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ORIGINAL ARTICLE

New Insulins, Biosimilars, and Insulin Therapy

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Introduction

EXTENDING THE DURATION of action of basal insulins and shortening the time to peak action of fast-acting insulins may have advantages for many individuals with type 1 and type 2 diabetes. This year's attention focused on the long-acting analogs insulin degludec (Tresiba®) and U300 insulin glargine (Toujeo®) as large studies have been published and these insulins became available for many patients. This may take longer for another long-acting analog, peglispro, as Lilly announced a delay in their planned submission to FDA and EMA for market approval. But just how much these incremental improvements mean for the daily lives of the patients and at what cost for the health-care system is discussed vividly during the recent scientific meetings. This cost-effectiveness discussion will become even more intense as biosimilar insulins will become available like the glargine product developed by Eli Lilly and Boehringer Ingelheim (Abasaglar®), which has received market authorization in 2014. In contrast, the discussion on the long-term safety of the approved new insulins that has been the part of many recent yearbook articles has quieted down. Presently no worrisome safety signals have become available. As we reported last year, technosphere inhaled insulin (Afrezza®) has been approved for use in patients with type 1 and type 2 diabetes, but long-term studies of pulmonary safety and surveillance for malignancy as well as studies to assess the optimal time-dosing regimen are still needed, so that Afrezza® did not have a major impact on clinical practice yet. On the horizon are ultra-fast-acting insulins, fast-acting insulin aspart (FiAsp, NovoNordisk), BioChaperone® Lispro, and HinsBet®. Presently no new information became available on the citrate/zinc-ion chelator combination employed by Biodel, Inc., reported in earlier articles.

The first full article on FiAsp, containing the excipients nicotinamide and L-arginine to speed up the monomer formation, was published recently. It indicated approximately twice as fast an onset of appearance in the bloodstream and two-fold higher early exposure within the first 30 minutes. We look forward to the results of the phase 3 trials of this ultra-fast insulin, which is likely to be the first of its kind to be approved, possibly as early as next year. Finally, as a long shot, new approaches to achieve a smart insulin have received a lot of attention in recent months. This is a form of insulin that circulates in the bloodstream or is deposited in the subcutaneous tissue and turns on when it's needed to lower blood sugars and off when blood sugars are at safe levels. Twenty years after the introduction of Lispro as the first commercially available rapid-acting insulin analog, the pipeline of new insulins for diabetes therapy remains exciting.

Key Articles Reviewed for this Article

New insulin glargine 300 units · mL^{-1} provides a more even activity profile and prolonged glycemic control at steady state compared with insulin glargine 100 units · mL^{-1}

Becker RH[1], Dahmen R[1], Bergmann K[1], Lehmann A[1], Jax T[2], Heise T[2]

*Diabetes Care 2015; **38**: 637–43*

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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 hypoglycemia in a 6-month randomized controlled trial (EDITION 1)

Riddle MC[1], Bolli GB[2], Ziemen M[3], Muehlen-Bartmer I[3], Bizet F[4], Home PD[5], on behalf of the EDTION 1 Study Investigators

*Diabetes Care 2014; **37**: 2755–62*

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

Riddle MC[1], Yki-Järvinen H[2], Bolli GB[3], Ziemen M[4], Muehlen-Bartmer I[4], Cissokho S[5], Home PD[6]

*Diabetes Obes Metab 2015; **17**: 835–42*

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)

Yki-Järvinen H[1], Bergenstal R[2], Ziemen M[3], Wardecki M[4], Muehlen-Bartmer I[3], Boelle E[5], Riddle MC[6], on behalf of the EDITION 2 Study Investigators

*Diabetes Care 2014; **37**: 3235–43*

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)

Bolli GB[1], Riddle MC[2], Bergenstal RM[3], Ziemen M[4], Sestakauskas K[5], Goyeau H[6], Home PD[7], on behalf of the EDITION 3 study investigators

*Diabetes Obes Metab 2015; **17**: 386–94*

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)

Home PD[1], Bergenstal RM[2], Bolli GB[3], Ziemen M[4], Rojeski M[5], Espinasse M[6], Riddle MC[7]

Diabetes Care 2015. [Epub ahead of print] 10.2337/dc15-0249

Insulin degludec in combination with bolus insulin aspart is safe and effective in children and adolescents with type 1 diabetes

Thalange N[1], Deeb L[2], Iotova V[3], Kawamura T[4], Klingensmith G[5], Philotheou A[6], Silverstein J[7], Tumini S[8], Ocampo Francisco A-M[9], Kinduryte O[9], Danne T[10]

*Pediatr Diabetes 2015; **16**: 164–76*

Comparison of insulin degludec/insulin aspart and biphasic insulin aspart 30 in uncontrolled, insulin-treated type 2 diabetes: a phase 3a, randomized, treat-to-target trial

Fulcher GR[1], Christiansen JS[2], Bantwal G[3], Polaszewska-Muszynska M[4], Mersebach H[5], Andersen TH[5], Niskanen LK[6], on behalf of the BOOST: Intensify Premix I Investigators

*Diabetes Care 2014; **37**: 2084–90*

The advent of biosimilars for the treatment of diabetes: current status and future directions

Giovanni Polimeni[1], Gianluca Trifirò[2], Ylenia Ingrasciotta[2], Achille P. Caputi[1,2]

*Acta Diabetologica 2015; **52**: 423–31*

Insulin biosimilars: the impact on rapid-acting analogue-based therapy

Franzè S, Cilurzo F, Minghetti P

*BioDrugs 2015; **29**: 113–21*

Biosimilar insulins: guidance for data interpretation by clinicians and users

Heinemann L[1], Home PD[2], Hompesch M[3]

*Diabetes Obes Metab 2015; **17**: 911–8*

An Overview of Current Regulatory Requirements for Approval of Biosimilar Insulins

Heinemann L[1], Khatami H[2], McKinnon R[3], Home P[4]

*Diabetes Technol Ther 2015; **17**: 510–26*

The biosimilar insulin landscape: current developments

Lavalle-González FJ[1], Khatami H[2]

*Postgrad Med 2014; **126**: 81–92*

Faster-acting insulin aspart: earlier onset of appearance and greater early pharmacokinetic and pharmacodynamic effects than insulin aspart

