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Jointly presented by
The Johns Hopkins University School of Medicine
and the Institute for Johns Hopkins Nursing

Supported by educational grants from
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eDiabetes Review
VOLUME 2, ISSUE 2

BEYOND BASAL INSULIN: COMBINATION THERAPY WITH GLP-1 RAs

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In this Issue...

In patients with poorly controlled type 2 diabetes, insulin has historically been viewed as the most effective glucose-lowering agent. When therapeutic intensification beyond basal insulin plus oral agents is required, the addition of prandial insulin has generally been used. However, newer data are likely to shift the treatment paradigms toward greater use of GLP-1 receptor agonists (RAs).

In this issue we review recent publications describing:
- A meta-analysis of 15 trials investigating GLP-1 RAs in combination with basal insulin
- GLP-1 RA/basal insulin combinations across a wide range of insulin titration
- The efficacy and safety differences between short-acting (intermittent) versus longer-acting (continuous) GLP-1 RAs in combination with basal insulin
- The effects on glycemic control, adverse events, and weight when combining basal insulin with GLP-1 RAs vs prandial insulin.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Describe the glucose lowering effects of GLP-1 receptor agonists (GLP-1 RA) added on basal insulin.

- Compare the safety and efficacy of GLP-1 RA and prandial insulin in combination with basal insulin.

- Identify the physiologic differences between continuous and intermittent GLP-1 RA, alone and in combination with basal insulin.

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GUEST AUTHOR OF THE MONTH

Commentary:

Kathleen Dungan, MD, MPH
Associate Professor,
Associate Division Director of Clinical Services
Division of Endocrinology, Diabetes and Metabolism
The Ohio State University
Columbus, Ohio

Guest Faculty Disclosure

Kathleen Dungan, MD, MPH has indicated that she has received grant/research funding from AstraZeneca, GlaxoSmithKline, Merck & Co., Inc., and Sanofi-Aventis; has served as a paid member of committees, panels, or boards for Eli Lilly and Company; has served as a consultant for GlaxoSmithKline; and has received honorarium from UpToDate ®.

Program Information
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Accreditation
Credit Designations
Intended Audience
Learning Objectives
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Disclaimer Statement

Length of Activity
1.0 hour Physicians
1.0 contact hour Nurses

Launch Date
September 24, 2015

Expiration Date
September 23, 2017

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Unlabeled/Unapproved Uses

Kathleen Dungan, MD, MPH has indicated that there will be references to the unlabeled/unapproved uses of IDegLira, degludec, and lixisenatide.

Program Directors' Disclosures

IN THIS ISSUE

Program Directors

Nestoras Mathioudakis, MD
Assistant Professor of Medicine
Division of Endocrinology, Diabetes, & Metabolism
Associate Director, Inpatient Diabetes Management Service Program
Johns Hopkins University School of Medicine
Baltimore, Maryland

Kathleen Dungan, MD, MPH
Associate Professor, Associate Division Director for Clinical Services
Division of Endocrinology, Diabetes and Metabolism
The Ohio State University
Columbus, Ohio

Susan Porter, MSN, CRNP, CDE
Clinical Nurse Practitioner and Certified Diabetes Educator
Johns Hopkins University School of Medicine
Baltimore, Maryland

COMMENTARY

Patients with type 2 diabetes frequently do not reach HbA1c targets, despite the growing arsenal of glucose lowering agents.[1,2] Professional society guidelines recommend initial therapy with metformin, followed by intensification with any of several classes of agents, based on an assessment of efficacy, hypoglycemia risk, contraindications, cost, and preference.[3,4] However, therapeutic inertia may occur in routine practice as treatment regimens become more complex and time-consuming.[5,6] Because of the chronic, progressive nature of type 2 diabetes, many patients require insulin therapy. In this setting, GLP-1 RAs provide multiple potential advantages when combined with insulin.

