Treatment Satisfaction and Quality of Life With Insulin Glargine Plus Insulin Lispro Compared With NPH Insulin Plus Unmodified Human Insulin in Individuals With Type 1 Diabetes

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OBJECTIVE — The purpose of this study was to compare quality of life (QoL) and treatment satisfaction using insulin glargine plus insulin lispro with that using NPH insulin plus unmodified human insulin in adults with type 1 diabetes managed with multiple injection regimens.

RESEARCH DESIGN AND METHODS — As part of a 32-week, five-center, two-way crossover study in 56 individuals with type 1 diabetes randomized to evening insulin glargine plus mealtime insulin lispro or to NPH insulin (once or twice daily) plus mealtime unmodified human insulin, the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and the Audit of Diabetes Dependent Quality of Life questionnaire were completed at baseline and at weeks 16 and 32, with additional interim DTSQ measurements.

RESULTS — For all patients combined, the mean baseline present QoL score was 1.3, reflecting "good" QoL. Present QoL improved with glargine + lispro but did not change with NPH + human insulin (1.6 ± 0.1 [mean ± SEM] vs. 1.3 ± 0.1, difference 0.3 [95% CI 0.1–0.6]; $P = 0.014$). Baseline mean average weighted impact score (AWI) of diabetes on QoL was −1.8, indicating a negative impact of diabetes on QoL. The AWI score at end point improved significantly with glargine + lispro but changed little with NPH + human insulin (−1.4 ± 0.1 vs. −1.7 ± 0.1, 0.3 [0.0–0.6]; $P = 0.033$). Treatment satisfaction (DTSQ 36-0 scale score) at end point was markedly greater with glargine plus lispro compared with that for NPH plus human insulin (32.2 ± 3.4 vs. 23.9 ± 7.2, 8.6 [6.5–10.6]; $P < 0.001$).

CONCLUSIONS — Insulin glargine plus insulin lispro improves treatment satisfaction, reduces the negative impact of diabetes on QoL, and improves QoL in comparison with NPH insulin plus unmodified human insulin in type 1 diabetes.

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A list of participating investigators in this study can be found in the APPENDIX.

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Abbreviations: ADDQoL, Audit of Diabetes Dependent Quality of Life; AWI, average weighted impact; DAFNE, Dose Adjustment For Normal Eating; DTSQ, Diabetes Treatment Satisfaction Questionnaire; DTSQc, DTSQ change version; DTSQs, DTSQ status version; ITT, intention-to-treat; QoL, quality of life.

The primary aim for most physicians advising patients on the management of type 1 diabetes is to help the individual to achieve good blood glucose control without excessive hypoglycemia. One of the management strategies that can be used to achieve this aim is the use of analog insulin preparations in a multiple daily injection regimen. However, many physicians are concerned that the increased number of injections might have a negative impact on individual quality of life (QoL) (1), although others have anticipated the QoL benefits that may follow from a regimen that allows flexible eating and insulin dosing (23). The maintenance, or indeed improvement, in psychological outcomes such as QoL and treatment satisfaction should thus be an additional but related goal in the management of patients with type 1 diabetes (4). Rapid- and extended-acting insulin analogs have been shown to improve blood glucose control in individuals with type 1 diabetes (5–10). However, it cannot be assumed that these therapies concurrently improve psychological outcomes. The evaluation of QoL and, more specifically, treatment satisfaction is thus an important part of the assessment of new insulin preparations.

The combination of insulin glargine with a rapid-acting insulin analog such as insulin lispro provides a more physiological replacement of mealtime and basal insulin compared with previous insulin regimens. It was previously shown, in the same study participants as those involved in the present report, that insulin glargine in combination with insulin lispro improves overall glycemic control, as assessed by A1C and 24-h plasma glucose monitoring, to a clinically significant degree, together with a reduction in nocturnal hypoglycemia (8). Although psychological outcomes have been evaluated in studies comparing insulin glargine with NPH insulin (4) and rapid-acting insulin analogs with unmodified human

Table 1—*Characteristics of the modified, randomized, and treated ITT sample with type 1 diabetes*