Heise T[1], Hövelmann U[1], Brøndsted L[2], Adrian CL[2], Nosek L[1], Haahr H[2]

*Diabetes Obes Metab 2015; **17**: 682–88*

Glucose-responsive insulin activity by covalent modification with aliphatic phenylboronic acid conjugates

Chou DH[1–3], Webber MJ[1,3], Tang BC[1,3], Lin AB[1,3], Thapa LS[1,3], Deng D[1,3], Truong JV[1,3], Cortinas AB[2], Langer R[1–5], Anderson DG[1–5]

*Proc Natl Acad Sci U S A 2015; **112**: 2401–6*

Microneedle-array patches loaded with hypoxia-sensitive vesicles provide fast glucose-responsive insulin delivery

Yu J[1,2], Zhang Y[1,2], Ye Y[1,2], DiSanto R[1,2], Sun W[1,2], Ranson D[1], Ligler FS[1], Buse JB[3], Gu Z[1,2,3]

*Proc Natl Acad Sci U S A 2015; **112**: 8260–65*

ULTRA-LONG-ACTING INSULIN ANALOGS

Glargine U300 approved by EMA and FDA

New insulin glargine 300 units · mL^{-1} provides a more even activity profile and prolonged glycemic control at steady state compared with insulin glargine 100 units · mL^{-1}

Becker RH[1], Dahmen R[1], Bergmann K[1], Lehmann A[1], Jax T[2], Heise T[2]

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*Diabetes Care 2015; **38**: 637–43*

Background

To compare the pharmacokinetic and pharmacodynamic characteristics of the new insulin glargine 300 units/mL formulation (Gla-300) with the original glargine 100 units/mL formulation (Gla-100) in patients with type 1 diabetes.

Methods

A randomized, double-blind crossover trial in 30 patients with type 1 diabetes. Following 8 days of once-daily subcutaneous administration of 0.4 units·kg^{-1} of either insulin Gla-300 or Gla-100 (with a wash-out period of 5–19 days between the treatment periods), a euglycemic clamp was performed over a period of 36 h. Glucose infusion rates (GIR) and serum insulin concentrations were determined.

Results

After 8 days of administration, at steady state, serum insulin concentrations and GIR profiles of Gla-300 were more constant and more evenly distributed over 24 h than those with Gla-100, and with a prolonged duration of action beyond 24 h. Sustained, tight blood glucose control ($\leq$ 105 mg·dL^{-1}) was observed for about 5 h longer (median 30 h) with Gla-300 than with Gla-100.

Conclusions

At steady state, Gla-300 offers more evenly distributed pharmacokinetic and pharmacodynamic profiles and a longer duration of action than Gla-100, resulting in blood glucose control beyond 24 h.

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 hypoglycemia in a 6-month randomized controlled trial (EDITION 1)

Riddle MC[1], Bolli GB[2], Ziemen M[3], Muehlen-Bartmer I[3], Bizet F[4], Home PD[5], on behalf of the EDTION 1 Study Investigators

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Diabetes Care 2014; 37: 2755–62

This article is also discussed in the article on New Medications for the Treatment of Diabetes, p. S-125.

Background

To compare the efficacy and safety of insulin glargine 300 units/mL (Gla-300) with glargine 100 units/mL (Gla-100) in patients with type 2 diabetes on basal (≥ 42 units per day) and mealtime insulin therapy.

Methods

The trial was a multinational 6-month, open-label, parallel-group study. A total of 807 patients with type 2 diabetes (mean age 60 years; diabetes duration 16 years; BMI 36.6 kg/m^2) on basal/bolus insulin treatment—with or without combination with metformin—with HbA1c 7.0–10.0% were randomized 1:1 to once daily Gla-300 or Gla-100, with dose titration aiming for a fasting plasma glucose of 4.4–5-6 mmol/L. Primary end point was HbA1c reduction from baseline. Main secondary endpoint was percentage of patients with one or more confirmed (≤ 3.9 mmol/L) or severe nocturnal hypoglycemic events from week 9 to end of trial.

Results

The decrease in mean HbA1c was similar in both study groups (from 8.15% to 7.3%); the least square mean difference being − 0.00% [95% CI − 0.11 to 0.11] (0.00 mmol/mol [− 1.2 to 1.2]), thus meeting the noninferiority criterion. Fewer patients experienced one or more confirmed or severe nocturnal hypoglycemic episodes between week 9 and month 6 with Gla-300 (36%) than with Gla-100 (46%); relative risk ratio 0.79 ([0.67 to 0.93]; $p < 0.005$). Incidence and event rates of nocturnal hypoglycemia were also lower with Gla-300 during the first 8 weeks of the trial. Tolerability and safety profiles were comparable between the two glargine formulations.

Conclusions

Gla-300 provides similar glucose control to Gla-100 in patients with type 2 diabetes on basal/bolus insulin therapy, with less risk of nocturnal hypoglycemia.

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

Riddle MC[1], Yki-Järvinen H[2], Bolli GB[3], Ziemen M[4], Muehlen-Bartmer I[4], Cissokho S[5], Home PD[6]

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Diabetes Obes Metab 2015; 17: 835–42

Background

To evaluate the efficacy and safety of insulin glargine 300 U/mL (Gla-300) versus glargine 100 U/mL (Gla-100) over a 12-month period in patients with type 2 diabetes on basal plus meal-time bolus insulin therapy.

Methods

Patients who had completed the 6-month study period in the EDITION 1 trial continued as initially randomized to receive Gla-300 or Gla-100 once daily as basal insulin supplementation for a 6 month extension phase. Assessments at 12 months included changes in glucose control, insulin dose, hypoglycemic events, and body weight.

