Requirements for Insulin Glargine 300 U/mL for Patients with Type-1 Diabetes Mellitus Previously Treated with Insulin Glargine 100 U/mL, According to the Number of Daily Injections Given Previously

Mercè Albareda*, Mercè Lara, Raquel Barnés, Yolanda Torres, Gemma Francisco and Lluís Vila

Endocrinology Department, Hospital de Sant Joan Despí Moisés Broggi, Consorci Sanitari Integral, Barcelona, Spain

*Corresponding Author: Mercè Albareda, Endocrinology Department, Hospital de Sant Joan Despí Moisés Broggi, Consorci Sanitari Integral, Barcelona, Spain.

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Abstract

Aims: To assess the requirement for insulin glargine 300 U/mL (Gla-300) in people with Type 1 diabetes mellitus (Type 1 DM) previously treated with glargine 100 U/mL (Gla-100), depending on the prior number of daily injections of insulin. The secondary goal is to observe the differences in HbA1c and hypoglycaemia after 6 months of treatment with Gla-300.

Methods: Cross-sectional observational study of people with type 1 DM treated with basal-bolus therapy. Group 1: participants treated with a single dose of insulin Gla-100. Group 2: participants treated with two doses a day. Following medical criteria, all subjects were switched to insulin Gla-300.

Results: 133 participants with type 1 DM: 73 in Group 1 and 60 in Group 2. The participants in Group 2 required a significantly higher dose of basal insulin than those in Group 1, both on a baseline level and at 6 months. No differences in mealtime insulin were observed. There was a significantly increase in insulin dose of Gla-300 than previous doses of Gla-100 in both groups: 18.2% in Group 1 vs 6.4% in Group 2 (p < 0.001). No changes in HbA1c were observed in the two groups at 6 months of treatment and there was a significant reduction in hypoglycaemia in Group 1 (6 vs 4 per month).

Conclusion: Group 2 participants needed a lower increase in their dose of insulin on switching to Gla-300 than subjects in Group 1. The subjects in Group 1 presented less hypoglycaemia after switching treatment, without changes in HbA1c levels.

Keywords: Type 1 Diabetes; Insulin Glargine; Basal-Bolus Therapy; Hypoglycaemia

Abbreviations

BMI: Body Mass Index; Gla-100: Insulin Glargine 100 U/mL; Gla-300: Insulin Glargine 300 U/mL; Type 1 DM: Type 1 Diabetes Mellitus

Introduction

Clinical and pharmacological studies have demonstrated that the effective action of Gla-100 lasts under 24 hours in certain participants with Type 1 DM [1,2]. Such could be the case of 15 - 30% of patients [1-3]. An improvement in metabolic control has been observed when administering two daily injections of insulin Gla-100 [2-4]. One such study, with a longer follow-up period, describes Type 1 DM people treated with two doses of insulin Gla-100 requiring a far higher dose of insulin [3].

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Currently, Gla-300 is already available, and it displays a flatter and more prolonged pharmacokinetic and pharmacodynamic profile for Type 1 DM people, with an action which lasts approximately 3 hours longer than Gla-100 and offers approximately 5 hours more of precise glycaemic control [5]. The EDITION 4 multi-centre study carried out with Type 1 DM subjects, showed neither differences in metabolic control nor fewer episodes of hypoglycaemia when comparing Gla-300 and Gla-100 [6], as opposed to the EDITION JP1 Study, performed with a Japanese population, which describes a reduction in the number episodes of hypoglycaemia with Gla-300 [7]. Both studies observed a greater need for Gla-300 than Gla-100 amongst the subjects studied [6,7].

Aim of the Study

The main goal of the present study is to assess the requirement for insulin Gla-300 in Type 1 DM people previously treated with basal-bolus insulin therapy with Gla-100 as their basal insulin, depending on the prior number of daily injections of the basal insulin. The secondary goal is to assess metabolic control by determining HbA1c and the number of episodes of hypoglycaemia after 6 months of treatment with Gla-300.

Materials and Methods

Patients

Observational prospective study performed at the Endocrinology Department of Hospital Moisès Broggi, Sant Joan Despí (Barcelona). The study protocol was approved by the appropriate local ethics committee.

