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Clinical value of glargine 300 U/mL based on randomized trials and routine medical practice

ABSTRACT

The paper presents available evidence on the clinical use of glargine 300 IU/mL, the latest addition to the diabetes care armamentarium. (Clin Diabetol 2016; 5, 6: 203–207)

Key words: glargine, type 2 diabetes, insulin therapy

Introduction

Economical availability of modern antidiabetic therapies in Poland continues to be limited. Thus reimbursement of a new basal insulin product, next generation glargine, Toujeo® (insulin glargine 300 U/mL, Gla-300) must be greeted with special satisfaction. Toujeo® is a new insulin glargine product indicated for the treatment of adults with diabetes mellitus that received marketing authorization in February 2015 in the USA and in April 2015 in EU countries. It contains insulin glargine at three times the concentration of the conventional form 100 U/mL. This paper outlines this product based on randomized clinical trials performed before the manufacturing authorization was granted and presents available data from observational studies.

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Basal insulins, current status

Isophane insulin (NPH) continues to be the most commonly used basal insulin in Poland. Despite many limitations related to its pharmaceutical form and pharmacokinetic/pharmacodynamic (PK/PD) profile, it is fully reimbursed and thus constitutes the cheapest insulin therapy option. Available long-acting insulin analogs, such as glargine 100 U/mL (Gla-100), (Lantus, Sanofi; Abasaglar, Eli Lilly) and detemir (Levemir, Novo Nordisk) are still used rarely, in particular in type 2 diabetes mellitus. Such condition is mainly a result of economic side of therapy, since long acting analogs, unlike human insulins, are only partially reimbursed, with 30% payment for the patients. Such restrictions make it impossible for patients with type 2 diabetes mellitus, uncontrolled on oral drugs, who require insulin therapy, to obtain reimbursed long acting analogs.

New analogs with even more prolonged activity and flat PK/PD profile, glargine 300 U/mL (Toujeo, Sanofi), degludec (Tresiba, Novo Nordisk) continue to be new agents on Polish market and are rarely used. Reimbursement of the medicinal product Toujeo is an opportunity to make this modern therapy more common. However, it must be emphasized that restrictions of reimbursement remain the same as for the other long acting analogs and furthermore apply only to adults.

Pharmacokinetics and pharmacodynamics of glargine 300 U/mL

Mechanism of prolonged activity of glargine, irrespective of its concentration, involves precipitation in neutral pH of the subcutaneous tissue and formation

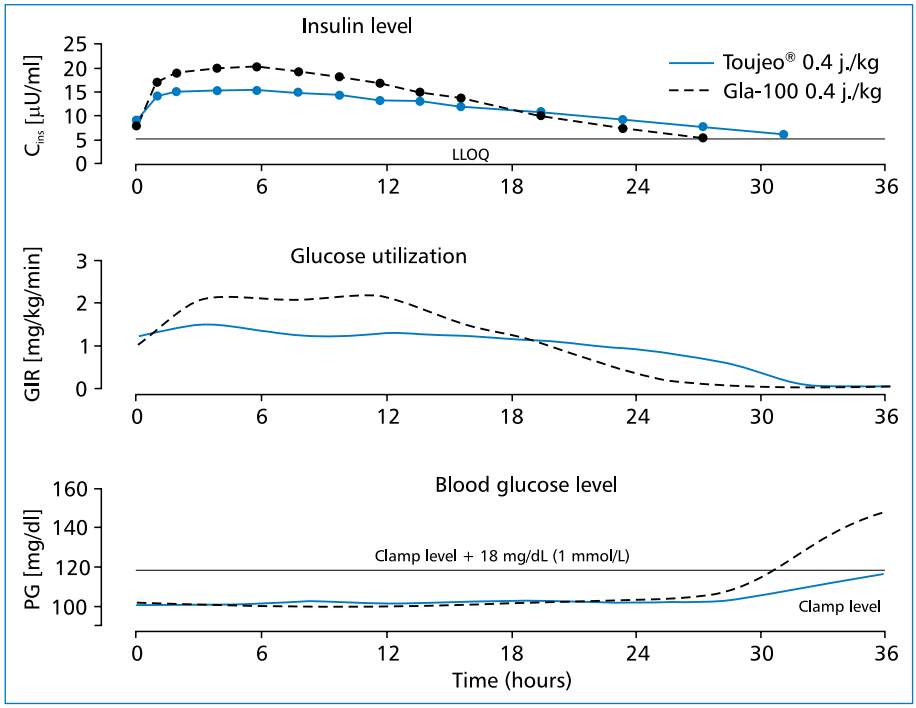

Figure 1. Steady state PK/PD parameters for Gla-300 *vs.* Gla-100 [6]

