians rated the treatment safety of insulin glargine as satisfactory or unsatisfactory, and 95.9% rated treatment safety with insulin glargine as very good or good for the rated aspects of therapy (Table 4) – quality of life (94.1%), BG control (87.6%) and weight management (68.9%). Physicians also reported that the demands placed on their time with insulin glargine were either very good or good (89.7%).

In the full data set, continuation of insulin glargine therapy was planned for 6163 patients (97.7%) at the end of the observation period. Of the 116 patients who stopped therapy with insulin glargine, the most common reasons were ‘inadequate BG control’ (n = 53), ‘change of therapy’ (n = 42), ‘patient lost to follow-up’ (n = 28) or ‘treatment no longer considered necessary at the end of observation’ (n = 5). For 29 patients, there was no information on whether insulin glargine treatment was continued at the end of the observation period. In the insulin glargine + OAD set, continuation of insulin glargine plus OAD therapy was planned for 4929 patients (97.7%).

Discussion

Here, we describe a non-interventional, non-randomised observational study that was undertaken to document postmarketing experience of transferring patients with T2DM from premixed insulin to insulin glargine. This study demonstrates for the first time in daily clinical practice that initiation of insulin glargine with or without OADs improves glycemic control in patients with T2DM who were poorly controlled with premixed insulin prior to the observation period. Significant improvements in both HbA1c and FBG were observed during the 12-week observation period in patients treated with insulin glargine with or without OADs. Furthermore, body weight was reduced over the 12-week observational period with relatively small increases in daily insulin dose. The improvements in FBG, HbA1c and body weight were also observed in the subsets of the full data population, including the insulin glargine + OAD set.

The results presented in this observational study were broadly consistent, irrespective of the patient subsets, and show that the initiation of insulin glargine in patients previously treated with premixed insulin was associated with significant improvements
in FBG, HbA1c and body weight, irrespective of whether or not patients were previously taking OADs.

In a recent observational study of 12,216 patients with T2DM poorly controlled with OADs alone [HbA1c: 8.7 ± 1.4%; FBG: 11.2 ± 3.1 mmol/l (202 ± 56 mg/dl)], addition of once-daily insulin glargine was associated with improvements in FBG [7.4 ± 1.8 mmol/l (133 ± 33 mg/dl)] and HbA1c (7.2 ± 0.9%) at 3 months, which were maintained at 9 months (6). In our study, we show that switching from premixed insulin to insulin glargine is associated with significant improvements in FBG and HbA1c after only 12 weeks. Furthermore, the majority of patients achieved the target FBG, HbA1c, or PPBG.

Premixed insulin is a common therapy for T2DM and approximately 40% of patients are treated with premixed insulin worldwide (1), while a recent German study suggested that premixed insulin constitutes the majority (> 80%) of insulin usage in patients with either T1 or T2DM (7).

In the transition to insulin glargine therapy, OADs are typically used in combination. In the present study, some of the patients previously treated with premixed insulin (with or without oral antidiabetic agents) switched to insulin glargine, but did not take