	Glargine + lispro in first treatment period	NPH + human in first treatment period
n	22	26
Sex (male/female)	7/15	11/15
Age (years)	41.7 ± 13.9	42.2 ± 9.1
BMI (kg/m^2)	26.3 ± 2.8	25.8 ± 3.0
Weight (kg)	72.9 ± 11.1	73.5 ± 9.6
Duration of diabetes (years)	22.3 ± 15.5	21.5 ± 10.7
A1C	8.1 ± 0.8	8.0 ± 0.8
Prestudy insulin therapy		
Basal insulin		
Once-daily NPH insulin	12 (55)	17 (65)
Twice-daily NPH insulin	5 (23)	6 (23)
Insulin zinc suspension	3 (14)	2 (8)
Unknown/other	2 (9)	1 (4)
Meal-time insulin		
Unmodified human insulin	14 (64)	16 (62)
Rapid-acting insulin analog	8 (36)	9 (35)
Unknown	0	1 (4)
ADDQoL scores		
Present Qol	1.4 ± 0.8	1.2 ± 1.3
Diabetes-specific QoL	−1.7 ± 1.1	−1.8 ± 1.0
Average weighted impact of diabetes on QoL	−0.7 ± 0.5	−0.9 ± 0.5
DTSQ scores		
Treatment satisfaction	29.4 ± 5.0	28.2 ± 6.3
Perceived frequency of hyperglycemia	3.9 ± 1.0	3.6 ± 1.4
Perceived frequency of hypoglycemia	2.9 ± 1.5	2.3 ± 1.2

Data are means ± SD or *n* (%). All randomized participants who received at least one dose of the study medication and had at least one postbaseline efficacy measurement of treatment satisfaction or QoL in each treatment period are included. There were no statistically significant differences between groups.

insulin (11–14), there are no comprehensive reports of psychological outcomes comparing a combined rapid-acting and long-acting analog regimen with NPH insulin plus unmodified human insulin.

Here we report treatment satisfaction, overall QoL, and the impact of diabetes on QoL in a randomized clinical trial comparing once-daily insulin glargine + insulin lispro with once- or twice-daily NPH insulin + unmodified human insulin in adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS

— A 32-week, open, randomized, two-way cross-over clinical trial in individuals with type 1 diabetes was conducted in five U.K. sites. The study was approved by local ethics committees, and written informed consent was obtained from all participants before the study began. The study design and metabolic outcome measures have been reported in detail previously (8). Here we present the psychological outcome measures recorded during the study.

Seventy-one individuals were recruited (by examination of their medical records with regard to inclusion criteria followed by invitation to enter the study). Two withdrew before random assignment, and 13 did not fulfill study inclusion criteria. Fifty-six individuals were randomized. Two individuals withdrew after random assignment but before receiving the study treatment(one in each group). Neither knew the treatment they had been randomized to receive; 54 individuals were thus randomized and treated. Three individuals withdrew during the study (two randomized to glargine plus lispro, and one to NPH plus unmodified human insulin, all during the first treatment period), and 51 completed the study. One individual withdrew because of an adverse event, one felt unable to continue with the demands of the study protocol, and one was unable to complete the 24-h in-patient studies.

A modified intention-to-treat (ITT) sample was used for all psychological analyses, consisting of all randomized participants who received at least one dose of the study medication and had at least one postbaseline efficacy measurement of treatment satisfaction or QoL in each treatment period. This sample consisted of 48 individuals, 22 randomized to insulin glargine plus insulin lispro for the first treatment period and 26 to NPH insulin plus unmodified human insulin (Table 1). Insufficient questionnaire data were collected for the remaining 3 participants to allow inclusion. There were no clinically significant differences between the recorded characteristics of the modified ITT sample for the QoL analysis and those of the main efficacy study sample. The modified ITT sample for the QoL analysis consisted of 18 men and 30 women, aged 18–65 years with type 1 diabetes and no previous experience of insulin glargine, who had been using a multiple insulin injection regimen for at least 1 year (mean ± SD 10.5 ± 8.4 years) before randomization. Participants had a random C-peptide level of ≤ 0.10 nmol/l and A1C of 7.0–9.5% (nondiabetic <5.9%). Two of the study centers and thus some of the participants recruited at these sites had previously taken part in the Dose Adjustment For Normal Eating (DAFNE) study and had thus been trained in insulin dose adjustment to allow considerable dietary freedom. It has been shown that DAFNE training resulted in significant improvements in treatment satisfaction using the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and both present QoL and the impact of diabetes on QoL measured by the Audit of Diabetes Dependent Quality of Life (ADDQoL) (15). There were no statistically significant differences in baseline characteristics between the two randomized groups.

