A Comparison of 1-Year Treatment Costs in Patients with Type 2 Diabetes Following Initiation of Insulin Glargine or Insulin Detemir in Argentina

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**A B S T R A C T**

**Objective:** To estimate and compare type 2 diabetes mellitus treatment costs in insulin-naive patients following initiation of therapy with either insulin glargine (IG) or insulin detemir (ID) over 1-year time horizon from a payers’ perspective in Argentina. **Methods:** We used a pharmacoeconomic model based on a randomized trial comparing IG and ID (Rosenstock J, Davies M, Home PD, et al. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetologia 2008;51:408–16) and Argentinean sources. Clinical, resource use, and cost data were combined to estimate direct medical costs (insulin, test strips, and needles) during the first year. Price per international unit of insulin is similar for IG and ID in the local market. Deterministic analysis was performed on insulin unit cost and probabilistic sensitivity analyses on clinical, resource use, and unit costs to evaluate contribution to variance on the difference in total annual treatment cost. **Results:** Annual mean treatment cost (Argentinean pesos 2013) was AR $6229 for IG and AR $9257 for ID, showing 33% total cost reduction with IG (AR $3028; exchange rate US $1.00 = AR $5.30). Probabilistic sensitivity analysis showed that IG was cost saving in 88% of the simulations. The most influential parameter was the difference in insulin dose requirements. Threshold analysis showed that if the unit price of ID is reduced by 43%, ceteris paribus, the total annual costs per person for both insulin regimens would be the same. **Conclusions:** From a payer’s perspective in Argentina, cost savings related to the use of IG represented one third of total treatment costs. Sensitivity analyses confirmed the robustness of these results. **Keywords:** cost comparison, insulin detemir, insulin glargine, type 2 diabetes.

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**Introduction**

Type 2 diabetes mellitus (T2DM) is a serious public health problem due to its high prevalence and the development of chronic complications (retinopathy, nephropathy, peripheral vascular disease, ulcers, diabetic foot and amputations, cardiovascular disease, and stroke), which increases resource use and socioeconomic costs, especially in developed countries [1]. The economic burden raised by diabetes is challenging health care systems. According to the World Health Organization, direct health care cost of diabetes-related illnesses ranged from 5% to 13% of a country’s annual health care budget, depending on local prevalence and treatment costs [2]. In Argentina, diabetes affects 11.9% of the population [3] and is estimated to represent a high proportion of total health expenditure [2].

It has been clearly established that the development and progression of complications can be effectively prevented or delayed through tight glycemic control [4–6]. A number of landmark randomized controlled trials and meta-analysis of randomized controlled trials (RCTs) established that intensive glucose-lowering treatment reduces microvascular complications, and follow-up data from these studies suggest that intensive treatment also lowers macrovascular risk in T2DM [5,7–11]. When considering effectiveness, tolerability, and cost of the various diabetes treatments, insulin is not only the most potent but also the most cost-effective intervention [12,13].

In spite of the existing evidence, there has been a stepwise introduction of glucose-lowering interventions, with the final step of insulin therapy being administered 10 to 15 years after diagnosis [14]. Both patients and physicians are often reluctant to start insulin because of fears of painful injections, hypoglycemia, and weight gain [15–17]. In recent years, long-acting insulin analogues, insulin glargine (IG) and insulin detemir (ID), were introduced and proposed as a therapeutic alternative with the potential to overcome some of these barriers as data from trials...
...and meta-analysis showed a lower rate of symptomatic, overall, and nocturnal hypoglycemia in patients treated with either IG or ID compared with neutral protamine hagedorn (NPH) insulin [18].

According to the American Diabetes Association and the European Association for the Study of Diabetes guidelines for the management of T2DM, insulin could be initiated with either once-daily NPH insulin or long-acting insulin analogues [19]. Regimes involving long-acting insulin analogues can achieve clinically important improvements in glycemic control similar to those achieved with NPH, but with less risk of hypoglycemia [20,21].

Studies that compared IG and ID in patients with T2DM showed that both analogues did not differ in efficacy and safety profiles [22-25].

The economic impact of the use of these insulins was estimated in Spain by Guisasola et al. [26] on the basis of the only 52-week randomized trial to date (Rosenstock et al.) [22], which compared clinical outcomes related to the addition of basal insulin analogues ID or IG in a sample of 582 insulin-naive patients with T2DM who were inadequately controlled with oral glucose-lowering drugs. In this study, it was found that the use of IG instead of ID would result in annual saving on treatment costs of 34% or 534.96 (€ 2006) for a patient with T2DM.

