Control of Glycemia With a Basal-Plus Regimen in People With Type 2 Diabetes Mellitus Insufficiently Controlled by Previous Treatment

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is often characterized by insulin resistance and progressive β-cell deterioration. With longer duration of T2DM most patients treated with oral antihyperglycemic drugs (OADs), in monotherapy or in combination, will ultimately require basal insulin therapy and even further prandial intensification later on. The basal-plus regimen is one of the proposed approaches for treatment intensification by adding one injection of prandial rapid-acting insulin to basal insulin. The CONBA+ study aimed to collect real-world data of glycemic control of T2DM patients uncontrolled on insulin/OAD therapy using the basal-plus approach in Morocco.

Methods: CONBA+ study was a national, prospective, non-interventional, multicenter study involving 50 endocrinologists from Morocco. The study, conducted between June 2015 and June 2017, enrolled T2DM patients uncontrolled on their previous regimen (hemoglobin A1c (HbA1c) ≥ 7.5% on two OADs, glargine 100 U/mL and OADs or once daily premixed insulin). Patients continued or newly initiated once-daily insulin glargine 100 U/mL (Gla-100) and also received one injection of insulin glulisine (Glu) at the main meal in replacing any previous treatment. Demographics, glycated hemoglobin (hemoglobin A1c (HbA1c)), fasting blood glucose (FBG), postprandial glucose (PPG), insulin doses and the frequency of hypoglycemia were assessed at baseline and at 12 and 24 weeks after study entry.

Results: Overall, 854 people (46.8% men) fulfilled the inclusion criteria. At baseline, mean age was 59.0 ± 9.4 years, mean duration of diabetes 10.8 ± 6.7 years (range: 1 - 45 years), mean body mass index (BMI) 27.4 ± 4.0 kg/m\textsuperscript{2} and mean HbA1c 9.50±1.51%. After 24 weeks, 33.0% of patients achieved target HbA1c < 7.0% (primary endpoint). In addition, mean FPG and postprandial blood glucose (PPBG) improved significantly at week 24 (change from baseline: -88 mg/dL and -108 mg/dL respectively; P < 0.001) while the number of reported severe hypoglycemia was low.

Conclusions: The use of a basal-plus regimen consisting of insulin glargine 100 U/mL and insulin glulisine injected at the main meal resulted in significant improvements of glycemic parameters. In addition, the basal-plus approach showed a good safety profile with a low risk of hypoglycemia.

Keywords: Treatment intensification; Insulin glargine; Insulin glulisine; Glycemic control; Hypoglycemia

Introduction

Type 2 diabetes mellitus (T2DM) is a complex disease often associated with insulin resistance and progressive β-cell deterioration. As β-cell function declines, most patients will require insulin as they will fail to obtain and maintain an adequate glycemic control with only lifestyle changes and oral antihyperglycemic drugs (OADs) [1]. The addition of basal insulin is considered to be the simplest way to start insulin therapy in those patients [1, 2]. Nevertheless, only approximately half of all patients treated with basal insulin will achieve target glycated hemoglobin (hemoglobin A1c (HbA1c)) goals indicating a need for additional treatment [3]. Starting with premixed insulin may be an effective option, but it is frequently linked to an increased risk of hypoglycemia, weight gain and fixed meal schedules [4].

As an alternative, the approach known as “basal-plus strategy” has been developed. This approach considers the addition of a single daily prandial injection of rapid-acting insulin before the meal of the day that produces the largest postprandial glucose excursions. The effectiveness of the basal-plus regimen is supported by the fact that one major prandial glucose excursion occurs daily in patients with T2DM especially at mid-morning after breakfast [5]. In addition, several clinical trials have demonstrated the efficacy and safety of this approach as it allows achieving a good therapeutic response with a low risk of hypoglycemia and weight gain, regardless of the patient’s age or BMI [6-10].

There are no data in Morocco concerning glycemic con-
The present real-world study aimed to collect data on the number of T2DM patients who were uncontrolled on various previous treatments including two OADs only, basal insulin with OADs, or once daily premixed insulin who achieved HbA1c < 7.0% after 6 months with a basal-plus regimen.

Results

Overall, 854 patients (46.8% men) fulfilled the selection criteria and were included in the study. At study entry, the mean age was 59.0 ± 9.4 years with almost half of participants (48.6%) aged over 60 years. The time between diagnosis of T2DM and inclusion in the study ranged between 1 to 45 years; and 27.3% of participants were not overweighted or obese.