After a 4-week screening period during which previous insulin therapy was continued, individuals were randomized to bedtime insulin glargine (Lantus; sanofi-aventis, Paris, France) in combination with premeal insulin lispro (Humalog; Eli Lilly, Indianapolis, IN) (glargine + lispro) or to NPH insulin (HOE 36HPR; sanofi-aventis) in combination with premeal unmodified human insulin (HOE 31HPR; sanofi-aventis) (NPH + human). Randomizing was by telephone using a central computer randomization program.

The first 4 weeks of the 16-week treatment period consisted of a dose titration period during which study visits occurred weekly. In the subsequent 12

weeks, visits were fortnightly or more frequently if necessary. At each consultation self-monitored blood glucose levels and insulin doses were reviewed, and insulin doses were titrated according to a target-driven algorithm that was identical for all study sites and both insulin regimens. Target blood glucose levels were identical for each regimen: preprandial and postprandial targets were 4.0–6.5 mmol/l in the absence of hypoglycemia. The blood glucose target for 0300 h was ≥5.0 mmol/l.

Insulin glargine was initially given at bedtime but could be injected earlier in the evening if blood glucose levels were frequently high or rising at bedtime or 0300 h. All individuals randomized to the human insulin regimen received NPH insulin once daily at bedtime or twice daily at bedtime and breakfast, the frequency of injection being determined by the individual's prior dosing frequency. Insulin lispro was recommended to be given immediately before meals, whereas participants were recommended to inject unmodified human insulin 30 min before eating. The OptiPen Pro-1 injection device (sanofi-aventis) was used to give all insulin injections except insulin lispro (HumaPen Ergo; Eli Lilly).

At the end of the 16-week treatment period, participants were admitted for a 24-h in-patient plasma glucose assessment. At the end of the first 24-h study, participants began the alternative insulin regimen, and the study sequence was repeated.

Questionnaires

The DTSQ andADDQoL questionnaire are self-administered instruments that have demonstrated validity and reliability in diabetes patient populations (4,14,16–19).

Treatment satisfaction was assessed using the DTSQ (18,19). This is an eight-item questionnaire in which each item is scored on a 7-point scale. The treatment satisfaction score is the sum of six of the items of the DTSQ for each respondent. The additional two items measure perceived frequency of hyperglycemia and hypoglycemia and are considered separately.

The DTSQ status version (DTSQs) assesses treatment satisfaction over the few weeks before its completion. Each item is scored from 6 to 0 with a higher score indicating greater satisfaction. The treatment satisfaction score can thus range from 36 (very satisfied) to 0 (very dissatisfied). The two additional items measuring perceived frequency of hypo- and hyperglycemia are scored from 0 (none of the time) to 6 (most of the time). The DTSQs can be limited by a ceiling effect when treatment satisfaction is high at baseline (20). The DTSQ change version (DTSQc) uses the same eight-item stems as the DTSQs but has different response options and asks respondents to assess changes in treatment satisfaction with their current treatment compared with their previous treatment and thus overcomes any ceiling effect that may occur with the DTSQs (14). Each of the six items of the DTSQc is scored from +3 (e.g., much more satisfied now) to −3 (e.g., much less satisfied now). The DTSQc treatment satisfaction change score can thus range from +18 to −18. The items measuring perceived frequency of hypo- and hyperglycemia were scored from −3 (much less of the time now) to +3 (much more of the time now) such that a higher score indicates more hyper- or hypoglycemia.

The DTSQs was completed at baseline and at weeks 8 and 16 of each 16-week treatment period. The DTSQc was completed once at the end of the study.

