THE USE OF LONG-ACTING INSULIN DEGLUDEC IN ADULT PATIENTS WITH TYPE 2 DIABETES MELLITUS IN REAL CLINICAL PRACTICE IN RUSSIA

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BACKGROUND: Effective glycaemic control remains the most important task in managing the risks of Diabetes type 2 complications development. In this regard, the choice of insulin preparations with minimal variability of action is of utmost importance since this approach allows achieving the maximum treatment effectiveness and adequate safety level.
AIM: The aim of this study was to investigate insulin degludec treatment effect on glycemic control in adult patients with Diabetes Mellitus (DM) type 2 in a real-world clinical setting in the Russian Federation.
MATERIALS AND METHODS: The open prospective study was conducted in 2020–2021 in 35 clinical centers in 31 cities of the Russian Federation. The study included adult patients with type 2 DM treated according to Russian routine clinical practice. The prospective follow-up period was 26 weeks. The main study endpoints were changes in HbA_{1c} level, fasting plasma glucose, insulin daily doses, number, and characteristics of different types of hypoglycaemia episodes and adverse events (AEs), and patient preferences compared to previous treatment.
RESULTS: The study enrolled 494 patients. By the end of follow-up period:
- The mean HbA_{1c} decrease was 1.6% ($p<0.0001$).
- Fasting plasma glucose level decreased by 3.4 mmol/L ($p<0.0001$).
- Daily basal and prandial insulin doses decreased by 1.6 IU/day ($p<0.0001$) and 2.1 IU/day ($p<0.01$), respectively.
- Severe episodes of hypoglycemia did not occur, while the incidence of nonsevere episodes decreased significantly.
- 76 patients (15.4%) had 105 AEs, of which 41 (in 33 patients, 6.7%) were serious.
- COVID-19 was the most frequent AE reported in 21 patients (4.3%).
- Only in one case insulin degludec was withdrawn due to the patient's pregnancy and the AEs that arose from it.
- Most patients (98.6%) preferred insulin degludec to previous treatment.

CONCLUSION: The study demonstrated a statistically significant improvement in glycemic control, accompanied by basal insulin dose decrease combined with the absence of severe episodes of hypoglycemia, and significant decrease of nonsevere episodes (total and nocturnal). These results led to a large proportion of patients wanting to continue insulin degludec treatment preferring the medicine over previous treatment.

KEYWORDS: insulin degludec; glycated hemoglobin; hypoglycemia; diabetes mellitus type 2

ПРИМЕНЕНИЕ ИНСУЛИНА СВЕРХДЛИТЕЛЬНОГО ДЕЙСТВИЯ ДЕГЛУДЕК У ВЗРОСЛЫХ ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ 2 ТИПА В РЕАЛЬНОЙ КЛИНИЧЕСКОЙ ПРАКТИКЕ В РОССИИ

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ОБОСНОВАНИЕ. Эффективный контроль гликемии остается важнейшей задачей управления рисками развития осложнений сахарного диабета 2 типа (СД2). В связи с этим выбор препаратов инсулина с минимальной вариабельностью действия приобретает крайне важное значение, поскольку такой подход позволяет достичь максимальной эффективности лечения при должном уровне безопасности.
Данная работа является первым исследованием применения инсулина деглудек в реальной клинической практике в России.
ЦЕЛЬ. Изучение влияния на гликемический контроль лечения инсулином деглудек у взрослых пациентов с СД2, получающих лечение в условиях реальной клинической практики в Российской Федерации.
МАТЕРИАЛЫ И МЕТОДЫ. Открытое проспективное исследование проведено в 2020–2021 гг. в 35 клинических центрах, расположенных в 31 городе Российской Федерации. В исследование включали взрослых пациентов с СД2, получавших лечение в соответствии с рутинной клинической практикой в России. Основными конечными точками исследования были изменения уровней гликированного гемоглобина (HbA_{1c}), глюкозы плазмы натощак, суточных доз препаратов инсулина, количество эпизодов различных видов гипогликемии, количество и характеристики нежелательных явлений (НЯ), а также предпочтения пациентов по сравнению с предыдущим лечением.
РЕЗУЛЬТАТЫ. В исследование были включены 494 пациента. К концу периода наблюдения:

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- среднее снижение HbA_{1c} составило 1,6% (p<0,0001);
- уровень глюкозы плазмы натощак уменьшился на 3,4 ммоль/л (p<0,0001);
- суточные дозы базального и прандиального инсулина снизились на 1,6 Ед/сут (p<0,0001) и 2,1 Ед/сут (p<0,01) соответственно;
- тяжелые эпизоды гипогликемии не возникали, в то время как частота возникновения нетяжелых эпизодов гликемии (включая ночные) существенно снижалась;
- у 76 (15,4%) из 494 пациентов зарегистрировано 105 НЯ, из которых 41 (у 33 пациентов, 6,7%) было классифицировано как серьезное;
- наиболее частым НЯ, зарегистрированным у 21 (4,3%) пациента, стало заболевание COVID-19;
- инсулин деглудек отменен только в 1 случае из-за беременности пациентки и НЯ, возникших на ее фоне;
- большинство пациентов (98,6%) предпочли инсулин деглудек предыдущему лечению.

