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Optimization of Treatment with Exenatide once Weekly versus Basal Insulins for Patients with Type 2 Diabetes: A Budget Impact Analysis

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Abstract

Purpose: Diabetes is an increasing and relevant public health problem due to the increasing prevalence and incidence. Despite the recommendations, a large proportion of patients do not achieve the desired level of glycemic control even after starting basal insulin. In the past years new therapeutic options have been made available, providing an alternative to insulin treatment initiation after the failure of oral therapy; for these reason, we performed an economic evaluation to estimate the impact on the Italian National Health Service (INHS) expenditure of treating with exenatide once weekly those patients for whom basal insulin would be the treatment of choice.

Patients and Methods: A budget impact model based on Italian data (drug market composition, healthcare resource use and costs) was developed as indicated by international guidelines.

Results: Hypothesizing a greater uptake of exenatide once weekly versus basal insulin's, even considering the high cost of exenatide once weekly, the model estimates a relevant saving for INHS expenditure due to the reduction in use and related costs for consumables, outpatients and hospitalization. The reduction in healthcare expenditure is estimated at national level in €5.8 million the first year, €15.5 million the second year and €27.3 million the third.

Conclusions: The increased use of exenatide once weekly as a possible effective and safe treatment option in patient's candidate to basal insulin, by reducing healthcare resource use as hospitalizations, outpatients and consumables, could be associated with a reduction in total healthcare expenditure in Italy.

Introduction

National and international clinical practice guidelines emphasize the importance of achieving and maintaining a good glycemic control to avoid long-term diabetes complications [1,2]. In addition to its clinical impact, a prolonged poor glycemic control can also affect patient's quality of life, causing frustration, distress, lack of motivation and reduced self-care activities, pessimism toward therapy and depression [3-6].

Despite the recommendations, many patients do not achieve the desired level of control, and patient and physician inertia has been often described as a barrier to therapy intensification [7-10]. In Italy, data from the AMD Annals initiative [11], documented that patients with Type 2 Diabetes (T2D) starting basal insulin had an average HbA1c level of 8.9%; of these patients, around 50% already had a HbA1c >8.0% (> 64 mmol/mol) two years before adding basal insulin [12]. Even after starting basal insulin, around 50% of the patients still showed HbA1c levels >8.0% (> 64 mmol/mol) after one year and after two years.

Therapeutic inertia may be driven by physician and patient concerns about hypoglycaemia, weight gain, fear of needles, lack of confidence in how to start insulin, and the complexities of living with diabetes [13-16].

Recently, new therapeutic options have been made available, providing an alternative to insulin treatment initiation after the failure of oral therapy [17]. In particular, GLP1 receptor agonists have been proven to be effective in improving glycemic control, while minimizing the risk of hypoglycemia and leading to a reduction in body weight [18,19]. The cardiovascular safety of this class of drugs has been also clearly demonstrated [20].

Considering the relevant burden of treatment with insulin in terms of costs related to the management (e.g. hospitalizations, consumables), we performed a budget impact analysis to evaluate the impact on the Italian National Health Service (INHS) expenditure of treating with exenatide once weekly (Bydureon®, AstraZeneca SpA) those patients for whom basal insulin would be the treatment of choice.

The present analysis is based on the results of the DURATION-3 study, an open label, randomized trial comparing exenatide once weekly (subcutaneous injections, 2 mg) with insulin glargine in patients not adequately controlled with metformin with or without sulfonylurea at maximum tolerate dosages [21]. This study highlighted that patients treated with exenatide once weekly had a better HbA1c control and a lower incidence of hypoglycaemia than patients treated with insulin glargine in a 3-year period. Moreover, these patients achieved and maintained weight loss during the study.

Methods

A budget impact analysis needs an estimation of the present and future forecasted market shares of different therapeutic approaches indicated for a specific disease/therapy line, the identification of the target population for whom the drug is indicated and the unit cost per patient of the different treatment options in order to evaluate the related healthcare costs (according to the International Society for Pharmacoeconomics and Outcomes Research Task Force on Good Research Practice) [22].