Information was obtained on patients with Type 1 DM aged ≥ 18 years and previously treated with basal-bolus insulin, using Gla-100 as the basal insulin, and who had attended follow-up appointments in the period March 2016 to December 2016. We enrolled those patients previously treated with 1 or 2 daily injections of insulin Gla-100 who were switched to treatment with Gla-300 for clinical reasons (to reduce the number of injections of insulin per day for patients previously treated with 2 doses of insulin Gla-100, to reduce nocturnal hypoglycaemia, to reduce the amount of insulin administered to subjects with high insulin requirements, to reduce glycaemic variability). We excluded those subjects treated with other basal insulin or mixes of insulin. The mealtime insulin used was lispro, aspart or glulisine.

In regular clinical practice of our department, the switch from insulin Gla-100 to insulin Gla-300 is performed in the following way: with patients previously treated with a single daily injection of Gla-100 (Group 1), the dose of insulin Gla-300 is calculated by adding 15% to the previous dose of insulin Gla-100. For those treated with two doses of Gla-100 daily (Group 2), the dose is calculated by adding the previous daily dose of Gla-100. Patients are recommended to increase their weekly basal insulin intake by 2 UI if their pre-breakfast self-monitored plasma glucose is > 140 mg/dL and they do not present nocturnal hypoglycaemia. For patients previously poorly controlled (HbA1c ≥ 8%), it is recommended that they attend a follow-up visit at 2 - 3 months from switching, while for those subjects with HbA1c < 8%, it is recommended that they send in an email of their test results at one month from the switch, to control or modify the titration of the treatment. All patients are asked to attend a follow-up visit at 6 months from the switch. During the insulin switchover and at the 6-month follow-up appointment the following information is collected: weight, height, BMI, basal insulin dose, dose of fast mealtime insulin analogue, number of episodes of hypoglycaemia and severe hypoglycaemia (noted and glucometer) and HbA1c level. We have taken hypoglycaemia as any glycaemia under 70 mg/dL and severe hypoglycaemia as any hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery.

Statistical analysis

Categorical variables were described as percentages, while continuous variables were summarized as mean and standard deviation or median and minimum and maximum values.

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The comparison of the variables of the two groups (1 or 2 prior doses of insulin Gla-100) was made using a bivariate analysis, applying $\chi^2$ tests for categorical variables and Student’s t-Test or Mann-Whitney, whenever normality assumptions did not hold, for continuous variables.

The differences found in the individual patient were compared, looking at the variables in a baseline situation and then at 6 months from switching treatment with a Student’s t-Test for paired data.

Throughout, the level of significance was taken at 5%.

Statistical analysis was performed with IBM SPSS version 19.

**Results**

Data was collected on 133 Type 1 DM subjects: 73 from group 1 and 60 from group 2. 93% of group 1 subjects administered Gla-100 at night. The characteristics of the subjects and the bivariate study are shown in table 1. Group 2 subjects had a higher weight and BMI and a longer duration of DM. No differences were observed between the groups at the outset of the study with respect to metabolic control, when HbA1c level and number of episodes of hypoglycaemia were compared.

<table>
<thead>
<tr>
<th></th>
<th>1 injection Gla-100</th>
<th>2 injections Gla-100</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 73</td>
<td>N = 60</td>
<td></td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>34/39</td>
<td>25/35</td>
<td>ns</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46.8 ± 15.6</td>
<td>49.8 ± 15.4</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>DM duration (years)</td>
<td>16 ± 12.5</td>
<td>24.8 ± 14.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>73.1 ± 13.9</td>
<td>79 ± 18.4</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>26.6 ± 4.2</td>
<td>28.1 ± 5.6</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.7 ± 0.9</td>
<td>7.7 ± 0.8</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemia Number/ month</td>
<td>6 (0 - 58)</td>
<td>5 (0 - 30)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Median (min-max)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 1:** Characteristics of type 1 DM patients according to the number of injections of basal Gla-100 received prior to switching treatment.

**Insulin requirements**

The subjects in group 2 required a baseline dose of insulin Gla-100 significantly higher than those in group 1 prior to the switch (0.41 ± 0.15 U/kg/day vs 0.3 ± 0.09 U/kg/day; p < 0.001). No differences were observed with respect to the dose of mealtime insulin at that moment (0.3 ± 0.13 U/kg/day vs 0.29 ± 0.15 U/kg/day; ns).

