Long-term cost-effectiveness analysis of liraglutide vs GLP-1 added to basal insulin as intensification therapies in type 2 diabetes mellitus in Spain

INTRODUCTION

- Current guidelines for the treatment of type 2 diabetes mellitus (T2DM) recommend choosing anti-diabetic drugs that control bodyweight and reduce the risk of hypoglycemia as well as they control glycemia [1].

- Liraglutide (Lira) is an analogue of the glucagon-like peptide 1 (GLP-1) that has shown HbA1c reductions between 0.8 and 1.5%, weight reduction and low hypoglycemia rates in T2DM patients uncontrolled with other oral anti-diabetic drugs both in clinical trials [2,3,4,5,6] and real-world setting [7].

- Insulin degludec (IDeg): a long-acting insulin analogue non-anterior to insulin glargine (IGlar) in terms of long-term glycaemic control in T2DM, with statistically significantly lower rates of hypoglycaemia [8,9].

- Limitations related to weight gain and hypoglycemia exist, however, with the use of basal insulin regimens, while issues on the efficacy of GLP-1 analogues when used alone have also been raised [10].

- A fixed-ratio combination of IDeg and Lira (IDegLira) has been developed as a once-daily subcutaneous injection, which has shown to be effective and well tolerated and seems to countercouple limitations of its individual components [11,12,13].

OBJECTIVE

- To compare the long-term clinical and costs outcomes associated with IDegLira versus GLP-1 added to basal insulin in T2DM patients uncontrolled on basal insulin from the perspective of the Spanish National Health System (NHS).

METHODS

Model description and time horizon

- The IMS Health CORE model [14,15,16] was used to simulate the long-term (Hiltime up to 50 years) outcomes of treating T2DM patients with IDegLira vs. IGlar+Lira.

Patients’ characteristics

- An hypothetical cohort of 1,000 T2DM patients.

- Baseline characteristics of patients were based on patients receiving IDegLira in the DUAL II trial [13].

Treatment

- First 5 years: patients were treated with either IDegLira or IGlar+Lira (Fig. 1).

- Following years: it was assumed that glycemic control failed and both treatment arms were switched to a basal-bolus insulin regimen with either IDeg or IGlar once daily intensified by insulin aspart (IDep) three times a day with mean (Fig.1).

Table 1. Treatment effects for the first year of the simulation in uncontrolled patients on basal insulin.

<table>
<thead>
<tr>
<th>Changes from baseline</th>
<th>IDegLira</th>
<th>Basal-bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (mean [SD])</td>
<td>-1.66 (0.96)</td>
<td>-1.32 (0.96)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg) (mean [SD])</td>
<td>-8.86 (13.20)</td>
<td>-4.67 (13.20)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL) (mean [SD])</td>
<td>-10.13 (30.28)</td>
<td>-12.66 (30.28)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL) (mean [SD])</td>
<td>0.52 (6.79)</td>
<td>-0.77 (6.79)</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL) (mean [SD])</td>
<td>-6.65 (23.83)</td>
<td>-9.07 (23.83)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL) (mean [SD])</td>
<td>-25.74 (103.73)</td>
<td>-18.99 (103.73)</td>
</tr>
<tr>
<td>Body mass index (kg/m²) (mean [SD])</td>
<td>-1.04 (1.34)</td>
<td>-1.39 (1.34)</td>
</tr>
<tr>
<td>Event rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe hypoglycemia (events per 100 patient/year)</td>
<td>0.84</td>
<td>0.00</td>
</tr>
<tr>
<td>Non-severe hypoglycemia (events per 100 patient/year)</td>
<td>125.05</td>
<td>124.46</td>
</tr>
</tbody>
</table>

**Statistically significant difference: SD, standard deviation**

- Years 1-5: Benefits in terms of HbA1c and weight were assumed to persist while patients receive initial therapies and were annulled after treatment switching. Blood pressure and serum lipids effects followed the natural progression algorithms built into the CORE Diabetes Model.

