Improved Treatment Satisfaction and Quality of Life with Insulin Glargine + Lispro compared with NPH Insulin + Regular Human Insulin in Patients with Type 1 Diabetes

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Abstract

Diabetes has a significant negative impact on the quality of life (QoL) of patients. This was a multicenter, open-label, randomized crossover clinical trial comparing insulin glargine (LANTUS®) + insulin lispro (Humalog®), with NPH insulin + regular human insulin, in patients with type 1 diabetes. Objectives were to compare once-daily insulin glargine + lispro (glargine + lispro) with once- or twice-daily NPH + regular insulin (NPH + regular) in terms of treatment satisfaction (using the Diabetes Treatment Satisfaction Questionnaire [DTSQ], 6 items of which provide a Treatment Satisfaction score, ranging from 0 (very dissatisfied] to 36 (very satisfied]) and measures of present QoL and perceived impact of diabetes on QoL (average weighted impact [AWI] scores) from the Audit of Diabetes Dependent QoL. Lispro or regular insulin was given before meals. Patients (n=48; 62.5% female; mean age 42 ± 11.4 years) were randomized to receive either Treatment Sequence A (glargine + lispro [treatment period 1] followed by NPH + regular [treatment period 2]; n=22) or Treatment Sequence B (NPH + regular [treatment period 1] followed by glargine + lispro [treatment period 2]; n=26) for a total of 32 wks (16 wks per treatment period). Patient-reported outcomes were assessed initially and after each treatment period. Statistical tests used were analysis of variance, with a model including terms for treatment, period, sequence and subjects within sequence. Treatment satisfaction increased during treatment with glargine + lispro, regardless of which period it was administered in (Graph). For the total treatment period, Treatment Satisfaction scores were significantly higher with glargine + lispro compared with NPH + regular (mean: 32.2 ± 3.4 vs 23.9 ± 7.2; p<0.0001). Present QoL was also significantly better with glargine + lispro compared with NPH + regular (mean:1.6 vs 1.3; p=0.014), and patients reported significantly less negative impact of diabetes on QoL following glargine + lispro compared with NPH + regular treatment (mean AWI: −1.34 vs −1.64; p=0.033). In conclusion, this study shows that insulin glargine + lispro improves QoL and treatment satisfaction.

Introduction

- The maintenance and improvement of quality of life (QoL) is a goal of diabetes care with similar importance to blood glucose control
- The Diabetes Treatment Satisfaction Questionnaire (DTSQ) is recommended by the World Health Organization (WHO) and International Diabetes Federation (IDF) to measure satisfaction with treatment and perceptions of blood glucose control in patients with diabetes[1]
- The status version of the DTSQ (DTSQs) measures current treatment satisfaction and perceived frequency of hyper – and hypoglycemia[2,3]
- Relative change in satisfaction with treatment is assessed with a change version of the DTSQ (DTSQc)[4], which is more sensitive to changes in satisfaction than the DTSQs alone[2,5]
- The Audit of Diabetes-dependent Quality of Life (ADDQoL) is a questionnaire that measures the perceived impact of diabetes on QoL, both generally, and in individual life domains, such as social life and working life[7,8]
- A 32-week multicenter, open, randomized, 2-way cross-over clinical trial, comparing the effects of insulin glargine + insulin lispro (lispro) versus NPH insulin (NPH) + regular human insulin (regular) on psychological outcomes, has been conducted in patients with type 1 diabetes on a mealtime (31% on lispro or another fast-acting insulin analog prior to randomization) + basal insulin regimen (mostly NPH insulin; none using insuline glargine prior to randomization)
- The study also compared glycemic control between the two treatment groups and found that insulin glargine + lispro both improved overall glycemic control and reduced nocturnal hypoglycemia to a clinically significant degree compared with NPH + regular[9]

Study Objectives

- To show improvements in treatment satisfaction using the DTSQs and c in patients treated with insulin glargine + lispro versus NPH + regular
- To show, using the ADDQoL, that the perceived negative impact of diabetes on QoL is reduced with insulin glargine + lispro versus NPH + regular