The baseline patient characteristics are summarized in Table 1. All participants were intended to receive a basal plus therapy consisting of once-daily Gla-100 and one injection of glulisine at the main meal at the discretion of the participating physician between 1 and 3 months prior to inclusion. However, a few patients were switched to twice daily (BID) Gla-100 (n = 2; 0.2%) or two (n = 46; 5.4%) or three (n = 12; 1.4%) injections of glulisine at the beginning of the study (Table 2). The number of patients with more than one glulisine injection per day further increased towards the end of the study (BID: n = 122; 14.3%; thrice daily (TID): n = 54; 6.3%). The analysis of results included all participants regardless of injection frequency of basal or prandial insulin in order to reflect daily routine practice in Morocco.

Changes in HbA1c levels

A significant improvement in glycemic control was observed during the study after initiation of a basal-plus regimen with Gla-100 and glulisine. HbA1c decreased from 9.50±1.51% to 8.08±1.06% at 12 weeks (P < 0.001) and to 7.37±0.88% at 24 weeks (P < 0.001). Likewise, mean change from baseline in HbA1c was -1.42% (95% CI: -1.53%, -1.30%) and -2.13% (95% CI: -2.25%, -2.02%); P < 0.001 at 12 and 24 weeks respectively (Table 3). The percentage of patients who achieved target HbA1c level < 7.0% increased from 10.2% (95% CI: 8.1% - 12.2%) at 12 weeks to 33.0% (95% CI: 29.7% - 36.1%) at 24 weeks (P < 0.001; Table 3).

Only 3.5% (95% CI: 2.3-4.8%) and 14.5% (95% CI: 12.0-16.9%) of patients achieved HbA1c values ≤ 6.5% at 12 and 24 weeks, respectively.

Materials and Methods

Study design and patients population

This was an open-label, prospective, observational study carried out from June 2015 to June 2017 in 50 sites that were randomly selected among 150 endocrinologists in Morocco. A total of 1,000 patients were planned to be included in the study to obtain a representative and sufficient sample size.

Physicians who agreed to participate were asked to enroll the first 20 T2DM patients aged at least 18 years, who were known to be diabetic since at least 1 year and presenting with HbA1c ≥ 7.5%, for whom the physician has recently (between one and three months prior to inclusion in the study) decided to prescribe a basal insulin (insulin glargine 100 U/mL, Gla-100) and a rapid-acting insulin injection (insulin glulisine) at main meal due to a suboptimal glycemic control with the previous regimen (two OADs, Gla-100 with OADs or once daily premixed insulin).

Patients were to be excluded if they were not willing, or not able to perform self-monitoring blood glucose or to self-titrate basal insulin under physician’s guidance; if they had any serious underlying illness, were hospitalized or taking steroids or any other medication known to elevate or lower glycemia. Moreover, pregnant or breastfeeding women were not allowed to participate in the study.

All patients provided written informed consent before entering the study. The study was non- interventional; the decision of results included all participants regardless of injection frequency of basal or prandial insulin in order to reflect daily routine practice in Morocco.

Data collection

During the study, data were collected on standardized paper case report forms (CRFs) at three different outpatient visits: at the moment of inclusion (visit 1) then at 12 and 24 weeks after entering the study (visit 2 and visit 3, respectively). Demographics, vital signs, bodyweight, HbA1c, insulin doses, use of OADs and of concomitant non-insulin antidiabetic drugs were reported. Moreover, the frequency of symptomatic and nocturnal (defined as occurring between midnight and 6:00 am) hypoglycemia and adverse events were recorded. Finally, records for fasting (FBG) and postprandial blood glucose (PPBG) were collected.

Statistical analysis

The statistical analysis was descriptive. Results were presented as number of available observations, means, standard deviations (SD) and minimum and maximum values for quantitative variables. Categorical variables were presented as percentages. The 95% confidence interval (CI) was given. Differences between means were assessed by the paired t-tests for continuous variables while the McNemar test was used for comparison of percentages. P values < 0.05 were considered statistically significant.
After the 6 months observational period, mean FBG levels dropped significantly (P < 0.001) from 198 ± 65 mg/dL at inclusion to 148 ± 40 mg/dL at 12 weeks and to 129 ± 32 mg/dL at 24 weeks. Similarly, mean change from baseline for FBG was -57 mg/dL (95% CI: -79 to -35 mg/dL) and -88 mg/dL (95% CI: -110 to -66 mg/dL) at 12 and 24 weeks, respectively (Table 4). Mean PPBG values decreased significantly from 277 ± 72 mg/dL (baseline) to 200 ± 51 mg/dL (P < 0.001) at 12 weeks (Δ = -78 mg/dL) and to 168 ± 41 mg/dL (P < 0.001) at 24 weeks (Δ = -108 mg/dL) (Table 4).