Pucherer et al. [27] compared treatment costs of IG with those of ID, both combined with bolus insulin as part in patients with T2DM in Germany. The authors concluded that IG may represent a cost-saving option for patients with T2DM in this country, with potential annual cost savings of €684 (15%) per patient compared with ID at 2008 prices.

In contrast, a retrospective cohort analysis of health care claims data in a large US managed care organization (since May to December 2006) found that patients receiving ID incurred lower diabetes-related medical costs ($707 vs. $1510; P = 0.03) and total health care costs ($2261 vs. $3408; P = 0.03) than did those using IG [28].

We found many other similar cost comparison studies between these insulins for many countries [26,27,36], but none of them was for any Latin American country. The Latin-American Diabetes Association guidelines recommend the use of insulin analogues when hypoglycemia is limiting glycemic control [29]. Up to date, no studies in Latin America have compared the economic impact of the use of IG versus ID.

This study attempts to estimate and compare the economic implications of IG and ID therapy initiation in insulin-naive patients with T2DM with 1-year time horizon, from a payer’s perspective in Argentina incorporating a probabilistic sensitivity analysis (PSA).

**Methods**

We used a pharmacoeconomic exercise based on Guisasola et al. [26], and Pucherer et al. [27] constructed on MS Excel based on the results of Rosenstock et al. [22]. Although other trials comparing the efficacy and safety of both insulin have been published [23-25], the study by Rosenstock et al. [22] is the only trial to date that compared IG and ID in an annual duration of treatment in insulin-naive patients with T2DM.

Clinical, resource use, and cost data were combined in the model to estimate annual direct medical costs associated with the use of insulin, test strips, and needles required during the first year of insulin treatment in T2DM.

**Clinical Parameters**

Table 1 lists the clinical parameters for each insulin regime. At the end of follow-up, 55% of the patients treated with ID required twice-daily application. All patients treated with IG required once-daily injections.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Insulin glargine</th>
<th>Insulin detemir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial mean body weight (kg)</td>
<td>87.4</td>
<td>87.4</td>
</tr>
<tr>
<td>Final weight (kg)</td>
<td>91.3</td>
<td>89.7</td>
</tr>
<tr>
<td>Initial doses (IU)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Final doses (IU/kg)</td>
<td>0.44</td>
<td>0.52</td>
</tr>
<tr>
<td>Average dose (IU)</td>
<td>26.09</td>
<td>29.32</td>
</tr>
<tr>
<td>Note. Estimated and adapted from Rosenstock et al. [22].</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This trial informed the initial and final doses of each insulin regimen, so an average total dose per each insulin regimen was estimated on the basis of the initial dose (12 international unit [IU] for all patients) and the final dose per insulin regimen reported in Rosenstock et al. [22] considering a linear titration over the 52 weeks. This is a conservative assumption, given that 80% of the patients requiring ID twice daily (n = 103) were transferred to this scheme during the first 12 weeks of treatment.

Average total dose

\[
\text{Average total dose} = \frac{\text{Initial dose per kg} + \text{Final dose per kg} - \text{Initial dose per kg}}{2} \times \text{Final body weight}
\]

As the equation shows, mean dose per each insulin regimen was calculated using patient’s final weight. As in Rosenstock et al. [22], only the mean initial and incremental body weight from baseline at 52th week were reported and the final body weight was estimated as the initial plus the incremental one. As in the case of the average total dose, this estimation was also a conservative assumption for IG because the final body weight estimated was higher for IG than for ID per each insulin regime.

Because the difference in hypoglycemic events was neither clinical nor statistically significant among both regimens (0.04 episodes per patient-year) [22], it was not considered in the model.

Costs associated with the change in body weight of each insulin regimen are a relatively new issue and usually not included in the literature, and they were not considered in ours because of the difficulty in identifying an unbiased cost estimate for the Argentinean context.

**Utilization of Resources and Cost Parameters**

The commercial forms considered for insulins were Lantus Solo-star and Levemir FlexPen for IG and ID, respectively. This decision is based on the fact that both presentations are the only ones available in the Argentinean market that contain the same quantity of insulin (five prefilled pens of 3 mL with 100 IU/mL).