- Following years: HbA1c and weight benefits in both arms were replaced with those associated with basal bolus insulin regimens.

Resource use, costs and perspective

- Costs (in €, 2013) were computed from the perspective of the Spanish NHS.

- Pharmacy, diabetes-related complications and concomitant patient management costs were included.

- Spanish pharmacy discount ex-factor cost per day with IDegLira and IGlar+Lira were €5.09 and €5.85, respectively, which included the cost of medication plus metformin, 1,500mg/day nebido, 1 and 25mg, respectively, and one self-monitoring blood glucose (SMBG) strip and lancet per day.

- After therapy intensification, the cost of IGlar was assumed for the basal insulin treatment and the use of SMBG tests a day was assumed giving a total cost of €4.98/day for both arms.

- Patient management was assumed to be the same in both treatment arms and included concomitant medications (aspirin, statins and angiotensin-converting enzyme (ACE) inhibitors), screening for renal disease, retinopathy and diabetic foot complications, and post-complication management.

- The cost of diabetes-related complications in the year of event and during the years of follow-up were identified through literature reviews and searches of Spanish diagnosis-related groups.

Utilities

- The additive CORE Default Method was applied, which implies taking the lowest utility associated with existing complications and subtracting utilities for events that occur in that year, estimating annual utility scores for each simulated patient [14].

Discounting

- A yearly discount rate of 3% in costs and utilities was applied.

Outcomes

- The Waitime (50 years) outcomes estimated (1,000 simulations) by the model were: life years (LY), quality-adjusted life years (QALY), cumulative incidence of diabetes-related complications, time to onset of diabetes-related complications and costs, incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratio (ICUR).

Sensitivity analysis

- One-way sensitivity analysis (OWSA) tested the impact on ICER and ICUR of the main model assumptions.

- Probabilistic sensitivity analysis (PSA) was also performed. Cohort characteristics, treatment effects, complication costs and utilities were sampled from distributions and 1,000 cohorts of 1,000 patients were simulated using a second order Monte Carlo approach.

RESULTS

Long-term effectiveness

- IDegLira was associated with an improvement of 0.06 LYs and 0.07 QALYs compared to IGlar+Lira (Table 2), resulting from a reduced incidence of diabetes complications.

- Further cost savings were associated to avoided treatment of diabetes-related complications (IDegLira €15,646 vs. IGlar+Lira €16,307), particularly uro and nephropathy complications.

Long-term cost-effectiveness

- IDegLira was dominant over IGlar+Lira as it was more effective and less costly (Table 2).

Table 2. Long-term cost-effectiveness results.

<table>
<thead>
<tr>
<th>Differences</th>
<th>LYs</th>
<th>QALYs</th>
<th>Discounted direct costs (€)</th>
<th>ICER (€/LY)</th>
<th>ICUR (€/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDegLira vs Basal insulin plus bolus (Mean) vs IDegLira</td>
<td>14.34</td>
<td>14.28</td>
<td>0.06</td>
<td>Dominant</td>
<td>Dominant</td>
</tr>
<tr>
<td>Basal insulin plus bolus vs Basal insulin plus Lira</td>
<td>9.25</td>
<td>9.18</td>
<td>0.07</td>
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</table>

Sensitivity analysis

- All variables tested in the OWSA gave dominant ICER and ICUR for IDegLira except for insulin daily dose that resulted in an ICER of €3,553/QALY, which can be considered cost-effective for Spain (commonly accepted threshold €30,000/QALY).

- In PSA, the majority of the simulations fell into the dominant quadrant (Fig. 2), and the 75.4% of the simulation was cost-effective with a willingness-to-pay threshold of €30,000/QALY (Fig. 3).

CONCLUSION

- IDegLira is a less costly and more effective alternative for the treatment of patients with T2DM uncontrolled on basal insulin compared with GLP-1 added to basal insulin (IGlar+Lira), from the perspective of the National Health System in Spain.

REFERENCES