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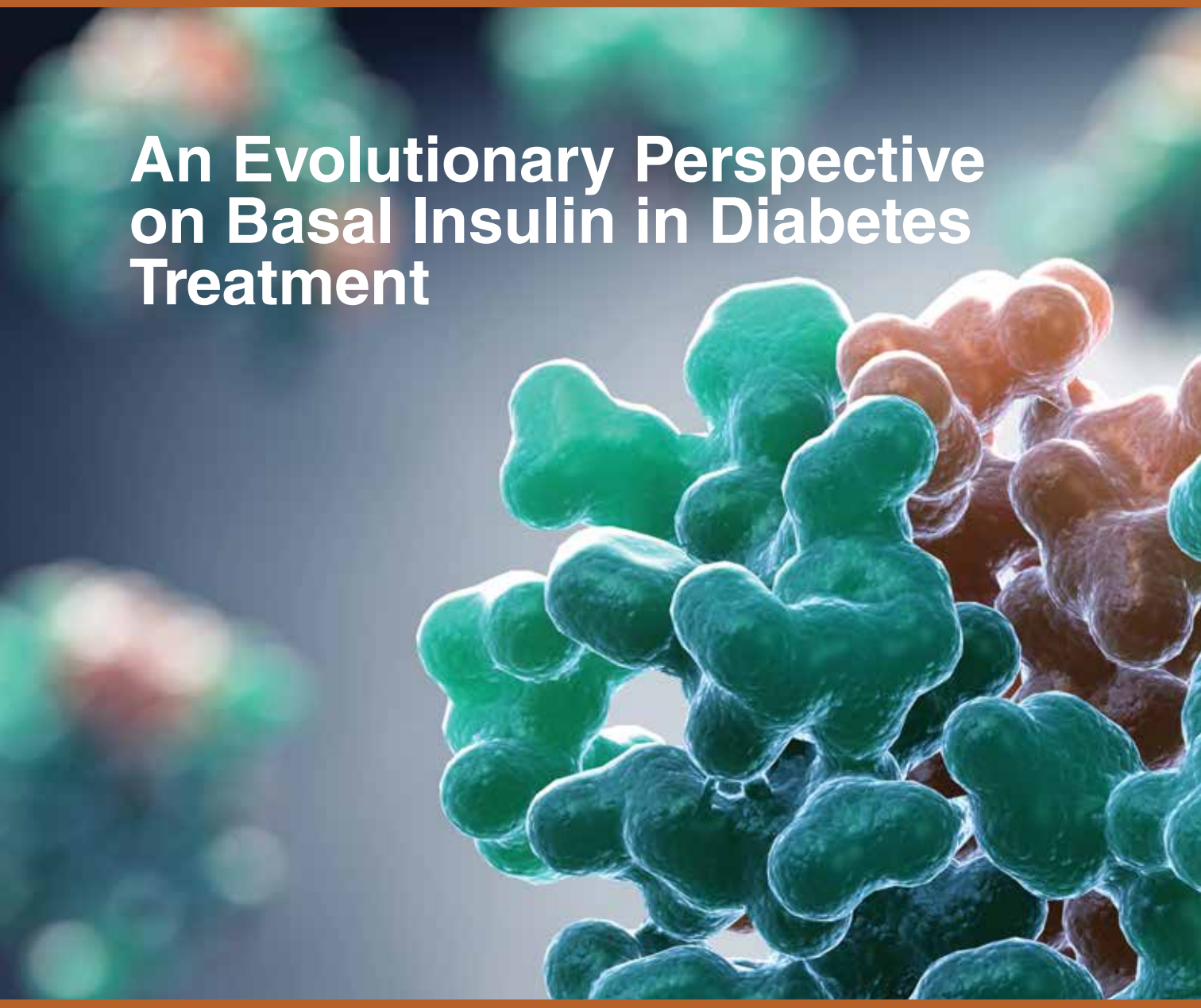
An Evolutionary Perspective on Basal Insulin in Diabetes Treatment



An Evolutionary Perspective on Basal Insulin in Diabetes Treatment

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LEARNING OBJECTIVES

- Provide an overview of the role of insulin as described in current practice guidelines for the management of persons with diabetes
- Describe the benefits of early initiation of insulin in persons with type 2 diabetes
- Implement effective physician-patient dialogues into strategies to identify and resolve patient barriers to insulin
- Describe the unmet clinical needs with human and older basal insulin analogs
- Describe the efficacy, safety, and tolerability of recently approved basal insulin analogs
- Initiate new basal insulin analogs in appropriate patients to address patient barriers or improve outcomes

INTRODUCTION

Helena W. Rodbard, MD, FACP, MACE
Eden M. Miller, D.O.
Athena Philis-Tsimikas, MD
John E. Anderson, MD

ROLE OF INSULIN THERAPY IN DIABETES

Helena W. Rodbard, MD, FACP, MACE
Medical Director, Endocrinology and Metabolic Consultants
Rockville, Maryland
Past President, American Association of Clinical Endocrinologists
Past President, American College of Endocrinology

Dr. Rodbard discloses that she is on the advisory board for AstraZeneca; Janssen Pharmaceuticals, Inc.; Merck & Co., Inc.; Novo Nordisk Inc.; Regeneron Pharmaceuticals, Inc.; and sanofi-aventis U.S. LLC. She is on the speakers' bureaus for AstraZeneca; Merck & Co., Inc.; and Novo Nordisk Inc. and does contracted research for Boehringer Ingelheim-Eli Lilly and Company; Merck & Co., Inc.; Novo Nordisk Inc.; Regeneron Pharmaceuticals, Inc.; and sanofi-aventis U.S. LLC.

BASAL INSULIN IN PRIMARY CARE

Eden M. Miller, D.O.
Executive Director and Co-founder Diabetes Nation
High Lakes Health Care
St. Charles Hospital
Bend, Oregon

Dr. Miller discloses that she is on the advisory board for Abbott; AstraZeneca; Boehringer Ingelheim; Eli Lilly and Company; Janssen Pharmaceuticals, Inc.; and Novo Nordisk Inc. She and her spouse are on the speakers' bureaus for Abbott; AstraZeneca; Boehringer Ingelheim; Eli Lilly and Company; Janssen Pharmaceuticals, Inc.; and Novo Nordisk Inc.

INNOVATIONS IN INSULIN: INSULIN DEGLUDEC U-100 AND U-200

Athena Philis-Tsimikas, MD
Scripps Whittier Diabetes Institute
San Diego, California

Dr. Philis-Tsimikas discloses that she is on the advisory board for AstraZeneca; Dexcom, Inc.; Eli Lilly and Company; Novo Nordisk Inc.; and sanofi-aventis U.S. LLC.

INNOVATIONS IN INSULIN: INSULIN GLARGINE U-300

John E. Anderson, MD
Past President
The Frist Clinic
Nashville, Tennessee

Dr. Anderson discloses that he is on the advisory board and speakers' bureaus for AstraZeneca; Boehringer Ingelheim; Eli Lilly and Company; Janssen Pharmaceuticals, Inc.; and sanofi-aventis U.S. LLC. He is also on the advisory board for Abbott.

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Cover Image: Photo Researchers 2016. Stylized illustration of 2HIU insulin. Computer generated image.

Introduction

The discovery and introduction of insulin in the management of patients with type 1 diabetes mellitus (T1DM) in 1922 was a major advance in medicine. The insulin administered to the first patient was a thick brown muck that lowered the blood glucose—but also caused severe abscesses. Much has changed with insulin over the nearly 100 years since the first use in humans. No longer extracted from animal pancreatic tissues, the insulin formulations available today are synthesized using DNA technology and highly purified.

The devices used to administer insulin also have evolved and are far more patient-friendly than the vials and syringes that were used for decades. Today's reusable pen devices enable accurate selection of the dose and, in conjunction with the short, ultra-fine needles now available, allow for simple, relatively painless self-injection.

This supplement begins with Dr. Helena Rodbard highlighting the role of insulin in managing patients with type 1 diabetes and focuses on how the role of insulin in type 2 diabetes mellitus has evolved over the past 2 decades. Dr. Rodbard offers her insight into the factors contributing to this evolution, emphasizing the benefits of early vs late use of insulin in type 2 diabetes mellitus, as well as the cardiovascular benefits associated with insulin.

In the second article, Dr. Eden Miller discusses the provider, patient, and family barriers to insulin that contribute to its lower than recommended usage in the primary care setting. Dr. Miller offers physician-patient communication dialogues that can be incorporated into strategies to identify and then overcome some of the most common barriers in patients with type 2 diabetes mellitus, including treatment complexity and intrusiveness, hypoglycemia, and weight gain. Dr. Miller concludes by outlining unmet needs with human insulin and older basal insulin analogs.

The third and fourth articles in the supplement include case vignettes to focus on the 2 most recently available basal insulins, insulin degludec and insulin glargine U-300. Discussion focuses on degludec and glargine U-300 used alone and not in combination with glucagon-like peptide-1 receptor agonists or premixed with prandial insulin.

In the third article, Dr. Philis-Tsimikas discusses the clinical pharmacology of insulin degludec and the clinical relevance of key pharmacokinetic and pharmacodynamic properties, including its long duration of glucose-lowering effect and low intra- and inter-patient glycemic variability. The phase 3 program of clinical trials is reviewed, particularly long-term efficacy and safety in patients with type 2 diabetes mellitus, focusing on hypoglycemia and cardiovascular safety. Dr. Philis-Tsimikas concludes by summarizing the improvements in patient reported outcomes observed when on treatment with insulin degludec, including the benefits of alternative dose timing.

The final article by Dr. John Anderson provides similar information about insulin glargine U-300, beginning with a comparison of the clinical pharmacology with insulin glargine U-100. The phase 3 program of clinical trials in patients with type 1 or type 2 diabetes mellitus is outlined. Emphasis is placed on long-term efficacy and safety, particularly hypoglycemia and cardiovascular safety. Patient quality of life and treatment satisfaction compared with insulin glargine U-100 are provided, as are dosing considerations.

An Evolutionary Perspective on Basal Insulin in Diabetes Treatment should provide you with insights that help you individualize treatment of patients with diabetes mellitus. ●

Helena W. Rodbard, MD, FACP, MACE, Medical Director, Endocrinology and Metabolic Consultants, Rockville, Maryland, Past President, American Association of Clinical Endocrinologists, Past President, American College of Endocrinology

Eden M. Miller, DO, Executive Director and Co-founder Diabetes Nation, High Lakes Health Care, St. Charles Hospital, Bend, Oregon

Athena Philis-Tsimikas, MD, Scripps Whittier Diabetes Institute, San Diego, California

John E. Anderson, MD, Past President, The Frist Clinic, Nashville, Tennessee

DISCLOSURES

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Dr. Philis-Tsimikas discloses that she is on the advisory board for AstraZeneca; Dexcom, Inc.; Eli Lilly and Company; Novo Nordisk Inc.; and sanofi-aventis U.S. LLC.

Dr. Anderson discloses that he is on the advisory board and speakers' bureaus for AstraZeneca; Boehringer Ingelheim; Eli Lilly and Company; Janssen Pharmaceuticals, Inc.; and sanofi-aventis U.S. LLC. He is also on the advisory board for Abbott.

Role of Insulin Therapy in Diabetes

Helena W. Rodbard, MD, FACP, MACE

INTRODUCTION

The ideal insulin therapy would mimic the body's own physiology, with a very rapid release of insulin at the time of food intake, as well as a sustained availability of insulin throughout the entire 24 hours to provide a basal level of insulin needed even when there is no immediate food intake. Although there have been numerous improvements in insulin formulations since becoming available nearly 100 years ago, this ideal has not yet been achieved.

Insulin was originally prepared from crude extracts of beef and pork pancreases. Over decades, the methods to purify insulin improved, leading to better reliability, fewer local reactions, and less antigenicity. Longer acting forms of insulin were developed, such as neutral protamine Hagedorn (NPH, isophane). In the 1980s, major progress occurred when it became possible to manufacture human insulin using recombinant DNA methodology. This resulted in native human insulin, thereby avoiding problems due to inter-species differences, and providing essentially an insulin molecule identical to that secreted in humans. Another benefit of recombinant DNA technology is that it made possible modification of the insulin molecule, resulting in insulin analogs with desired pharmacokinetic and pharmacodynamic characteristics. These include more rapid absorption and onset of action for use as a prandial or bolus insulin or slower absorption and prolonged duration of action for use as basal insulin (**TABLE**).[1-18]

Helena W. Rodbard, MD, FACP, MACE, Medical Director, Endocrinology and Metabolic Consultants, Rockville, Maryland
Past President, American Association of Clinical Endocrinologists,
Past President, American College of Endocrinology

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BASAL INSULINS

Since most basal insulins have a fairly consistent rate of absorption and long duration of action, they can mimic the relatively constant rate of endogenous insulin secretion over the course of the day. Consequently, basal insulins are used to control glycemia throughout the 24-hour period, and are usually monitored by following the fasting blood glucose.

Until recently, insulin detemir and insulin glargine U-100 were the only 2 long-acting basal insulin analogs available. In 2015, the new molecular entity degludec U-100 and U-200 and a concentrated formulation of insulin glargine, glargine U-300, were approved in the United States as long-acting basal insulin analogs (see: *Innovations in Insulin: Insulin Degludec U-100 and U-200* on page S14 and *Innovations in Insulin: Insulin Glargine U-300* on page S23).

