Short Report: Treatment

Fasting plasma glucose 6–12 weeks after starting insulin glargine predicts likelihood of treatment success: a pooled analysis

D. Karl1, R. Zhou2, A. Vlajnic3 and M. Riddle4

1The Endocrine Clinic, Portland, OR, 2Medpace Inc., Cincinnati, OH, 3Sanofi US, Bridgewater, NJ and 4Oregon Health and Science University, Portland, OR, USA

Accepted 6 March 2012

Abstract

Aims To evaluate whether fasting plasma glucose values measured early during insulin therapy can identify patients with Type 2 diabetes who may not achieve adequate glycaemic control after 6 months and will require additional treatment.

Methods Patient-level data from seven prospective, randomized, controlled studies using treat-to-target methods were pooled to evaluate the efficacy of insulin glargine. Fasting plasma glucose was measured at baseline, week 6 or 8 (6/8) and week 12. HbA1c was measured at week 24 to assess glycaemic control.

Results One thousand and thirty-six patients (56% male, 81% white) were included in the analysis (mean age 56.3 years; duration of diabetes 8.4 years). Baseline mean fasting plasma glucose was 11.2 mmol/L and mean HbA1c was 73 mmol/mol (8.8%). After 24 weeks of treatment, mean HbA1c decreased to 53 mmol/mol (7.0%); 56% of patients reached a target HbA1c ≤ 53 mmol/mol (7.0%). Significant correlations with week 24 HbA1c were obtained for fasting plasma glucose measured at week 6/8 and week 12 (r = 0.32; P < 0.0001 for both). Patients with fasting plasma glucose > 10 mmol/L at week 6/8 or week 12 were significantly less likely to achieve the HbA1c target at the end of treatment than patients with fasting plasma glucose < 8.9 mmol/L (P < 0.0001 for both). If fasting plasma glucose was > 10 mmol/L at week 6/8 or week 12, patients had only a 27% chance of reaching the HbA1c goal.

Conclusions Fasting plasma glucose remaining > 10 mmol/L after 6–12 weeks of glargine therapy indicates that reaching target HbA1c ≤ 53 mmol/mol (7.0%) is unlikely and calls for individualized attention to consider further therapeutic options.

Diabet. Med. 29, 933–936 (2012)

Keywords fasting plasma glucose, glycated haemoglobin, HbA1c, insulin glargine, Type 2 diabetes

Introduction

Many patients treated with lifestyle modifications and oral anti-diabetic drugs eventually require insulin therapy [1]. Adding titrated insulin glargine to the drugs reduces HbA1c to < 53 mmol/mol (7.0%) for many patients, but some require additional therapy [2,3]. Early identification of patients for whom glargine and oral anti-diabetic drugs may not be sufficient would be helpful.

Concurrent measurements of fasting plasma glucose and HbA1c levels during stable therapy are strongly correlated, [4,5]. However, when treatment is intensified, fasting plasma glucose values improve immediately, whereas HbA1c values lag behind, not reaching a stable new value for 4 months or more. Therefore, fasting plasma glucose measured at early follow-up visits might predict future success in reaching HbA1c targets. To test this concept, we performed a pooled analysis of patient-level data obtained in studies in which treatment with glargine was started using similar treat-to-target methods.

Patients and methods

Study selection

Sixty-three studies in adults with Type 2 diabetes completed between 1997 and 2007 were evaluated. For inclusion in the pooled analysis, a study had to have a prospective, randomized,
controlled design conducted according to Good Clinical Practice standards; using basal insulin therapy with glargine (but without prandial insulin) added to lifestyle alone or stable oral anti-diabetic drug therapy, and a treat-to-target strategy with a predefined insulin titration algorithm targeting fasting plasma glucose < 5.6 mmol/l; and including fasting plasma glucose measurements at baseline, week 6 or 8 (6/8) and week 12 as well as systematic collection of reports of hypoglycaemia. Seven studies met these criteria [2,6–11] (data on file; Sanofi US, Bridgewater, NJ, USA). For studies with longer duration, only data from the first 24 weeks were used. Participants were eligible for analysis if fasting plasma glucose values at baseline, week 6/8 and week 12 and HbA1c measurements at week 24 were all available. Patient level data for 1036 participants were included.