Table 4 Physician assessment of insulin glargine therapy

| Factor                  | Full data set (n = 6308) | Prior premixed insulin – OADs (n = 3098) | Prior premixed insulin + OADs (n = 3210) | Insulin glargine + OAD set (n = 5045) |
|------------------------|--------------------------|----------------------------------------|----------------------------------------|-------------------------------------|
|                        | n | %     | n | %     | n | %     | n | %     |
| Quality of life        |   |        |   |        |   |        |   |        |
| Very good              | 2615 | 41.5  | 1308 | 42.2  | 1307 | 40.7  | 2085 | 41.3  |
| Good                   | 3320 | 52.6  | 1626 | 52.5  | 1694 | 52.8  | 2673 | 53.0  |
| Satisfactory           | 277  | 4.4   | 118  | 3.8   | 159  | 5.0   | 221  | 4.4   |
| Unsatisfactory         | 19   | 0.3   | 7    | 0.2   | 12   | 0.4   | 15   | 0.3   |
| No response given      | 77   | 1.2   | 39   | 1.3   | 38   | 1.2   | 51   | 1.0   |
| Blood glucose control  |   |        |   |        |   |        |   |        |
| Very good              | 2921 | 46.3  | 1479 | 47.7  | 1442 | 44.9  | 2310 | 45.8  |
| Good                   | 2606 | 41.3  | 1259 | 40.6  | 1347 | 42.0  | 2103 | 41.7  |
| Satisfactory           | 602  | 9.5   | 274  | 8.8   | 328  | 10.2  | 491  | 9.7   |
| Unsatisfactory         | 118  | 1.9   | 58   | 1.9   | 60   | 1.9   | 101  | 2.0   |
| No response given      | 61   | 1.0   | 28   | 0.9   | 33   | 1.0   | 40   | 0.8   |
| Weight management      |   |        |   |        |   |        |   |        |
| Very good              | 1691 | 26.8  | 863  | 27.9  | 828  | 25.8  | 1335 | 26.5  |
| Good                   | 2655 | 42.1  | 1335 | 43.1  | 1320 | 41.1  | 2136 | 42.3  |
| Satisfactory           | 1455 | 23.1  | 675  | 21.8  | 780  | 24.3  | 1182 | 23.4  |
| Unsatisfactory         | 422  | 6.7   | 183  | 5.9   | 239  | 7.5   | 334  | 6.6   |
| No response given      | 85   | 1.4   | 42   | 1.4   | 43   | 1.3   | 58   | 1.2   |
| Safety                 |   |        |   |        |   |        |   |        |
| Very good              | 3426 | 54.3  | 1683 | 54.3  | 1743 | 54.3  | 2765 | 54.8  |
| Good                   | 2625 | 41.6  | 1280 | 41.3  | 1345 | 41.9  | 2093 | 41.5  |
| Satisfactory           | 164  | 2.6   | 92   | 3.0   | 72   | 2.2   | 123  | 2.4   |
| Unsatisfactory         | 19   | 0.3   | 8    | 0.3   | 11   | 0.3   | 15   | 0.3   |
| No response given      | 74   | 1.2   | 35   | 1.1   | 39   | 1.2   | 49   | 1.0   |
| Demand on time         |   |        |   |        |   |        |   |        |
| Very good              | 2051 | 32.5  | 1036 | 33.4  | 1015 | 31.6  | 1592 | 31.6  |
| Good                   | 3608 | 57.2  | 1744 | 56.3  | 1864 | 58.1  | 2959 | 58.7  |
| Satisfactory           | 528  | 8.4   | 258  | 8.3   | 270  | 8.4   | 408  | 8.1   |
| Unsatisfactory         | 32   | 0.5   | 13   | 0.4   | 19   | 0.6   | 25   | 0.5   |
| No response given      | 89   | 1.4   | 47   | 1.5   | 42   | 1.3   | 61   | 1.2   |

As some patients had incomplete data the numbers of patients with valid data for each characteristic are given. Reasons for missing data were not collected. Results are n and per cent. Full data set = all patients who fulfilled the inclusion criteria; prior premixed insulin – OAD = all patients who were treated with premixed insulin without OADs prior to the observational study; prior premixed insulin + OAD = all patients who were treated with premixed insulin plus OADs prior to the observational study. Insulin glargine + OAD set = all patients who were treated with insulin glargine plus OADs during the observational period. OADs, oral antidiabetic agents.
concomitant oral therapy. In those who switched from premixed insulin without or with OADs to insulin glargine without OADs, improvements in HbA1c, FBG and PPBG were consistent with the insulin glargine + OAD and the full data sets (data not shown).

