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Original article

Willingness to pay for diabetes drug therapy in type 2 diabetes patients: based on LEAD clinical programme results

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Abstract

Objective:
The purpose of this study was to investigate the preferences of people with diabetes for liraglutide vs other glucose lowering drugs, based on outcomes of clinical trials.

Methods:
Willingness to pay (WTP) for diabetes drug treatment was assessed by combining results from a recent WTP study with analysis of results from the Liraglutide Effect and Action in Diabetes (LEAD) programme. The LEAD programme included six randomised clinical trials with 3967 participants analysing efficacy and safety of liraglutide 1.2 mg (LEAD 1–6 trials), rosiglitazone (LEAD 1 trial), glimepiride (LEAD 2–3 trials), insulin glargine (LEAD 5 trial), and exenatide (LEAD 6 trial). The WTP survey used discrete choice experimental (DCE) methodology to evaluate the convenience and clinical effects of glucose lowering treatments.

Results:
People with type 2 diabetes were prepared to pay an extra €2.64/day for liraglutide compared with rosiglitazone, an extra €1.94/day compared with glimepiride, an extra €3.36/day compared with insulin glargine, and an extra €0.81/day compared with exenatide. Weight loss was the largest component of WTP for liraglutide compared with rosiglitazone, glimepiride, and insulin glargine. Differences in the administration of the two drugs was the largest component of WTP for liraglutide (once daily anytime) compared with exenatide (twice daily with meals). A limitation of the study was that it was based on six clinical trials where liraglutide was the test drug, but each trial had a different comparator, therefore the clinical effects of liraglutide were much better documented than the comparators.

Conclusions:
WTP analyses of the clinical results from the LEAD programme suggested that participants with type 2 diabetes were willing to pay appreciably more for liraglutide than other glucose lowering treatments. This was driven by the relative advantage of weight loss compared with rosiglitazone, glimepiride, and insulin glargine, and administration frequency compared with exenatide.

Introduction

There is increasing evidence that people with type 2 diabetes have sub-optimal disease control. For example, control of glycated haemoglobin A_{1c} (HbA_{1c}) values has been deteriorating in people with diabetes for the last 4 years in Sweden[1]. Failure to obtain maximum benefit from drug treatment, inadequate management, and poor treatment adherence contribute to worsening HbA_{1c} levels and the increasing risk of developing future complications associated with diabetes[2–4].

It is important that patients are prescribed a treatment that is effective and convenient in order to increase adherence and achieve good control of blood glucose levels. The value that people with type 2 diabetes place on different attributes of treatment can be assessed by measuring their so-called willingness to pay (WTP) for these attributes. Combining these WTP data with clinical trial data is an established method for investigating the value of treatment in diabetes[5–8]. Discrete choice experiments (DCEs) is one approach that can be used to measure the value people with diabetes place on each attribute of diabetes treatment[5,7]. DCEs can then be used to calculate a person's WTP for the defined treatment attributes. In a previous WTP study of the importance of different treatment attributes, people with type 2 diabetes placed a relatively large value on the attributes of treatments to prevent weight gain, reduce or avoid hypoglycaemia, and reach HbA_{1c} goals[7].

The purpose of this study was to investigate the preferences of people with diabetes for liraglutide vs other glucose lowering drugs, based on outcomes of clinical trials with liraglutide in people with type 2 diabetes.

Methods

WTP for diabetes drug treatment in people with type 2 diabetes was assessed by combining results from an analysis of liraglutide compared with other diabetes drug therapies in the Liraglutide Effect and Action in Diabetes (LEAD) programme and a WTP study assessing important aspects of diabetes medication in people with type 2 diabetes[7]. In these clinical trials, liraglutide was compared with different commonly used glucose lowering agents for the treatment of type 2 diabetes.

