A Clinical Review of Concentrated Insulins for Type 1 and Type 2 Diabetes Mellitus

Author:

Jennifer N. Clements,

PharmD, BCPS, CDE, BCACP (Corresponding Author)

Associate Professor

Presbyterian College School of Pharmacy
Department of Pharmacy Practice
307 North Broad Street
Clinton, South Carolina 29325
Phone: 864-938-3870
Fax: 864-938-3903

Email: jclements@presby.edu

Abstract

Insulin therapy is cornerstone treatment for the management of type 1 diabetes mellitus and often, is initiated for patients with type 2 diabetes inadequately controlled with oral antidiabetic medications or with severe hyperglycemia. Concentrated insulin products are available to address the volume concerns with high doses of insulin U-100 (100 units per milliliter) due to poor or unpredictable absorption. Humulin R U-500 has been available for 20 years, but has been underutilized in clinical practice due to conversions into a U-100 syringe or tuberculin syringe with the vial. Now, its use may increase as a pre-filled pen and U-500 syringe have recently become available. In addition, two additional concentrated insulins were approved in 2015 - insulin glargine U-300 (300 units per milliliter) and insulin degludec U-200 (200 units per milliliter). These specific products are alternative insulin options for type 1 or type 2 diabetes, especially among patients with high doses of insulin therapy and high risk of hypoglycemia. Insulin glargine U-300 and insulin degludec U-200 have similar A1c reduction to active comparators, but have a lower risk of hypoglycemia and nocturnal hypoglycemia. This article evaluates and summarizes the indications, dosing, recent clinical evidence and role of insulin regular U-500, insulin glargine U-300 and insulin degludec U-200 for type 1 and type 2 diabetes mellitus.

Keywords: insulin glargine U-300; insulin degludec U-200; insulin U-500; concentrated insulin; type 1 diabetes; type 2 diabetes; diabetes mellitus

Running Head: Concentrated Insulin for Diabetes

1. Background

1.1. Basal insulin has been the mainstay of diabetes management since its discovery in 1920 by Frederick Bunting (Bliss 1982). Even though it has not been 100 years since its discovery, there have been several medical advances with insulin including approval of insulin analogs, availability of pre-filled devices, and discovery of other delivery systems (i.e., inhaled insulin). More recently, two additional basal, concentrated insulin products were approved by the Food and Drug Administration (FDA) for use among patients with type 1 diabetes (T1DM) and type 2 diabetes mellitus (T2DM). However, the use of insulin as the sole therapy for diabetes management has varied from 26% to 17.8%, respectively, for the year 1997 and 2011 (Centers for Disease Control 2012).

1.2. Due to rapid absolute destruction of beta cells in the pancreas, patients with T1DM require insulin therapy indefinitely through vial-syringe, pre-filled pens, or insulin pumps as the delivery system. A combination of basal and bolus insulin are essential to mimic endogenous insulin production. For the management of T2DM, the pathophysiology is multifactorial, but has key defects involving insulin resistance and progressive decline of pancreatic beta cell function over time (DeFronzo 2010). Insulin therapy is often considered for the management of T2DM when there is inadequate glycemic control despite oral medications (i.e., mono-, dual, or triple-therapy), presence of contraindications, history of intolerances, or glucotoxicity (Inzucchi 2015). Basal insulin does not have to be considered a last option for patients with T2DM as there is evidence to support early initiation for preservation of pancreatic beta cell function (Owens 2013). Early initiation can also improve insulin sensitivity and prevent disease progression over time (Owens 2013).

1.3. American Diabetes Association

1.3.1. While the most common, clinically-utilized guidelines may vary slightly in the recommendations on insulin initiation for a patient with T2DM, the ideal basal insulin for initiation should have a low risk of weight gain and hypoglycemia, along with flexible dosing for once-daily injection. Specifically focusing on the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), basal insulin is a second-line option, equal to sulfonylureas (SUs), thiazolidinediones (TZDs), dipeptidyl peptidase-IV inhibitors (DPP-IVi), sodium glucose co-transporter 2 inhibitors (SGLT2i), and glucagon-like peptide-1 receptor agonists (GLP-1RAs) (Inzucchi 2015). These medications are options based on specific factors (i.e., A1c reduction, risk of hypoglycemia), following a 3-month trial of metformin. This specific set of guidelines recommends the initiation of basal insulin for those that have poorly controlled diabetes, based on glucose values or A1c which is equal to or above 9% (Inzucchi 2015). Basal insulin therapy is preferably recommended for those that may be showing signs of hyperglycemia. According to the ADA and EASD, patients should be started on a basal-bolus insulin regimen, if there is the presence of severe hyperglycemia indicated by a blood glucose level equal to or above 300 mg/dL or an A1c concentration equal to or above 10% (Inzucchi 2015). Concerns with insulin therapy are related to adverse events, such as hyperglycemia and weight gain. More recently, one of the

biggest limitations or concerns with insulin therapy is the high co-pay or cost, which has been steadily increasing over the past 20 years.