Weight gain is a seemingly unavoidable occurrence with initiation of insulin therapy in T2DM (8). In a 28-week study comparing initiation of insulin therapy with either biphasic insulin aspart (70/30) or insulin glargine, once-daily insulin glargine was associated with significantly less weight gain compared with twice-daily biphasic insulin aspart (+3.5 vs. +5.4 kg; p < 0.01) (9). Furthermore, educational programmes, if combined with insulin glargine therapy, may help prevent the weight gain otherwise associated with insulin therapy (10). In this study, the authors used a programme comprising 90-min lessons over a 12-week duration, with focus on various topics, such as ‘insulin dosing and injection’, ‘BG self-monitoring’, ‘food and diet’, ‘physical exercise’ and ‘diabetic complications’. Patients were monitored for 30 months and were not to make dietary adjustments as part of the study. No weight gain was seen in the overall study population. In our study, we show that weight loss can be achieved in the overall study population. In our study, only 16 patients reported an episode of hypoglycaemia, of which 13 were classed as ADRs. However, this may partly be due to the less stringent target levels used in everyday clinical practice compared with the study by Janka et al. (4), which set target values of HbA1c ≤ 7.0% and FBG ≤ 5.6 mmol/l (≤ 100 mg/dl).

In a 28-week RCT comparing insulin glargine with NPH insulin in patients who were inadequately controlled (HbA1c 7.0–12.0%) with insulin, < 30% of patients achieved target FBG levels [< 6.7 mmol/l (< 120 mg/dl)] at the study end (12). The authors reported that this may have been due to reluctance of the investigators and/or subjects to intensively titrate the insulin dose likely because of fear of hyperglycaemia or weight gain. In our study, almost 50% of patients achieved FBG levels of ≤ 6.7 mmol/l (≤ 120 mg/dl) and > 70% achieved HbA1c levels of ≤ 7.5%.

There are limitations of the study that mean care should be taken when interpreting our results. First, as this was an observational study and not controlled by the inclusion of a comparator arm, it is likely that some of the improvements observed may be related to a study effect rather than the therapeutic regimen based on insulin glargine plus OADs. Unfortunately, as this study was uncontrolled, it is not possible to delineate between the study effect and the regimen used. Nevertheless, the improvements in glycaemic control over the study period are consistent with RCTs (13,14).

Second, the duration of the observation period was restricted to 12 weeks; however, subsequent follow ups are planned at 1 year to address longer-term benefits of insulin glargine plus OADs in clinical practice, particularly on the overall weight loss and low incidence of hypoglycaemia observed here.

In the present study, the target HbA1c was ≤ 7.5% and was achieved by almost 75% of the patients. However, the International Diabetes Federation (15) and the American Diabetes Association (16) have set target HbA1c levels of ≤ 6.5% and ≤ 7.0%, respectively. It is likely that if the target HbA1c had been set at equivalent levels, a more intensive treatment algorithm would be needed, which may, however, increase risk of hypoglycaemia. Thus, the low incidence of hypoglycaemia observed in the present study may reflect the less stringent titration targets used [i.e. FBG < 6.7 mmol/l (< 120 mg/dl) and HbA1c < 7.5%]. However, a number of trials have demonstrated that greater improvements in FBG and/or HbA1c can be achieved with insulin glargine vs. NPH insulin, with a lower risk of hypoglycaemia, even with intensive insulin titration regimens.
(13,14,17). The incidence of hypoglycaemia may also reflect the self-report methods used, as patients and physicians were not requested to provide specific details of each episode. Thus, the occurrence of hypoglycaemia may have been underreported by patients in the present study.

In the present study, approximately 75% of patients met our target HbA1c level of ≤ 7.5%, with a mean of 7.2% for the full data set. While this is close to the ADA target (and undoubtedly, some patients will have met the ADA, and possibly IDF targets), we suggest that further intensification of therapy, perhaps by adding one or more bolus insulin injections, would help improve glycaemic control further (18). Indeed, the improvements observed in the present study provide a foundation on which further therapies should be added.

