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Basal Insulin Analogues: The Next Generation

Alice YY Cheng
MD, FRCPC

Endocrinologist
Credit Valley Hospital and St Michael's Hospital
Associate Professor, University of Toronto
Toronto, Ontario, Canada

Basal insulins have greatly evolved from traditional NPH, to first generation basal insulin analogues (glargine 100u/mL, detemir), and now to the next generation of basal insulin analogues (glargine 300 u/mL, degludec). With each generation, basal insulin profiles become flatter, and last longer. The clinical benefit this provides is less hypoglycemia for our patients. This article will review the method of protraction, evidence for clinical benefit, and then focus on the comparison between the two second-generation basal insulin analogues, Glargine 300 u/mL (Gla-300; Toujeo™) and Degludec (IDeg; Tresiba™).

WHAT IS A METHOD OF PROTRACTION?

To better understand how insulins differ, it is important to remember that the behaviour of insulin in circulation is similar, regardless of its source. What creates the different time-action profiles is the behaviour of the insulin after it is injected in the subcutaneous space. After glargine is injected, human pH causes the insulin solution to form micro-crystals. These micro-crystals of insulin slowly "dissolve" over time releasing insulin monomers, which are absorbed into circulation. In the case of glargine 300 units/mL, a different formulation results in tighter micro-crystals that are slower to dissociate resulting in a longer, flatter time-action profile compared to that of glargine 100 u/mL. The other second-generation basal insulin analogue, insulin degludec, creates protraction in the subcutaneous space by forming multihexamers upon injection. Over time, zinc used to bind the insulin molecules dissociates, and the monomers are released. Due to these different methods of protraction, both second-generation basal insulin analogues have longer, flatter time-action profiles (see Table 1).

Table 1: Types of Basal Insulin

	Onset	Peak	Duration
Intermediate-acting Insulins (cloudy) *Insulin neutral protamine Hagedorn (Humulin®-N, Novlin®ge NPH)	1-3h	5-8h	Up to 18h
Long-acting Insulins (clear) * Insulin detemir (Levemir®) * Insulin glargine U-100 (Lantus®) * Insulin glargine U-300 (Toujeo®) * Insulin glargine biosimilar (Basaglar®) * Insulin degludec U-100, U-200 (Tresiba®)	90min	Not applicable	U-100 glargine 24h, detemir 16-24h U-300 glargine > 30h degludec 42h

SECOND-GENERATION VS. FIRST-GENERATION BASAL INSULIN ANALOGUES

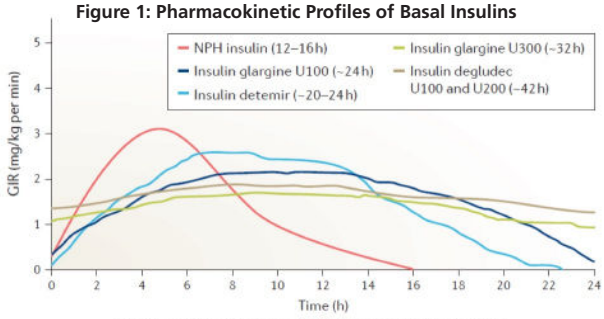
When compared to first-generation basal insulin analogues, the second-generation insulins have been shown to cause less hypoglycemia. The EDITION clinical trial program demonstrated this with Gla-300 compared to glargine 100 u/mL. The BEGIN clinical trial program and SWITCH studies

also demonstrated hypoglycemia reduction with IDeg compared to glargine 100 u/mL. In addition, the DEVOTE cardiovascular outcome trial with IDeg was able to show reduction in severe hypoglycemia compared to first-generation glargine 100 u/mL. Such a meaningful, statistically significant difference between 2 highly regarded basal insulins was only possible due to DEVOTE's large study population and lengthy follow-up period. Real world studies have also consistently shown less hypoglycemia with Gla-300 or IDeg compared to previous generation basal insulin analogues. With this wealth of evidence, one can confidently conclude that the second-generation basal insulin analogues are superior in causing less hypoglycemia. However, the more interesting question is how do the two second-generation basal insulin analogues compare to each other?

COMPARISON OF GLARGINE 300 U/ML VS INSULIN DEGLUDEC

Two head-to-head pharmacokinetic/pharmacodynamics studies have been published comparing these 2 insulins with conflicting results. Comparisons between the EDITION and BEGIN programs are not appropriate since the fasting glucose targets and definitions of hypoglycemia were different. However, the best way to answer the question is with a direct head-to-head randomized controlled trial. The BRIGHT study is the first such trial conducted in insulin-naïve patients with type 2 diabetes.

