RESOLUTION OF NATIONAL ADVISORY BOARD «THE PLACE OF ADVANCED INSULIN THERAPY IN GEORGIA»

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The National Advisory Board (NAB) dedicated to «The place of advanced insulin therapy in Georgia» was held with the support of Novo Nordisk (Denmark) in Tbilisi, on October, 2, 2020

The National Advisory Board consisting of the chairman Prof. R. Kurashvili, Director of National Centre for Diabetes Research, and members of the NAB: Prof. E. Giorgadze, Director of National Institute of Endocrinology; Prof. D. Metreveli, Prof. D. Metreveli, Head of the Department of Endocrinology, Tbilisi State Medical University; Prof. M. Gordeladze, Head of the Department of Endocrinology, Zhvania Clinic; PhD T. Zerekidze, endocrinologist at National Institute of Endocrinology; PhD L. Nikoleishvili, Head of dep. at Diacor Clinic; PhD M. Khubua, Leading specialist at Inova; PhD E. Patsatsia, Zhvania Clinic; Prof. A. Y. Kulikov, 1-st MMA by Sechenov, Moscow, Russia.

The aim of the NAB was to discuss current unmet needs on treatment of diabetes, the place of innovative insulin therapy, and in particular new possibilities that insulin degludec can bring to people with diabetes in Georgia, both in terms of efficacy and cost-effectiveness.

Insulin degludec is a new-generation basal insulin analogue with an unique mode of protraction, with proven clinical benefits such as reduced glycaemic variability, hypoglycaemia, indicated for patients with type 1 and type 2 and children as young as 1 year of age.

Welcoming the NAB, the chairman Prof. R. Kurashvili noted that the number of patients with diabetes has been steadily increasing to reach 700 million in 2045, according to experts' estimate [1].

Despite the emergence of new highly effective noninsulin medicine, the needs for insulin therapy is increasing, which is associated with the peculiarities of diabetes development.

Prof R. Kurashvili mentioned Swedish trial published in Lancet in 2018 where five replicable clusters of patients with diabetes were identified, which had significantly different patient characteristics, risk of diabetic complications and the initiation of treatment.

According to data-driven cluster analysis based on BMI, age at onset of diabetes, homoeostasis model assessment (HOMA) with estimation of β-cell function (HOMA2-B) and insulin resistance (HOMA2-IR) based on C-peptide concentrations calculated with the HOMA calculator, presence or absence of GADA, 24% of patients with onset diabetes need insulin therapy [2].

At the same time, as modern guidelines emphasize, in order to minimize risk of hypoglycaemia, recommended to use basal insulins with a lower risk of hypoglycaemia, which certainly includes insulin degludec [3].

Prof. R. Kurashvili also focused on the new criteria for compensation of glycaemic control TIR (time in range), generally refers to the time spent in an individual's target glucose range (usually 70–180 mg/dL, but occasionally 70–140 mg/dL) [4]. Optimal TIR is 70%. Time below TIR, assessed as hypoglycaemia, should be no more than 4% without severe hypoglycaemia [5].

Reducing the time spent in target glycaemic range during the day increases the frequency of microalbuminuria and retinopathy [6].

Prof. Ramaz Kurashvili shared with the participants the first experience of treatment of the patients with high rate of hypoglycaemia including the patients with oncological diseases, received specific chemical therapy with high glycaemic variability. The use of insulin degludec made it possible to improve, achieve a more stable level of glycaemia and reduce the rate of hypoglycaemia.

Continuing the topic of the importance of adequate insulin therapy in type 2 and 1, Prof D. Metreveli drew the attention of the audience to 3 main challenges of insulin therapy: variability, hypoglycaemia and lack of flexibility in insulin therapy.

Variability of glycaemia "within - day" 3,4 mmol/l [61,2 mg/dl] and more increases the risk of cardiovascular outcomes more than 2,5 times [7]. Variability in FPG ("day-to-day") is predictive of decreased survival in patients with type 2 [8]. Variability has a direct correlation with the frequency of hypoglycaemia [9].

Hypoglycaemia has long been recognised as a dangerous side-effect of treatment of diabetes with insulin. With its potential to disrupt cerebral function, hypoglycaemia can have a major effect on peoples' lives. Study findings have suggested that hypoglycaemia is associated with an increased risk of cardiovascular events and mortality. Different mechanisms by which hypoglycaemia might provoke cardiovascular events have been identified in experimental studies, and in clinical studies cardiac arrhythmias have been reported to be induced by hypoglycaemia [10].