of a compact depot [1]. Due to 3 × higher concentration, a volume of Gla-300 injection is by 2/3 lower than that of Gla-100. As a result, area of subcutaneous drug depot is reduced by half [2]. This slows down the rate of glargine release into the circulation. Thus pharmacokinetics and pharmacodynamics (PK/PD) of Gla-300 is different than that of Gla-100. Its activity profile is milder and prolonged and drug action extends for more than 24 hours [3, 4]. As a result of this prolonged residence time in the subcutaneous tissue higher exposure to enzymatic inactivation occurs resulting in lower systemic bioavailability of Gla-300. The mechanism is similar to this observed earlier with NPH insulin [5].

In a steady-state study (single center, randomized, controlled, double blind, cross-over), 30 patients with type 1 diabetes mellitus received doses of 0.4 or 0.6 U/kg b.wt. Gla-300 or 0.4 U/kg b.wt. Gla-100 [6]. Results obtained in this study are consistent with results of a single dose study. Plasma insulin profile over the dosing interval (24 hours) was more stable and homogeneous than for Gla-100. Furthermore amplitude of variation of insulin level was lower for Gla-300 than for Gla-100.

With regard to pharmacodynamic parameters, Gla-300 in a steady state was characterized by more stable, homogenous reduction of blood glucose level over 24 hours. After administration of the last dose, hypoglycemic activity persisted longer and the assumed level of euglycemic clamp ≤ 105 mg/dL for the doses 0.4 and 0.6 U/mL persisted for more than 24 hours (29.5 and 32.3 hours, respectively) (Fig. 1).

Basal insulin in diabetes mellitus should ensure relatively stable reduction of blood glucose level with minimum within-day and between-day variability. Furthermore, interindividual variability of hypoglycemic effect should be as low as possible. These parameters for Gla-300 were tested in a randomized, controlled, double blind clinical study conducted in 50 patients with type 1 diabetes mellitus [7]. The parameters obtained in a euglycemic clamp indicate homogeneous distribution of the hypoglycemic effect throughout 24 hours. This is indicated by glucose utilization (AUC_{GIR}) turing subsequent 6-hour periods. The effect variability coefficient over 24 hours (fluctuations) was 1 mg/kg/ /min and average variability rate GIR-$AUC_{0–24\,h}$ for individual patients was 33%, while the same coefficient for interindividual variability was 43% (Fig. 2).

This resulted in more stable control of blood glucose level throughout 24 hours. Lower daily blood glucose fluctuations are more beneficial since, as multiple studies indicate, lower variability of blood glucose results in limitation of vascular damage, reducing the risk of vascular complications of diabetes [8–10].

Clinical evaluation of utility of glargine 300 U/mL

Effectiveness of Toujeo® was evaluated in a comprehensive clinical trial program called EDITION [11–14].

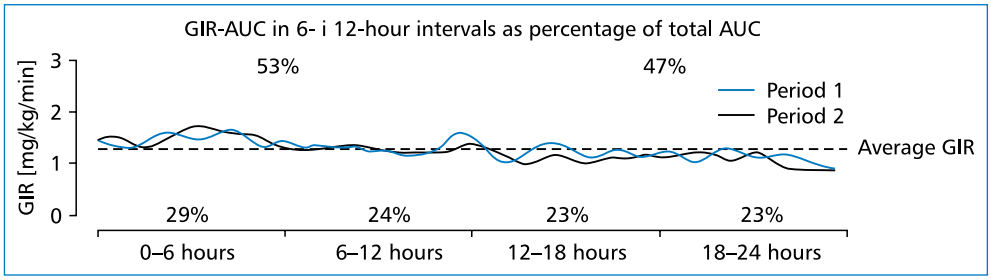

Figure 2. Distribution of the hypoglycemic effect over time [7]

