IDegLira Improves Metabolic Control in Patients with Type 2 Diabetes Previously Treated with Premix Insulin

Amela Dizdarevic-Bostandzic, Vanja Karlovic Beslic, Ismana Surkovic, Sefkija Balic, Tanja Dujic, Zeljija Velija-Asimi, Azra Burekovic

ABSTRACT

Background: IDegLira (fixed combination of GLP 1 receptor agonist and insulin) has been shown to be effective in improving the glucoregulation in patients previously treated with oral therapy as well as individual components, GLP-1 receptor agonist or basal insulin. Objective: The aim of this study is to examine the parameters of metabolic control in patients treated with IDegLira who were previously treated with premix insulin in several daily doses and to compare them with patients whose premix insulin dose was increased. Methods: The study included 100 patients who had been previously treated with two or three daily doses of premix insulin. Half of the patients were switched to IDegLira (group I), and half (group II) had their insulin dose increased according to the clinical assessment of the physician. Fasting glucose, 2h postprandial glucose, Hba1c, BMI and insulin dose were determined at baseline and at follow-up after 6 months. Results: Patients treated with IDegLira compared to patients whose insulin dose was increased achieved significantly lower fasting glucose (p <0.001), postprandial glucose (p <0.001), Hba1c (p <0.001), BMI (p <0.001) with a significantly lower insulin dose (p <0.001). Comparison of the same parameters within the groups of patients at the beginning and after 6 months showed that patients who were switched from insulin premix to IDegLira achieved significantly lower fasting blood glucose (p <0.001), postprandial glucose (p <0.001), Hba1c (p < 0.001), BMI (p <0.001) with significantly lower insulin dose within the fixed combination (p <0.001). Patients with gradually increased insulin dose achieved significant reduction in fasting glucose (p = 0.021) and postprandial glucose (p = 0.036), but with a significantly higher insulin dose (p = 0.005). There was also a slight increase in BMI that was not statistically significant (p = 0.267). Conclusion: The obtained data suggest that switching patients from a complex insulin regimen to a fixed combination of basal insulin and GLP 1 receptor agonist in comparison to increases in insulin dose results in a significant improvement in fasting glucose, postprandial glucose, Hba1c, and BMI. The results were achieved with a significantly lower daily insulin dose.

Keywords: IDegLira, Premix insulin, Diabetes mellitus type 2.

1. BACKGROUND

The progressive nature of type 2 diabetes necessitates that treatment is intensified as the disease advances (1). Treatment intensification is one of the most challenging and frequently observed clinical issues which is attributable to several factors, including the evolution of the disease, patient’s compliance, handling and safety of the treatment, effectiveness of treatment and durability (2). Characteristics such as glycated haemoglobin (Hba1c), fasting plasma glucose (FPG), and body mass index (BMI) are often taken into consideration when individualizing treatment; therefore, information on how specific therapies perform with regard to such characteristics is essential in order to individualize diabetes treatment options (3). Many individuals with type 2 diabetes (T2D) will eventually require insulin therapy to help achieve and maintain adequate glycemic control. However, the use of insulin can be associated with adverse effects such as hypoglycemia and weight gain, and in some patients the addition of insulin to treatment regimens is often still insufficient to achieve target glycemic control (4). Increase in body weight, worsen glycemic control, thus creating a vicious circle of poor glucoregulation with
worsening cardiovascular risk factors. Despite novel therapeutic options, many people with type 2 diabetes do not achieve their HbA1c targets. Premix insulins remain frequently used, either as initial injectable therapy or as intensification from basal insulin. Premix insulin injections can potentially provide significant glycaemic improvements to basal insulin but at the expense of increased hypoglycaemia and weight gain and the need for multiple daily doses, which may affect treatment adherence (5). A fixed combination of basal insulin degludec and glucagon-like peptide-1 receptor agonist (GLP-1RA) liraglutide (IDegLira; 50 units degludec/1.8 mg liraglutide) has been developed as a once daily injection for the treatment of type 2 diabetes (6). Titratable fixed-ratio co-formulations of basal insulin and a GLP-1 receptor agonist have been shown to improve glycemic control, with less complex dosing schedules, possibly increasing treatment adherence. Data from clinical trials show that titratable fixed-ratio co-formulations improve glycemic control, allowing more patients with T2D (both insulin-naive and insulin-experienced) to reach their glycemic targets when compared with each medication used separately (7-9). IDegLira provides additional options for clinicians and patients that may help ameliorate some of the side effects seen with insulin therapy by itself, while still providing clinically robust A1C improvements (10).

2. OBJECTIVE

The aim of this study is to examine the parameters of metabolic control in patients treated with ideglira who were previously treated with premix insulin in several daily doses and to compare them with patients whose premix insulin dose was increased.