The present analysis aimed to evaluate the economic impact on expenditure in charge to INHS of the use of exenatide once weekly as alternative therapy in patients not adequately controlled using oral glucose-lowering drugs and candidate to the first use of insulin.

In our analysis, two different scenarios were compared: the current scenario with exenatide once weekly with a limited forecasted increase in sales and a more thriving one. Considered time horizon is 3 years.

As consequence of the hypothesized place in therapy for exenatide once weekly (in substitution to the beginning of the first insulin treatment), the reference market considered is the basal insulin market (degludec insulin, detemir insulin, glargine insulin–with both originator and biosimilar considered-estimated based on IMS Health data, year 2015).

The market growth of the entire insulin market over the three years period considered (+1.2%, +1.8% and +2.0%), was estimated on the basis of the previously years' trend. The uptake of the biosimilar of glargine (Abasaglar®, Eli Lilly SpA), was estimated considering the average uptake for biosimilar products reported in the "National Report on Medicines use in Italy" [23].

Among total insulin treated patients, the percentage with Type II Diabetes Mellitus was identified through IMS Health data to be 63.7%.

Starting from IMS Health data in terms of number of packs sold, the potential number of patients treated per year was estimated considering a daily consumption of insulin of 15 Units (U). This daily consumption was determined based on the Italian real-world data published by CINECA Osservatorio SID-ARNO: the incidence of population treated with basal insulin versus total observed population was reported to the entire Italian population (Italian National Institute of Statistics, ISTATdata) and then, by using IMS Health sales data, the average yearly and daily dosage per patient were estimated [24,25].

The average consumption per patient/year of insulin was estimated in 15U/patient on the basis of the sales of the three available types of basal insulin's. From the economic point of view, this data is conservative as for all basal insulin the Defined Daily Dose (DDD) established by World Health Organization (WHO) is 40U [26].

For the purpose of the budget impact estimates, as exenatide once weekly is already on the market, we considered a first scenario with a growth in line with current sales (1.3% of the basal insulin market at year zero, 1.6% the first year, 1.8% the second year and 2.0% the third year) which was compared with a more aggressive scenario where, starting from the same market share at year zero (as scenario 1), forecasted for exenatide an uptake of 2.5%, 4.2% and 6% in the first three years. This hypothesis (scenario 2) is in line with the maximum number of new patients starting basal insulin treatment per year and considers that exenatide once weekly treated patients remain on treatment the following year (Table 1).

Both scenarios consider that exenatide once weekly achieves additional market share by the basal insulin available proportionally with market composition during years, except for the biosimilar of insulin glargine, which is hypothesized to grow in the same way in the two scenarios taking its market shares by all other basal insulins (also the ones for which the biosimilar is not yet available).

Unitary costs

Costs considered in the model were the ones in charge to INHS: drugs, estimated using the ex-factory price in charge to INHS net from mandatory price reductions (table 2); consumables for blood glucose monitoring (in order to reflect the INHS perspective, as each Italian Region have different approaches in terms of acquisition costs and number of consumables delivered for free to patients, the per patient annual cost was estimated as an average cost weighted by regional population); hospitalizations and outpatients (estimated using real world data reported by a recently published Italian study [27]: 3034€ for basal insulins (ATC class A10A associated with ATCA10B, 2479€ for hospitalizations and 555€ for outpatients) and 1320€ for

Table 1: Forecasted market shares.

	Scenario 1: current evolution of exenatide once weekly market				Scenario 2: increased evolution of exenatide once weekly market			
	Year 0	Year 1	Year 2	Year 3	Year 0	Year 1	Year 2	Year 3
degludec (TresibaFlext®, Novo Nordisk SpA)	11.0%	11.0%	10.9%	10.9%	11.0%	10.9%	10.7%	10.5%
detemir (LevemirFlex®, Novo Nordisk SpA)	17.2%	17.1%	17.1%	17.1%	17.2%	17.0%	16.7%	16.4%
glargine (Abasaglar®, Novo Nordisk SpA)	0.0%	8.0%	14.5%	15.6%	0.0%	8.0%	14.5%	15.6%
glargine (Lantus®, Eli Lilly SpA)	70.5%	62.4%	55.6%	54.5%	70.5%	61.7%	53.9%	51.5%
exenatide once weekly (Bydureon®, AstraZeneca SpA)	1.3%	1.6%	1.8%	2.0%	1.3%	2.5%	4.2%	6.0%
Total	100%	100%	100%	100%	100%	100%	100%	100%

Table 2: Summary of drugs cost and average daily dosage considered in the model.

