DE-ESCALATION OF COMPLEX INSULIN REGIMENS WHILE PRESERVING GOOD GLYCEMIC CONTROL IN TYPE 2 DIABETIC PATIENTS

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Summary of PhD Thesis

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Relevant publications

Full papers

I. **Taybani Z**, Bótyik B, Katkó M, Gyimesi A, Várkonyi T. Simplifying Complex Insulin Regimens While Preserving Good Glycemic Control in Type 2 Diabetes. Diabetes Therapy. 2019;10(5):1869-1878. **(impact factor: 2.827)**

II. **Taybani Z**, Bótyik B, Katkó M, Gyimesi A, Várkonyi T, Kempler P. De-escalation of complex insulin regimens in well controlled patients with type 2 diabetes in everyday clinical practice. Diabetes, Stoffwechsel und Herz. 2019;28(6):354-359. **(impact factor: 0.082)**

III. **Taybani Z**, Bótyik B, Katkó M, Gyimesi A, Kempler P, Várkonyi T. Komplex inzulinkezelési rezsimek deeszkalációja a jó glikémiás kontroll megőrzésével 2-es típusú diabetes mellitusban [De-escalation of complex insulin regimens while preserving good glycemic control in type 2 diabetes]. Diabetologia Hungarica. 2020. (in press)

Published abstracts

- **Taybani Z**, Bótyik B, Katkó M, Gyimesi A. Simplifying complex insulin regimens with preserving good glycemic control in type 2 diabetes. Diabetes Technology & Therapeutics. 2018;20(S1):145-146.
- **Taybani Z**, Bótyik B, Katkó M, Gyimesi A. Simplification of complex insulin regimens with preserving good glycaemic control in type 2 diabetes. Diabetologia. 2018;61(S1):S414.
- **Taybani Z**, Bótyik B, Gyimesi A, Katkó M. Komplex inzulinkezelési rezsimek egyszerűsítése a jó glikémiás kontroll megőrzésével 2-es típusú diabetesben [Simplifying complex insulin regimens with preserving good glycemic control in type 2 diabetes]. Diabetologia Hungarica. 2018;26(S1):95-96.
- Veres A, Bótyik B, Fehértemplomi K, Szerencsi R, **Taybani Z.** A túlkezelés rizikója hypoglykaemizáló szerekkel kezelt idős 2-es típusú diabetes mellitusos betegekben [Risk of potential overtreatment in older adults with type 2 diabetes treated with hypoglycemic medications]. Diabetologia Hungarica. 2019;27(S1):63-64.

Introduction

Patients with type 2 diabetes (T2D) suffering from severe hyperglycemia are often put on multiple daily insulin injections (MDI). If the glucose toxicity resolves, the complex regimen may potentially be simplified, but there are no specific guidelines regarding this procedure and a lot of patients are left on MDI for years meanwhile a considerable proportion of them become overtreated.

In general overtreatment is defined as the use of a treatment even when the potential harms exceed the possible benefits. Patients with T2D who are treated with hypoglycemic agents too aggressively and have HbA_{1c} values permanently lower than their individual target range are considered to be overtreated and overcontrolled. Overtreatment of T2D with hypoglycemic medications particularly in frail and elderly patients with comorbidities is potentially harmful because it may increase the risk of hypoglycemia and weight gain, poses excess treatment burden on them and worsens their quality of life. Many recent studies demonstrated that overtreatment is a common but generally unrecognized problem in patients with T2D.

Another type of overtreatment is when well-controlled T2D patients are using unnecessarily complex insulin regimens instead of simpler alternatives which would ensure the same glycemic control with significantly less treatment burden.

Deintensification or de-escalation is a process to simplify, reduce or withdraw medications to avoid overtreatment in order to reduce the risk of polypharmacy and associated adverse events. In spite of the high rates of overtreatment with complex medications, deintensification in everyday clinical practice is infrequent. On the other hand evidence based strategies to prevent overtreatment in people with T2D and to simplify MDI regimens are still scarce.