Study Design and Methods

Study design

- Multicenter (5 UK centres), open-label, randomized, controlled, 2-way, cross-over study including a 4-week screening phase and two 16-week treatment periods during which patients received one of the following treatment regimens:
  - Insulin glargine given once daily in the evening and lispro injected shortly (0–5 minutes) before meals
  - NPH given either once daily at bedtime or twice daily in the morning and at bedtime and regular given within 30 minutes prior to meals
- Patients were randomized (1:1) to one of the following treatment sequences:
  - Insulin glargine + lispro in treatment period 1 and NPH + regular in treatment period 2
  - NPH + regular in treatment period 1 and insulin glargine + lispro in treatment period 2
- Insulin glargine, NPH and mealtime insulins were titrated to achieve blood glucose levels near to or within the normal range
- The clinical outcomes have been reported elsewhere[9]

Patients

- Men and women with type 1 diabetes
- Aged 18–65 years
- HbA_{1c} 7.0–9.5%
- >1 year on daily intensified multiple insulin injection regimens
- Able to self-monitor blood glucose (SMBG), interpret SMBG results and perform insulin dose adjustments

Psychological outcome measures

- DTSQs
  - 8-item questionnaire that measures current treatment satisfaction (6 items) and 2 separate items: perceived frequency of hyper – and hypoglycemia (Table 1)
  - Patients completed the DTSQs at baseline, weeks 8 and 16 during treatment period 1 and at weeks 24 and 32 during treatment period 2
- DTSQc
  - Uses the same 8 items as the DTSQs (Table 1) but patients are asked to indicate their degree of satisfaction with their current treatment as compared with their prior treatment, thus measuring relative change in satisfaction
  - Patients completed the DTSQc at week 32 only, thereby comparing the treatment used in period 2 with the treatment used in period 1
- ADDQoL
  - Individualised questionaire with:
  - Single overview item measuring present QoL on a scale from 3 (excellent) through 0 (neither good nor bad) to −3 (extremely bad)
  - 18 specific life domains, such as social life and working life[8], where impact of diabetes on specific domains is weighted by importance for QoL and averaged across all applicable domains to provide an average weighted impact (AWI) score ranging from −9 (maximum negative impact) through 0 (no impact) to +9 (maximum positive impact)
  - Patients completed the ADDQoL at baseline and at weeks 16 and 32 (i.e. at the end of each treatment period)

Table 1. Diabetes Treatment Satisfaction Questionnaire contents and format

The Diabetes Treatment Satisfaction Questionnaire status and change versions: DTSQs and DTSQc
A one-page 8-item measure of satisfaction with diabetes treatment, including any medication and diet.

Six items to be summed into a Treatment Satisfaction scale score (0 very dissatisfied to +36 very satisfied) on the DTSQs or summed into the Change in Treatment Satisfaction scale score (−18 much less satisfied now to +18 much more satisfied now) on the DTSQc:

- Current treatment (shown as example below)
- Convenience
- Flexibility
- Understanding of your diabetes
- Recommend to others
- Satisfaction to continue current treatment

Two separate items (2 and 3, see below), to measure Perceived Blood Glucose Control:

- Perceived Frequency of Hyperglycaemia ("Perceived Hypers" 0 to 6 on the DTSQs) or Change in Perceived Hypers (−3 to +3 on the DTSQc)
- Perceived Frequency of Hypoglycaemia ("Perceived Hypos" 0 to 6 on the DTSQs) or Change in Perceived Hypos (−3 to +3 on the DTSQc)

Examples of question format:

1. How satisfied are you with your current treatment?
   very satisfied 6 5 4 3 2 1 0 very dissatisfied (DTSQs)
   much more satisfied now 3 2 1 0 −1 −2 −3 much less satisfied now (DTSQc)

2/3. How often have you felt that your blood sugars have been unacceptably high/low recently?
   most of the time 6 5 4 3 2 1 0 none of the time (DTSQs)
   much more of the time now 3 2 1 0 −1 −2 −3 much less of the time now (DTSQc)

Statistical analysis

- A modified intent-to-treat (ITT) population (all randomized patients who received at least one dose of study medication with at least one post-baseline (efficacy) measurement in both treatment periods) was used for all analyses
- QoL variables from the DTSQs and ADDQoL were analyzed by analysis of variance (ANOVA) using a standard crossover model
- DTSQc scores were analyzed by analysis of covariance (ANCOVA) adjusting for the effect of baseline DTSQs
- All statistical tests were performed at a 2-sided significance level of α=5%