Drug	Average daily dose	pack	Ex-factory price in charge to INHS (€)	Average daily cost per patients (€)	Average yearly cost per patient (€)
degludec (TresibaFlext®)	15 U	5 pens 3ml 100U/ml	83.05	0.83	303.14
detemir (LevemirFlex®)	15 U	5 pens 3ml 100U/ml	45.96	0.46	167.77
glargine (Abasaglar®)	15 U	5 cartridge 100U/ml 3ml	36.77	0.37	134.22
glargine (Lantus®)	15 U	5 cartridge 100U/ml 3ml	45.96	0.46	167.77
exenatide once weekly (Bydureon®)	0.286 mcg	4 pens 2mg 0.65 ml RP	89.96	3.21	1172.72

U: units; mcg: micrograms.

exenatide once weekly (ATC class A10B, 941€ for hospitalizations and 379€ for outpatients). We assumed that in the proposed place in therapy (before the beginning of insulin use), hospitalizations and outpatients' costs of exenatide once weekly were the same as oral agents (all ATCA10B drugs); in the above mentioned study [27], in fact, exenatide was included in this class due to its tolerability profile which is similar to that of oral agents; this assumption could also be considered as conservative as in the class of oral agents also sulfonyl ureas, characterised by a greater prevalence of hypoglycaemia episodes, are included. Moreover, this approach could be considered conservative as other real world recent Italian studies highlights even lower costs associated with exenatide use [28,29].

Regarding drugs cost, whereas both exenatide and basal insulin treatments is additional to similar baseline therapy also in randomized clinical trials, we did not monetize other glucose lowering drug costs by considering them the same in both groups.

We also performed sensitivity analysis, in order to test the robustness of the results of the model, setting the daily costs of all insulins at current price of the biosimilar of glargine (0.37€/day, the lowest price of all basal insulins) and increasing hospitalizations and outpatients' costs for exenatide once weekly by 50% and 80%.

Results

The summary of the results of the present budget impact analysis is reported in table 3.

The increased uptake of exenatide once weekly in patients candidate to the initiation of a treatment with basal insulin (scenario 2), even if associated with higher drug costs, leads to a total reduction of INHS expenditure due to the reduction in consumables, outpatients and hospitalization related expenditure.

With the hypothesized market shares, increased use of exenatide once weekly before the beginning of basal insulin treatment, could lead to a total saving ranging from €5.8 million the first year to €27.3 million the third year (mainly due to reduction in hospitalizations).

Sensitivity analysis considering for all insulins the daily costs of biosimilar of insulin glargine substantially confirms the results of the base case (year 1: €5.5 million saving; year 2: €14.8 million saving and year 3: €26.1 million saving). Moreover, in order to test the sensitivity of the model to the costs of hospitalizations and outpatients associated to the treatment with exenatide once weekly, those were increased

Table 3: Summary of results.