ЗАКЛЮЧЕНИЕ. Исследование продемонстрировало статистически значимое улучшение гликемического контроля, сопровождавшееся снижением базальной дозы инсулина в сочетании с отсутствием тяжелых эпизодов гипогликемии, а также достоверным снижением частоты возникновения нетяжелых эпизодов (общих и ночных). Данные результаты привели к тому, что большая часть пациентов предпочли продолжить лечение инсулином деглудек по сравнению с предыдущим лечением.

КЛЮЧЕВЫЕ СЛОВА: инсулин деглудек; гликированный гемоглобин; гипогликемия; сахарный диабет 2 типа

BACKGROUND

Diabetes mellitus (DM) is one of the important socially significant diseases, largely due to the high incidence rate. According to the Russian National Federal Register, at the beginning of 2021 the number of patients with DM doubled compared to 2000 and amounted to almost 4.8 million people, or more of 3% of the Russian population. Of these, more than 4.4 million had type 2 diabetes mellitus (T2DM)[1]. In this regard, the control of T2DM in such a large number of patients is an important therapeutic task.

The main parameter for assessing disease control has long been the level of glycated hemoglobin (HbA1c), which reflects the average glycemic index over the past 3 months. However, even with satisfactory HbA1c values in a patient during these 3 months, there may be significant fluctuations in the glycemic index during the day (high variability)[2]. Reduction of glycemic variability is considered as an important therapeutic goal in the treatment of DM. High variability is associated not only with poor health accompanying episodes of hyper- and hypoglycemia, but also with an increased risk of developing cardiovascular complications that worsen the prognosis of the disease[3].

All of the above necessitates developing both new methods for continuous monitoring of glucose levels[2, 4], and new drugs that have a long-term, stable effect with minimal variability in action[3]. The issue of low variability is especially relevant for basal insulins, whose action extends not only to the day, but also to the night, when the patient cannot independently influence the consequences of the drug action variability.

Insulin degludec (Tresiba®) is a long-acting basal insulin analog (with a duration of action more than 42 hours) that has been specifically developed for low variability of action. The latter has been confirmed in a number of randomized clinical trials (RCTs) and meta-analyses[5–8].

Insulin degludec is characterized by high efficacy in glycemic control, low risk of hypoglycemia, proven cardiovascular safety and dosing flexibility, which distinguishes it from insulin analogues of previous generation[9–12]. It is worth noting that the results of RCTs are consistent with data from several real world trials (RWTs) conducted in European countries[13, 14]. However, there is no information about the results of such trials in the territory of the Russian Federation.

Recently, especially after the decision of the Food and Drug Administration of the United States Department of Health (FDA) and a little later the European Medical Agency (EMA) to consider the results of RWTs, when making regulatory decisions, more and more attention is paid to these RWTs.

Such attention to RWTs is due to the limitations of RCTs, which are largely determined by strict limits, control over the possibility of statistical errors, the collection of large amounts of data, and careful selection of patients.

Regardless of the study therapy in RCTs, patients who meet strict inclusion and exclusion criteria tend to have a less severe course of the underlying disease, fewer co-morbidities, and greater compliance with the study protocol compared to patients in real world practice. Moreover, the strict scope of the RCT protocol does not take into account the conditions of the specific health care system, the clinical practice that has developed in the country, and the medical care system[15].

RWTs, on the contrary, due to less strict selection criteria for participants with a larger number of participants, allow to most fully cover those patients who seek help from a clinician, more realistically assess the frequency of adverse events (AEs), identify those AEs that are not found in RCTs, take into account the peculiarities of the local clinical practice and medical care system[16].

Under such conditions, it is also possible to study the subjective experience of patients without being influenced by the usual restrictions imposed by participation in RCTs, which may affect both the patient's lifestyle and the nature of the interactions between the patient and the doctor, which can be used to assess not only the results of treatment, but also the quality of medical services[17].

Moreover, data and evidence from real world practice are considered as one of the most important elements in substantiating the value of any medicinal products, since they allow clarifying and making more generalizable assessments of the efficacy, safety and economic characteristics ratio.

PURPOSE OF THE STUDY

The purpose of this study was the following:

a. to study the effect of treatment with insulin degludec on glycemic control in adult patients with T2DM treated in real world setting in the Russian Federation;
b. as well as an analysis of individual preferences of patients in relation to the prescribed treatment.

MATERIALS AND METHODS

Study sites, start and end dates

An open-label prospective study was conducted in 2020–2021 in 35 study cites located in 31 cities of the Russian Federation (in the cities of Alushta, Belogorsk, Bryansk, Voskresensk, Vyksa, Dolgoprudny, Dyurtyuli, Ivanovo, Kazan, Kaluga, Krasnodar, Krasnoyarsk, Lipetsk, Lyskovo, Magnitogorsk, Moscow, Nizhny Novgorod, Odintsovo, Penza, Rostov-on-Don, Samara, St. Petersburg, Saratov, Sergiev Posad, Sovetsky, Syktyvkar, Tula, Ufa, Chapaevsk, Chelyabinsk, Elista).