Results

In total, 89% of the patients initially allocated to receive Gla-300 and 88% of those who were assigned to Gla-100 completed the 6-month extension trial. The improvements in glucose control observed at 6 months were maintained at 12 months in both groups (HbA1c 7.24% with Gla-300 and 7.42% with Gla-100, respectively); the reduction in HbA1c at 12 months being greater with Gla-300 than with Gla-100 (least squares mean difference Gla-300 versus Gla-100 − 0.17% [95% CI: − 0.30 to − 0.05]). The mean daily dose of basal insulin at 12 months was 1.03 U/kg with Gla-300 and 0.90 U/kg with Gla-100. Lower percentages of patients on Gla-300 therapy experienced ≥ 1 confirmed (≤ 3.9 mmol/L) or severe hypoglycemic events at any time of the day (86 versus 92%; relative risk 0.94 [0.89 to 0.99]) and during nighttime (54 versus 65%; relative risk 0.84 [0.75 to 0.94]), whereas the annualized rates of overall and nocturnal hypoglycemic events were comparable with Gla-300 and Gla-100. No differences in adverse events were observed between the treatment groups.

Conclusions

In patients with type 2 diabetes on basal plus meal-time insulin treatment, glucose control was better maintained and fewer patients experienced hypoglycemic events over a 12-month period with Gla-300 than with Gla-100. The mean daily dose of basal insulin was higher with Gla-300 compared with Gla-100, while total numbers of hypoglycemic episodes and tolerability were similar between treatments.

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)

Yki-Järvinen H[1], Bergenstal R[2], Ziemen M[3], Wardecki M[4], Muehlen-Bartmer I[3], Boelle E[5], Riddle MC[6], on behalf of the EDITION 2 Study Investigators

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Diabetes Care 2014; **37**: 3235–43

This article is also discussed in the article on New Medications for the Treatment of Diabetes, p. S-125.

Background

To compare the efficacy and safety of basal insulin therapy with insulin glargine 300 units/mL (Gla-300) in patients with type 2 diabetes on existing therapy with basal insulin (≥42 units per day) in combination with oral hypoglycemic agents (OADs). Comparison was made with insulin glargine 100 units/mL.

Methods

Multicenter, open-label, parallel-group trial. In total, 811 patients with type 2 diabetes (mean age 58 years, duration of diabetes 13 years, BMI 34.8 kg/m^2, HbA1c 8.24%) with ongoing treatment with basal insulin plus OADs were randomized to once-daily injections of Gla-300 or Gla-100 for 6 months. Primary endpoint was HbA1c change from baseline. Main secondary endpoint was percentage of patients with one or more nocturnal confirmed (≤70 mg/dL) or severe hypoglycemia from week 9 to month 6.

Results

HbA1c was lowered in a similar way with both glargine formulations: least squares mean HbA1c (SD) decrease from baseline was −0.57% (0.09) with Gla-300 and −0.56% (0.09) with Gla-100 (mean difference −0.01% [95% CI −0.14 to 0.12]. This was achieved with a 10% higher dose of Gla-300. A lower percentage of patients reported ≥1 nocturnal confirmed or severe hypoglycemic event with Gla-300 from week 9 to month 6 (relative risk 0.77 [0.61 to 0.99]; $p=0.038$), as well as during the initial 8 weeks. Less frequent nocturnal and overall (24 h) hypoglycemic events were observed during the total 6-month study period. Weight gain was significantly less in patients treated with Gla-300 than in those treated with Gla-100 ($p=0.015$). No differences in safety profiles between the treatment groups were observed.

Conclusions

Gla-300 was as effective as Gla-100 in terms of glucose control, but with reduced risks of nocturnal and overall hypoglycemic events.

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)

Bolli GB[1], Riddle MC[2], Bergenstal RM[3], Ziemen M[4], Sestakauskas K[5], Goyeau H[6], Home PD[7], on behalf of the EDITION 3 study investigators

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Diabetes Obes Metab 2015; **17**: 386–94

Background

To compare the efficacy and safety of ad-on basal insulin therapy with insulin glargine 300 units/mL (Gla-300) versus glargine 100 units/mL (Gla-100) in patients with type 2 diabetes using oral antidiabetic agents (OADs).

Methods

Multicenter, open-label, parallel group trial, where 878 patients with type 2 diabetes (mean age 57.7 years, diabetes duration 9.8 years, BMI 33.0 kg/m^2, HbA1c 8.54%) using OADs were randomized to Gla-300 or Gla-100 once daily. On-going therapy with sulphonylureas and glinides was discontinued, whereas treatment with metformin and/or dipeptidylpeptidase-4-inhibitors was continued. Insulin doses were titrated to attain fasting plasma glucose 4.4–5.6 mmol/L). Primary endpoint was HbA1c change from baseline to month 6. Main secondary endpoint was percentage of patients with one or more nocturnal confirmed (≤3.9 mmol/L) or severe hypoglycemia from week 9 to month 6.

Results

At 6 months, HbA1c had decreased in a similar way with both glargine formulations (about −1.4%): the least squares mean difference in HbA1c change from baseline was −0.04% [95% CI −0.09 to 0.17]. Numerically, smaller number of patients on GLA-300 reported ≥1 nocturnal confirmed or severe hypoglycemic events from week 9 to study end (relative risk 0.89 [0.66 to 1.20], but a significant reduction between the two groups was found for the full 6-month study period (relative risk 0.76 [0.50 to 0.99]). No differences in safety parameters between the treatment groups were found.

Conclusions

In patients with type 2 diabetes on OADs, ad-on basal insulin therapy with Gla-300 is as effective as Gla-100, with less risk of hypoglycemic events.

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)

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Diabetes Care 2015. [Epub ahead of print] 10.2337/dc15-0249

Background

To compare the efficacy and safety of basal insulin therapy with insulin glargine 300 units/mL (Gla-300) versus glargine 100 units/mL (Gla-100) in patients with type 1 diabetes.

Methods

In total, 549 patients with type 1 diabetes (mean age 47 years, duration of diabetes 21 years, HbA1c 8.1%, and BMI 27.6 kg/m^2) on basal/bolus insulin treatment were randomized open-label to Gla-300 or Gla-100 and to morning or evening basal insulin administration, and were followed over a 6-month period. Prestudy mealtime insulin analogs were continued.