Fixed-ratio combinations (FRCs) consisting of a long-acting basal insulin and a GLP-1-RA represent a novel approach to insulin therapy. One of these combinations, IDegLira is the titratable fixed-ratio combination of a second-generation ultra long-acting basal insulin analog (insulin degludec, 100 units/mL) and the GLP-1-RA liraglutide (3.6 mg/mL). Compared to basal-bolus therapy IDegLira has similar glycemic efficacy with less hypoglycemic risk and more favourable effect on body weight in T2D patients previously treated unsuccessfully with a basal insulin plus oral glucose lowering agents. On the basis of these observations it is

reasonable to think that IDegLira can be a potential tool for simplifying complex insulin regimens in selected T2D patients.

Our hypothesis was that in everyday clinical practice switching from MDI to once-daily IDegLira in relatively well controlled ($HbA_{1c} \leq 7.5\%$) T2D subjects using a low total daily insulin dose (TDD) is feasible, safe and effective. We performed a prospective clinical trial to confirm our hypothesis.

Our main goals were:

- to describe the characteristics of those well-controlled T2D patients treated with MDI who are eligible for medication de-escalation,
- to demonstrate that in everyday clinical practice switching from MDI to IDegLira in selected T2D patients is feasible,
- to prospectively examine the safety of switching from MDI to once-daily IDegLira in relatively well controlled subjects with T2D,
- to prospectively examine the glycemic efficacy of switching from MDI to once-daily IDegLira in relatively well controlled subjects with T2D,
- to examine the effect of de-escalation on body weight, risk of hypoglycemia and daily insulin need.

Patients and methods

This was a real-world setting, prospective, single-arm clinical trial of patients with T2D. It was conducted at the Diabetes Center of the Békés County Central Hospital – Dr. Réthy Pál Member Hospital (Békéscsaba, Hungary) from 2016 January.

The T2D patients included were ≥18 years old and had detectable random, non-fasting serum C-peptide levels (≥1.1 ng/mL; normal range 1.1-4.1 ng/mL) and an $HbA_{1c} \leq 7.5\%$. The patients enrolled were treated with MDI (stable daily doses of insulin had been administered at least for 90 days prior to the baseline visit [BV]) ± metformin (MF) and were using relatively low TDD. At BV low TDD was defined as TDD≤70 IU/day and TDD≤0.6 IU/kg/day at the same time. Clearly overinsulinised individuals who had severe or repeated symptomatic hypoglycemia

during the month before BV using TDD≤70IU/day and 0.8>TDD>0.6 IU/kg/day could also be admitted to the study.

At BV previous insulins were stopped and once daily IDegLira was started at any time, independent of meals, repeated approximately at the same time each day. DegLira was started with 16 units (each unit contains 1 unit of insulin degludec and 0.036 mg of liraglutide) and patients titrated every 3 days with 2 units to achieve a pre-breakfast self-measured blood glucose (SMBG) range of 5-6 mmol/L. The maximum daily dose of IDegLira was 50 units. MF was initiated or continued and titrated up with 500 mg weekly to 3000 mg or to the maximal tolerated dose. Patients were asked to test blood glucose daily in a structured manner (one measurement before breakfast and one test before lunch or dinner) and to record SMBG measurements in their diary.

Participants returned to the Diabetes Center 2 weeks after switching of therapy, at which point self-titration and adverse events were rechecked (Visit 0). Patients were monitored over the course of their routine diabetes care. Clinical characteristics were assessed at baseline and at 3, 7 and 12 months after initiating IDegLira. So far the 3 months and 7 months data were analysed and published.

The primary endpoint was the change in HbA_{1c} at 3 months (Visit 1), at 7 months (Visit 2) and at 12 months (Visit 3) from baseline. Secondary outcomes included change in body weight, TDD, and incidence of documented (SMBG<3.9 mmol/L) or symptomatic hypoglycemia during the follow-up. Severe hypoglycemia requiring external assistance and clinically meaningful adverse events were also recorded.