Study populations

A single population of patients who met the inclusion and exclusion criteria was studied.

Inclusion criteria.

- Adults (18 years of age and older) with T2DM who signed an informed consent and received hypoglycemic therapy with and without various insulins.
- By the time informed consent is obtained:
  - the diagnosis of T2DM should have been established;
  - patients were observed by investigators, received treatment in accordance with routine clinical practice in Russia;
  - treatment with any antidiabetic drug other than insulin degludec should have been initiated no earlier than 26 weeks prior to obtaining informed consent and the initial visit (Visit 1);
  - the decision to start treatment with commercially available insulin degludec was made by the patient and the attending physician before and regardless of the decision to enroll the patient in the study with poor control of diabetes;
  - all patients should have had HbA1c data for at least 12 weeks prior to initiation of insulin degludec treatment.

Exclusion criteria.

- Previous participation in this study (presence of prior informed consent).
- Mental incapacity, unwillingness, or language barriers preventing adequate understanding or cooperation from the patient.
- Hypersensitivity to the active substance or to any of the excipients of the drug with the active substance insulin degludec.

Population sampling method

A random sampling method was used in this study.

Study design

The study was multicenter, observational, dynamic, prospective (follow-up period 26–36 weeks), one-sample and uncontrolled.

Patients received commercially available insulin degludec in a pre-filled syringe in accordance with routine clinical practice according to the instructions for medical use and the recommendations of the attending physician.

Dose changes or discontinuation of hypoglycemic drugs, including insulin degludec, during the study were allowed only at the discretion of the attending physician. No additional diagnostic or monitoring procedures beyond the scope of routine clinical practice were performed on the patients included in the study.

The study design is schematically shown in Figure 1.

The study design included Visit No. 1 to obtain informed consent and initiate treatment with insulin degludec. The follow-up period after Visit No. 1 for each patient was 26 weeks, with intervening visits where insulin degludec and other hypoglycemic agents were titrated in accordance with routine clinical practice. The study was completed between the 26th and 36th weeks from the start of the study with Visit No. 3, at which the final data collection was carried out. The data collection period continued for all participating patients, including those who discontinued insulin degludec treatment, unless the patients withdrew their informed consent. If a patient stopped treatment with insulin degludec, information was collected on the reasons for discontinuing treatment.

Primary endpoints (when compared with baseline scores).

- Efficacy.
  - **Changes in HbA1c level over time.**
  - Changes in fasting plasma glucose over time.
  - Changes in daily doses of insulin over time (degludec, prandial and total daily dose).
- Safety
  - Changes in the number of episodes of non-severe hypoglycemia over time registered by patients.
  - Changes in the number of nocturnal episodes of hypoglycemia over time.
  - Changes in the number of severe episodes of hypoglycemia over time.
  - AE.
  - Reasons for discontinuing treatment with insulin degludec during the treatment period (if applicable).
- Patient preference over prior treatment.

Fasting plasma HbA1c and glucose levels were determined at the laboratories of each study site. Confirmation of an episode of hypoglycemia was carried out using individual glucometers calibrated by blood plasma.

Since episodes of hypoglycemia were self-registered by patients, they were understood as cases of subjectively poor health against the background of a decrease in blood glucose levels, while severe hypoglycemia was understood as episodes when the patient needed outside help.

Subjective experience, namely the patient's preference over prior treatment, was assessed by recording responses to two questions asked at the study end at Visit No. 3: "Will you continue treatment with insulin degludec?" (yes/no) and "Do you prefer insulin degludec over prior treatment?" (yes/no).

Statistical analysis

Descriptive statistics were used to represent patient characteristics at the start of insulin degludec treatment: quantitative characteristics were described as means, standard

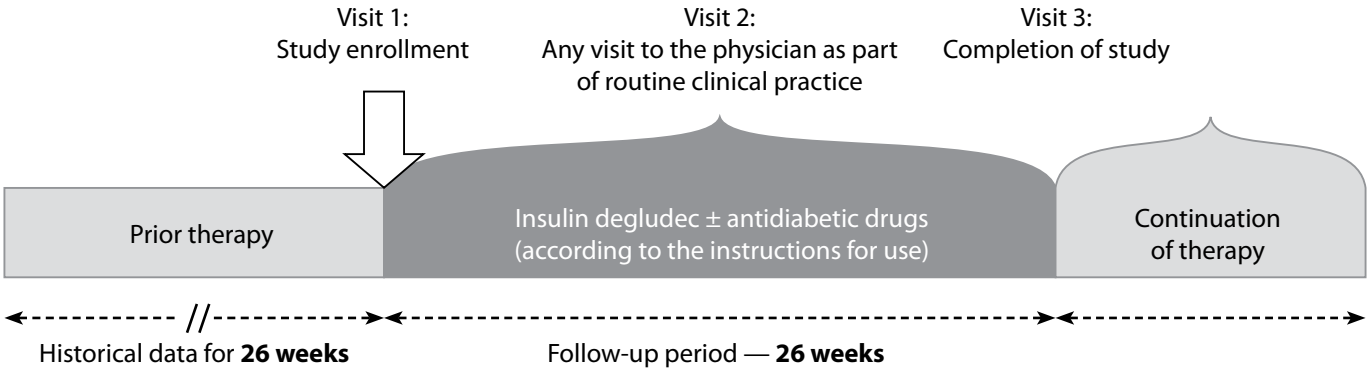

Figure 1. Study design.

deviation, median and range, qualitative or categorical – as the number of observations and the proportion of the number of patients with available data of the corresponding type.

