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GUEST EDITORIAL

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NEW APPROACHES TO DIABETES MANAGEMENT: INHALED INSULIN

Clinical studies have confirmed that the intensive management of hyperglycemia in type 2 diabetes mellitus (T2DM) can lead to significant reductions in long-term complications such as neuropathy and retinopathy. In light of these findings, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recently issued new management guidelines advocating a more aggressive approach to achieve and maintain glycemic goals. For most patients, this new algorithm recommends initial lifestyle intervention combined with metformin therapy, followed by the timely addition of basal insulin, a sulfonylurea, and/or a thiazolidinedione. The third treatment step consists of insulin initiation or intensification as needed to achieve or sustain target A1C levels.

The ADA/EASD's recommendation for earlier and more intensive insulin use distinguishes these guidelines. Insulin treatment has historically been introduced late in the course of disease progression, but recognition of the benefits of early, physiologic insulin therapy is critical if we are to overcome patient and physician obstacles to multiple daily injection regimens. To that end, there has been increased interest in noninvasive routes of insulin administration, including oral, nasal, transdermal, and pulmonary delivery. The oral, nasal, and transdermal approaches have shown proof of concept in small-scale studies, but significant hurdles still exist. By contrast, the lung's large, vascular, highly per-

meable alveolar surface area makes it an excellent environment for efficient insulin absorption. Furthermore, the pharmacodynamics of inhaled insulin, which include an onset of action comparable to that of rapid-acting injectable insulin, with peak plasma levels achieved in 15 to 40 minutes, and a duration of action intermediate between rapid-acting and regular insulin, make it well suited for prandial use.

Although pulmonary insulin administration was first attempted over 50 years ago, it did not become a clinical reality until recently, when partnerships between pharmaceutical companies and pulmonary drug delivery device manufacturers led to the development of a number of inhaled insulin products (Table 1). Some of these systems are either commercially available or have reached phase 3 clinical testing, while others are still in the early stages.

Emerging evidence indicates that not only is the efficacy and safety of inhaled insulin comparable to conventional syringe-injected (SI) insulin but inhaled insulin has also been associated with increased treatment satisfaction and quality of life. Recent research, discussed below, provides long-term assessments of the efficacy and safety of inhaled insulin, as well as evaluations of new pulmonary delivery systems. It is important to note that no

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ABOUT THE COUNCIL FOR THE ADVANCEMENT OF DIABETES RESEARCH AND EDUCATION

The Council for the Advancement of Diabetes Research and Education (CADRE) is a nonprofit organization committed to reducing the devastating complications of both type 1 and type 2 diabetes through achievement of tight metabolic control.

To achieve this goal, CADRE provides health care professionals with scientific information and educational programs to enable them to manage and empower their patients with diabetes.

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published clinical trials conducted to date have directly compared inhaled insulin with pen-injected insulin analogs.

Recent Research on Inhaled Insulin

Exubera: The results of several clinical trials evaluating Exubera dry-powder inhaled insulin (currently the only commercially available system) were presented at the ADA's 66th Annual Scientific Sessions and the EASD's 42nd Annual Meeting, both held in 2006. In a 2-year, open-label, parallel-group, multicenter study of Exubera in T2DM, patients were randomized to regimens consisting of basal insulin combined with either Exubera (n=319) or SI or pen-injected (PI) prandial insulin (n=316). The Exubera and injectable insulin groups achieved similar A1C reductions, from 7.7% and 7.8%, respectively, at baseline to a mean of 7.3%.

Table 1. Inhaled Insulin Products Available or in Development

Product trade name	Type of product and inhaler	Product developer/partners	Current development status
Exubera®	Dry powder; passive inhaler	Nektar Therapeutics/Pfizer	Approved by the US Food and Drug Administration (FDA)
AERx® iDMS	Liquid aerosol; microprocessor-controlled inhaler	Aradigm/Novo Nordisk	Phase 3
HIIP®	Dry powder; passive inhaler	Alkermes/Eli Lilly	Phase 3
Technosphere®	Dry powder microparticles; passive inhaler	MannKind	Phase 3
Unnamed	Dry crystals; propellant inhaler	Kos Pharmaceuticals	Phase 1/2
ProMaxx®	Dry powder microspheres	Baxter BioPharma Solutions, Epic Therapeutics	Phase 1
Alveair®	Liquid aerosol; generic inhaler	CoreMed	Phase 1
BioAir®	Coated dry particles	BioSante Pharmaceuticals	Preclinical testing
Aerodose®	Liquid aerosol; passive inhaler	Nektar Therapeutics, Aerogen	Unknown
MicroDose DPI®	Dry powder; breath-activated electronic inhaler	MicroDose Technologies/Novartis	Unknown

Adapted from de Galan BE, et al. *Neth J Med.* 2006;64(9):319-325.