GLP-1 RAs produce robust HbA1c reduction stimulating endogenous insulin secretion and inhibiting the inappropriate postmeal glucagon response in a glucose-dependent manner. These agents have a low hypoglycemia risk as a result. GLP-1 RAs promote weight loss in part through signaling in appetite centers of the hypothalamus.[7,8] Five agents are currently approved by the Food and Drug Administration (FDA), and these may be categorized according to whether they activate the GLP-1 receptor intermittently (exenatide twice daily) or continually (liraglutide [daily], exenatide once weekly, albiglutide [weekly], or dulaglutide [weekly]).[9-11] Another intermittent agent (lixisenatide [daily]), is expected to be submitted to the FDA within the year.[10]

As the HbA1c drops below 8%, postprandial glucose contributes more to HbA1c, and therefore agents that specifically target postprandial glucose may be of value.[12-14] While all GLP-1 RAs lower postprandial glucose, intermittent agents may lower postprandial glucose better than continuous agents, possibly because constitutive activation of the GLP-1 receptor may lead to attenuation of the effects on gastric emptying.[15] This is demonstrated directly in the reviewed article by Meier and colleagues and indirectly in the Diamant article. However, the postprandial glucose advantage is only observed at the meal immediately postdose and does not translate to better HbA1c reduction or weight loss. On the other hand, continuously activating agents tend to lower fasting glucose more than intermittently activating agents, often leading to better HbA1c reduction. Other, generally small, differences in HbA1c lowering, weight loss, tolerability, and ease of use are notable among individual agents in this class, as noted by recent reviews.

Historically, intensification of therapy after failure of basal insulin begins with the addition of prandial insulin.[5,6] However, the meta-analysis by Eng and colleagues (reviewed herein) demonstrates that GLP-1 RAs may be a compelling alternative strategy by lowering HbA1c without increasing the risk of hypoglycemia or weight gain. Several studies indicate that a single injection of prandial insulin at the largest meal each day provides only marginally less HbA1c reduction than three injections per day and minimizes hypolgycemia.[16-18] However, the Mathieu article demonstrates that GLP-1 RA therapy is associated with similar HbA1c reduction, with significantly fewer hypoglycemic events and less weight gain compared to a single injection of prandial insulin per day.

Moreover, GLP-1 RAs generate HbA1c reductions that are similar to or better than that produced by adding multiple injections of prandial insulin per day, as shown by the Eng, Diamant, and Rosenstock articles. These reviewed articles also report a lower risk of hypoglycemia compared to thrice daily prandial insulin when either is added to basal insulin. One potential criticism of the Rosenstock article was that prandial insulin titration was not performed optimally. However, the findings arguably still surpass the real-world setting, in which prandial insulin initiation and titration are less likely to be performed optimally.[19-21] In the article by Buse and colleagues, the investigators demonstrate that even among patients who require extensive insulin titration, the HbA1c lowering capability of exenatide is retained due to additional postprandial glucose reduction. While weight loss was attenuated at higher insulin titration increments, exenatide still prevented the weight gain that was observed with glargine alone.

In clinical practice, when GLP-1 RAs are added to existing insulin therapy, it is important to reduce the daily insulin dose by 10-20%, particularly if the HbA1c is < 8.0%.[22] Fixed dose combinations of basal insulin and GLP-1 RAs, as described in the Mathieu article, are in development and may reduce the number of daily injections per day.[23] There are currently few data to support the combination of basal-prandial insulin with GLP-1 RAs. However, one recent trial demonstrated that the addition of dulaglutide to prandial insulin provided similar HbA1c reduction with less weight gain and nocturnal hypoglycemia compared to basal-prandial insulin.[24]

The drawbacks of GLP-1 RAs should be considered. Treatment does involve additional injections and prescription coverage may vary. The class of drugs causes gastrointestinal side effects in a significant number of recipients, though this adverse effect tends to resolve over time. Contraindications include advanced renal failure, gastroparesis, and pancreatitis. The drugs demonstrate a small but measurable increase in heart rate, although the clinical relevance of this remains unclear.[25-27] Cardiovascular outcomes studies are under way and will provide more evidence of the long-term safety of these agents. In the first of these studies, lixisenatide demonstrated a neutral effect on major cardiovascular events and no change in the risk of heart failure.[28,29]

In summary, the addition of GLP-1 RAs with basal insulin is an effective glycemic control strategy which minimizes the risk of hypoglycemia and weight gain incurred by traditional basal-bolus insulin therapy.