Results

After 6 months, the change in HbA1c was comparable in the Gla-300 and Gla-100 treatment groups (about −0.4%); the difference between the groups being 0.04% [95% CI 0.10 to 0.19] (0.4 mmol/mol [−1.1 to 2.1], showing noninferiority for Gla-300. Similar findings were observed irrespective of injection times (morning or evening) in the two treatment groups. Results on glucose control were also the same when morning and evening injections of Gla-300 were compared, including overlapping eight-point profiles of self-measured plasma glucose. In the first 8 weeks of the trial, nocturnal confirmed (≤70 mg/dL) or severe hypoglycemia was less common with Gla-300 (risk ratio 0.69 [0.53 to 0.91]; otherwise there were no differences in rates of nocturnal or overall rates of hypoglycemia between the treatment groups. Frequency of hypoglycemia was similar whether glargine U300 was administered in the morning or in the evening. At 6 months, the basal insulin dose was slightly higher for Gla-300. The adverse event profile was comparable with the two glargine formulations, and independent of the timing of the Gla-300 injection. Weight gain was less apparent with Gla-300 (0.5 kg) than with Gla-100 (1.0 kg); treatment difference −0.6 kg [−1.1 to −0.03; $p=0.037$].

Conclusions

In patients with type 1 diabetes of long duration, Gla-300 offers similar glucose control as compared with Gla-100, with less risk of hypoglycemia after transfer from other basal insulins, whether administered in the morning or in the evening, and with less weight gain.

INSULIN DEGLUDEC APPROVED FOR USE IN CHILDREN

Insulin degludec in combination with bolus insulin aspart is safe and effective in children and adolescents with type 1 diabetes

Thalange N[1], Deeb L[2], Iotova V[3], Kawamura T[4], Klingensmith G[5], Philotheou A[6], Silverstein J[7], Tumini S[8], Ocampo Francisco A-M[9], Kinduryte O[9], Danne T[10]

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Pediatr Diabetes 2015; **16**: 164–76

Background

To compare the efficacy and safety of basal insulin supplementation with insulin degludec (IDeg) once daily with insulin detemir (IDet) once or twice daily in children with type 1 diabetes.

Methods

In this treat-to-target, controlled trial, 350 children with type 1 diabetes, aged 1–17 years, were randomized 1:1 stratified by age to IDeg once daily (same time each day) or IDet once or twice daily, together with prandial insulin aspart (adjusted according to a sliding scale or in line with an insulin versus carbohydrate ratio and a plasma glucose correction factor), and followed for 26 weeks. In total, 280 of the children also took part in an extension study for an additional 26-week period.

Results

At 26 weeks, the estimated treatment difference regarding HbA1c between the study groups was 0.15% [95% CI; −0.03 to 0.32], confirming noninferiority. After 52 weeks, the mean decrease in HbA1c was comparable for IDeg (−0.27%) and IDet (−0.22%), whereas the change in fasting plasma glucose was greater for IDeg (−1.29 mmol/L) than for IDet (+1.10 mmol/L): the estimated treatment difference being −1.62 mmol/L ([−2.84 to −0.41]; $p=0.009$). The mean basal insulin dose was higher with IDet (0.55 U/kg) than with IDeg (0.38 U/kg), and 64% of the children on IDet required twice daily injections to attain glycemic targets. Rates of confirmed (self-measured plasma glucose ≤3.1 mmol/L), severe or nocturnal hypoglycemic episodes did not differ significantly between the two groups, whereas the frequency of hyperglycemia with ketosis (plasma glucose >11.1 mmol/L and capillary blood ketones >1.5 mmol/L) was significantly lower with IDeg than with IDet (0.7 vs. 1.1 events/patient-years of exposure [0.22 to 0.78]; $p=0.0066$). No differences in adverse event profiles were found.

Conclusions

Basal insulin therapy with IDeg in children with type 1 diabetes attained comparable long-term glycemic control (HbA1c) as compared with IDet, with significant reduction in fasting plasma glucose and 30% lower basal insulin requirement. Rates of hypoglycemia were not significantly

different, whereas the frequency of hyperglycemia and ketosis was significantly reduced with IDeg.

Comparison of insulin degludec/insulin aspart and biphasic insulin aspart 30 in uncontrolled, insulin-treated type 2 diabetes: a phase 3a, randomized, treat-to-target trial

Fulcher GR[1], Christiansen JS[2], Bantwal G[3], Polaszewska-Muszynska M[4], Mersebach H[5], Andersen TH[5], Niskanen LK[6], on behalf of the BOOST: Intensify Premix I Investigators

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*Diabetes Care 2014; **37**: 2084–90*

Background

To compare the efficacy and safety of the premixed combination of insulin degludec/insulin aspart (IDegAsp; 70% insulin degludec and 30% insulin aspart) with biphasic insulin aspart 30 (BIAsp 30; mixture of 70% of a protamine form of insulin aspart and 30% of the soluble form of insulin aspart) in patients with type 2 diabetes inadequately controlled with once- or twice-daily pre- or self-mixed insulin ± oral antidiabetic drugs.

Methods

Multinational, open-label, treat-to-target trial, where patients with type 2 diabetes (mean age 58.7 years, duration of diabetes 13 years, BMI 29.3 kg/m^2, HbA1c 8.4%) were randomized to twice-daily injections (breakfast and main evening meal) of IDegAsp ($n = 224$) or BIAsp ($n = 222$) for 26 weeks. Insulin doses were titrated to attain self-measured, premeal plasma glucose of 4.0–5.0 mmol/L.

Results

After 26 weeks, mean HbA1c was reduced to 7.1% in both groups with an estimated treatment difference (ETD) of −0.03% [95% CI −0.18 to 0.13], that is, achieving the prespecified noninferiority margin. Treatment with IDegAsp was more effective in reducing fasting plasma glucose (ETD: −1.14 mmol/L [−1.53 to −0.76], $p < 0.001$), and the final mean daily insulin dose was significantly lower (ETD 0.89 [0.83 to 0.96], $p = 0.002$). Rates of overall confirmed (< 3.1 mmol/L), nocturnal confirmed, and severe hypoglycemic events were 32% ($p = 0.0049$), 73% ($p < 0.0001$), and 50% ($p =$ not significant) lower, respectively, with IDegAsp than with BIAsp.

Conclusions

Premixed IDegAsp administered twice daily improves glycemic control (HbA1c and fasting plasma glucose) with less risk of hypoglycemia as compared to BIAsp in patients with type 2 diabetes previously inadequately controlled with once- or twice-daily pre- or self-mixed insulin therapy.