At six months from switching, the dose of insulin Gla-300 was likewise higher for group 2 subjects (0.44 ± 0.17 U/kg/day vs 0.36 ± 0.01 U/kg/day, p < 0.001), with no difference observed for the dose of mealtime insulin (0.29 ± 0.12 U/kg/day vs 0.29 ± 0.1 UI/day, ns).

In both groups there was a significant increase in the dose of insulin Gla-300 required, compared to insulin Gla-100, but the increase was far greater amongst subjects from group 1: they required an average increase in dose of 18.2% (-25, 57) with respect to the insulin

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dose prior to the switch, as opposed to the 6.4% (-24, 57) increase observed in Group 2 subjects (p < 0.05). In neither group was any increase in the dose of mealtime insulin observed at 6-month follow-up (Table 2).

<table>
<thead>
<tr>
<th>Period</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal insulin dose</td>
<td>Baseline</td>
<td>6 Months</td>
</tr>
<tr>
<td>Units/day</td>
<td>22.4 ± 9</td>
<td>27.1 ± 11†</td>
</tr>
<tr>
<td>Units/kg/day</td>
<td>0.3 ± 0.09</td>
<td>0.36 ± 0.01†</td>
</tr>
<tr>
<td>Prandial insulin dose</td>
<td>Units/day</td>
<td>22 ± 12</td>
</tr>
<tr>
<td>Units/kg/day</td>
<td>0.29 ± 0.15</td>
<td>0.29 ± 0.1</td>
</tr>
</tbody>
</table>
| Insulin dose change (%) | 18.2 (-25, 57) | 6.4 (-24, 57)‡

Table 2: Basal and mealtime insulin before and 6 months after switch from Gla-100 to Gla-300

†p < 0.05 with respect to group 1 baseline and ‡p < 0.05 with respect to Group 1 at 6 months
§p < 0.05 with respect to group 2 baseline.

Metabolic control at 6 months

No differences were observed in HbA1c with respect to baseline levels or between the groups at the six months follow up. With regard to hypoglycaemia, group 1 subjects presented a lower number of episodes than with the previous treatment (6 (0 - 58) vs 4 (0-44) p = 0.004). No such difference was observed in group 2. There were also no differences in the number of severe hypoglycaemias in both groups, this was probably due to the small number of episodes. In neither group, changes in weight nor BMI were observed (Table 3).

<table>
<thead>
<tr>
<th>Period</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>7.7 ± 0.9</td>
<td>7.5 ± 0.8</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>7.7 ± 0.8</td>
<td>7.8 ± 0.9</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>6 (0 - 58)</td>
<td>4 (0 - 44)†</td>
</tr>
<tr>
<td>Number/month Median (min-max)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Severe hypoglycaemia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>73.1 ± 13.9</td>
<td>73.3 ± 13.3</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>73.1 ± 13.9</td>
<td>73.3 ± 13.3</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>26.6 ± 4.2</td>
<td>26.7 ± 4.2</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>26.6 ± 4.2</td>
<td>26.7 ± 4.2</td>
</tr>
<tr>
<td>28.1 ± 5.6†</td>
<td>28.4 ± 4.4‡</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Parameters for metabolic control and weight prior to and six months after switching treatment from insulin Gla-100 to Gla-300.

†p < 0.05 with respect to group 1 basal and ‡p < 0.05 with respect to group 1 at 6 months.

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Discussion

Pharmacokinetic and pharmacodynamic studies of subjects, both with and free from diabetes, have observed the action of Gla-100 to last under 24 hours \[1,8\] while clinical studies presented a significant percentage of subjects with Type 1 DM requiring more than one injection of insulin Gla-100 a day \[2-4\]. Some of these studies have also shown improvement in glycaemic control in a subgroup of patients \(15\) and \(24.2\)% when changing from one to two doses of Gla-100 \[2,3\]. At eight weeks follow-up, the Ashwell., \textit{et al}.
study \[2\] described no difference in the requirement for insulin Gla-100 between subjects with \(1\) or \(2\) doses of basal insulin, as opposed to the Albright., \textit{et al}.
study, with a longer follow-up \(12\) - \(15\) months), which showed an increase in the dose of insulin Gla-100 of \(70\)% for subjects taking two doses \[3\]. The differences between the findings of these two studies are most probably due to the length of the follow-up and how that may relate to improved titration of the dose of insulin and assessment of the changes in HbA1c in the study with the longer follow-up period.

