New Insulins, Biosimilars, and Insulin Therapy

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Introduction

ADVANCES IN INSULIN FORMULATIONS continue to be important for diabetes management, but clinical safety and efficacy need to be established. Today, the increased availability of continuous glucose monitoring already allows a more intricate analysis of clinical insulin action than was previously possible. This permits an assessment of whether these new insulins provide a better means for achieving optimal glycemic control beyond HbA1c, which is increasingly receiving scientific and regulatory acceptance. This comes at a time when rapid developments in the device area, as showcased by the U.S. Food and Drug Administration (FDA) approval of the hybrid closed loop (MiniMed 670G, Medtronic) in September 2016, ask for pharmacological advances to facilitate the development of closed-loop pump systems (i.e., artificial pancreas) potentially being a treatment option for insulin-dependent patients with both type 1 and type 2 diabetes.

At the same time insulin may no longer be the only treatment approved for type 1 diabetes, as sotagliflozin (Lexicon/Sanofi), a novel, oral antidiabetic agent has achieved success in several phase 3 clinical trials. Indeed, Jorge Insuasty, senior vice president and head of global development at Sanofi, announced in the summer of 2017 that they will be pursuing regulatory submissions for the adjunct treatment of type 1 diabetes worldwide, which may have a significant impact on the way we treat type 1 diabetes in the future.

This year's attention focused on the first-ever next-generation mealtime insulin to be launched globally. Fiasp (NovoNordisk) is the brand name for fast-acting insulin aspart. After the ultra-fast rapid-acting insulin aspart was approved by the European Commission and other authorities early in 2017, it was launched in April in Canada, Germany, and the United Kingdom and will be coming soon to more European countries, while the FDA approval process is still ongoing. At the same time, clinicaltrials.gov lists completed phase 1 trials with Eli Lilly's new ultra-rapid insulin LY900014, which have yet to be published. In contrast, the December 2014 Collaboration Research and License Agreement between Lilly and Adocia for the development of BioChaperone Lispro, Adocia's ultra-rapid insulin for treatment in people with type 1 and type 2 diabetes, was terminated in January 2017.

Regarding the long-acting analogs, the year provided evidence for their efficacy in reducing the hypoglycemia risk with the ultra-long-acting insulins Toujeo (Sanofi) and Tresiba (NovoNordisk) as well as for the cardiovascular safety of Tresiba, providing reassuring data for clinical practice.

In the second year after the first biosimilar insulin (BioIns) got market approval in the European Union and the United States (not as a BioIns due to the current regulatory situation in the United States), some changes in the insulin marketplace occurred, but nothing overwhelming happened. In the United States some insurance companies switched from Lantus to Basaglar (insulin glargine by Lilly/Boehringer Ingelheim). Most probably this was driven by cost considerations; however, it is not

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clear how much lower the price for this BioIns is in comparison with the originator, Lantus. In some European countries Abasaglar (this is the name of the same BioIns in the EU) has gained significant market share, but no dramatic shift in the market shares of the insulin manufacturer were observed. In the EU price differences between Abasaglar and Lantus vary considerably between countries, up to a maximum of 30%.

An issue with insulin is that there are many myths, barriers, and fears around this drug. Therapy with insulin is more complex than with most other drugs. This leads to inertia in progressing with insulin therapy (i.e., increase the dose, add an insulin, etc., but also switching to a “new” insulin, meaning BioIns). All in all, in the most recent year the field of new insulins and insulin therapy is still moving forward on the research side, but these potential advances need to be accompanied by action on the advocacy front when it comes to important issues like access and affordability.

Key Articles Reviewed for the Article

Efficacy and safety of degludec versus glargine in type 2 diabetes

Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, Pratley RE, Haahr P-M, Lange M, Brown-Frandsen K, Moses A, Skibsted S, Kvist K, Buse JB; for the DEVOTE Study Group

[N Engl J Med 2017; 377: 723–732](#)

Efficacy and safety of once-daily insulin degludec/insulin aspart compared with once-daily insulin glargine in participants with type 2 diabetes: a randomized treat-to-target study

Kumar S, Jang HC, Demirağ NG, Skjøth TV, Endahl L, Bode B

[Diabet Med 2017; 34: 180–188](#)

Insulin degludec/aspart once daily in type 2 diabetes: a comparison of simple or stepwise titration algorithms (BOOST: SIMPLE USE)

Park SW, Bebakar WMW, Hernandez PG, Macura S, Hersløv ML, de la Rosa R

[Diabet Med 2017; 34: 174–179](#)

Glycaemic control and hypoglycaemia during 12 months of randomized treatment with insulin glargine 300 U/mL versus glargine 100 U/mL in people with type 1 diabetes (EDITION 4)

Home PH, Bergenstal RM, Bolli GB, Ziemer M, Rojeski M, Espinasse M, Riddle MC

[Diabetes Obes Metab 2018; 20: 121–128 \[Epub 2017 Aug 8\]](#)

Comparison of insulin glargine 300 units/mL and 100 units/mL in adults with type 1 diabetes: continuous glucose monitoring profiles and variability using morning or evening injections

Bergenstal RM, Bailey TS, Rodbard D, Ziemer M, Guo H, Muehlen-Bartmer I, Ahmann AJ

[Diabetes Care 2017; 40: 554–560](#)

Insulin degludec: lower day-to-day and within-day variability in pharmacodynamics response compared with insulin glargine 300 U/mL in type 1 diabetes

Heise T, Nørskov M, Nosek L, Kaplan K, Famulla S, Haahr H

[Diabetes Obes Metab 2017; 19: 1032–1039](#)

Hypoxia and H₂O₂ dual-sensitive vesicles for enhanced glucose-responsive insulin delivery

Yu J, Qian C, Zhang Y, Cui Z, Zhu Y, Shen Q, Ligler FS, Buse JB, Gu Z

[Nano Lett 2017; 17: 733–739](#)

Red blood cells for glucose-responsive insulin delivery

Wang C, Ye Y, Sun W, Yu J, Wang J, Lawrence DS, Buse JB, Gu Z

Adv Mater 2017; **29**: 1606617

Duration of action of two insulin glargine products, LY2963016 insulin glargine and Lantus insulin glargine, in subjects with type 1 diabetes mellitus

Linnebjerg H, Lam EC, Zhang X, Seger ME, Coutant D, Chua L, Kapitza C, Heise T

Diabetes Obes Metab 2017; **19**: 33–39

Similar pharmacokinetics and pharmacodynamics of rapid-acting insulin lispro products SAR342434 and US- and EU-approved Humalog in subjects with type 1 diabetes

Kapitza C, Nowotny I, Lehmann A, Bergmann K, Rotthaeuser B, Nosek L, Becker RHA

Diabetes Obes Metab 2017; **19**: 622–627

Efficacy and safety of Biosimilar (SAR342434 insulin lispro) in adults with type 1 diabetes also using insulin glargine-SORELLA 1 study

Garg S, Wernicke-Panten K, Rojeski M, Pierre S, Kirchhein Y, Jedynasty K

Diabetes Technol Ther 2017; **19**: 516–526

A pooled analysis of clinical pharmacology trials investigating the pharmacokinetic and pharmacodynamic characteristics of fast-acting insulin aspart in adults with type 1 diabetes

Heise T, Pieber TR, Danne T, Erichsen L, Haahr H

Clin Pharmacokinet 2017; **56**: 551–559

Faster-acting insulin aspart provides faster onset and greater early exposure vs. insulin aspart in children and adolescents with type 1 diabetes mellitus