At the same time, Prof. D. Metreveli highlighted, there is a problem of non-recognition of hypoglycaemia by patients and underestimation of the importance of hypoglycaemia by health care professionals.

It was noted HAT study, involving 27,5 thousand patients in real clinical practice, demonstrated that deterioration of glycaemic control and an increase of HbA1c are accompanied by an increase of hypo incidents [11].

Inflexible dosing regimens can make it difficult to take insulin as prescribed and may lead to patients omitting or altering insulin doses. Based on the GAPP™ survey, 27.6% of patients who missed insulin doses indicated they had difficulty taking their insulin at the prescribed time. Furthermore, one-third of patients reported insulin omission/non-adherence at least 1 day in the last month, with an average of 3.3 days. Among physicians, three quarters reported that their typical patient does not take their insulin as prescribed and most (87.6%) agreed that many insulin-treated patients do not have adequate blood glucose control. Most (85.8%) physicians said they wished insulin treatments could be more flexible. The number of injections taken and taking insulin at prescribed times were the two most commonly reported (by patients and physicians) difficulties patients have with insulin treatment. Thus, a more flexible dosing regimen may reduce the burden of insulin treatment and encourage adherence [12].

Prof. D. Metreveli noted that longer insulin half-life, providing an extended duration of action without increased risk of hypoglycaemia, could therefore simplify management, increase flexibility in dosing and better accommodate the needs of patients than current insulins.

Speaking about the application of clinical benefits of degludec in real clinical practice, Prof E. Giorgadze noted, that degludec is a new-generation basal insulin with an ultra-long duration of action.

Due to its structure and formulation, degludec forms stable and soluble multihexamers upon injection. Insulin monomers then slowly and gradually dissociate from the multihexamers and are subsequently absorbed into the bloodstream to provide an ultra-long duration of action more than 42 hours [13].

A number of clinical pharmacological studies have shown that degludec exhibits flat and stable steady-state pharmacokinetic and pharmacodynamic profiles in patients with diabetes [14,15]. The flat and stable profile of degludec was preserved in children, adolescents and elderly patients [16]. The pharmacokinetic profiles were similar in patients with renal or hepatic impairment to normal individuals [17,18].

Euglycemic glucose clamp studies conducted in patients with type 1 diabetes demonstrated that degludec presents significantly lower variability in blood glucose-lowering effect between injections than glargine U100 and U300 [19,20].

As a result insulin degludec has very low risk of hypoglycaemia. It was confirmed in BEGIN trials where the risk of nocturnal hypos were lower on insulin degludec on 26% compared with insulin glargine U100 [21].

Crossover, double-blinded SWITCH 1&2 trial proved undeniable profits of insulin degludec for patients with high risk of hypoglycaemia by reducing the risk of nocturnal and sever hypoglycaemia by more than a third for type 1 and more than 45% for type 2 [22,23].

These results have been confirmed in real-life clinical practice study. When compared with insulin glargine U100 (EU-TREAT study), the risk of all hypos on degludec was 21% lower in type 1 and 60% lower in type 2. The risk of severe hypoglycaemia was 85% lower in type 1 and 92% lower in type 2[24].

CONCLUDE study showed a dramatic reduction in the number of severe hypoglycaemia as well as the number of patients with hypos on degludec (-80%) compared with insulin glargine U300 [25].

Thus, Prof. E. Giorgadze noted, using insulin degludec we can get closer to solve the one of the problem of insulin therapy – hypoglycaemia.

The efficacy and safety of degludec were demonstrated in force- flexible regime with intervals of injection 8 and 40 hours in the frame of BEGIN 3a phase [26]. It means that we can allow patients for whom it is important to use a flexible regime of insulin therapy with degludec, Prof. E. Giorgadze highlighted, improving quality of life without compromising glycaemic control.

Also cardio-vascular safety of insulin degludec proven in DEVOTE study were discussed by the members of the advisory board. It was noted the benefit of insulin degludec in patients with type 2 and chronic kidney disease (CKD) in the form of reduced risk of hypoglycaemia and cardiovascular mortality [27].

In conclusion, Prof. E. Giorgadze focused on the following benefits of insulin degludec:

- Simplicity of titration
- Stable and effective profile
- Low variability
- Low risk of hypos
- Safe flexible regime
- Cardio-vascular safety
- Additional benefit for patients with CKD.