1.4. Insulin Products and Formulations

1.4.1. There are several traditional basal insulin products, with traditional interpreted as U-100 (100 units per milliliter). Neutral Protamine Hagedorn - marketed as Novolin N and Humulin N - is an intermediate-acting insulin with a duration of 8 to 12 hours, requiring twice daily injections (Humulin N package insert 2015; Novolin N package insert 2016). There are several long-acting products with similar onsets of 1 to 3 hours, variable (insulin detemir [Levemir]) to no peak (insulin glargine [Lantus], insulin degludec [Tresiba]), and 24-hour duration, allowing for once daily injection (Levemir package insert 2015; Lantus package insert 2016; Tresiba package insert 2016). In clinical practice, there is a concern for severe insulin resistance leading to titration and higher prescribed doses of basal insulin as a U-100 formulation. As the dose increases, there may be decreased and/or unpredictable absorption or potential leakage at the site of subcutaneous injection (i.e., abdomen, upper thigh, or arm). Higher doses of basal insulin U-100 may require more than one injection per day, which may be additional discomfort to the patient (Lamos 2016). Therefore, concentrated insulins have been developed, investigated, and approved in the United States (US) for use in the management of T1DM and T2DM. These specific agents may be particularly favored among patients with T2DM due to concerns of insulin resistance and greater body weights, leading to higher insulin doses to combat the progressive decline in endogenous insulin production (Lamos 2016). Lastly, concentrated insulins address the volume challenges, such as the need for multiple injections per dose and a larger amount dispensed per prescription.

1.5. Purpose of Article

1.5.1. A recent survey was conducted by the American Pharmacists Association which targeted its membership of pharmacists to determine knowledge and skills related to diabetes services and insulin therapy (American Pharmacists Association 2016). An interesting finding was 80% and 87% of respondents were very familiar with insulin detemir and insulin glargine, respectively. Fifty-three percent of the respondents were very familiar with the concentrated formulation of insulin glargine U-300 (Toujeo). In addition, 48% of the respondents were very familiar with insulin regular U-500. Insulin degludec was not included in this particular survey (American Pharmacists Association 2016). There is no other evidence to show the familiarity of existing and newer insulin products among other health care professionals. This article aims to summarize the clinical evidence and define the role of concentrated insulin – insulin regular U-500, insulin glargine U-300, and insulin degludec U-200.

2. Concentrated Insulin - Regular U-500

2.1. Introduction

2.1.1. Insulin regular U-500 (500 units per 1 milliliter [mL]) is marketed as Humulin R U-500 by Eli Lilly, LLC and received FDA-approval in 1994 (Humulin R U-500 package insert 2016). Insulin regular

U-500 was the first concentrated insulin to become available and be an alternative option for resolving volume challenges that are encountered in clinical practice. This specific concentrated insulin has a reduced hexamer formation that allows for faster dissociation and absorption at the subcutaneous site of injection (Humulin R U-500 package insert 2016). The characteristics of insulin regular U-500 are its ability to mimic bolus and basal insulin activity with a peak effect within 20 to 30 minutes (Humulin R U-500 package insert 2016). The half-life of the drug is approximately 4 hours with a duration of 7 to 24 hours, allowing for flexible dosing (Humulin R U-500 package insert 2016).

2.2. Indications

2.2.1. Insulin regular U-500 is indicated for the management of type 1 or type 2 diabetes among the pediatric and adult population, specifically for patients with severe insulin resistance injecting more than 200 units of insulin per day (Humulin R U-500 package insert 2016). Currently, insulin regular U-500 insulin is available as a 20 milliliter (mL) vial which contains 10,000 units and a 3-mL pre-filled, disposable FlexPen containing 1500 units. The vial-syringe regimen can be prescribed as 5 to 250 units per injection, whereas the pre-filled pen can inject 5 to 300 units per injection. The pre-filled pen has an advantage of the vial-syringe combinations, as actual doses are displayed, eliminating the need for dosing conversions (Humulin R U-500 package insert 2016).

