New Insulins, Biosimilars, and Insulin Therapy

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Introduction

THE PAST YEAR DEMONSTRATED how developing pharmacological solutions for better ways of insulin substitution and making those drugs commercially available for patients with all forms of diabetes are becoming more and more complex issues worldwide in the light of increasing patient numbers and rising health-care costs. Meanwhile, the two first rapid-acting analogs are celebrating their 20th (insulin lispro (1)) and 15th (insulin aspart (2)) anniversaries of commercial approval. The discussion on the long-term safety concerns of insulin analogs has quieted down considerably and only further reassuring data regarding mitogenicity have become available lately (3). In 2013 the U.S. Food and Drug Administration (FDA) had requested additional cardiovascular data from a dedicated cardiovascular outcomes trial before the review of the New Drug Application for the long-acting insulin degludec could be completed. Degludec had received marketing authorization valid throughout the European Union (EU) and other countries already early 2013. In September 2015, the FDA approved Tresiba (insulin degludec injection) and Ryzodeg 70/30 (insulin degludec/insulin aspart injection) after reassuring data from the DEVOTE trial. But marketing approval does not necessarily translate into reimbursement. After degludec was denied a benefit in the health technology assessment of the German Institute for Quality and Efficiency in Health Care (IQWIG) as part of the so-called AMNOG process (Gesetz zur Neuordnungsgesetz des Arzneimittelmarkt-''Pharmaceuticals Market Reorganisation Act'') for new drug entities in Germany, the German authorities were unwilling to accept a price premium over other long-acting insulins because the benefit was considered marginal. Hence Novo Nordisk took the difficult decision to pull degludec from the German market in January 2016 because other markets (e.g., China) set their price on the basis of Germany. As a consequence, 40,000 German patients on degludec—many of the claiming significant improvements over their previous therapy – had to be transferred to another insulin regimen. In contrast, Toujeo, the U300 insulin glargine approved by the European Agency for the Evaluation of Medicinal Products (EMEA) and the Food and Drug Administration (FDA) in 2015 is not considered a new drug entity and therefore had not to undergo an IQWIG assessment or the AMNOG process and is currently reimbursed in Germany and many other countries. The ultra-fast-acting insulins, such as fast-acting insulin aspart (FiAsp, i.e., NN-1218 or ultra-fast-acting insulin aspart, Novo Nordisk) and Bio-Chaperone Lispro remain on the horizon. However, the communication of the results of clinical studies so far has been dominated by congress presentations and company announcements and the peer-reviewed evidence to date remains scarce. In the year one after the first biosimilar insulin (BioIns) got market approval in the EU and the United States, one has to acknowledge that not too much has happened from a general perspective. This version of insulin glargine developed by Eli Lilly and Boehringer Ingelheim (Abasaglar in the EU and Basaglar in the United States) is not on the market in the United States until now (summer 2016, but will come shortly) and has gained significant market share in some countries in the EU only. In such countries the

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decrease in prices observed is quite different, with a maximum of up to 30%. In March of 2016 the Holy Grail promise of a ''smart'' insulin, or glucose-responsive insulin, was the focus of a joint investment from the Juvenile Diabetes Research Foundation (JDRF) and Sanofi. The $4.6 million in funding over three years will support early research from four researchers developing new and discrete approaches to glucose-responsive insulin. JDRF has prioritized this area of research for several years now, and more collaborations may be announced in the next few months.

Key Articles Reviewed for the Article

New insulin glargine 300 U/mL versus glargine 100 U/mL in Japanese adults with type 1 diabetes using basal and mealtime insulin: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 1)

Matsuhisa M, Koyama M, Cheng X, Takahashi Y, Riddle MC, Bolli GB, Hirose T; on behalf of the EDITION JP 1 study group

Diabetes Obes Metab 2016; ***18****: 375–383*

Glycaemic control and hypoglycaemia with new insulin glargine 300 U/mL versus insulin glargine 100 U/mL in people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: the EDITION 2 randomized 12-month trial including 6-month extension

Yki-Järvinen H, Bergenstal RM, Bolli GM, Ziemen M, Wardecki M, Muehlen-Bartmer I, Maroccia M, Riddle MC

Diabetes Obes Metab 2015; ***17****: 1142–1149*

Insulin degludec improves long-term glycaemic control similarly to insulin glargine but with fewer hypoglycaemic episodes in patients with advanced type 2 diabetes on basal-bolus insulin therapy

Hollander P, King AB, Del Prato S, Sreenan S, Balci MK, Muñoz-Torres M, Rosenstock J, Hansen CT, Niemeyer M, Garber AJ

Diabetes Obes Metab 2015; ***17****: 202–206*

Safety and efficacy of insulin glargine 300 U/mL compared with other basal insulin therapies in patients with type 2 diabetes mellitus: a network meta-analysis

Freemantle N, Chou E, Frois C, Zhuo D, Lehmacher W, Vlajnic A, Wang H, Chung H, Zhang Q, Wu E, Gerrits C

BMJ Open 2016; ***6****: e009421*

Safety and efficacy of insulin degludec/insulin aspart with bolus mealtime insulin aspart compared with standard basal-bolus treatment in people with type 1 diabetes: 1-year results from a randomized clinical trial (BOOST® T1)

Hirsch IB, Franek E, Mersebach H, Bardtrum L, Hermansen K

Diabet Med 2016; Jan 16. DOI 10.1111/dme.13068. [Epub ahead of print]

Pharmacokinetic and prandial pharmacodynamics properties of insulin degludec/insulin aspart in children, adolescents, and adults with type 1 diabetes

Biester T, Danne T, Bläsig S, Remus K, Aschemeier B, Kordonouri O, Bardtrum L, Haahr H

Pediatr Diabetes 2016; ***17****: 642–649*

Effects of high-intensity interval exercise versus moderate continuous exercise on glucose homeostasis and hormone response in patients with type 1 diabetes mellitus using novel ultra-long-acting insulin

Moser O, Tschakert G, Mueller A, Groeschl W, Pieber T, Obermayer-Pietsch B, Koehler G, Hofmann P

PLoS ONE 2015; ***10****: e0136489*

Similar risk of exercise-related hypoglycaemia for insulin degludec to that for insulin glargine in patients with type 1 diabetes: a randomized cross-over trial

Heise T, Bain SC, Bracken RM, Zijlstra E, Nosek L, Stender-Petersen K, Rabøl R, Rowe E, Haahr HL

Diabetes Obes Metab 2016; ***18****: 196–199.*

Randomized clinical trial comparing basal insulin lispro and insulin glargine in patients with type 2 diabetes previously treated with basal insulin: IMAGINE 5

Buse JB, Rodbard HW, Trescoli Serrano C, Luo J, Ivanyi T, Bue-Valleskey J, Hartman ML, Carrey MA, Chang AM; for the IMAGINE 5 Investigators

Diabetes Care 2016; ***39****: 92–100*

Basal insulin peglispro versus insulin glargine in insulin-naïve type 2 diabetes: IMAGINE 2 randomized trial

Davies MJ, Russell-Jones D, Selam J-L, Bailey TS, Kerényi Z, Luo J, Bue-Valleskey J, Iványi T, Hartman ML, Jacobson JG, Jacober SJ; for the IMAGINE 2 Study Investigators

Diabetes Obes Metab 2016; ***18****: 1055–1064*

Comparison of the pharmacokinetics and pharmacodynamics of LY2963016 insulin glargine and European Union- and U.S.-approved versions of Lantus insulin glargine in healthy subjects: three randomized euglycemic clamp studies

Linnebjerg H, Chen Quin Lam E, Seger ME, Coutant D, Chua L, Lan Chong C, Ferreira MM, Soon D, Zhang X

Diabetes Care 2015; ***38****: 2226–2230*

Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus®) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study

Blevins TC, Dahl D, Rosenstock J, Ilag L, Huster W, Zielonka J, Pollom R, Prince M