Generally utilized as a basal insulin, NPH is a synthetic human insulin that should be considered as intermediate-acting because of its shorter duration of action compared with the basal insulin analogs. NPH can be administered once or twice daily, though is generally administered twice a day. The time-action curve of NPH in terms of glucose lowering (transport of glucose out of the circulation into cells) shows a very distinct peak at about 8 hours and its action is virtually complete within 12 hours.[7,8] Further, NPH is associated with very marked intra- and interpatient pharmacodynamic variability in glucose-lowering. The interpatient variability may result in as much as a two-fold (or larger) ratio of effectiveness in different people. Together, the short time course of action and large intra- and interpatient variability are responsible for a relatively high rate of hypoglycemic events in people using NPH alone or in premixed insulin preparations.[8]

PRANDIAL INSULINS

The modern prandial or bolus insulins have a rapid onset and fairly short duration of action and are used to reduce postprandial hyperglycemia. They can mimic the intermittent secretion of insulin in humans in response to food intake. In addition, prandial insulins inhibit glucose production by the liver, stimulate glucose uptake by the liver, and promote

TABLE Time-action profiles of insulin formulations[1-18]

Generic Name	Form	Time of Action (h)		
		Onset	Peak	Duration
Rapid-acting (Prandial)[1-4]				
Aspart	Analog	<0.25	1-3	3-5
Glulisine	Analog	<0.25	0.7-3	3-5
Lispro U-100, U-200	Analog	<0.25	0.5-1.5	3-6
Regular, powder, metered	Human	<0.25	0.5-1.5	2.7
Short-acting (Prandial)[5,6]				
Regular	Human	0.25-1.25	1.5-3.5	8
Intermediate-acting (Basal)[7,8]				
Neutral protamine Hagedorn	Human	1-2	4-12	10-16
Long-acting (Basal)[7-18]				
Degludec U-100, U-200	Analog	1-2	Relatively peakless	≥42
Detemir	Analog	1-2	Relatively peakless	≤24
Glargine U-100	Analog	1-2	Relatively peakless	24
Glargine U-300	Analog	6	Relatively peakless	≥24

glucose uptake by cells throughout the body, especially by muscle and fat cells.

The prandial insulin analogs, aspart, glulisine, and lispro, are considered rapid-acting, as is regular human insulin when formulated as technosphere insulin for inhalation. In contrast, the time-action profile of injectable regular human insulin is much longer; thus it is considered a short-acting insulin. The use of injectable regular insulin should be discouraged because its time-action profile generally does not match the rate of absorption of food from the gastrointestinal tract. This commonly results in a marked increase in blood glucose shortly after starting a meal, and may be followed by a decrease in blood glucose as the regular human insulin begins to work. This problem is largely, but not entirely, solved by the current generation of rapid-acting insulins. To overcome this limitation, current research is focused on developing prandial insulins that act even more rapidly.

The rapid-acting insulins are also used in insulin pumps. In this role, they can be used for the pre-meal or meal-associated bolus, as well as providing for the longer acting insulin profiles corresponding to the basal insulins.

COMBINING BASAL AND PRANDIAL INSULIN

Using currently available forms of therapy, approximately 60% of patients with type 2 diabetes mellitus (T2DM) can achieve a glycated hemoglobin A1c (HbA1c) ≤7.0% by combining basal insulin and oral agents, provided the patient is adherent to medications, diet, and other lifestyle interventions.[19] When basal insulin once or twice daily is not adequate to achieve the individualized target level for glycemic control, prandial insulin can be administered once daily, beginning with the meal that causes the largest postprandial rise in blood glucose (designated as basal-plus). Prandial insulin can be added at a second (basal-plus 2) or third (basal-bolus) meal depending on patient needs. The stepwise progression from basal insulin- only to basal-bolus, (and possibly additional "correction" boluses), is easy for physicians to implement and for patients to self-adjust the insulin dose.[20]

EVOLUTION IN TREATMENT OF TYPE 2 DIABETES

The improvements in insulin formulations have been part of an overall advancement in the treatment of patients with diabetes, particularly T2DM. This is largely the result of two factors. The first is a greater understanding of the disease pathophysiology, making it clear that multiple mechanisms may disrupt glucose homeostasis in T2DM.[21] The second is the availability of 11 classes of medications in addition to insulin that target different pathophysiologic mechanisms. Considering that these medications can be used as mono-, dual, or triple therapy with or without one or two types of insulin, leads to a large number of possible combinations.[22] With these advances—and greater complexity—came the

need to understand how the medications could be best used to care for patients with T2DM.

In 1989, the American Diabetes Association (ADA) issued its first *Standards of Medical Care for Patients with Diabetes Mellitus* as a means of identifying basic medical care for people with diabetes.[23] In 1994, the American Association of Clinical Endocrinologists (AACE) published its *System of Intensive Diabetes Self-Management*.[24] Both the ADA and AACE publications discussed factors to consider in managing patients with diabetes mellitus, but provided little information to guide pharmacologic management. This changed in 2006 when the ADA, in collaboration with the European Association for the Study of Diabetes (EASD), published a consensus algorithm for the metabolic management of T2DM.[25] Subsequently, in 2009, AACE, in collaboration with the American College of Endocrinology (ACE), published consensus panel recommendations in the form of a diabetes algorithm for glycemic control.[26] The AACE/ACE algorithm introduced the concept that insulin should be used as initial therapy for patients with T2DM and HbA1c greater than 9.0% with symptoms attributable to hyperglycemia. This concept remains an important recommendation in the most recent ADA/EASD and AACE/ACE algorithms.[27,28] The 2015 ADA/EASD algorithm extends the recommendation to include patients who exhibit catabolic features such as weight loss or ketosis, in which case, the combination of basal and prandial insulin is preferred. The ADA/EASD algorithm also recommends that consideration should be given to initiating combination injectable therapy with insulin when the blood glucose is 300 to 350 mg/dL or greater and/or the HbA1c is 10% to 12%.[27]

Although glucose control is a major focus of treatment in patients with T2DM, controlling glucose must be done in the context of overall cardiovascular risk reduction. This consists of adoption of healthy lifestyle habits, including smoking cessation, as well as rigorous control of blood pressure and lipids, generally in combination with pharmacotherapy. Accordingly, treatment individualization that balances the benefits of glycemic control with its potential risks, including hypoglycemia, is essential. Patient factors such as age, health status and life expectancy, duration of diabetes, comorbidities, interests, and capabilities, may influence the HbA1c target for glucose control as well.[27] Some of these factors are modifiable while others may not be for an individual patient. Each patient's degree of motivation, education, attitude, and access to resources and support systems are unique and may change over time.

The 2015 ADA/EASD algorithm was included in a position statement that was developed based on the best available evidence and, where solid support did not exist, using the experience and insight of the writing group.[27] The position statement also included extensive review by additional experts. Adopting a more patient-centered approach to management, the writing committee noted that their recommendations were less prescriptive than and not as algorithmic as prior guidelines due to a lack of relevant comparative-effectiveness research.

The 2016 AACE/ACE algorithm was included as part of a consensus statement.[28] Where there were no randomized controlled trials or specific US Food and Drug Administration labeling for issues in clinical practice, the participating clinical experts utilized their judgment and experience. Every effort was made to achieve consensus among the committee members. The writing committee indicated that the intent of the AACE/ACE position statement was to provide guidance, but that it should not be considered prescriptive for any individual patient and should not replace the judgment of a clinician.

ROLE OF INSULIN IN TREATMENT

Type 1 Diabetes Mellitus

The body's inability to produce insulin in patients with T1DM necessitates the administration of basal and prandial insulins in all patients to meet physiologic needs. The only exception might arise during a "honeymoon period" shortly after diagnosis, and in some patients with latent autoimmune diabetes of adulthood who have some residual insulin secretory capacity. For basal insulin therapy, the analogs are generally preferred because there is a smaller risk of moderate and severe hypoglycemia compared with NPH insulin.[29]

Type 2 Diabetes Mellitus

Insulin is the most potent glucose-lowering agent available. The decision to start insulin is made in collaboration with the patient and depends on several factors, including the patient's motivation, cardiovascular and other microvascular complications, age, general well-being, risk of hypoglycemia, overall health status, and cost.[28]

BENEFITS OF INSULIN THERAPY IN TYPE 2 DIABETES MELLITUS

Early vs Late Use of Insulin

The ability of insulin to provide rapid and sustained glucose control has led to investigations examining the benefits of early insulin replacement. Some investigations have focused on the longevity of benefits derived from early, short-term treatment with insulin. One study involved people newly diagnosed with T2DM (FPG 239 mg/dL at baseline) who were treated with multiple daily injections (MDI) of insulin to achieve an FPG <108 mg/dL and 2-hour postprandial glu-

cose <126 mg/dL. Treatment was continued for 2 to 3 weeks, after which insulin was discontinued. After 1 year, the mean FPG was 121 mg/dL. Forty-four percent of patients maintained glycemic control for up to 1 year with diet therapy alone.[30] Compared with oral agents, MDI for 6 months also has been shown to result in significantly greater reduction of HbA1c (from 11.3% at baseline to 7.84% vs 11.9% at baseline to 6.78%, respectively), and higher proportion of patients achieving HbA1c targets.[31] Beta-cell function was better maintained with basal insulin therapy compared with oral agents.

Early initiation of intensive insulin therapy (either as MDI or continuous subcutaneous insulin infusion [CSII]) has been shown to partially restore beta-cell function and greatly improve insulin sensitivity.[32] Another investigation comparing basal insulin monotherapy with CSII in patients newly diagnosed with T2DM showed that both groups experienced similar improvement in glycemic control (HbA1c and fasting plasma glucose) and beta-cell function.[33] This latter study particularly shows the success, practicality, and affordability of a very simple approach (basal insulin monotherapy) that can be readily implemented and maintained long-term in primary care.

The benefits of early vs late use of basal insulin analog therapy have been confirmed in a meta-analysis by Fonseca et al.[34] Patients (N=928) with a mean HbA1c of 8.69% were treated with insulin glargine in combination with oral agents for 24 weeks. The likelihood of achieving the HbA1c target was significantly greater with the early addition of insulin glargine to baseline metformin monotherapy compared with later addition to the combination of metformin and sulfonylurea (log odds ratio 0.738; *P*=.005). Similarly, the risk of hypoglycaemia was lower with earlier addition of insulin glargine (log odds ratio -0.546; *P*=.001).

Cardiovascular Outcomes

A possible association of insulin with cardiovascular events has been investigated in several large prospective studies, with results showing no associated risk. Among the most recent, the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial investigated the occurrence of cardiovascular events in patients with prior T2DM (mean 5.2 years), impaired fasting glucose, or impaired glucose tolerance.[35] All patients (N=12,443; 82.4% with prior T2DM) were at high cardiovascular risk since a history of prior cardiovascular events was required. Patients were randomized to treatment with basal insulin (target fasting plasma glucose ≤95 mg/dL) or standard care, consisting of the investigator's best judgment and local guidelines.

The median HbA1c was 6.4% in both groups at baseline and 6.2% and 6.5% at study end in the insulin glargine and standard care groups, respectively. There were 2 co-primary composite cardiovascular outcomes. The first was cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; the second was a composite of these events, a revascularization procedure, or hospitalization for heart failure. The results of ORIGIN showed that over a median follow-up of 6.2 years, the risks of either co-primary outcome, as well as all-cause mortality or microvascular events, were similar in the insulin glargine and standard care groups.

The study concluded that basal insulin does not increase the incidence of cardiovascular events in people with prediabetes or short-duration T2DM at high cardiovascular risk. Although treatment with basal insulin was associated with increased risks of severe and non-severe hypoglycemia, the relative risk of severe hypoglycemia with a major adverse cardiovascular outcome was significantly lower with basal insulin compared with standard care.[36]

Further insight regarding the long-term impact of insulin therapy on cardiovascular outcomes was reported from the Veterans Affairs Diabetes Trial (VADT). The VADT investigated the impact of intensive vs standard glucose control (to achieve HbA1c less than 6% or less than 9%, respectively) on cardiovascular outcomes in 1791 military veterans with T2DM.[37] The study was conducted because previous investigations observed an inconsistent association between intensive glucose control and cardiovascular disease. The primary outcome of VADT was the time to first occurrence of a composite of cardiovascular events (myocardial infarction; stroke; cardiovascular death; new or worsening heart failure; surgical intervention for cardiac, cerebrovascular, or peripheral vascular disease; inoperable coronary artery disease; and amputation for ischemic gangrene).

Key baseline characteristics of patients in VADT included T2DM for an average of 11.5 years, HbA1c 9.4-9.5%, and a previous cardiovascular event in approximately 40%.[38] An initial report covering a median of 5.6 years of follow-up had shown no difference in the primary outcome between intensive glucose lowering compared with standard therapy.[37,38] The difference in HbA1c reduction between the intensive and standard therapy groups averaged about 1.5% during the trial and declined to 0.2% to 0.3% by 3 years after the trial ended.[38]

In contrast, the recent report of long-term follow-up (median 9.8 years) showed that the risk of the primary outcome was significantly lower in the intensive therapy group compared with the standard therapy group (hazard ratio 0.83; *P*=.04).[38] There was, however, no difference in the overall survival rate.

The mechanisms underlying the cardiovascular outcomes associated with insulin therapy are unclear. A sub-

study of ORIGIN evaluated the effects of insulin glargine on carotid intima-media thickness (CIMT) and found no significant difference in CIMT progression between treatment with basal insulin or standard care.[39] Similarly, there were no differences in the changes in CIMT among patients with T2DM treated using basal-only (detemir), basal-bolus (detemir + aspart), or premixed (aspart/aspart protamine) therapy for 18 months.[40]

SUMMARY

The availability of human insulin and subsequently insulin analogs that more closely mimic the body's physiology have contributed to increased safety in patients with diabetes and a greater role in patients with T2DM. This greater role is supported by clear evidence that early use of insulin in T2DM results in long-term improvements in glycemic control and beta-cell function compared with oral agents.