Fath M, Danne T, Biester T, Erichsen L, Kordonouri O, Haahr H

Pediatr Diabetes 2017; **18**: 903–910 [Epub 2017 Feb 6]

Fast-acting insulin aspart improves glycemic control in basal-bolus treatment for type 1 diabetes: results of a 26-week multicenter, active-controlled, treat-to-target, randomized, parallel-group trial (onset 1)

Russell-Jones D, Bode BW, De Block C, Franek E, Heller SR, Mathieu C, Philis-Tsimikas A, Rose L, Woo VC, Østerskov AB, Graungaard T, Bergenstal RM

Diabetes Care 2017; **40**: 943–950

Faster aspart versus insulin aspart as part of a basal-bolus regimen in inadequately controlled type 2 diabetes: the onset 2 trial

Bowering K, Case C, Harvey J, Reeves M, Sampson M, Strzinek R, Bretler DM, Bang RB, Bode BW

Diabetes Care 2017; **40**: 951–957

Adding fast-acting insulin aspart to basal insulin significantly improved glycaemic control in patients with type 2 diabetes: a randomized, 18-week, open-label, phase 3 trial (onset 3)

Rodbard HW, Tripathy D, Vidrio Velázquez M, Demissie M, Tamer SC, Piletič M

Diabetes Obes Metab 2017; **19**: 1389–1396

Improved postprandial glycemic control with faster-acting insulin aspart in patients with type 1 diabetes using continuous subcutaneous insulin infusion

Bode BW, Johnson JA, Hyveled L, Tamer SC, Demissie M

Diabetes Technol Ther 2017; **19**: 25–33

UTLRA-LONG-ACTING INSULIN ANALOGS: CARDIOVASCULAR SAFETY, CLINICAL CHARACTERISTICS, AND TITRATION ALGORITHMS

Efficacy and safety of degludec versus glargine in type 2 diabetes

Marso SP¹, McGuire DK², Zinman B³, Poulter NR⁴, Emerson SS⁵, Pieber TR⁶, Pratley RE⁷, Haahr P-M⁸, Lange M⁸, Brown-Frandsen K⁸, Moses A⁸, Skibsted S⁸, Kvist K⁸, Buse JB⁹; for the DEVOTE Study Group

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N Engl J Med 2017; **377**: 723–732

This manuscript is also discussed in the article on New Medications for the Treatment of Diabetes, page S-139.

Background

The DEVOTE trial was a dedicated cardiovascular outcomes trial assessing the cardiovascular safety of insulin degludec compared with insulin glargine in patients with type 2 diabetes at high risk of cardiovascular events.

Methods

In this double-blind, treat-to-target, event-driven cardiovascular outcomes trial, 7637 patients with type 2 diabetes (mean age 65 years, mean duration of diabetes 16.4 years, mean HbA1c $8.4 \pm 1.7\%$, 83.9% with ongoing insulin therapy) were randomly randomized 1:1 to insulin degludec or glargine U100 once daily (between dinner and bedtime). Of the participants, 85.2% had proven cardiovascular disease, chronic renal disease, or both. The primary composite outcome was the first occurrence of a major cardiovascular event (death from cardiovascular causes or nonfatal myocardial infarction or stroke), with a predefined inferiority margin of 1.3. Events of severe hypoglycemia (necessitating assistance from another person for recovery) were a multiplicity-adjusted secondary outcome.

Results

The primary outcome occurred in 8.5% of the patients in the degludec group and in 9.3% in the glargine group, respectively (hazard ratio 0.91 [95% CI 0.78–1.06]; $P < 0.001$ for non-inferiority). At 24 months, mean HbA1c was $7.5 \pm 1.2\%$ in both study groups, whereas mean fasting plasma glucose in the degludec group (128 ± 56 mg/dL) was significantly lower than that in the glargine group (136 ± 57 mg/dL; $P < 0.001$). Severe hypoglycemia occurred in 4.9% of the degludec users and 6.6% of the glargine users (rate ratio 0.60, $P < 0.001$ for

superiority; odds ratio 0.73, $P < 0.001$ for superiority). Rates of adverse events were similar in the two groups.

Conclusions

In patients with type 2 diabetes at high risk for cardiovascular events, the use of insulin degludec was noninferior to insulin glargine therapy regarding occurrence of major cardiovascular events.

Efficacy and safety of once-daily insulin degludec/insulin aspart compared with once-daily insulin glargine in participants with type 2 diabetes: a randomized treat-to-target study

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Diabet Med 2017; **34**: 180–188

Background

The aim of this study was to assess the efficacy and safety of the soluble combination of insulin degludec/insulin aspart (IDegAsp) once daily compared with insulin glargine U100 (IGlar) once daily in adult subjects with type 2 diabetes who were on inadequate treatment with oral antidiabetic agents (OADs) and basal insulin.

Methods

A 26-week, open-label, treat-to-target trial was conducted, in which the participants were randomized 1:1 to once-daily IDegAsp ($n = 232$) or IGlar ($n = 233$) administered with the main meal of the day (most commonly in the evening) in combination with preexisting OADs. Insulin titration was done weekly to attain mean prebreakfast plasma glucose between 3.9 and 4.9 mmol/L.

Results

After 26 weeks, the reduction in HbA1c was similar in both groups (mean estimated treatment difference -0.03% [95% CI $-0.20, 0.14$]). The self-measured evening postprandial plasma glucose excursion was lower with IDegAsp than with IGlar (-1.32 mmol/L [$-1.93, -0.72$]; $P < 0.05$). The overall frequency of confirmed hypoglycemia (< 3.1 mmol/L) was greater with IDegAsp than with IGlar (estimated rate ratio 1.43 [1.07, 1.92]; $P < 0.05$), whereas the rate of confirmed nocturnal hypoglycemia tended to be lower with IDegAsp (estimated rate ratio 0.80 [0.49, 1.30]; $P =$ not significant).

Conclusions

In adults with type 2 diabetes inadequately treated with basal insulin, transition to once-daily IDegAsp therapy improved

glucose control and was noninferior to IGLar once daily. IDegAsp was associated with higher frequency of daily hypoglycemia, whereas rates of nocturnal hypoglycemia did not differ significantly between once-daily IDegAsp or IGLar.

Insulin degludec/aspart once daily in type 2 diabetes: a comparison of simple or stepwise titration algorithms (BOOST: SIMPLE USE)

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Diabet Med 2017; **34**: 174–179

Background

This study compared the efficacy and safety of two different titration algorithms after initiation of once-daily administration of insulin degludec/aspart (IDegAsp) together with metformin in adults with insulin-naïve type 2 diabetes.

Methods

In this 26-week, multicenter, open-label, treat-to-target trial, 276 adults with type 2 diabetes treated with metformin with or without other OADs were switched to combination therapy with metformin and once-daily IDegAsp and randomized 1:1 to either of two different insulin titration algorithms: a “simple algorithm” where IDegAsp was titrated twice weekly based on a single self-recorded prebreakfast plasma glucose measurement, or a “stepwise algorithm” where IDegAsp was titrated once weekly based on the lowest of three days’ successive prebreakfast plasma glucose values. In both groups, the titration algorithm aimed to achieve a prebreakfast plasma glucose of 4.0–5.0 mmol/L. Primary outcome was change in HbA1c at the end of the trial.