Diabetes, Obesity and Metabolism 2015; ***17****: 726–733.*

Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus®) in patients with type 2 diabetes who were insulin-naïve or previously treated with insulin glargine: a randomized, double-blind controlled trial (the ELEMENT 2 study)

Rosenstock J, Hollander P, Bhargava A, Ilag LL, Pollom RK, Zielonka JS, Huster WJ, Prince MJ

Diabetes, Obesity and Metabolism 2015; ***17****:* 734–741

Evaluation of immunogenicity of LY2963016 insulin glargine compared with Lantus® insulin glargine in patients with type 1 or type 2 diabetes mellitus

Ilag LL, Deeg MA, Costigan T, Hollander P, Blevins TC, Edelman SV, Konrad RJ, Ortmann RA, Pollom RK, Huster WJ, Zielonka JS, Prince MJ

Diabetes, Obesity and Metabolism 2016; ***18****: 159–168*

Efficacy and safety of LY2963016 insulin glargine in patients with type 1 and type 2 diabetes previously treated with insulin glargine

Hadjiyianni I, Dahl D, Lacaya LB, Pollom RK, Chang CL, Ilag LL

Diabetes Obes Metab 2016; ***18****: 425–429*

Effect of insulin analogues on frequency of non-severe hypoglycaemia in patients with type 1 diabetes prone to severe hypoglycaemia: the HypoAna trial

Agesen RM, Kristensen PL, Beck-Nielsen H, Nørgaard K, Perrild H, Christiansen JS, Jensen T, Hougaard P, Parving HH, Thorsteinsson B, Tarnow L, Pedersen-Bjergaard U

Diabetes Metab 2016; ***42****: 249–255*

Short-acting insulin analogues versus regular human insulin for adults with type 1 diabetes mellitus

Fullerton B, Siebenhofer A, Jeitler K, Horvath K, Semlitsch T, Berghold A, Plank J, Pieber TR, Gerlach FM

Cochrane Database of Systematic Reviews 2016; Issue 6. Art. No.: CD012161.

Improving efficacy of inhaled technosphere insulin (Afrezza) by post meal dosing: in-silico clinical trial with the University of Virginia/Padua type 1 diabetes simulator

Visentin R, Giegerich C, Jäger R, Dahmen R, Boss A, Grant M, Dalla Man C, Cobelli C, Klabunde T

*Diabetes Technol Ther 2016; **18**: 574–585.*

ULTRA-LONG-ACTING INSULIN ANALOGS GLARGINE U300 and DEGLUDEC: NEW DATA AND LONGER FOLLOW-UPS

New insulin glargine 300 U/mL versus glargine 100 U/mL in Japanese adults with type 1 diabetes using basal and mealtime insulin: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 1)

Matsuhisa M[1], Koyama M[2], Cheng X[3], Takahashi Y[2], Riddle MC[4], Bolli GB[5], Hirose T[6]; on behalf of the EDITION JP 1 study group

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*Diabetes Obes Metab 2016; **18**: 375–383*

Background

The aim of this trial was to compare the efficacy and safety of the new insulin glargine 300 U/mL (Gla-300) versus the original insulin glargine 100 U/mL (Gla-100) in Japanese adult subjects with type 1 diabetes.

Methods

A multicenter, open-label, phase 3 trial over six months. Two-hundred and forty-three adults with type 1 diabetes on basal/bolus insulin therapy were randomized to Gla-300 or Gla-100 in combination with prestudy meal-time insulin. Basal insulin was titrated to achieve fasting plasma glucose between 4.4 to 7.2 mmol/L.

Results

Glycemic control (HbA1c) over the six month study period was comparable between Gla-300 and Gla-100 [least squares mean difference 0.13% (95% CI −0.03 to 0.29)], demonstrating noninferiority. The annualized rate of confirmed (self-measured plasma glucose ≤3.9 mmol/L) or severe hypoglycemia was lower with Gla-300 than with Gla-100 at night time (rate ratio 0.66 [95% CI 0.48–0.92]) and at any time of the day (rate ratio 0.80 [95% CI 0.65–0.98]); the difference being most marked during the first eight weeks of the study. At six months, the daily basal insulin dose had increased in both groups to 0.35 U/kg with Gla-300 and 0.29 U/kg with Gla-100. Body weight change was less pronounced with Gla-300 than with Gla-100 [least square mean difference −0.6 kg (95% CI −1.1 to −0.0); $P=0.035$. Adverse events were comparable between the groups.

Conclusions

In Japanese adults with type 1 diabetes on multiple injection therapy, basal insulin supplementation with Gla-300 attained comparable glycemic control (HbA1c) as compared with Gla-100, with significantly less daily hypoglycemia and, in particular, less nocturnal hypoglycemia.

Glycaemic control and hypoglycaemia with new insulin glargine 300 U/mL versus insulin glargine 100 U/mL in people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: the EDITION 2 randomized 12-month trial including 6-month extension

Yki-Järvinen H[1,2], Bergenstal RM[3], Bolli GM[4], Ziemen M[5], Wardecki M[6], Muehlen-Bartmer I[5], Maroccia M[7], Riddle MC[8]

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*Diabetes Obes Metab 2015; **17**: 1142–1149*

Background

The aim of this study was to compare the long-term efficacy and safety of insulin glargine 300U/mL (Gla-300) with glargine 100 U/mL (Gla-100) in adults with type 2 diabetes using combination therapy with basal insulin and oral antihyperglycemic drugs (OADs).

Methods

Multicentre, open-label, parallel group trial, where adults with type 2 diabetes were randomized to once-daily injections

of Gla-300 or Gla-100 together with OADs (with the exception of sulphonylureas) for six months, and for an additional six month extension period.

Results

Seventy-eight percent of the participants in the Gla-300 group and 77% in the Gla-100 group completed the full 12 month study period. The reduction in HbA1c was maintained over 12 months in both groups; the least squares mean change from basal being −0.55% with Gla-300 and −0.50% with Gla-100 (least squares mean difference −0.06% [95% CI −0.22–0.10]). The annualized rate of nocturnal confirmed (self-measured plasma glucose ≤3.9 mmol/L) or severe hypoglycemia was significantly lower with Gla-300 than with Gla-100 (rate ratio 0.63 [95% CI 0.42–0.96]; $P=0.031$), and the percentage of participants experiencing ≥1 event was lower with Gla-300 (relative risk 0.84 [95% CI 0.71–0.99]). Weight gain was less pronounced with Gla-300 than with Gla-100 (least squares mean difference −0.7 kg (95% CI −1.3 to −0.2); $P=0.009$). Adverse event patterns were similar in the two groups.

Conclusions

In adults with type 2 diabetes using combination therapy with basal insulin plus OADs, the improvement in glycemic control is maintained over 12 months with Gla-300 and Gla-100, but with less nocturnal hypoglycemia with Gla-300.

Insulin degludec improves long-term glycaemic control similarly to insulin glargine but with fewer hypoglycaemic episodes in patients with advanced type 2 diabetes on basal-bolus insulin therapy

Hollander P[1], King AB[2], Del Prato S[3], Sreenan S[4], Balci MK[5], Muñoz-Torres M[6], Rosenstock J[7], Hansen CT[8], Niemeyer M[9], Garber AJ[10]

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*Diabetes Obes Metab 2015; **17**: 202–206*

Background

The aim of this extension study was to evaluate the long-term efficacy and safety of insulin degludec in adults with type 2 diabetes, using basal/bolus insulin therapy with or without the addition of metformin and/or pioglitazone. Comparison was made with insulin glargine 100U/mL as basal insulin.

Methods

In the original 52 week trial, 1006 adults with type 2 diabetes previously treated with any kind of insulin regimen, with or without metformin and/or pioglitazone, were randomized (3:1) to basal insulin supplementation with once-daily insulin degludec (IDeg) or insulin glargine (IGla); all together with mealtime insulin aspart. Basal insulin doses were titrated to attain prebreakfast plasma glucose between 3.9 to 4.9 mmol/L. Seventy-five percent of the participants in the IDeg group and 76% in the IGla group continued their assigned treatment for an additional 26 week extension period.