Endpoint analysis was performed in two populations: in the full analysis set (FAS), which included all eligible patients who signed an informed consent and started treatment with degludec; and in the complete on-treatment analysis set (CTAS), which included all patients treated with degludec at Visit No. 3.

The FAS was used to characterize the patients in the study, the primary and secondary HbA1c analyses, additional endpoints and patient preference studies, and safety assessments (AEs). The CTAS population was used for additional analysis of HbA1c and values of different types of hypoglycemia episodes (severe, non-severe and non-severe nocturnal). In this article, data on HbA1c are given in the FAS population. This was done since the number of patients who did not complete the study was insignificant (1.6%) and there were no statistically significant differences in the data of this parameter in both populations.

Primary endpoints analysis was carried out both for the entire group as a whole and depending on the experience of insulin therapy (insulin-naive and insulin-experienced). Stratified analysis by baseline treatment regimen for the adjusted model was analyzed in the same way as the primary endpoints, except that baseline treatment regimen was omitted as a covariate.

Primary endpoint analysis was performed in FAS using a mixed model repeated measures (MMRM). **An approximate model** (ANCOVA) included baseline HbA1c and time of HbA1c measurement as covariates. To assess the deviation from linearity, a random coefficient model was used with time and time squared as fixed coefficients and random coefficients «patient» and «patient*time».

The adjusted model additionally included the following original covariates: age, gender, duration of diabetes, body mass index (BMI), and baseline treatment regimen (insulin-experienced and insulin-naive patients). Study sites were included in the model to account for correlations within the study site. An unstructured covariance matrix was used to describe the repeated measures variability for a patient. For this model, the estimated difference between HbA1c levels at the end of the study compared to baseline was presented along with an appropriate two-sided 95% confidence interval (CI) and an adjusted two-tailed p-value, which defaulted to 0.05 to test all statistical hypotheses. Adjustments for multiple comparisons were not applied. Graphs were plotted using GraphPad Prism 5.0 software (GraphPad Software, USA).

Due to the absence of statistically significant differences in the assessment of endpoints using the approximate and adjusted MMRM models in this article, the results of the endpoints are given using the adjusted model.

Ethical review

The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Pharmacoepidemiological Practice; before the start of the study, all necessary documents were reviewed and approved by the local ethics committees of the clinics included in this study.

RESULTS

Demographic characteristics

All 494 patients (59.9% women, 40.1% men) who signed informed consent were included in the study and were included in the FAS; 486 (98.4%) patients completed the study. The main baseline characteristics are summarized in Table 1. The study included patients with an average age of 60.7±9.41 years, body weight 87.6±17.06 kg and BMI 31.4±5.46 kg/m^2. Most of the patients included in the study were obese (BMI>30 kg/m^2: n=287; 58.1%) or were overweight (BMI=25–30 kg/m^2: n=156; 31.6%). The average duration of T2DM at the time of inclusion was 11.7±6.33 years, and the average levels of HbA1c and fasting glycemia reached 9.4±1.44% and 10.8±3.35 mmol/L, respectively.

Changes in the glycated hemoglobin level over time

Changes in the glycated hemoglobin level over time are shown in Figure 2.

The majority of patients included in the study (≈80%) had an HbA1c level of more than 8% at baseline, but by the time they completed the study, the proportion of such patients had decreased to 26%. More than 69% of patients had a decrease in HbA1c of at least 1% from baseline. Thus, after 26–36 weeks of treatment with insulin degludec, the HbA1c level (arithmetic mean±standard error) was 7.7 ± 0.04%, and the mean change in the parameter was -1.6% (95% CI -1.69–- 1.55), which was a statistically significant decrease (p<0.0001). Changes in HbA1c levels were statistically significant both in insulin-experienced patients (mean decrease of 1.6%; p<0.0001) and in insulin-naive patients (mean decrease of 2.1%; p< 0.0001).