Outcome measures

Laboratory measurements of fasting plasma glucose from samples collected at study sites were divided into three categories: < 8.9, ≥ 8.9 to < 10 or ≥ 10 mmol/l. Correlations between site fasting plasma glucose values and those obtained at home by patient self-measurements were determined. Treatment was considered successful if HbA1c at week 24 was ≤ 53 mmol/mol (7.0%). Symptomatic hypoglycaemia was defined as all events reported with symptoms. Glucose-confirmed symptomatic hypoglycaemia included events with concurrent glucose < 2.8 mmol/l. Severe hypoglycaemia comprised all symptomatic events for which the patient required assistance and had either a blood glucose level < 2 mmol/l or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.

Statistical analysis

Summary statistics were calculated for HbA1c at baseline and week 24. Independent analyses of fasting plasma glucose values were performed for the correlation between week 6/8 fasting plasma glucose and week 24 HbA1c, and the correlation between week 12 fasting plasma glucose and week 24 HbA1c. For each, week 24 HbA1c and change in HbA1c from baseline to week 24 were analysed continuously using an analysis of covariance model, with study as a factor and post-baseline visit to week 24 were analysed continuously using an analysis of covariance model, with study as a factor and post-baseline visit to week 24 as a covariate. Week 24 HbA1c was covariate model, with study as a factor and post-baseline visit to week 24 were analysed continuously using an analysis of available. Patient level data for 1036 participants were included.

The 1036 participants were 56% male and 81% white with mean ± sd age 56.3 ± 9.9 years and duration of diabetes 8.4 ± 5.9 years. Prior (and continued) therapies included 1–3 oral anti-diabetic drugs (metformin, sulphonylurea, thiazolidinedione). Mean HbA1c was 73 mmol/mol (8.84 ± 1.03%) and mean fasting plasma glucose was 11.2 ± 3.0 mmol. Examined by ranges of HbA1c at baseline, 63% of patients had fasting plasma glucose ≥ 10 mmol/l, 13% had fasting plasma glucose from 8.9 to < 10 mmol/l and 24% had fasting plasma glucose < 8.9 mmol/l. Measurements at home (mean ± sd; 8.85 ± 3.39 mmol/l) correlated strongly with laboratory measurements (8.65 ± 3.18 mmol/l; r = 0.778; P = 0.0001).

Adding glargine to oral anti-diabetic drugs reduced both measures of glycaemic control, but with differing patterns (Table 1). Mean fasting plasma glucose declined to 7.3 mmol/l at 6/8 weeks, 6.8 mmol/l at 12 weeks and 6.7 mmol/l at 24 weeks. Mean HbA1c was 56 mmol/mol (7.3%) at 12 weeks and 53 mmol/mol (7.0%) at 24 weeks, with 56% of patients at or below that level.

Fasting plasma glucose as a predictor of treatment outcome

The correlation between baseline fasting plasma glucose and week 24 HbA1c considered as continuous variables was weak but statistically significant in this large sample (r = 0.169; P < 0.0001). The correlation with week 24 HbA1c was stronger for fasting plasma glucose measured at week 6/8 (r = 0.319; P < 0.0001) and week 12 (r = 0.317; P < 0.0001).

When the ability of baseline fasting plasma glucose to predict later attainment of the HbA1c target level was examined by range of fasting plasma glucose, the limited predictive power of this measurement was evident (Fig. 1). Percentages of participants obtaining the HbA1c target for those starting with fasting plasma glucose < 8.9, 8.9 to < 10 and ≥ 10 mmol/l were 61, 66 and 52%. However, corresponding percentages at week 6/8 were 61, 48 and 26.5%; at 12 weeks they were 60, 40 and 27%. For the general association between reaching target HbA1c and these fasting plasma glucose categories, P-values were 0.001, < 0.0001 and < 0.0001 for the fasting plasma glucose categories at baseline, week 6/8 and week 12, respectively.