Comment

Sanofi's new ultra-long-acting basal insulin analog, glargine U300, is a higher-strength formulation (300 units/mL) of the original insulin glargine U100 product (Lantus®), resulting in flatter pharmacokinetic and pharmacodynamic profiles and prolonged duration of action (> 24 h) because of a more gradual and protracted release from the more compact subcutaneous depot, as was also shown at steady-state pharmacokinetic conditions by Becker and coworkers. The metabolism of glargine U300 is the same as that of glargine U100, with the M1 metabolite (21^A-Gly-human insulin) being the main active, circulating moiety (1,2). This is important as it implies that the neutral safety profile with regard to cardiovascular outcomes and cancer incidence that was demonstrated for glargine U100 in the ORIGIN trial (3) should also be applicable for the new glargine U300 formulation.

In 2015, glargine U300 (Toujeo®) was approved by the European Medicines Agency (EMA) and by the U.S. Food and Drug Administration (FDA), and received marketing authorization in Europe and the United States for adult patients with type 1 and type 2 diabetes. The approvals were based mainly on the EDITION clinical trial program, where the efficacy and safety of glargine U300 have been compared with glargine U100 in a series of multinational, open-label, treat-to-target phase 3 studies of up to 26 weeks with 6 months extension periods in patients with type 1 diabetes and in patients with type 2 diabetes with different insulin treatment regimens; the presently referenced EDITION 1–4 trials being the ones that until now have been published as full articles. Across these trials, the improvement in glycemic control (HbA1c) was comparable between glargine U300 and glargine U100 after 6 months (thus fulfilling the noninferiority criterion), and after 12 months in the EDITION 1 extension study the reduction in HbA1c was even slightly better sustained with glargine U300 than with the comparator.

Although not totally consistent, the findings in the type 2 diabetes trials indicate a reduced risk of hypoglycemia, and especially nocturnal hypoglycemia, with glargine U300. Accordingly, in a patient-level meta-analysis of the EDITION 1, 2, and 3 trials (4), annualized rates of confirmed or severe hypoglycemia were lower with glargine U300 than with glargine U100 any time of the day (rate ratio 0.86 [95% CI 0.77 to 0.97]; $p = 0.0116$) and during nighttime (rate ratio 0.69 [0.57 to 0.84]; $p = 0.0002$). In patients with type 1 diabetes, the so-far limited published data with glargine U300 showed less frequent nocturnal hypoglycemia in the first 8 weeks after treatment initiation, but otherwise the risk of overall and nocturnal hypoglycemia was comparable with that of glargine U100. Hopefully, data from other trials in patients with type 1 diabetes will clarify this issue in greater detail. With regard to effects of glargine U300 on body weight, the overall findings suggest less or similar weight gain as with glargine U100. Adverse event profiles and tolerability were also comparable. Lastly, it seems that a slightly higher dose of glargine

U300 is required to achieve the same glycemic control as that with glargine U100, which might be a consequence of the longer residence time in the subcutaneous depot with higher propensity for enzymatic inactivation by local tissue peptidases, and, hence, a somewhat lower bioavailability. To sum up, insulin glargine 300 u/mL offers pharmacokinetic and pharmacodynamic advantages compared with the original glargine 100 U/mL, which appears to translate into effective glycemic control with less risk of hypoglycemic events. However, more data from long-term studies are needed—especially in patients with type 1 diabetes—to fully disclose its potential clinical benefits.

In previous Yearbooks, we have reviewed extensively about insulin degludec (Tresiba®). Developed by Novo Nordisk, degludec was the first of the new generation of ultra-long-acting insulin analogs, and has been available for adult patients with type 1 and type 2 diabetes in Europe and elsewhere around the globe for a couple of years. In the United States, however, FDA in early 2013 requested additional cardiovascular outcome data before the review of a new drug application. Recently, it was announced that FDA now has accepted for review a class II resubmission for Tresiba® and the premixed insulin degludec/insulin aspart formulation (Ryzodeg®), based on an interim analysis of the ongoing dedicated cardiovascular outcomes trial (DEVOTE trial), which is expected to be completed in the second half of 2016. Meanwhile, in Europe, Tresiba® has recently received approval for basal insulin supplementation also in children and adolescents aged 1–17 years. It has previously been shown that the pharmacokinetic properties of insulin degludec are essentially the same in children and adolescents as in adults (5), and the referenced study by Thalange and coworkers clearly demonstrated that degludec once daily was well tolerated in children aged 1–17 years and achieved similar glucose control with smaller daily doses of basal insulin as compared to insulin detemir administered once or twice daily. Rates of overall and nocturnal hypoglycemic events were comparable, while episodes of hyperglycemia and ketosis were less frequent with degludec. Conceivably, the ultra-long-action profile of degludec, allowing a less stringent timing of insulin injections from day to day, may be an advantageous option for younger patients.

As already mentioned, a premixed formulation consisting of 70% insulin degludec and 30% insulin aspart is also available on the market (Ryzodeg®). This coformulation has previously been tested in a short-term, proof-of-concept study as an add-on to metformin therapy in patients with type 2 diabetes, which showed similar glucose control and less risk of hypoglycemia compared to biphasic insulin aspart 30 (6). In the presently referenced larger trial, the earlier findings were clearly confirmed, demonstrating a notable reduction in overall and nocturnal rates of hypoglycemic events with the degludec/aspart premix. Notably, this was achieved in parallel with a marked lowering of HbA1c and with smaller insulin doses and less weight gain than with biphasic insulin aspart.

As is readily observed, most trials evaluating the efficacy and safety of the ultra-long-acting basal insulin analogs degludec and glargine U300 have had the original glargine U100 or in some cases insulin detemir as comparator. Bearing in mind that both analogs now are available for clinical use, a direct head-to-head comparison between the two is much awaited.