Results

At 26 weeks, the change in HbA1c was -14.6 mmol/mol (-1.3%), to 52.4 mmol/mol (6.9%), in participants using the simple algorithm and -11.9 mmol/mol (-1.1%), to 54.7 mmol/mol (7.2%), in the stepwise algorithm group; the estimated between-group change being -1.97 mmol/mol [95% CI -4.1 to 0.2] (-0.2% [95% CI -0.4 to 0.02]), confirming noninferiority. Mean reduction in fasting plasma glucose and eight-point profiles of self-measured plasma glucose were comparable between the groups. Frequency of confirmed hypoglycemic events (<3.1 mmol/L) was higher with the simple algorithm (3.3 per patient years of exposure [PYE]) than with the stepwise algorithm (2.1 PYE), with the estimated rate ratio being 1.8 [95% CI 1.1 to 2.9]. Rates of nocturnal hypoglycemia were similar, and no severe hypoglycemic events were registered.

Conclusions

Using a simple titration algorithm when initiating once-daily IDegAsp therapy in adults with insulin-naïve type 2

diabetes improved HbA1c as effectively as a stepwise titration algorithm. Frequency of hypoglycemia was lower with the stepwise algorithm.

Glycaemic control and hypoglycaemia during 12 months of randomized treatment with insulin glargine 300 U/mL versus glargine 100 U/mL in people with type 1 diabetes (EDITION 4)

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Diabetes Obes Metab 2018; **20**: 121–128 [Epub 2017 Aug 8]

Background

This study is an extension of the 6-month, multicenter, open-label, randomized phase 3 trial EDITION 4, comparing the efficacy and safety of insulin glargine 300 U/mL (Gla-300) versus glargine 100 U/mL (Gla-100) in people with type 1 diabetes.

Methods

Of the 549 originally randomized participants, 444 completed the trial and this 6-month extension (80% remaining in the Gla-300 group and 82% in the Gla-100 group). Mean HbA1c reductions from baseline to 12 months were comparable in the two groups (estimated treatment difference 0.02% [95% CI -0.13 , 0.17]; 0.2 mmol/mol [-1.5 , 1.9]). At 12 months the mean HbA1c was 7.86% (62.4 mmol/mol) in both study groups. Comparing morning versus evening injection, there was no difference in HbA1c lowering with Gla-100, whereas with Gla-300 the reduction of HbA1c was greater with morning than with evening injection (difference -0.25% [-0.47 , -0.04]; -2.7 mmol/mol [95% CI -5.2 , -0.4]). Results of eight-point self-measured plasma glucose measurements improved in a similar way in both groups. Basal insulin requirement was 20% higher with Gla-300 than with Gla-100. Overall and nocturnal rates of hypoglycemic events over 12 months were comparable in the two groups and irrespective of injection timing. Adverse event profiles were also comparable.

Conclusions

In people with type 1 diabetes, basal insulin supplementation with Gla-300 offers comparable glucose control as compared with Gla-100 and allows administration any time of the day.

Comparison of insulin glargine 300 units/mL and 100 units/mL in adults with type 1 diabetes: continuous glucose monitoring profiles and variability using morning or evening injections

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Diabetes Care 2017; **40**: 554–560

Background

The aim of this study was to compare daily glucose control archived with insulin glargine 300 U/mL (Gla-300) and glargine 100 U/mL (Gla-100) administered either in the morning or in the evening together with mealtime insulin in adults with type 1 diabetes, using masked continuous glucose monitoring (CGM).

Methods

The study design was a 16-week, open-label, parallel-group, two-period crossover trial. Fifty-nine adults with type 1 diabetes were evenly randomized into four different arms to once-daily Gla-300 or Gla-100 administered in the morning or in the evening. After 8 weeks, the participants crossed over to the alternate timing of the same basal insulin analog. The primary outcome was the mean percentage of time in the optimum target glucose range (defined as 80–140 mg/dL), analyzed from the CGM recordings during the last 2 weeks of each 8-week period. Secondary endpoints included other CGM-based glycemic metrics, hypoglycemic events confirmed by self-measurements of plasma glucose, and adverse events.

Results

There was no difference between Gla-300 and Gla-100 therapies with regard to the mean percentage of time in the target glucose range. The increase in CGM-derived glucose during the last 4 hours of the once-daily injection interval was significantly smaller with Gla-300 than with Gla-100 (least squares mean difference -14.7 mg/dL [95% CI: -26.9 , -2.5]). Mean 24-h glucose curves showed a narrower range of fluctuations with Gla-300 compared with Gla-100, regardless of morning or evening injection. The rate of nocturnal, confirmed hypoglycemia (<54 mg/dL) or severe hypoglycemic events was lower for Gla-300 users than for those with Gla-100 (4.0 versus 9.0 events per patient-year; rate ratio 0.45 [95% CI 0.24, 0.82]).

Conclusions

In comparison with Gla-100, the use of Gla-300 showed less increase in CGM-derived glucose levels during the last 4 hours of the once-daily injection interval, smoother mean 24-h glucose profiles irrespective of morning or evening injection time, and lower frequency of nocturnal hypoglycemic events.

Insulin degludec: lower day-to-day and within-day variability in pharmacodynamics response compared with insulin glargine 300 U/mL in type 1 diabetes

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Diabetes Obes Metab 2017; **19**: 1032–1039

Background

The objective of this study was to compare the pharmacodynamics characteristics, including day-to-day and within-day variability, of insulin degludec (IDeg) and insulin glargine 300 U/mL (IGlar-U300) in adults with type 1 diabetes.

Methods

Participants in this double-blind, crossover study were randomly assigned to administer 0.4 U/kg of IDeg or IGlar-U300 once daily for 12 days. Following a 7–21 days washout period, there was a complete crossover to the other insulin analog during a second 12 day period. Pharmacodynamic parameters were assessed at steady-state from glucose infusion rate profiles obtained during three consecutive 24 h euglycemic glucose clamps at days 6, 9, and 12 during each treatment period.

Results

Fifty-seven participants completed the study protocol (342 clamp sessions). The potency of IGlar-U300 was 30% lower than IDeg (estimated ratio 0.70 [95% CI: 0.61 to 0.80]; $P < 0.0001$). The relative 24 h distribution of the glucose-lowering effect, as assessed across 6 h intervals, was stable for IDeg (24–26%), whereas IGlar-U300 showed more pronounced effects in the first and last intervals (35% and 28%, respectively) compared with the second (20%) and third (17%) 6 h period. Within-day variability was 37% lower with IDeg than with IGlar-U300 (estimated ratio 0.63 [95% CI 0.54 to 0.73]; $P < 0.0001$). The day-to-day variability in glucose-lowering effect was four times lower for IDeg than for IGlar-U300 (variance ratio IGlar-300/IDeg: 3.70 [95% CI: 2.42 to 5.67]; $P < 0.0001$). As assessed in 2 h intervals over 24 h, the day-to-day variability with IDeg was consistently small, whereas it increased gradually with IGlar-U300 to maximum values at the 10–12 h and 12–14 h intervals after administration (variance ratios 12.4 and 11.4, respectively).

Conclusions

Compared with IGlar-U300, IDeg shows lower day-to-day and within-day variability and a more stable glucose-lowering effect. These pharmacodynamics characteristics might simplify insulin titration and allow lower glycemic targets with less risk of hypoglycemia.