2.3. Evidence

2.3.1. In expert opinions, there has been a variety of prescribing doses for insulin regular U-500 based on the total daily amount of insulin U-100 (Cochran 2005; Neal 2005; Garg 2006; Cochran 2008; Lane 2009; Segal 2010). As an example, insulin regular U-500 could be dosed as two or three times a day, if the total daily amount of insulin is between 200 to 299 units. These dosing percentages have varied from 40 to 45% before breakfast, 30 to 40% before lunch, and 20 to 30% before dinner (Cochran 2005; Neal 2005; Garg 2006; Cochran 2008; Lane 2009; Segal 2010). A more recent study was able to compare twice daily and three times a day of insulin regular U-500 in 24-week, open label, randomized trial (Hood 2015). Within the study, patients were eligible for randomization based on the following criteria: 18 to 75 years of age, diagnosis of T2DM, A1c between 7.5 to 12%, 200 to 600 units of insulin U-100 per day, and body mass index (BMI) equal to or above 25 kg/m^2. From the baseline characteristics, the average age was 55.4 years, 15-year history of diabetes, A1c of 8.7%, mean insulin dose of 287.5 units per day, and BMI of 41.9 kg/m^2. From baseline, twice daily dosing resulted in a 1.3% reduction in A1c compared to 1.2% reduction with three times a day dosing. The difference of -0.1% (95% confidence interval [CI] -0.33% to 0.12%) was neither statistically nor clinically significant. However, it established the clinical equivalency between these two different dosing regimen of insulin regular U-500 to be implemented into clinical practice. With regards to insulin regular U-500 in general, weight gain was observed (average of 4.9 kg) and hypoglycemic episodes occurred as 0.5 per person per week (Hood 2015).

2.4. Dosing

2.4.1. From the U-500 Initiation Trial, an evidence-based approach can be

extrapolated and used for dosing calculations in clinical practice for the total daily amount of this concentrated insulin (Hood 2015). If the A1c is above 8% and 7-day self-monitoring blood glucose levels are above 183 milligrams per deciliter (mg/dL), then 100% of insulin U-100 could be calculated and converted to insulin regular U-500. However, if the A1c is equal to or less than 8% or 7-day self-monitoring glucose values have been less than 183 mg/dL, then 80% of insulin U-100 should be taken into account for the calculation and conversion to insulin regular U-500. As the next step, it would be important to determine dose proportions for two- or three times a day dosing. Based on the U-500 Initiation Trial, twice-daily dosing of insulin regular U-500 is recommended to be prescribed as 60% before breakfast and 40% before dinner. For three times a day dosing, the following percentages would be recommended for breakfast, lunch, and dinner, respectively – 40%, 30%, and 30%. Based on the same trial, there is an algorithm dose titration rounded to the nearest five unit increment, which can be used for either dosing schedule (Hood 2015).

2.4.2. When initiating insulin regular U-500, patients should receive adequate counseling on dosing and administration. Insulin regular U-500 should be injected within 30 minutes of eating (Humulin R U-500 package insert 2016). Patients should be informed about the specific dosing units of the pre-filled pen or markings of the syringe. If a U-100 syringe is preferred, the actual units should be divided by five to indicate the markings within the syringe, whereas the prescribed amount would be divided by 500 to know the volume (mL) within a tuberculin syringe. As of November 2016, B-D developed a U-500 syringe for use with 20-mL vial. With the newly available pre-filled FlexPen and B-D U-500 syringe, both devices allow a prescriber to skip the calculated steps of converting a patient from U-100 insulin to U-500 insulin. The new B-D syringe may be beneficial for "new starts" of insulin regular U-500 in order to prevent further confusion. Patients currently injecting insulin regular U-500 with a tuberculin or U-100 syringe could be educated about this new syringe to determine if a switch to the new delivery device is desired. This general opinion for initiation or switches can also be applied to the pre-filled FlexPen.

2.5. Role in Diabetes Management

2.5.1. Insulin regular U-500 can have a definite role in the management of diabetes mellitus, particularly among individuals with T2DM and severe insulin resistance. One of the challenges in clinical practice has been underutilization of insulin regular U-500 most likely due to the unfamiliarity with its pharmacokinetic profile and dosing, along with the need for calculated dosing conversions. There have been several expert opinion articles indicating how to convert insulin U-100 to insulin regular U-500 using the U-100 syringe or tuberculin syringe (Cochran 2005; Neal 2005; Garg 2006; Cochran 2008; Lane 2009; Segal 2010). Now with the pre-filled FlexPen and B-D U-500 syringe, the use of insulin regular U-500 may increase as the calculations for new initiations would not be applied to its dosing.

3. Concentrated Insulin - Insulin glargine U-300

3.1. Introduction

3.1.1. Insulin glargine U-300 (300 units per mL) is one of the newer long-acting insulin analog products. It is marketed as Toujeo in the United States (US) and was approved by the FDA in February 2015 (Toujeo package insert 2015). This concentrated insulin is an acidic solution, which will become neutralized after injection into a subcutaneous area. Following subcutaneous injection, it forms a depot, allowing for slow release of insulin glargine over time. Specifically, insulin glargine U-300 has a unique characteristic of post-administration dissolution rate from the formation of microprecipitate. The microprecipitate is concentration dependent. Based on its pharmacokinetic profile, it has an onset of 6 hours with no peak, and has a duration of 36 hours. The half-life is estimated to be 18 to 19 hours (Toujeo package insert 2015). Insulin glargine U-300 provides more consistent absorption and a longer duration of action, particularly compared to insulin glargine U-100; therefore, insulin glargine U-300 can be dosed at any time of the day (Becker 2015; Becker 2015; Shiramoto 2015).