Baseline demographics

Table 2. Patient demographics at baseline (ITT population)

	Total treated (n=48)
Male	18 (37.5%)
Female	30 (62.5%)
Mean age ± SD (years)	42 ± 11.4
Mean age at onset of diabetes ± SD (years)	21 ± 11.2
Mean duration of diabetes ± SD (years)	22 ± 13.0
No. of patients prior to randomization who were using: – NPH insulin – fast-acting insulin analog experience	 40 (83.3%) 15 (31%)

SD=Standard deviation

Results

DTSQs: treatment satisfaction

- The distribution of treatment satisfaction scores at baseline was comparable for both treatment sequence groups (Table 3; Figure 1)
- For patients receiving insulin glargine + lispro in treatment period 1, treatment satisfaction increased by 3.6 points from baseline to cross-over, and then decreased by 11.5 points in treatment period 2 (Table 3)
- In patients receiving NPH + regular in treatment period 1, treatment satisfaction decreased by 2.5 points from baseline to cross-over and then increased by 5.9 points with insulin glargine + lispro treatment during period 2 (Table 3)
- For the total treatment period, treatment satisfaction was significantly higher with insulin glargine + lispro (32.2 ± 3.4) than with NPH + regular (23.9 ± 7.2), regardless of the treatment period in which it was administered (p <0.0001; Figure 1)

Figure 1. Change in DTSQs treatment satisfaction score following insulin glargine + lispro or NPH + regular

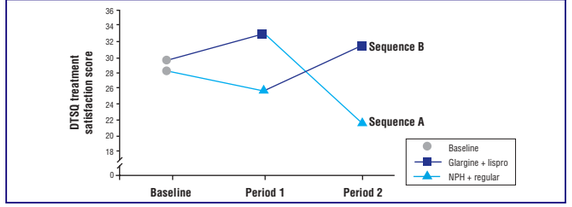


Table 3. DTSQs treatment satisfaction scores after 16 weeks' treatment with each regimen

DTSQs score (mean ± SD)	Sequence A: insulin glargine + lispro/NPH + regular	Sequence B: NPH + regular/ insulin glargine + lispro
Baseline	29.4 ± 4.98 (n=22)	28.2 ± 6.32 (n=26)
End of treatment period 1	33.0 ± 3.06 (n=22)	25.7 ± 6.50 (n=26)
End of treatment period 2	21.5 ± 7.51 (n=21)	31.6 ± 3.62 (n=26)

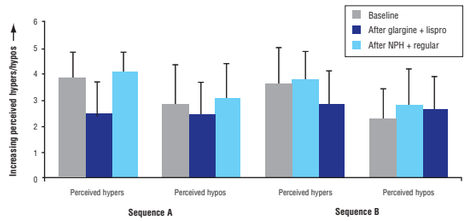
DTSQs: perceived frequency of hyperglycemia

- Perceived frequency of hyperglycemia was measured with item 2 of the DTSQs (Table 1)
- The mean perceived frequency of hyperglycemia for all patients was 3.7 at baseline, reflecting a high frequency of hyperglycemia (Figure 2)
- For the total treatment period, perceived frequency of hyperglycemia was significantly lower after treatment with insulin glargine + lispro than after NPH + regular (p <0.0001; 95% confidence interval [CI] −1.80; −0.92; Figure 2)

DTSQs: perceived frequency of hypoglycemia

- Perceived frequency of hypoglycemia was measured with item 3 of the DTSQs (Table 1)
- The mean perceived frequency of hypoglycemia for all patients at baseline was 2.6, reflecting a moderately high frequency of hypoglycemia (Figure 2)
- Between-treatment comparison showed a trend for perceived frequency of hypoglycemia to be lower with insulin glargine + lispro than with NPH + regular, but this did not reach significance (p=0.078; Figure 2)

Figure 2. DTSQs perceived frequency of hyperglycemia and hypoglycemia after 16 weeks treatment with each regimen



Sequence A: insulin glargine + lispro (period 1), NPH + regular (period 2)
Sequence B: NPH + regular (period 1), insulin glargine + lispro (period 2)
Data shown are mean ± standard deviation