Figure 1: Pharmacokinetic Profiles of Basal Insulins



Pharmacodynamic Action Profiles of Long-Acting Insulins

Source: Mathieu, Chantal; Gillard, Pieter; Benhalima, Katrien. Insulin analogues in type 1 diabetes mellitus: getting better all the time. Nature Reviews Endocrinology 2017/04/21/online http://dx.doi.org/10.1038/nrendo.2017.39 (Used with permission)

BRIGHT STUDY

The BRIGHT study was a multicenter, 24-week trial with 929 patients receiving either Gla-300 or IDeg. Both groups were treated to a fasting self-monitored plasma glucose (SMPG) target goal of 4.4-5.6 mmol/L.. The weekly titration schedule was identical for the two groups with an expectation that the majority of patients would achieve the fasting SMPG target in the first 12 weeks of the study (titration period) although adjustments could continue to be made in the latter 12 weeks (maintenance period). The initial doses were based on the product monographs in the various countries, and therefore were slightly different with Gla-300 started at 0.2 units/kg and IDeg started at 10 units per day. The primary endpoint was non-inferiority for A1C and prespecified safety endpoints of hypoglycemia for the entire study, titration and maintenance periods. At baseline, the mean age was 60.5 years with 10.6 years of diabetes and mean A1C of 8.64%. More than 80% of the study population was on ≥2 antihyperglycemic agents with similar proportions using sulfonylurea (65.7%) at baseline.

At 24 weeks, the A1C decreased significantly from baseline for both groups with no difference between them (least squares mean difference -0.05% (95% CI -0.15 to 0.05) (non-inferiority P<0.0001) (Figure 1). The fasting plasma glucose levels were slightly different at baseline (Gla-300 10.6 ±2.7; IDeg 10.1±2.8 mmol/L). This small difference was maintained throughout the study. The significance of this is unclear since the fasting SMPG levels, upon which titration decisions were made, were similar between the 2 groups. At 24 weeks, the insulin dose was higher by 0.11 units/kg with the Gla-300 group, consistent with a higher initial dose based on product monographs in various enrolling countries. Despite the higher dose of Gla-300, there was no difference in body weight between the groups.

> With this wealth of evidence, one can confidently conclude that the second-generation basal insulin analogues are superior in causing less hypoglycemia.

For the overall study period (24 weeks) and the maintenance period (12-24 weeks), hypoglycemia (anytime or nocturnal) incidence and rate were comparable between the groups. The only notable exception was during the titration period (0-12 weeks), the period of greatest A1C reduction and insulin dose increase, when the incidence and rate of anytime (24-hour) confirmed hypoglycemia were lower with Gla-300 (Figure 2).

INTERPRETATION AND CLINICAL IMPLICATIONS OF BRIGHT

This head-to-head trial comparing Gla-300 and IDeg in insulin-naïve patients with type 2 diabetes demonstrated that the insulins have more similarities than differences (15). The following are some key learnings and interpretations from BRIGHT.

> This head-to-head trial comparing Gla-300 and IDeg in insulin-naïve patients with type 2 diabetes demonstrated that the insulins have more similarities than differences

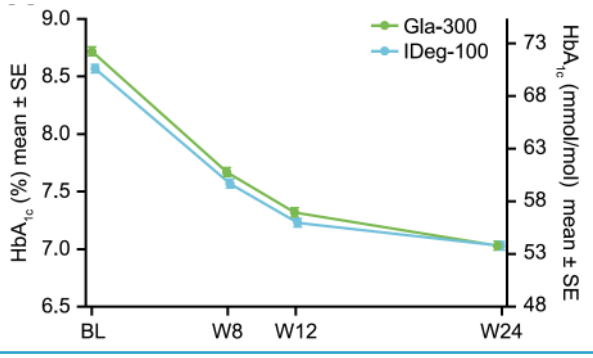
1. Proper titration of either basal insulin is effective for lowering glucose

Both insulins are effective basal insulins that when properly titrated, can effectively lower A1C from mean baseline of 8.6% to close to 7.0% in 12 weeks and achieve 7.0% by 24 weeks. These results are not typically seen in real life due to inadequate titration.