Statistical analysis was performed using GraphPad Prism 6 software (GraphPad Software, San Diego, CA, USA). Data are presented as mean ± standard deviation (SD) or median with 25th and 75th percentiles (interquartile range, IQR) for continuous variables in case of normal and non-normal distribution, respectively, and as n (%) for frequency data. During the analysis of the 3 months data clinical and demographic variables measured before and after switching therapy were compared using two-tailed paired t-test for normal distributed data and Wilcoxon signed rank test for non-normal distributed data. P values < 0.05 were considered to indicate statistical significance.

During the analysis of the 7 months data variables at baseline, at 3 months and 7 months were compared using repeated measures ANOVA with Tukey post-hoc test for data with normal distribution and Friedman test with Dunn post-hoc test for data with non-normal distribution. P values < 0.05 were considered to indicate statistical significance.

Our trial conformed to the recommendations of the Declaration of Helsinki and the International Council on Harmonization Good Clinical Practice norms with regard to medical research in humans. The study protocol was approved by the local institutional and by the Hungarian National Medical Research Council's ethical review board. All patients provided written informed consent form before they were enrollment.

Results

Results of the 3 months analysis

Between February 2016 and July 2018, 69 T2D patients meeting the trial's inclusion criteria were switched to IDegLira. Soon after switching, 3 patients ceased the therapy for financial reasons, 1 patient gradually reduced and finally stopped IDegLira due to low SMBG values before visit 1 and remained well controlled on MF monotherapy, 1 patient discontinued the medication after a few days due to moderate adverse gastrointestinal effects, and 2 patients did not return to the scheduled control. Thus, 62 patients (baseline age 64.06 ± 10.24 years, HbA_{1c} 6.42 ± 0.68%, body mass index [BMI] 33.53 ± 6.90 kg/m^2, body weight 93.81 ± 19.26 kg, TDD 43.31 ± 10.99 IU/day, insulin requirement 0.47 ± 0.13 IU/kg, duration of diabetes 10.84 ± 7.50 years, mean ± SD) attended an assessment 3 months after initiating IDegLira (visit 1) and were included in the analysis

At baseline, 49 (79%) patients were on a basal-bolus regimen using 1 dose of basal insulin and 3 doses of prandial insulin (38 used human and 11 used an analog insulin), and 13 (21%) patients were treated with two or three doses of human or analog premix insulins. At BV, 38 (61%) patients were taking MF (median dose was 1500 [0–2000] mg), the mean number of insulin injections daily was 3.69 ± 0.69, and the mean C-peptide was 4.00 ± 2.52 ng/mL.

After a mean follow-up of 99.2 days, HbA_{1c}, body weight, and BMI had decreased significantly. Mean HbA_{1c} decreased by 0.30% to $6.12 \pm 0.65\%$ ($p < 0.0001$), body weight decreased by 3.11 kg to 90.70 ± 19.12 kg ($p < 0.0001$), and BMI decreased to 32.39 ± 6.71 kg/m^2 ($p < 0.0001$).

After 3 months of follow-up, the mean dose of IDegLira was 20.76 ± 6.60 units (the mean dose of liraglutide was 0.75 mg), the median dose of MF was 2000 [1000 – 2000] mg, and the mean insulin requirement decreased to 0.23 ± 0.08 IU/kg.

IDegLira + MF combination was found to be safe and generally well tolerated. Transient gastrointestinal adverse events (lack of appetite, nausea, or diarrhea) were reported by 14 patients (22.5%), and 1 patient had transient dysthymia.

During the month before BV, 28 patients (45%) had at least one episode of documented (self-measured plasma glucose < 3.9 mmol/L) or symptomatic hypoglycemia, while only 6 (9.67%) patients reported a total of 13 documented (1 asymptomatic and 12 mild) episodes during the follow-up. Severe hypoglycemia requiring external assistance did not occur.

The mean daily number of injections changed from 3.69 to 1, and the patients reported a substantial decrease in the number of blood glucose tests performed each day.