For subjects with type 1 DM, insulin Gla-300 has been shown to have flatter and more prolonged pharmacokinetic and pharmacodynamic profiles compared to Gla-100 \[5\], but also to require greater insulin dose. In the EDITION 4 and JP1 studies, subjects with Type 1 DM required higher doses of Gla-300 than their previous basal insulin requirements, with increases of \(17.5\)% and \(20.5\)% respectively. The greatest difference was observed when comparing the night time dose of Gla-300 and Gla-100, as subjects treated with morning Gla-100 also required \(20\)% more insulin than those treated with night time Gla-100 \[6,7\]. It has been suggested that the increased dose could be secondary to Gla-300 offering lower bioavailability, since the more compact subcutaneous insulin deposits are more exposed to tissue peptides as absorption is more prolonged \[6\]. In the EDITION studies, although most subjects had been previously treated with insulin Gla-100, a smaller percentage had been treated with other basal insulins. Moreover, the patients had been following a regimen of \(1\) or \(2\) injections of basal insulin, with percentages varying from one study to the other \(15.2\) and \(17.8\)% in the EDITION 4 study and \(31.1\) and \(32.2\)% in the EDITION JP1 study \[6,7\]. A pilot study carried out with a smaller number of Type 1 DM patients, did not show a higher requirement for Gla-300 than Gla-100 \[9\]. The differences could possibly be due to the morning administration of Gla-100 which, as mentioned above, has been observed to require higher doses \[6\].

Real-life studies with patients with type 1 diabetes have been recently published, all of them have showed no increase or a lower increase of insulin Gla-300 than in the EDITION studies \[10-12\]. In a UK study there was no changes in the dose of basal insulin. In this study, at baseline \(86\)% of participants were on a basal bolus regimen, \(35\)% were on twice-daily basal insulin doses and Gla-100 was the basal insulin in \(55\)% of the regimens \[10\]. In another observational study by Pujante Alarcón., \textit{et al}.
, patients were switched from one dose of Gla-100 to one dose of Gla-300 administered at the same schedule \(11\)% morning dose, \(48.8\)% lunch dose and \(39\)% bedtime dose) and the change in total dose of basal insulin was of \(+7.24\)% at 6-month follow-up \[11\]. Oriot., \textit{et al}.
also analysed the dose increase according to the number of previous injections of Gla-100. They described a significant slightly higher dose in the group treated with one dose of Gla-100 and no difference was seen in the group of subjects previously treated with \(2\) doses of Gla-100 at 6 months of switching to Gla-300, but the differences between the two groups were small \(+6.1\) vs \(+4\)% \[12\].

In our study we observed a clear difference between the two groups with respect to the Gla-300 required. It was far higher amongst subjects from group 1, who showed increases similar to those described in the EDITION 4 and JP1 studies. The subjects in group 2 required a lesser increase than that described, probably due to the fact that they started from a position of higher baseline Gla-100 requirements, in line with the findings of the abovementioned Albright., \textit{et al}.
study, which observed a need for higher doses of insulin Gla-100 amongst Type 1 DM patients treated with \(2\) doses of insulin Gla-100 \[3\] and in addition, these results are similar to those of the Belgian study \[12\]. The differences between the studies could be partially due to the daytime administration of Gla-100 in a significant number of patients \[9,11\] which, as mentioned above, has been observed to require higher doses \[6\]. In addition, at baseline some patients were

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treated with twice-daily basal insulin doses [10,12] and according to our results, these patients could require a smaller increase in insulin dose.

With regard to metabolic control, no differences in HbA1c were observed in either of the groups at 6 months after switching, in line with the findings of the EDITION 4 and JP1 studies [6,7]. However, some real-life studies have shown a reduction of HbA1c at 6 month follow-up, one of them with very modest decrease [10,12].

Group 1 subjects of this study presented a lower number of hypoglycaemic episodes than with their previous treatment. A decrease in the number of hypoglycaemic episodes was also observed in the EDITION 1JP7 and real-life studies [11,12], as well as in other studies performed with Type 2 diabetes patients [13], but not in the EDITION 4 study [6]. The authors of the EDITION JP1 study attribute the variations in the results of the EDITION 4 study to differences in diet and lifestyle, as well as in the time of administration of the basal insulin. In EDITION 4 it was given before breakfast or supper, while in the EDITION JP1 study, it was only given before supper.