Results

After 78 weeks, improvement in glycemic control (HbA1c) was sustained and comparable in both groups. The overall rate of hypoglycemia (defined as plasma glucose <3.1 mmol/L or severe hypoglycemia) was 24% lower ($P=0.011$), and the rate of nocturnal hypoglycemia 31% lower ($P=0.016$), in the IDeg group. Total insulin doses and rates of adverse events were comparable in the two groups.

Conclusions

Throughout 18 months of basal insulin supplementation with insulin degludec in combination with mealtime insulin aspart ± oral antidiabetic drugs (OADs), improvement in glycemic control was maintained in the same way as with insulin glargine, but with less risks of overall and nocturnal hypoglycemia.

Safety and efficacy of insulin glargine 300 U/mL compared with other basal insulin therapies in patients with type 2 diabetes mellitus: a network meta-analysis

Freemantle N[1], Chou E[2], Frois C[3], Zhuo D[3], Lehmacher W[4], Vlajnic A[5], Wang H[2], Chung H[6], Zhang Q[2], Wu E[3], Gerrits C[2]

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Background

The aim of this study was to compare the efficacy and safety of insulin glargine 300 U/mL (Gla-300) with other basal insulins (NPH, detemir, premixed insulins, and degludec) in adults with type 2 diabetes. In the absence of direct head-to-head comparative trials, this was done by a comprehensive literature review and network meta-analysis to estimate comparative effects of multiple interventions using indirect evidence.

Methods

Network meta-analysis of randomized clinical trials of basal insulin therapies in subjects with type 2 diabetes, identified by a systematic literature review of several

databases. Outcome measures included changes in glycemic control (HbA1c) and body-weight, and rates of nocturnal and documented symptomatic hypoglycemia.

Results

Altogether 41 studies were included in the network meta-analysis. Change in HbA1c was comparable between Gla-300 and all comparator basal insulins. Change in body weight was similar between Gla-300 and detemir and NPH and degludec, respectively, but lower compared with premixed insulin (−1.83 kg [95% Credible Interval (CrI) −2.85 to −0.75]). Rate of nocturnal hypoglycemia was lower with Gla-300 versus NPH (risk ratio 0.18 [95% CrI 0.05–0.55]) and premixed insulin (risk ratio 0.36 [95% CrI 0.14–0.94]), but not significantly different from that with detemir or degludec. Rates of documented symptomatic hypoglycemia were not significantly different between Gla-300 and NPH, detemir, or degludec.

Conclusions

The findings of this network meta-analysis suggest that basal insulin supplementation in type 2 diabetes with Gla-300 is associated with less risk of nocturnal hypoglycemia compared with NPH and premixed insulin, with glycemic control being comparable to all the comparator basal insulins.

PREMIXED INSULIN DEGLUDEC/INSULIN ASPART IN TYPE 1 DIABETES

Safety and efficacy of insulin degludec/insulin aspart with bolus mealtime insulin aspart compared with standard basal-bolus treatment in people with type 1 diabetes: 1-year results from a randomized clinical trial (BOOST® T1)

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Background

Insulin degludec/insulin aspart (IDegAsp) is a premixed coformulation of insulin degludec and insulin aspart (70/30 ratio). The aim of this study was to assess the long-term safety and efficacy of IDeg/Asp once daily (at main meal) in combination with insulin aspart at remaining meal times versus a conventional multiple daily injection therapy with insulin detemir (IDet; once or twice daily) together with insulin aspart (IAsp) at mealtimes in adult subjects with type 1 diabetes.

Methods

Multicenter, parallel-group, open-label, phase 3 trial, where adult subjects with type 1 diabetes (n = 548) were randomized (2:1) to IDegAsp + IAsp or IDet + IAsp for 26 weeks followed by a 26 week extension period. Insulins were titrated to achieve plasma glucose < 5 mmol/L before breakfast (IDegAsp- and IDet-doses) and before meals (IAsp-doses).

Results

At week 52, the mean HbA1c decrease from baseline was −0.7% with IDeg/Asp + IAsp and −0.6% with IDet + IAsp, to a final mean HbA1c of 7.6% and 7.7%, respectively. The rate of overall confirmed hypoglycemia (plasma glucose < 3.1 mmol/L) was comparable with both insulin regimens (31.8 episodes/patient-years of exposure [PYE] with IDegAsp + IAsp and 36.7 episodes/PYE with IDet + IAsp), whereas the rate of nocturnal confirmed hypoglycemia was significantly lower with IDeg/Asp + IAsp (3.1 episodes/PYE) than with IDet + IAsp (5.4 episodes/PYE); ($P < 0.05$). The mean total daily dose of insulin was smaller with IDeg/IAsp + IAsp than with IDet + IAsp; the ratio between the groups being 0.87 (95% CI 0.79–0.95; $P = 0.0026$). Rates of adverse events were comparable.

Conclusions

Once-daily administration of the IDeg/Asp coformulation together with IAsp at remaining meals improved glycemic control equally good as a standard multiple daily injections (MDI)-regimen with IDet plus meal IAsp, but with significantly less risk of nocturnal confirmed hypoglycemia in adults with type 1 diabetes.

Pharmacokinetic and prandial pharmacodynamics properties of insulin degludec/insulin aspart in children, adolescents, and adults with type 1 diabetes

Biester T[1], Danne T[1], Bläsig S[1], Remus K[1], Aschemeier B[1], Kordonouri O[1], Bardtrum L[2], Haahr H[3]

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*Pediatr Diabetes 2016; **17**: 642–649*

Background

The aim of this study was to assess the pharmacokinetic and pharmacodynamics characteristics of insulin degludec/insulin aspart (IDeg/Asp) in children (age 6 to 11 years), adolescents (12 to 17), and adults (18 to 65) with type 1 diabetes.

Methods

Single-center, open-label, single-dose trial. The participants (38 in total) were given a single subcutaneous injection of IDeg/Asp (0.5 U/kg) immediately before a standardized liquid meal adjusted for body weight. Plasma glucose (PG) and insulin concentrations (IDeg and IAsp) were followed up to 57 hours after insulin administration.

Results

The mean postprandial PG profiles after the standardized meal test − including the PG lowering effect, the maximum

PG excursion, and the maximum PG concentration—were comparable for all age groups. Estimated ratios (ER) for total exposure area under the curve (AUC) $_{IAsp,\ 0–12h,\ SD}$) and maximum concentration ($C_{max,\ IAsp,\ SD}$) of IAsp were 1.69 (95% CI: 1.02–2.80) and 1.66 (95% CI: 1.10–2.51), respectively, for children/adults, and 1.14 (95% CI: 0.76–1.69) and 1.16 (95% CI: 0.84–1.61), respectively, for adolescents/adults. ERs for total exposure ($AUC_{IDeg,\ 0-\infty,\ SD}$) and maximum concentration ($C_{max,\ IDeg,\ SD}$) of IDeg were 1.42 (95% CI: 0.94–2.16) and 1.38 (95% CI: 1.09–1.76), respectively for children/adults, and 1.23 (95% CI: 0.96–1.58) and 1.16 (95% CI: 0.95–1.42), respectively, for adolescents/adults.

Conclusions

The rapid onset of the prandial coverage of the IAsp component and the protracted pharmacokinetic profile of the IDeg component of IDeg/Asp were similar in children and adolescents, as compared with adults. Exposure to both IAsp and IDeg was higher in children than in adults, but there were no differences in the PG lowering effect. Accordingly, the IDeg/IAsp-coformulation may be a treatment alternative in children and adolescents with type 1 diabetes.

ULTRA-LONG-ACTING INSULIN ANALOGS AND EXERCISE

Effects of high-intensity interval exercise versus moderate continuous exercise on glucose homeostasis and hormone response in patients with type 1 diabetes mellitus using novel ultra-long-acting insulin

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This manuscript is discussed also in Article Advances in Exercise, Physical Activity, and Diabetes Mellitus, page S-94.