WTP survey and analysis of LEAD clinical programme

The analysis included six randomised clinical trials with 3967 participants in the LEAD programme, which analysed efficacy and safety of liraglutide 1.2 mg (LEAD 1–6 trials)[9–14], rosiglitazone (LEAD 1 trial)[11], glimepiride (LEAD 2–3 trials)[10,12], insulin glargine (LEAD 5 trial)[13], and exenatide (LEAD 6 trial)[9]. Changes in HbA_{1c} levels, systolic blood pressure (SBP), and body weight were analysed with Intention-To-Treat methodology for the first 26 study weeks in the trials. Hypoglycaemia was measured as the event rate, and nausea as a percentage of patients with the documented event. Differences between the treatments were calculated arithmetically, and the data used in conjunction with values from the DCEs.

The WTP survey used a DCE methodology (where respondents were asked to choose between two hypothetical treatments) to evaluate the convenience and clinical effects of treatments in type 2 diabetes[7]. The design of the questionnaire and the DCE methodology has been published in detail elsewhere[7,15]. However, briefly, a questionnaire was developed in co-operation with a panel of diabetes experts in Sweden and the questionnaire including wording and payment range was tested in a pilot study of patients with diabetes. The questionnaire was divided into five sections: (1) questions on the patient's current conditions, the medications they take, visits to the doctor, mode of administration, and need for self-measurement of blood glucose levels; (2) a series of four 'choice sets' on convenience attributes; (3) questions about the patient's current clinical profile and a series of six 'choice sets' on clinical attributes; (4) a number of other aspects of diabetes treatment, including weight loss and the use of blood test strips were rated from 1–10; and (5) background questions, including those on the risks of uncontrolled HbA_{1c}, gender differences, and the impact of smoking. The hypothetical payment levels were documented as direct 'out-of-pocket' costs per patient. Hypothetical payment-estimates were also recorded with the understanding that they were per month payments of ongoing payments for a chronic condition.

The respondents were presented four convenience and six clinical scenarios each, which is standard practice, to keep the duration of the questionnaire short, and this did not bias the results in any way. Respondents were asked for their preference of a hypothetical drug compared with their own current medication.

The questionnaire was implemented using an electronic questionnaire system. Data collection was provided by the independent research company GfK Health Care. The respondents were recruited using an existing e-mail panel, and the questionnaires were completed over the internet. The respondents were fully anonymous, and no names or other identifying personal information were collected. The selection process for the respondents for the DCEs is shown in Table 1. In order for a patient's questionnaire responses to be included for analysis, the patient had to confirm diagnosis of type 2 diabetes and use of medication for his or her diabetes (Table 1).

WTP data from Jendle *et al.*[7] were summarised into total values for each attribute measured, using a currency rate of €1 = SEK9.52. The questionnaire was divided into five sections: questions on the patient's current status; choice scenario questions on convenience attributes; choice scenarios on clinical attributes; choice scenarios on more intangible aspects of diabetes management; and background questions. As previously described, in order to reduce the number of choice sets an orthogonal, fractional, factorial design was produced[7].

The DCEs provided monetary values for each attribute, while the analysis of the clinical trials provided the clinical differences between the treatments for these attributes.

Table 1. Selection of respondents for the discrete choice experiments/willingness to pay questionnaire.

Category	Number of respondents
Gross sample	10,540
Not diabetic	9572
Type 1 diabetes	128
Type 2 diabetes	840
Did not complete survey	177
Do not use diabetes medication	126
Net sample type 2 with medication	537
Failed test question	76
Relevant sample	461

So the analysis of the LEAD clinical programme showed a difference between two treatments, while the DCE showed the value of the difference.

Results

The number of participants included in the analysis from the LEAD clinical programme were 898 on liraglutide 1.2 mg, 492 on glimepiride 4–8 mg, 232 on rosiglitazone 4 mg, 234 on insulin glargine, and 231 on exenatide 10 μg BID.