The impact of diabetes on QoL was assessed using the ADDQoL questionnaire. Eighteen of the 20 items of the ADDQoL concern specific life domains such as social life and working life and are scored on a 7-point impact scale, accompanied by a related importance rating scale for each domain used to assess the importance of each aspect of life for the individual's QoL. The impact of diabetes on each of these life domains is then weighted by the domain's importance for the respondent's QoL and the resulting weighted impact scores are averaged across all applicable domains to provide an average weighted impact (AWI) score. Weighted impact scores for single domains and the AWI score can range from +9 (maximum positive impact of diabetes) to −9 (maximum negative impact of diabetes). The two remaining overview items are scored separately and include a single diabetes-specific QoL item measuring the impact of diabetes on QoL that is scored from +3 (maximum positive impact of diabetes) to −3 (maximum negative impact of diabetes) and a single item, present QoL, that is scored from +3 (excellent) to −3 (extremely bad) to measure overall QoL. The ADDQoL was completed at baseline and at the end point of each treatment period (weeks 16 and 32).

To achieve a high response rate, participants were asked to complete the questionnaires during trial visits and to return them to the investigators in a sealed envelope. The completed questionnaires were not inspected by the investigators but were analyzed by a statistician blinded to the randomized group.

Statistical analysis

Sample size was calculated using A1C, the primary end point of the main study (8). Participant-reported outcomes from the ADDQoL and DTSQ were analyzed by an ANOVA model including period and sequence effects. All statistical tests were performed at a two-sided significance level of $\alpha = 5\%$. Data provided are means ± SEM and mean difference (95% CI) unless otherwise stated. Analysis was performed using SAS software (SAS Institute, Cary, NC). The model included fixed effects for treatment, sequence, and period, as well as a random effect to account for subjects within sequence.

RESULTS

ADDQoL

The mean ± SD present QoL score for the whole study sample at baseline was 1.3 ± 1.1, reflecting "good" rather than "very good" or "excellent" QoL. The AWI score ± SD at baseline was −1.8 ± 1.2, indicating an overall negative impact of diabetes on QoL.

The present QoL score increased by 0.3 points during treatment with glargine + lispro but did not change with NPH + human (end point scores 1.6 ± 0.1 [mean ± SEM) vs. 1.3 ± 0.1, difference 0.3 [95% CI 0.1–0.6]; $P = 0.014$) (Fig. 1*A*). Diabetes-specific QoL at end point did not differ between treatment groups (−1.4 ± 0.1 vs. −1.5 ± 0.1, 0.2 [−0.1 to 0.5], NS).

The AWI score improved by 0.4 points with glargine + lispro but changed little with NPH + human (end point scores −1.4 ± 0.1 vs. −1.7 ± 0.1, difference 0.3 [95% CI 0.0–0.6]; $P = 0.033$). The AWI score followed a pattern during the study similar to that of present QoL (Fig. 1*A*). The negative impact of diabetes on QoL in the following domains was improved with glargine + lispro compared with NPH + human: social life (−0.8 ± 0.2 vs. −1.8 ± 0.2, 1.0 [0.3–1.7]; $P = 0.007$), sex life (−0.8 ± 0.2 vs. −1.5 ± 0.2, 0.6 [0.1–1.2]; $P = 0.023$), society's reaction (−0.7 ± 0.1 vs. −1.1 ± 0.1, 0.4 [0.0–0.7]; $P = 0.048$), and enjoyment of

