

Original Research

Cost-effectiveness of intermediate or long-acting insulin versus Exenatide in type 2 diabetes mellitus patients not optimally controlled on dual oral diabetes medications

Krystal L. EDWARDS, Brian K. IRONS, Tom XU.

ABSTRACT*

Objective: To better understand exenatide's role in the treatment of type 2 diabetes, this analysis assessed its cost-effectiveness in comparison to an intermediate (NPH) and long-acting insulin (glargine). Exenatide is a recently approved medication for the treatment of type 2 diabetes for use in addition to frequently used oral diabetes medications.

Methods: Two studies were identified by a Medline search (1996-Oct 2005) that were similar in study duration, baseline glycemic control, population size, and primary outcomes to appropriately assess the cost-effectiveness of either insulin in comparison to exenatide on both glycemic and weight control.

Results: Both NPH and glargine appear to be more cost effective than exenatide with respect to glycemic control (incremental CE ratios -1,968 and -65,520 respectively). Exenatide appears to be more cost effective for reductions in body weight than either NPH (CE ratio 235) or glargine (CE ratio 128).

Conclusions Compared to intermediate and long-acting insulin therapies, exenatide does not appear to be as cost effective for the treatment of type 2 diabetes.

Keywords: Diabetes. Exenatide. Insulin. Glargine. Insulin Isophane. Cost-Benefit Analysis.

RESUMEN

Objetivo: Comprender el papel del exenatide en el tratamiento de la diabetes tipo 2, analizando su coste-efectividad comparado con insulina intermedia (NPH) y de larga duración (glargina). Exenatide es una medicación recientemente aprobada para el tratamiento de la diabetes tipo 2, para ser usada además de los antidiabéticos orales frecuentemente usados.

Métodos: Para evaluar apropiadamente el coste-efectividad de las insulinas comparadas con exenatide, tanto en control glucémico como de peso, se identificaron dos estudios en una búsqueda en Medline (1996 a octubre 2005) que eran similares en duración, control de la glucemia basal, tamaño de la población y resultados principales.

Resultados: Tanto la NPH como la glargina parecen ser más coste-efectivos que el exenatide en relación al control glucémico (ratio CE incremental -1968 y -65520 respectivamente). El exenatide parece ser más coste-efectivo para la reducción del peso corporal que la NPH (Ratio CE 235) o la glargina (ratio CE 128).

Conclusiones: Comparada con la insulina intermedia y de larga duración, exenatide no parece ser más coste-efectivo para el tratamiento de la diabetes tipo 2.

Palabras clave: Diabetes. Exenatide. Insulina. Glargina. Insulina isofánica. Análisis coste-beneficio.

(English)

INTRODUCTION

Attaining glycemic control in type 2 diabetes mellitus is the primary therapeutic goal of therapy.¹ Intensive glycemic control in type 2 diabetes has shown statistical reductions in microvascular complications, including reduced risks of both retinopathy and nephropathy.^{2,3} As well, there has been a trend toward reduction in macrovascular complications which includes the leading cause of death in type 2 diabetes, cardiovascular disease.¹⁻³ To achieve and maintain optimal glycemic control, most type 2 diabetes patients will require multiple diabetes agents. In the United Kingdom Prospective Diabetes Study, about 50% of patients were able to sustain their glycemic control after 3 years and only

* Krystal L. EDWARDS. Assistant Professor. Department of Pharmacy Practice and Veterans Administration North Texas Health Care System. School of Pharmacy Texas Tech University Health Sciences Center. Dallas, TX (USA).

Brian K. IRONS. Division Head – Primary Care. Assistant Professor. Department of Pharmacy Practice, School of Pharmacy. Texas Tech University Health Sciences Center. Dallas, TX (USA).

Tom XU. Assistant Professor. Department of Family and Community Medicine, School of Medicine. Texas Tech University Health Sciences Center. Dallas, TX (USA).

25% at 9 years with monotherapy.⁴ This loss of glycemic control is often due to a decline in beta-cell function and explains the failure of some oral agents in type 2 diabetes patients and the requirement of two or more diabetes agents. Failure to obtain or maintain adequate glycemic control using two oral agents has historically left clinicians with the options of adding a third oral agent, adding an intermediate or long acting insulin, or discontinuing all oral agents and switching to insulin alone. Bedtime insulin with either insulin glargine or NPH (neutral protamine hagedorn) offers the convenience of once-daily insulin regimens in addition to oral therapy. Combinations of oral therapy with once-daily insulin may be the preferred regimen due to improvement in glycemic control and lower insulin dose compared to insulin monotherapy.⁵