When the discrete choice values from the WTP study were applied to the treatment attributes in the analysis (last observation carried forward, Intention-To-Treat analysis set used, Table 2), it was revealed that, overall, participants with type 2 diabetes were willing to pay more for liraglutide compared with comparator treatments (Table 3).

Participants with type 2 diabetes were prepared to pay an extra €2.64/day for liraglutide (1.2 mg once daily subcutaneous [SC] injection) compared with rosiglitazone (4 mg once daily oral administration [OAD]), an extra €1.94/day compared with glimepiride (4 or 8 mg once daily OAD), an extra €3.36/day compared with insulin glargine (on average 24 international units once daily SC injection), and an extra €0.81/day compared with exenatide (10 μg twice daily SC injection) (Table 3).

Weight loss was the largest component of WTP for liraglutide compared with rosiglitazone, glimepiride, and insulin glargine (Table 3). Once daily administration of liraglutide (anytime, not limited to administration with meals) was the main component driving WTP compared with exenatide (twice daily administration with meals). Gastrointestinal adverse effects were of special interest for liraglutide and exenatide and nausea was the most frequent adverse event. Although the proportion of patients with nausea was initially similar for both liraglutide and exenatide, nausea resolved more quickly in patients treated with liraglutide[9]. The analysis calculated the mean percentage of patients with nausea over the course of the clinical trial (Table 2).

Discussion

The results of our analysis demonstrate and confirm that people with type 2 diabetes put a high value on improving their glucose lowering medication, particularly in relation to avoiding weight gain and in administration of fewer injections. A previous study showed that, in addition to avoiding weight gain, reduction in hypoglycaemic events, reduction in HbA_{1c}, convenience of dosing regimen, and clinical efficacy were significant predictors of WTP for diabetes treatment[7]. The current analysis combined results from that study in combination with an analysis of the LEAD programme to suggest that WTP for liraglutide was appreciably higher compared with other treatments in the LEAD clinical programme. The main drivers for this were weight loss compared with rosiglitazone, glimepiride, and insulin glargine, and number and timing of subcutaneous injections compared with exenatide.

In the LEAD 2 trial, liraglutide was shown to significantly reduce weight both in monotherapy or added to metformin compared with glimepiride in patients with type 2 diabetes[16]. In a sub-population of this study and LEAD 3, the percentage of fat of the body weight with liraglutide 1.2 and 1.8 mg plus metformin was significantly reduced compared with glimepiride plus metformin ($p < 0.05$), but not compared with placebo[16]. Visceral and subcutaneous adipose tissue areas were reduced from baseline in all liraglutide/metformin arms. Except with liraglutide 0.6 mg/metformin, reductions were significantly different compared with changes seen with glimepiride ($p < 0.05$), but not with placebo[16].

In a separate study, there was also a significant WTP for weight control treatment in women, which was negatively linked with age, personal income, and perceptions about current and optimal weight[17]. In fact, applying the WTP data from the Jendle *et al.*[7] study to the LEAD clinical data shows that weight may be a major factor in WTP for liraglutide over other treatments that cause weight gain.

Rates of cardiovascular disease and mortality from ischaemic heart disease are disproportionately high in people with diabetes[18]. Patients with type 2 diabetes who show pronounced weight gain during treatment have a higher risk of cardiovascular or metabolic complications of diabetes compared with patients who have no or minimal weight gain[19]. In this respect, even a weight loss of less than 10% of total body weight is associated with significant risk reduction for cardiovascular disease in people with type 2 diabetes[20,21]. Some studies have shown that weight loss is also strongly associated with improved glycaemic control and lower blood pressure[22,23], and,

Table 2. Main results from the meta-analysis.