Background

The influence of ultra-long-acting insulins on hypoglycemia counter-regulation and hypoglycemia risk is not very well evaluated. The aim of this study was to assess blood glucose and counter-regulatory hormonal responses to aerobic high-intensity interval exercise (HIIE) and moderate continuous exercise (CON) matched for load and duration in subjects with type 1 diabetes using insulin degludec as basal insulin.

Methods

Seven trained males with type 1 diabetes first performed a maximal incremental exercise test and then 30 min HIIE and CON tests at three different mean intensities; each test being separated by one week. Prior to the exercise tests, the participants had been adjusted to basal insulin supplementation with insulin degludec once daily (evening). Before exercise, standardized meals were given, and the short-acting insulin dose was reduced by 25% to 75%, depending on the exercise intensity. Blood glucose (BG) and counter-regulatory hormonal responses together with blood lactate, heart rate, and pulmonary gas exchange variables were measured during the tests, and glucose control over 24 h after exercise was registered by a continuous glucose monitoring system.

Results

Compared to CON, the lowering of BG during HIIE was significantly smaller at the intermediate exercise intensity, and tended to be smaller during the other two intensities. No differences between HIIE and CON were seen with regard to counter-regulatory hormone responses, carbohydrate utilization or postexercise glucose control. No hypoglycemic events (glucose < 3.3 mmol/L) were observed during or after the various tests. Increases in blood lactate and respiratory exchange ratios were significantly higher during HIIE than during CON at the two lower exercise intensities, but not at the highest.

Conclusions

HIIE and CON was performed without hypoglycemic events during or after exercise in subjects with type 1 diabetes using insulin degludec as basal insulin and applying standardized carbohydrate intake and reductions of bolus insulin doses before the tests. While both exercise modes were matched for mean load and duration, HIIE resulted in less pronounced BG decrease compared to CON, although higher peak workloads were applied in HIIE. Therefore, HIIE and CON could both be safely recommended.

Similar risk of exercise-related hypoglycaemia for insulin degludec to that for insulin glargine in patients with type 1 diabetes: a randomized cross-over trial

Heise T[1], Bain SC[2], Bracken RM[2], Zijlstra E[1], Nosek L[1], Stender-Petersen K[3], Rabøl R[3], Rowe E[4], Haahr HL[3]

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*Diabetes Obes Metab 2016; **18**: 196–199*

Background

The aim of this study was to compare changes in blood glucose (BG) and susceptibility to hypoglycemia during and after exercise in subjects with type 1 diabetes using insulin degludec (IDeg) or insulin glargine (IGla) as basal insulin.

Methods

Randomized, open-label, two-period, crossover trial in 40 subjects with type 1 diabetes. Following individual titration and steady-state dosing with each of the two basal insulins in random order, the subjects performed a 30 min moderate-intensity cycle ergometer exercise test (65% peak

rate of oxygen uptake). BG, counter-regulatory hormones, and hypoglycemic events (plasma glucose ≤3.1 mmol/L or requiring assistance) were recorded during and for 24 h after exercise.

Results

BG lowering during exercise was comparable with IDeg and IGla [estimated treatment difference for maximum BG decrease 0.14 mmol/L (95% CI −0.15 to 0.42; $P=0.34$)], as was the mean BG [estimated treatment difference −0.16 mmol/L (95% CI −0.36 to 0.05; $P=0.13$)]. No hypoglycemic event was registered during the exercise test. Postexercise mean BG and counter-regulatory hormonal responses were similar with both insulins. Likewise, the number of hypoglycemic episodes within 24 h after starting exercise was comparable; 18 events in 13 subjects with IDeg, and 23 events in 15 subjects with IGla.

Conclusions

In subjects with type 1 diabetes using basal/bolus insulin treatment, the risk of hypoglycemia provoked by moderate-intensity exercise is small and similar for IDeg and IGla.

INSULIN PEGLISPRO: END OF THE STORY

Randomized clinical trial comparing basal insulin lispro and insulin glargine in patients with type 2 diabetes previously treated with basal insulin: IMAGINE 5

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*Diabetes Care 2016; **39**: 92–100*

Background

The aim of this study was to assess the long-term safety and efficacy of the ultra-long-acting basal insulin peglispro (BIL) compared with insulin glargine in subjects with type 2 diabetes previously treated with basal insulin alone or in combination with oral antihyperhyperglycemic drugs.

Methods

Fifty-two week, phase 3, open-label, treat-to-target trial where subjects with a mean HbA1c of 7.42% (57.6 mmol/mol) were randomized to basal insulin supplementation with BIL (n = 307) or glargine (n = 159). Primary outcome was change from baseline HbA1c from baseline.

Results

At 26 weeks, the lowering of HbA1c was greater with BIL (−0.82% [−8.9 mmol/mol]) than with glargine (−0.29% [−3.2 mmol/mol]); the least square mean difference being −0.52%, 95% CI: −0.67 to −0.38 (−5.7 mmol/mol, 95% CI: −7.3 to −4.2); $P<0.001$. At 52 weeks, the greater reduction in HbA1c with BIL was sustained, and more subjects in the BIL group achieved HbA1c less than 7% (53 mmol/L) at 26 and 52 weeks ($P<0.001$ at both time points). At both 26 and 52 weeks, BIL subjects experienced 60% less nocturnal hypoglycemia ($P\leq0.001$), more subjects achieved the treatment goal (HbA1c < 7%; 53 mmol/mol) without nocturnal hypoglycemia ($P<0.001$), and glucose variability was lower ($P<0.01$), as compared with glargine. At 52 weeks, total rate of hypoglycemia was lower with BIL than with glargine ($P<0.03$). At weeks 26 and 52, insulin dose ($P<0.001$) was higher with BIL than with glargine. Triglycerides and aminotransferases were also significantly higher with BIL ($P<0.05$). Liver fat content (investigated in a subset of 162 subjects), was increased from baseline with BIL versus glargine ($P<0.001$), with unchanged levels between week 26 and 52.

Conclusions

BIL therapy resulted in greater improvement in glycemic control versus glargine, with less nocturnal and total rates of hypoglycemia and lower glucose variability, and lead to increased triglycerides, aminotransferases, and liver fat content.

Basal insulin peglispro versus insulin glargine in insulin-naïve type 2 diabetes: IMAGINE 2 randomized trial

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*Diabetes Obes Metab 2016; **18**: 1055–1064*

Background

The aim of this study was to compare the long-term safety and efficacy of basal insulin peglispro versus insulin glargine as add-on to oral hypoglycemic drugs in insulin-naïve, type 2 diabetic subjects.

Methods

Phase 3, multi-national, double-blind, trial. One thousand five hundred and thirty-eight subjects were randomized (2:1) to treatment with peglispro or glargine for 52 weeks, with an additional 26 week extension period (n = 920). The primary outcome was noninferiority of peglispro to glargine in terms of HbA1c reduction (margin 0.4%). There were also several gated secondary outcomes with statistical multiplicity adjustments regarding glycemic control and safety. Liver fat content was assessed by magnetic resonance imaging (MRI) in a subset of 168 subjects.

Results

Compared with glargine, peglispro treatment resulted in a statistically significant greater reduction of HbA1c

($P < 0.001$), but within the prespecified noninferiority margin (least squares mean difference (-0.29%, 95% CI: -0.40 to -0.19). Peglispro subjects experienced lower rate of nocturnal hypoglycemia (relative rate 0.74 [95% CI: 0.60–0.91]; $P = 0.005$), and more subjects achieved HbA1c $< 7\%$ (odds ratio (OR) 1.97 [95% CI: 1.57–2.47]; $P < 0.001$) and HbA1c $< 7\%$ without nocturnal hypoglycemia (OR 2.15 [95% CI: 1.60–2.89]; $P < 0.001$). Incidence of total hypoglycemia and fasting serum glucose were comparable between the two groups. At 52 weeks, subjects on peglispro had higher triglyceride (1.9 vs. 1.7 mmol/L, alanine transaminase (34 vs. 27 IU/L), and aspartate transaminase (27 vs. 24 IU/L) levels. At 52 weeks, least square mean liver fat content had not changed from basal values in peglispro subjects but had decreased by 3.1% in glargine subjects (difference 2.6% [95% CI: 0.9–4.2]; $P = 0.002$). Adverse injection site reactions were more common in the peglispro group (3.5% vs. 0.6%; $P < 0.001$).