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GLP-1 RA PLUS BASAL INSULIN: META-ANALYSIS OF 15 RCTS

Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. *Lancet*. 2014 Dec 20;384(9961):2228-2234.

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This systematic review and meta-analysis of randomized controlled trials examined the effect of combining GLP-1 receptor agonists and basal insulin on hemoglobin A1c, hypoglycemia, and weight gain. Fifteen studies of four different drugs (three exenatide, seven liraglutide, four lixisenatide, and one albiglutide) were included in the analysis. Studies were 12 to 36 weeks in duration.

• Six trials compared GLP-1 RA with placebo in combination with basal insulin.
• Three trials examined the use of basal or basal-bolus insulin with or without a GLP-1 RA (no placebo comparator).
• One trial compared basal insulin plus GLP-1 RA to basal insulin plus a single injection of bolus insulin.
• One trial compared a pre-mixed fixed-ratio combination of GLP-1 RA and basal insulin to placebo.
• Three studies compared basal insulin plus GLP-1 RA to intensive basal-bolus insulin therapy and was a pre-specified sensitivity analysis.

In both the overall analysis and in the prespecified sensitivity analysis, the combination of GLP-1 RA and basal insulin was associated with a greater mean reduction in HbA1c than produced by other treatment strategies (treatment difference - 0.44 [-0.602, - 0.29] overall and -0.10 [-0.172, -0.02] in the prespecified sensitivity analysis). In the overall analysis, there was evidence of between-study heterogeneity and publication bias, but further

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analyses determined that these factors did not affect the estimates. Patients were more likely to achieve a HbA1c less than 7% in the overall analysis but not in the sensitivity analysis.

There was no significant difference in relative risk of hypoglycemia in the overall analyses, though there was significant between-study heterogeneity. However, in the sensitivity analysis, GLP-1 RA in combination with basal insulin was associated with a lower risk of hypoglycemia compared to multiple prandial insulin injections per day (relative risk 0.67 [0.56 - 0.80]).

The overall analysis as well as the sensitivity analysis of studies comparing GLP-1 RA to multiple prandial insulin injections per day showed that the GLP-1 RA resulted in greater mean reduction in weight (treatment difference - 3.2 [- 4.90 to - 1.54] kg in the overall analysis and - 5.66 [- 9.80 to - 1.51] kg) compared with other therapies, with significant between-study heterogeneity.

The authors note that these findings were consistent in these studies, despite differences in background glucose lowering therapy, type of GLP-1 RA, and sequence of initiation relative to basal insulin. Furthermore, heterogeneity was likely due to these study differences, since it was eliminated during the sensitivity analysis. This meta-analysis is limited by the inclusion of trials that were relatively short in duration and some trials that were open label in design.

GLP-1 RA SAFETY AND EFFICACY ACROSS A RANGE OF INSULIN TITRATION

Buse JB, Han J, Miller S, MacConell L, Pencek R, Wintle M. Addition of exenatide BID to insulin glargine: a post-hoc analysis of the effect on glycemia and weight across a range of insulin titration. *Curr Med Res Opin*. 2014 Jul;30(7):1209-1218.