A new injectable agent, exenatide, is now available that offers an additional option to augment a failing oral therapy regimen. Exenatide is a glucagon-like peptide-1 (GLP-1) mimetic which has multiple mechanisms of action including glucose-dependent stimulation of insulin secretion, suppression of glucagon secretion, enhancement of beta-cell mass, slowing gastric emptying, inhibition of food intake, and modulation of glucose trafficking in peripheral tissues.⁶ Exenatide has been studied in type 2 diabetes patients with uncontrolled glycemic control on an existing regimen of a sulfonylurea, metformin, or the combination of the two agents.⁷⁻⁹ It has shown improved glycemic control compared to placebo and also results in modest weight loss rather than weight gain, a common side effect of many oral diabetes medications.¹⁰ Exenatide has also been directly compared to insulin glargine therapy for efficacy and adverse effect differences.¹¹ However, no cost-effectiveness studies of exenatide have been performed. With the increasing impact that diabetes has on the health care economy^{12,13} and the fact that improved glycemic control may reduce health care costs and utilization¹⁴, efforts to improve diabetes control using cost-effective treatment modalities are very prudent. To better understand exenatide's role in the treatment of type 2 diabetes, this analysis assesses exenatide's cost-effectiveness compared to intermediate or long-acting insulins in patients uncontrolled on two oral diabetes medications.

METHODS

A Medline (1996-October 2005) search was performed to identify clinical trials directly comparing exenatide with any insulin on glycemic efficacy in type 2 diabetes subjects already receiving dual oral diabetes therapy with a sulfonylurea and metformin. Dual oral therapy, as opposed to monotherapy, was chosen for baseline diabetes therapy as the authors felt this is the more likely application of exenatide in clinical practice. Only one study was found in the clinical literature that met this criteria and compared exenatide to glargine insulin.¹¹ In addition, randomized trials assessing the glycemic efficacy of NPH insulin in addition to sulfonylurea / metformin therapy were also identified and selected for analysis based on

the following similarities with the above exenatide / glargine study: 1) similar study duration, 2) similar baseline glycemic control, 3) comparative population size, and 4) similar primary outcomes. Only one study fit all four of these criteria for adequate cost-effectiveness analysis.¹⁵ Details of the study designs, size, primary inclusion criteria, treatment strategies, demographics, and changes in glycemic and weight control are described in Table 1. Dosing strategies for NPH and glargine in both trials used frequent dose titrations aimed to lower fasting glucose levels to <100 mg/dl. Exenatide was administered using fixed doses (5 mcg twice daily for four weeks titrated to 10 mcg twice daily thereafter based on tolerance).

Comparisons between NPH and exenatide and between glargine and exenatide were made. First, the characteristics of the NPH, glargine and exenatide groups were compared to investigate whether they differed in any aspects at baseline. The statistical significance level was set at $\alpha=0.05$. The characteristics of the different groups included demographics and baseline glycosylated A1c hemoglobin (HbA1C). Second, cost-effectiveness analyses (CEA) were conducted to compare exenatide with NPH or glargine. The effectiveness was measured by HbA1C and weight reductions. The unit costs of exenatide, glargine and NPH were based on United States average wholesale prices as of September 2005. The total cost of each treatment group was calculated by multiplying the unit cost by the average daily treatment units used in the two studies.

Due to data limitations, it was impossible to perform a formal cost-effectiveness analysis (e.g., the full decision tree and statistical inferences) because only the aggregated data, i.e., means, were available from these two published studies. A simplified CEA was employed. As in a conventional CEA, incremental CE ratios were used. The incremental CE ratio was defined as the difference in the cost between exenatide and NPH (or glargine) divided by the difference in the effectiveness. Although rigorous statistical inferences could not be obtained using aggregated means from these two studies, one-way sensitivity analyses were conducted to address the uncertainty of the parameters in the CE ratios. The effectiveness, either HbA1C or weight reduction, of exenatide was assumed to be 110% and 120%, respectively, of the mean reported. Weight is compared in this study as exenatide promotes weight loss whereas insulin can cause weight gain, thereby leading to increased insulin resistance. In addition, the cost of exenatide was assumed to be 90% and 80%, respectively, in the sensitivity analyses.

RESULTS

Table 1 reports the comparisons for weight and glycemic changes between the exenatide, glargine and NPH groups from the two studies. In the comparison between the exenatide and the glargine groups, the only statistically significant difference in subjects' baseline characteristics was age; the

Edwards KL, Irons BK, Xu T. Cost-effectiveness of intermediate or long-acting insulin versus Exenatide in type 2 diabetes mellitus patients not optimally controlled on dual oral diabetes medications. *Pharmacy Practice* 2006; 4(3): 129-133.

exenatide group was older (mean=59.8) than the glargine group (mean=58.0). In the comparison between the exenatide and the NPH groups, subjects in the exenatide group were statistically

significantly older, had lower body mass index (31.4 vs. 32.2 kg/m²) and had lower HbA1C (8.2 vs. 8.56 %).