Conclusions

Compared to glargine, treatment with peglispro lead to a statistically significant greater reduction in HbA1c, more subjects attaining HbA1c target, lower incidence of nocturnal hypoglycemia, comparable rates of total hypoglycemia, higher triglyceride and aminotransferase levels, and more frequent injection site reactions.

Comment

In the last years, we have reviewed comprehensively about the two newest ultra-long-acting insulin anlogs on the market; glargine 300 U/mL (Tuejo) from Sanofi and degludec (Tresiba) from Novo Nordisk. As the U.S. Food and Drug Administration (FDA) in September 2015 approved Tresiba (and the premixed combination of degludec and the rapid-acting analog aspart; Ryzodeg 70/30) after an interim analysis of a dedicated cardiovascular outcomes trial (DEVOTE), both analogs are now available in Europe and in the United States.

This year, we present data from extension studies of previously-published phase 3 trials with both analogs, which show that improvements in glycemic control (HbA1c) are maintained over longer periods of time. Moreover, reduced risk of hypoglycemia – and especially nocturnal hypoglycemia – seems to be a consistent finding also after longer follow ups, and no alarming safety issues have been observed. Unfortunately, there is still no head-to-head comparison between glargine 300 U/ml and degludec. By using data from several randomized, controlled trials in a network meta-analysis, Freemantle and coworkers indirectly compared the effectiveness of different basal insulins, including Tuejo and Tresiba. According to their analysis, there were no apparent differences with regard to glycemic control or risk of hypoglycemia between the two new analogs. However, randomized, controlled, treat-to-target trials directly comparing the ultra-long-acting analogs in both type 1 and type 2 diabetes are necessary to make any firm conclusions and are much awaited.

As mentioned, Novo Nordisk has also developed a soluble coformulation consisting of 70% degludec and 30% aspart (Ryzodeg). Previous studies have demonstrated that this combination provides both the stable and protracted glucose-lowering effect of degludec and the rapid prandial effect of aspart, and that there is a clear dose-response relationship for both components (4). In clinical testing, a marked improvement in glucose control together with notable reductions in rates of total and nocturnal hypoglycemia compared with biphasic insulin aspart have also been shown in subjects with type 2 diabetes (5). The presently referenced trials, suggest that Ryzodeg may also be used as part of a multiple daily injection treatment regimen in both young and adult subjects with type 1 diabetes. The advantages include fewer injections and, according to the results of Hirsch et al.'s study, less risk of hypoglycemia. It should be borne in mind, however, that fixed dosing limits the possibility of adjusting prandial insulin in relation to meal demands, planned physical activity etc. In this regard, the influence of ultra-long-acting insulin analogs on hypoglycemia risk during or after exercise is a very important clinical question. In both the two referenced studies, the rapid-acting, prandial insulin dose before exercise was reduced in relation to the work intensity, according to therapy recommendations (6). In the study by Moser and coworker, no hypoglycemia event was recorded during or within 24 h after high-intensity interval exercise or moderate continuous exercise matched for work load and duration in subjects with type 1 diabetes using degludec. Notably, however, the mean blood glucose level before exercise was rather high (about 11–13 mmol/L), i.e., with a rather large buffer zone against hypoglycemia. In the study by Heise et al., hypoglycemia was registered postexercise in about one-third of the participants in both the degludec group and the glargine group, with most of the events occurring during the night. While no information was given regarding their general propensity for hypoglycemia, this frequency of exercise-associated hypoglycemia appears rather high. Conceivably, more data regarding the optimum insulin adjustments in conjunction with exercise in subjects using ultra-long-acting insulin analogs are needed.

In previous Yearbooks we have also commented extensively on another new ultra-long-acting basal insulin analog, namely insulin peglispro, in development by Lilly. Early trials with this analog with a more hepato-preferential mode of action showed promising results with regard to glycemic parameters, with even better improvements of HbA1c and lower frequency of nocturnal hypoglycemia as compared to insulin glargine; findings that now have been corroborated in the presently-referenced studies of longer duration. However, elevations of triglycerides, liver enzymes and liver fat content have been observed in parallel, which may be the consequence of reduced peripheral action of peglispro and thereby increased fatty acid delivery to the liver. Based on this potentially deleterious side effect, Lilly in December 2015 announced that the development program of peglispro has been terminated.

BIOSIMILAR INSULIN

Comparison of the pharmacokinetics and pharmacodynamics of LY2963016 insulin glargine and European Union- and U.S.-approved versions of Lantus insulin glargine in healthy subjects: three randomized euglycemic clamp studies

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*Diabetes Care 2015; **38**: 2226–2230*

Background

The insulin glargine products LY2963016 (LY IGlar) and Lantus (IGlar) are manufactured by distinct processes but they have an identical primary structure. Three studies evaluated the pharmacokinetic (PK) and pharmacodynamic (PD) similarity of both of these glargines (one glargine was studied in two versions: one approved in the EU and the other approved in the United States).

Methods

Three single-site, randomized, double-blind, two-treatment, four period, crossover, euglycemic glucose clamp studies were conducted. In each study, healthy subjects received subcutaneous (SC) injections of 0.5 units/kg of the insulin glargines on two occasions each, following a randomized sequence. PD was assessed by a euglycemic glucose clamp lasting up to 24 h.

Results

A total of 211 subjects participated in the three studies. The PK (area under the curve; maximum observed concentration) and PD (maximum glucose infusion rate; total glucose infusion during the clamp) were observed to be similar between LY IGlar and IGlar. The ratios of geometric means ranged from 0.90 to 0.95 for PK parameters and from 0.91 to 0.99 for PD parameters across the three studies. In all cases, the 90% confidence intervals relating to the ratios of the geometric means were totally contained within the prespecified acceptance limits of 0.80–1.25. Adverse events were observed to be similar between the treatments.

Conclusions

In healthy subjects the PK and PD properties of LY IGlar and IGlar were similar after single 0.5 units/kg s.c. doses, contributing to the totality of evidence supporting similarity of these products.

Comment

The PK and PD properties of the first approved BioIns were studied in three glucose clamp studies with healthy subjects and the main results obtained with a high insulin dose (0.5 U/kg) were presented in this summary publication. In two comments the performance of these studies and the interpretation were challenged (20,21). Nevertheless, the PK and PD data presented make clear that this biosimilar insulin glargine is quite similar to the originator insulin. However, the variability of the individual responses observed (see the large error bars) also highlights the magnitude to which these differ.

Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus®) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study

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*Diabetes, Obesity and Metabolism 2015; **17**: 726–733*.

Background

The aim of this study was to compare the efficacy and safety of LY2963016 insulin glargine (LY IGlar) and the originator insulin (insulin glargine; IGlar) in patients with type 1 diabetes (T1D).

Methods

In this phase III, randomized, open-label, 52-week study 535 patients with T1D were enrolled (HbA1c $\leq 11\%$). These are treated with multiple daily injections, i.e., basal insulin (once daily) and bolus insulin. Patients were randomized to receive once-daily LY IGlar (n = 268) or IGlar (n = 267).