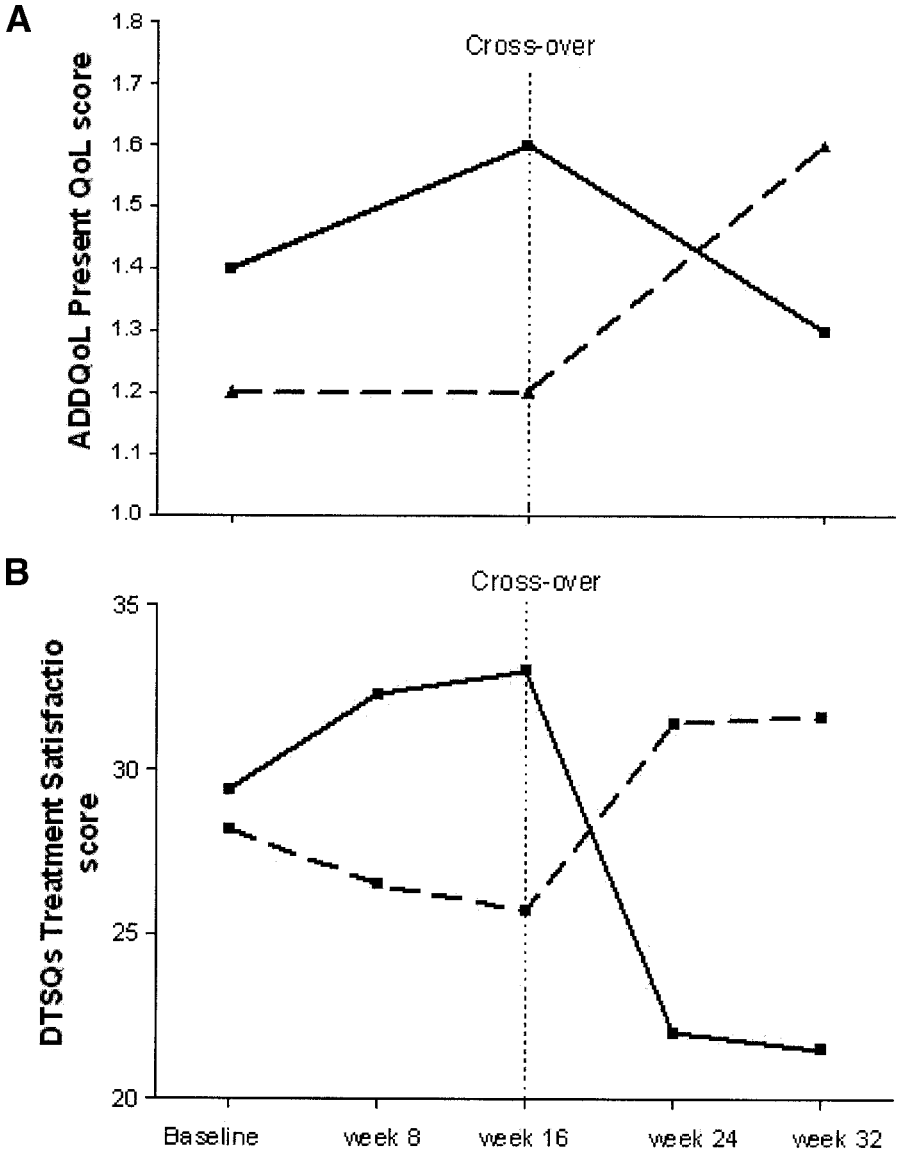

Figure 1—*ADDQoL present QoL score* (A) *and DTSQs treatment satisfaction score* (B) *in those who used glargine + lispro (——) and in those who used NPH + human (– – –) in period one of the study, switching to the alternative insulin regimen in period 2.*

food [−1.6 ± 0.1 vs. −2.1 ± 0.1, 0.5 [0.1– 0.9]; $P = 0.014$).

DTSQ

Treatment satisfaction at baseline was high in this population, with a mean DTSQ treatment satisfaction score of 28.8 ± 5.7. Nineteen individuals (39.6%) had a baseline DTSQ summary score between 31 and the maximum of 36.

Treatment satisfaction increased by 3.2 points with glargine + lispro, but decreased by 4.9 points with NPH + human: 32.3 ± 0.7 vs. 23.7 ± 0.7 (8.6 [6.5–10.6]; $P < 0.001$). The treatment satisfaction score showed a progressive increase from baseline to end point during treatment with glargine + lispro. Conversely, with NPH + human, there was a progressive decrease in treatment satisfaction through the course of the treatment period (Fig. 1*B*).

Significant differences favoring glargine + lispro were found for five of the six items of the treatment satisfaction scale: current satisfaction with treatment (5.4 ± 0.2 vs. 3.8 ± 0.2; $P < 0.001$), convenience of treatment (5.3 ± 0.1 vs. 4.1 ± 0.1; $P < 0.001$), flexibility of treatment (5.2 ± 0.1 vs. 3.9 ± 0.2; $P < 0.001$), recommend to others (5.5 ± 0.2 vs. 3.7 ± 0.2; $P < 0.001$), and satisfaction to continue current treatment (5.7 ± 0.2 vs. 3.2 ± 0.2; $P < 0.001$).