Comments

In September 2015, the U.S. FDA approved the ultra-long-acting insulin analog degludec (Tresiba) and the soluble coformulation of insulin degludec/insulin aspart (Ryzodeg) after an interim analysis of a dedicated cardiovascular outcomes trial in patients with type 2 diabetes at high risk of cardiovascular events; the DEVOTE trial. Now, the final results of the completed DEVOTE trial have been published by Marso and coworkers, reassuringly showing no evidence of cardiovascular safety

concerns with insulin degludec. In the trial, insulin glargine U100 was used as comparator, as this basal insulin had previously been shown to have a neutral cardiovascular safety profile in the ORIGIN trial (1). The rate of severe hypoglycemic events was also less apparent with insulin degludec than with glargine U100 in the DEVOTE trial. As extensively reviewed in earlier ATTD Yearbooks, this finding is in line with several previous phase 3 trials in both type 1 and type 2 diabetes cohorts where the frequency of hypoglycemia—and especially nocturnal hypoglycemia—was lower with insulin degludec therapy than with glargine U100. More recently, this was also corroborated in two short-term, cross-over designed trials in type 1 (2) and type 2 diabetes (3).

Regarding the use of the premixed combination of insulin degludec and insulin aspart and risk of hypoglycemia in type 2 diabetes, the data are less consistent. This may partly be explained by the chosen comparator insulin and timing of the insulin administration, and probably also by the characteristics of the included participants (i.e., insulin-naïve, switch from other types of insulin regimens, combination therapy with other antidiabetic drugs, and so on), and—as shown by Park and coworkers—by the type of titration algorithm used. In the referenced study by Kumar et al., type 2 diabetic subjects with inadequate glycemic control using basal insulin once-daily (detemir, glargine U100, or NPH insulin) plus metformin, and in most cases additional OADs, were included and randomized to once-daily insulin degludec/aspart or glargine U100 administered with the main meal together with preexisting OADs. Perhaps not surprisingly given the rapid-acting insulin aspart component of the coformulation, the rate of overall confirmed hypoglycemia was higher with Ryzodeg than with Lantus, whereas there was no difference in frequency of nocturnal confirmed hypoglycemia. In another recently published trial with similar design, where insulin-naïve people with type 2 diabetes were assigned either degludec or glargine once-daily together with metformin, the total daily rate of confirmed hypoglycemic events was 86% higher and the frequency of nocturnal confirmed hypoglycemia 75% lower after 52 weeks with Ryzodeg versus Lantus (4). Evidently, the generalizability of findings from a single trial in type 2 diabetes should be considered cautiously.

Previous yearbook articles have also reviewed in detail the trials assessing the efficacy and safety of the newer, more concentrated insulin glargine U300 analog (Toujeo), which offers a smoother and more protracted pharmacodynamics profile. While reduced risk of hypoglycemia—and in particular nocturnal hypoglycemia—has been verified in several trials composed of various cohorts with type 2 diabetes, the data concerning type 1 diabetes have been more variable. Similar rates of overall and nocturnal hypoglycemic events were registered in the first phase 3 randomized controlled EDITION 4 trial in type 1 diabetes (5), and the same findings were observed in the presently referenced extension study by Home and co-workers after one year.

By contrast, another trial in Japanese adults with type 1 diabetes showed significant reductions in confirmed hypoglycemic events at any time of the day and in particular during nighttime (6). Accordingly, the study by Bergenstal et al. using masked CGM recordings observed less daily fluctuations in glucose control together with reduced nocturnal confirmed hypoglycemia. Seemingly, more data are required to fully elucidate the effectiveness of Toujeo on reducing the risk of hypoglycemia in type 1 diabetes, preferably with the use of CGM to reveal clinically important improvements in daily glucose control and variability.

The fact that both ultra-long-acting insulin analogs Tresiba and Toujeo are now available globally for clinical use makes it highly desirable to have a direct, head-to-head comparison between the two. The data provided by Heise and coworkers, in their extensive assessment of the pharmacodynamic profiles of the two analogs (altogether 342 24-h euglycemic clamps in 57 participants with type 1 diabetes during the short-term cross-over study) suggest that insulin degludec has lower day-to-day and within-day variability than insulin glargine U300. Whether these findings translate into clinical benefits in terms of less glucose variability and risk of hypoglycemia, and therefore a greater likelihood to achieve more stringent glycemic targets, remains to be proven in randomized, controlled trials.

SMART INSULINS ON THE HORIZON?

Hypoxia and H₂O₂ dual-sensitive vesicles for enhanced glucose-responsive insulin delivery

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Nano Lett 2017; **17**: 733–739

Background

This study describes the development of a glucose-responsive insulin delivery system that imitates endogenous beta-cell activity.

Methods

The device was composed of a painless microneedle-array patch containing vesicles loaded with insulin and sensitive to

hypoxia and H_2O_2 generated by glucose conversion by glucose oxidase. This in turn facilitates a solubility switch of the polymersome-based vesicles and insulin release.

Results

In vivo experiments in diabetes mice using this device showed effective regulation of glucose control for 10 h in mice with streptozotocin-induced diabetes.

Conclusions

The findings suggest that this smart insulin patch shows potential for a glucose-responsive insulin delivery system.

Red blood cells for glucose-responsive insulin delivery

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Background

This report describes the development of a new glucose-responsive insulin delivery system that utilizes the cell membrane of erythrocytes.

Methods

A glucose derivative-modified insulin was constructed by conjugating glucosamine to insulin. This Glc-insulin effectively binds to erythrocyte cell membranes (probably to glucose transporter molecules). This binding is reversible, and the Glc-insulin, which retains its normal glucose-lowering effect, is rapidly released by competitive interaction of free glucose to the transporter protein when circulating glucose levels are increasing.

Results

In vitro experiments demonstrated reversible binding of Glc-insulin and membranes, and rapid release of insulin from the cellular carriers. A glucose-responsive release of insulin from the erythrocytes resulting in blood glucose lowering was also shown in *in vivo* experiments in mice with streptozotocin-induced diabetes.

Conclusions

This glucose-responsive insulin delivery system is the first to utilize erythrocyte membranes to attain rapid insulin release.

Comments

The development of a smart glucose-responsive insulin delivery system that can mimic the normal beta-cell to regulate the release of insulin according to the ambient circulating glucose level has been an area of research interest for many years, and in March 2016 the Juvenile Diabetes Research Foundation together with Sanofi agreed on a major investment for funding to support researchers in this field. One such smart insulin candidate from Merck Sharp & Dohme entered a phase 1 human trial a couple of years ago to assess its safety and pharmacokinetics and pharmacodynamics. According to ClinicalTrials.gov, the study was completed in August 2016, but up to now no data have been published.

The presently referenced publications describe two different smart insulin concepts: one with an external microneedle device that delivers insulin-containing vesicles sensitive to hypoxia and H_2O_2 which release insulin in response to enzymatic conversion of glucose, and another that utilizes red blood cells that bind a glucose derivate-modified insulin that can be rapidly released from the cell membrane by competitive interaction of free glucose to the binding sites. Both concepts were tested in short-term *in vivo* experiments in diabetic mice, and proved to effectively regulate blood glucose control.

While there is still a long way to go until the smart insulin concept might be a clinical reality, the data are encouraging and further developments in this area will most certainly be covered in future Yearbooks.

BIOSIMILAR INSULIN

Duration of action of two insulin glargine products, LY2963016 insulin glargine and Lantus insulin glargine, in subjects with type 1 diabetes mellitus

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Background

The insulin glargine products LY2963016 (LY IGLar) and Lantus (IGlar) are manufactured using different processes but with identical amino acid sequences. In a glucose clamp study of patients with type 1 diabetes mellitus (T1DM), the duration of action of both insulins were compared.