Results

Both treatment groups had similar and significant ($P < 0.001$) within-group decreases in mean HbA1c values from baseline. LY IGlar met the noninferiority criteria compared with IGlar for change in HbA1c from baseline to 24 weeks (-0.35% vs. -0.46%, least squares mean difference 0.108% [95% CI -0.002 to 0.219], $P > 0.05$). There were no significant treatment differences in other efficacy measures, including proportion of patients reaching HbA1c $< 7\%$, daily mean blood glucose, and insulin dose at 24 and 52 weeks. At 52 weeks, similar findings were observed between LY IGlar and IGlar for safety outcomes, including adverse events, allergic reactions, hypoglycemia, weight change, and insulin antibodies.

Conclusion

Both insulin glargines, when used in combination with mealtime insulin lispro, provided effective and similar glucose control and similar safety profiles.

Comment

Eli Lilly and Boehringer Ingelheim performed two large clinical trials to get market approval in the United States (these studies would not have been required for market approval in the European Union). They named these studies ELEMENT 1 and ELEMENT 2, in relation to the patient group studied. In this study with patients with type 1 diabetes no relevant differences were observed in clinical endpoints (metabolic control and frequency of hypoglycemic events) and side effects at the end of the study. However, after 12 weeks significant higher HbA1c values were observed with the BioIns, indicating that the treating physicians in this open-label study were somewhat reluctant to adjust the insulin dose as rapidly as they did with the originator insulin. In combination with the PK/PD data, the study results indicate that this BioIns can be used like the originator insulin.

Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus®) in patients with type 2 diabetes who were insulin-naïve or previously treated with insulin glargine: a randomized, double-blind controlled trial (the ELEMENT 2 study)

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Diabetes, Obesity and Metabolism 2015; ***17***: 734–741

Background

The aim of this study was to compare the efficacy and safety of LY2963016 insulin glargine (LY IGlar) and the reference product (Lantus) insulin glargine (IGlar) in combination with oral antihyperglycaemic medications (OADs) in patients with type 2 diabetes (T2D).

Methods

This phase 3, randomized, double-blind, 24-week study enrolled patients with T2D who were insulin-naïve (HbA1c ≥ 7 and $\leq 11.0\%$) or previously treated with a basal insulin (HbA1c $\leq 11\%$) and treated with ≥ 2 OADs. Patients were randomized to receive once-daily LY IGlar (n = 376) or IGlar (n = 380) for 24 weeks.

Results

Both treatment groups had similar and significant ($P < 0.001$) within-group decreases in mean HbA1c values from baseline. LY IGlar met noninferiority criteria compared with IGlar for change in HbA1c from baseline (-1.29% vs. -1.34%; respectively). The mean difference in HbA1c was 0.052% (95% CI -0.070 to 0.175; $P > 0.05$). There were no significant differences in fasting plasma glucose, proportion of patients reaching HbA1c $< 7\%$, or insulin dose at 24 weeks. Also adverse events, allergic reactions, weight change, hypoglycemia, and insulin antibodies were similar between treatment groups. Similar findings were observed in patients who were insulin-naïve or previously treated with IGlar at baseline.

Conclusions

Both LY IGlar and IGlar, when used in combination with OADs, provided effective and similar glucose control with similar safety profiles in patients with T2D.

Comment

As long-acting insulin analogues are widely used for insulin therapy in patients with type 2 diabetes, it is clear that also a clinical study in this patient group was performed. The study results would have been easier to interpret if two separate studies would have been performed, one study with patients that were not on an insulin-therapy previously (but on OADs) and one study with patients with previous insulin therapy. However, the data presented again showed that both insulin glargines induce quite similar clinical outcomes.

Evaluation of immunogenicity of LY2963016 insulin glargine compared with Lantus® insulin glargine in patients with type 1 or type 2 diabetes mellitus

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Diabetes, Obesity and Metabolism 2016; ***18****: 159–168*

Background

Aim of these studies was to compare the immunogenicity profiles and the potential effects on clinical outcomes of LY2963016 insulin glargine (LY IGlar) and the originator insulin glargine (IGlar) in patients with type 1 or type 2 diabetes mellitus (T1DM or T2DM).

Methods

Anti-insulin glargine antibodies (measured as percent binding) were compared between treatments in 52 week (open-label) and 24 week (double-blind) randomized studies in patients with T1DM (n = 535) and T2DM (n = 756), respectively. In patients with type 2 two subgroups were studied: insulin-naïve patients and those reporting prestudy IGlar treatment (prior IGlar). Relationships between insulin antibody levels and clinical outcomes were assessed using analysis of covariance and partial correlations. Treatment comparisons for treatment-emergent antibody response (TEAR) and incidence of detectable antibodies were analyzed using Fisher's exact test.

Results

No significant differences were observed for insulin antibody levels, incidence of detectable anti-insulin glargine

antibodies, or incidence of TEAR in patients with T1DM or patients with T2DM, including the insulin-naïve subgroup. A significant difference was noted in the overall incidence of detectable antibodies but not at endpoint nor in TEAR for the prior IGlar subgroup of patients with T2DM. Insulin antibody levels were low (<5%) in both treatment groups. Insulin antibody levels or TEAR was not associated with clinical outcomes.

Conclusions

Both glargine have similar immunogenicity profiles. Anti-insulin glargine antibody levels were low with both glargine, with no observed effect on efficacy and safety outcomes.

Comment

As stated above, the immunogenicity of BioIns is a major concern and therefore the evaluation of the antibody formation in the two ELEMENT studies is of high interest. At least under such study conditions both insulin glargines do not differ in stimulation of the immunological response. The question remains, if this holds true for all patients, it might be that small patient groups act differentially and that this is not seen when analyzing all patients as one group. Depending on the quality of the pharmacovigilance system that is in place in the given country, an increase in antibody titers to a level that clinically relevant differences in insulin doses etc. show up in such patients will be detected or not. Without a structured and systematic evaluation (including measurement of antibody titers), such patients will not be detected in daily life. The question is who is willing to pay for such an approach?

Efficacy and safety of LY2963016 insulin glargine in patients with type 1 and type 2 diabetes previously treated with insulin glargine

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*Diabetes Obes Metab 2016; **18**: 425–429*

Background and Methods

The safety and efficacy of LY2963016 insulin glargine (LY IGlar) and originator insulin glargine (IGlar) were assessed in subgroups of patients with type 1 (T1D, n = 452) or type 2 diabetes (T2D, n = 299) that used IGlar prior to their participation in a 52 week open-label study (ELEMENT-1) or a 24 week double-blind study (ELEMENT-2). At randomization, patients were switched from their prestudy IGlar to equivalent doses of LY IGlar or IGlar. Primary efficacy (change in HbA1c from baseline to 24 weeks), other efficacy and select safety outcomes of LY IGlar were compared with those of IGlar.

Results

No statistically significant treatment differences were identified for efficacy and safety outcomes except for weight change (T1D), overall incidence of detectable insulin antibodies (T2D), and serious adverse events (T2D). These differences were neither consistently observed across both studies nor observed in the total study populations, and their magnitude suggests they were not clinically meaningful.

Conclusions

LY IGlar and IGlar show similar efficacy and safety profiles in patients using IGlar prior to study participation.

Comment

This additional analysis of patients with prestudy IGlar treatment who were randomized to biosimilar insulin glargine treatment showed no differences in efficacy and safety outcomes to those of patients receiving IGlar during the study. The difference in weight gain observed with LY IGlar is worth a follow-up evaluation in daily practice. Also the significant difference in overall antibody incidence of LY IGlar-treated patients with T2D; this might be due to an imbalance in baseline antibody levels. It is worth acknowledging that neither study was designed to prospectively compare LY IGlar and IGlar in patients with diabetes reporting prestudy IGlar treatment. The results cannot be considered sufficient to support interchangeability.

CONCLUDING COMMENT

Next BioIns

The next BioIns that most probably will come to the market in the European Union and the United States is another insulin glargine currently under development by Merck-US. Merck has not published any data until now; however, data presented at the American Diabetes Association (ADA) in 2015 and 2016 document the similarity of this BioIns with the originator insulin. Also other insulin glargines are in clinical development (one by Biocon is in late phases of the development) and also a BioIns of insulin lispro (developed by Sanofi).