In addition, glycemic control of T2DM patients was significantly improved regardless of the pre-treatment regimen used prior to the inclusion into the study (Table 5).

### Blood glucose

After the 6 months observational period, mean FBG levels dropped significantly (P < 0.001) from 198 ± 65 mg/dL at inclusion to 148 ± 40 mg/dL at 12 weeks and to 129 ± 32 mg/dL at 24 weeks. Similarly, mean change from baseline for FBG was -57 mg/dL (95% CI: -79 to -35 mg/dL) and -88 mg/dL (95% CI: -110 to -66 mg/dL) at 12 and 24 weeks, respectively (Table 4). Mean PPBG values decreased significantly from 277 ± 72 mg/dL (baseline) to 200 ± 51 mg/dL (P < 0.001) at 12 weeks (Δ = -78 mg/dL) and to 168 ± 41 mg/dL (P < 0.001) at 24 weeks (Δ = -108 mg/dL) (Table 4).

In addition, glycemic control of T2DM patients was significantly improved regardless of the pre-treatment regimen used prior to the inclusion into the study (Table 5).

### Insulin doses

Of 854 patients treated with Gla-100 and glulisine, information

### Table 1. Baseline Characteristics of the Study Participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>848</td>
<td>59.0 ± 9.4</td>
<td>30 - 87</td>
</tr>
<tr>
<td>Gender</td>
<td>835</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>444(53.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>391(46.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>846</td>
<td>167.2 ± 8.6</td>
<td>142 - 192</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>850</td>
<td>76.5 ± 11.8</td>
<td>43 - 117</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>846</td>
<td>27.4 ± 4.0</td>
<td>16.7 - 50.0</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>853</td>
<td>10.8 ± 6.7</td>
<td>1 - 45</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>823</td>
<td>77.3 ± 8.6</td>
<td>54 - 128</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>844</td>
<td>133.4 ± 14.8</td>
<td>93 - 230</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>838</td>
<td>75.6 ± 9.7</td>
<td>50 - 120</td>
</tr>
</tbody>
</table>

N: number of subjects/available data; SD: standard deviation. Results were reported taking into account available data. Missing data were not counted in the total number of subjects or percentages.

### Table 2. Gla-100 and Glulisine Doses (Mean ± SD) Throughout the Study

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Units/day</td>
<td>N Units/day</td>
<td>N Units/day</td>
</tr>
<tr>
<td>Gla-100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OD</td>
<td>849 20.7 ± 8.5</td>
<td>837 22.7 ± 8.9</td>
<td>815 23.5 ± 9.0</td>
</tr>
<tr>
<td>BID</td>
<td>2 33.0 ± 9.9</td>
<td>3 28.0 ± 11.1</td>
<td>2 29.5 ± 9.2</td>
</tr>
<tr>
<td>Glulisine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OD</td>
<td>725 9.7 ± 4.2</td>
<td>659 10.7 ± 3.9</td>
<td>612 11.5 ± 4.9</td>
</tr>
<tr>
<td>BID</td>
<td>46 10.1 ± 4.4</td>
<td>120 14.4 ± 7.1</td>
<td>122 14.8 ± 6.9</td>
</tr>
<tr>
<td>TID</td>
<td>12 10.0 ± 4.5</td>
<td>26 15.6 ± 9.0</td>
<td>54 16.6 ± 10.3</td>
</tr>
</tbody>
</table>

SD: standard deviation; OD: once daily; BID: twice daily; TID: thrice daily. N: number of subjects/available data. Results were reported taking into account available data. Missing data were not counted in the total number of subjects or percentages.