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Basal Insulin in Primary Care

Eden M. Miller, DO

Insulin is the most potent treatment available for diabetes mellitus. Yet, the usage of insulin has declined over the past 2 decades. In 1994, 38% of patients with diabetes mellitus were treated with insulin, whereas data from the National Health Interview survey from 2010 to 2012 show that 14.0% of patients with diabetes were treated with insulin alone and 14.7% with the combination of insulin and oral glucose-lowering medication.[1,2] The declining usage of insulin is contrary to the greater role recommended in current guidelines for the treatment of patients with type 2 diabetes mellitus (T2DM).[3,4] (see *Role of Insulin therapy in Diabetes* on page S3)

This article focuses on the factors that contribute to the lower than recommended usage of insulin and how they might be overcome in primary care. Also discussed will be unmet needs with human and older insulin analogs.

BARRIERS TO BASAL INSULIN

Numerous studies and surveys have been conducted to identify the barriers to diabetes care, including insulin therapy, among providers and patients with T2DM and their families. The second Diabetes Attitudes, Wishes, and Needs (DAWN2) survey, the Hypoglycemia Assessment Tool (HAT) study, and the Global Attitudes of Patients and Physicians (GAPP) survey are among the most recent.

2nd Diabetes Attitudes, Wishes, and Needs Survey

DAWN2 was a multinational study of over 15,000 healthcare providers (HCPs), patients, and family members in 17 countries. The primary objective of DAWN2 was to assess potential barriers and facilitators of active and successful management of diabetes.[5]

Eden M. Miller, DO, Executive Director and Co-founder Diabetes Nation, High Lakes Health Care, St. Charles Hospital, Bend, Oregon

DISCLOSURE

Dr. Miller discloses that she is on the advisory board for Abbott; AstraZeneca; Boehringer Ingelheim; Eli Lilly and Company; Janssen Pharmaceuticals, Inc.; and Novo Nordisk Inc. She and her spouse are on the speakers' bureaus for Abbott; AstraZeneca; Boehringer Ingelheim; Eli Lilly and Company; Janssen Pharmaceuticals, Inc.; and Novo Nordisk Inc.

Health Care Providers

Among HCPs (N=4785), only one-third agreed that health care is well-organized for the management of patients with chronic conditions such as diabetes.[6] Nearly two-thirds of HCPs reported the need for formal training in effective communication with their patients with diabetes. Nearly two-thirds also agreed that improvements are needed in patient self-monitoring of blood glucose, a skill that is essential to guide insulin therapy. HCPs generally agreed that although self-management education was considered to be important, it was generally not provided. Finally, psychosocial support was considered a key aspect of diabetes care, but HCPs lack adequate resources, training, and reimbursement to provide it.

Patients with Diabetes Mellitus

Among the 8596 patients included in DAWN2, 1368 (15.9%) had type 1 diabetes mellitus (T1DM) and 7228 (84.1%) had T2DM.[7] Of the patients with T2DM, 35.9% were treated with insulin. Of all patients with diabetes in the United States, one-quarter reported high diabetes-related distress, which was associated with suboptimal self-management. One-third reported being worried about the risk of hypoglycemia and nearly one-quarter indicated that their diabetes treatment interfered with their normal life. Patients in the United States reported testing their blood sugar on fewer than 5 of the previous 7 days recommended by their provider.

Family Members

DAWN2 included 2057 family members of people with diabetes.[8] In the United States, supporting a family member with diabetes was perceived as a burden by one-quarter, and one-quarter experienced a high level of diabetes distress. In addition, nearly one-half worried about the risk of hypoglycemia. These data likely contribute to the finding that one-third of US family members report a high level of frustration in not knowing how to help the individual with diabetes.

Hypoglycemia Assessment Tool Study

The HAT study was a multinational study that assessed self-reported hypoglycemia and associated predictive factors in adults with T1DM (n=8022) or T2DM (n=19,563) treated with

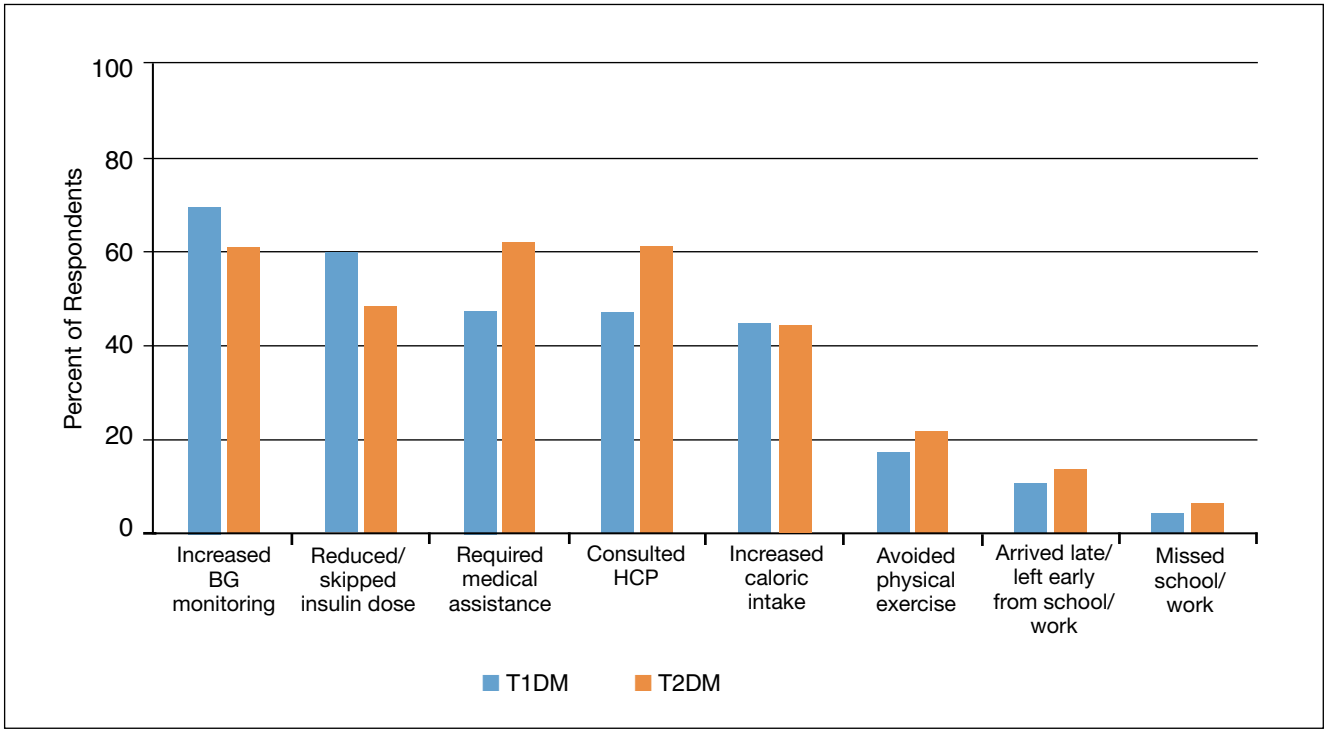
insulin for ≥12 months.[9,10] Most patients with T1DM (83.4%) and half of the patients with T2DM (50.8%) experienced ≥1 hypoglycemic event during the 4 weeks before baseline. During the 4 weeks after baseline, a greater percentage of patients with T1DM vs T2DM reported any (83.0% vs 46.5%), nocturnal (40.6% vs 15.9%), or severe (14.4% vs 8.9%) hypoglycemia.[9] The estimated annual hypoglycemia incidence rates were 73.3 and 19.3 events/patient-year of exposure for T1DM and T2DM, respectively.[10] On a 10-point scale (0, not afraid at all; 10, absolutely terrified), patients quantified their level of fear of hypoglycemia as 4.7±2.95 for T1DM and 4.4±3.05 for T2DM.[10] Increased blood glucose monitoring was the most frequent response to a hypoglycemic event (**FIGURE**).[10] Many patients modified their insulin dosing regimen or increased their caloric intake, which may have a significant impact on achieving glycemic control and associated long-term benefits.[10] Additionally, 1 in 5 individualss with T2DM avoided physical exercise as a consequence of a hypoglycemic event, which is a concern because physical exercise is a cornerstone of treatment.

Global Attitudes of Patients and Physicians Survey

The GAPP survey was an Internet survey of 1250 physicians (n=650 primary care) and a telephone survey of 1530 insulin-treated patients (n=1350 with T2DM) in 8 countries, including the United States.[11] Three-quarters of physicians reported that patients do not take their basal insulin as prescribed (an average of 4.3 days per month) nor their prandial insulin (5.7 days per month). Physicians and patients agreed that the top 5 reasons for non-adherence were: too busy, traveling, skipped meals, stress or emotional problems, and public embarrassment. Taking insulin at the prescribed time or with meals every day and the number of daily injections were the top negative perceptions of patients about insulin. Physicians reported that the possibility of hypoglycemia limits treatment intensification and that balancing efficacy and safety is difficult.

DAWN2, HAT, and GAPP reaffirm that numerous barriers exist to the management of patients with T1DM or T2DM. In addition to approaching the management of patients with diabetes as a chronic disease, using a collaborative care model, HCPs identified the need to better communicate with and support patients in their diabetes self-management, especially related to insulin. Effective communication and support are extremely important since both patients and their families see diabetes as a heavy burden. Moreover, high levels of frustration and distress

FIGURE Patient actions in response to a hypoglycemic event[10]



Abbreviations: BG, blood glucose; HCP, health care professional; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

are common, particularly regarding hypoglycemia, since hypoglycemia is associated with many negative outcomes, including causing patients to reduce treatment intensity with insulin.

STRATEGIES TO ADDRESS PATIENT BARRIERS TO INSULIN IN TYPE 2 DIABETES MELLITUS

Providing care to patients with diabetes is based on the knowledge that both T1DM and T2DM are chronic diseases that are largely self-managed.[12] Consequently, the major roles of the primary care provider and health care team are to advise, coach, and generally support the patient and family. In these roles, it is especially important to help patients identify barriers to self-management, find acceptable solutions, and successfully implement them. This may be best accomplished through a process of shared decision-making.

The willingness and ability of patients to participate in shared decision-making varies among patients and is influenced by their relationship with their provider. If not done previously, the process of shared decision-making can begin at the time of diabetes diagnosis. Some patients may be reluctant to participate in shared decision-making initially, but are likely to become more willing as they become more comfortable with the process and their own ability to self-manage. Discussion about shared decision-making regarding the treatment of T2DM and the use of insulin might be started as follows: "Patients often find it helpful when we work together to make decisions about their care. To do this, it is important that they have a good understanding about their diabetes, including the different medications like insulin that can be used for treatment. It's also most helpful when we talk about any concerns you might have. What do you think about this?"

Regardless of the extent to which shared decision-making is undertaken, asking each patient about their concerns, including those about insulin, can lead to a process of collaborative problem-solving. One approach is to ask "What comes to your mind when you think of insulin?" or "Can you see yourself injecting insulin? If not, why not?" The answer is useful to guide further discussion ultimately leading to resolution of the barrier and successful initiation of insulin. While this discussion needs to begin at the time of diagnosis of T1DM, it is advisable to do the same with patients with T2DM as it is likely to de-stigmatize insulin and allay patient concerns.

Once barriers to insulin are identified, the following strategies might be implemented to address some of the more common concerns of patients with T2DM.

Confusion About Role of Insulin in Therapy

PCP: Now that we've reviewed your glucose levels over the past ten to twelve months and see that your HbA1c is slowly rising, it's clear that your current medications aren't adequate to control your blood glucose. What do you think about starting insulin?

Patient: Please don't talk to me about going on insulin. I promise I will take my medications when I should.

PCP: The need for insulin isn't because you have forgotten to take your medications from time to time. It's because the medications you have been taking are no longer helping you to keep your blood glucose under control. This is common in patients with type 2 diabetes and is a result of your body losing its ability to produce insulin. It's very much like putting gasoline in your car. Your car needs gasoline to run, so when your gas tank approaches empty, you fill it with gasoline. That's what we're doing by administering insulin, supplying the insulin your body needs but isn't producing.

Patient: Okay, that makes sense, but I've heard about people starting insulin and dying soon after. Or maybe they lose a toe. I can't bear to think that's going to happen to me.

PCP: It's true that some patients die or lose a toe soon after starting insulin. But insulin didn't cause it. It's because their blood glucose hadn't been well controlled for many years and their body developed complications as a result. It's likely that they should have started insulin many years before they did. I want to help you avoid this situation by keeping your blood glucose under control. Starting insulin earlier than it used to be done will help us do that.

Comment: Talking with patients with T2DM about the progressive nature of the disease and the benefits of good glucose control are of paramount importance, starting at the time of diagnosis.

Treatment Complexity

PCP: How do you think your treatment is going? Are you having any difficulties?

Patient: I guess it's going okay, although I thought my blood glucose would be under control by now like we talked about. My real difficulty is that my feet are feeling a little numb.

PCP: The numbness is a complication of your diabetes called neuropathy. For that reason and the fact that your blood glucose isn't where we'd like it to be, perhaps it's time to make a change with your medications. Perhaps we should consider starting insulin.