In previous articles, we have also commented on another novel ultra-long-acting basal insulin analog, peglispro from Lilly. Interestingly, this analog has been shown to provide a more hepato-preferential mode of action, thus resembling endogenous insulin. Early clinical phase 2 studies with basal insulin lispro in patients with type 1 and type 2 diabetes showed comparable or even better glucose control, less glucose variability, and lower risk of nocturnal hypoglycemia than with glargine U100 (7,8). In later (hitherto unpublished) phase 3 trials, these findings have been corroborated. However, observed increases in liver enzymes and liver fat with peglispro have been a matter of concern, and in February 2015 Lilly announced a delay in their planned submission to FDA and EMA to delineate in more detail the hepatic action of the analog and out-role any potential liver toxicity. The length of the postponement could not be specified, but Lilly anticipated that the regulatory filing will likely be submitted after 2016.

BIOSIMILAR INSULIN

The advent of biosimilars for the treatment of diabetes: current status and future directions

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As patents of major branded insulin products will expire in the next few years, there is an increase in the discussions on the biosimilar insulins that will be introduced as an alternative to the treatment of diabetes. Issues relating to this topic are being addressed in this article.

Insulin biosimilars: the impact on rapid-acting analogue-based therapy

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*BioDrugs 2015; **29**: 113–21*

Summary

The introduction of biosimilar insulins, mainly the rapid-acting ones, is being discussed in this article, suggesting that

as being cheaper than the branded insulins, it will become the preferred choice of physicians.

Biosimilar insulins: guidance for data interpretation by clinicians and users

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*Diabetes Obes Metab 2015; **17**: 911–8*

Summary

Biosimilar insulins have some advantages over the branded insulin, which may include greater market competition and potential cost reduction. As such, these are a welcome addition to diabetes therapy.

However, clinicians and users lack a clear perspective on ''biosimilarity'' for insulins. Public data on this is quite scarce.

The authors of this manuscript suggest that all comparative data will be put in the public domain and that clinical studies are performed to address batch-to-batch variability, delivery devices, interchangeability in practice, as well as long-term efficacy and safety.

An overview of current regulatory requirements for approval of biosimilar insulins

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*Diabetes Technol Ther 2015; **17**: 510–26*

Summary

Insulin analog patent expiry is liable to mean that, more and more, copies of original biopharmaceutical products will be submitted for authorization. Experience with biosimilars in other therapeutic areas suggests that careful regulation and caution are needed. Published guidelines of regulatory authorities around the world on approval of biosimilars and, where available, insulin biosimilars were reviewed. Information was sourced through Internet searching and cross-referencing guidelines. As of August 2014, general biosimilar and insulin-specific guidelines are available in 34 countries and two countries/regulatory domains, respectively. Areas covered by these guidelines are fairly consistent, covering preclinical, pharmacokinetic (PK), and pharmacodynamic (PD) studies in humans and clinical areas; however, there are differences in emphasis. From a global perspective, this area of drug regulation is heterogeneous and evolving, and the authors call for an initiative aimed at harmonizing the requirements for biosimilar insulins.

The biosimilar insulin landscape: current developments

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*Postgrad Med 2014; **126**: 81–92*

Summary

This is a review on the field of biosimilar insulin. Copies of branded insulins have great potential for increasing their share in the market of diabetes. It is therefore very important that biosimilars should be as safe and efficient as the original branded insulins.

Some companies are developing biosimilar insulins or even producing these products in emerging markets with different regulatory requirements. However, for insulin biosimilars to be licensed in more established markets, manufacturers will need to meet the strict criteria set out by agencies, such as the European Medicines Agency and the U.S. Food and Drug Administration, and fulfill several preclinical, clinical, and pharmacovigilance surveillance criteria.

Comment

At the end of 2014 the first biosimilar insulin (BioIns) received market approval in the EU. This is an insulin glargine product developed by Eli Lilly and Boehringer Ingelheim (Abasaglar®). In the coming years, more BioIns will come to the highly regulated markets in Europe and the United States. After a number of years with unsuccessful attempts to get a BioIns approved, the insulin market will change in coming years. Not only will there be more insulin formulations on the market (with the risk of confusion for patients and the diabetes team), also more manufacturers will be active. Clearly a major driver for the market uptake of Abasaglar® (and the other BioIns in the years to come) will be the costs. Especially in the United States, the prices for the originator insulins were increased massively in recent years. If the price of BioIns is considerably lower than that of the originator insulin, the costs for insulin therapy might decline for the first time in decades. With other biosimilars, a decline in price of 40 to 50% was observed, the guess is that this will be in the 20 to 30% range with BioIns. Market introduction of the first BioIns will clearly increase the interest in this topic in general.

BioIns should have similar pharmacokinetic and pharmacodynamic properties to the originator insulins; however, they might differ to a given extent, and we will have to see if such differences are of clinical relevance or not. In addition, such insulins might differ in their immunogenic properties, that is, they might stimulate generation of (neutralizing) insulin antibodies. A topic on its own are the devices used to apply BioIns. Most probably all BioIns will come to the market in combination with an insulin pen. However, a pen by another company (the originator of the insulin) might also be used if the insulin cartridge fits into this pen. The switch from one pen to another one is associated with an

additional teaching and training burden for the diabetes team. Patients might have difficulties understanding why they should use a different pen with probably other features. From a liability point of view, it is not completely clear who is liable if issues arise, the manufacturer of the BioIns or the pen manufacturer?

A search for original articles reporting data from clinical trials with BioIns was not successful, that is, no such study was published. It is clear that this will change in the following years. Not only the data from the clinical studies performed with Abasaglar® will be published, also other insulin manufacturers most probably will publish their data. However, some comments/reviews were published about BioIns, reflecting on different topics from different points of view (9–12). It is of interest to note that, due to the paucity of published data, such publications reflect more or less the opinions of the authors (the statements are eminence based) and not scientifically sound information.

One extensive review addresses a crucial aspect— the regulatory situation. It is somewhat annoying that patients with diabetes around the globe are treated with BioIns that does not have to fulfill the same regulatory requirements (13). From our point of view the WHO should initiate an attempt to harmonize the requirements; currently these are quite heterogeneous.