Results from the DTSQc were similar to those obtained with the DTSQs: predominantly negative scores for items 1 and 4–8 with NPH + human indicated worsened treatment satisfaction compared with previous treatment with glargine + lispro (Table 2 of the online appendix available at http://dx.doi.org/10.2337/dc07-1183).

Perceptions of blood glucose control

Perceived frequency of hyperglycemia at end point (DTSQs) was lower with glargine + lispro compared with NPH + human (2.7 ± 0.2 vs. 4.0 ± 0.2; $P < 0.001$). The DTSQc showed a decrease in perceived frequency of hyperglycemia with insulin glargine + lispro and an increase with NPH + human at end point when respondents compared their experience of treatment in period 2 with that in period 1 (−0.8 ± 0.5 vs. 0.5 ± 0.5; $P = 0.043$) (Table 2 of the online appendix).

Perceived frequency of hypoglycemia at end point (DTSQs and DTSQc) did not differ between glargine + lispro and NPH + human (Table 2 of the online appendix).

CONCLUSIONS

— In this study we compared treatment satisfaction and QoL in individuals with type 1 diabetes randomized to insulin glargine plus insulin lispro or to NPH insulin plus unmodified human insulin, using a 32-week, open, multicenter, two-way crossover design. Together with observed improvements in blood glucose control with insulin glargine plus insulin lispro (8), QoL and treatment satisfaction also improved compared with NPH insulin plus unmodified human insulin. Present QoL increased with the analog compared with the human insulin regimen, and the negative impact of diabetes on QoL, particularly on social life, sex life, society's reaction, and enjoyment of food, was reduced. Treatment satisfaction improved progressively through the study with insulin glargine plus insulin lispro, with notable improvements in flexibility and convenience.

Participants using glargine plus lispro reported a significantly reduced perception of the frequency of hyperglycemia, but there was no difference between treatment groups in perceived frequency of hypoglycemia on the DTSQs. However, self-monitored and in-patient–assessed hyperglycemia as well as symptomatic nocturnal hypoglycemia were reduced

with the analog compared with the human insulin regimen (8). Episodes of all recalled/diary-monitored symptomatic hypoglycemia did not differ between treatment groups. The DTSQ does not assess severity of hypoglycemia. It is thus possible that, when completing the DTSQ, respondents would be influenced more by frequent minor symptoms of daytime hypoglycemia than by less frequent but more troublesome instances of more severe (e.g., nocturnal) hypoglycemia to the extent that participants did not indicate any difference in overall hypoglycemia between treatments.

The study was not blinded because of differences in the appearance of the basal insulin preparations. It is thus possible that some of the observed improvements in treatment satisfaction and QoL might have simply reflected participant expectations of a new insulin regimen. Although this possibility cannot be entirely discounted, the improvements in treatment satisfaction with insulin glargine plus insulin lispro increased progressively throughout the study. This result indicates that any expectations of the perceived benefits of the analog insulin regimen held by participants are likely to have been met and that such benefits were not transient but maintained and indeed improved further through the course of the study. Although it would have been technically possible, although difficult, to blind the study, it was felt that this would not have been acceptable to participants. In addition, blinded study designs have major limitations in studying psychological outcomes relating to insulin therapy. For example, convenience and flexibility were improved with the analog insulin regimen, reflecting differences between analog and human insulin regimens in the frequency of insulin injections and their timing in relation to meals. A blinded design would have been unable to detect such differences in treatment satisfaction between regimens as such a design would require the necessity for placebo injections, which create an artificial experience of treatment that is more demanding than either treatment in clinical reality.

Three of the 51 patients randomized to the main study did not complete any QoL or treatment satisfaction questionnaires. Although there were no clinically significant differences between the recorded characteristics of this sample of 48 used for the QoL and treatment satisfaction analysis and the sample of 51 used for the main efficacy study sample, subtle differences cannot be excluded. As in all such studies, ascertainment bias as a result of the recruitment of patients motivated to enter this clinical trial also cannot be excluded.