Patient: Wouldn't that be worse? My life is complicated enough without adding insulin to it. As it is, I have trouble remembering to take my metformin at dinnertime. And I certainly can't see giving myself shots every day.

PCP: It's true that administering insulin is a bit more involved than taking medications by mouth. But most of my patients who take insulin tell me it's worth it. In fact, most tell me that taking insulin is a lot easier than they imagined. Most of them also tell me that they barely feel the needle and that the pen device is very easy to use. I can show you before you leave today. You would start with giving yourself an injection once a day at dinnertime along with your metformin. You could discontinue your two other oral medications.

Patient: Okay, but isn't it complicated to figure out how much insulin to inject?

PCP: No, not really. You would start with what's called basal insulin. Basal insulin is given to replace the background insulin that your body needs over a 24-hour period. I will give you simple directions to adjust your dose up or down when that's needed. Adjusting your insulin dose will be based on your blood glucose monitoring just as you do now. You will need to monitor your blood glucose more frequently than you do now, but generally not more than once a day. If you have any questions as you do this, please give me a call.

Comment: Teaching patients to self-titrate their insulin dose enables them to make more timely adjustments. It also can improve adherence since the patient more readily sees changes in their glycemic control as they change the insulin dose.

Intrusiveness on Daily Activities

PCP: We've talked for some time about the possibility of needing to start insulin to keep your blood glucose under control. We've tried several types of medications, but we can't seem to lower your HbA1c to less than 8.0%. So, in this case, I think we need to start insulin to get your blood glucose under control.

Patient: Using insulin is just going to be too difficult for me.

PCP: Why do you think that?

Patient: It's common knowledge that using insulin disrupts people's lives. You have to figure out how much insulin to use, administer it several times a day, and monitor your blood glucose several times a day. Between work and all the things I do at home, I just can't.

PCP: Most patients with type 2 diabetes gain control of their blood glucose with one or two doses of insulin per day. Also, most of my patients tell me they feel better within a few weeks after starting insulin. That's because the body is no longer being attacked with high levels of blood glucose.

Patient: Although that sounds great, I'm still worried about how it will affect my life.

PCP: I often hear that from my patients and find that it's because they feel overwhelmed when they don't know what to do or why they are doing it. That's understandable. My job is to help you not feel overwhelmed. My job is to help you feel that you are in control of your diabetes.

Patient: I'd like to be in control of my diabetes.

PCP: Good. Let's talk about your activities on a typical day, especially your eating and physical activity. From there we can decide together how best to begin insulin.

Comment: In shared decision-making, it's important not to solve problems *for* patients, but rather *with* patients.

Concerns About Hypoglycemia

PCP: At your last visit, we talked about the possible need to start insulin. Have you thought about it?

Patient: What concerns me most is hypoglycemia. I hear stories about people on insulin fainting or having to be rushed to the hospital because their blood sugar was too low. I've experienced hypoglycemia a few times and it scared me.

PCP: I understand your concern about hypoglycemia. This is another reason why it's important that we work together to do all we can to reduce your risk of hypoglycemia, especially hypoglycemia that causes severe symptoms.

Patient: I know my family is also worried about hypoglycemia. The last time I had an episode, my wife was so upset because she didn't know what to do.

PCP: I can help you and your family handle that better. Let's review the symptoms of hypoglycemia and what you and your family should do in the event that you experience hypoglycemia. Let's also talk about when to monitor your blood glucose level.

Patient: Okay.

PCP: I also need your help in another way. It's important that you follow the treatment plan that we develop together, including eating and exercising. If you find it difficult or you have a problem, please let me know. We can make further adjustments to your medications. There are also other ways to help you monitor your blood glucose.

Comment: Educating patients is a powerful tool that helps improve their acceptance of treatment, as well as better self-management.

Concerns About Weight Gain

PCP: Now that you've been taking basal insulin with dinner for about a month, how do you think you're doing?

Patient: I see that my blood glucose levels are better, particularly before breakfast. But I am concerned because your nurse tells me that I've gained nearly three pounds.

PCP: Patients often gain 3-4 pounds over the first few months. This is because insulin helps your body better utilize food. Some patients don't gain any weight, especially those who maintain a healthy lifestyle. That's why it's important that you continue the healthy eating you've been doing and exercise regularly. If you do, there's a good chance you won't gain any further weight. However, if you do, we may be able to make further adjustments to your medications to help minimize the weight gain.

Comment: A healthy lifestyle is a cornerstone of treatment and should be reinforced regularly.

UNMET NEEDS WITH HUMAN INSULIN AND OLDER INSULIN ANALOGS

As discussed in the previous article in this supplement, *Role of Insulin Therapy in Diabetes*, insulin formulations have undergone dramatic improvements over the past century to improve their safety and make it so that they more closely resemble the time-action profile of insulin secretion in humans. Nonetheless, limitations exist.

Key limitations with currently available basal insulins in patients with T2DM are hypoglycemia, including nocturnal hypoglycemia, and weight gain.[3,13] Although less common with detemir and glargine U-100 compared with NPH, these limitations remain a concern of providers and patients.[14-16] The differences in the risk of hypoglycemia are due, in part, to greater variability in the blood glucose level with NPH compared with detemir and glargine.[13,14,17] Another factor contributing to hypoglycemia is the less than ideal duration of action among the basal insulins, particularly NPH. NPH generally requires twice-daily administration, while detemir and glargine can be administered once-daily in most patients.[13,14] In some patients, however, once-daily administration of detemir or glargine U-100 is not sufficient to control the FPG and the blood glucose level rises in the hours prior to the next daily dose. In an effort to extend the duration of action to 24 hours, and to better control the FPG, some providers progressively increase the dose of detemir and glargine U-100. This has the unfortunate consequence of increasing the risk of hypoglycemia, particularly nocturnal hypoglycemia.

SUMMARY

The DAWN2, HAT, and GAPP studies reaffirm that providers, patients, and family members experience numerous barriers to diabetes care, including the use of insulin. Strategies are provided as part of a shared decision-making process to help address some of the more common barriers experienced by patients. ●

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Innovations in Insulin: Insulin Degludec U-100 and U-200

Athena Philis-Tsimikas, MD

CLINICAL PHARMACOLOGY

Insulin degludec (IDeg) is a long-acting basal human insulin analog produced using recombinant DNA technology. The insulin structure is modified at the B30 position to allow a di-hexamer conformation in the presence of phenol and zinc. Following subcutaneous injection, the phenol disperses allowing the di-hexamers to self-associate and form a stable depot of multi-hexamer chains at the injection site (**FIGURE 1**).[1]As the zinc diffuses, the multi-hexamer chains gradually disassociate, leading to a slow and continuous delivery of IDeg monomers into the systemic circulation. More than 99% of IDeg is bound to albumin, but the relatively low concentration of IDeg relative to albumin (<1/10,000) precludes it from being affected by the binding of other drugs to albumin.[2]

Pharmacokinetics and Pharmacodynamics

Following once-daily subcutaneous administration of IDeg at doses of 0.4, 0.6, and 0.8 units/kg in patients with type 2 diabetes mellitus (T2DM), the terminal elimination half-life ranges from 24.4 to 26.8 hours at steady-state, indicating that clearance is independent of dose within this range.[3] At these same doses, steady state is reached after 2-3 days. Steady state represents the condition where the amount of drug administered is equal to the amount of drug cleared between two doses. The elimination half-life in patients with type 1 diabetes mellitus (T1DM) is approximately 25 hours.[4] The long elimination half-life observed with IDeg contributes to a longer duration of glucose-lowering effect that enables once-daily administration.

Despite the long elimination half-life, the overall exposure of IDeg at steady-state is unchanged from day to day demonstrating that "stacking," ie, excessive accumulation leading to hypoglycemia, does not occur.[5] Overall exposure is similar following administration of a single 0.4 unit/kg dose of IDeg in the thigh, deltoid, or abdominal wall in healthy subjects.[6] In addition, there is no significant difference in the glucose-lowering effect among the three sites of administration.

AP is a 19-year-old college student diagnosed with type 1 diabetes mellitus (T1DM) when he was 7 years old. Treatment with once-daily basal insulin at bedtime and mealtime prandial insulin has provided good glycemic control until he went away to college (HbA1c now 7.4%). Review of his blood glucose log shows that his fasting plasma glucose ranges from 106 to 152 mg/dL and his blood glucose rises late in the afternoon (range 158 to 208 mg/dL). These observations suggest that his dose of basal insulin needs to be increased and that once-daily administration may not be adequate. AP objects to adding a dose of basal insulin in the morning saying that his variable eating and sleeping schedule makes it difficult for him to adhere to his current insulin regimen.

The duration of action of insulin detemir (IDet) and insulin glargine (IGlar) U-100 enables once-daily dosing in most, but not all, patients. Adding a second dose of basal insulin before breakfast is an option, but may not be practical for all patients.

Euglycemic glucose clamp studies show that the glucose-lowering effect of IDeg extends beyond 42 hours at steady state at doses of 0.4, 0.6, and 0.8 units/kg in patients with T1DM (N=49).[7] Euglycemic glucose clamp studies measure insulin absorption and insulin activity following insulin administration through intravenous infusion of glucose to maintain a constant glucose level. Further euglycemic glucose clamp studies were conducted in patients with T1DM (N=54) to compare the day-to-day variability in glucose-lowering with IDeg and IGlar U-100 at a dose of 0.4 units/kg once daily for 12 days.[8] Clamp studies on days 6, 9, and 12 showed that the within-subject day-to-day variability was 20% for IDeg and 82% for IGlar U-100 (P<.0001).

Euglycemic clamp studies were also conducted in patients with T2DM showing that the average glucose infusion rate profiles are flat and stable over 24 hours at doses of 0.4, 0.6, and

Athena Philis-Tsimikas, MD, Scripps Whittier Diabetes Institute, San Diego, California

DISCLOSURE

Dr. Philis-Tsimikas discloses that she is on the advisory board for AstraZeneca; Dexcom, Inc.; Eli Lilly and Company; Novo Nordisk Inc.; and sanofi-aventis U.S. LLC.

0.8 units/kg.[3] Further indication of a consistent glucose-lowering effect over 24 hours is shown by minimal variability among each of the four 6-hour intervals (**FIGURE 2**).[3]

Age and Race

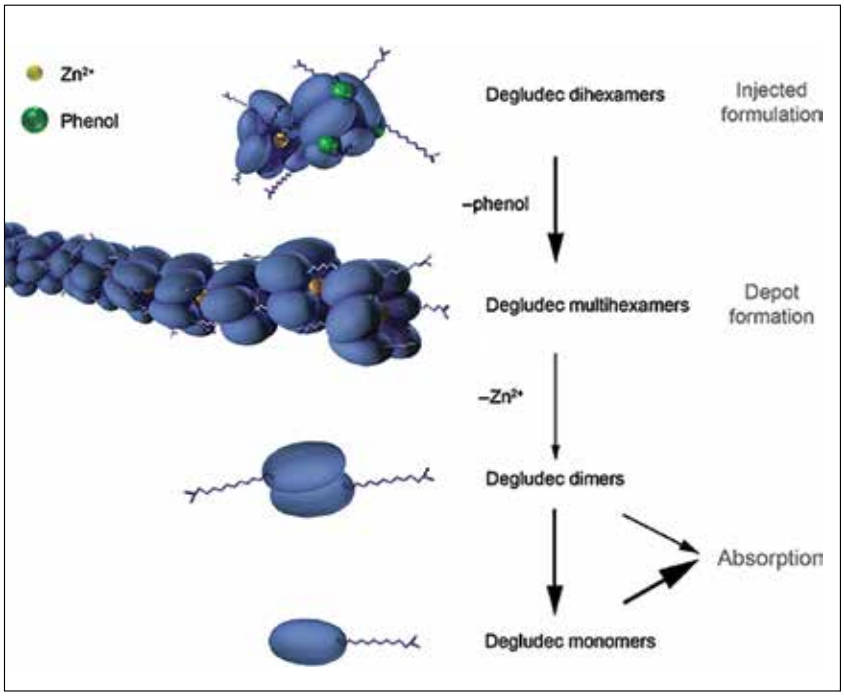
Age has no apparent effect on the pharmacokinetics and pharmacodynamics of IDeg. In the elderly, steady-state was reached after 2 to 3 days and the overall exposure of IDeg at steady state during once-daily dosing has been shown to be similar in younger adult and elderly patients with T1DM. Correspondingly, the glucose-lowering effect was similar and was found to be evenly distributed across the first and second 12-hour intervals following once-daily dosing.

Race/Ethnicity also have no apparent effect as the pharmacokinetics and pharmacodynamics of IDeg have been shown to be similar in African Americans, Hispanic/Latino, and Japanese patients as in Caucasians.[9,10]

Kidney and Liver Impairment

In patients (11 of 30 with T2DM) with varying degrees of renal dysfunction, including those requiring hemodialysis, no differences in IDeg pharmacokinetics were observed following a single 0.4 unit/kg dose.[11] Maximum serum IDeg concentration (C_{max}), exposure, and clearance were all unaffected by the degree of renal impairment. These endpoints were similarly unaffected in patients with varying levels of hepatic impairment (normal, Child-Pugh grade A, B, or C); subjects with liver impairment could have diabetes.[12]

FIGURE 1 Absorption schema of insulin degludec[1] an ultra-long-acting basal insulin



Schematic representation of the hypothesis for the mode of retarded absorption of insulin degludec: Insulin degludec is injected subcutaneously as a zinc phenol formulation containing insulin degludec dihexamer in the T3R3 conformation. Rapid loss of phenol changes the degludec hexamers to T6 configuration and multi-hexamer chains form. With slow diffusion of zinc, these chains break down into dimers, which quickly dissociate into readily absorbed monomers.