Table 1. Demographic and other baseline characteristics of patients

Characteristic	Insulin-naive patients (n=52)	Insulin-experienced patients (n=442)	Overall population (n=494)
Age, years	59.8±9.61	60.8±9.39	60.7±9.41
Sex (M/F), %	48.1/51.9	39.1/60.9	40.1/59.9
BMI, kg/m^2	30.3±5.01	31.5±5.50	31.4±5.46
Overweight (BMI=25–30 kg/m^2), %	40.4	30.5	31.6
Obese (BMI≥30 kg/m^2), %	48.1	59.3	58.1
Duration of disease, years	10.2±7.00	11.9±6.23	11.7±6.33
HbA1c, %	10.0±1.53	9.3±1.41	9.4±1.44
Fasting glucose, mmol/L	12.2±2.56	10.6±3.39	10.8±3.35

Note: data are presented as means and standard deviation or as a percentage (%) of the number of observations in the respective subgroup. M/F — male/female; BMI — body mass index; HbA1c — glycated hemoglobin.

Changes in fasting plasma glucose over time

Changes in fasting plasma glucose over time are shown in Figure 3.

After 26 weeks of treatment with insulin degludec, fasting plasma glucose (arithmetic mean±standard error) decreased to 7.4 ± 0.08 mmol/L, and the mean change was -3.4 mmol/L (95% CI -3.54–-3.27), which was a statistically significant decrease (p<0.0001). The change in fasting plasma glucose in insulin-naive patients was more pronounced than in insulin-experienced patients (-4.5 mmol/L vs. -3.3 mmol/L).

Changes in insulin doses over time

Most of the patients included in the study used basal insulin at a dose of 33.4±14.26 U (0.4±0.16 U/kg) prior to the initiation of insulin degludec, and only a third of patients (164 patients out of 442) used prandial insulin at a dose of 30.3±15.92 U (0.4±0.15 U/kg). The mean duration of insulin degludec use was 204.4±29.00 days (6 to 253 days). Information about the changes in daily insulin doses over time during the observation period in insulin-experienced patients is shown in Figure 4.

At the end of study completion, the daily dose of **basal insulin** was 31.9 ± 0.29 U/day, the average dose change was -1.6 U/day (95% CI -2.17–-1.04), which was statistically significant decrease (p<0.0001). The daily dose of **prandial insulin** after 26–36 weeks of insulin degludec use was 28.2 ± 0.56 U/day, the average dose change reached -2.1 U/day (95% CI -3.22–-1.00 U/day), which was also a statistically significant decrease (p<0.01).

Hypoglycemia episodes

Prior to treatment, severe episodes of hypoglycemia were experienced by 50 patients (including 2 insulin-naive patients), while non-severe episodes were reported by 229 patients (including 4 insulin-naive patients) and non-severe nocturnal episodes by 138 patients (including 1 insulin-naive patient). During the study, severe episodes of hypoglycemia did not occur, while the incidence of non-severe episodes of glycemia (including nocturnal) was significantly reduced (see Tables 2 and 3).

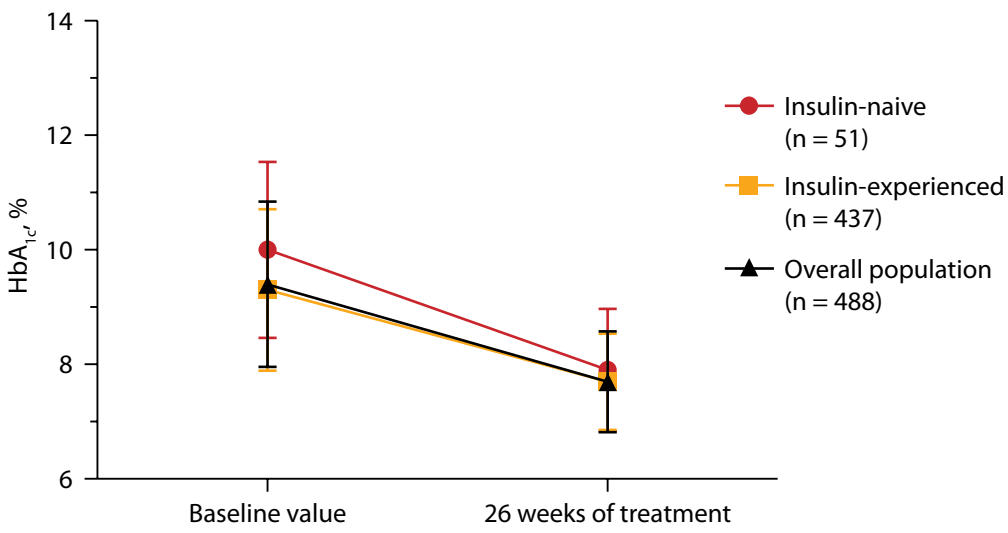

Figure 2. Changes in the glycated hemoglobin level over time.

Note. Hereinafter in Figures 3, 4: data are presented as means and standard deviation.