Another critical topic is the pharmacovigilance systems that we have in place. It is clear that, for example, with the regulatory requirements BioIns have to fulfil in the EU, only relatively small numbers of patients with diabetes are studied. It's possible that other patient groups that did not participate in these studies, or with a small number, could show, for example, immunological reactions. In order to be able to detect these, adverse events should be reported to the authorities. However, the question is if this happens in daily practice. Reporting of adverse events is quite a time-consuming and challenging procedure. Therefore, there is a high risk of underreporting of adverse events. This is not an issue for BioIns alone; this holds true for all drugs (also for the originator insulins). With other biosimilars (proteins that are used to treat other diseases) severe adverse events were detected more or less by chance (14). There were anecdotal reports about adverse events/differences in insulin doses with insulin copies in countries with relatively low regulatory requirements, for example, in Mexico (15). In a case report from this country the authors describe a hypersensitivity reaction of a 51-year-old woman with type 2 diabetes to a BioIns, an insulin glargine copy (16). In this case the active pharmaceutical ingredient is from China; however, the insulin is formulated and marketed by a local company. The hypersensitivity reaction could be confirmed by laboratory measurements (abnormal basophil degranulation tests). The question is, is this reaction due to patient-specific conditions and/or quality issues of the insulin glargine used. Another critical question is if each batch of BioIns manufactured has the same quality. As the control mechanisms to check and guarantee this quality are more or less in the hands of the manufacturer (with concern. We will have to see how the BioIns story will develop in the coming years; most probably this will become a hot topic.

ULTRA-RAPID INSULINS—THE NEW KID ON THE BLOCK

Faster-acting insulin aspart: earlier onset of appearance and greater early pharmacokinetic and pharmacodynamic effects than insulin aspart

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Aims

In a randomized, single-center, double-blind study, the authors evaluated the pharmacokinetics and pharmacodynamics of faster-acting insulin aspart and insulin aspart.

Methods

In a three-way crossover design (3–12 days washout between dosing), fifty-two patients with type 1 diabetes (mean age 40.3 years) each received a single 0.2 U/kg subcutaneous dose of faster-acting insulin aspart, insulin aspart, or another faster aspart formulation (not selected for further development) under glucose-clamp conditions.

Results

Faster-acting insulin aspart had a faster onset of exposure compared with insulin aspart, shown by a 57% earlier onset of appearance [4.9 vs. 11.2 min; ratio 0.43, 95% confidence interval (CI) 0.36; 0.51], a 35% earlier time to reach 50% maximum concentration (20.7 vs. 31.6 min; ratio 0.65, 95% CI 0.59; 0.72), and a greater early exposure within 90 min after dosing. The greatest difference occurred in the first 15 min, when area under the serum insulin aspart curve was 4.5-fold greater with faster-acting insulin aspart than with insulin aspart. Both treatments had a similar time to maximum concentration, total exposure, and maximum concentration. Faster-acting insulin aspart had a significantly greater glucose-lowering effect within 90 min after dosing (largest difference: area under the curve for the glucose infusion rate [AUCGIR], 0–30 min ratio 1.48, 95% CI 1.13; 2.02) and a 17% earlier time to reach 50% maximum glucose infusion rate (38.3 vs. 46.1 min; ratio 0.83, 95% CI 0.73; 0.94). The primary endpoint (AUCGIR, 0–2 h) was 10% greater for faster-acting insulin aspart, but did not reach statistical significance (ratio 1.10, 95% CI 1.00; 1.22). Both treatments had similar total and maximum glucose-lowering effects, indicating similar overall potency.

Conclusions

Faster-acting insulin aspart was found to have earlier onset and higher early exposure than insulin aspart, and

a greater early glucose-lowering effect, with similar potency.

Comment

Rapid-acting insulin analogs were introduced 20 years ago and are now a well-established therapeutic entity despite remaining shortcomings in onset and duration compared to insulin secreted from the beta cell. A growing number of severely overweight patients and patients with severe insulin resistance require higher insulin dosage. For these patients, there is a need to develop concentrated insulin solutions in order to inject higher doses. Consequently, Humalog® 200 units/mL KwikPen® (insulin lispro 200 units/mL; U200), the first and only concentrated mealtime insulin analog in the United States, became recently available in pharmacies. It holds twice as many units of insulin (600 units vs. 300 units) as the U100 formulation in the same three-milliliter cartridge volume, offering patients a pen that lasts longer, which facilitates fewer pen changes every month apparently without major differences in the pharmacokinetic and pharmacodynamic profile compared to the U100 formulation.

In previous volumes of the yearbook we followed the development of ultra-rapid mealtime insulins, aiming at more closely following the physiological insulin secretion profile. The article by Heise et al. is the first full publication on fast-acting insulin aspart (FIAsp). The well-characterized excipients nicotinamide and L-arginine (to stabilize the molecule) are added to the established rapid-acting insulin analog insulin aspart, leading to a greater early glucose-lowering effect, as the article of Heise et al. shows. According to preliminary data presented at scientific meetings the ultra-rapid effect of adding nicotinamide is not mediated through changes in local blood flow but rather by causing a more rapid monomer formation leading to a quick uptake into the blood stream. Particularly as this may offer better mealtime coverage and more dosing flexibility, such a profile may be particularly advantageous in the most intensive insulin therapies, such as CSII or the artificial pancreas. The appropriate phase 3 studies will become available next year.

Another approach to ultra-rapid mealtime insulin action has been discussed at the recent scientific meetings with BioChaperone® Lispro, an ultra-rapid formulation of insulin lispro—although, a full article is not yet available. This insulin is developed in cooperation between Lilly and the French clinical-stage biotechnology company Adocia. According to the company website, BioChaperone® is a library of polysaccherides mimicking the properties of heparin. The capacity of heparin, a natural polysaccharide, to form molecular complexes with growth factors was discovered over a decade ago. This physical association through electrostatic interactions may improve a hormone or growth factors activity in three main ways: increasing solubility, protecting against enzymatic degradation, and extending the time of action. The interactions of BioChaperone® polymers, oligomers, and small organic compounds with proteins are claimed to form physical complexes that are reversible and do not modify the protein. Adocia is currently developing four insulin-based products using BioChaperone®: BioChaperone® Lispro U100 and U300, HinsBet®, (an ultra-fast human insulin accelerating the pharmacokinetic profile of human insulin with BioChaperone®, obtaining comparable performances to a rapid insulin analog with human insulin) and a BioChaperone® Glargine-based combo (a combination of prandial and basal insulin based on insulin glargine). Data presented so far at meetings indicate that BioChaperone ®Lispro U100 is significantly faster than Humalog in type 1 diabetic patients, with an onset of action 30% earlier and a 69% stronger early metabolic. We are awaiting the publication of the data.