Rapid-acting insulin analogs have been shown to improve treatment satisfaction compared with unmodified human insulin in individuals with type 1 diabetes, with reported between-group differences in the DTSQs treatment satisfaction score of 1.6–2.3 (11–14). Similar studies have reported improvements in the DTSQs treatment satisfaction score with insulin glargine compared with NPH insulin of 0.9–1.8 (4,21). In the current study, however, the between-group difference in the DTSQs treatment satisfaction score was much greater, at 8.6. The between-group differences in each of the items of the DTSQs in the current study were also much greater than those reported in previous studies comparing insulin glargine with NPH insulin or rapid-acting insulin analogs with unmodified human insulin (4,13,22). This result suggests that the combination of insulin glargine and a rapid-acting insulin analog might have a synergistic benefit on treatment satisfaction. However, the use of carbohydrate-counting skills and prandial insulin dose adjustment by some of the participants of the present study might have contributed to these improved QoL results.

The DAFNE study provided individuals with type 1 diabetes with an educational package, at the heart of which was the acquisition of skills to count carbohydrate and adjust rapid-acting insulin doses accordingly, thus allowing dietary flexibility (15). The improvements in measures of QoL in individuals who undertook this course compared with the control group who were yet to do so are similar to those recorded in the present study comparing analog and human insulin regimens: DTSQs treatment satisfaction score improved by 8.8 and perceived frequency of hyperglycemia by 1.1 in the DAFNE study. The AWI score improved by 0.4 and present QoL by 0.3. The only difference between DAFNE and the present study is the improvement in the item "freedom to eat as I wish" that was much greater in DAFNE. Two of the five centers involved in the present study (that together contributed 39% of the total study sample) had previously taken part in the DAFNE study. Some of the investigators and participants enrolled in the present study at these sites had thus undergone DAFNE training. Although carbohydrate-counting and rapid-acting dose adjustment skills were not an inclusion criterion of the present study and were not taught during the study, a high proportion of participants recruited from these two study sites would be likely to have previously acquired these skills. Some of the improved QoL and treatment satisfaction benefits observed in the present study (which were markedly greater that those seen in previous studies comparing insulin glargine with NPH insulin or rapid-acting insulin analogs with unmodified human insulin) might thus relate to the combined benefits of an insulin analog regimen and dietary freedom in the participants who were DAFNE trained. A post hoc analysis comparing QoL and treatment satisfaction in DAFNE compared with non-DAFNE centers is problematic owing to the small number of centers (two versus three), but ADDQoL AWI score, freedom to eat, and present QoL did not differ between sites (data not shown).

It may be noted that individuals in the present study tended to show worsened satisfaction with the conventional insulin regimen during the study. This is most marked after exposure to the combined analog regimen (Fig. 1*B*) and reflects the commonly observed disappointment with the previously satisfactory control treatment after experiencing a treatment that participants preferred (23).

In summary, insulin glargine in combination with a rapid-acting insulin analog improves both biomedical and psychosocial outcomes compared with NPH insulin plus unmodified human insulin. These data reinforce the suggestion that the use of combined insulin analog therapy should be considered as an option for all individuals with type 1 diabetes.

APPENDIX

Participating investigators in this study were Professor Philip Home, Professor Stephanie Amiel, Professor Rudy Bilous, Dr. Simon Heller, and Dr. David Hepburn.