3. PATIENTS AND METHODS

Participants

The study included 100 patients who had previously received two or three daily doses of premix insulin. Half of the patients were switched to ideglira (group I), and half had their insulin dose increased (group II) according to the clinical assessment of the attending physician. The study included patients with type 2 diabetes and unregulated glycemia (HbA1c ≥ 8%). Exclusion criteria were patients who could not tolerate IDeGLira, patients who had previously been treated with either basal insulin or a GLP 1 receptor agonist, and patients who had some of the acute complications of diabetes during the follow-up period. Patients were tested for fasting glucose, 2h postprandial glucose and HbA1c, body weight and height were measured and total daily insulin dose, and IdegLira dose determined at baseline and at follow-up visits after 6 months.

Research methods

The level of fasting glucose, 2h postprandial glucose, and HbA1c were determined in the Central Laboratory of the Clinical Centre University of Sarajevo in the beginning and after six month treatment. BMI was calculated as weight (kg)/height in m². The dose of ideglira is expressed in dose steps, and the number of dose steps corresponds to insulin units within a fixed combination. In both groups insulin dose was determined for the purpose of comparison.

Statistical analysis

The statistical program IBM SPSS Statistic 23 was used for statistical calculations. The Mann-Whitney test was used to compare the parameters between the two groups of subjects, and the Wilcoxon test was used to compare the parameters within the group in two different periods. P < 0.05 was considered statistically significant.

4. RESULTS

In the group receiving Ideglira (group I) there were 20 men and 30 women, and in the group receiving insulin (group II) there were 19 men and 31 women. The average age of patients in group I was 63 years, and in group II 62 years, there was no difference between groups (p = 0.666). The duration of diabetes for group I was 15 years, and for group II 14 years, there was no difference between groups (p = 0.419). The initial average fasting glucose in group I was 13.2 mmol / l and in group II 13 mmol / l (p = 0.677). At the follow-up examination after 6 months, the average glucose in group I was 8.16 mmol / l, and in group II 11.9 mmol / l. The difference between the groups was statistically highly significant (p < 0.001). Postprandial glucose in group I was 17.3 mmol / l, and in group II 17.09 mmol / l (p = 0.687).

At the control examination after 6 months, the average postprandial glucose in group I was 12.1 mmol / l, and in group II 15.9 mmol / l. The difference between the groups was statistically highly significant (p < 0.001). The initial value of HbA1c was 10.9% in group I and 10.8% in group II (p = 0.751). After 6 months, HbA1c was 8.9% in group I and 10.4% in group II (p < 0.001). The initial BMI was 36.19 in group I and 36.10 in group II (p = 0.741). After 6 months, the BMI in group I was 33.8 and in group II 36.5 (p < 0.001). The initial insulin dose was 68 IU in group I and 66 IU in group II (p = 0.586). After 6 months, the insulin dose in group I was 46 IU, and in group II 78 IU (p < 0.001) (Table 1) The above parameters were also compared within the groups at the beginning and at the six-month control. In group I fasting glucose at the beginning of the study was 13.2 mmol / l, at control after 6 months 8.6 mmol / l (p < 0.001). Postprandial glucose was initially 17.3 mmol / l, at the six-month control 12.1 (p < 0.001). HbA1c was initially 10.9% at control after 6 months 8.9% (p < 0.001). BMI was initially 36.19, at the six-month control 33.8 (p < 0.001). The insulin dose was initially 68 IU, at the six-month control 46 IU (p < 0.001) (Table 2).

In group II fasting glucose was 13.0 at the beginning of the study, at control after 6 months 11.9 mmol / l (p = 0.021). Postprandial glucose was 17.09 at the beginning of the study, and 15.9 at the six-month control (p = 0.036). HbA1c was 10.8% at baseline, at control after 6 months 10.4 % (p = 0.220). BMI was 36.1 at baseline, at control after 6 months 36.5 (p = 0.267). The insulin dose was 66 IU at the beginning of the study, and was statistically significantly higher (78 IU) at the six-month follow-up (p = 0.005) (Table3).
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### Table 1. Patients characteristics and comparison of examined parameters in IDegLira (I group) and insulin (group II)