The proportions of the patients who had achieved $HbA_{1c} \leq 7\%$ and $HbA_{1c} \leq 6.5\%$ were 92% ($n = 57$) and 66% ($n = 41$), respectively. The proportions of the patients who achieved $HbA_{1c} \leq 7\%$ and $HbA_{1c} \leq 6.5\%$ without any weight gain were 79% ($n = 49$) and 53% ($n = 33$), respectively. The proportions of the patients who attained $HbA_{1c} \leq 7\%$ and $HbA_{1c} \leq 6.5\%$ without hypoglycemia were 82.25% ($n = 51$) and 56.45% ($n = 35$), respectively. Finally, the proportions of the patients who realized $HbA_{1c} \leq 7\%$ and $HbA_{1c} \leq 6.5\%$ without weight gain and without hypoglycemia were 72.58% ($n = 45$) and 46.77% ($n = 29$), respectively.

Results of the 7 months analysis

Between February 2016 and July 2019, 89 MDI treated patients with T2D meeting the trial's inclusion criteria were switched to IDegLira. Soon after switching 4 patients ceased the therapy due to financial reasons, 3 patients gradually reduced and finally stopped IDegLira due to low SMBG values before visit 1, and remained well-controlled on non-insulin therapy, 3 patients

discontinued IDegLira in a few days due to moderate gastrointestinal adverse effects (abdominal pain, nausea) and 3 patients did not return to the scheduled controls. 8 patients on IDeglira were still before Visit 2 so their data could not be included in the analysis. Finally 68 patients (55% female, baseline age 64.01 ± 9.72 years, HbA_{1c} 6.36 ± 0.7 %, BMI 33.48 ± 6.73 kg/m^2, body weight 93.88 ± 19.18 kg, TDD 43.77 ± 11.3 IU/day, insulin requirement 0.47 ± 0.12 IU/kg, duration of diabetes 10.29 ± 7.49 years, mean±SD) completed visit 2 before August 2019 and were included in this analysis.

At BV the mean number of daily insulin injections was 3.75 ± 0.63 and mean C-peptide was 3.91 ± 2.48 g/mL. At baseline 56 (82%) patients were on a basal-bolus regimen using one dose of basal and 3 doses of prandial insulins (63% used human and 19% used analog insulins), 12 (18%) patients were treated with 2 or 3 doses of human or analog premix insulins.

After 7 months (mean follow-up of 220 days) HbA_{1c} changed from 6.36 ± 0.71% to 6.20 ± 0.64% (estimated mean difference -0.16% [-0.33 ─ 0.01], p=0.07). Body weight decreased from 93.88 ± 19.18 kg to 89.61 ± 19.31 kg (estimated mean difference -4.27 [-5.65 ─ -2.89], p<0.0001) and BMI 33.48 ± 6.73 kg/m^2 at baseline decreased to 31.93 ± 6.64 kg/m^2 (estimated mean difference -1.55 [-2.04 ─ -1.06], p<0.0001]) at Visit 2. After 7 months of follow-up mean dose of IDegLira was 21.44 ± 7.64 units (mean dose of liraglutide was 0.77 mg), median dose of MF was 2000 mg, and mean insulin requirement decreased from 0.47 ± 0.12 IU/kg to 0.24 ± 0.08 IU/kg.

IDegLira + MF combination therapy was safe and generally well tolerated. Transient gastrointestinal adverse events (lack of appetite, abdominal pain, nausea or diarrhoea and in one case vomitus) were reported by 17 patients (25%) and 2 patients (3%) had transient dysthymia.

During the month before BV 32 patients (47%) had at least one documented (self-measured plasma glucose<3.9 mmol/L) or symptomatic hypoglycemia, while during the 7 month follow-up only 12 patients (18%) reported 30 documented (1 asymptomatic and 29 mild) episodes in all. Severe hypoglycemia requiring external assistance did not occur.

Mean daily number of injections changed from 3.75 ± 0.63 to 1, and the patients substantially reduced the daily number of blood glucose testing also. During the 7 months follow-up 58 patients (85%) lost weight.