Insulin degludec is indicated for patients with type 1 and 2, who have high risk of hypoglycaemia or labile diabetes, flexible regime of injections, cardiovascular diseases or CKD, failure of prior therapy.

According to the opinion of Prof. M. Gordeladze, insulin degludec may take a special place in the treatment of diabetes in children and adolescents.

Prof. M. Gordeladze noted that the use of insulin in children and adolescents

with type 1 diabetes is a challenge because of the heterogeneity of these patients and their lifestyles, with consequent unpredictability in blood glucose level.

Hypoglycemia is the most often acute complication of type 1 in children.

The rates and duration of hypos increase in 6 year children and younger [28].

Hypoglycemia in childhood impairs brain functions and decrease cognitive capability. Long sever night hypoglycemia increases the risk “dead-in- bed -syndrome” [29].

Hyperglycaemia with ketoacidosis (DKA) is another dangerous acute complication of type 1 in children. Cerebral injury is the major cause of mortality and morbidity and cerebral edema accounts for 60% to 90% of all DKA deaths. From 10% to 25% of survivors of cerebral edema have significant residual morbidity.

Children without overt neurological symptoms during DKA treatment may have subtle evidence of brain injury, particularly memory deficits, after recovery from DKA. Magnetic resonance imaging (MRI), spectroscopy, and cognitive assessments show morphologic and functional brain changes that are associated with adverse neurocognitive outcomes in the medium term [30].

A new ultralong-acting basal insulin, insulin degludec, has the potential to mitigate some of these challenges, notably variability in the glucose-lowering action of the basal insulin component of an insulin regimen, and consequent risks of hypo- and hyperglycaemia with ketoacidosis.

Prof. M. Gordeladze mentioned that BEGIN Young study (degludec + aspart OD, versus detemir + aspart BID) showed a numerical reduction in the rates of ketosis with degludec when compared with insulin detemir (41%) in two phase 3b clinical trials in pediatric patients with diabetes. Thus, use of degludec might also form a useful therapeutic strategy in children with type 1, particularly those with recurrent ketosis events [31].

It was noted that the pharmacokinetic of degludec is equivalent in adults and children [32]. It is worth to note , despite the physiological differences between these age groups, the results of the Flex T1 study in adults with T1D may be for paediatrics’ practice. The Flex T1 study demonstrated that once steady state is achieved, there is considerable latitude to vary the dosing interval at the patient’s convenience (±16 h giving a range of 8-40 h between injections), provided that the patient continues to receive, on average, one injection every 24 h. These properties may give degludec a flexibility in dose timing in children, that is not available with other basal insulins that have a shorter half-life and sometimes very important for improving glycaemic control, quality of life and adherence to treatment.

According to the Prof. M. Gordeladze, insulin degludec will have definite advantages for treatment children with non-stable diabetes, frequent hypoglycaemia, a tendency to hyperglycaemia with ketosis, as well as who needs a flexibility in dose timing.

The implementation of innovative medicine in real clinical practice is impossible without pharmacoeconomic analysis including the estimation of value and impact of new products to healthcare system.

Prof. A. Kulikov, as a pharmacoeconomist, presented cost–effectiveness and budget impact analysis of insulin degludec. Globally, the prevalence of diabetes is increasing and this imposes a major economic burden upon healthcare systems. A significant proportion of this expenditure is as a result of treating the micro- and macro-vascular complications arising from prolonged exposure to high blood glucose concentrations [33].

Prof. Kulikov noted that that pharmacoeconomic analysis is an effective approach to make decision on the procurement of innovative medicines by states .

Currently, health authorities of developed countries are more interested not in the value of treatment of diabetes, but in the value of the treatment results such as a decrease of acute and chronic complications, quality and duration of life.

Using the results of the real-world clinical study EU-TREAT such as decrease of HbA1c, rate of hypoglycaemia and quality of life, cost-effectiveness finalises with assessment of the impact on the budget of insulin degludec compared with glargine U100 were carried out in UK and Sweden. Both health economic assessments shown that treatment with degludec was less costly and more efficient [34,35].

In Russian Federation the same analysis showed that insulin therapy with degludec had greater efficacy compared with insulin glargine U100 and U 300 for the considered efficacy indicators. According to the efficiency criterion "lowering the level of HbA1c", the use of degludec was economically beneficial. According to the efficiency criterion, the quality-adjusted life-year - QALY, the use of insulin degludec was cost-effectiveness.