Abbreviation: Zn^{2+}, zinc ion.

Reproduced from: Jonassen I, Havelund S, Hoeg-Jensen T, Steensgaard DB, Wahlund PO, Ribel U. *Pharm Res*. 2012;29:2104-2114.

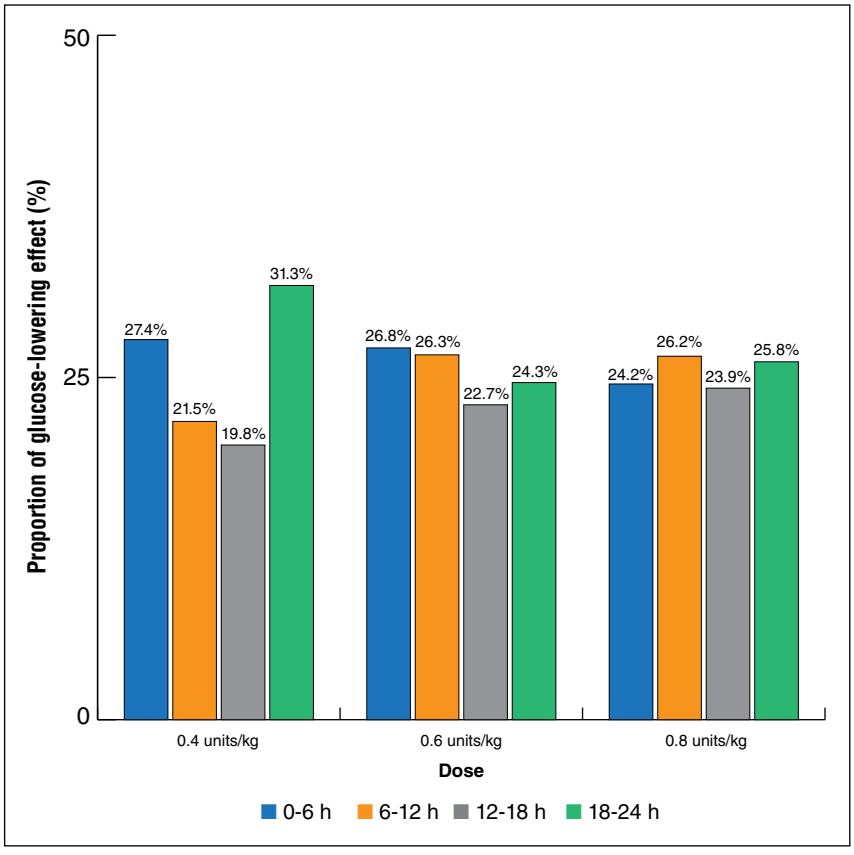
Degludec U-100 vs U-200

KT is a 53 year-old obese male (body mass index 38.6 kg/m^2) diagnosed with T2DM 3 years ago. Current medications: metformin 1000 mg twice daily, basal insulin 80 units (0.69 units/kg) with dinner. His blood glucose levels have decreased significantly since starting basal insulin, but his HbA1c remains elevated at 7.8%; FPG has ranged from 92 mg/dL to 166 mg/dL over the past month. He has not experienced hypoglycemia since starting basal insulin.

Since the patient is at the maximum dose (80 units) that can be delivered with a single injection of detemir, IGlar U-100, or IGlar U-300 using a pen device and his blood glucose levels are not at goal, further intensification of basal insulin is needed. One option is to add a second dose of basal insulin before breakfast. Another option is to switch to IDeg U-200, which delivers the same dose in half the volume as IDeg U-100, since up to 160 units can be given in one injection. Switching from another basal insulin to IDeg U-100 or U-200 is done using the same unit dose as this has been shown to result in similar or greater HbA1c reduction, as well as rates of confirmed or severe and nocturnal hypoglycemia.[13,14]

Comparison of IDeg U-100 with U-200 shows that the two formulations are interchangeable, with no conversion needed, and have similar pharmacodynamic profiles at steady-state.[15] In a post hoc analysis, the U-200/U-100 ratios for area under the steady-state serum IDeg concentration-time curve and maximum steady-state IDeg concentra-

FIGURE 2 **Distribution of glucose-lowering effect of degludec over 24 hours at steady state[3]**



tion over 24 hours are 0.99 (90% confidence interval [CI] 0.91-1.07) and 0.93 (90% CI 0.84-1.02), respectively, which are well within the accepted ratio range of 0.80 to 1.25. For both formulations, comparable glucose infusion rates were observed and the glucose-lowering effect was evenly distributed between the first and second 12-hour post-dosing intervals. These data indicate that IDeg U-100 and U-200 can be used interchangeably in clinical practice on a dose basis.

In summary, the results of these investigations demonstrate that IDeg delivered via subcutaneous administration has a duration of action >24 hours at steady state with a smooth and stable pharmacokinetic profile and low day-to-day intra-patient glycemic variability in patients with T1DM or T2DM. IDeg U-100 and U-200 are interchangeable and no dose conversion is needed. Dose stacking does not occur at steady-state. No adjustment in dosing is needed in patients with renal or hepatic impairment or based on race/ethnicity. The U-200 formulation allows administration of a dose up to 160 units in a single injection.

EFFICACY AND SAFETY

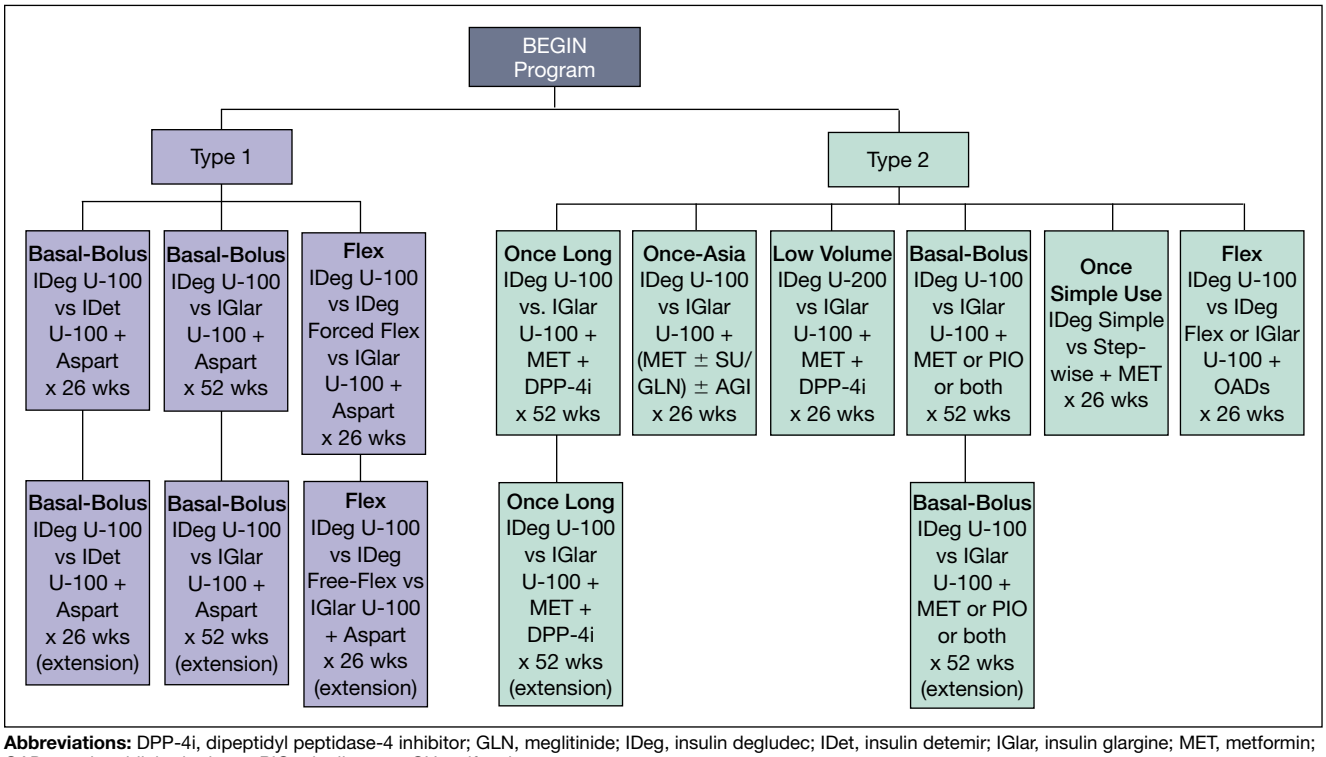
Insulin degludec U-100 and U-200 is approved in the United States to improve glycemic control in adults with diabetes mellitus.[16] Approval was largely based on the BEGIN program of nine phase 3 clinical trials that included nearly 5500 patients with T1DM or T2DM (**FIGURE 3**)[17-29]. Patients were from North America, South America, Europe, Africa, and Asia. The primary objective was to establish the non-inferiority of IDeg versus comparator in terms of glycemic control by measuring the change in HbA1c from baseline. A finding of non-inferiority demonstrates that there is no difference between groups. A non-inferiority design was used as required by the US Food and Drug Administration for evaluating new insulins. The trials were randomized, controlled, multicenter, using a treat-to-target approach. IGlar U-100 was given once daily at the same time every day, mostly between dinner and bedtime, except in 4 studies as described below. Insulin doses were titrated to achieve a self-measured fasting plasma glucose (FPG) level of 70 to 90 mg/dL. Overall confirmed hypoglycemia was classified as episodes in which the plasma glucose was <56 mg/dL (irrespective of symptoms) or severe (requiring assistance). Hypoglycemia that occurred between 00:01 am and 05:59 am (inclusive) was classified as nocturnal. Nocturnal hypoglycemia is an important endpoint because it is often associated with high doses of basal insulin at dinner or bedtime.

Type 1 Diabetes

The efficacy and safety of IDeg in patients with T1DM have been investigated in numerous phase 3 clinical trials, including three basal-bolus trials as part of the phase 3a program. Two of the trials utilized a fixed dose administration time, while the third investigated an alternative dose-timing regimen.[17-21]

In the two fixed dose administration time trials, patients with T1DM and HbA1c ≤10% had been treated with basal-bolus insulin for at least 1 year prior to randomization. In one trial, patients were randomized to IDeg or IDet for 26 weeks with a 26-week extension.[17,18] In the other trial, patients were randomized to IDeg or IGlar U-100 for 1 year with a 1-year extension.[19,20] In both, insulin aspart was taken before each

FIGURE 3 BEGIN program of phase 3 clinical trials of insulin degludec U-100 or U-200 in type 1 and type 2 diabetes mellitus[17-29]



Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; GLN, meglitinide; IDeg, insulin degludec; IDet, insulin detemir; IGlar, insulin glargine; MET, metformin; OADs, oral antidiabetic drugs; PIO, pioglitazone; SU, sulfonylurea.

meal and titrated to achieve a preprandial and bedtime blood glucose of 70 to 90 mg/dL. At the end of the 26-week comparison with IDet and the 1-year comparison with IGlar, glycemic control with IDeg was noninferior to the comparator except that IDeg provided significantly greater reduction in FPG compared with IDet.[18] In both extension studies, glycemic control was comparable between IDeg and comparator. In the maintenance phase of both extension trials, the rates of overall confirmed hypoglycemia and severe hypoglycemia were similar for IDeg vs IDet and IGlar, but the rate of nocturnal hypoglycemic episodes was significantly (27%) lower with IDeg (number needed to treat = 76).[19] Weight gain with IDeg was higher compared with IDet but similar in comparison with IGlar.

Type 2 Diabetes

Clinical trials in patients with T2DM in the BEGIN program also confirm the non-inferiority of IDeg to IGlar U-100 in insulin-naïve and insulin-exposed patients on basal or basal-bolus therapy (**TABLE**).[22-29] Reductions in the FPG were similar or significantly greater with IDeg than IGlar U-100. The risk of overall and nocturnal hypoglycemia was lower with IDeg compared with IGlar U-100 at equivalent HbA1c levels.[30] Weight gain was small and similar with IDeg and IGlar U-100. The total daily dose of IDeg was similar or less than IGlar U-100.

Alternative Dose-Timing

SW is a 48-year-old salesman who covers upstate New York for a national hardware manufacturer. He was diagnosed with T2DM 6 years ago; current treatment is metformin + insulin detemir with dinner. During review of the patient's blood glucose log for the past month, his primary care physician (PCP) notes wide variability in his fasting blood glucose level. The PCP also notes that SW is not monitoring his blood glucose as often as they had agreed. SW admits that he is having difficulty remembering to administer his insulin because of his work schedule.