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When a GLP-1 RA is combined with insulin, the resulting glucose control, weight gain, and hypoglycemia may depend upon the degree of insulin titration that is required. The objective of this posthoc analysis was to further investigate this possibility. The original study was a 30-week phase 3 trial in which patients with type 2 diabetes on preexisting insulin glargine (at least 20 units/day) with or without metformin or pioglitazone were randomized to placebo (N = 123) or exenatide twice daily (N = 138). The glargine dose was initially reduced by 20% in subjects with a baseline HbA1c of < 8%. Glargine was titrated according to a published algorithm after the exenatide dose was optimized.1 Patients were divided into tertiles (T) based on the change in insulin dose from baseline to study end.

The mean insulin dose titration in the exenatide and glargine groups respectively was - 7 and - 5 units in T1, +11 and +10.5 units in T2, and +35 and +41 units in T3. Fasting glucose was reduced similarly between the exenatide and glargine groups within each tertile, indicating adequate titration of glargine. However, there was a larger reduction in HbA1c with exenatide twice daily compared to placebo across all tertiles (- 1.18% vs. - 0.78% in T1, P = .081, - 1.65% vs - .85%, P = .0001 in T2, - 1.65 vs - 1.12 P = .012 in T3), and was statistically significant in T2 and T3. This was a result of greater reductions in postmeal glucose levels with exenatide in all tertiles, mainly following breakfast and dinner. More subjects obtained an HbA1c of less than 7% in all tertiles, although it was only significant in T2 and T3. There was significantly more weight loss with exenatide than with placebo in T1 (- 0.286 vs. - 0.12 kg, P = .0006) and T2 (- 1.64 vs + 0.02 kg, P = .0133), and exenatide prevented insulin-associated weight gain in T3 (- 0.09 vs. =1.96 kg, P = .0006). Weight gain was associated with just 5 units of additional insulin in the placebo group compared to 33 units in the exenatide group. Hypoglycemia was numerically less frequent with exenatide twice daily across all tertiles but this was not statistically significant. Gastrointestinal side effects were more common with exenatide twice daily than with placebo, and this was not affected by insulin titration.

The results should be interpreted in light of their posthoc nature. This analysis demonstrates that GLP-1 RAs provide better glycemic control without more hypoglycemia when substantial insulin titration (more than 5 units/day) is required. Exenatide was associated with weight loss at smaller insulin adjustments and avoidance of weight gain that is commonly observed with larger insulin adjustments.

SHORT-ACTING VS LONG-ACTING GLP-1 RA IN COMBINATION WITH BASAL INSULIN

Meier JJ, Rosenstock J, Hincelin-Méry A, et al. Contrasting effects of lixisenatide and liraglutide on postprandial glycemic control, gastric emptying, and safety parameters in patients with type 2 diabetes on optimized insulin glargine with or without metformin: A randomized, open-label trial. *Diabetes Care*. 2015 Jul;38(7):1263-1273.

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This multicenter, randomized, controlled trial compared the short-acting GLP-1 RA lixisenatide 20 mcg once daily, to longer-acting liraglutide at 1.2 or 1.8 mg once daily for eight weeks in combination with optimally titrated basal insulin glargine. Patients (N = 149) with type II diabetes and HbA1c of 6.5-9.5% who were receiving NPH or glargine for three months prior to screening (plus or minus metformin) were eligible. Following a four to 11 week basal insulin glargine optimization period, patients were randomized to one of the three treatment arms, stratified by baseline HbA1c. The glargine dose was reduced by 20% if the HbA1c was less than 7.5% and subsequently titrated upward as needed to maintain a fasting glucose of 80 mg/dL -100 mg/dL.