	Scenario 1: current evolution of exenatide once weekly market				Scenario 2: increased evolution of exenatide once weekly market			
	Year 0	Year 1	Year 2	Year 3	Year 0	Year 1	Year 2	Year 3
Number of patients								
Insulin degludec (TresibaFlext®)	62,976	63,736	64,886	66,185	62,976	63,164	63,360	63,532
Insulin detemir (LevemirFlex®)	98,446	99,634	101,432	103,463	98,446	98,739	99,045	99,315
Insulin glargine (Abasaglar®)	-	46,340	86,203	94,463	-	46,340	86,203	94,463
Insulin glargine (Lantus®)	404,210	362,727	330,222	330,285	404,210	358,982	320,127	312,507
exenatide once weekly (Bydureon®)	7677	9212	10,752	11,839	7677	14,425	24,785	36,436
Total number of patients	573,309	581,650	593,520	606,253	573,309	581,650	593,520	606,253
INHS Expenditure								
Drugs (€)	112,422,066	113,912,594	116,266,244	119,394,310	112,422,066	119,074,144	130,166,747	143,757,431
Consumables (€)	251,085,815	254,185,393	258,835,425	264,059,473	251,085,815	252,158,362	253,390,198	254,502,803
Hospitalizations and outpatients (€)	1,726,261,700	1,748,937,542	1,782,233,112	1,819,027,889	1,726,261,700	1,740,002,262	1,758,257,680	1,776,919,702
Total INHS expenditure(€)	2,089,769,581	2,117,035,528	2,157,334,780	2,202,481,672	2,089,769,581	2,111,234,768	2,141,814,624	2,175,179,936
Expenditure difference for scenario 2 versus scenario 1 (€)						**- 5,800,761**	**-15,520,157**	**-27,301,735**

INHS: Italian National Health Service.

by 50% and 80%: in both cases the budget impact result in saving associated to the use of exenatide once weekly varying in the three years period from €2.3 million to €11 million and from € 0.3 million to €1.3 million respectively.

Discussion

Resource consumption and cost associated with the treatment of diabetes and its complications have a relevant burden on Italian National Health Service (INHS) with increasing costs associated to increasing co-morbidities [28-31]. Optimizing diabetes treatment through the use of drugs associated with a favourable risk-benefit profile can help overcome clinical inertia and facilitate the attainment of the desired therapeutic goals, with a positive clinical, social and economic impact.

The increased use of exenatide once weekly as a possible effective and safe treatment option in patient's candidate to basal insulin, by reducing the use of healthcare resource as hospitalizations, outpatients and consumables, could be associated with a reduction in total healthcare expenditure although associated with higher drug costs. Several economic evaluations have been performed comparing exenatide versus basal insulin across different Countries and Health care Settings [32-36]. The cost-effectiveness of exenatide twice daily vs. insulin glargine as add-on to oral therapy was documented in UK,Germany, Spain, China, and Switzerland [37-41]. More recently, the cost effectiveness of once weekly exenatide vs. insulin glargine was also documented in different countries; in all these analyses, the cost per QALY gained for weekly exenatide when compared with insulin glargine in type 2 diabetes was within the range normally considered cost effective [33,34,42,43].

Furthermore, an observational study found a reduction in total healthcare costs related to the treatment with exenatide once weekly versus basal insulin [44].

While cost-effectiveness analyses are based on long-term projections of the benefits documented in clinical trials, our analysis shows that increasing the use of exenatide once weekly as an alternative to beginning basal insulin treatment could lead to cost savings starting from the first year, with even larger savings the third year. These findings have important clinical and economic implications, considering that in Italy over 30% of patients on dual or triple oral therapy show HbA1c levels over 8.0% [12]. Patient and physician reluctance to initiate insulin therapy, mainly driven by the fear of hypoglycemia and weight gain and to the added complexity of treatment, determine a substantial delay in therapy intensification, thus leading to long periods of exposure to elevated blood glucose levels. On the other hand, the initiation of insulin therapy is responsible for additional costs related to the need for more frequent blood glucose self-monitoring and increased healthcare resource utilization, mainly related to hypoglycemic episodes. In this respect, weekly exenatide represents a valuable alternative option, due to its efficacy and safety profile. Furthermore, its weekly administration and the lack of need for additional blood glucose self-monitoring adds a low level of complexity to the everyday management of the disease, thus facilitating treatment compliance. These positive aspects overcome the higher costs of treatment as compared to insulin glargine, translating into substantial cost savings for the national healthcare system.

In conclusion, our budget impact study shows that in the Italian national healthcare system weekly exenatide represents an important option for patients not adequately controlled with oral agents and candidate to basal insulin therapy. The higher costs of the treatment are offset by the savings deriving from the lower use of healthcare resources such as hospitalizations, outpatients and consumables. Future studies should evaluate the comparative effectiveness of GLP-1 receptor agonists vs. basal insulin strategies in community settings to facilitate more precise estimation of clinical and economic tradeoffs.

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