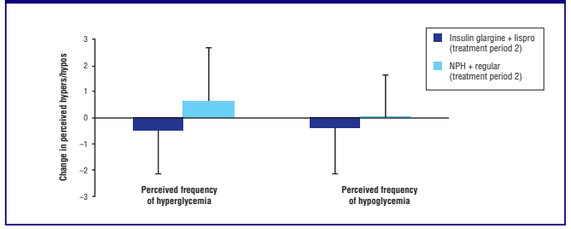
DTSQc: treatment satisfaction

- Patients completed the DTSQc at week 32 (after the end of treatment period 2) to provide a comparison of their experience of their current treatment with their experience of treatment during period 1
- Mean change in treatment satisfaction measured at the end of treatment period 2 was:
  - 13.8 ± 3.68 when using insulin glargine + lispro in treatment period 2, indicating a large increase in treatment satisfaction
  - 0.1 ± 8.73 when using NPH + regular in treatment period 2, indicating, on average, no change in treatment satisfaction
- The improvement in treatment satisfaction following insulin glargine + lispro during treatment period 2 was significantly greater than that following NPH + regular (p <0.0001; CI 9.39; 18.32)

DTSQc: perceived frequency of hyper- and hypoglycemia

- In order to assess change in perceived frequency of hyper- and hypoglycemia, patients provided scores between +3 ("much more of the time now") to −3 ("much less of the time now") on the DTSQc (See Table 1)
- Perceived frequency of hyperglycemia decreased during treatment with insulin glargine + lispro (−0.5 ± 1.63) in treatment period 2 and increased during treatment with NPH + regular (0.6 ± 2.03) in treatment period 2 (Figure 3). The difference in perceived frequency of hyperglycemia between the two treatments was significant (p=0.043; CI −2.54; −0.04; Figure 3)
- Perceived frequency of hypoglycemia decreased after treatment with insulin glargine + lispro (−0.4 ± 1.69) in treatment period 2 and did not change after treatment with NPH + regular (0.0 ± 1.62; Figure 3). The difference between treatment regimens was not statistically significant

Figure 3. Change in perceived frequency of hyper- and hypoglycemia between treatment periods 1 and 2 (minus scores show decreased perceived hyper/hypoglycemia)



ADDQoL: present QoL and average weighted impact of diabetes on QoL

- For all patients combined, the mean present QoL baseline score was 1.3, reflecting good present QoL
- After the total treatment period, present QoL increased by 0.3 after treatment with insulin glargine + lispro and did not change after treatment with NPH + regular. For the total treatment period, present QoL was significantly higher with insulin glargine + lispro versus NPH + regular (p=0.014; Table 5)
- The AWI of diabetes on QoL was significantly improved after treatment with insulin glargine + lispro versus NPH + regular for the total treatment period (p=0.033; Table 5)

Table 5. ADDQoL: present QoL and average weighted impact (AWI) of diabetes on QoL score for the total treatment period

	Insulin glargine + lispro	NPH + regular	p value*
Present QoL	1.6 ± 0.83	1.3 ± 1.01	0.014
Average weight impact of diabetes on QoL	−1.4 ± 0.98	−1.7 ± 1.21	0.033

*Between-group comparison; values presented are mean ± standard deviation

Conclusion

- Insulin glargine + lispro improved treatment satisfaction in patients with type 1 diabetes
- Insulin glargine + lispro reduced the negative impact of diabetes on QoL and improved QoL *per se*
- Perceived frequency of hyperglycaemia was also significantly reduced by insulin glargine + lispro compared to NPH + regular
- The combination of insulin glargine + lispro allows patients a high degree of lifestyle flexibility including, most importantly, dietary freedom, while maintaining control of blood glucose levels: a broad spectrum of psychological outcomes are improved
- The patient reported outcomes demonstrate further benefits of insulin glargine + lispro over and above the benefits apparent from the clinical outcomes from this study (i.e. A1c, self-monitored blood glucose, blood glucose profile and episodes of severe hypoglycemia)[10]. The combination of insulin glargine + lispro demonstrated statistically significant superiority over NPH + regular in all the key biomedical outcomes, treatment satisfaction and QoL

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