Baseline characteristics were similar with HbA1c of 7.8 ± 0.8%. Fasting glucose at randomization was 94 mg/dL - 96 mg/dL in all treatment arms, indicating adequate glargine titration. Lixisenatide was associated with greater reduction in the area under the curve for postprandial glucose following the start of a standardized breakfast (30 minutes after injection through four hours postmeal, $P < .0001$ for comparisons with both doses of liraglutide). A 24-hour plasma glucose profile demonstrated a significant reduction postbreakfast for lixisenatide compared to both liraglutide doses, but similar glucose levels across treatment arms the rest of the day. The change in fasting glucose was similar across the three treatment arms. HbA1c decreased to a mean of 6.1% - 6.2% in all three treatment arms but decreased slightly more with liraglutide 1.8 mg compared to lixisenatide (marginal mean treatment difference of -0.2% [95% one-sided CI -0.3, -0.04, $P = .007$]). The 1.2 mg dose of liraglutide was no different (marginal mean treatment difference -0.1% [95% one-sided CI -0.2, 0.04, $P = .17$] from lixisenatide. Glucagon was reduced similarly in all three treatment arms, while C-peptide was reduced with lixisenatide and increased with both doses of liraglutide. The marginal mean ±SE reduction in weight for lixisenatide, liraglutide 1.2 mg, and liraglutide 1.8 mg was + 1.6 ± 0.5, - 1.6 ± 0.5, and - 2.4 ± 0.5 kg respectively and was similar across groups.

Gastric emptying was delayed to a greater extent with lixisenatide compared to both doses of liraglutide. Symptomatic hypoglycemia tended to be more common with lixisenatide compared to liraglutide (29 vs. 19% - 21%), but there tended to be fewer gastrointestinal side effects with lixisenatide. Heart rate was increased to a greater degree with liraglutide (9.3 and 9.2 beats per minute for 1.2 and 1.8 mg doses) and displayed nocturnal predominance compared to lixisenatide, which increased heart rate 3.3 beats per minute and showed a daytime pattern ($P < .0001$ for both). Likewise, pancreatic enzymes were increased significantly more, with both liraglutide doses compared to lixisenatide.

The study was limited by short treatment duration, open label design and mostly Caucasian population. Lixisenatide is currently available in Europe but not in the U.S. In conclusion both lixisenatide and liraglutide, when combined with basal insulin glargine, results in improved glycemic control with slightly different safety and efficacy profiles that are consistent with other short-acting and longer-acting GLP-1 RAs, respectively.

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GLP-1 RA VS A SINGLE INJECTION OF PRANDIAL INSULIN

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Traditional means of treatment intensification for patients with type 2 diabetes requiring basal insulin involve addition of prandial insulin, and improvement in glycemic control can often be sufficient with a single injection of prandial insulin per day. In this 28-week study, investigators compared basal insulin treatment intensification with once-daily liraglutide to the addition of a single dose of prandial insulin daily.

Subjects who completed 104 weeks of optimized basal insulin titration (basal insulin degludec, currently not FDA approved) in the BEGIN ONCE-LONG trial with an HbA1c > 7% were eligible. Subjects were randomized to either liraglutide (N = 88) or rapid acting insulin analogue (RAIA, aspart, N=89), and all continued basal insulin and metformin. A third, nonrandomized arm (N =236) with an HbA1c < 7% continued basal insulin and metformin alone. In the liraglutide arm, the initial dose of basal insulin was reduced by 20% at randomization to prevent hypoglycemia. Liraglutide was titrated up to a dose of 1.8 mg to meet fasting glucose < 5 mmol/L. Basal insulin was titrated according to a published algorithm after six weeks. In the aspart arm, the initial dose was 4 units per day with the largest meal and titrated weekly.

The two randomized groups had similar baseline characteristics, except slightly higher weight in the liraglutide arm. By trial end the mean basal insulin dose was 0.65 unit/kg/day in the liraglutide arm and remained lower than the pre-randomization value. The mean basal and prandial dose was 0.64 and 0.21 unit/kg/day in the aspart arm. The basal insulin dose remained stable in the nonrandomized arm, 0.59 unit/kg/day. Liraglutide reduced HbA1c more than a single daily injection of aspart (-0.74 vs. -0.39%, P = .0024). Fasting glucose and nine-point self-monitored blood glucose profiles were similar in both groups. Liraglutide subjects had significantly less confirmed (estimated rate ratio 0.13, 95% CI 0.05,0.40, P = .002) and nocturnal confirmed hypoglycemia, as well as greater weight loss than subjects in the aspart arm (- 2.8 vs. +0.9 kg, P < .0001). More patients in the liraglutide group achieved HbA1c < 7.0% without hypoglycemia or weight gain (49.4 vs 7.2%, P < .0001). In the nonrandomized subjects, fasting glucose, HbA1c, and nine-point self-monitored blood glucose profiles remained stable. Adverse effects were mainly gastrointestinal in the liraglutide group but otherwise similar between groups.