### Table 3. Mean HbA1c Changes Throughout the Study and Percentage of Patients Achieving Target Values

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n = 851)</th>
<th>12 weeks (n = 835)</th>
<th>24 weeks (n = 809)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.50 ± 1.51</td>
<td>8.08 ± 1.06</td>
<td>7.37 ± 0.88</td>
</tr>
<tr>
<td>ΔHbA1c (%)</td>
<td>-1.42 (-1.53, -1.30)</td>
<td>-2.13 (-2.25, -2.02)</td>
<td></td>
</tr>
<tr>
<td>HbA1c &lt; 7.0%</td>
<td>0%</td>
<td>10.2% (8.1, 12.2)</td>
<td>33.0% (29.7, 36.1)</td>
</tr>
<tr>
<td>HbA1c ≤ 6.5%</td>
<td>0%</td>
<td>3.5% (2.3, 4.8)</td>
<td>14.5% (12.0, 16.9)</td>
</tr>
</tbody>
</table>

All differences (means or percentages) between visits are significant (P < 0.001). Confidence intervals at 95% are presented between round brackets. HbA1c: hemoglobin A1c.
on injection frequency and/or insulin doses was missing in 74 (8.7%) patients at baseline, and missing data further increased during the course of the study (Table 2). The mean daily glulisine and Gla-100 doses did not change significantly between the start and the end of the study in patients with available data indicating a lack of appropriate insulin titration during the study (Table 2).

Safety

Overall, 19.5% of the participants had experienced at least one symptomatic hypoglycemic event from study entry to week 12, and 21.1% between week 12 and 24. A total of 19 severe hypoglycemic events (requiring third party assistance) were reported in 18 patients during the study: eight subjects reported one severe hypoglycemic event and one patient described two severe hypoglycemic episodes at week 12. Another nine severe hypoglycemic events were reported in nine patients until week 24. Daytime symptomatic hypoglycemia episodes were more frequently reported than nocturnal episodes.

Patients previously treated with two OADs experienced more hypoglycemic events than patients using other treatment regimens prior to study entry.

Discussion

The basal-plus approach has been validated by several clinical trials as a simple, effective and safe method of intensifying basal insulin therapy in patients failing to meet glycemic targets on basal insulin alone or in combination with OADs [9-14]. The results of this 24-week national, open-label, observational study shows that the use of basal insulin together with rapid-acting insulin at main meal improved glycemic control in uncontrolled T2DM Moroccan patients using two OADs or basal insulin ± OAD, or once daily premixed insulin as previous therapy. Despite the fact that about 20% of participants in

Table 4. Mean FBG and PPBG Values Over the Course of the Study

<table>
<thead>
<tr>
<th></th>
<th>FBG (mg/dL)</th>
<th>PPBG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong> Baseline 12 weeks 24 weeks</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>FBG (mg/dL)</td>
<td>198 ± 65</td>
<td>277 ± 72</td>
</tr>
<tr>
<td>ΔFBG (mg/dL)</td>
<td>-57 (-79, -35)</td>
<td>-78 (-84, -72)</td>
</tr>
<tr>
<td>PPBG (mg/dL)</td>
<td>200 ± 51</td>
<td>676</td>
</tr>
<tr>
<td>ΔPPBG (mg/dL)</td>
<td>-88 (-110, -66)</td>
<td>-108 (-114, -102)</td>
</tr>
</tbody>
</table>

N: number of subjects/available data. Results were reported taking into account available data. Missing data were not counted in the total number of subjects or percentages. FBG: fasting blood glucose; PPBG: postprandial blood glucose.