| Parameter                                      | Group/ Treatment | N  | Mean Rank | Σ of Ranks | Mann-Whitney U | p-value |
|------------------------------------------------|------------------|----|-----------|------------|----------------|---------|
| Fasting glucose- initial (mmol/L)              | Ideglira         | 50 | 51.71     | 2585.50    | 1189.500       | 0.677   |
|                                                 | Insulin          | 50 | 49.29     | 2464.50    |                |         |
| Postprandial glucose-initial (mmol/L)           | Ideglira         | 50 | 51.67     | 2583.50    | 1191.500       | 0.687   |
|                                                 | Insulin          | 50 | 49.33     | 2466.50    |                |         |
| HbA1c- initial (%)                              | Ideglira         | 50 | 51.42     | 2571.00    | 1204.000       | 0.751   |
|                                                 | Insulin          | 50 | 49.58     | 2479.00    |                |         |
| Body Mass Index- initial (kg/m2)                | Ideglira         | 50 | 51.46     | 2573.00    | 1202.000       | 0.741   |
|                                                 | Insulin          | 50 | 49.54     | 2477.00    |                |         |
| Insulin dose- initial (IU)                      | Ideglira         | 50 | 52.08     | 2604.00    | 1171.000       | 0.586   |
|                                                 | Insulin          | 50 | 48.92     | 2446.00    |                |         |
| Age (years)                                     | Ideglira         | 50 | 51.75     | 2587.50    | 1187.500       | 0.666   |
|                                                 | Insulin          | 50 | 49.25     | 2462.50    |                |         |
| Disease duration (years)                        | Ideglira         | 50 | 52.84     | 2642.00    | 1133.000       | 0.419   |
|                                                 | Insulin          | 50 | 48.16     | 2408.00    |                |         |
| Fasting glucose-6 month control (mmol/L)        | Ideglira         | 50 | 36.10     | 1805.00    | 530.000        | <0.001  |
|                                                 | Insulin          | 50 | 64.90     | 3245.00    |                |         |
| Postprandial glucose-6 month control (mmol/L)   | Ideglira         | 50 | 33.84     | 1692.00    | 417.000        | <0.001  |
|                                                 | Insulin          | 50 | 67.16     | 3358.00    |                |         |
| HbA1c- 6 month control (%)                      | Ideglira         | 50 | 41.02     | 2051.00    | 776.000        | 0.001   |
|                                                 | Insulin          | 50 | 59.98     | 2999.00    |                |         |
| Body Mass Index- 6 month control (kg/m2)        | Ideglira         | 50 | 36.14     | 1807.00    | 532.000        | <0.001  |
|                                                 | Insulin          | 50 | 64.86     | 3243.00    |                |         |
| Insulin dose- 6 month control (IU)              | Ideglira         | 50 | 27.86     | 1393.00    | 118.000        | <0.001  |
|                                                 | Insulin          | 50 | 73.14     | 3657.00    |                |         |

Table 2. Initial and six months control parameters in IDegLira group (group I)

| Parameter                                      | Mean | SD  | Ranks | N  | Mean Rank | Σ of Ranks | Z-value | p-value |
|------------------------------------------------|------|-----|-------|----|-----------|------------|---------|---------|
| Fasting glucose (mmol/L)                       | Initial | 13.20 | 2.5805 | Positive | 44 | 27.55 | 1212.00 | -5.546 | <0.001 |
| Control                                        | 8.60 | 2.0927 | Negative | 6 | 10.50 | 63.00 | 0 |       |
| Ties                                           | 0 | | | | | | | |
| Postprandial glucose (mmol/L)                  | Initial | 17.30 | 2.5126 | Positive | 47 | 26.80 | 1259.50 | -6.005 | <0.001 |
| Control                                        | 12.10 | 2.5113 | Negative | 3 | 5.17 | 15.50 | 0 |       |
| Ties                                           | 0 | | | | | | | |
| HbA1c (%)                                      | Initial | 10.90 | 1.9815 | Positive | 41 | 27.22 | 1116.00 | -5.010 | <0.001 |
| Control                                        | 8.90 | 1.7728 | Negative | 8 | 13.63 | 109.00 | 0 |       |
| Ties                                           | 1 | | | | | | | |
| Body Mass Index (kg/m2)                        | Initial | 36.19 | 2.7851 | Positive | 41 | 27.74 | 1137.50 | -5.223 | <0.001 |
| Control                                        | 33.80 | 2.4055 | Negative | 8 | 10.94 | 87.50 | 0 |       |
| Ties                                           | 1 | | | | | | | |
| Insulin dose (IU)                              | Initial | 68.00 | 19.571 | Positive | 42 | 26.49 | 1112.50 | -5.382 | <0.001 |
| Control                                        | 46.00 | 5.2683 | Negative | 6 | 10.58 | 63.50 | 0 |       |
| Ties                                           | 2 | | | | | | | |
5. DISCUSSION