The study was limited by lack of blinding and relatively small sample size. These limitations may explain why there is a difference in HbA1c and hypoglycemia but nonsignificant differences in self-monitored blood glucose levels. In conclusion, this study suggests that better glycemic control can be achieved with the addition of a GLP-1 RA with lower risk of hypoglycemia or weight gain compared to prandial insulin.

SHORT-ACTING GLP-1 RAS VS THRICE DAILY PRANDIAL INSULIN

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In this 30-week, open-label, randomized, noninferiority trial, 627 patients with HbA1c greater than 7.0% who underwent optimal titration of basal insulin glargine plus metformin were randomized to exenatide or thrice daily prandial insulin lispro. Sulfonylureas were

discontinued prior to a 12 week lead-in period, in which glargine was titrated to a fasting glucose target of 5.6 mmol/L (101 mg/d). The glargine dose was reduced 10% if the HbA1c was < 8.0% prior to initiation of exenatide and by 30% - 50% prior to initiation of lispro. Lispro was started at a daily dose equal to the reduction in dose of glargine and was titrated to a premeal glucose of 5.6 to 6.0 mmol/L. Exenatide was added to the two largest meals of the day and titrated to 10 mcg per meal. Titration algorithms for both glargine and lispro were prespecified to ensure consistency.

In the lead-in phase, 92 of 917 patients enrolled achieved an HbA1c < 7% and were excluded from randomization. Of the 825 patients remaining, 652 were randomized to either intervention, and 627 ultimately continued in the study. Discontinuation rates were 17% in the glargine and 14% in the exenatide arms, respectively. Baseline characteristics were similar across treatment groups, with 36.2% having previously taken a sulfonylurea and had mean HbA1c levels of 8.2%. In the per-protocol population, both groups demonstrated a reduction in HbA1c of 1.13 (95% CI - 1.24, -1.03) for exenatide and - 1.10 (95% CI - 1.20, - 1.00) for lispro, resulting in a - 0.04% (95% CI - 0.18, 0.11) treatment difference, meeting the prespecified criteria for noninferiority, with an upper bound of the confidence interval < 0.3%. Similar results were observed in the intention to treat population. Achievement of HbA1c ≤ 7.0 % was similar at 49.6% and 49.0% in the exenatide and lispro groups, respectively; but fasting glucose reduction was greater with exenatide. Postprandial glucose reductions were similar at breakfast and supper, but greater at lunch in the lispro group. Weight decreased by 2.5 ± 0.3 kg in the exenatide group and increased 2.1 ± 0.2 kg in the glargine group (treatment difference - 4.6 kg [95% CI -5.2, -3.9]. The median glargine dose was 57 and 52 units in the exenatide and lispro groups, respectively, and the median dose of lispro was 34 units at endpoint. While both groups reported improvements in treatment satisfaction, the exenatide group reported greater improvement in perceived frequency of hyperglycemia, hypoglycemia, and impact of weight on quality of life.

Treatment-emergent adverse events were more common with exenatide and were largely gastrointestinal (47% vs. 13%). Hypoglycemia was 41% vs 30% in the lispro and exenatide groups overall and 34% vs 15% for confirmed nonnocturnal events.