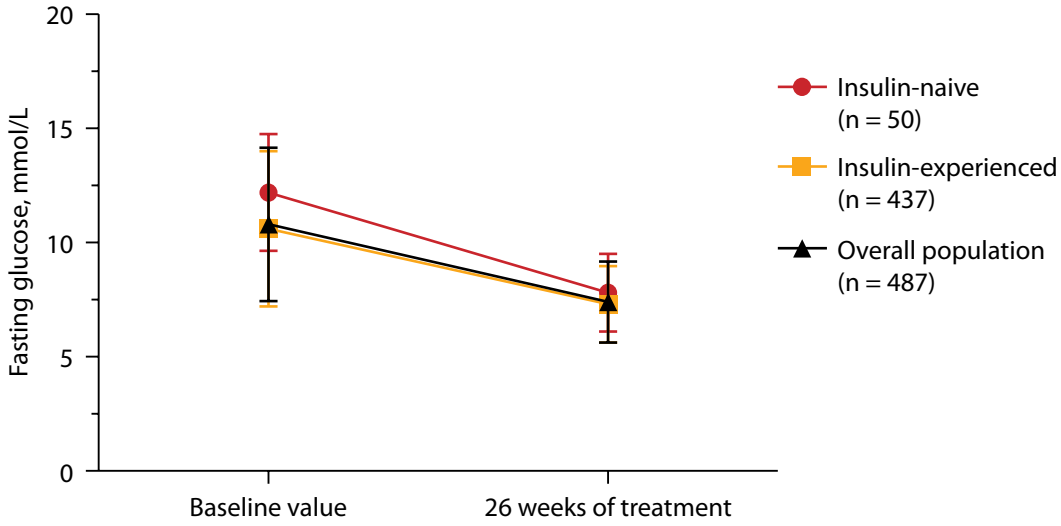

Figure 3. Changes in fasting plasma glucose over time.

During the 26 weeks prior to the initiation of insulin degludec, 113 episodes of severe hypoglycemia were recorded among insulin-experienced patients, while no such episodes occurred during the 26 weeks from the initiation of insulin degludec. The number of non-severe episodes of hypoglycemia during the 4 weeks before the initiation of insulin degludec was 877 episodes, while during the 4 weeks before the completion of the study, this figure decreased to 62 episodes. The estimated incidence ratio of total non-severe hypoglycemic episodes was 0.07 (95% CI 0.05–0.10), which was statistically significant (p<0.0001). In similar time periods, the number of nocturnal non-severe episodes of hypoglycemia was 320 and 10 episodes, respectively, and the incidence ratio was 0.03 (95% CI 0.02–0.06; p<0.0001). Thus, the use of insulin degludec was accompanied by a decrease in the incidence of episodes of hypoglycemia of all types.

Treatment discontinuation

Of 494 patients treated with insulin degludec, 4 (0.8%) patients discontinued treatment. The reasons for discontinuation of treatment in 2 (0.4%) cases were the termination of follow-up due to concomitant trauma unrelated to the underlying disease and moving to another region. In other cases, due to pregnancy or poor glycemic control in a non-compliant patient.

Adverse events

During the follow-up period, 105 AEs were registered in 76 (15.4%) patients (Table 4), of which 41 (in 33 patients, 6.7%) were classified as serious AEs (SAEs).

In 6 cases, SAEs led to the death of patients, but their association with insulin degludec was unlikely: in 4 cases, the cause of death was coronavirus infection COVID-19, in 2 cases, a cardiovascular accident.

COVID-19 disease was the most common AE reported in 21 (4.3%) patients; in 12 cases, this AE was classified as an SAE.

Withdrawal of insulin degludec was carried out only in 1 case due to the patient's pregnancy and 7 AEs that occurred against her background. These AEs included maternal exposure during pregnancy, fetal exposure during pregnancy, hypertension (SAE), diabetic nephropathy (SAE), diabetic

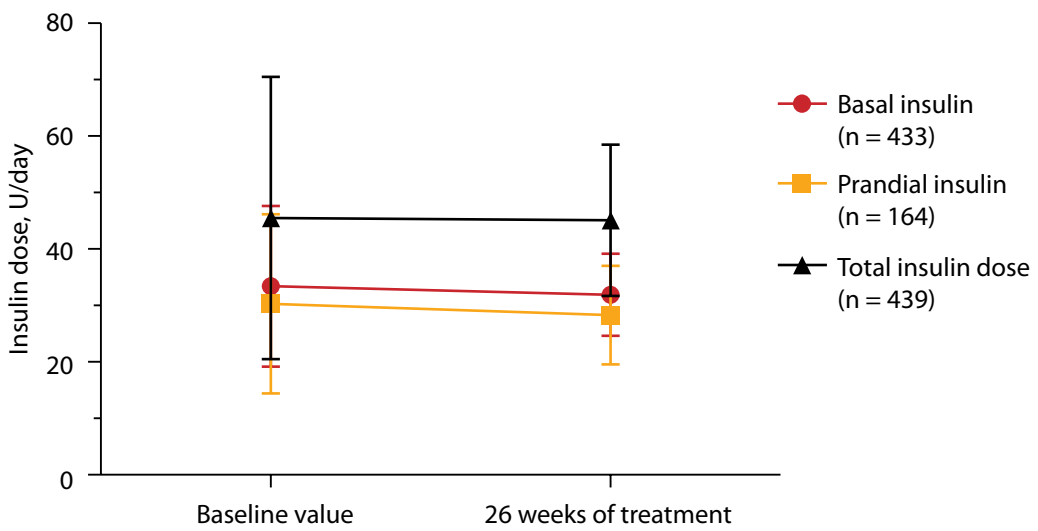

Figure 4. Changes in daily insulin doses over time in insulin-experienced patients.

fetopathy (SAE), diabetic fetopathy (SAE), and malformation of the gastrointestinal tract (SAE). All of the AEs and SAEs listed were mild to moderate in severity and, in the investigator's judgment, are unlikely to be related to the study drug.