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References

1. Speight J, Bradley C: DAFNE: improved quality of life as a result of intensified treatment is counter-intuitive to many clinicians [article online], 2002. Available from http://bmj.com/cgi/eletters/325/7367/746#26769. Accessed 15 April 2008
2. Bradley C, Pierce MB, Hendrieckx C, Riazi A, Barendse S: Diabetes mellitus. In *Health Psychology*. Johnston M, Johnston DW, Eds. [Vol. 8 in *Comprehensive Clinical Psychology*. Bellack AS, Hersen M, Eds.] Oxford, U.K., Elsevier Science, 1998, p. 277–304
3. Howorka K: Preface. In *Functional Insulin Treatment,* 2nd ed. Berlin, Springer Verlag; Authors preface. 1996
4. Witthaus E, Stewart J, Bradley C: Treatment satisfaction and psychological well-being with insulin glargine compared with NPH in patients with type 1 diabetes. *Diabet Med* 18:619–626, 2001
5. Ahmed A, Home P: Optimal provision of daytime NPH insulin in patients using the insulin analog lispro. *Diabetes Care* 21: 1707–1713, 1998
6. Ciofetta M, Lalli C, Del Sindaco P, Torlone E, Pampanelli S, Mauro L, Chiara DL, Brunetti P, Bolli GB: Contribution of postprandial versus interprandial blood glucose to HbA_{1c} in type 1 diabetes on physiologic intensive therapy with lispro insulin at mealtime. *Diabetes Care* 22: 795–800, 1999
7. Lalli C, Ciofetta M, Del Sindaco P, Torlone E, Pampanelli S, Compagnucci P, Bartocci L, Brunetti P, Bolli GB: Long-term intensive treatment of type 1 diabetes with the short-acting insulin analog lispro in variable combination with NPH insulin at mealtime. *Diabetes Care* 22:568–477, 1999
8. Ashwell SG, Amiel SA, Bilous RW, Dashora U, Heller SR, Hepburn DA, Shutler SD, Stephens JW, Home PD: Improved glycaemic control with insulin glargine plus insulin lispro. *Diabet Med* 23:285–292, 2006
9. Porcellati F, Rossetti P, Pampanelli S, Fanelli CG, Torlone E, Scionti L, Perriello G, Bolli GB: Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with type 1 diabetes mellitus given meal-time lispro insulin. *Diabet Med* 21:1213–1220, 2004
10. Rossetti P, Pampanelli S, Fanelli C, Porcellati F, Costa E, Torlone E, Scionti L, Bolli GB: Intensive replacement of basal insulin in patients with type 1 diabetes given rapid-acting insulin analog at mealtime. *Diabetes Care* 26:1490–1496, 2003
11. Home PD, Lindholm A, Riis A: Insulin aspart vs. human insulin in the management of long-term blood glucose control in type 1 diabetes mellitus: a randomized controlled trial. *Diabet Med* 17:762–770, 2000
12. DeVries JH, Lindholm A, Jacobsen JL, Heine RJ, Home PD: A randomized trial of insulin aspart with intensified basal NPH insulin supplementation in people with type 1. *Diabet Med* 20:312–318, 2003
13. Bott U, Ebrahim S, Hirschberger S, Skovlund SE: Effect of the rapid-acting insulin analogue insulin aspart on quality of life and treatment satisfaction in patients with type 1 diabetes. *Diabet Med* 20:626–634, 2003
14. Howorka K, Pumprla J, Schlusche C, Wagner-Nosiska D, Schabmann A, Bradley C: Dealing with ceiling baseline treatment satisfaction level in patients with diabetes under flexible, functional insulin treatment: assessment of improvements in treatment satisfaction with a new insulin analogue. *Qual Life Res* 9:915–930, 2000
15. DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomized controlled trial. *BMJ* 325:746, 2002
16. Bradley C, Todd C, Gorton T, Symonds E, Martin A, Plowright R: The development of an individualized questionnaire measure of perceived impact of diabetes on quality of life: the ADDQoL. *Qual Life Res* 8:79–91, 1999
17. Bradley C, Speight J: Patient perceptions of diabetes and diabetes therapy. *Diabetes Metab Res Rev* 18 (Suppl. 3):S64–S69, 2002
18. Bradley C, Lewis K: Measures of psychological well-being and treatment satisfaction developed from the responses of people with tablet-treated diabetes. *Diabet Med* 7:445–451, 1990
19. Bradley C: The Diabetes Treatment Satisfaction Questionnaire. In *Handbook of Psychology and Diabetes: A Guide to Psychological Measurement in Diabetes Research and Practice*. Bradley C, Ed. Chur, Switzerland, Harwood Academic Publishers, 1994, p. 111–132
20. Bradley C: Diabetes treatment satisfaction questionnaire: change version for use alongside status version provides appropriate solution where ceiling effects occur. *Diabetes Care* 22:530–532, 1999
21. Bradley C, Witthaus E, Stewart J: Treatment satisfaction and psychological well-being in patients with type 1 diabetes treated with a new long-acting insulin glargine. *Diabetes* 48:A353, 1998
22. Tamas G, Marre M, Astorga R, Dedov I, Jacobsen J, Lindholm A: Glycaemic control in type 1 diabetic patients using optimised insulin aspart or human insulin. *Diabetes Res Clin Pract* 54:105–114, 2001
23. Bradley C: Psychological issues in clinical trial design. *Ir J Psychol* 18:67–87, 1997