One common difficulty identified by patients treated with basal insulin, ie, NPH, IDet, IGlar U-100 or U-300, is the need to administer the dose at the same time every day.[31-33] In contrast, IDeg has been approved for once-daily administration at any time of the day.[16] The alternative dose-timing

TABLE Summary of key clinical outcomes in patients with T2DM[22-29]

Population/Baseline Treatment	Trial Treatment	Blood Glucose Changes from Baseline	% Achieving HbA1c <7%	Weight Change from Baseline (kg)	Confirmed Hypoglycemia (episodes/ patient-year)	TDD* (units/kg/ day)
Once Long[22] Insulin-naïve inadequately controlled with metformin with/without SU, GLN, DPP-4i, AGI, TZD Baseline: HbA1c 8.2%, FPG 173-175 mg/dL N=1030	Metformin with/ without DPP-4i+ IDeg U-100 QD with dinner or IGlar U-100 QD for 52 weeks	HbA1c: -1.06% vs -1.19% FPG: -68 mg/dL vs -59 mg/dL	52% vs 54% Without hypoglycemia (last 12 weeks): 42% vs 46% Without nocturnal hypoglycemia (last 12 weeks): 53% vs 54%	2.4 vs 2.1	Overall: 1.52 vs 1.85 Nocturnal: 0.25 vs 0.39 Severe: 0.003 vs 0.023	0.59 vs 0.60
Once Long *(extension)*[**23] Insulin-naïve inadequately controlled with metformin with/without SU, GLN, DPP-4i, AGI, TZD Baseline: HbA1c 8.2%, FPG 173-175 mg/dL N=725	Metformin with/ without DPP-4i+ IDeg U-100 QD with dinner or IGlar U-100 QD for 52 weeks (total 104 weeks)	HbA1c: -1.1% vs -1.3% FPG: -75 mg/dL vs -64 mg/dL	NR	2.7 vs 2.4	Overall: 1.72 vs 2.05 Nocturnal: 0.27 vs 0.46 Severe: 0.006 vs 0.021	0.63 vs 0.63
Once-Asia[24] Insulin-naïve inadequately controlled with metformin and/or SU/GLN with/without AGI or DPP-4i Baseline: HbA1c 8.4%-8.5%, FPG 151-155 mg/dL N=435	Metformin and/ or SU/GLN with/ without AGI+ IDeg U-100 QD in evening or IGlar U-100 QD for 26 weeks	HbA1c: -1.24% vs -1.35% FPG: -52 mg/dL vs -53 mg/dL	41% vs 49% Without hypoglycemia (last 12 weeks): 29% vs 32%	1.3 vs 1.4	Overall: 3.0 vs 3.7 Nocturnal: 0.8 vs 1.2	0.28 vs 0.35
Low Volume[25] Insulin-naïve inadequately controlled with metformin with/ without SU, GLN, DPP-4i, AGI Baseline: HbA1c 8.2%-8.3%, FPG 172-174 mg/dL N=457	Metformin with/ without DPP-4i+ IDeg U-200 QD with dinner or IGlar U-100 QD for 26 weeks	HbA1c: -1.3% vs -1.3% FPG: -67 mg/dL vs -61 mg/dL	52% vs 56% Without hypoglycemia (last 12 weeks): 45% vs 45%	1.9 vs 1.5	Overall: 1.22 vs 1.42 Nocturnal: 0.18 vs 0.28 Severe: 0 vs 0	0.53 vs 0.60

TABLE Summary of key clinical outcomes in patients with T2DM[22-29] (*continued*)

Population/Baseline Treatment	Trial Treatment	Blood Glucose Changes from Baseline	% Achieving HbA1c <7%	Weight Change from Baseline (kg)	Confirmed Hypoglycemia (episodes/ patient-year)	TDD* (units/kg/ day)
Basal-Bolus[26] Basal and/or prandial insulin ≥3 months with/ without oral agents Baseline: HbA1c: 8.3%-8.4%, FPG 166 mg/dL N=1006	Metformin or pioglitazone or both + insulin aspart+ IDeg U-100 QD with dinner or IGlar U-100 QD for 52 weeks	HbA1c: -1.10% vs -1.18% FPG: -41 mg/dL vs -36 mg/dL	49% vs 50%	3.6 vs 4.0	Overall: 11.09 vs 13.63 Nocturnal: 1.39 vs 1.84 Severe: 0.06 vs 0.05	1.46 vs 1.42
Basal-Bolus (extension)[27] Basal and/or prandial insulin ≥3 months with/ without oral agents Baseline: HbA1c: 8.3%-8.4%, FPG 166 mg/dL N=757	Metformin or pioglitazone or both + insulin aspart+ IDeg U-100 QD with dinner or IGlar U-100 QD for 26 weeks (total 78 weeks)	HbA1c: -1.0% vs -1.2% FPG: -43 mg/dL vs -40 mg/dL	NR	NR	Overall: 9.84 vs 12.76 Nocturnal: 1.27 vs 1.77 Severe: 0.05 vs 0.06	1.5 vs 1.5
Once Simple Use[28] Insulin-naïve inadequately controlled with metformin with/ without SU, GLN, DPP-4i, AGI, TZD Baseline: HbA1c 8.1%-8.2%, FPG 167-169 mg/dL N=222	Metformin+ IDeg U-100 QD (Simple)† or IDeg U-100 QD (Step-wise)† for 26 weeks	HbA1c: -1.09% vs -0.93% FPG: -59 mg/dL vs -48 mg/dL	57% vs 41% Without hypoglycemia: 41% vs 35%	1.6 vs 1.1	Overall: 1.60 vs 1.17 Nocturnal: 0.21 vs 0.10	0.61 vs 0.50
Flex[29] OADs or basal insulin with/without OADs Baseline: HbA1c 8.4%-8.5%, FPG 158-162 mg/dL N=687	Baseline OADs+ IDeg U-100 QD (Flex)‡ or IDeg U-100 QD with dinner or IGlar U-100 QD for 26 weeks	HbA1c: -1.28% vs -1.07% vs -1.26% FPG: -58 mg/dL vs -54 mg/dL vs -50 mg/dL	38.9% vs 40.8% vs 43.9%	1.5 vs 1.6 vs 1.3	Overall: 3.6 vs 3.6 vs 3.5 Nocturnal: 0.6 vs 0.6 vs 0.8	0.6 vs 0.6 vs 0.6 (receiving insulin prior to study) 0.5 vs 0.5 vs 0.5 (insulin-naïve prior to study)

Abbreviations: AGI, alpha-glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; FPG, fasting plasma glucose; GLN, meglitinide; HbA1c, glycated hemoglobin 1c; NR, not reported; OAD, oral antidiabetic drug; QD, once daily; SU, sulfonylurea; TZD, thiazolidinedione.

*Total daily dose of insulin at end of study.

**Data are from baseline through 104 weeks.

†Doses were given at any time of the day with a minimum of 8 h and a maximum of 40 h between doses. Self-adjustment of IDeg dose was performed once-weekly. Dose adjustment was based on a single pre-breakfast SMBG measurement (Simple arm) or lowest of 3 consecutive days' pre-breakfast SMBG measurements (Step-wise arm).

‡Doses were given once-daily according to a pre-specified, rotating morning and evening dosing schedule creating a minimum of 8 h and a maximum of 40 h between doses.

regimen of IDeg is supported by clinical trials in patients with T1DM or T2DM.

Patients with T1DM were randomized to: (1) IDeg U-100 once-daily at the same time every day (IDeg fixed); (2) IDeg once-daily using a forced alternative dose-timing schedule (IDeg forced-alternative); or (3) IGlar U-100, all in combination with mealtime insulin aspart (N=493).[21] The forced-alternative dose-timing schedule created dosing intervals of at least 8 but not more than 40 hours between injections. After 26 weeks, reductions in HbA1c were 0.41%, 0.40%, and 0.58% in the IDeg fixed, IDeg forced-alternative, and IGlar U-100 groups, respectively, confirming non-inferiority of IDeg forced-alternative with IGlar U-100. The FPG decreased 46 vs 23 vs 24 mg/dL, respectively. In a 26-week extension phase, all IDeg patients utilized an alternative dose-timing regimen in which they could take IDeg at any time of day provided that doses were separated by at least 8 but not more than 40 hours. After the additional 26 weeks, the HbA1c increased slightly from 26-week levels, but remained lower than baseline in both groups. Confirmed hypoglycemia rates were similar, while the rate of nocturnal hypoglycemia was lower with IDeg compared with IGlar at weeks 26 (40% lower) and 52 (25% lower).

In patients with T2DM, Meneghini et al randomized patients to the same regimen: a) IDeg U-100 once-daily at the same time each day (IDeg fixed); 2) IDeg once-daily using the forced-alternative dose-timing schedule (IDeg forced-alternative); or 3) IGlar U-100 once-daily at the same time each day.[29] After 26 weeks, reductions in the HbA1c level were 1.07%, 1.28%, and 1.26%, respectively, confirming non-inferiority of IDeg forced-alternative with IGlar U-100. The rates of overall (3.6 vs 3.6 vs 3.5 episodes/patient-year) and nocturnal (0.6 vs 0.6 vs 0.8 episodes/patient-year) hypoglycemia were similar in the IDeg fixed, IDeg forced-alternative, and IGlar U-100 groups, respectively. A more recent trial in Japanese patients yielded similar results.[34]

Safety

MZ is a 64-year-old woman diagnosed with T2DM 4 years ago. She is accompanied by her husband at the current office visit. Both express concern that MZ experiences frequent episodes of confirmed hypoglycemia. One of these occurred a week ago at which time MZ was awoken by her husband because she seemed particularly restless; her blood glucose was 58 mg/dL.

Hypoglycemia

Numerous studies and surveys show that hypoglycemia due to insulin is one concern of providers, patients, and family members (see *Basal Insulin in Primary Care* on page S8). As a consequence, patients often become poorly adherent to therapy. The occurrence of hypoglycemia has been extensively investigated in clinical trials involving IDeg.

A pre-defined, patient-level, meta-analysis of seven trials included in the phase 3a program showed that among insulin-naïve patients with T2DM, the rate ratios (RR) of IDeg vs IGlar U-100 for overall (0.83), nocturnal (0.64), and severe (0.14) hypoglycemia were significantly lower in favor of IDeg.[30] In the overall T2DM population, significantly lower rate ratios of overall (0.83) and nocturnal (0.68) hypoglycemia also were in favor of IDeg. In patients with T1DM, the rate ratio (0.75) of nocturnal hypoglycemia also was significantly in favor of IDeg compared with IGlar U-100 during maintenance treatment following titration; the rate ratio for overall confirmed hypoglycemia was not significantly different (1.02).

A meta-analysis of seven randomized phase 3 clinical trials involving patients with T1DM or T2DM age ≥65 years (N=917) showed that the rates of overall (RR 0.76) and nocturnal (RR 0.64) hypoglycemia were significantly lower with IDeg than IGlar U-100.[35]

Results of the SWITCH 1 and 2 clinical trials were reported at the 2016 American Diabetes Association annual meeting showing lower rates of several categories of hypoglycemia with IDeg compared with IGlar U-100.[36,37] Both were randomized, double-blind trials involving a 16-week titration phase followed by a 16-week maintenance phase after which patients were crossed over to the alternate basal insulin. SWITCH 1 involved 501 patients with T1DM and SWITCH 2 involved 721 patients with T2DM. During the maintenance period, SWITCH 1 showed a significantly lower rate of severe or confirmed hypoglycemia (11%), severe or confirmed nocturnal hypoglycemia (36%), and severe hypoglycemia (35%) with IDeg vs IGlar U-100.[36] During the maintenance period, SWITCH 2 showed a significantly lower rate of severe or confirmed hypoglycemia (30%) and severe or confirmed nocturnal hypoglycemia (42%) with IDeg vs IGlar U-100.[37]

Cardiovascular Safety

A comprehensive review of the cardiovascular safety of IDeg was undertaken in 2012 as part of the FDA's review of the application for approval.[38] This review included a meta-analysis of 16 therapeutic confirmatory trials with IDeg or IDeg with aspart (IDegAsp). The results of the meta-analysis showed an incidence rate of pre-defined major adverse cardiovascular events (MACE) (non-ST-elevation myocardial infarction, ST-elevation myocardial infarction, stroke, or cardiovascular death) of 1.48 events per 100 patient years of exposure in the IDeg and IDegAsp group compared with 1.44 events per 100 patient-years of exposure in the comparator group (HR 1.10; 95% CI 0.68-1.77). The meta-analysis

was updated by the FDA by restricting the MACE definition and including additional MACE data over a longer reporting period for events. Both the initial and updated post hoc meta-analyses suggested an increased cardiovascular risk with IDeg, of which the lower bounds of the 95% CI for MACE are near or above 1. Since an increased cardiovascular risk could not be confirmed nor excluded, the FDA required additional investigation in a pre-approval phase 3 clinical trial.

The DEVOTE trial (NCT01959529) was launched in 2013 to compare the cardiovascular safety of IDeg with IGlar U-100 in subjects with T2DM at high risk of cardiovascular events. Interim results of DEVOTE were not made publicly available, but were shared with the FDA in early 2015 as part of agreed submission of the new drug application for IDeg. This resubmission led to approval of IDeg by the FDA in September 2015. The DEVOTE trial is scheduled to be completed in September 2016.

Other Adverse Events

The safety of IDeg has been extensively evaluated in phase 3 clinical trials. None of the trials has shown either more or serious adverse events with IDeg compared with IGlar U-100.[39] Adverse events other than hypoglycemia observed in ≥5% of patients are nasopharyngitis, upper respiratory tract infection, headache, diarrhea, and sinusitis.[16]

PATIENT REPORTED OUTCOMES

Use of IDeg has been shown to improve several patient reported outcomes versus comparators. In patients with T1DM, 16 weeks of treatment with IDeg compared with IGlar U-100 resulted in statistically significant improvement in the SF-36 mental component score. This difference was due to significant improvement in social functioning and mental health with IDeg.[40] Improvements in physical functioning and other domains were similar between the two treatments.