Subjective experience with insulin degludec

Of the 494 patients who used insulin degludec, 486 patients participated in the treatment preference assessment. Of these, 479 (98.6%), including 51 insulin-naive patients, preferred insulin degludec to the previous treatment. Three insulin-experienced patients (0.6%) preferred the previous/other treatment. In 4 cases, (0.9%) patients discontinued insulin degludec and their responses were not considered.

DISCUSSION

Representativeness of sample

The power of the study was calculated on the basis of current standards and recommendations for the organization of studies by epidemiologists and medical statisticians.

Clinical significance of the results

This RWT of insulin degludec use in the treatment of patients with T2DM was the first in the Russian Federation. It is gratifying that its results are consistent with the data of similar studies conducted abroad, which indicates both a certain generality of the approaches used to manage such patients and the efficacy of insulin, regardless of the conditions for its use.

Comparison with other publications

The use of the drug in this study was accompanied by a statistically significant decrease in HbA1c, by an average of 1.6%, and a decrease in the basal insulin dose by 1.6 U/day (with a baseline dose of basal insulin of 33.5±14.48 U/day). At the same time, in insulin-naive patients the decrease in HbA1c was more pronounced than in insulin-experienced patients (-2.1% vs. -1.6%). In studies conducted abroad, the decrease in HbA1c levels was less pronounced. In particular, T. Siegmund et al. (2017) in the RWT in European countries, which included more than 800 patients with T2DM, within 6 months registered a decrease in HbA1c levels by an average of 0.51% with a decrease in the basal insulin dose by 0.88 U/day (with a baseline insulin dose of 32.0 ±18.9 U/day in patients using basal insulin alone (22.4%) or 38.5±26.5 U/day in patients using basal insulin plus prandial insulin (74.5%))[14], and S. Harris et al. (2021) in a study with a similar design conducted in Canada, noted a decrease in HbA1c levels by 0.4% and only a slight decrease in the basal insulin dose by an average of 0.6 U/day (with a baseline dose of 51.8 ± 39.2 U/day)[18].

Table 2. Changes over time in the number of patients experiencing hypoglycemia at baseline and by the end of the study

Characteristic, n (%)	Insulin-naive patients (n=52)		Insulin-experienced (n=442)		Overall population (n=494)	
	prior the treatment	end of the study	prior the treatment	end of the study	prior the treatment	end of the study
Severe episodes of hypoglycemia (during the previous 26 weeks)	2 (3.8)	0	48 (10.9)	0	50 (10.1)	0
Non-severe episodes of hypoglycemia (during the previous 4 weeks)	4 (7.7)	2 (3.8)	225 (50.9)	27 (6.1)	229 (46.4)	29 (5.9)
Non-severe nocturnal episodes of hypoglycemia (during the previous 4 weeks)	1 (1.9)	1 (1.9)	137 (31.0)	5 (1.1)	138 (27.9)	6 (1.2)

Table 3. Changes over time in the number of episodes of hypoglycemia among insulin-experienced patients at baseline and by the end of the study

Characteristic, n (%)	Insulin-experienced (n=442)	
	number of episodes of hypoglycemia before treatment	number of episodes of hypoglycemia at the end of the study
Severe episodes of hypoglycemia (during the previous 26 weeks)	113	0
Non-severe episodes of hypoglycemia (during the previous 4 weeks)	877	62
Non-severe nocturnal episodes of hypoglycemia (during the previous 4 weeks)	320	10

Table 4. Characteristics of adverse events

System organ class/preferred term	Serious AEs		Non-serious AEs		Total AEs	
	%	n	%	n	%	n
All AEs	6.7	41	9.9	64	15.4	105
Infections and infestations	4.0	20	4.0	20	8.1	40
COVID-19	2.4	12	1.8	9	4.3	21
Pneumonia due to COVID-19	1.4	7	0.2	1	1.6	8
Upper respiratory infection			0.8	4	0.8	4
Erysipelas			(0.4	2	0.4	2
Viral infection of the upper respiratory tract			0.4	2	0.4	2
Cystitis			0.2	1	0.2	1
Otitis externa			0.2	1	0.2	1
Pneumonia	0.2	1			0.2	1
Other	0.2	1	2.8	21	3.0	22

Note. AE - adverse event.