It included 4 randomized, controlled phase 3 clinical trials, conducted in a population of patients with type 1 and type 2 diabetes mellitus. The primary end-point in these studies was to demonstrate non-inferiority of Toujeo® versus insulin glargine 100 U/mL with regard to reduction of HbA_{1c} level. This primary end-point was achieved in all EDITION studies. Furthermore, a phase with follow-up extended by 6 months demonstrated that diabetes controlled was unchanged until the end of the follow-up in type 2 diabetes mellitus patients. In month 12, HbA_{1c} level in the group treated with Toujeo® was significantly lower than in the group that received glargine 100 U/mL (average difference of least square means: –0.10%, 95% CI: –0.18 to –0.02%; p = 0.0174) [15]. This result was achieved without increasing the dose further from month 6 to month 12.

The EDITION studies demonstrated that comparable control of diabetes would require 10 to 18% higher dose of Toujeo® than that of glargine 100 U/mL. Several factors may underlie these differences in dosing. The above mentioned differences in PK/PD properties of both products affect nature of activity of these insulins. Flat, homogeneous activity over 24 hours, which is a desirable feature of the basal insulin, may make the effects of comparable doses weaker versus insulins that exhibit more or less pronounced peak activity. However benefits related to flat and prolonged activity, such as stable reduction of blood glucose level, lower variability and in particular lower risk of hypoglycemia (in particular during the night) and compensate the required higher dose. Second, rationale behind the studies in EDITION program and their protocols that specified very ambitious aims [fasting blood glucose levels in the range of 4.4–5.6 mmol/L (80–100 mg/dL)] and use of treat-to-target model of therapy that required high insulin doses (that usually are not used in routine medical practice) to achieve the specified control. Third, the patient population enrolled in the studies in EDITION program was very homogeneous, restricted to patients who met the inclusion and exclusion criteria. Such selection of patients favored achievement of reliable results with regard to assessment of treatment efficacy that are required to obtain marketing authorization, but do not necessarily reflect subsequent situation after the marketing authorization is granted. It must be emphasized that the EDITION studies were conducted in patients with type 2 diabetes mellitus and precluded use of sulphonylurea derivatives that, plus metformin, are the cornerstone of oral therapy of diabetes mellitus.

The Summary of Product Characteristics indicates equivalence of utilized doses, unit per unit, when glargine 100 U/mL is switched to Toujeo®. Furthermore it provides that "higher dose (by approximately 10 to 18%) of Toujeo® may be required to achieve the desired plasma glucose concentration". This fragment reflects the above mentioned observations from the studies in the EDITION program that will not have to be reflected by routine clinical practice.

Glargine 300 U/mL in studies in routine clinical practice

Data obtained in observational studies conducted in the USA do not support differences in dosing between glargine 300 U/mL and glargine 100 U/mL in patients with type 2 diabetes mellitus, switched to Toujeo® from other basal insulin (the patients received: 7.8% NPH, 65.9% insulin glargine 100 U/mL, 25.1% insulin detemir). A basal insulin was switched to Toujeo® in this study e.g. due to lack of treatment efficacy or hypoglycemia [16]. This study demonstrated that after a basal insulin was switched to Toujeo®, the insulin dose did not significantly change, while the number of daily injections was reduced — before switching to Toujeo®, 43.2% of patients used basal insulin twice daily, while after switching to Toujeo®, this was reduced to only 9.8%. The dosing did not significantly change in patients who used basal insulin once or twice daily before the switch. In patients who used their insulin once daily, the dose was 0.53 U/kg before the switch and 0.56 U/kg after the switch (difference of 0.03 U/kg, p = 0.684) and in patients who used their basal insulin twice daily the dose was 0.94 U/kg before the switch

and 0.76 U/kg after the switch (difference of 0.18 U/kg, $p = 0.230$). What should be emphasized, there was a significant reduction of HbA_{1c} by 0.96% ($p < 0.0001$) and the number of cases of hypoglycemia was significantly lower, RR = 0.23, $p < 0.0001$.

In summary, data from routine clinical practice support the observation that switching from other basal insulin to Toujeo® does not result in increased dose, but results in significant reduction of HbA_{1c} the number of cases of hypoglycemia, clearly demonstrating benefits of Toujeo versus currently available basal insulins.