In the BEGIN trials involving patients with T2DM, significantly greater improvement was observed with IDeg compared with IGlar U-100 in the SF-36 domain of bodily pain over 26 to 104 weeks.[25,26,41] Statistically significant improvement in physical functioning and vitality, also has been observed in the BEGIN Once Long and Low Volume trials, respectively.[25,41]

Patients in one phase 3b study (BEGIN Once Simple Use), which compared two different IDeg titration algorithms, were specifically queried about the FlexTouch IDeg pen device.[28] At weeks 12 and 26, more than 90% of patients expressed a high level of satisfaction with FlexTouch in several categories, including confidence in using the pen, ease in learning to use the pen, ease in holding the pen stable or seeing the dose scale while self-injecting, pushing down the injection button, and selecting the correct dose. At week 26, 98% of patients reported no problems using FlexTouch.

SUMMARY

Insulin degludec is a once-daily, long-acting basal human insulin analog with a flat and stable glucose-lowering effect with lower intrapatient variability when compared to insulin glargine U-100. Clinical trials in patients with type 1 and type 2 diabetes mellitus have shown the noninferiority of insulin degludec with insulin glargine U-100 and insulin detemir in terms of glycemic control. Rates of confirmed and severe, as well as nocturnal hypoglycaemia are significantly lower with insulin degludec than insulin glargine U-100 and insulin detemir in patients with type 1 or type 2 diabetes mellitus. These characteristics enable insulin degludec to be administered once-daily at any time of the day, with variable dose timing. The availability of a U-200, as well as U-100, formulation provides an option for insulin doses >80 units to be administered as a single injection. ●

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Innovations in Insulin: Insulin Glargine U-300

John E. Anderson, MD

CLINICAL PHARMACOLOGY

Insulin glargine 300 units/mL (IGlar U-300) is a long-acting basal human insulin analog produced using recombinant DNA technology. The insulin structure is the same as insulin glargine U-100. Both insulins have been modified from human insulin in that the asparagine at position A21 has been replaced with glycine and two arginines remain at the C-terminus of the B-chain. Insulin glargine is an acidic solution that is neutralized upon subcutaneous injection, forming a precipitate that slowly dissolves with slow release of insulin glargine. It is thought that the larger crystal size of IGlar U-300, and hence, greater surface area, compared with IGlar U-100 is responsible for the slower dissolution rate of IGlar U-300 compared with U-100.[1] Metabolism of IGlar U-300 is the same as IGlar U-100.[2]

Pharmacokinetics and Pharmacodynamics

JH is a 47-year-old woman diagnosed with T2DM 11 months ago (HbA1c 9.7%). At diagnosis, she was started on a combination of metformin and detemir; currently, metformin 1000 mg twice daily and detemir 26 units (0.40 units/kg/day) at bedtime. Her HbA1c is 7.9%. Review of her blood glucose log shows her fasting plasma glucose (FPG) ranges from 68 to 116 mg/dL. It also shows that her blood glucose level begins to rise during the late afternoon and early evening such that her pre-dinner blood glucose ranges from 156 to 192 mg/dL. Blood glucose monitoring following lunch indicates an acceptable rise in her blood glucose level.

Her rising blood glucose level during the late afternoon and early evening suggests that the effectiveness of the detemir is less than 24 hours. Increasing the dose is inappropriate because her fasting plasma glucose is well-controlled and would increase the risk of hypoglycemia, particularly during the night. Adding a second dose of detemir before breakfast or switching to IGlar U-100 or U-300 or insulin degludec are options.

John E. Anderson, MD, Past President, The Frist Clinic, Nashville, Tennessee

DISCLOSURE

Dr. Anderson discloses that he is on the advisory board and speakers' bureaus for AstraZeneca; Boehringer Ingelheim; Eli Lilly and Company; Janssen Pharmaceuticals, Inc.; and sanofi-aventis U.S. LLC. He is also on the advisory board for Abbott.

The pharmacokinetics and pharmacodynamics of IGlar U-300 are somewhat different from IGlar U-100. In patients with type 1 diabetes mellitus (T1DM) (N=30), the terminal elimination half-life was 19.0 hours with IGlar U-300 and 13.5 hours with IGlar U-100, both at a daily dose of 0.4 units/kg.[1] Findings from a separate cohort showed that the terminal elimination half-life of IGlar U-300 at a daily dose of 0.6 units/kg was 17.7 hours, compared with 10.8 hours for IGlar U-100 at a daily dose of 0.4 units/kg. A detectable insulin level was observed in more than 50% of patients treated with IGlar U-300 or U-100 until 32 hours and 28 hours, respectively, both at a dose of 0.4 units/kg-day. Steady-state with IGlar U-300 was estimated to be achieved after three to four days of once-daily dosing.[1] [Note: the prescribing information indicates that steady state of IGlar U-300 is reached by at least 5 days of once-daily subcutaneous administration of 0.4 to 0.6 units/kg.][3] Steady state represents the condition where the amount of drug administered is equal to the amount of drug cleared between doses.

Exposure to insulin was similar with IGlar U-300 than U-100 over 24 and 36 hours post-dose.[1] The total amount of glucose administered over the first 24 hours of a euglycemic glucose clamp study was lower than with IGlar U-100 (ratio 0.73), indicating the need for a higher dose of IGlar U-300 than IGlar U-100. Of key clinical importance was the finding that insulin exposure with IGlar U-300, at both 0.4 and 0.6 units/kg, was more evenly distributed over 36 hours post-dose, indicating a flatter profile with IGlar U-300 than U-100.

Intra-patient glycemic variability assessed using continuous glucose monitoring was found to be similar in a randomized, multiple-dose trial in Japanese adults with T1DM treated with basal-bolus insulin.[4] Over approximately 8 weeks of open-label, crossover treatment, glucose variability over 24 hours was comparable with IGlar U-300 compared with U-100 (ratio 0.96). Glucose variability at night was also similar (ratio 0.94).

Special Populations

No overall differences in safety and effectiveness have been observed across adult age groups, including those age

≥65 years.[3] Two non-head-to-head studies that used similar methodologies found that insulin exposure with IGlar U-300 was lower than IGlar U-100 in European compared with Japanese patients with T1DM.[5] It is not known if this difference is clinically important.

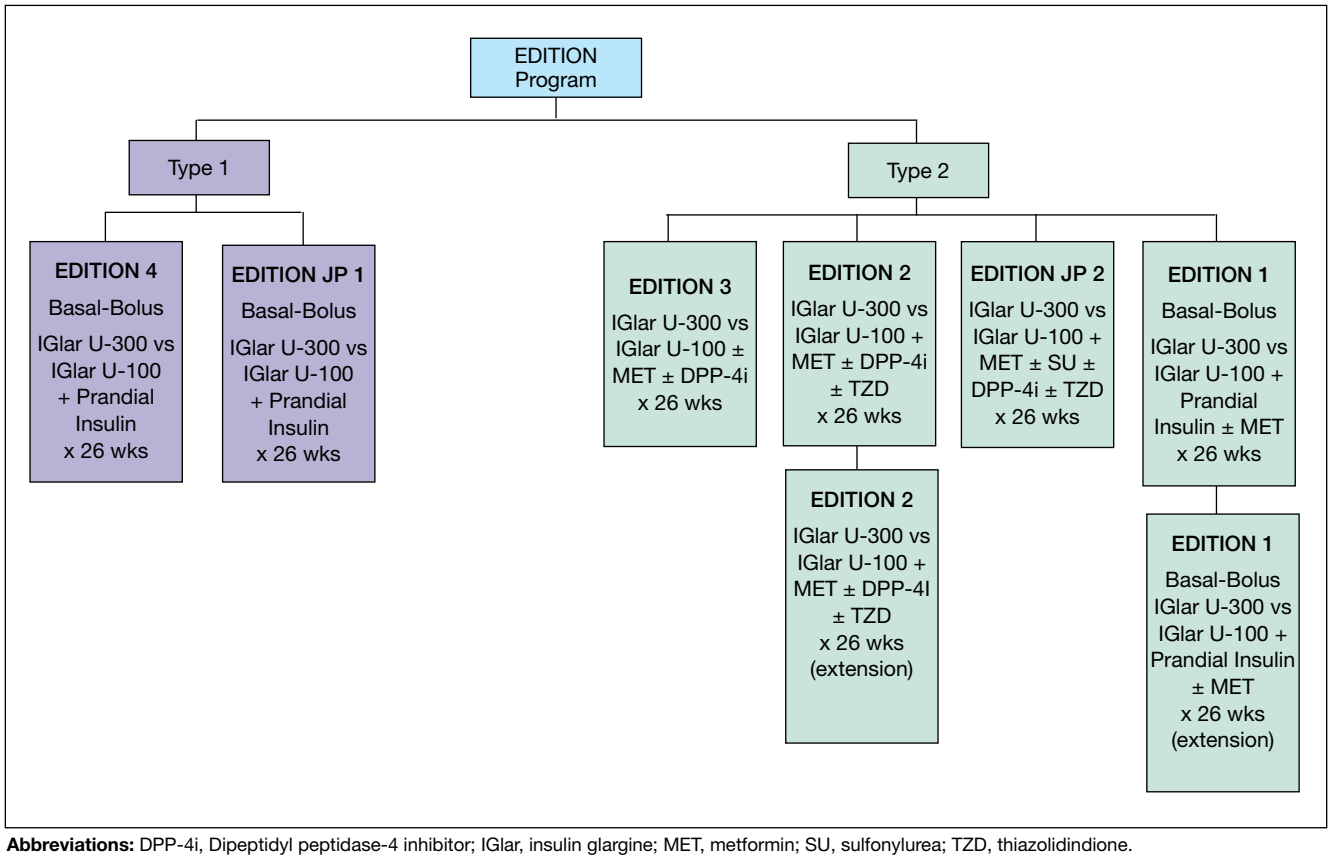
The safety and effectiveness of IGlar U-300 have not been established in children. The effect of renal or hepatic impairment on the pharmacokinetics of IGlar U-300 has not been studied.

EFFICACY AND SAFETY/TOLERABILITY

Insulin glargine U-300 is approved in the United States to improve glycemic control in adults with diabetes mellitus.[3] Approval was based largely on the EDITION program of phase 3 clinical trials that compared IGlar U-300 with U-100 (**FIGURE**)[6-13]. The EDITION program included more than 3000 patients with T1DM or T2DM from North America, South America, Europe, Asia, and Africa. The primary objective was to establish the noninferiority of IGlar U-300 vs IGlar U-100 in terms of glycemic control by measuring the change in HbA1c from baseline to 6 months. In the trials of patients with T2DM, a secondary objective was to compare the rates of nocturnal confirmed hypoglycemia.

The EDITION trials were randomized, controlled, multicenter, using a treat-to-target approach. A noninferiority design was used as required by the US Food and Drug Administration for evaluating new insulins. Patients were stratified by baseline HbA1c (<8.0% or ≥8.0%). IGlar U-100 was given once daily at the same time every day. Insulin doses were titrated to achieve a self-measured FPG level of 80 to 130 mg/dL (T1DM) or 80 to 100 mg/dL (T2DM). Confirmed hypoglycemia was classified as episodes in which the plasma glucose was less than or equal to 70 mg/dL (with or without symptoms) or severe (requiring assistance). Hypoglycemia that occurred between 00:00 am and 05:59 am (inclusive) was classified as nocturnal.

FIGURE EDITION program of phase 3 clinical trials of insulin glargine U-300 in type 1 and type 2 diabetes mellitus[6-13]



Abbreviations: DPP-4i, Dipeptidyl peptidase-4 inhibitor; IGlar, insulin glargine; MET, metformin; SU, sulfonylurea; TZD, thiazolidindione.

Type 1 Diabetes

EDITION 4 assessed the efficacy and safety of IGlar U-300 compared with IGlar U-100 in patients with T1DM (N=549).[6] Prandial insulin was titrated to achieve a 2-hour postprandial glucose less than 160 mg/dL. Patients had longstanding T1DM (mean 21 years) with a mean HbA1c of 8.1% and BMI of 27.6 kg/m^2. At six months, the mean change in HbA1c from baseline was -0.42% and -0.44% for IGlar U-300 and U-100, respectively, demonstrating noninferiority of IGlar U-300 with U-100. A similar percentage of patients achieved HbA1c less than 7.0% at 6 months (16.8% vs 15.0%, respectively). The FPG decreased from 185.9 mg/dL at baseline to 175.5 mg/dL at 6 months in the IGlar U-300 group, and from 199.3 mg/dL to 173.5 mg/dL in the IGlar U-100 group. The injection time (morning vs evening) of IGlar U-300 had no effect on HbA1c or FPG.

Rates of confirmed or severe (78.4 vs 72.5 episodes/patient-year) and nocturnal (8.0 vs 9.0 episodes/patient-year) hypoglycemia were similar in the IGlar U-300 and U-100 groups, respectively.[6] During the first 8 weeks of the study when dose titration occurred most frequently, the rate of confirmed or severe hypoglycemia was lower with IGlar U-300 (rate ratio 0.69). An increase in the basal insulin dose was observed in both groups from baseline to 6 months, but was greater with IGlar U-300 (from 0.38 to 0.47 units/kg/day for IGlar U-300 vs 0.37 to 0.40 units/kg/day for IGlar U-100). Nonetheless, the increase in body weight was significantly less with IGlar U-300 vs U-100 (0.5 vs 1.0 kg).