Persistence of higher fasting plasma glucose early in therapy was associated with the possibility of having very high HbA1c at 24 weeks. In the group with fasting plasma glucose < 8.9 mmol/l at 12 weeks just 8% of participants had HbA1c above 64 mmol/mol (8.0%) at 24 weeks. In contrast, in the group with fasting plasma glucose ≥ 10 mmol/l at 12 weeks, 39% had week 24 HbA1c above 64 mmol/mol (8.0%), 14.5% above 75 mmol/mol (9.0%) and 6.5% above 86 mmol/mol (10.0%).
Thus might benefit from re-evaluation of treatment options. Achieve HbA\textsubscript{1c} goals with glargine added to oral therapies and the course of treatment can identify patients who are unlikely to hypoalgalia. Hypoalgalia measured early in the course of therapy was reported by 65% of participants with 12-week fasting plasma glucose \( < 8.9 \text{ mmol/l} \) at week 24 at three stages of therapy, by range of fasting plasma glucose values at each stage: (7.0%) at week 24 at three stages of therapy, by range of fasting plasma glucose \( < 8.9 \text{ mmol/l} \) and glucose-confirmed events compared with \( \geq 10 \text{ mmol/l} \). Participants with 12-week fasting plasma glucose \( < 8.9 \text{ mmol/l} \) and \( < 5.6 \text{ mmol/l} \) and 7% likelihood of a single clinic-measured fasting plasma glucose value \( > 10 \text{ mmol/l} \) between 6 and 12 weeks after starting glargine was associated with \( \sim 2.5\% \) chance of attaining that target. Also, a fasting plasma glucose value of \( \geq 10 \text{ mmol/l} \) after 12 weeks of treatment suggested approximately 15% likelihood of ending with HbA\textsubscript{1c} \( > 75 \text{ mmol/mol (9.0\%)} \) and 7% likelihood of a final HbA\textsubscript{1c} higher than 86 mmol/mol (10.0\%). Not surprisingly, lower levels of fasting plasma glucose after 12 weeks of treatment with glargine were associated with more hypoglycaemia. However, the occurrence of severe hypoglycaemia was rare, even with intensive insulin therapy targeting fasting plasma glucose \( < 5.6 \text{ mmol/l} \). Thus, the occurrence of hypoglycaemia, when carefully managed, did not preclude intensification of insulin therapy.

These findings are potentially helpful despite the limitation inherent in their being based on only a single measurement of fasting plasma glucose for each patient at each time point. Collection of multiple self-measured values by the patient at home should provide a more substantial basis for evaluating the patient’s early response to insulin therapy. When, despite a systematic titration plan, glargine fails to reduce fasting plasma glucose below 10 mmol/l within the first 12 weeks, potentially important problems may be suspected. These might include development of a new medical problem that interferes with insulin’s effectiveness, frequent omission of insulin injections, inability to make systematic decisions on dose–titration, mishandling of insulin or faulty injection technique, or eating prior to measurement of fasting plasma glucose either at home or in the provider’s office. If such medical or behavioural factors are not identified, the possibility of markedly elevated postprandial glucose below10 mmol/l within the first 12 weeks, potentially important problems may be suspected. These might include development of a new medical problem that interferes with insulin’s effectiveness, frequent omission of insulin injections, inability to make systematic decisions on dose–titration, mishandling of insulin or faulty injection technique, or eating prior to measurement of fasting plasma glucose either at home or in the provider’s office. If such medical or behavioural factors are not identified, the possibility of markedly elevated postprandial

### Table 1 Changes in fasting plasma glucose during treatment

| Patients | Baseline | Week 6 or 8* | Week 12 | Week 24 |
|----------|----------|-------------|---------|---------|
| All patients, mean (sd) fasting plasma glucose, mmol/l | 11.1 (3.0) | 7.3 (2.2) | 6.8 (2.0) | 6.7 (1.9) |
| All patients, mean (sd) HbA\textsubscript{1c}, mmol/mol† | 73 \(8.84 (1.03)\) | — | 56 \(7.27 (0.90)\) | 53 \(7.03 (0.86)\) |
| Patients (n, %) and glucose [mean (sd), mmol/l] within each fasting plasma glucose group: | | | | |
| Fasting plasma glucose \( < 8.9 \text{ mmol/l} \) | n, % | 246 (23.7) | 827 (79.8) | 897 (86.6) | 923 (89.1) |
| Mean (sd) | 7.6 (0.9) | 6.5 (1.3) | 6.2 (1.3) | 6.2 (1.3) |
| HbA\textsubscript{1c}, % mean (sd) | 8.17 (0.71) | — | 7.16 (0.80) | 6.95 (0.80) |
| Fasting plasma glucose 8.9 to \( < 10 \text{ mmol/l} \) | n, % | 139 (13.4) | 107 (10.3) | 77 (7.4) | 57 (5.5) |
| Mean (sd) | 9.4 (0.3) | 9.4 (0.3) | 9.4 (0.3) | 9.3 (0.3) |
| HbA\textsubscript{1c}, % mean (sd) | 8.42 (0.82) | — | 7.72 (1.04) | 7.42 (0.90) |
| Fasting plasma glucose \( \geq 10 \text{ mmol/l} \) | n, % | 651 (62.8) | 102 (9.8) | 62 (6.0) | 56 (5.4) |
| Mean (sd) | 12.8 (2.4) | 11.8 (1.6) | 11.6 (1.4) | 11.7 (1.6) |
| HbA\textsubscript{1c}, %, mean (sd) | 9.18 (1.01) | — | 8.25 (1.24) | 7.9 (1.14) |

*HbA\textsubscript{1c} was not measured at week 6/8.
†Standard deviation (sd) is not calculable.