The Exubera group experienced slightly lower rates of hypoglycemia overall, with severe hypoglycemic events comparable between Exubera and injectable insulin. Furthermore, patients receiving Exubera experienced greater fasting plasma glucose (FPG) reductions compared with the injectable insulin group (-15.6 mg/dL versus -1.1 mg/dL, respectively) as well as less weight gain (+1.7 kg versus +3.0 kg, respectively). Minor changes in pulmonary function were observed early in the study among Exubera patients, but these were small and nonprogressive throughout the 2-year treatment period. The adverse event profiles for the 2 groups were similar except for an increased, mild cough observed in the Exubera group.

The results of an analogous study of Exubera in adults with type 1 diabetes mellitus (T1DM) were also presented. Participants were randomized to Exubera (n=291) or SI or PI insulin (n=291) plus basal NPH or glargine. Findings were sim-

ilar to those reported in the T2DM study, with comparable levels of glycemic control maintained in the Exubera and injectable insulin groups after 2 years.

Results from a 6-month retrospective analysis of the effects of Exubera on body weight in T1DM and T2DM were also reported at the 2006 EASD. Exubera combined with intermediate- or long-acting injectable insulin was compared with conventional injectable insulin regimens. Patients experienced less weight gain with Exubera compared with injectable insulin with comparable glycemic control and hypoglycemic event rates.

HIIP: The most recently published results on this dry-powder insulin formulation detailed an open-label, randomized, 7-period, crossover phase 1 trial comparing the pharmacokinetic and glucodynamic properties of HIIP with SI insulin lispro in healthy volunteers (n=20). HIIP demonstrated a longer time-action profile, but

Continued

a comparable overall exposure and metabolic effect compared with insulin lispro. HIIP was also safe and well tolerated, with no statistically significant effects on pulmonary function and no reported adverse events. A phase 2 trial randomized patients with T1DM to a 12-week treatment regimen of basal insulin glargine combined with either HIIP or SI lispro or regular insulin. Glycemic control and hypoglycemic events were comparable between the 2 groups, although FPG improvements with HIIP did trigger some nocturnal hypoglycemia, which was managed with diet and dosing adjustments. Small, reversible changes in pulmonary function were observed in the HIIP group and were believed to be not clinically significant.

Currently, HIIP is being evaluated in a phase 3 clinical program, which includes a 2-year evaluation of its efficacy and safety in patients with T1DM, a 1-year study in patients with T1DM or T2DM plus mild-to-moderate asthma or chronic obstructive pulmonary disease, and a 3-month study (with projected follow-up to 18 months) comparing HIIP with injectable insulin in patients with T2DM.

Technosphere: A 12-week, randomized, placebo-controlled trial of Technosphere dry-powder microparticle inhaled insulin (TII) in patients with T2DM was presented at the 66th Annual Scientific Sessions of the ADA. Results indicated that treatment with TII led to statistically significant improvements in both glycemic control and quality of life. A1C levels in the TII treatment group (n=48) decreased from 7.7% at baseline to 7.0%. Patients' attitudes toward insulin therapy also showed significant improvement following treatment with inhaled insulin.

In another study of TII in T2DM, patients received insulin glargine combined with either TII or rapid-acting insulin aspart. Study results, presented at the 2006 EASD, showed no statistically significant changes in pulmonary function with TII compared with injectable insulin following 6 months of treatment.

The TII phase 3 program is ongoing; enrollment was recently completed for a large (n>1800) randomized, long-term safety study evaluating TII in T1DM, T2DM, and individuals without diabetes.

AERx iDMS: Although no clinical research on the liquid aerosol insulin AERx was published or presented at major conferences in 2005 or 2006, recent announcements indicate that a large phase 3 program (n=3400) has been initiated.

Special Considerations With Inhaled Insulin

In its January 2006 approval of Exubera, the FDA emphasized the need for long-term follow-up studies of inhaled insulin. Clinical research continues to provide evidence of the safety and efficacy of this formulation; current findings indicate that

- The most common adverse event associated with dry-powder inhaled insulin is a mild-to-moderate postdosing cough that improves with continued treatment.
- In general, the risk of hypoglycemia and other side effects with inhaled insulin is comparable to that of injectable insulin.
- Small, nonprogressive reductions in both 1-second forced expiratory volume and carbon monoxide diffusing capacity have been observed with inhaled insulin therapy. However, these have been shown to be reversible with treatment discontinuation.
- Although increases in serum insulin antibody levels are greater with inhaled compared with injectable insulin, no clinically significant effects have been associated with altered antibody levels.

Other noteworthy observations between inhaled insulin therapy and injectable insulin regimens include less weight gain, greater FPG reductions, and improved treatment satisfaction.

Research indicates that inhaled insulin provides outcomes comparable to injectable insulin.

Conclusion

Research indicates that inhaled insulin used in the treatment of T1DM and T2DM provides outcomes comparable to injectable insulin. Patients also appear to prefer inhaled insulin due to its ability to overcome the injection barrier. Additional long-term efficacy and safety studies are underway, with all signs indicating that inhaled insulin is a promising alternative therapy for diabetes management.

Dr. Cefalu serves as a consultant to, is on the speakers' bureau for, and conducts research sponsored by Amylin Pharmaceuticals, Eli Lilly and Company, and Pfizer; he also conducts research sponsored by Novo Nordisk Pharmaceuticals.