The results of EDITION JP 1, which was conducted in 243 Japanese patients with T1DM, are very similar to EDITION 4. EDITION JP 1 also showed IGlar U-300 to be noninferior to IGlar U-100 in terms of HbA1c reduction (-0.30% vs -0.43%, respectively).[7] The rates of confirmed or severe hypoglycemia, as well as nocturnal hypoglycemia, were significantly lower with IGlar U-300. The increase in body weight was significantly less with IGlar U-300 despite a higher daily basal insulin dose.

Type 2 Diabetes

DT is a 51-year-old woman diagnosed with T2DM 9 years ago. She was managed with various combinations of oral therapy, but her HbA1c was never below 7.6%. A year and a half ago, her oral medications (except metformin) were discontinued and basal insulin once-daily with dinner started. Her basal insulin has been titrated to 34 units (0.43 units/kg/day). Her current HbA1c is 7.5% and her FPG has ranged from 125 to 162 mg/dL over the past 2 weeks. Additional blood glucose monitoring shows an acceptable rise in her blood glucose level following meals. Her primary care physician talks with her about intensifying her basal insulin, but DT resists, saying taking insulin has already made her life too complicated. She also expresses concern about further hypoglycemic episodes and weight gain.

The EDITION program of phase 3 trials compared the efficacy and safety of IGlar U-300 with IGlar U-100 in different populations of patients with T2DM. EDITION 1 and 2 enrolled patients treated with basal insulin; EDITION 1 included patients not adequately controlled with basal-bolus insulin, while EDITION 2 included patients not adequately controlled with basal insulin in combination with oral agents (**TABLE**).[8-13] EDITION 3 enrolled insulin-naïve patients not adequately controlled with oral agents only.[13]

General findings of EDITION 1, 2, and 3 are that, compared with IGlar U-100, glycemic control with IGlar U-300 is noninferior, the incidence of hypoglycemia, including nocturnal, is lower, and weight gain is less. The total daily dose of insulin is higher with IGlar U-300 compared with U-100.

Patient-Level Meta-Analysis

A patient-level meta-analysis examined the results in patients with T2DM in greater detail. The meta-analysis pooled the results of the 26-week EDITION 1, 2, and 3 trials.[14] Across the three studies, the mean change in HbA1c was -1.02% for both IGlar U-300 and IGlar U-100. The proportion of patients who achieved an HbA1c less than 7% was 36.2% and 35.5% in the IGlar U-300 and U-100 groups, respectively. The reduction in FPG was similar (36.7 mg/dL vs 40.7 mg/dL, respectively), as was the variability in the blood glucose levels. Overall, a treatment-related adverse event resulted in discontinuation in 1.4% and 1.3% of IGlar U-300 vs U-100 patients, respectively. The dose of IGlar U-300 and U-100 increased from baseline and was 0.85 and 0.76 units/kg/day at 26 weeks. Body weight increased 0.51 and 0.79 kg, respectively.[14]

Safety & Tolerability

RZ is a 71-year-old man diagnosed with T2DM 7 years ago. For the past 2½ years, he has been treated with metformin and basal insulin, which he takes twice daily. His HbA1c was 7.6% eight months ago and is 7.4% now. During the current office visit, his wife reports that RZ reduces his dose of morning insulin or eats a large breakfast before driving every Friday to visit their daughter who lives 3 hours away. RZ admits to doing this and states that he doesn't want to have an episode of hypoglycemia while driving.

Hypoglycemia

Hypoglycemia is one concern of providers, patients, and family members (see *Basal Insulin in Primary Care* on page S8). One of the ways in which patients manage this concern

TABLE Summary of key clinical outcomes in patients with T2DM[8-13]

Population/Baseline Treatment	Trial Treatment	Blood Glucose Changes from Baseline	% Achieving HbA1c <7%	Weight Change (kg)	Confirmed Hypoglycemia (episode/ patient-year)	TDD* (units/ kg/day)
EDITION 3[13] Insulin-naïve inadequately controlled with metformin, SU/GLN, and/or DPP-4i Baseline: HbA1c 8.5%, FPG 179-184 mg/dL N=878	Metformin and/or DPP-4i + IGlar U-300 QD or IGlar U-100 QD for 26 weeks	HbA1c: -1.42% vs -1.46% FPG: -61.4 mg/dL vs -68.4 mg/dL	43% vs 42%	0.49 vs 0.71	Confirmed/ Severe: 6.41 vs 8.50 Nocturnal: 1.31 vs 1.34 Severe: 0.02 vs 0.02	0.62 vs 0.53
EDITION 2[10] Basal insulin with/without metformin, SU, DPP-4i, TZD Baseline: HbA1c 8.2%-8.3%, FPG 142-148 mg/dL N=811	Metformin with/ without DPP-4i with/without TZD + IGlar U-300 QD or IGlar U-100 QD for 26 weeks	HbA1c: -0.57% vs -0.56% FPG: -20.5 mg/dL vs -19.1 mg/dL	30.6% vs 30.4%	0.08 vs 0.66	Confirmed/ Severe: 14.01 vs 18.14 Nocturnal: 1.89 vs 3.68 Severe: 0.03 vs 0.06	0.92 vs 0.84
EDITION 2 (extension)[11] Basal insulin with/without metformin, SU, DPP-4i, TZD Baseline: HbA1c 8.2%-8.3%, FPG 142-148 mg/dL N=693	Metformin with/ without DPP-4i with/without TZD + IGlar U-300 QD or IGlar U-100 QD for 26 weeks (total 52 weeks)	HbA1c: -0.55% vs -0.50% FPG: -14.7 mg/dL vs -18.0 mg/dL	NR	0.4 vs 1.2	Confirmed/ Severe: 11.60 vs 13.18 Nocturnal: 1.74 vs 2.77 Severe: 0.03 vs 0.03	0.97 vs 0.87
EDITION JP 2[12] Basal insulin with/without metformin, SU, DPP-4i, TZD Baseline: HbA1c 8.0%-8.1%, FPG 133-139 mg/dL N=241	Metformin with/ without SU with/ without DPP-4i with/without TZD + IGlar U-300 QD or IGlar U-100 QD for 26 weeks	HbA1c: -0.45% vs -0.55% FPG: -21.8 mg/dL vs -22.5 mg/dL	25.0% vs 24.2% Without hypoglycemia: 23.3% vs 22.5%	-0.6 vs 0.4	Confirmed/ Severe: 10.48 vs 16.52 Nocturnal: 2.18 vs 4.98 Severe: 0.05 vs 0.03	0.35 vs 0.30

is by reducing the doses of their glucose-lowering medications or eating more than normal prior to activities where hypoglycemia is thought to be more likely.[15-17]

The patient-level meta-analysis also found the rate of confirmed or severe hypoglycemia to be significantly lower with IGlar U-300 compared with IGlar U-100 (15.22 vs 17.73 episodes/patient-year) and was similar based on age (less than age 65 years vs age 65 years or greater).[14] Similarly, the rate of nocturnal confirmed hypoglycemia was significantly lower with IGlar U-300 (2.10 vs 3.06 episodes/patient-year, respectively). The reduction in confirmed or severe hypoglycemia with IGlar U-300 was apparent during the first 8 weeks of treatment, as well as during the maintenance period (week 9 to month 6).

Cardiovascular Safety

The review of IGlar U-300 conducted by the US Food and Drug Administration (FDA) during the new drug application process concluded that there is no safety concern with IGlar U-300 that suggests a cardiovascular risk.[18] Moreover, the review noted that there was a higher number of events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) with IGlar U-100 compared with IGlar U-300.

Other Adverse Events

The FDA review found that, other than hypoglycemia, nasopharyngitis and upper respiratory tract infection were the only treatment-related adverse events observed in 5% or more of patients treated with IGlar U-300.[3,18]

TABLE Summary of key clinical outcomes in patients with T2DM[8-13] (*continued*)

Population/Baseline Treatment	Trial Treatment	Blood Glucose Changes from Baseline	% Achieving HbA1c <7%	Weight Change (kg)	Confirmed Hypoglycemia (episode/ patient-year)	TDD[a] (units/ kg/day
EDITION 1[8] IGlar U-100/NPH and prandial insulin ± metformin for ≥1 year Baseline: HbA1c 8.2%, FPG 158-161 mg/dL N=807	Prandial insulin ± metformin + IGlar U-300 QD or IGlar U-100 QD for 26 weeks	HbA1c: -0.83% vs -0.83% FPG: -23.2 mg/dL vs -24.8 mg/dL	39.6% vs 40.9%	0.9 vs 0.9	Confirmed/ Severe: 25.48 vs 26.76 Nocturnal: 3.13 vs 4.20 Severe: 0.27 vs 0.24	1.53 vs 1.43
EDITION 1 (extension)[9] IGlar U-100/NPH and prandial insulin ± metformin for ≥1 year Baseline: HbA1c 8.2%, FPG 158-161 mg/dL N=745	Prandial insulin ± metformin + IGlar U-300 QD or IGlar U-100 QD for 26 weeks (total 52 weeks)	HbA1c: -0.86% vs -0.69% FPG: -29.6 mg/dL vs -26.0 mg/dL	NR	1.2 vs 1.4	Confirmed/ Severe: 22.34 vs 20.99 Nocturnal: 2.88 vs 3.19 Severe: 0.19 vs 0.14	1.58 vs 1.45

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin 1c; IGlar U-100, insulin glargine 100 units/mL; NPH, neutral protamine Hagedorn insulin; NR, not reported; QD, once daily; SU, sulfonylurea; TZD, thiazolidinedione.

*Total daily dose of insulin (basal and prandial, if taking prandial) at end of study.

PATIENT REPORTED OUTCOMES

LT is a 42-year-old man recently diagnosed with T2DM. Current medications include metformin and basal insulin analog twice daily. Two weeks after starting basal insulin, he experienced an episode of severe hypoglycemia requiring a 2-day hospitalization. Since that time, he has reluctantly agreed to continue basal insulin, but admits that he would rather live with mild hyperglycemia than experience another episode of severe hypoglycemia.

In patients with T2DM treated with IGlar U-300 or IGlar U-100 (EDITION 1, 2, 3), concerns about hypoglycemia, including perceived frequency of hypoglycemia, improved similarly.[8-11] Furthermore, similar improvement in treatment satisfaction was observed with IGlar U-300 and U-100, while health-related quality of life was unchanged from baseline.[8,9,13]

In patients with T1DM (EDITION 4), treatment satisfaction and quality of life were unchanged from baseline in patients treated with IGlar U-300 or U-100.[6]

Dosing Considerations

IGlar U-300 is 3 times the concentration of IGlar U-100, containing 300 units of insulin glargine per milliliter. As with IGlar U-100, the maximum dosage of IGlar U-300 per injection is 80 units.[3] When switching patients from IGlar U-100 to IGlar U-300, the dose of IGlar U-300 is the same initially as IGlar U-100. However, results of the EDITION trials showed that a mean 12% higher daily dose of IGlar U-300 is needed to maintain the same level of glycemic control as with IGlar U-100.[6-14] When switching patients from twice-daily NPH insulin, the starting dose of IGlar U-300 is 80% of the total daily NPH dose. Titration should be guided by blood glucose monitoring.

Dosing Time

IGlar U-300 should be given once-daily at the same time each day based on patient preference.[3] Although not stated in the prescribing information, if a dose of IGlar U-300 is missed, it can be given within 3 hours of the normal dose time. This dose time flexibility is based on a substudy of EDITION 1 and 2. Following 6 months of optimized treatment with IGlar U-300, eligible patients completing 6 months of optimized IGlar U-300 in EDITION 1 and 2 with a mean HbA1c of 7.3% were randomized to either increase variability of between-injection intervals by administering the IGlar U-300 dose within 3 hours of the dose time (flexible group) or to continue administering the IGlar U-300 dose at the same time each day (fixed group). At the end of 3 months, 41% and 12% of the between-injection intervals were outside the 23- to 25-hour range in the flexible and fixed groups, respectively. End-of-treatment differences between the flexible and fixed groups were: HbA1c 0.05%, FPG 2.7 mg/dL, and basal insulin dose

0.00 units/kg/day. Rates of confirmed or severe hypoglycemia (10.44 vs 14.81 episodes/patient-year) and nocturnal (2.30 vs 1.95 episodes/patient-year) were similar in the flexible and fixed groups, respectively.

Pen Device

The SoloSTAR pen used for IGlar U-100 has been modified to allow for the one-third volume of IGlar U-300 with the same push button dial stroke and reduced plunger travel.[19] This device, which is commercially available in the United States, is different from the pen device used in the EDITION program.

Prospective comparison of the modified IGlar U-300 SoloSTAR pen with FlexPen (insulin detemir) and KwikPen (insulin lispro) showed that all three pens met the International Organization for Standardization requirements for dosing accuracy at three dose levels (1 unit, half-maximal, maximal).[19] Between-dose variation was similar for the three pen devices. Both the mean plateau injection force and the mean maximum injection force for IGlar U-300 SoloSTAR were significantly lower than for FlexPen and KwikPen.

SUMMARY

Insulin glargine U-300 is a long-acting basal human insulin analog approved for once-daily administration due to a flat and stable glucose-lowering effect for more than 24 hours. The EDITION program of phase 3 clinical trials established comparable glycemic control with insulin glargine U-300 and insulin glargine U-100 in patients with type 1 or type 2 diabetes mellitus. Variability in the blood glucose levels is similar. Rates of confirmed and severe, as well as nocturnal, hypoglycemia are generally lower with insulin glargine U-300 than insulin glargine U-100, thereby reducing an important concern of providers and patients regarding insulin therapy. Although a higher dose of insulin glargine U-300 than U-100 is required in most patients, the observed increase in body weight is small and less than with insulin glargine U-100. ●

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