3.2. Indications

3.2.1. Insulin glargine U-300 is indicated as basal insulin for the management of T1DM and T2DM among adult patients (Toujeo package insert 2015). It is available as a SoloStar pen; each pen is 1.5 mL, and therefore, contains 450 units. A dose of 1 to 80 units per injection could be administered, as 1 unit or increment is indicated by 1 click with the pre-filled, disposable pen. Due to its concentration, insulin glargine U-300 will not be available in a vial to prevent medication errors in dosing and administration (Toujeo package insert 2015). If the pen is not in use, it should be stored in the refrigerator until its expiration date. Once the pen device has been used, it can be kept at room temperature for 28 days (Toujeo package insert 2015).

3.3. Evidence

3.3.1. Insulin glargine U-300 has only been studied in comparison to insulin glargine U-100 in the EDITION trials. The EDITION trials are a series of open-label, multinational, noninferiority, randomized-controlled trials, among patients with T1DM or T2DM. Among all the EDITION trials, the baseline A1c was approximately 8.1 to 8.5%. Particularly among patients with T2DM in the EDITION trials, baseline characteristics included average age of 59 years, BMI of 30 to 36 kg/m^2, and 9 to 16 year history of diabetes (Riddle 2014; Yki-Jarvinen 2014; Bolli 2015).

3.3.2. In the EDITION 1 trial, the two glargine concentrations were compared among patients with T2DM, inadequately controlled with a basal-bolus regimen (Riddle 2014). The basal-bolus regimen must have consisted of NPH insulin 42 units or more at the beginning of the trial - with mealtime insulin. Both insulin concentrations had similar A1c reduction after 6 months of therapy with a mean difference of 0.0%. Both insulin glargine U-300 and U-100 are effective options in lowering A1c; when the trial was extended for an additional 26 weeks, insulin glargine U-300 had a slightly greater A1c reduction, as the mean difference was -0.17% (95% CI -0.30% to -0.05%, p=0.007) (Riddle 2015).

While this result was statistically significant, it was not a clinically significant finding as both insulins would be effective and equivalent in lowering A1c concentrations among this specific patient population. The EDITION 2 trial was similar to EDITION 1, except patients with inadequately controlled glucose readings with NPH insulin 42 units or more were included in the trial (Yki-Jarvinen 2014). Oral antidiabetic medications were allowed with the exception of sulfonylureas. At the end of 26 weeks, insulin glargine U-300 and U-100 were similar in the primary endpoint (mean A1c difference of -0.01, 95% CI -0.14 to 0.12%); this same finding was observed for an extended period of time of 52 weeks (mean A1c difference of -0.06%) (Yki-Jarvinen 2014; Yki-Jarvinen 2015). The EDITION 3 trial evaluated the efficacy of insulin glargine U-300 to insulin glargine U-100 among insulin-naive patients with T2DM (Bolli 2015). Patients must have been prescribed oral antidiabetic medications for at least 6 months prior to enrollment. Following the study, insulin glargine U-300 produced a 1.42% A1c reduction, compared to insulin glargine U-100 (-1.46%). From this particular study, more patients achieved fasting glucose targets with insulin glargine U-100. However, more patients achieved a desired A1c of less than 7% with insulin glargine U-300, which is a similar finding from the EDITION 1 and 2 trials (Riddle 2014; Yki-Jarvinen 2014; Bolli 2015). While the active comparator was the same, the EDITION 4 trial included patients with T1DM on mealtime insulin for at least 3 months. At baseline, the average patient was 46.4 years of age with a 13-year history of diabetes, and weighed 82 kg. The baseline A1c concentration was 8.1% and after 26 weeks of therapy, insulin glargine U-300 produced a 0.42% A1c reduction, compared to insulin glargine (-0.44%, mean difference of 0.02%). This specific trial confirmed equivalency between these two glargine concentrations in lowering A1c concentrations, as the primary outcome.

3.3.3. When reviewing the EDITION series, it is important to also investigate the adverse effects of insulin glargine U-300 (Ritzel 2015). Specifically, weight gain occurred among patients with T2DM at an average of 0.2 kilograms (kg), compared to weight reduction among those with T1DM (average of 0.6 kg). In terms of hypoglycemia that may have occurred anytime of the day, insulin glargine U-300 did have a lower incidence than the comparator group of insulin glargine U-100 (15.2 versus 17.73 events per participant year). These results were calculated as a relative risk (RR) of 0.86, 95% confidence interval (CI) 0.77 to 0.97, indicating insulin glargine U-300 has a 14% lower risk of hypoglycemia. For nocturnal hypoglycemia, insulin glargine U-300 also had a 31% lower risk (2.1 events), compared to insulin glargine U-100 (3.06 events), with a RR of 0.69 (95% CI 0.57 to 0.84) (Ritzel 2015). In the EDITION trials, a higher total daily dose of insulin glargine U-300 was observed, compared to insulin glargine U-100. More specifically, approximately 11 to 15% of patients with T2DM and 17.5% of patients with T1DM have a higher dose of insulin glargine U-300 (Ritzel 2015).