In relation to the use of needles, we assumed a utilization rate of one per each insulin application. Finally, regarding the use of test strips, a consumption rate of three and six units per week for once-daily and twice-daily injection scheme, respectively, was assumed. Both assumptions were based on expert opinion of diabetes specialists. It is recognized that a lower number of applications may have advantages in terms of quality of life, but this issue will not be considered in monetary terms in this cost comparison exercise because it is out of scope of this article and because of the absence of local estimates.

Monetary values for insulins were obtained from the Argentinean market. Unit prices for the commercial forms considered...
were AR $1126.88 and AR $1066.54 for IG and ID, respectively, both valid since April 30, 2013. To customize the situation to our perspective, a 35% discount over market prices was used, assuming the presence of purchase power from large payers. Unit costs for test strips and needles were obtained from the Argentinean market; we considered Accu-chek active glucose per 50 strips from ROCHE (AR $6.4656 per strip) and NovoFone 30 G 100 and 70 (AR $1.5574 per needle). All unit prices and costs include value-added tax and are expressed in local currency, year 2013 (mean exchange rate US $1.00 = AR $5.30).

Annual costs were calculated for insulins, needles, and test strips. For each insulin, the cost per unit of insulin was multiplied by the corresponding average total dose, estimated by the equation, and by 365 days of treatment. Regarding needles and test strips, total annual costs for IG were calculated by multiplying the unit price per the utilization rate and 365; for ID, these were calculated in the same way as in the IG regimen up to the 12th week, and for the remaining 40 weeks, they were calculated in a similar way but ponderating by the proportion of people with once-daily and twice-daily dose, as expressed in the following equation:

\[
(12 \times 7 \times \text{Unit Cost} \times \text{Use}_{1}) + (40 \times 7) \times (\text{Use}_{2} \times \text{Unit Cost} \times \text{Use}_{2})
\]

where \text{Use}_{1} and \text{Use}_{2} refer to the utilization rate for those on a once-daily and twice-daily dose scheme with ID, respectively, and \%_{1} and \%_{2} refer to the proportion of people on a once-daily and twice-daily dose scheme with ID.

**Sensitivity Analysis**

Base-case values with their corresponding distributions, associated parameters, and commentaries are expressed in Table 2. Deterministic analysis was performed to evaluate the change in the unit price of ID so as to get a null difference in the total annual costs per person for each insulin regimen. Then, PSA was performed using Monte-Carlo technique and considering 1950 iterations at a confidence level of 95% for mean and SD; this number of trials was enough to reach an accurate forecast for our results.

Final doses of insulin in units per kilogram (IU/kg) were simulated under a normal distribution considering as base-case values those reported in Rosenstock et al. [22], with an inferior limit of 0.15 IU/kg [19], assuming a common SD of 50% for each regimen, which equals 0.22 IU/kg, 0.26 IU/kg, and 0.50 IU/kg for IG, ID once-daily, and ID twice-daily dose scheme, respectively. Because Rosenstock et al. [22] did not inform measures of dispersion for insulin doses, the proportion for the SD of final doses of insulin was based on Raskin et al. [25].

The proportion of patients treated with ID receiving once-daily dose was assumed to follow a beta distribution. Unit prices of insulins were not included in the PSA; instead, the discount over both market prices was included, assuming it to be similar for both insulins. The distribution type and parameters for this variable were derived from experts’ opinion.

Unit costs for test strips and needles are both assumed to follow a normal distribution considering as base-case values those from the sources already mentioned; the SD in both cases was assumed to be 50%.

**Results**

The overall annual treatment costs (insulin, needles, and test strips) per person in the first year were AR $6229 and AR $9257 for IG and ID, respectively (Table 3). The insulin component represented 75% of the total treatment cost for both insulin regimens. Although unit prices of insulins were very similar, treatment of