2. Comparable hypoglycemia between the insulins with less anytime confirmed hypoglycemia with Gla-300 in the titration period only

Overall and maintenance period hypoglycemia was comparable between the insulins but anytime confirmed hypoglycemia was reduced with Gla-300 during the titration period. This finding may be surprising for some so it is important to rule out some proposed explanations. The glycemic control achieved based on A1C and fasting SMPG were no different between the insulins at 12 weeks. FPG may have been slightly lower with IDeg at baseline by chance but that was maintained throughout the study yet hypoglycemia difference was only seen during the titration period. Therefore, glycemic control does not explain the difference. The titration schedule used was identical for both insulins, which occurred weekly and no more than 3 days apart, which is consis-

Figure 2: BRIGHT Study: A1C achieved at 24 weeks



tent with labels for both insulins. In fact, the doses of Gla-300 were higher initially and increased more quickly compared to that of IDeg, so titration does not explain the hypoglycemia difference. The use of sulfonylurea at baseline was similar between the two groups and the in-study use and doses of sulfonylurea were similar as well. At this point, an explanation for the difference in hypoglycemia remains unclear. However, from a clinical perspective, the titration period is important because patients are particularly vulnerable to basal insulin discontinuation in the first few months of starting basal insulin and any adverse effect will likely increase non-adherence or negatively impact future titration efforts. Therefore, minimizing potential issues early is worthwhile

3. Higher dose of Gla-300 may be required but do not assume every patient will require a higher dose

Consistent with findings in the EDITION program, the Gla-300 group required a slightly higher insulin dose than the IDeg group. Some of this is explained by the higher initial dose based on the labels in the countries. However, there is also a biologic explanation. The tighter micro-crystals seen with Gla-300 reside for a longer period of time in the subcutaneous space resulting in more time for degradation by tissue peptidases before absorption. In the clinical setting, not every patient will necessarily require a higher dose if their basal insulin is being changed. Therefore, it would be safer to make basal insulin switches as per the product monographs (either dose-for-dose or 80% reduction if moving from twice daily insulin), and to avoid increasing the dose pre-emptively to avoid hypoglycemia.

4. Is there consistency with real world evidence?

The DELIVER-D+ observational cohort study used large United States databases and identified patients with type 2 diabetes that switched to Gla-300, IDeg or others . This study demonstrated that the efficacy and hypoglycemia incidence of Gla-300 and IDeg were comparable. The CONFIRM study compared cohorts of insulin-naïve type 2 diabetes patients. In contrast, this study showed that IDeg had superior glycemic efficacy, less hypoglycemia and less discontinuation rates, but was limited since after propensity-score matching, A1C and hypoglycemia analyses were based on only part of the matched cohort. Interestingly, DELIVER-Naïve D, another observational study using the same database as CONFIRM and evaluating insulin-naïve patients with type 2 diabetes, found similar glycemic efficacy, hypoglycemia and discontinuation rates between the two insulins, and thus more consistent with the findings of BRIGHT.

5. Who are the patients in whom second-generation basal insulin analogues should be considered for use?

Assuming access is available, the second-generation basal insulin analogues are appropriate for the following patient scenarios:

- New basal insulin start in type 2 diabetes: In this scenario, the BRIGHT study would suggest that Gla-300 would be the preferred second-generation basal insulin analogue due to the potential for less anytime hypoglycemia during the titration period
- Currently taking twice-daily basal insulin: The longer half-lives of both of these insulins would allow for conversion to once daily dosing
- Currently taking basal insulin, and experiencing or suspected of having hypoglycemia
- Patient desiring smaller volume insulin as Gla-300 (300units/mL) and IDeg (200 units/mL) offer more concentrated options
- Patient requiring increased flexibility of insulin dosing: IDeg has been shown to be safe with flexible dosing in type 2 diabetes ranging from 8-40 hours . Gla-300 has only demonstrated safety +/- 3 hours

CONCLUSIONS

Both Gla-300 and IDeg are effective second-generation basal insulin analogues that are associated with less hypoglycemia compared to earlier generations. The BRIGHT head-to-head study of the 2 insulins in insulin-naïve patients with type 2 diabetes showed that there are more similarities than differences between the two insulins with comparable glycemic efficacy and overall hypoglycemia. The only notable differences were less anytime hypoglycemia with Gla-300 during the titration period and a slightly higher dose requirement with Gla-300. BRIGHT has provided useful clinical information to facilitate the choice between basal insulins. Many clinicians are already looking forward to upcoming head-to-head clinical trials in type 2 diabetes populations already using basal insulin that will provide further useful information.