	NPH Insulin ¹⁵	Insulin Glargine ¹¹	Exenatide ¹¹	
Sample Size (n)	389	267	282	
Study Duration (weeks)	24	24	24	
Inclusion Criteria	30-70 years old	30-75 years old	30-75 years old	
	BMI 26-40 kg/m ²	BMI 25-45 kg/m ²	BMI 25-45 kg/m ²	
	A1C 7.5-10.0%	A1C 7.0-10.0%	A1C 7.0-10.0%	
	Diabetes ≥ 2 years	≤ 10% weight variation in previous 3 months before screening	≤ 10% weight variation in previous 3 months before screening	
Treatment Strategy	Titrated to target FPG ≤ 100 mg/dl	Titrated to target FPG ≤ 100 mg/dl	5 mcg twice daily x 4 weeks then 10 mcg twice daily thereafter	
Age (years)	56 +/- 8.9	58.0 +/- 9.5	59.8 +/- 8.8*†	
Duration Diabetes Diagnosis (years)	9.0 +/- 5.6	9.2 +/- 5.7	9.9 +/- 6.0	
Weight (kg)	na	88.3 +/- 17.9	87.5 +/- 16.9	
BMI (kg/m ²)	32.2 +/- 4.8	31.3 +/- 4.6	31.4 +/- 4.4†	
Male Gender (%)	56	57	55	
Race (%)	Caucasian	83	81	80
	Black	13	1.1	0.7
	Asian	3	0.7	1.8
	Hispanic	6	15	16
	Other	1	2.6	2.1
Baseline HbA1C (%)	8.56 +/- 0.9	8.3 +/- 1.0	8.2 +/- 1.0†	
Baseline FPG (mg/dl)	194 +/- 47	187 +/- 52	182 +/- 47	

All values are mean +/- standard deviation unless otherwise noted.
 NPH: Neutral Protamine Hagedorn, BMI: Body Mass Index, A1C: Hemoglobin A1C, FPG: Fasting Plasma Glucose
 *: Baseline comparison statistically different (p>0.05) between exenatide group and glargine group
 †: Baseline comparison statistically different (p>0.05) between exenatide group and NPH group

During the 24-week period, for every 100 US dollars spent on exenatide, glargine or NPH, the reduction in HbA1C was 0.091, 0.655 and 0.201, respectively. For every 100 US dollars spent on exenatide, there was an average weight reduction of 0.19 kg. The use of glargine or NPH was associated with an increase in weight. The results from the cost-effectiveness analyses indicated that the use of exenatide achieved a smaller reduction in HbA1C at a higher cost as compared with NPH or glargine, leading to negative incremental CE ratios. The incremental CE ratio for exenatide vs. NPH was -1,968 and for exenatide vs. glargine, -65,520.

All the sensitivity analyses of the incremental CE ratios assuming that either exenatide was 10 or 20 percent cheaper, or exenatide was 10 or 20 percent more effective in HbA1C reduction, still resulted in negative incremental CE ratios of exenatide vs. NPH. In the results from the sensitivity analyses of exenatide vs. glargine, the incremental CE ratio remained negative when exenatide was assumed to be cheaper. However, if the effectiveness of exenatide was increased by 10 or 20 percent, the incremental CE ratios were 6,552 and 3,120, respectively. That is, in comparison to glargine, the additional reduction of 1% in HbA1C resulted from exenatide cost additional 6,552 US dollars or 3,120 US dollars.

In terms of weight reduction, the incremental CE ratio for exenatide vs. NPH was positive (235). It indicated that in comparison to NPH, the additional

reduction of 1 kg in weight resulted from exenatide cost 235 US dollars. The incremental CE ratio for exenatide vs. glargine was 128. The sensitivity analyses assuming that either exenatide was 10 or 20 percent cheaper, or exenatide was 10 or 20 percent more effective than NPH or glargine in weight reduction resulted in positive incremental CE ratios ranging from 81 to 223.