The risk of episodes of hypoglycemia in many cases becomes an obstacle for patients when switching to new therapy regimens and a factor that can significantly reduce patient compliance with prescribed therapy. Even mild episodes of hypoglycemia aggravate patients' well-being and reduce their quality of life, causing fear of recurring events that can lead to negative lifestyle changes, problems with driving and reduced work productivity[19, 20]. In this study, in insulin-experienced patients no severe episodes of hypoglycemia were recorded, while the overall frequency of episodes of non-severe hypoglycemia decreased by more than 7 times, and the frequency of nocturnal hypoglycemia episodes by 10 times, which also differed from foreign data: T. Siegmund et al. (2017) when switching from basal insulins to insulin degludec, observed a decrease in the frequency of severe episodes of hypoglycemia, the overall frequency of non-severe episodes of hypoglycemia and the frequency of non-severe episodes of nocturnal hypoglycemia by 1.26, 2.1 and 5.4 times, respectively[14].

As follows from the comparison of the described results, in the Russian population, insulin degludec had a more pronounced effect on the HbA1c level, which, however, did not lead to an increase in the frequency of hypoglycemia, but, on the contrary, was accompanied by a decrease in the frequency of all hypoglycemic events. It is possible that the observed differences may be related to social or cultural factors (for example, different attitudes of patients towards their physicians and/or differences in potential reasons for prescribing insulin degludec in the Russian Federation and in foreign countries), however, the establishment of such reasons was not part of this study and requires a deeper analysis of existing approaches to the interaction between physicians and patients.

Treatment with insulin degludec was well tolerated by patients, and discontinuation of the drug due to AEs was required in only one patient who developed them during pregnancy. It is worth noting that S. Harris et al. (2021) observed a similar frequency of discontinuation of the drug in 3 (0.9%) patients with T2DM (in 2 cases due to high cost, in 1 case due to diarrhea)[18], while T. Siegmund et al. (2017) noted a significantly higher rate of withdrawal from therapy: 3.7% of patients discontinued treatment due to high cost, 1.6% lack of efficacy, 0.5% dispensing device problems, 0.4% weight gain, 0.1% episodes of nocturnal hypoglycemia, and also 3.1% - for other reasons[14].

In the vast majority of cases (more than 98%), patients preferred the prescribed treatment over the previously administered one, and among patients who did not have experience with insulin and did not stop treatment, this figure was 100%. Thus, the favorable safety and tolerability profile of insulin degludec is combined not only with proper glycemic control, but also with high subjective assessments of the experience of using this drug, which is consistent with foreign data[21].

Study limitations

This study, like other non-interventional RWTs, has some limitations that should be considered when interpreting the results. The study protocol did not provide for a comparison group, so the observed clinical outcomes could be due not only to the use of insulin degludec, but also to other factors associated with participation in the clinical study and the limitations imposed by it.

It should also be considered that the assessment of the effect of insulin degludec treatment on the changes over time of glycemic control could be distorted due to the clinical prerequisites for initiating treatment with insulin degludec, namely, due to the presence of episodes of hypoglycemia, insufficient control and high variability in blood glucose values. However, every effort was made to ensure that the study had generic nature and that participating clinics accurately reflected real experience with insulin degludec. The study sites were chosen in different geographic regions to accurately reflect the target patient population in Russia, and a small number of inclusion and exclusion criteria were planned to ensure generalizability of the study results to the general adult population of T2DM patients living in Russia.

External circumstances (COVID-19 pandemic) also had a significant impact on the course of the study. In particular,

they affected the selection process of study sites, as some of the originally planned sites were repurposed to treat patients with COVID-19 or were subject to appropriate epidemiological restrictions. The available data suggested that the presence of DM is a factor that increases both the likelihood of COVID-19 disease and its severity[22, 23], so the planned ratio of face-to-face and remote visits was revised towards increasing the number of remote visits, and the enrollment period for the study was increased to 3 months.

Despite the measures taken, the epidemiological situation affected the overall assessment of the safety of the therapy and, apparently, significantly distorted it, since most of the reported AEs were related to the COVID-19 disease and in 3 cases caused the death of patients. At the same time, data collection related to COVID-19 was not planned, therefore, the relationship of some other reported AEs with this disease cannot be excluded. In particular, this may refer to the cardiovascular disorders or complications of the underlying disease due to the known contribution of COVID-19 to the progression of vascular complications and metabolic disorders, including the state of insulin resistance[24, 25].

CONCLUSION

This study demonstrated a statistically significant improvement in glycemic control (HbA1c and fasting glycemia) in patients treated with insulin degludec both with and without prandial insulin. After 26 weeks of treatment with insulin degludec, a statistically significant decrease in basal insulin dose was observed in both subgroups of insulin-naive and insulin-experienced patients. In insulin-experienced patients, when switching to insulin degludec, there was an improvement in glycemic control while maintaining the dose of basal insulin.

With the observed significant improvement in glycemic control, there were no episodes of severe hypoglycemia, and the incidence of non-severe episodes (general and nocturnal) after 26 weeks of treatment was significantly lower than baseline, which indicates the advantages of insulin degludec over previous treatment regimens.

Good glycemic control and fewer hypoglycemic episodes meant that a large proportion of patients wanted to continue treatment with insulin degludec and preferred treatment with insulin degludec over previous treatment.

Overall, insulin degludec was safe and well tolerated, and no new safety data were identified.

ADDITIONAL INFORMATION

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