In conclusion, both treatments improved glycemic control similarly, although exenatide was associated with better fasting glucose, less daytime hypoglycemia, greater weight loss, and better quality of life. A strength of the study is that the glargine was optimized prior to addition of lispro or exenatide. There was a slight difference in glargine dose between groups that was accounted largely by overnight hypoglycemia, suggesting that the inherent characteristics of GLP-1 agonists rather than lack of adequate titration per se was responsible for differences in fasting glucose. Previous protocols reduced the dose of glargine by 20% in patients with an HbA1c < 8 prior to initiation of GLP-1 agonists, but 10% was deemed appropriate in this study. Study limitations o include a complicated titration schedule for lispro, and practice patterns may vary with respect to intensification of glargine insulin from the number of injections to the degree of reduction in glargine dose. In addition, the study was short-term and did not address next steps in subjects who fail the exenatide/glargine combination.

LONG-ACTING GLP-1 RAS VS THRICE DAILY PRANDIAL INSULIN

Rosenstock J, Fonseca VA, Gross JL, et al; Harmony 6 Study Group. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. Diabetes Care. 2014 Aug;37(8):2317-2325.

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This 26 week, randomized, open label, phase 3 study compared the GLP-1 RA albiglutide once weekly to thrice daily prandial insulin, both in combination with optimized basal insulin glargine and metformin with or without pioglitazone or an alpha glucosidase

inhibitor. It is unclear how the dose of glargine was adjusted when albiglutide or lispro was added, and the initial lispro dosing and subsequent titration was left to investigator discretion. Glargine was titrated to a fasting glucose of < 5.6 mmol/L and lispro was titrated according to investigator discretion for a mean premeal glucose 4.4 mmol/L-7.2 mmol/L and peak postmeal glucose of < 10 mmol/L. Albiglutide dose was increased from 30 mg to 50 mg between 8-12 weeks if the HbA1c was > 8% and between 12-26 weeks if the HbA1c was > 7.5%.

Overall, 586 subjects were randomized and 566 received treatment. Baseline characteristics were similar, with a mean HbA1c of 8.5% in the albiglutide group and 8.4% in the lispro group. HbA1c was reduced 0.82 ± 0.06% in the albiglutide group and - 0.66% in the lispro group, for a treatment difference of - 0.16% (95%CI - 0.32, .00), meeting the prespecified non-inferiority criteria. HbA1c < 7% was achieved by 30% of the albiglutide group and 25% of the lispro group. The reduction in fasting glucose was numerically greater for albiglutide compared to lispro but not statistically significant. The mean glargine dose was 53 units and 51 units in the glargine and lispro arms, and the lispro dose was 31 units at study end. In total, 28% of albiglutide patients and 38% of lispro patients required rescue therapy. Subjects in the albiglutide arm lost 0.7 ± 0.2 kg and those in the lispro arm gained 0.8 &pllusmn; 0.2 kg (P < .0001). Adverse events were similar in both study arms. Gastrointestinal events were relatively low (< 5% in the albiglutide arm and even lower at study end) but were the most common reason leading to withdrawal. Injection site reactions were 9.5% in the albiglutide arm and 5.3% in the lispro arm and were mild or moderate. Hypoglycemia occurred in 16% of the albiglutide arm and 30% of the lispro arm.

In conclusion, once weekly albiglutide plus basal insulin was associated with similar improvement in HbA1c with greater weight loss and less hypoglycemia compared to lispro insulin. The advantages of albiglutide also includes fewer injections. The study was limited by open label design and possibly lack of strict enforcement of basal and prandial insulin titration.

KEY TAKEAWAYS

• The available evidence supports the use of GLP-1 receptor agonists (RAs) for use with basal insulin over conventional basal-prandial insulin regimens.
• The HbA1c reductions observed with GLP-1 RAs are robust, even among patients requiring large insulin doses.
• Though minor differences in efficacy (fasting glucose, postprandial glucose, and HbA1c) are observed across GLP-1 RAs, the choice of GLP-1 RA may vary based upon a number of other factors.

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