3.4. Dosing

3.4.1. When starting insulin glargine U-300, it is important to consider appropriate dosing for those patients considered insulin-naïve or insulin-

experienced. For insulin-naïve patients with T2DM, 0.2 units per kilogram daily should be the converting ratio when initiating insulin glargine U-300 (Toujeo package insert 2015). If a patient is being converted from once daily basal insulin (i.e., insulin glargine U-100), the ratio of 1:1 can be used in the conversion. If a patient is changing from twice daily NPH insulin, then 80% of the NPH total daily dose can be used to calculate the initial dose of insulin glargine U-300 (Toujeo package insert 2015). For those with T1DM, one-third to one-half total daily dose could be initiated as the basal dose for the basal-bolus regimen, which is approximately 0.2 to 0.4 units per kilogram per day. Based on its half-life, insulin glargine U-300 can be titrated every 3 to 4 days, after it has reached steady-state in 5 days, in order to target fasting glucose numbers (Toujeo package insert 2015).

3.4.2. There was a specific titration protocol for the EDITION trials, based on 3-day average of fasting blood glucose levels (Riddle 2014; Yki-Jarvinen 2014; Bolli 2015; Home 2015). It is important to note that the dose of insulin glargine U-300 was titrated over 12 weeks within these trials. If the 3-day average was equal to or above 140 mg/dL, then insulin glargine formulations were increased by 6 units. If the 3-day average was 100 to 139 mg/dL, then the insulin was increased by 3 units. Insulin doses were maintained at the current prescribed amount if the 3-day average was between 89 to 99 mg/dL. The amount or dose of insulin was decreased by 3 units if the fasting blood glucose average for 3 days was below 79 mg/dL. This specific titration schedule can be implemented into clinical practice for insulin glargine U-300 (Riddle 2014; Yki-Jarvinen 2014; Bolli 2015; Home 2015).

3.5. Role in Diabetes Management

3.5.1. Insulin glargine U-300 has been compared to insulin glargine U-100, in which both insulin concentrations had similar glycemic control in terms of A1c reduction. In addition, there are similar changes with weight between these two different insulin glargine concentrations. The main difference and advantage of insulin glargine U-300 over insulin glargine U-100 would be a lower risk of hypoglycemia. However, the statistically significant difference in this secondary outcome was not consistent among all the EDITION trials. There may be less volume to be injected due to the concentration of insulin glargine U-300 but higher doses would be required, as indicated from the clinical evidence in the EDITION series.

4. Concentrated Insulin - Insulin degludec U-200

4.1. Introduction

4.1.1. Insulin degludec is another long-acting human insulin analog, recently approved by the FDA (September 2015) for use in diabetes management (Tresiba package insert 2016). It is available as U-100, but also as a concentration of U-200, indicated as 200 units per milliliter. Based on its pharmacokinetic profile, insulin degludec is often considered an ultra-long acting insulin in clinical practice. After subcutaneous injection, formation of multi-hexamer chains occurs; zinc becomes depleted and individual hexamers will dissociate into monomers from the formation of a depot. Therefore, insulin degludec is slowly absorbed into the blood. It has an onset of 10 to 12 hours with no peak, half-life of 25 hours, and duration of

42 hours, allowing for once-daily dosing (Biester 2014; Haahr 2014; Korsatko 2014).

4.2. Indications

4.2.1. Insulin degludec U-200 is indicated as basal insulin for the management of T1DM and T2DM among pediatric and adult patients. Insulin degludec can be an option for those older than 1 year of age (Tresiba package insert 2016). It is available in a pre-filled, disposable FlexTouch pen with 3 mL of volume. Therefore, each pen contains 600 units of insulin degludec. The maximum dose per one injection is 160 units, as each dosing increment will equal 2 units. If the insulin degludec pen is not used but stored in the refrigerator, then it can be used until its expiration date. Once opened, insulin degludec can be stored at room temperature for 56 days (Tresiba package insert 2016).

4.3. Evidence

4.3.1. Insulin degludec U-200 has been studied in the BEGIN trials among participants with T1DM and T2DM (Garber 2012; Gough 2012; Gough 2013; Heller 2012; Mathieu 2013; Meneghini 2013; Onishi 2013; Zinman 2012). All of these trials were noninferiority, open-label, multinational, randomized-controlled with intention-to-treat for study design; only the BEGIN EARLY trial was designed in a superiority manner to compare insulin degludec to sitagliptin (Philis-Tsimikas 2013). Specifically, insulin degludec was compared to insulin glargine U-100 among patients with T1DM and T2DM, as part of a basal-bolus regimen, while a majority of the trials investigated insulin degludec as the basal insulin option with oral antidiabetic agents for T2DM (Garber 2012; Gough 2012; Gough 2013; Heller 2012; Mathieu 2013; Meneghini 2013; Onishi 2013; Zinman 2012).