The reduced number of episodes of hypoglycaemia found by the EDITION studies was during the first 8 weeks, that is, during the titration stage. It has been said that at the beginning of both EDITION 4 and JP1 studies, patients were undertreated since, on switching, they were treated with the same amount of Gla-300 as previously with Gla-100. However, the former required higher doses. This could explain the lower number of hypoglycaemic episodes during the titration stage [14]. In our study, the insulin switch was made together with an initial 15% increase in dose for the group previously treated with a single dose of insulin Gla-100. Moreover, a reduction in hypoglycaemic episodes was observed at six months of follow-up.

Limitation of the Study

The limitations to the present study are the fact that it is an observational study with a small number of patients. Being an observational study, the titration of the dose was carried out by the patient with a mid-term medical check-up, which in turn reflects the results of daily clinical practice, although it is probably less accurate than that performed by the physician. However, we should point out that the insulin switch and control over the first six months was performed by the same medical-educational team, using the same control and treatment criteria. Moreover, in most cases, insulin dose calculators were used to assess the doses administered and the number of hypoglycaemic episodes suffered by each patient, thus confirming the data in the patient’s written accounts. Another limitation is the lack of both a quality of life and a treatment satisfaction test to assess the impact of the reduced number of hypoglycaemic episodes amongst group 1 subjects, and the reduction to a regimen of just one basal insulin injection a day for Group 2 subjects. In addition, the time when hypoglycaemia occurred was not recorded, which would have been interesting to evaluate the differences in nocturnal hypoglycaemia.

The strength of the present study lies in the fact that all the patients were initially treated with the same basal insulin Gla-100, thus making it easier to assess the increased dose. The EDITION and UK real-life studies included patients previously treated with different basal insulins, although most were treated with Gla-100. In addition, most of the patients of group 1 (93%) administered previously Gla-100 at night, which reduce the need for higher doses of daytime administration of Gla-100. Our study showed that patients previously taking two injections of insulin had already required far higher doses of basal insulin.

Conclusion

To conclude, our results support the findings of EDITION studies with respect to the need to increase the dose of insulin when administering Gla-300 instead of Gla-100 but with clear differences between those subjects who had previously required two injections of Gla-100. However, there are significant differences between these results with the other real-life studies. The resulting cost-benefit of

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employing this insulin has been questioned due to the increase in the dose required to achieve the same level of control [14]. However, probably for subjects previously treated with two injections of Gla-100 it could prove cost-effective since the increase in dose is only small and it would mean eliminating one of the two daily injections of basal insulin, with the likely added perk of improved quality of life. Moreover, in clinical practice, the results could help to better calculate the initial dose of insulin Gla-300 when switching from insulin Gla-100, thus reducing not only the time required for titration with either of the two subject groups, but also the number of appointments and patient queries.

Acknowledgements

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Conflict of Interest

MA has received honoraria for consulting and/or speaking and/or registrations for Almirall, Astrazeneca, Boehringer Ingelheim, Janssen, Lilly, MSD, Novo Nordisk, and Sanofi. ML has received honoraria for consulting and/or speaking and/or registrations for Astrazeneca, MSD, NovoLab and Roche. RB has received honoraria for consulting and/or speaking and/or registrations for Astrazeneca, Novo Nordisk, Abbott, MSD and Sanofi. YT has received honoraria for speaking for Lilly. GF has received honoraria for consulting and/or speaking and/or registrations for Astrazeneca, Lilly, MSD, Novo Nordisk and Sanofi. LV has received honoraria for consulting and/or speaking and/or registrations for Abbott, Astrazeneca, Janssen, Lilly, Menarini, Merck, MSD, Novo Nordisk and Sanofi.

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*Citation:* Mercè Albareda, *et al.* “Requirements for Insulin Glargine 300 U/ML for Patients with Type-1 Diabetes Mellitus Previously Treated with Insulin Glargine 100 U/ML, According to the Number of Daily Injections Given Previously”. *EC Diabetes and Metabolic Research* 5.3 (2021): 02-09.