At vitist 2 the proportions of patients who had achieved $HbA_{1c} \leq 7\%$ and $HbA_{1c} \leq 6.5\%$ were 88% ($n = 60$) and 74 % ($n = 50$), respectively. The proportions of patients who achieved $HbA_{1c} \leq 7\%$ and $HbA_{1c} \leq 6.5\%$ without any weight gain were 78% ($n = 53$) and 66% ($n = 45$), respectively. The proportions of patients who attained $HbA_{1c} \leq 7\%$ and $HbA_{1c} \leq 6.5\%$ without hypoglycemia were 74% ($n = 50$) and 59% ($n = 40$), respectively. Finally, the proportions of patients who realized $HbA_{1c} \leq 7\%$ and $HbA_{1c} \leq 6.5\%$ without weight gain and without hypoglycemia were 65% ($n = 44$) and 53% ($n = 36$), respectively.

Discussion

The aim of our real-world prospective study was to examine the safety and efficacy of switching from MDI to once daily IDegLira in relatively well controlled subjects with T2D using low TDD. At baseline most of the patients using complex insulin regimens who were enrolled in our study had optimal glycemic control. De-escalation was performed in those cases to decrease treatment burden and to improve quality of life. However, as some of our patients had HbA_{1c} values that were too low, leading to high risk of hypoglycemia, reducing the frequency of hypoglycemia and achieving appropriate glycemic control were also objectives.

The results of a one-arm intervention study enrolling elderly T2D patients (n=65, baseline HbA_{1c} 7.7%) with one or more episodes of hypoglycemia confirmed with continuous glucose monitoring demonstrated that switching MDI to a single dose of basal insulin (glargine U100) combined with non-insulin glucose-lowering agents if required can decrease the risk of hypoglycemia and disease-related distress without compromising glycemic control. In our study, instead of a single long-acting basal insulin, we used IDegLira for de-escalation because it was demonstrated that it produces significantly greater improvement in overall glycemic control than a basal insulin (due to the fasting and prandial effects of liraglutide) as well as significantly reduced frequency of confirmed hypoglycaemia and a more favourable effect on body weight. Other works in the literature also encouraged us to use IDegLira to simplify MDI. For instance, the DUAL VII trial demonstrated that IDegLira exerts comparable glycemic effects to MDI on patients with uncontrolled T2D who are on glargine U100 plus MF. That trial

showed that IDegLira provided lower hypoglycemia rate and weight loss versus weight gain compared to MDI treatment.

C-peptide is a commonly used measure of pancreatic beta cell function. We only included patients into our study with detectable levels of C-peptide. Mean TDD in T2D can vary considerably with the level of insulin resistance and residual beta-cell function, but Caucasian patients treated with MDI regimens usually have a TDD between 0.9 and 1.4 unit/kg. We supposed that a normal or near normal HbA_{1c} achieved with a low TDD is associated with some degree of preserved endogenous insulin secretion. We defined a low insulin need as an average TDD≤0.6 IU/kg and used this definition together with the positive C-peptide level to identify potential candidates for our study. The safety of our patients was ensured by the study design as the maximal daily dose of IDeglira was 50 units, and we only enrolled patients with a TDD≤70 units/day at BV to be able to cover the effects of the previous complex regimens.

In our first analysis we reported the short-term (3 months) follow-up data of 62 well-controlled (or overcontrolled) T2D patients whose low dose MDI regimens were switched to IDegLira. We demonstrated the very first time that in everyday clinical practice de-escalation of MDI regimens with IDegLira in selected T2D patients is feasible and safe. We described the characteristics of those T2D patients who are eligible for a successful treatment deintensification and we showed that on short-term the simplified treatment conferred similar or better glycemic control with less hypoglycemia and weight loss versus weight gain compared to the MDI regimens used previously. The process of de-escalation and the IDegLira+MF combination was safe and generally well tolerated. Transient non-serious gastrointestinal adverse events were reported by 14 patients (22.5%) and 1 patient had transient dysthymia. The safety profile was as expected from previous trials with IDegLira. Only one SAE occurred which was not related to IDegLira therapy. We confirmed that simplification of complex insulin regimens can be performed successfully in adult T2D patients who have an HbA_{1c}≤7.5%, treated with low dose (TDD≤0.6 IU/kg and TDD≤70 IU/day) MDI, and have a detectable (≥1.1ng/mL) random, non-fasting serum C-peptide level, indicating that there is some degree of preserved endogenous insulin secretion. After a mean follow-up of 99.2 days, HbA_{1c}, body weight, and BMI had decreased significantly. Despite the low baseline TDD, the combined application of degludec and liraglutide resulted in a further reduction of TDD. There are two main explanations for the insulin sparing-effects of liraglutide. On the one hand liraglutide has a strong glucose-lowering effect deriving from the glucose-dependent enhancement of insulin