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Perspectives on Canada's New Food Guide 2019

By Ashley Spegel, RD, CDE

Healthy dietary habits can reduce your patient's HbA1c by up to 2%; more potent than any available antihyperglycemic agent. This is great news for patients looking to improve their glycemic control with lifestyle modification. The 2019 edition of Canada's Food Guide (CFG) was released in February, and it's the ideal tool to help patients control blood sugar, promote heart health, and optimize weight management.

Canada's Food Guide has Two Areas of Focus:

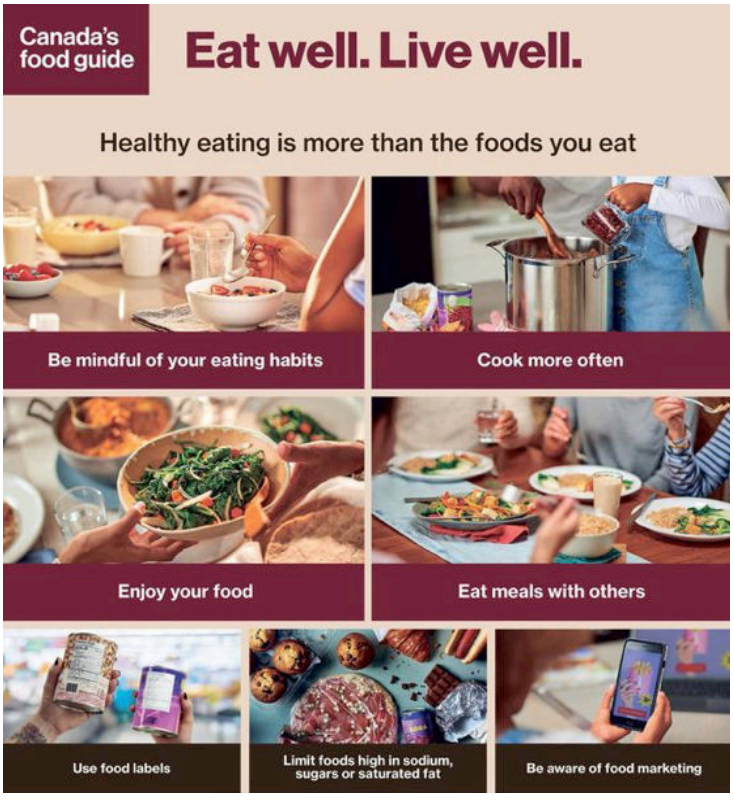
1 The Plate

Divided into three components: the Plate recommends each meal consist of 50% vegetables and fruit, 25% lean protein sources, and 25% whole grain carbohydrates and starches. These recommendations parallel those of Diabetes Canada. One premise behind the Plate's distribution is attributed to the undeniably favourable effects of fibre, which makes up 75% of the plate via veggies, fruit, and whole grains. Observational research has repeatedly confirmed that consuming high-fibre carbohydrates, as opposed to cutting them out completely, has significant benefits for managing blood sugar, and preventing diseases like type 2 diabetes, stroke, heart disease, and colon cancer. The Plate also encourages Canadians to consume lean protein at all meals and snacks, and emphasizes choosing plant-based proteins most often. Nuts, seeds, lentils, legumes, and soy can all reduce cholesterol, and blood sugar for patients with type 1 and type 2 diabetes. Next to the Plate is a glass of water. It's recommended all Canadians, and especially for those with diabetes, to hydrate with water, and avoid fruit juices to limit their intake of added sugar.

2 The Social and Emotional Aspects of Eating

Following in the footsteps of Brazil's acclaimed food guide, CFG highlights the psychosocial forces driving our food choices, which can impact health in the same way as diet. Tips to ensure healthy eating patterns include:

- Eating meals with others, especially loved ones
- Cooking at home more often so that nutritious eating becomes a priority
- Eating mindfully to avoid overeating.
- Enjoying your food



These simple recommendations that most of us don't follow, can even help mitigate stress and enhance emotional wellbeing. These are paramount for those facing the day-to-day challenges of diabetes. The simplicity of CFG – and its overlap with nutritional recommendations from the 2018 Diabetes Canada clinical practice guidelines -- give patients and practitioners tangible recommendations, applicable to all cultures and age groups.