Methods

Twenty patients participated in this randomized, double-blind, single-dose, two-period, crossover 42 hour euglycemic clamp study. The patients received a single subcutaneous 0.3 U/kg dose of either LY IGLar or IGLar insulin. Duration of action was defined as the time required for blood glucose levels to rise consistently above a predefined cutoff of 8.3 mmol/L (150 mg/dL) from euglycemic glucose levels.

Results

End of action was reached within 42 hours in 26 of 40 clamps (13 LY IGlár and 13 IGlár). Mean duration of action (calculated using only patients who reached end of action) was 23.8 and 25.5 hours and median duration of action for all subjects was 37.1 and 40.0 hours for LY IGlár and IGlár respectively. The duration of action was similar between the treatments using time-to-event analysis (log-rank test of equality $P=0.859$).

Conclusion

LY IGlár and IGlár had similar duration of action and comparable pharmacodynamic parameters in subjects with T1DM.

Comments

This publication adds to similar publications from the previous year in which pharmacokinetic (PK) and pharmacodynamic (PD) properties of the first approved BioIns were studied in glucose clamp studies with healthy studies. These data add to the totality of evidence that this BioIns is quite similar to the originator insulin. However, again the variability of the individual responses observed also highlights the magnitude to which these differ.

Similar pharmacokinetics and pharmacodynamics of rapid-acting insulin lispro products SAR342434 and US- and EU-approved Humalog in subjects with type 1 diabetes

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Diabetes Obes Metab 2017; **19**: 622–627

Background

This study compared the pharmacokinetic (PK) and pharmacodynamic (PD) properties of three rapid-acting insulin lispro analogs: SAR342434, U.S.-approved Humalog, and EU-approved Humalog.

Methods

A single-center, randomized, double-blind, three-treatment, three-period, six-sequence, crossover, euglycemic clamp study was carried out in 30 adult male patients with type 1 diabetes. Participants were randomized to receive 0.3 U/kg of one of the three insulins under fasted conditions. Glucose clamps lasted up to 12 hours.

Results

Mean serum insulin concentration [insulin (INS)-C] and glucose infusion rate (GIR) profiles were similar for all three insulins. Exposure (INS-C_{max}, INS-AUC_{last}, and INS-AUC) and activity (GIR_{max} and GIR-AUC_{0–12h}) were similar as well (point estimates of treatment ratios, 0.95–1.03 and 1.00–1.07 for PK and PD parameters respectively). For the ratios of

geometric least squares means, the 90% CIs were within the prespecified bioequivalence limit [0.80, 1.25]. Across the clamps, within-subject variability of exposure and activity was low, signifying high day-to-day reproducibility in clamp performance. Additionally, adverse events were similar across all three insulin products.

Conclusions

This study showed similarity in PK and PD profiles for all three insulin lispro versions, supporting the use of SAR342434 as a BioIns.

Efficacy and safety of biosimilar (SAR342434 insulin lispro) in adults with type 1 diabetes also using insulin glargine-SORELLA 1 study

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Diabetes Technol Ther 2017; **19**: 516–526

Background

SAR342434 (SAR-Lis) is a biosimilar (follow-on) of Humalog insulin lispro (Ly-Lis). The objective of this study was to show that the two have similar safety, efficacy, and immunogenicity in adult type 1 diabetes (T1DM) patients treated with multiple daily injections while using basal insulin glargine (Lantus; GLA100GLA-100).

Material and Methods

SORELLA-1 (clinical trial number NCT02273180) was a 6-month, randomized, open-label phase 3 study with a 6-month safety extension. Patients who completed the main study continued, as randomized, on SAR-Lis or Ly-Lis for the 6-month extension. Data were gathered regarding change in HbA1c, fasting plasma glucose (FPG), seven-point self-monitored plasma glucose (SMPG) profiles, hypoglycemic events, treatment-emergent adverse events (TEAEs), and anti-insulin antibodies (AIA).

Results

In total, 507 patients were randomized (n=253 for SAR-Lis; n=254 for Ly-Lis). At week 26 (from baseline; primary endpoint) the change in HbA1c least square mean (LS [standard error]) was similar in both treatment groups (SAR-Lis, −0.42% [0.051]; Ly-Lis, −0.47% [0.050]). Noninferiority at prespecified 0.3% noninferiority margin and inverse noninferiority were demonstrated (LS mean difference of SAR-Lis vs. Ly-Lis, 0.06% [95% CI −0.084, 0.197]). At the end of the extension period (week 52), a small increase in HbA1c (vs. week 26) was observed in both groups. FPG and seven-point SMPG profile changes, including postprandial glucose excursions, were similar between groups. Similar changes in basal insulin doses and mean daily mealtime were observed at week 52, and TEAEs,

TABLE 1. BIOSIMILAR BASAL INSULIN

<i>Sponsor</i>	<i>Drug Name</i>	<i>Type</i>	<i>Status</i>	<i>Timeline</i>
Lilly/Boehringer Ingelheim	Basaglar/Abasaglar	Biosimilar insulin glargine	Approved	Launched ex-U.S. as Abasaglar; approved in United States and will launch December 15, 2016, under terms of patent lawsuit settlement agreement with Sanofi
Biocon/Mylan	Undisclosed	Biosimilar insulin glargine	Phase 3	U.S. and EU filing expected by end of year; launched in Japan (where it's not partnered with Mylan)
Merck	Lusduna	Biosimilar insulin glargine	Approved	Phase 3 data presented at ADA 2016; Approved in EU; NDA filed August 2016 with U.S. FDA decision expected June 2017; Sanofi files patent infringement lawsuit September 2016
Arecor	Insulin glargine with improved thermostability	Biosimilar insulin glargine	Preclinical	Preclinical program listed on company website
Arecor	Ultra-long-acting insulin glargine	Biosimilar insulin glargine	Preclinical	Preclinical program listed on company website

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hypoglycemia, and AIAs (incidence, prevalence) did not differ between the two groups.

Conclusions

This controlled study found similar efficacy and long-term safety (including immunogenicity) for SAR-Lis and Ly-Lis in adults with T1DM also using GLA-100.

Comments

It is of interest to note that Sanofi is the first company that will bring a BioIns of a prandial insulin to market. It is this company's basal insulin that most other companies are "copying" to create their own BioIns.

COMMENTS ON BIOSIMILARS

In the last year another insulin glargine (Lusduna) developed by Merck-USA received market approval as a BioIns in the EU and the US; however, Lusduna is not on the market yet. The results of the clinical studies performed with Lusduna were not published until now. More BioIns of insulin glargine are known to have progressed considerably in clinical development; for example, a BioIns by Biocon might get market approval soon (Tables 1 and 2). Also, the first BioIns of the rapid-acting insulin analog insulin lispro

(SAR342434 developed by Sanofi) has got market approval in the EU and the United States.

It remains to be seen whether the introduction of more BioIns will induce more drastic changes in the insulin market, as these newcomers will try to gain market share. It is worth mentioning that only with production of a certain amount of insulin per year (> 100 kg?) is it worth doing so. If the various companies do not reach such a level, there is a risk that they might withdraw from the market in the long run. The market uptake of the different BioIns will also depend on the pressure put behind a lowering of insulin prices by insurance companies and/or the health-care system in the given countries (7). There is an ongoing discussion about the high insulin prices in the United States; however, it has become clear that the price increases for originator insulins in the United States was not driven by the manufacturer companies alone, but also by the pharmacy benefit managers. When it comes to cost of insulin therapy, each country has its own complex reimbursement system for drugs in place, which makes it difficult to compare the situation (=price) in one country with that in another country.