4.3.2. Based on the BEGIN trials, insulin degludec U-200 is similar to insulin glargine U-100 for A1c reduction among patients with T1DM, T2DM with oral agents, and T2DM with basal-bolus regimens (mean differences -0.04%, -0.01%, and -0.05%, respectively) (Vora 2014). In a meta-analysis, there was no statistically significant difference in mean insulin doses at the end of the trials with patients receiving insulin degludec U-200 or insulin glargine U-100 for T1DM or T2DM as part of the basal-bolus regimen. However, insulin degludec doses were 10% lower among insulin-naive patients with T2DM ($p=0.0004$) (Vora 2014). In terms of safety, insulin degludec U-200 had an average weight gain of 1.5 to 3.6 kg. In some studies, this weight gain was similar to the comparator arm of insulin glargine U-100. However, there was a reduction with weight (average of -0.4 kg) for those receive sitagliptin in the BEGIN EARLY trial, whereas insulin degludec U-200 caused weight gain (Garber 2012; Gough 2012; Gough 2013; Heller 2012; Mathieu 2013; Meneghini 2013; Onishi 2013; Philis-Tsimikas 2013; Zinman 2012).

4.3.3. The biggest differences in insulin degludec U-200 and insulin glargine U-100 for clinical implications occurred with the secondary and safety endpoints of hypoglycemia and nocturnal hypoglycemia. Insulin degludec U-200 did have lower incidence of hypoglycemia and nocturnal hypoglycemia, in comparison to insulin glargine U-100. Statistically significant findings for hypoglycemia were observed among patients with T2DM, as insulin degludec U-200 had a 17% lower risk in a

basal-bolus regimen, compared to insulin glargine U-100. Among insulin-naive patients with T2DM, insulin degludec was associated with a 20% reduction of hypoglycemia in the maintenance phase of the BEGIN trials (Vora 2014). In terms of nocturnal hypoglycemia, insulin degludec U-200 had a 17%, 25%, and 36% lower risk of this endpoint among patients with T1DM, insulin-experienced T2DM, and insulin-naive T2DM, respectively (Vora 2014). This finding was seen throughout the BEGIN trials, but more specifically, insulin degludec was also associated with a 25%, 29% and 49% lower risk of nocturnal hypoglycemia during the maintenance phase of the BEGIN trials among patients with T1DM, insulin-experienced T2DM, and insulin-naive T2DM, respectively (Vora 2014). It is important to note a higher risk of nocturnal hypoglycemia with insulin degludec U-200 versus sitagliptin (Philis-Tsimikas 2013). This finding would be predicted as DPP-IV inhibitor has minimal to no risk of hypoglycemia when used with other agents, such as metformin.

4.3.4. There was a meta-analysis of major adverse cardiovascular events for the insulin degludec U-200 showing a nonstatistically significant risk, but potential trend (hazards ratio [HR] 1.10 (95% CI 0.68 to 1.77)) (Thuiller 2015). Additional studies will be completed to provide more evidence regarding the cardiovascular safety of insulin degludec (Marso 2016).

4.4. Dosing

4.4.1. The initiation and titration of insulin degludec is similar to insulin glargine U-300. Among insulin-naive patients with T2DM, the starting dose of insulin degludec would be 10 units subcutaneously daily at anytime of the day (Tresiba package insert 2016). For those with T1DM, one-third to one-half of the total daily dose could be used, which is approximately 0.2 to 0.4 units per kilogram per day. If a patient is being changed from an intermediate- or long-acting basal insulin, then the conversion ratio is 1:1 when switching to insulin degludec U-200. Steady-state would be achieved after 2 to 3 days of administration; following this period, insulin degludec can be titrated every 3 to 4 days in order to target fasting blood glucose levels (Tresiba package insert 2016).

4.5. Role in Diabetes Management

4.5.1. Due to its ultra-long duration of action, insulin degludec U-200 may have flexible dosing as one of the newest concentrated insulins. However, it will most likely be initiated as a once-daily basal insulin in clinical practice. It has comparable glycemic control and weight changes, when compared to insulin glargine U-100. Insulin degludec U-200 was not a fair comparator, as basal insulin, to a post-prandial oral medication, indicating better glycemic control than sitagliptin. There was a lower risk of nocturnal hypoglycemia based on its pharmacokinetic profile when insulin degludec was compared to insulin glargine. Insulin degludec may be a preferred basal insulin for patients desiring flexible dosing or may be on low doses of insulin, as insulin degludec has a longer storage expiration date when the pre-filled pen is being used. Lastly, insulin degludec U-200 would be an option for patients requiring high-dose basal insulin due to its availability as a concentrated insulin.