Table 5. Sub-Analysis of Glycemic Control in Participants According to Their Previous Type of Antidiabetic Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>12 weeks</th>
<th>24 weeks</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal insulin ± OADs (n = 470)</td>
<td>HbA1c &lt; 7.0%</td>
<td>0%</td>
<td>9.2%</td>
<td>31.6%</td>
</tr>
<tr>
<td></td>
<td>HbA1c ≤ 6.5%</td>
<td>0%</td>
<td>3.0%</td>
<td>12.8%</td>
</tr>
<tr>
<td></td>
<td>HbA1c (%)</td>
<td>9.29 ± 1.40</td>
<td>8.06 ± 1.06</td>
<td>7.41 ± 0.90</td>
</tr>
<tr>
<td></td>
<td>FBG (mg/dL)</td>
<td>178 ± 63</td>
<td>140 ± 39</td>
<td>126 ± 32</td>
</tr>
<tr>
<td></td>
<td>PPBG (mg/dL)</td>
<td>264 ± 72</td>
<td>191 ± 48</td>
<td>163 ± 39</td>
</tr>
<tr>
<td>2 OADs (n = 272)</td>
<td>HbA1c &lt; 7.0%</td>
<td>0%</td>
<td>13.3%</td>
<td>33.2%</td>
</tr>
<tr>
<td></td>
<td>HbA1c ≤ 6.5%</td>
<td>0%</td>
<td>5.5%</td>
<td>16.0%</td>
</tr>
<tr>
<td></td>
<td>HbA1c (%)</td>
<td>9.77 ± 1.51</td>
<td>8.06 ± 1.03</td>
<td>7.37 ± 0.85</td>
</tr>
<tr>
<td></td>
<td>FBG (mg/dL)</td>
<td>223 ± 62</td>
<td>158 ± 40</td>
<td>134 ± 33</td>
</tr>
<tr>
<td></td>
<td>PPBG (mg/dL)</td>
<td>293 ± 68</td>
<td>213 ± 52</td>
<td>175 ± 40</td>
</tr>
<tr>
<td>Premixed insulin ± OADs (n = 35)</td>
<td>HbA1c &lt; 7.0%</td>
<td>0%</td>
<td>8.6%</td>
<td>51.4%</td>
</tr>
<tr>
<td></td>
<td>HbA1c ≤ 6.5%</td>
<td>0%</td>
<td>0.0%</td>
<td>31.4%</td>
</tr>
<tr>
<td></td>
<td>HbA1c (%)</td>
<td>9.13 ± 1.16</td>
<td>7.98 ± 0.93</td>
<td>6.98 ± 0.89</td>
</tr>
<tr>
<td></td>
<td>FBG (mg/dL)</td>
<td>199 ± 47</td>
<td>148 ± 34</td>
<td>122 ± 24</td>
</tr>
<tr>
<td></td>
<td>PPBG (mg/dL)</td>
<td>252 ± 55</td>
<td>193 ± 40</td>
<td>174 ± 50</td>
</tr>
</tbody>
</table>

FBG: fasting blood glucose; OAD: oral antihyperglycemic drugs; PPBG: postprandial blood glucose; HbA1c: hemoglobin A1c.
this study received a more intensified treatment than just basal-
plus (more than one injection of glulisine per day), the signifi-
cant improvements in glycemic control after 12 and 24 weeks
of treatment with Gla-100 and glulisine are very comparable to
results previously reported in several basal-plus studies [9-14].

Overall, 33% of patients achieved the primary endpoint of
the study of HbA1c levels < 7.0% after 24 weeks of treatment.
However, only 14.5% of participants achieved target HbA1c ≤ 6.5% at 24 weeks. This might be explained by a high baseline
HbA1c at study entry (9.5%). The absolute mean HbA1c was
considerably lowered by -2.13% at 24 weeks indicating a good
effectiveness of the basal-plus strategy in real-world practice in
Morocco.

The percentage of people achieving target HbA1c < 7.0% (33%) or ≤ 7.0 % (38%) at 6 months in our real-world
study were slightly lower to that one observed after 6 months
in the OPAL clinical study using a basal-plus regimen with
Gla-100 and glulisine as well [14]. In the OPAL study, 44%
of patients achieved HbA1c ≤ 7.0% at the end of the study.
However, the OPAL study showed a high proportion of pa-
tients (30%) achieving an HbA1c target of 6.5% in compar-
tion to our study. This may be, in part, to the different
selection criteria used in relation to baseline HbA1c levels. In
fact, while subjects had to show HbA1c values > 6.5-9.0% to
be eligible for the OPAL study, the CONBA+ study required
HbA1c values > 7.5% at study entry. Moreover, our study was
of non-interventional, observational nature without providing
any guidance on proper insulin titration compared to the OPAL
interventional study design. Therefore, it is not surprising that
in our study, the mean daily glulisine and Gla-100 doses did
not change significantly throughout the study indicating a lack
of adequate insulin titration during the observational period.
Moreover, in the CONBA+ study, patients on basal-plus regi-
men received a higher mean daily glulisine dose at study start
(9.7 ± 4.2 U/day) compared to patients in the OPAL study (5.0 ± 2.3 U/day), while glulisine doses at end of study, were com-
parable between OPAL and CONBA+ (OPAL: 12.0 ± 7.0 U/
day CONBA+: 11.5 ± 4.9 U/day). In contrast, Gla-100 doses
were higher in the OPAL study both at start and end of study
(26.5 ± 13.2 U vs. 20.7 ± 8.5 U at study start and 26.9 ± 13.2
UI vs. 23.5 ± 9.0 UI at end of study for OPAL and CONBA+
study, respectively). In addition, a total of 58 patients were al-
tready treated with more than one daily injection of glulisine at
the beginning of the study and increased to 176 patients at the
end of the study. On the other hand, in our study, the change
from baseline to the end of study for HbA1c was greater than
the values observed in clinical trials assessing the efficacy of
the basal-plus approach. The analysis of pooled data from four
multicenter clinical trials where patients with poor glycemic
control on OADs have initiated a basal-plus regimen for up to 6
months, showed a significant decrease of -0.4% in HbA1c (vs.
-2.13% for the CONBA+ study) over a follow-up of 6 months
[14]. However, patients included in this analysis were already
receiving once-daily injection of basal insulin (and OADs) and
the single injection of insulin glulisine at the main meal was
added at patient’s inclusion in the corresponding studies.