Clinical experience

It is of interest to note that no reports about the clinical experience of patients with diabetes using Basaglar/Abasaglar in daily practice were published until now. No new data about immunological aspects of BioIns were published in the last

TABLE 2. BIOSIMILAR RAPID-ACTING INSULINS

<i>Sponsor</i>	<i>Drug Name</i>	<i>Type</i>	<i>Status</i>	<i>Timeline</i>
Sanofi	Insulin Lispro Sanofi (R)	Biosimilar insulin lispro (Lilly's Humalog)	Approved in Europe	On the market in Germany since October 2017
Biocon	Undisclosed	Biosimilar insulin lispro (Lilly's Humalog)	Preclinical	Preclinical program listed on company website
Biocon	Undisclosed	Biosimilar insulin aspart (Novo Nordisk's NovoLog)	Preclinical	Phase 1 study being planned

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year. Also, no data about the quality of different batches of (originator) insulins and BioIns were published.

Interchangeability

Switching from one insulin to another is a decision made by the treating physician, to exchange one insulin for another with the same therapeutic intent in a given patient (8). Interchangeability refers to the practice of substituting one insulin for another that is expected to achieve the same blood glucose lowering effect in any patient with diabetes on the initiative or with the agreement of the physician. This requires that the insulin can be regarded as interchangeable (i.e., as a property of a given insulin). In contrast, substitution is a process at the pharmacy level in which another insulin (a BioIns) is dispensed instead of the prescribed insulin without consulting the prescribing physician. Currently there is no “substitutability determination” in the EU; that is, there is no automatic substitution in practice in the EU whereby a pharmacist is obliged to dispense a BioIns instead of a prescribed insulin. Interesting differences exist between individual U.S. states when it comes to guidelines for market allowance of BioIns. Early in 2017 the FDA issued drafts of guidelines for interchangeability. No BioIns fulfill these requirements and Eli Lilly has not tried to get approval for Basaglar as an interchangeable BioIns.

Devices

In daily practice for patients, diabetologists, and nurses, the devices (most often insulin pens) used for application of insulin are of high relevance (9,10). Each manufacturer of BioIns comes to the market with a combination of their insulin glargine with an insulin pen. The switch from the pen(s) of the originator insulin to another one is associated with an additional teaching and training burden for the diabetes team. Such aspects are of high relevance from a practical point of view.

Clinical trials

Only two original articles reporting data from clinical trials with BioIns were published in the last year (11,12). However, some comments and reviews were published about BioIns, mainly focusing on the situation in other countries, for example, Germany (13,14) and Europe (15), or more general to the introduction of BioIns (7,16). Also, preclinical data for Abasaglar were published (17).

Knowledge about BioIns

One relatively small study (with 58 diabetologists) was published in which the knowledge of physicians about biosimilars and BioIns appeared to be relatively good (18). However, there is a high risk with such surveys (selection bias), and it might very well be that the knowledge differs between specialties and countries.

Summary

Compared with other indication areas (oncology, rheumatology, dermatology, etc.) it is a relatively late event that biosimilars for diabetes and BioIns became available. We have to see whether the market introduction of more BioIns

will change the situation. What is missing is a dialogue about this topic with patients, politicians, etc. Also, it is annoying that the medical associations have not made any position statements about BioIns. The availability of different BioIns might lower the price for insulin, making it more accessible and affordable for many patients with diabetes. However, this expansion of the repertoire for insulin therapy will also lead to some confusion for users, as there will be a number of insulins on the market with the term glargine in their name. We have to see how the naming of products will be handled; differences in naming between countries would increase the chance for confusion, and this in turn might also have an impact on the reporting of any side effects observed (i.e., pharmacovigilance).

ULTRA-RAPID INSULINS: THE FIRST-IN-CLASS IS ON THE MARKET

A pooled analysis of clinical pharmacology trials investigating the pharmacokinetic and pharmacodynamic characteristics of fast-acting insulin aspart in adults with type 1 diabetes

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Background

Fast-acting insulin aspart (faster aspart) is a new formulation of insulin aspart (IAsp) developed to more closely mimic the rapid release of endogenous prandial insulin than other currently available insulin analogs. The aim of this *post hoc* analysis was to compare the pharmacological characteristics of faster aspart and IAsp using pooled data from six clinical pharmacology trials.

Methods

Data from six randomized, double-blind, crossover trials comprising 218 adult subjects with type 1 diabetes were included in the analysis. In all trials, participants received 0.2 U/kg of faster aspart and IAsp via subcutaneous dosing. In the three trials included in the pharmacodynamic analysis, a 12-h euglycemic clamp was performed (target 5.5 mmol/L; 100 mg/dL).

Results

The pharmacokinetic and pharmacodynamic profiles were shifted to the left for faster aspart compared with IAsp. Onset of appearance was 4.9 min earlier for faster aspart vs. IAsp [95% CI −5.3, −4.4], $P < 0.001$), offset of exposure ($t_{\text{Late } 50\% \text{ C}_{\text{max}}}$) occurred 12.2 min earlier [−17.9, −6.5] ($P < 0.001$), and early exposure ($\text{AUC}_{\text{IAsp}, 0-30\text{min}}$) was twice as great (estimated ratio faster aspart/IAsp, 2.01 [1.87, 2.17], $P < 0.001$). Consequently, onset of action occurred 4.9 min earlier [−6.9 to −3.0] ($P < 0.001$), offset of glucose-lowering effect ($t_{\text{Late } 50\% \text{ GIR}_{\text{max}}}$) took place 14.3 min earlier [−22.1, −6.5] ($P < 0.001$), and early glucose-lowering effect

(AUC_{GIR,0-30min}) was 74% greater (1.74 [1.47, 2.10], $P < 0.001$) for faster aspart compared with IAsp. There was not a significant difference in total exposure or total glucose-lowering effect between treatments.

Conclusions

In adults with type 1 diabetes, faster aspart has the potential to more closely mimic the pattern of endogenous prandial insulin secretion in healthy adults and thereby to improve postprandial glucose control versus IAsp.

Faster-acting insulin aspart provides faster onset and greater early exposure vs. insulin aspart in children and adolescents with type 1 diabetes mellitus

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This manuscript is also discussed in the article on Diabetes Technology and Therapy in the Pediatric Age Group, page S-114.

Background

Faster-acting insulin aspart (faster aspart) is insulin aspart (IAsp) with additional excipients (L-arginine and niacinamide). This new formulation allows faster aspart to provide more rapid onset and higher early exposure and action in adult patients compared with IAsp.

Aim

The pharmacological properties of faster aspart vs. IAsp were investigated in a randomized, double-blind, two-period crossover trial of 40 patients with type 1 diabetes mellitus: 12 children (6–11 years), 13 adolescents (12–17 years), and 15 adults (18–64 years).

Methods

Immediately prior to a standardized meal (17.3 g carbohydrate/100 mL; amount adjusted by body weight), each participant received 0.2 U/kg subcutaneous dosing (mean of 8.3, 12.8, and 15.6 U for children, adolescents, and adults, respectively).

Results

For faster aspart vs. IAsp, onset of appearance occurred 5–7 minutes earlier (about twice as quickly) and early exposure (AUC_{IAsp,0-30min}, area under the IAsp curve from 0 to 30 minutes) increased by 78–147% consistently across age groups, with no treatment differences in total exposure (AUC_{IAsp,0-t}) or maximum concentration (C_{max}). Additionally, two-hour postmeal plasma glucose excursion was less for faster aspart vs. IAsp; however, statistical significance was only reached in children. AUC_{IAsp,0-t} for faster aspart was lower in children vs. adults (estimated ratio children/adults

0.59 [95% CI 0.50, 0.69], $P < 0.001$) and adolescents vs. adults (0.78 [0.67, 0.90], $P = 0.002$), in accordance with the absolute dose for each age group. There were no age group differences in C_{max} (0.91 [0.70, 1.17], $P = 0.445$, and 0.99 [0.77, 1.26], $P = 0.903$), and the age effect on AUC_{IAsp,0-t} and C_{max} did not differ statistically significantly between treatments. Both faster aspart and IAsp were tolerated well.