As a result of the complementary effects of its components, which target different pathophysiological defects of type 2 diabetes, IDegLira helps patients achieve glycemic control and provides the additional benefits of weight loss or weight neutrality and low rates of hypoglycemia (11). Modest weight-loss (≥ 5% but < 10%) can minimize and reduce diabetes-associated complications, and significant weight-loss can potentially resolve disease. Antihyperglycemia therapies have considerable effects on patient weight, prompting careful consideration of weight-loss or weight-neutral therapies for patients with T2D who also have obesity. Insulins are associated with weight gain (12). There are till now just several studies that included patient who were treated with ideglira after premix insulins. IDegLira initiation resulted in improved HbA1c and weight loss in japanese patients (13). The findings from the Italian study show that in a real-world setting, the switch to IDegLira treatment is a valid option for patients who are failing to achieve glycemic control targets and/or struggling with the side effects, such as weight gain and hypoglycemia, of other insulin therapies (14). In real-world practice, after 6 months and at a moderate dose, in patients previously on insulin treatment IDegLira resulted in substantial reductions in HbA1c and body weight, with a reduced risk of hypoglycaemia (15). Our study compared parameters of metabolic control in diabetic patients on two or three doses of premix insulin (an insulin regimen containing both basal and bolus components) with patients who were switched to a fixed combination containing basal insulin and GLP 1 receptor agonist. Increasing insulin dose in patients showed improvement in fasting and postprandial glycemia, but much less than in the group treated with ideglira, and in addition it led to an increase in BMI, which is due to the increase in insulin doses. In contrast to this group of patients, in the other group who was switched to a fixed combination of basal insulin and GLP 1 receptor agonist, the improvement in fasting glycemia and postprandial glycemia as well as HbA1c was highly statistically significant. All this was achieved with a significantly lower dose of daily insulin, which resulted in a statistically significant decrease in BMI. Although this study did not deal with this, in addition to lowering BMI, there is usual a common and beneficial effect on other cardiovascular risk factors, which should certainly be proven in a differently designed study with such groups of patients. Also, with lowering the insulin dose to achieve glycemic control goals, a significantly lower rate of hypoglycemic incidents is expected.

6. CONCLUSION

The data obtained in the study suggest that switching patients from a complex insulin regimen to a fixed combination degludec/liraglutide results in significant improvement in fasting glycemia, postprandial glycemia, HbA1c, and decreased BMI. The results were achieved with a significantly lower daily dose of insulin.

- **Patient Consent Form:** All participants were informed about subject of the study.
- **Author’s contribution:** A.D.B. gave substantial contributions to the conception and design of the work. A.D.B., V.K., I.S., S.B, and A.B gave substantial contribution to acquisition of data. A.D.B., T.D., Z.V.A. and A.B gave substantial contribution to analysis and data interpretation. A.D.B., V.K., I.S. and S.B. had a part for drafting the article. A.D.B., T.D., Z.V.A. gave substantial contribution in critically revising and approval final version to be published.
- **Conflicts of interest:** There are no conflicts of interest.
- **Financial support and sponsorship:** None.

| Parameter               | Mean   | SD    | Ranks | N   | Mean Rank | Σ of Ranks | Z-value | p-value |
|-------------------------|--------|-------|-------|-----|-----------|-----------|---------|---------|
| Fasting glucose (mmol/L)| Initial| 13.00 | 2.9756| Positive | 31 | 27.26 | 845.00 | -2.313 | 0.021 |
|                        | Control| 11.90 | 3.0852| Negative | 18 | 21.11 | 380.00 |        |        |
|                        | Ties   |       |       | 1    |           |           |         |         |
| Postprandial glucose (mmol/L)| Initial| 17.09 | 2.6569| Positive | 30 | 25.40 | 762.00 | -2.095 | 0.036 |
|                        | Control| 15.90 | 2.8175| Negative | 17 | 21.53 | 366.00 |        |        |
|                        | Ties   |       |       | 3    |           |           |         |         |
| HbA1c (%)              | Initial| 10.80 | 2.0966| Positive | 29 | 24.40 | 707.50 | -1.226 | .220  |
|                        | Control| 10.40 | 2.3776| Negative | 19 | 24.66 | 468.50 |        |        |
|                        | Ties   |       |       | 2    |           |           |         |         |
| Body Mass Index (kg/m2) | Initial| 36.10 | 2.3872| Positive | 22 | 23.75 | 522.50 | -1.110 | .267  |
|                        | Control| 36.50 | 2.2302| Negative | 28 | 26.88 | 752.50 |        |        |
|                        | Ties   |       |       | 0    |           |           |         |         |
| Insulin dose (IU)      | Initial| 66.00 | 17.603| Positive | 16 | 19.53 | 312.50 | -2.827 | 0.005 |
|                        | Control| 78.00 | 17.252| Negative | 32 | 26.98 | 863.50 |        |        |
|                        | Ties   |       |       | 2    |           |           |         |         |

Table 3. Initial and six months control parameters in insulin group (group II)
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