Both FBG and PPGB contribute to HbA1c levels, and
therefore, inadequate control of either parameter will have
a negative impact on overall glycemic control. Normalizing
FBG is a long-established goal of basic glycemic control in
the treatment of T2DM. Nevertheless, evidence suggests that
postprandial glucose (PPG) levels are the major contributor
to overall glycemic control in patients with well-to-moderately
controlled HbA1c (< 7%) in patients with T2DM [15]. In our
study, after 24 weeks, both mean levels of FBG and PPGB
decreased significantly in comparison to baseline levels. These
results are in agreement with those described in other studies
[9-14].

Finally, as described in previous studies [9-14], the CON-
BA+ study has shown that the basal-plus approach, as a first
step in introducing prandial insulin therapy, was well tolerated
with a low rate of severe hypoglycemia and no specific safety
concern. For those needing further intensification of insulin
therapy given individual clinical requirements based on diabe-
tes duration, age and risk of macrovascular disease; advancing
to full basal-bolus treatment may be needed [16, 17].

Our study has some limitations given its observational
non-controlled design. Some of the data were missing for a
number of variables and subjects. The hypoglycemic events
were self-reported by the study patients leading to a potential
underestimation of the frequency of these events. Furthermore,
the effect of the basal-plus approach on patients’ weight could
not be assessed during our study as this variable has not been
reported at final visit. In addition, the study population includ-
ed 58 patients on the basal-bolus regimen. Lastly, although the
results of our study were examined in view of those reported in
published clinical trials, a direct comparison of the CONBA+
study outcomes with other studies cannot be established due
to differences in trial design, primary endpoints and assessed
patient populations.

Nevertheless, despite these limitations, the results of this
study have shown that the basal-plus approach using insulin
glulisine in addition to basal insulin glargine is a relevant opti-
onion for T2DM patients even when considering the most recent
2018 recommendations from the American Diabetes Associa-
tion (ADA), where the preferred option for intensification of
insulin therapy is the addition of GLP-1 receptor agonists to
basal insulin. As a matter of fact, the ADA states that compared
with basal-plus insulin, “basal insulin plus GLP-1 RAs are as
associated with less hypoglycemia and with weight loss instead
of weight gain but may be less tolerable and have a greater
cost” [18]. Tolerability and particularly treatment cost may in-
deed be important factors for treatment decision making in the
population of Moroccan T2DM patients.

In conclusion, the results of our study suggest that, fol-
lowing the real-life clinical practice, the use of the basal-plus
approach in Moroccan patients with uncontrolled T2DM on
previous therapy, improves significantly glycemic control while
showing a good safety profile with a low risk of severe
hypoglycemia. However, additional educational initiatives are
needed to further improve insulin titration practice and overall
glycemic control in Morocco.

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References
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Conflict of Interest

H. Iraqi received grant support and/or served as a consultant for Sanofi, Eli Lilly and Novo Nordisk, Servier, Abbott, Merck, MSD and Astra-Zeneca. N. El Ansari received grant support and/or served as a consultant for Sanofi, Eli Lilly, Novo Nordisk, MSD and Astra-Zeneca.

Informed Consent

Obtained.

Author Contributions

H. Iraqi: validation of the protocol, analyzing the data, and writing; N. El Ansari: review of the manuscript.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

References