DISCUSSION

Based on this analysis, intermediate (NPH) or long-acting insulin (glargine) is more cost effective with respect to glycemic control than exenatide in patients with type 2 diabetes not optimally controlled on both a sulfonylurea and metformin. Exenatide, on the other hand, was more cost effective with respect to weight changes than either NPH or glargine. While the intent of the analysis was to compare the two insulins to exenatide, it should be noted that glargine was less cost-effective than NPH for both HbA1C reduction and weight changes (CE ratios -644 and -309 respectively)

The primary limitation of this analysis is that the NPH data used is not derived from a specific comparative study directly assessing the effectiveness on glycemic control between NPH and exenatide. Rather the data is derived from two separate studies and, while very similar in patient characteristics and baseline glycemic control, does not guarantee differences in patient parameters and

therapies had no effect on the outcomes of this analysis. The NPH data was obtained from a study directly comparing NPH with glargine.¹⁵ In that study, both NPH and glargine were found to be equally effective in lowering HbA1C levels. The average daily dose of glargine to obtain this control was higher than the doses found in the comparative exenatide / glargine study (47 versus 25 units daily respectively). The two studies, however, used different dose titration strategies to reach optimal glycemic control and, along with differences in baseline characteristics, could explain the differences in HbA1C changes between the two studies.

Exenatide, while more costly than NPH or glargine, has a role in treating type 2 diabetes due to its unique mechanism of action compared to the other currently available agents on the market. It is efficacious in treating hyperglycemia, is associated with weight loss rather than gain, and adds to our armament in treating a disease that is often uncontrolled.¹⁶ However, exenatide has several limitations compared to treating patients with insulin. It is only indicated in the treatment of type 2 diabetes for patients not optimally controlled with a sulfonylurea, metformin, or the combination of the two agents. It has a limited fixed-dose strategy which does not allow it to be continually titrated to obtain a specific glycemic target. It has not been directly compared to NPH insulin therapy or studied for use with insulin, thiazolidinediones, meglitinides, or alpha-glucosidase inhibitors. Nausea and hypoglycemia are the two most common adverse events in the longer term exenatide studies.⁷⁻⁹

Intermediate and long-acting insulins, on the other hand, offer quick and effective dose titration to obtain appropriate glycemic control and can often be injected once daily in addition to a failing type 2 diabetes regimen with oral agents. Like exenatide, insulin is associated with the risk of hypoglycemia, but unlike exenatide, is frequently associated with weight gain.¹⁷ This increase in weight may have a negative effect on insulin resistance, a hallmark of type 2 diabetes.

The present study provides useful information in decisions regarding adding exenatide to formularies. From this data, NPH and glargine both are more cost effective in lowering blood glucose. When taking medication costs to patients and health care plans into consideration, the study also has clinical implications in medication selection by practitioners when patients have failed dual therapy. Future clinical trial information directly assessing the glycemic effect and cost-effectiveness of other insulin therapies compared to exenatide are needed to more appropriately distinguish exenatide's place in therapy of type 2 diabetes and on formulary decisions. In addition, longer-term studies assessing the potential weight benefits of exenatide on clinical outcomes are needed.

DISCLAIMER

The funding for this study was provided by salary support via Texas Tech University Health Sciences Center. None of the authors have a conflict of interest.

References

1. American diabetes association. Standards of medical care in diabetes – 2006. *Diabetes Care* 2006;29(Supp1):s4-42
2. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854-65.
3. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53.
4. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *JAMA* 1999;281:2005-12.
5. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. *JAMA* 2002;287:360-72.
6. Nielsen LL, Young AA, Parkes DG. Pharmacology of exenatide (synthetic exendin-4): a potential therapeutic for improved glycemic control of type 2 diabetes. *Regul Peptid* 2004;117:77-88.
7. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 2005;28:1092-100.
8. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD; Exenatide-113 Clinical Study Group. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* 2005;27:2628-35.
9. Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* 2005;28:1083-91.
10. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 1999;131:281-303.
11. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG; GWAA Study Group. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes. *Ann Intern Med* 2005;143:559-69.
12. American Diabetes Association. Economic costs of diabetes in the US in 2002. *Diabetes Care* 2003;26:917-32.
13. Gilmer TP, O'Connor PJ, Manning WG, Rush WA. The cost to health plans of poor glycemic control. *Diabetes Care* 1997;20:1847-53.
14. Wagner EH, Sandhu N, Newton KM, McCulloch DK, Ramsey SD, Grothaus LC. Effect of improved glycemic control on health care costs and utilization. *JAMA* 2001;285:182-9.
15. 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;26:3080-6.

Edwards KL, Irons BK, Xu T. Cost-effectiveness of intermediate or long-acting insulin versus Exenatide in type 2 diabetes mellitus patients not optimally controlled on dual oral diabetes medications. *Pharmacy Practice* 2006; 4(3): 129-133.

16. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA* 2004;291:335-42.
17. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: Scientific review. *JAMA* 2003;289:2254-64.