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base value</th>
<th>Distribution</th>
<th>Parameters</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final dose per kilogram for insulin glargine (IU/kg)</td>
<td>0.44</td>
<td>Normal</td>
<td>Mean = 0.44 (\text{SD} = 0.22) (\text{Min} = 0.15)</td>
<td>Mean extracted from Rosenstock et al. [22]. SD was assumed equal to 50% based on Raskin et al. [25]. Minimum value was assumed according to general local practice.</td>
</tr>
<tr>
<td>Final dose per kilogram for once-daily injection for insulin detemir (IU/kg)</td>
<td>0.52</td>
<td>Normal</td>
<td>Mean = 0.52 (\text{SD} = 0.26) (\text{Min} = 0.15)</td>
<td>As above</td>
</tr>
<tr>
<td>Final dose per kilogram for twice-daily injection for insulin detemir (IU/kg)</td>
<td>1</td>
<td>Normal</td>
<td>Mean = 1.00 (\text{SD} = 0.50) (\text{Min} = 0.15)</td>
<td>As above</td>
</tr>
<tr>
<td>Completers with once-daily injections with insulin detemir (%)</td>
<td>45%</td>
<td>Beta</td>
<td>(\text{Min} = 0) (\text{Max} = 100%) (\alpha = 105) (\beta = 129)</td>
<td>Parameters extracted from Rosenstock et al. [22]. Completers with twice-daily injections were calculated as 1 minus this variable.</td>
</tr>
<tr>
<td>Discount over unit price of insulins (%)</td>
<td>35%</td>
<td>Beta</td>
<td>(\text{Min} = 15%) (\text{Max} = 50%) (\alpha = 5) (\beta = 4)</td>
<td>Parameters were set to shape local expert’s opinion.</td>
</tr>
<tr>
<td>Unit cost of test strips (AR $)</td>
<td>6.4656</td>
<td>Normal</td>
<td>(\text{Min} = 0) (\text{Max} = 50) (\text{Mean} = 6.46) (\text{SD} = 3.2328)</td>
<td>Extracted from Argentinean market. SD assumed to reach 50% according to personal communication with experts.</td>
</tr>
<tr>
<td>Unit cost of needle (AR $)</td>
<td>1.5574</td>
<td>Normal</td>
<td>(\text{Min} = 0) (\text{Max} = 50) (\text{Mean} = 1.55) (\text{SD} = 0.7787)</td>
<td>Extracted from Argentinean market. SD assumed to reach 50% according to personal communication with experts.</td>
</tr>
</tbody>
</table>

IU, international unit; max, maximum; min, minimum.
patients with T2DM initiating IG was 33% less costly than of those with T2DM initiating ID, mainly due to daily doses requirement.

The results of a deterministic threshold analysis indicated that if the unit price of ID net of the discount was reduced by 43% of its original, ceteris paribus, the total annual costs per person for both insulin regimens in the base case would be the same. This price reduction would be enough to offset those savings generated by the IG regime on needles and on self-monitoring blood glucose costs.

In the PSA, the estimated mean value for the difference in total annual treatment costs between IG and ID under a lognormal distribution was marginally higher than the estimated value in the base case (AR $3114.6 vs. AR $3028.2). Fig. 1 shows density and cumulative distributions, respectively, for the difference in total annual treatment cost. This difference was positive, meaning that IG was cost saving, in 87% of the simulations.

Table 4 summarizes the sensitivity of the results (correlation and contribution to variance) of the assumptions made in the model, that is, the influence of each variable incorporated into PSA over mean difference in total annual treatment costs. In our estimations, final doses per kilogram of both insulin regimens were main determinants for the variance in our result. All these variables had the expected sign and the expected strength over them. As shown, variations in the final doses (IU/kg) of ID had a growing effect over the variance in our result as we moved from once-daily dose to twice-daily dose scenarios.

Discussion

In our study, mean total annual costs in the first year after initiating insulin treatment among insulin-naive patients with T2DM were lower when treated with IG than with ID, AR $6229 and AR $9257 for IG and ID, respectively (Table 3). But when patients were treated with once-daily dose of ID or IG, such difference narrowed in a significant way (5%).

Because the unit prices of commercial forms used for both insulins were similar, this difference in cost was mainly explained by the difference in insulin dose requirement. Costs were also higher in the ID group for strips and needles, mainly as a result of twice-daily dosing in 55% of the patients who initiate insulin therapy with ID.

Costs associated with hypoglycemic events and other complications were not accounted for in this analysis because the difference in hypoglycemic events was neither clinical nor statistically significant among both regimens in the trial [22].