#### Discussion

This pooled analysis of patient-level data confirmed the hypothesis that fasting plasma glucose measured early in the course of treatment can identify patients who are unlikely to achieve HbA\textsubscript{1c} goals with glargine added to oral therapies and thus might benefit from re-evaluation of treatment options.
glucose values leading to wide daily variations of glucose should be considered, and addition of rapid-acting insulin or other prandial treatment may be indicated.

In conclusion, these analyses verify that attention to fasting plasma glucose changes in the first 12 weeks after starting treatment with glargine may allow earlier identification of patients unlikely to attain HbA1c targets, leading to individualized attention and more timely and effective changes in management.

Competing interests
DK has received honoraria for consulting from Sanofi US. RZ is an employee of Medpace Inc. AV is an employee of Sanofi US. MR has received research grant support and honoraria for consulting or speaking from Sanofi US, research grant support from Eli Lilly and Company and honoraria for consulting from Novo Nordisk.

Acknowledgement
Study funding was provided by Sanofi US. Editorial support was provided by Stacey J. P. Ullman MHS, of Embryon, LLC, and was funded by Sanofi US.

References
1 Dailey G. A timely transition to insulin: identifying Type 2 diabetes patients failing oral therapy. Formulary 2005; 40: 114–130.
2 Riddle MC, Rosenstock J, Gerich J. Insulin Glargine 4002 Study Investigators. 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: 3080–3086.
3 Yki-Järvinen H, Jaurinen L, Alvarsson M, Bystrud T, Caldwell I, Davies M et al. Initiate Insulin by Aggressive Titration and Education (INITIATE): a randomized study to compare initiation of insulin combination therapy in Type 2 diabetic patients individually and in groups. Diabetes Care 2007; 30: 1364–1369.
4 Bonora E, Calcaterra F, Lombardi S, Bonfante N, Formentini G, Bonadonna RC et al. Plasma glucose levels throughout the day and HbA1c interrelationships in Type 2 diabetes: implications for treatment and monitoring of metabolic control. Diabetes Care 2001; 24: 2023–2029.
5 Monami M, Lamanna C, Lamberti L, Longo R, Cocca C, Addante F et al. Fasting and post-prandial glycemia and their correlation with glycated hemoglobin in Type 2 diabetes. J Endocrinol Invest 2006; 29: 619–624.
6 Gerstein HC, Yale J-F, Harris SB, Issa M, Stewart JA, Dempsey E. A randomized trial of adding insulin glargine vs. avoidance of insulin in people with Type 2 diabetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas. The Canadian INSIGHT (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) Study. Diabet Med 2006; 23: 736–742.
7 Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G. Triple therapy in Type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. Diabetes Care 2006; 29: 554–559.
8 Meneghini LF, Traylor L, Schwartz SL. Improved glycemic control with insulin glargine versus pioglitazone as add-on therapy to sulfonylurea or metformin in patients with uncontrolled Type 2 diabetes mellitus. Endocr Pract 2010; 16: 588–599.
9 Janka HU, Plewe G, Riddle MC, Klüebe-Frisch C, Schweitzer MA, Yki-Järvinen H. 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: 254–259.
10 Yki-Järvinen H, Kauppinen-Mäkelin R, Tikkainen M, Vahatalo M, Virtamo H, Nikkilä K et al. Insulin glargine or NPH combined with metformin in Type 2 diabetes: the LANMET study. Diabetologia 2006; 49: 442–451.
11 Sanofi-Aventis. Lantus Versus Humalog Mix as Add-On Therapy in Type 2 Diabetes Patients Failing Sulfonylurea and Metformin Combination Treatment. 2001. Trial identifier: NCT01336751. Available at http://clinicaltrials.gov/ct2/show/NCT01336751 Last accessed 11 November 2011.