Budget impact analysis showed that an increase in the share of degludec up to 30% would lead to a decrease in direct medical costs by 0.62% for type 1 diabetes and a slight increase in costs within 4% for type 2 diabetes [36]. Based on the health economic outcome results, Health authority of Russian Federation approved insulin degludec as a vital medicine with cost coverage by the state.

In the discussion that followed the presentations, the members of Advisory board were discussing the place of insulin degludec in Georgia.

PhD L. Nikoleishvili shared with the participants the first experience of treatment of the patients with high rate of hypoglycaemia. The use of insulin degludec made it possible to improve glycaemic control, achieve a more stable level of glycaemia and reduce the rate of hypoglycaemia. The expert emphasized the simplicity and safety of titration.

PhD E. Patsatsia highlighted the benefits of insulin degludec in children with type 1: low risk of hypos, low variability and low risk of ketoacidosis.

PhD T. Zerekidze drew the attention of the members of advisory board to the clinical and pharmacoeconomic benefit of insulin degludec in patients with type 1, nothing complicated in managing of these patients on degludec.

All members of Advisory board agreed that insulin degludec is an innovative ultra-long-action insulin with proven clinical benefits: reducing of glycaemic variability, rate of hypoglycaemia and ketoacidosis, improvement of glycaemic control in clinical trials and real –life clinical practice.

Health-economic outcomes have proven the economic efficacy of insulin degludec and positive influence budget in long-term by improving control and reducing the risk of acute and chronic complications despite the relatively high price.

Insulin degludec has the unique PK profile and offers solutions to a wide spectrum of issues faced by such challenging patient population as children and adolescents . The stability and flexibility of degludec can help patients and caregivers address issues most commonly associated with this population, i.e., unpredictable lifestyle, poor treatment adherence, and higher risk of hypoglycaemia and hyperglycaemia with ketoacidosis.

Taking into account all mentioned above experts agreed that insulin degludec need to be provided a wide access for children and adolescents through state reimbursement channel.

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SUMMARY

RESOLUTION OF NATIONAL ADVISORY BOARD «THE PLACE OF ADVANCED INSULIN THERAPY IN GEORGIA»

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On October 2, 2020, by Novo Nordisk initiative, an expert council was held in Tbilisi, Georgia, dedicated to the problems of introducing innovative insulin therapy on the example of insulin degludek into the clinical practice.

The council chaired by prof. R. Kurashvili included seven leading endocrinology experts in Georgia and a specialist in the field of pharmaco-economics from Russian Federation Prof. A. Kulikov.

During the expert council, important scientific, clinical and economic emphases were made on the benefits of using insulin degludec associated with its unique structure and mechanism of action. Special emphasis was placed on the difficulty in managing children and adolescents with type 1 diabetes. The meeting provided compelling evidence that insulin degludec reduces the incidence of hypoglycemia and diabetic ketoacidosis, thereby contributing to overall health and the prevention of vascular complications in children and adolescents with diabetes.

The members of the council resolved to petition the Georgian Ministry of Health to include insulin degludek in the state program for children and adolescents with diabetes.

РЕЗЮМЕ

РЕШЕНИЕ НАЦИОНАЛЬНОГО КОНСУЛЬТАТИВНОГО СОВЕТА «ПЕРСПЕКТИВЫ ИНСУЛИНОВОЙ ТЕРАПИИ В ГРУЗИИ»

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Второго октября 2020 г. в Тбилиси состоялся Совет экспертов, инициированный компанией Ново Нордиск, посвященный проблеме внедрения инновационной инсулинотерапии на примере инсулина деглудек в реальную клиническую практику.

В Совет под председательством проф. Р. Курашвили вошли 7 ведущих экспертов Грузии в области эндокринологии, а также приглашен специалист в области фармако-экономики проф. А. Куликов из России.

В ходе Совета экспертов сделаны значимые научные, клинические и экономические акценты преимущества применения инсулина деглудек, связанные с его уникальной структурой и механизмом действия. Сделан акцент на сложности при ведении детей и подростков с сахарным диабетом 1 типа. На встрече предоставлены убедительные доказательства того, что инсулин деглудек снижает частоту гипогликемий и диабетического кетоацидоза, чем способствует общему здоровью и предотвращению сосудистых осложнений у детей и подростков с сахарным диабетом.

Члены Совета приняли решение о ходатайстве перед Минздравом Грузии о включении инсулина деглудек в государственную программу для детей и подростков с сахарным диабетом.