SMART INSULIN—AN INSULIN THAT REGULATES GLUCOSE WITHOUT CAUSING HYPOGLYCEMIA

Glucose-responsive insulin activity by covalent modification with aliphatic phenylboronic acid conjugates

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Abstract

Exogenous insulin has greatly changed the outlook for patients with diabetes ever since its discovery and isolation. Yet, serious complications can result as patients experience both hyperglycemic and hypoglycemic states, even when they strictly follow an insulin regimen. Several chemically or genetically modified insulins have been developed that tune the pharmacokinetics of insulin activity for personalized therapy. In this article, we demonstrate a strategy for the chemical modification of insulin intended to promote both long-lasting and glucose-responsive activity through the incorporation of an aliphatic domain to facilitate hydrophobic interactions, as well as a phenylboronic acid for glucose sensing. These synthetic insulin derivatives enable rapid reversal of blood glucose in a diabetic mouse model following glucose challenge, with some derivatives responding to repeated glucose challenges over a 13 h period. The best-performing insulin derivative provides glucose control that is superior to native insulin, with responsiveness to glucose challenge improved over a clinically used long-acting insulin derivative. In addition, continuous glucose monitoring reveals responsiveness matching that of a healthy pancreas.

This synthetic approach to insulin modification could afford both long-term and glucose-mediated insulin activity, thereby reducing the number of administrations and improving the fidelity of glycemic control for insulin therapy. This study is to our knowledge the first demonstration of a glucose-binding modified insulin molecule with glucose-responsive activity verified in vivo.

Microneedle-array patches loaded with hypoxia-sensitive vesicles provide fast glucose-responsive insulin delivery

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Abstract

The quality of life and health in diabetics has potential for great improvement with a glucose-responsive ''closed-loop'' insulin delivery system mimicking the function of pancreatic cells. This article reports a novel glucose-responsive insulin delivery device using a painless microneedle-array patch (''smart insulin patch'') containing glucose-responsive vesicles (GRVs; with an average diameter of 118 nm), which are loaded with insulin and glucose oxidase (GOx) enzyme. The GRVs are self-assembled from hypoxia-sensitive hyaluronic acid (HS-HA) conjugated with 2-nitroimidazole (NI), a hydrophobic component that can be converted to hydrophilic 2-aminoimidazoles through bioreduction under hypoxic conditions. The reduction of HS-HA, which rapidly triggers the dissociation of vesicles and subsequent release of insulin, is promoted by the local hypoxic microenvironment, caused by the enzymatic oxidation of glucose in the hyperglycemic state. The smart insulin patch effectively regulated the blood glucose in a mouse model of chemically induced type 1 diabetes. This study is the first demonstration, to our knowledge, of a synthetic glucose-responsive device using a hypoxia trigger for regulation of insulin release. The faster responsiveness of this approach holds promise in avoiding hyperglycemia and hypoglycemia if translated for human therapy.

Comment

The discussion on ''Smart'' insulin goes back to the year 2003 when chemists at the Massachusetts Institute of Technology (MIT) founded a company called SmartCells to develop ''Smart'' insulin. This insulin acts only when the blood glucose is high, but stops as soon as the glucose reaches normal levels. SmartCells has received significant funding by the JDRF, and recently several different approaches have been proposed leading to renewed attention to this mechanistic approach. In the meantime Merck has acquired SmartCells, and *clinicaltrial.gov* lists two clinical human trials of the ''Smart'' insulin substance MK-2640 between November 2014 and summer 2015, with a total of 58 probands (17). These studies are looking at the glucose-lowering effect of intravenous administration of various doses of MK-2640 in healthy individuals, followed by a comparison of the effects of MK-2640 to regular insulin in patients with type 1 diabetes. Information on these ongoing studies are currently not available. Chou et al. describe in their article the development and testing of a new insulin called Ins-PBA-F, which was able to normalize glucose levels for up to 13 h in diabetic mice after subcutaneous injection. Using techniques of adding molecules to the insulin molecule, comparable to those used for making long-acting insulin analogs like insulin detemir (Levemir®), they attached aliphatic phenylboronic acid conjugates. Elevated glucose levels lead to glucose binding to phenylboronic acid thereby releasing insulin from the protein binding until the glucose levels return to normal.

A third approach is the ''Smart'' insulin. Microneedle-array patches for drug delivery have been known for years. These arrays are optimized to penetrate only the shallow layers of the skin, avoiding close proximity to pain receptors, making the system extremely comfortable for the patient to wear. The study by Yu et al. is the first to combine a microneedle patch with a glucose-driven biochemical reaction to control insulin release. Insulin was placed within nanoparticles containing glucose oxidase. When glucose levels reach a critical level, the glucose oxidase begins consuming oxygen and creating a hypoxic local environment around the nanoparticles, which becomes active in the presence of high glucose levels. The nanoparticle walls contain 2-nitroimidazole, which changes from hydrophobic to hydrophilic when oxygen levels are low. This alters the nanoparticles' conformation in a way that releases the insulin within. At this point it remains difficult to judge which ''Smart'' insulin approach will eventually not only be safe in long-term human use but also able to release insulin following very small changes in glucose concentration as would be needed to treat human diabetes. Nevertheless, this concept holds the great promise of an insulin therapy without the risk of severe hypoglycemia.

Author Disclosure Statement

JB has received honoraria for consulting and/or lecture fees from Abbott Diabetes Care, AstraZeneca, Integrity Applications, Lilly and Sanofi.

LH is a consultant for a number of diagnostic and pharmaceutic companies developing novel options for diabetes therapy. He is also a member of numerous advisory boards of different companies. He is a partner of Profil Institut fuer Stoffwechselforschung, Neuss, Germany and Profil Institute for Clinical Research, San Diego, CA, USA.

TD has received speakers honoraria, research support and has consulted for Abbott, Bayer, BMS/AstraZeneca, Boehringer Ingelheim, DexCom, Eli Lilly, Medtronic, Novo Nordisk, Sanofi and Roche. He is a shareholder of DreaMed Ltd.

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