Prices

Market introduction of BioIns has not induced drastic changes in the insulin market until now; however, once more BioIns enter the market the increase in competition will most probably change this. We will have to see if the prices start a race to the bottom as it took place with test strips for blood glucose measurement systems in the last years. This 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. It is of interest to note that prices for originator insulins—which have gone up especially in the United States massively in the last years—are not driven up by the manufacturer companies, but also by the pharmacy benefit managers (7,8).

Clinical Experience

One can assume that in the near future the first reports about the clinical experience of patients with diabetes will be presented that have used the BioIns of insulin glargine in daily practice; hopefully the manufacturer will present data from their pharmacovigilance systems also.

Immunological Aspects

Market approval of BioIns means that these insulins have similar pharmacokinetic and pharmacodynamic properties in comparison to the originator insulins. During the approval process also the preclinical data are evaluated carefully (see the extended documentation of the EMA for Abasaglar); however, a matter of concern is the question if BioIns might differ in their immunogenic properties from the originator insulin. Also this is studied during the approval process, a clinical study with a limited number of subjects (300) over a limited period of time (6 or 12 months) has to be performed. The question remains if with such a study all relevant patient groups are studied for a sufficient period of time. A major concern is that at least in some patient's formation of (neutralizing) insulin antibodies is stimulated. Differences in immunological responses might be induced by certain differences between the BioIns and the originator insulin (9).

Quality

In the same line of thinking it would be of interest to know how good the quality of different batches of (originator) insulins and BioIns is over time. Insulin is manufactured in batches and these might differ considerably from each other as a reflection of the complexity of the manufacturing process. The amount of information that companies are reporting about this topic is quite limited (10–12).

Interchangeability

Switching from one insulin to another is a decision made by the treating physician to exchange one insulin with another insulin with the same therapeutic intent in a given patient (13,14). Interchangeability means the practice of changing 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 in which, at the pharmacy level, without (!) consulting the prescribing physician another insulin (a BioIns) is dispensed instead of the prescribed insulin. Currently there is no ''substitutability determination'' in the European Union, i.e., there is no automatic substitution in practice in the European Union whereby a pharmacist is obliged to dispense a BioIns instead of a prescribed insulin. Interesting differences exists between states in the United States when it comes to guidelines for market allowance of BioIns (12).

Devices

In daily practice for patients, diabetologists, and nurses the devices (most often insulin pens) used for application of insulin are of high relevance. 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

A number of original articles reporting data from clinical trials with BioIns were published in the last year, mainly data from the clinical studies performed for approval of Abasaglar were reported (15–19). However, also some comments and reviews were published about BioIns, mainly directed towards the usability of long glucose clamps for evaluation of the pharmacodynamic (PD) properties of basal insulins (20,21) and specific aspects like costs and interchangeability (8,13,22).

Summary

These are early days for BioIns. It can be taken for granted that this story will gain more attention and momentum in the next years. This will be mainly driven by cost aspects. Lower insulin prices mean also that more patients can afford to buy insulin or has access to it (23).

RAPID AND ULTRA-RAPID-ACTING INSULINS: THE ONGOING DILEMMA OF PROVING A CLINICAL MEANINGFUL BENEFIT OF A NEW DRUG CLASS

Effect of insulin analogues on frequency of non-severe hypoglycaemia in patients with type 1 diabetes prone to severe hypoglycaemia: the HypoAna trial

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Aim

Compared with human insulin, insulin analogues reduce the risk of hypoglycemia in patients with type 1 diabetes

(T1D) and minor hypoglycemia problems. The HypoAna trial has illustrated that for patients with recurrent severe hypoglycemia, the risk of severe hypoglycemia is reduced when treatment based on insulin analogues is employed. The present study aims to assess whether this also applies to nonsevere hypoglycemia events at night and during the day.

Methods

This investigator-initiated multicenter, prospective, randomized, open, blinded endpoint (PROBE) trial that took place over 2 years, involved participants with T1D who had had at least two episodes of severe hypoglycaemia during the previous year. These patients were randomized to basal-bolus therapy based on analogue (detemir/aspart) or human (NPH/regular) insulins using and balanced crossover design. In total 114 patients were included. Endpoints were the number of both nonsevere and severe hypoglycemic events, including documented symptomatic and asymptomatic episodes occurring during the day and at night.

Results

A 6% overall relative-risk reduction for nonsevere hypoglycemia resulted from analogue-based treatment (2%–10%; $P = 0.0025$). This was a result of a 39% (32%–46%; $P < 0.0001$) reduction of nonsevere nocturnal hypoglycemia, which was observed for both symptomatic (48% [36%–57%]; $P < 0.0001$) and asymptomatic (28% [14%–39%]; $P = 0.0004$) nocturnal hypoglycemia episodes. There were no clinically significant differences in hypoglycemia occurrence observed between the insulin regimens during the day. To avoid one episode (TNT1) of nonsevere nocturnal hypoglycemia, the time needed to treat one patient with insulin analogues was approximately three months.

Conclusion

In T1D patients prone to severe hypoglycemia, treatment with analogue insulin reduced the risk of nonsevere nocturnal hypoglycemia compared with human insulin.

Short-acting insulin analogues versus regular human insulin for adults with type 1 diabetes mellitus

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Background

As reflected in a number of scientific debates, the use of short-acting insulin analogue for people with diabetes remains controversial.

Objectives

The aim of this study was to assess the effects of short-acting insulin analogues versus regular human insulin in adults with type 1 diabetes.

Search Methods

Electronic searches were carried out through Ovid searching the following databases simultaneously: Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) (1946 to 14 April 2015), the Cochrane Central Register of Controlled Trials (CENTRAL; March 2015), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, EMBASE (1988 to 2015, week 15), ClinicalTrials.gov and the European (EU) Clinical Trials register (both March 2015), Ovid MEDLINE(R).

Selection Criteria

All randomized controlled trials with an intervention duration of at least 24 weeks and that compared regular human insulins with short-acting insulin analogues in the treatment of adults with type 1 diabetes who were not pregnant were included.

Data Collection and Analysis

Independently, two review authors assessed trials and extracted data for risk of bias, and differences were resolved by consensus. We graded the overall study quality using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) instrument. Random-effects models were used for the main analyses and the results presented as odds ratios (OR) with 95% confidence intervals (CI) for dichotomous outcomes.

Main Results

Nine trials that fulfilled the inclusion criteria, including 2693 participants, were identified. Intervention duration ranged from 24 to 52 weeks, with a mean of approximately 37 weeks. Participants exhibited some diversity, mainly with regard to diabetes duration and inclusion/exclusion criteria. Most of the trials were performed in the 1990s and participants were recruited from Europe, North America, Africa, and Asia. None of the trials was carried out in a blinded manner so that the risk of performance bias, especially for subjective outcomes such as hypoglycemia, was present in all of the trials. Several of the trials exhibited inconsistencies in the reporting of results and methods. The mean difference (MD) in glycosylated hemoglobin A1c (HbA1c) was −0.15% (95% CI −0.2% to −0.1%; *P* value

< 0.00001; 2608 participants; 9 trials; low-quality evidence) in favor of insulin analogues. Comparison of the risk of severe hypoglycemia between the two treatment groups demonstrated an OR of 0.89 (95% CI 0.71 to 1.12; *P* value = 0.31; 2459 participants; 7 trials; very low quality evidence). For overall hypoglycemia, also taking into account mild forms of hypoglycemia, most of the data were of a low quality, but also did not indicate substantial group differences. In relation to nocturnal severe hypoglycemic episodes, two trials reported statistically significant effects in favor of the insulin analogue, insulin aspart. However, inconsistent reporting in publications and trial reports means that the validity of the result are questionable. There was also no clear evidence for a substantial effect of insulin analogues on health-related quality of life. However, there were few results only based on subgroups of the trial populations. In none of the trials were substantial effects regarding weight gain or any other adverse events reported. None of the trials were designed to investigate possible long-term effects (such as all-cause mortality, diabetic complications), in particular in people with diabetes-related complications.