Studies suggest that higher doses of insulin are required for patients with T2DM when using ID than when using other basal insulins [30–32]. Higher requirements of insulin doses for ID (0.82 IU/kg vs. 0.59 IU/kg) were observed in a 52-week target-to-treat trial that compared IG versus ID efficacy and safety in a basal-bolus regimen with mealtime insulin as part in patients with T2DM [23]. Similar results were found in a 24-week treat-to-target

| Table 3 – Base case: Total annual costs per treatment. |
|---------------------------------|-----------------|-----------------|-----------------|
| Annual costs ( AR $)            | Insulin glargine | Insulin detemir | Difference (insulin detemir – insulin glargine) |
| Insulin                         | 4649.43         | 7008.68         | 2359.24         |
| Test strips                     | 1011.40         | 1439.66         | 428.25          |
| Needles                         | 568.45          | 809.15          | 240.70          |
| Total                           | 6229.29         | 9257.48         | 3028.19         |

Fig. 1 – Probabilistic sensitivity analysis: Density and cumulative distributions of difference on total annual costs (insulin detemir – insulin glargine). Density and cumulative distributions are plotted in relation to the absolute and relative frequency of iterations, respectively.
trial comparing initiation of IG once daily versus ID twice daily [24]. Raskin et al. [25], however, showed no differences in insulin doses (0.70 vs. 0.67) in the subgroup of insulin-naïve patients with T2DM when treated with insulin as part in a basal–bolus regimen.

A study conducted in Argentina that included 607 insulin-treated patients with T2DM followed by diabetes specialists showed that 82% of 51 patients treated with IG received one daily dose and 18% two daily doses. Regarding ID, 65% of 45 patients received two daily doses and 34% only one daily dose. Mean daily doses of insulin reported in this study were 20.7 ± 17.9 U/d for IG and 36.1 ± 23.8 U/d for ID; no distinction was made for patients who received one or two daily injections [33]. Although once-daily and twice-daily insulin regimens for IG and ID were similar to those reported in Rosenstock et al. [22], the mean daily dose of ID differed. In Rosenstock et al. [22], this value doubled the dose reported in this study.

The reasons for the increased dose requirement for ID are not clear, but it is likely to be related to the pharmacologic properties of the analogue [34,35].

We decided to include in our study the only RCT that evaluated clinical outcomes in insulin-naïve patients with T2DM treated with IG and ID as add-on therapy to glucose-lowering agents. We excluded trials using less rigorous methods, such as quasi-experimental studies or nonrandomized studies because RCTs provide stronger and more unbiased estimations of the effect of interventions. We also decided not to use the study that described insulin therapy in Argentina because it has an observational design and included a small number of patients with IG and ID treated by diabetes specialists. This restriction clearly limited the eligibility of studies for this exercise to only one RCT with 582 participants.

Our results are consistent with those described in cost comparison studies in other countries and with a cohort study in which patients with T2DM who initiated a basal-bolus insulin regimen with IG had reduced costs of treatment than did those treated with ID in UK routine general practice [36]. In this study, the median cost of prescriptions for classifiable antidiabetic therapy was 28.1% lower among those treated with IG than in those treated with ID (£1014 vs. £1410), a difference of £397 per person-year. The largest single contribution to this difference arose from the difference in insulin cost (32% lower), reagent cost (16% lower), pen delivery devices (50% lower), and sharps (16% lower) in the IG group compared with the ID group.

These findings may have coverage and policy implications. As studies to date show that ID and IG have similar efficacy [22,24], at similar commercial unit cost, treatment with IG over ID would be preferred in insulin-naïve patients with T2DM as part of a basal-bolus regimen because this decision could achieve a substantial cost saving. Our results based on the study by Rosenstock et al. [22] state that per 1000 patients treated with IG, an overall cost saving per year of AR $3,028,190 could be expected. Also, in the case that a broader perspective as the societal one was considered, this difference in cost would probably be higher, due to the extra time and discomfort associated with a more frequent dosing scheme of ID [37].

Further research, however, needs to be undertaken to evaluate real-world utilization, the long-term cost and cost-effectiveness of IG over ID, as well as the consistency of the finding of different dosing requirements between these insulins in our country. Our findings analyze treatment costs in insulin-naïve patients with T2DM during the first year of initiating a therapy with either IG or ID.

This study estimated the annual difference in treatment cost of ID and IG schemes in patients with T2DM in Argentina. Initiating insulin treatment with IG in patients with T2DM was associated with lower costs compared with ID use. T2DM requires substantially higher doses of ID, which translates into higher insulin costs.

From a payer’s perspective, cost savings related to the use of IG represented one third of total treatment costs. Sensitivity analyses confirmed the robustness of these results.

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