Variable	Liraglutide 1.2 mg ($n=898$)	Rosiglitazone 4 mg ($n=232$)	Glimepiride* 4–8 mg ($n=492$)	Insulin glargine** ($n=234$)	Exenatide 20 μg ($n=231$)
Change in HbA_{1c} at 26 weeks (%)†	−1.01	−0.35	−0.71	−0.98	−0.82
Change in systolic blood pressure at 26 weeks (mmHg)	−2.57	−0.35	0.41	1.64	−3.89
Weight change at 26 weeks (kg)	−1.52	1.94	1.04	1.57	−2.29
Hypoglycaemia event rate	0.284	0.134	1.365	1.403	2.669
Blood glucose measure (tests per day)	0.77	0.77	0.77	1.63	0.77
Nausea (% of patients)	4.1	0.2	0.8	0.1	12.2

*Glimepiride 4 mg/day (LEAD 2), 8 mg/day (LEAD 3); **Insulin glargine dose variable dependent on patient's clinical requirements; †HbA_{1c} in DCCT aligned units (%).

Table 3. Willingness to pay (WTP) for liraglutide 1.2 mg per day compared with other standard therapies (€ per day).

Variable	WTP for liraglutide 1.2 mg per day versus other glucose lowering treatments, € per day			
	Rosiglitazone 4 mg	Glimepiride* 4–8 mg	Insulin glargine**	Exenatide 20 μg
Change in HbA_{1c} at 26 weeks (%)†	0.95	0.43	0.04	0.27
Change in systolic blood pressure at 26 weeks (mmHg)	0.34	0.46	0.65	−0.20
Change in body weight at 26 weeks (kg)	2.70	1.87	2.35	−0.46
Minor hypoglycaemia event rate (minor + major per patient per year)	0.00	0.03	0.03	0.07
Administration	−1.30	−0.82	0.00	1.04
Blood glucose measure (tests per day)	0.00	0.00	0.33	0.00
Nausea (% of patients)	−0.04	−0.03	−0.04	0.08
Total	**2.64**	**1.94**	**3.36**	**0.81**

*Glimepiride 4 mg/day (LEAD 2), 8 mg/day (LEAD 3): **Insulin glargine dose variable dependent on patient's clinical requirements: †HbA_{1c} in DCCT aligned units (%).
The positive values mean that treatment with liraglutide is preferred to the alternative, i.e., the willingness to pay for liraglutide is positive. The negative values imply a willingness to pay to avoid, i.e., the alternative treatment is preferred to liraglutide when looking at that parameter.

therefore, weight loss may be one factor that may help to reduce mortality in people with type 2 diabetes[24,25]. In addition, weight loss has been shown to reduce medical and pharmaceutical costs in people with diabetes[26]. Even a modest 1% loss of weight significantly reduced costs related to diabetes management[27]. It has been suggested that weight loss in overweight people with diabetes may be the most important thing they can do to preserve health and prolong life[24]. The importance overweight people with diabetes place on weight loss is in line with it being, along with glycaemic control, an important therapeutic objective in diabetes disease management[24].

DCE is the recognised approach to establish WTP between two hypothetical scenarios and is designed to make it difficult for respondents to answer strategically[28]. A limitation of this analysis, however, is that the analysis was based on six clinical trials and, while liraglutide was a test drug in all six trials, the comparator data were derived from one trial (rosiglitazone–LEAD 1; insulin glargine–LEAD 5; exenatide–LEAD 6) and two trials for glimepiride (LEAD 2–3), which meant that the clinical effects of liraglutide were much better documented compared with the comparators, and which might have been a source of bias. Another potential limitation is that rosiglitazone was included as a comparator in the LEAD 1 trial; however, the LEAD 1 trial was designed at a time when rosiglitazone was widely used and before the safety limitations of the drug were made public. There is also a risk that respondents answered the questionnaire by giving different preferences to those that might have been given in an everyday situation[29].

Conclusions

Results from this analysis suggest that people with type 2 diabetes may place considerably more value on liraglutide than other standard treatments. The main motivations driving the WTP were decrease in weight compared with rosiglitazone, glimepiride, and insulin glargine, and administration frequency compared with exenatide.

Transparency

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