5. Conclusion

5.1. Overall, concentrated insulins can have an impact on T1DM and T2DM management. Specifically with insulin regular U-500, there should be policies and procedures for clinical practice and healthy-system practice in order to have appropriate prescribing, transcribing, ordering, dispensing, and administration. In addition, there need to be appropriate order sets, clinical reminders, and double or triple checks among the multidisciplinary team. With the other concentrated insulin products, there are also other benefits for use in clinical practice. As these insulins are available in a pre-filled device, they may be more preferable for certain individuals. However, the most useful benefits include a lower risk of hypoglycemia, potential lower risk of weight gain, and daily dosing.

6. References

Pharmacists' knowledge and skills to provide diabetes services and educate patients about insulin. In: Practice Insights, American Pharmacists Association. Washington, DC; December 2016.

Becker RH, Dahmen R, Bergmann K, et al. New insulin glargine 300 units/mL provides a more even activity profile and prolonged glycemic control at steady state compared with insulin glargine 100 units/mL. Diabetes Care. 2015;38:637–43.

Becker RH, Nowotny I, Teichert L, et al. Low within- and between-day variability in exposure to new insulin glargine 300 U/ml. Diabetes Obes Metab. 2015; 17:261–7.

Biester T, Blaesig S, Remus K, et al. Insulin degludec's ultra-long pharmaco-kinetic properties observed in adults are retained in children and adolescents with type 1 diabetes: insulin degludec in children/adolescents. Pediatr Diabetes. 2014;15:27–33.

Bliss M. The Discovery of Insulin. University of Chicago Press; Chicago, IL; 1982.

Bolli GB, Riddle MC, Bergenstal RM et al. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). Diabetes Obes Metab. 2015;17:386-94.

Centers for Disease Control and Prevention (CDC), National Center for Health Statistics, Division of Health Interview Statistics, data from the National Health Interview Survey. Retrived from https://www.cdc.gov/diabetes/statistics/meduse/fig2.htm.

Cochran E, Musso C, Gorden P. The use of U-500 in patients with extreme insulin resistance. Diabetes Care. 2005;28(5): 1240-1244.

Cochran E, Gorden P. Use of U-500 insulin in the treatment of severe insulin resistance. Insulin. 2008;3(4):211-218.

DeFronzo RA. Current issues in the treatment of type 2 diabetes. Overview of newer agents: where treatment is going. Am J Med 2010 Mar;123(3 Suppl):S38-48. doi: 10.1016/j.amjmed.2009.12.008.

Garber AJ, King AB, Del Prato S, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal–Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet. 2012;379: 1498–1507. doi: 10.1016/S0140-6736 (12)60205-0.

Garg R, Johnston V, McNally PG, et al. U-500 insulin: why, when and how to use in clinical practice. Diabetes Metab Res Rev. 2006;23(4):265-268.

Gough SC, Bhargava A, Jain R, et al. Low-Volume Insulin Degludec 200

Units/mL once daily improves glycemic control similarly to insulin glargine with a low risk of hypoglycemia in insulin-naive patients with type 2 diabetes: a 26-week, randomized, controlled, multinational, treat-to-target trial: The BEGIN Low Volume trial. Diabetes Care. 2013; 36:2536–2542. doi: 10.2337/dc12-2329.

Haahr H, Heise T. A review of the pharmacological properties of insulin degludec and their clinical relevance. Clin Pharmacokinet. 2014;53:787–800.

Heller S, Buse J, Fisher M, et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal–Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet. 2012;379:1489–1497. doi: 10.1016/S0140-6736(12)60204-9.

Home PD, Bergenstal RM, Bolli GB et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 1 diabetes: a randomized, Phase 3A, open-label clinical trial (EDITION 4). Diabetes Care. 2015;38:2217-25.

Hood RC, Arakaki RF, Wysham C, et al. Two treatment approaches for human regular U-500 insulin in patients with type 2 diabetes not achieving adequate glycemic control on high-dose U-100 insulin therapy with or without oral agents: A randomized, titration-o-treat clinical trial. Endocr Pract 2015 Jul;21(7):782-93. doi: 10.4158/EP15612.OR. Epub 2015 Mar 26.

Humulin N [package insert]. Indianapolis, IN; Eli Lilly, USA, LLC, 2015.

Humulin R U-500 [package insert]. Indianapolis, IN; Eli Lilly, USA, LLC, 2016.

Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2015;38:140–9.

Korsatko S, Deller S, Mader JK, et al. Ultra-long pharmacokinetic properties of insulin degludec are comparable in elderly subjects and younger adults with type 1 diabetes mellitus. Drugs Aging. 2014;31:47–53.

Lamos EM, YounkLM, Davis SN. Concentrated insulins: the new basal insulins. Ther Clin Risk Manag 2016 Mar 9;12:389-400. doi: 10.2147/TCRM.S99855.