Discussion

Thus, how this paradoxical data conflict can be resolved? It is probably a result of different approach to patient therapy in randomized clinical trials and routine clinical practice. Clinical trials aim at achievement of an established glycemic goal, while less emphasis is put on hypoglycemic episodes (that are uncommonly used as an endpoint). This implies using relatively high insulin doses. However, the risk of hypoglycemia determines the therapeutic goal in a specific patient in routine clinical practice, which is emphasized in recommendations of Polish Diabetes Association, 2016 [17]. This is consistent with the principle of individualization of diabetes treatment goals and methods, also reflected by international guidelines [18]. Thus use of insulin in routine clinical practice is quite different than in the presented results of randomized clinical trials and data from routine practice better reflect eventual outcomes of treatment of diabetic patients.

Similar difference also exist between other basal insulins (e.g. doses of insulin detemir higher by an average of 35% are required to achieve similar control of diabetes versus glargine) [19–21]. Differences between results of randomized clinical trials and routine clinical practice were also demonstrated in this case. Despite increased requirement for insulin detemir versus glargine to achieve the same efficacy in clinical trials, doses of both drugs used in routine clinical practice are similar [22, 23].

Benefits of more flat and prolonged pharmacodynamic profile also include limitation of the risk of hypoglycemia, in particular nocturnal hypoglycemia. As studies in the EDITION program revealed, Toujeo® reduces the incidence of confirmed [≤ 70 mg/dL (≤ 3.9 mmol/L)] nocturnal or severe hypoglycemia (assessed as the number of patients experiencing at least one episode) in patients with type 2 diabetes mellitus by 25% (RR: 0.75; 95% CI: 0.68–0.83) and overall hypoglycemia (at any time over 24 hours) by 9% (RR: 0.91; 95% CI: 0.87–0.96). This effect is particularly clear during the initial period of the therapy when titration occurs and patients establish their adequate insulin dose. Gla-300 allows to increase the dose to the effective level with lower risk of hypoglycemia.

Severe nocturnal hypoglycemia episodes are particularly dangerous, since patients are unaware of them and cannot undertake appropriate corrective actions. This was shown to threaten their lives (risk of death increased two-fold) and cause brain damage, impairing their cognitive skills and facilitating development of dementia [24]. Occurrence of hypoglycemia has negative effect on quality of life of patients and their social functioning [25, 26].

Higher flexibility of Toujeo® dosing versus other basal insulins is also significant for the patients [27]. A patient does not have to strictly adhere to 24-hour dosing intervals but can inject his insulin up to 3 hours before and 3 hours after the scheduled time of administration, without loss of efficacy.

Despite the fact that both products, Toujeo® and glargine 100 U/mL, contain the same substance, their profiles differ and this difference is reflected by significant benefits related to Toujeo®. These benefits are both clinical and economical.

Limitation of clinical utility of glargine 300 U/mL is lack of comparative studies with other basal insulins. Lack of randomized, controlled clinical trials in this area is somewhat compensated by a network metaanalysis, which was presented at 76th Scientific Sessions of American Diabetes Association in New Orleans in 2015 [28]. In this presentation Wang and associated presented results of indirect comparison of glargine 300 U/mL with other comparators, including glargine 100 U/mL, insulin detemir, insulin NPH, insulin degludec and insulin mixtures. The compared parameters included: HbA_{1c} level, effect on body weight and incidence of hypoglycemia episodes. No statistically significant differences were found for HbA_{1c} change and effect on body weight between the compared therapies. The comparison of incidence of nocturnal hypoglycemia episodes (defined as any episode [confirmed or symptomatic] occurring during the night) revealed 43% risk reduction for glargine 300 U/mL versus glargine 100 U/mL (RR = 0.57; 95% CI: 0.33–0.98), 79% risk reduction versus insulin NPH (RR = 0.31; 95% CI: 0.1–0.44) and 58% risk reduction versus insulin mixtures (RR = 0.42; 95% CI: 0.21–0.81). The conducted sensitivity analyses confirmed consistence of obtained results. In view of lack of direct head-to-head comparisons, results of this analysis may provide insight into benefits related to use of glargine 300 U/mL in patients with diabetes.

Extension of availability of new therapeutic options favors individualization of diabetes therapy. Wider use of safer therapeutic methods will result in improved

diabetes control, looking better not only in statistical summaries, but also affecting lives of individual patients suffering from diabetes.

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