Conclusion

Previous studies have shown the benefits of faster aspart vs. IAsp in adults. The results of this trial in children and adolescents suggest that faster aspart has potential to improve postprandial glycemia over current rapid-acting insulins in younger age groups as well.

Fast-acting insulin aspart improves glycemic control in basal-bolus treatment for type 1 diabetes: results of a 26-week multicenter, active-controlled, treat-to-target, randomized, parallel-group trial (onset 1)

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Objective

A multicenter, treat-to-target, phase 3 trial was conducted in adult patients with type 1 diabetes to evaluate the safety and efficacy of fast-acting insulin aspart (faster aspart) compared with conventional insulin aspart (IAsp).

Research Design and Methods

Following the conclusion of an 8-week run-in, participants underwent double-blind, randomized assignment (1:1:1) to mealtime faster aspart (n = 381), IAsp (n = 380), or open-label postmeal faster aspart (n = 382), each with insulin detemir. The primary endpoint was change in HbA1c from baseline to 26 weeks.

Results

In both treatment groups, HbA1c was reduced, and the reduction was statistically significant for mealtime faster aspart

vs. IAsp ($P=0.0003$). Both mealtime and postmeal faster aspart were confirmed as noninferior to IAsp (estimated treatment difference [ETD] faster aspart-IAsp: mealtime, -0.15% [95% CI $-0.23, -0.07$]; postmeal, 0.04% [$-0.04, 0.12$]). Postprandial plasma glucose (PPG) increments were statistically significantly lower with mealtime faster aspart at both 1 and 2 hours after the meal test (1-h ETD -1.18 mmol/L [95% CI $-1.65, -0.71$], -21.21 mg/dL [$-29.65, -12.77$], $P<0.0001$; 2-h ETD -0.67 mmol/L [$-1.29, -0.04$], -12.01 mg/dL [$-23.33, -0.70$], $P=0.0375$) and for PPG at 2 h, mealtime faster aspart was confirmed superior to IAsp. Safety profiles were similar between treatments, as were the overall rates of severe or blood glucose-confirmed (plasma glucose <3.1 mmol/L [56 mg/dL]) hypoglycemic episodes.

Conclusions

Faster aspart improved HbA1c effectively, and superior PPG control with mealtime faster aspart demonstrated its noninferiority to IAsp. Participants who received postmeal faster aspart for all meals maintained HbA1c noninferior to that obtained with mealtime IAsp.

Faster aspart versus insulin aspart as part of a basal-bolus regimen in inadequately controlled type 2 diabetes: the onset 2 trial

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Diabetes Care 2017; **40**: 951–957

Objective

A multicenter, double-blind, treat-to-target, phase 3 trial was carried out in adult patients with type 2 diabetes receiving basal insulin and oral antidiabetic agents to examine the safety and efficacy of fast-acting insulin aspart (faster aspart) vs. insulin aspart (IAsp).

Research Design and Methods

An 8-week run-in was conducted to optimize basal insulin. After the run-in participants were randomized in equal proportions to either mealtime faster aspart ($n=345$) or IAsp ($n=344$), titrated using a simple daily patient-driven algorithm, along with insulin glargine U100 and metformin. HbA1c change from baseline after 26 weeks of treatment was the primary endpoint.

Results

HbA1c decreased by 1.38% with faster aspart and by 1.36% with IAsp. The mean HbA1c for both groups was 6.6% . Faster aspart was found to be noninferior in reducing HbA1c

vs. IAsp (ETD [95% CI] -0.02% [$-0.15, 0.10$]). Postprandial plasma glucose (PPG) control was improved with both treatments. For faster aspart, results of the PPG increment/liquid meal test were statistically significant after 1 h (ETD -0.59 mmol/L [$-1.09, -0.09$]; -10.63 mg/dL [$-19.56, -1.69$]; $P=0.0198$) but not after 2–4 h. In body weight, fasting plasma glucose, and overall severe/blood glucose-confirmed hypoglycemia change in rates from baseline (rate ratio [95% CI] 1.09 [$0.88, 1.36$]) were similar between treatments. The postmeal (0–2 h) hypoglycemia rate for faster aspart was 2.27 and for IAsp 1.49 per patient-year of exposure (rate ratio 1.60 [$1.13, 2.27$]).

Conclusions

Both faster aspart and IAsp were confirmed noninferior for HbA1c change from baseline in a basal-bolus regimen. Faster aspart improved PPG at 1-h but at 2 h and 4 h showed no differences vs. IAsp. Hypoglycemia rates were similar overall except for an increase in 0- to 2-h postmeal hypoglycemia with faster aspart.

Adding fast-acting insulin aspart to basal insulin significantly improved glycaemic control in patients with type 2 diabetes: a randomized, 18-week, open-label, phase 3 trial (onset 3)

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Diabetes Obes Metab 2017; **19**: 1389–1396

Aim

An onset 3 trial was conducted to confirm that mealtime fast-acting insulin aspart (faster aspart) in a basal-bolus (BB) regimen provides superior glycemic control vs. basal-only insulin.

Material and Methods

This was a randomized, open-label, 18-week trial across 51 sites in 6 countries. Participants were adults ($n=236$) with inadequately controlled type 2 diabetes (T2D; mean HbA1c $\pm$ SD: $7.9 \pm 0.7\%$ [63.1 ± 7.5 mmol/mol]) receiving basal insulin and oral antidiabetic drugs. Following an 8-week optimization of prior once-daily basal insulin, participants were randomized 1:1 to begin a BB regimen with faster aspart ($n=116$) or to continue their once-daily basal insulin ($n=120$), both with metformin. HbA1c change from baseline after treatment for 18 weeks was the primary endpoint. Postprandial plasma glucose (PPG) change and overall PPG increment (all meals), treatment-emergent adverse events, body weight, and hypoglycemic events were secondary endpoints.

Results

In all, 94.1% of participants completed the trial. In the BB group HbA1c decreased from 7.9% (63.2 mmol/mol) to 6.8%

(50.7 mmol/mol), while in the basal-only group HbA1c decreased from 7.9% (63.2 mmol/mol) to 7.7% (60.7 mmol/mol); estimated treatment difference [95% CI] -0.94% [-1.17 , -0.72]; -10.3 mmol/mol [-12.8 , -7.8]; $P < 0.0001$. For all meals, reductions in overall mean 2-hour PPG and overall PPG increment from baseline (self-measured plasma glucose profiles) were statistically significant in favor of BB treatment ($P < 0.0001$). The rate of severe/blood glucose-confirmed hypoglycemia (12.8 vs. 2.0 episodes per patient-years of exposure) was higher with BB vs. basal-only treatment. Total daily insulin (1.2 vs. 0.6 U/kg) was also greater with BB than with basal-only treatment, as was weight gain (1.8 vs. 0.2 kg).

Conclusions

In adults with T2D, faster aspart in a BB regimen provided superior glycemic control vs. basal-only insulin, although patients using the BB regimen also experienced modest weight gain and an increased frequency of hypoglycemia.