Lane WS, Cochran EK, Jackson JA, et al. High dose insulin therapy: is it time for U-500 insulin? Endocr Pract. 2009; 15(1):71-79.

Lantus [package insert]. Bridgewater, NJ; Sanofi-Aventis, Inc., 2015.

Levemir [package insert]. Plainsboro, NJ; Novo Nordisk, Inc., 2015.

Marso SP, McGuire DK, Zinman B, et al. Design of DEVOTE (Trial comparing cardiovascular safety of insulin degludec

vs insulin glargine in patients with type 2 diabetes at high risk of cardiovascular events) - DEVOTE 1. Am Heart J 2016 Sep;179:175-83. doi: 10.1016/j.ahj. 2016.06.004. Epub 2016 Jun 18.

Mathieu C, Hollander P, Miranda-Palma B, et al. Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. J Clin Endocrinol Metab. 2013;98:1154–1162. doi: 10. 1210/jc.2012-3249.

Meneghini L, Atkin SL, Gough SC, et al. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: a 26-week, randomized, open-label, parallel-group, treat-to-target trial in people with type 2 diabetes. Diabetes Care. 2013;36:858–864. doi: 10.2337/dc12-1668.

Neal JM. Analysis of effectiveness of human U-500 insulin in patients unresponsive to conventional insulin therapy. Endocr Pract. 2005;11(5):305-307.

Novolin N [package insert]. Plainsboro, NJ; Novo Nordisk, Inc., 2016.

Onishi Y, Iwamoto Y, Yoo SJ, Clauson P, Tamer SC, Park S. Insulin degludec compared with insulin glargine in insulin-naïve patients with type 2 diabetes: a 26-week, randomized, controlled, Pan-Asian, treat-to-target trial. J Diabetes Invest. 2013;4:605–612. doi: 10.1111/jdi.12102.

Owens DR. Clinical evidence for the earlier initiation of insulin therapy in type 2 diabetes. Diabetes Technol Ther 2013 Sep;15(9):776-85. doi: 10.1089/dia. 2013.0081. Epub 2013 Jun 20.

Philis-Tsimikas A, Del Prato S, Satman I, et al. Effect of insulin degludec versus sitagliptin in patients with type 2 diabetes uncontrolled on oral antidiabetic agents. Diabetes Obes Metab. 2013;15:760–766. doi: 10.1111/dom.12115.

Riddle MC, Bolli GB, Zieman M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypo-glycemia in a 6-month randomized, controlled trial (EDITION 1). Diabetes Care. 2014;37:2755-62.

Riddle MC, Yki-Jarvinen H, Bolli GB, et al. One-year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal-time insulin: the EDITION 1 12-month randomized trial, including 6-month extension. Diabetes Obes Metab. 2015;17:835-42.

Ritzel R, Roussel R, Bolli GB et al. Patient-level meta-analysis of the EDITION 1, 2, and 3 studies: glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes. Diabetes Obes Metab. 2015;17:859-67.

Segal AR, Brunner JE, Burch FT, et al. Use of concentrated insulin human regular for patients with diabetes. Am J

Health Syst Pharm. 2010;67(18):1526-1535.

Shiramoto M, Eto T, Irie S, et al. Single-dose new insulin glargine 300 U/ml provides prolonged, stable glycaemic control in Japanese and European people with type 1 diabetes. Diabetes Obes Metab. 2015;17:254–60.

Thuillier P, Alavi Z, Kerlan V. (2015). Long-term safety and efficacy of insulin degludec in the management of type 2 diabetes. Diabetes, Metabolic Syndrome and Obesity 2015;8:483–493. http://doi.org/10.2147/DMSO.S54953.

Toujeo [package insert]. Bridgewater, NJ; Sanofi-Aventis, Inc., 2015.

Tresiba [package insert]. Plainsboro, NJ; Novo Nordisk, Inc., 2016.

Vora J, Christensen T, Rana A, Bain SC. Insulin degludec versus insulin glargine in type 1 and type 2 diabetes mellitus: A meta-analysis of endpoints in Phase 3a trials. Diabetes Ther 2014 Dec;5(2):435-46. doi: 10.1007/s13300-014-0076-9. Epub 2014 Aug 1.

Yki-Jarvinen H, Bergenstal R, Ziemen M et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). Diabetes Care. 2014;37:3235-43.

Yki-Jarvinen H, Vergenstal RM, Bolli GB et al. Glycaemic control and hypoglycaemia with new insulin glargine 300 U/mL versus glargine 100 U/mL in people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs (EDITION 2 randomized 12-month trial including 6-month extension). Diabetes Obes Metab. 2015; 17:1142-9.

Zinman B, Philis-Tsimikas A, Cariou B, et al. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long) Diabetes Care. 2012;35:2464–2471. doi: 10.2337/dc12-1205.