Conclusions

Our analysis suggests that there is only a minor benefit of short-acting insulin analogues on blood glucose control in people with type 1 diabetes. To draw conclusions regarding the effect of short-acting insulin analogues on long-term patient-relevant outcomes, long-term efficacy and safety data are needed.

Improving efficacy of inhaled technosphere insulin (Afrezza) by post meal dosing: in-silico clinical trial with the University of Virginia/Padua type 1 diabetes simulator

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Background

Technosphere insulin (TI), which is an inhaled human insulin with a fast-action onset, provides a novel option for the control of prandial glucose. The University of Virginia (UVA)/Padua simulator was used in order to investigate, *in silico*, the potential benefit of different dosing regimens on postprandial glucose (PPG) control with the aim of supporting the design of further clinical trials. Tested dosing regimens included at-meal or post meal dosing, or dosing before and after a meal (split dosing).

Methods

We compared various dosing regimens of TI to each other and to insulin lispro in 100 virtual type 1 patients. For each regimen, individual doses were identified following different titration rules. The postprandial glucose profiles that resulted were analyzed to quantify efficacy and to assess the risk for hypoglycemic events.

Results

The approach allowed us to compare results with simulations of insulin lispro and to assess the benefit/risk for each TI dosing regimen. We identified a new titration rule for TI that could significantly improve the efficacy of treatment with TI.

Conclusion

Clinical trials, *in silico*, which compared the effect of treatment with different dosing regimens with TI and of insulin lispro suggest that splitting or post meal dosing of TI, together with an appropriate titration rule, can achieve better postprandial glucose control while at the same time yielding a lower risk for hypoglycemic events than that achievable with conventional treatment with subcutaneously administered rapid-acting insulin products.

Comment

Learnings of two decades of experience with rapid-acting insulin analogs show how difficult it is to scientifically prove meaningful clinical benefits despite general acceptance of the pharmacokinetic advantages of the rapid-acting analogs. The Danish HypoAna trial confirmed the benefit of these drugs in high-risk patients for severe hypoglycemia. The time needed to treat one patient with insulin analogues to avoid one episode of nonsevere nocturnal hypoglycemia was approximately three months. Also the most recent analysis of the Cochrane group suggests only a minor benefit of short-acting insulin analogues on blood glucose control mainly because of criticisms of study design and data quality. Possibly *in silico* approaches will be able to guide the assessment of future new drugs, both in terms of the development of new trials as well as characterizing patient subgroups that are likely to profit most from such a drug. Regarding the efficacy of inhaled technosphere insulin (Afrezza) such in silico testing has demonstrated that post meal dosing or split dosing might be the best approach. In light of the reimbursement discussion and criticisms of study design and proof of efficacy with current trial earlier use *in silico* studies may help to better design studies and save resources and time. For technosphere insulin this may be too late as it still is lacking impact on clinical practice in spite of regulatory approval.

Already last year we reported on the first published data on faster aspart (24). This new formulation with two well-known additional excipients, L-arginine and niacinamide, provides a stable formulation with faster initial absorption after subcutaneous administration. As it is not an entirely new drug entity this may help both regulatory approval and reimbursement scenarios. Both excipients appear on the U.S. Food and Drug Administration list of approved inactive ingredients, in products for injection that makes additional safety concerns unlikely (25). The Onset program is a phase 3 clinical

program with faster-acting insulin aspart that consists of several trials encompassing more than 2100 people with type 1 and type 2 diabetes. First results were presented at the 2016 Scientific Sessions of the American Diabetes Association. The Onset 1 trial (1143 people randomized) is a 26 + 26 week randomized, partially double-blind, basal-bolus, treat-to-target trial investigating faster-acting insulin aspart dosed at mealtime or 20 minutes after starting a meal compared with NovoLog dosed at mealtime, both in combination with a basal insulin in adults with type 1 diabetes. Only the data from the first 26 weeks were reported at the 76th Annual Scientific Sessions of the ADA in New Orleans. The primary endpoint was change from baseline HbA1c versus NovoLog, and a secondary endpoint was change from baseline in 2 hour PPG increment versus NovoLog. In Onset 1, after 26 weeks of randomized therapy, faster-acting insulin aspart showed statistically significantly greater HbA1c reduction versus NovoLog in adults with type 1 diabetes when dosed at mealtime ([95% confidence interval (CI)] −0.15 [−0.23; −0.07]). Faster-acting insulin aspart also showed comparable HbA1c reduction when dosed 20 minutes after starting a meal, compared with NovoLog dosed at mealtime ([95% CI] 0.04 [−0.04; 0.12]). Trial results for Onset 1 also showed superior reduction in 2 hour PPG increment ([95% CI] −0.67 [−1.29; −0.04] mmol/L) versus NovoLog. The change in 1 hour PPG increment, a secondary supportive endpoint, was also reduced ([95% CI] −1.18 [−1.65; −0.71] mmol/L) (26).

The Onset 2 trial (689 people randomized): a 26 week randomized, double-blind, basal-bolus, treat-to-target trial investigating faster-acting insulin aspart compared with NovoLog, both dosed at mealtime and in combination with a basal insulin and metformin in adults with type 2 diabetes. The primary endpoint was change from baseline HbA1c versus NovoLog, and a secondary endpoint was change from baseline in 2 hour PPG increment versus NovoLog. In Onset 2, faster-acting insulin aspart demonstrated noninferiority in HbA1c reduction compared with NovoLog ([95% CI] −0.02 [−0.15; 0.10]) in adults with type 2 diabetes. Trial results could not confirm a statistically significant reduction in 2 hour PPG increment ([95% CI] −0.36 [−0.81; 0.08] mmol/L). However, a statistically significant reduction in 1 hour PPG increment was shown with faster-acting insulin aspart ([95% CI] −0.59 [−1.09; −0.09] mmol/L) (2) that was a secondary supportive endpoint (27).

At the same meeting the first outpatient 14-day study comparing the effect of multiple daily injections of BioChaperone Lispro and Humalog (insulin lispro rDNA origin) on postprandial glycemic control relative to solid standardized meals in 36 patients with type 1 diabetes was presented. The study also investigated the effects of different timing of administration, with treatments being injected either at mealtime, 15 minutes before, or 15 minutes after the start of a solid meal. Whereas commercialized fast-acting insulin analogs are usually injected before the meal, an ultra-rapid insulin aims to allow injection at the time of the meal, or even after the start of a meal, while maintaining a reduction in the magnitude of glycemic excursions. In this double-blind, randomized, crossover study, 36 patients with type 1 diabetes used individualized doses of either BioChaperone Lispro or Humalog as the short-acting insulin in their multiple daily injection regimen, over two periods of 14 days. At the beginning and the end of each period, patients were subject to a meal tolerance test in the clinic to compare postprandial blood glucose profiles after identical bolus injections immediately before the meal of either BioChaperone Lispro or Humalog relative to a solid standard meal. At the beginning of the study, when injected at the time of meal, BioChaperone Lispro demonstrated a statistically significant 31 percent reduction in blood glucose excursion over the first two hours compared to Humalog. After 14 days of treatment for each treatment, BioChaperone Lispro also demonstrated a statistically significant 42% reduction in blood glucose excursion over the first two hours compared to Humalog, when injected at the time of the meal (28).

It is likely that ultra-fast-acting insulin aspart will be the first of the class to be commercially available as NovoNordisk announced the submission to FDA and EMEA late in 2015. Overall, it is likely that these ultra-rapid-acting insulins will be able show their greatest benefit in continuous subcutaneous insulin infusion (CSII) or even closed-loop insulin therapy (29). In conclusion, the pipeline of new insulins and insulin therapy promises to remain interesting in the near future.

Author Disclosure Statement

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