Improved postprandial glycemic control with faster-acting insulin aspart in patients with type 1 diabetes using continuous subcutaneous insulin infusion

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Diabetes Technol Ther 2017; **19**: 25–33

This manuscript is also discussed in the article on Insulin Pumps, page S-30.

Background

Faster aspart is insulin aspart (IAsp) in a new formulation that contains the excipients niacinamide (vitamin B3) and L-arginine. When used in continuous subcutaneous insulin infusion (CSII) in subjects with type 1 diabetes, faster aspart has shown a faster onset and offset of glucose-lowering effect compared with IAsp.

Methods

A double-blind, randomized, crossover active-controlled trial was conducted in patients with type 1 diabetes. After 2 weeks of treatment using CSII with faster aspart or IAsp, 2-h postprandial plasma glucose (PPG) responses were compared. Participants ($n = 43$) had masked continuous glucose monitoring (CGM) throughout the study period. The primary endpoint was mean change in PPG 2 h after a standardized meal test ($\Delta\text{PG}_{\text{av},0-2\text{h}}$).

Results

The glucose-lowering effect following a standardized meal was statistically significantly greater for faster aspart vs. IAsp: $\Delta\text{PG}_{\text{av},0-2\text{h}}$ 3.03 mmol/L vs. 4.02 mmol/L (54.68 mg/dL vs. 72.52 mg/dL); estimated treatment difference (ETD) [95% CI] -0.99 mmol/L [-1.95 , -0.03] (-17.84 mg/dL [-35.21 , -0.46]; $P = 0.044$). PG levels at 1 h postmeal were -1.64 mmol/L (-29.47 mg/dL) lower with faster aspart vs. IAsp ($P = 0.006$). These findings were affirmed by the inter-

stitial glucose (IG) profiles: the largest differences in IG were observed at breakfast: 9.08 mmol/L for faster aspart vs. 9.56 mmol/L for IAsp (163.57 vs. 172.19 mg/dL; ETD -0.48 mmol/L [-0.97 , 0.01]; -8.62 mg/dL [-17.49 , 0.24]; $P = 0.057$). Periods of low IG levels (≤ 3.9 mmol/L [70 mg/dL] per 24 h) were statistically significantly shorter with faster aspart than with IAsp (2.03 h vs. 2.45 h; ETD -0.42 [-0.72 , -0.11]; $P = 0.008$). No unexpected safety findings were observed.

Conclusions

After a meal test, CSII delivery of faster aspart had lowered glucose more effectively than IAsp, resulting in less time spent with low IG levels. CGM results recorded throughout all meals supported this finding.

Comments

Fiasp's global progress is a very positive sign for insulin users looking to improve their mealtime glycemia. The pharmacokinetic and pharmacodynamic results of the individual phase 1 studies as well as the pooled analysis by Heise *et al.* revealed a uniform pharmacological picture. It has been preserved in children and adolescents as can be seen in the paper from Fath *et al.*, although the clinical pediatric regulatory study is still ongoing. In faster aspart, insulin was detectable twice as fast in the blood compared with injection of IAsp, and also the insulin concentration in the first 30 minutes was doubled or, when administered via CSII, tripled against IAsp. The glucose-lowering effect, measured by GIR, was increased by 74% for subcutaneous administration in these 30 minutes and by about 100% when using CSII. The more pronounced pharmacological effects in CSII compared with the subcutaneous administration route may be due to the continuous influx of niacinamide by the insulin basal rate.

The new insulin has a faster onset and offset than IAsp, meaning it should better control initial postmeal spikes in blood sugar and cause less hypoglycemia hours later. In standardized meal tests, improved pharmacological properties resulted in improved postprandial glycemic control, both in subcutaneous injection and in CSII (Bode *et al.*). For the standardized meal tests in three phase 1 studies, mean reductions of blood glucose of 1.0 to 1.5 mmol/L (18 to 27 mg/dL) were achieved with faster aspart in the first 2 hours, compared with IAsp.

Compared with those using IAsp, Fiasp users also saw slight A1c improvements in several studies, without a higher likelihood of severe hypoglycemia. Significantly better postprandial plasma glucose values 1 and 2 hours after a standardized meal when both insulins were used for the meal were also found in the clinical phase 3a study onset 1 trial in people with type 1 diabetes. In addition, in the onset 1 study, after 26 weeks the HbA1c value was improved by 0.15% by faster aspart compared with IAsp. Thus, an average HbA1c improvement was already achieved in the first major clinical study to the same extent that the Cochrane meta-analysis comparing short-acting insulin analogues in relation to human insulin (19) has been reported.

This also brings a convenience and flexibility win: Fiasp taken 20 minutes after the start of a standardized meal was as effective for HbA1c reduction as insulin aspart administered at mealtime and as effective for postprandial glucose lowering effect 2 hours after the meal as NovoRapid/NovoLog taken just before mealtime.

In patients with type 2 diabetes and multiple daily injections, the HbA1c reduction between faster aspart and IAsp was comparable in the clinical phase 3a study onset 2 after 26 weeks, whereas the standardized meal test showed a significantly reduced postprandial blood glucose increase in hour 1, while the hour 2 value had no difference (Bowering *et al.*, onset 2).

In both type 1 diabetes (onset 1) and type 2 diabetes (onset 2), overall hypoglycemia rate and weight development were comparable between faster aspart and IAsp. Comparable hypoglycemic rates were previously also found between short-acting insulin analogues and human insulin (19).

By further approximating the pharmacological profile to the physiological insulin profile and based on the first data from two phase 3a studies, a potential for an additional benefit of faster aspart compared with currently available short-acting insulin analogues is to be expected. This applies in particular to pump therapy (CSII). However, results of clinical phase 3 studies on faster aspart in CSII are still lacking.

A fast-acting insulin can also offer an advantage for the development of high-speed or fully automated insulin application systems (i.e., closed-loop systems) (20), since the algorithms for automatic insulin application with the previously available insulins do not yet have an optimal balance of postprandial control while avoiding hypoglycemia. In addition, compared with IAsp, faster aspart could provide more flexibility in meal scheduling, offering improved options for postprandial administration with similar effectiveness as insulin aspart given at the meal. This may be of particular importance for certain patient groups with difficulties foreseeing food intake during meals (e.g., toddlers or fussy eaters).

While the FDA regulatory process differs from international regulatory processes, hopefully Fiasp's approval in Canada and in European countries will help the drug's future in the United States. If approved, it is also expected that Fiasp could be rapidly included in automated insulin delivery studies, since faster insulin could enable better automated control after meals. Regarding the other ultra-rapid insulins, such as Bio-Chaperone Lispro or LY900014, so far only abstracts from congress presentations are available.

With this first-in-class ultra-rapid insulin conventionally assessed blood glucose levels an hour after mealtime averaged about 10 mg/dL lower. With CGM outcome reporting becoming more standardized hopefully future trials of ultra-rapid insulin analogs or adjunct therapies to insulin will use the advanced metrics of assessing continuous glucose data (21). There is now widespread agreement that the identification of hypoglycemia is as important as the measurement of time in and out of range in clinical trials. Quantifying the duration and magnitude

of hypo- and hyperglycemic excursions provides another means of assessing glucose control and should be uniformly reported when studying new insulins, biosimilars, and insulin therapy.

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Lutz Heinemann is a consultant for a number of companies that develop novel diagnostic and therapeutic options for the treatment of patients with diabetes. He owns shares of the Profil Institut für Stoffwechselforschung, Neuss, Germany and ProSciento, San Diego, CA.

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