secretion and inhibition of glucagon secretion. On the other hand, substantial weight loss is associated with liraglutide treatment, leading to a lower insulin requirement. De-escalation of MDI regimens with IDegLira performed in the eligible overtreated T2D patients led to substantially reduced risk of hypoglycemia and at the 3-months visit the proportion of patients achieving an $HbA_{1c} \leq 7\%$ was 92% moreover 73% reached that target without weight gain or hypoglycemia.

Our first observations were very promising, but we wanted to confirm the results over a longer follow-up period in a larger group of patients. In our subsequent analysis we reported longer-term (7 months) follow-up data of 69 well-controlled (or overcontrolled) T2D patients whose MDI regimens were de-escalated with IDegLira. The new results unambiguously confirmed the conclusions derived from our shorter-term follow-up data. Our longer-term observations further supported that de-escalation with IDegLira is safe and the treatment is generally well tolerated. We managed to preserve good glycemic control and substantially decreased the risk of hypoglycemia. The therapeutic success was also observed in significant weight loss during the 7 months follow-up. Insulin requirement decreased by almost 50% from BV to visit 1 and remained near the same at visit 2. The benefits of de-escalation were emphasized by the fact that at the 7-months visit the proportion of patients achieving an $HbA_{1c} \leq 7\%$ was 88% and 65% reached that target without weight gain or hypoglycemia.

According to our results measuring HbA_{1c}, C-peptide and calculation of TDD can help clinicians in identifying well-controlled but overtreated patients who will benefit from medication deintensification. We showed that switching MDI to IDegLira is feasible as our selected overtreated patients achieved similar or better HbA_{1c}, had fewer hypoglycemia, lost weight and used only one injection daily with IDegLira compared to the previously used complex insulin regimens. The once versus two-to-four times injection and the lower risk of hypoglycemia appreciably improves quality of life and adherence to therapy.

Our real-world setting prospective before-after study has several limitations. It was a non-randomised, non-blinded, uncontrolled, one-centered study. The sample size was relatively low. Besides the initiation of IDegLira the titration of MF also affected the HbA_{1c} efficacy achieved. We are not able to estimate separately the effects of IDegLira and MF, anyway our goal was not to test a certain drug but to study the strategy of de-escalation.

Conclusions and new findings

I. Well-controlled T2D patients who are using unnecessarily complex insulin regimens instead of simpler alternatives which would ensure the same glycemic control with significantly less treatment burden should (also) be considered overtreated (besides their overcontrolled counterparts).

II. Measuring HbA_{1c}, C-peptide and calculation of TDD can help clinicians in identifying well-controlled but overtreated patients who will benefit from medication deintensification. Simplification of complex insulin regimens can be performed successfully in adult T2D patients who have an $HbA_{1c} \leq 7.5\%$, treated with low dose MDI, and have a detectable random, non-fasting serum C-peptide level.

III. In everyday clinical practice, switching the eligible well-controlled (or overcontrolled) T2D patients of different ages from MDI to IDegLira, a fixed ratio combination of insulin degludec and liraglutide is feasible and safe.

IV. De-escalation of MDI regimens with IDegLira in the selected overtreated T2D patients ensures similar or better glycemic control and may induce weight loss.

V. De-escalation of MDI regimens with IDegLira performed in the eligible overtreated T2D patients leads to substantially reduced insulin requirement and a reduced risk of hypoglycemia.

VI. De-escalation of complex insulin regimens with IDegLira decreases treatment burden and may improve adherence to therapy.

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