In summary, in this observational study of everyday clinical practice, we have shown here for the first time that once daily insulin glargine plus OADs is an effective therapeutic regimen with a good safety profile for patients with T2DM who were inadequately controlled with premixed insulin. Furthermore, in a clinical setting, improvements in glycaemic control can be achieved with low risk of weight gain and with a low prevalence of hypoglycaemia in a large study population (6308 patients). It remains to be seen whether these improvements are maintained after a longer duration of time in this cohort of patients.

Acknowledgements

This study was supported by sanofi-aventis. Editorial support for this article was provided through the global publications group of sanofi-aventis. We would like to thank all of the investigators for their commitment to this study.

References

1 Koivisto VA, Tuominen JA, Ebeling P. Lispro Mix25 insulin as premeal therapy in type 2 diabetic patients. Diabetes Care 1999; 22: 459–62.

2 Garber AI. Premixed insulin analogues for the treatment of diabetes mellitus. Drugs 2006; 66: 31–49.

3 Roach P, Trautmann M, Arora V et al. Improved postprandial blood glucose control and reduced nocturnal hypoglycaemia during treatment with two novel insulin lispro-protamine formulations, insulin lispro mix25 and insulin lispro mix50. Mix50 Study Group. Clin Ther 1999; 21: 523–34.

4 Janka HU, Plewe G, Riddle MC et al. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Diabetes Care 2005; 28: 254–9.

5 sanofi-aventis. LANTUS: Summary of Product Characteristics, 2006. http://www.emea.europa.eu/humandocs/Humans/EPAR/lantus/lantus.htm (accessed May 2007).

6 Schreiber SA, Haak T. Insulin glargine benefits patients with type 2 diabetes inadequately controlled on oral antidiabetic treatment: an observational study of everyday practice in 12,216 patients. Diabetes Obes Metab 2007; 9: 31–8.

7 Hauner H, Koster I, von Ferber L. Outpatient care of patients with diabetes mellitus in 2001. Analysis of a health insurance sample of the AOK in Hesse/KV in Hesse. Dtsch Med Wochenschr 2003; 128: 2638–43.

8 Larger E. Weight gain and insulin treatment. Diabetes Metab 2005; 31 (4 part 2): 4551–6.

9 Raskin P, Allen E, Hollander P et al. Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. Diabetes Care 2005; 28: 260–5.

10 Schreiber SA, Russmann A. Insulin glargine and educational intervention in patients with type 2 diabetes in clinical practice: long-term improvement in glycaemic control without weight gain. Exp Clin Endocrinol Diabetes 2006; 114: 41–2.

11 Zammit NN, Frier BM. Hypoglycaemia in type 2 diabetes: pathophysiology, frequency, and effects of different treatment modalities. Diabetes Care 2005; 28: 2948–61.

12 Rosenstock J, Schwartz SL, Clark CM Jr et al. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. Diabetes Care 2001; 24: 631–6.

13 Yki-Jarvinen H, Kauppinen-Makelin R, Tiikkainen M et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. Diabetologia 2006; 49: 442–51.

14 Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003; 26: 3080–6.

15 IDF Clinical Guidelines Task Force. Global Guideline for Type 2 Diabetes. Brussels: International Diabetes Federation, 2005.

16 American Diabetes Association. Standards of medical care in diabetes. Diabetes Care 2006; 29 (Suppl. 1): 54–42.

17 Elsaschewitz FG, Calvo C, Valbuena H et al. Therapy in type 2 diabetes: insulin glargine vs. NPH insulin both in combination with glimepiride. Arch Med Res 2006; 37: 495–501.

18 Raccah D, Bretzel RG, Owens D, Riddle M. When basal insulin therapy in type 2 diabetes mellitus is not enough – what next? Diabetes Metab Res Rev 2007; 23: 257–64.