Suggested Reading

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DIABETES TACTICS

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BENEFITS OF EARLY COMBINATION THERAPY IN TYPE 2 DIABETES

Case Presentations

Two patients—Mr. Smith and Mr. Patterson—visit their respective physicians on the same day. Both are 58 years of age; report engaging in moderate, occasional physical activity (eg, bowling, golfing); and have had T2DM treated with lifestyle management alone for about 3 years. They have nearly identical metabolic profiles and lab results (Table 1), including A1C levels of 8.3%.

Mr. Smith's physician starts him on metformin 500 mg twice daily and asks the patient to return in 3 months for reevaluation. At that time, Mr. Smith's A1C is 7.8%, whereupon his metformin dose is increased to 1000 mg twice daily. This is the metformin dose typically associated with maximal effect. At Mr. Smith's

Table 1. Cases: Vital Statistics

	Mr. Smith	Mr. Patterson	Ms. Anderson	Ms. Ortiz
BMI (kg/m²)	32.3	32.5	28.2	28.6
A1C level (%)	8.3	8.3	9.8	9.8
FPG (mg/dL)	130	125	180	190
PPG (mg/dL)	220	225	250	260
Blood pressure (mm Hg)	130/89	127/77	145/88	142/88
LDL cholesterol (mg/dL)	110	104	110	100
HDL cholesterol (mg/dL)	41	38	48	50
Triglycerides (mg/dL)	110	110	150	130

BMI = body mass index; FPG = fasting plasma glucose; PPG = postprandial glucose; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

next 3-month visit, his A1C level is 7.4%. Mr. Smith's physician adds the sulfonylurea glimepiride 2 mg/day to his regimen. Three months later, Mr. Smith's A1C is 6.8%. It has taken 9 months for Mr. Smith to achieve satisfactory glycemic control.

The other patient, Mr. Patterson, is started immediately on a twice-daily glipizide/metformin combination pill (doses, 2.5 mg and 1000 mg, respectively). At his 3-month follow-up visit, Mr. Patterson's A1C has decreased by 1.5%, to 6.8%.

Ms. Anderson and Ms. Ortiz also visit their respective physicians on the same day. These women are 67 years old, their physical activity is limited to household activities, and both have had T2DM for 8 years. They also have substantially elevated A1C levels (9.8%), are currently taking only metformin at maximally effective dose (1000 mg twice daily), and share nearly identical metabolic profiles and lab results (Table 1).

Ms. Anderson's physician prescribes a sulfonylurea (glimepiride, 2 mg twice daily), which by 3-month follow-up has decreased her A1C to 8.3%. To improve glycemic control, basal insulin glargine is added next, starting at 10 U/day and titrated upward on a weekly basis using the Treat-to-Target methodology (illustrated in Table 2). This protocol combines bedtime insulin with existing oral agents

to target an FPG of ≤ 100 mg/dL (assessed through regular self-monitoring of blood glucose). Whenever a patient's mean FPG values over 2 days exceed this target, insulin dosage is adjusted. At her next 3-month visit, Ms. Anderson's A1C level is 7.4% and her glargine dose is adjusted. At her 9-month visit, her A1C is 6.9%.

Ms. Ortiz's physician immediately prescribes both a sulfonylurea (glimepiride, 2 mg twice daily) as well as basal insulin glargine titrated using the Treat-to-Target protocol. At her 3-month follow-up, Ms. Ortiz's A1C level is 6.7%.

Analysis

These cases demonstrate the importance of implementing appropriate treatment based on a patient's presenting A1C level. Despite evidence that a single agent was unlikely to be successful (discussed in more detail in the Recommendations section, below), only 1 treatment at a time was added to Mr. Smith's and Ms. Anderson's regimens.

These cases also illustrate the concept of clinical inertia, which can occur when too rigid an interpretation of stepwise T2DM treatment is imposed and/or when delays in therapeutic transition lead to prolonged periods of loss of glycemic control. Research has confirmed that physicians are likely to delay the transition to combination therapy until A1C levels are

Continued

Table 2. Treat-to-Target Insulin Titration Schedule

Start with bedtime basal insulin 10 U/day and adjust weekly	
Mean 2-day self-monitored FPG values (mg/dL)	Increase insulin dosage (IU/day)
>180	8
140-180	6
120-140	4
100-120	2

Adapted from Riddle MC, et al. *Diabetes Care*. 2003;26(11):3080-3086.

≥9%. Most recently, a report retrospectively evaluated a large, well-managed health management organization cohort (n=7208). They found that it was standard for patients with T2DM to experience a cumulative 10 years of A1C levels >7% (assessed as the time accrued between the failure of one treatment to control blood glucose levels and the correction of the problem). Although it took 9 months for Mr. Smith and Ms. Anderson to achieve their A1C targets, these hypothetical patients actually experienced a more rapid therapeutic transition than would be likely in many clinical practices.

Established evidence underscores the potential microvascular benefits associated with achieving and maintaining continuous glycemic control from early in the course of diabetes, while emerging evidence indicates that early, aggressive control may provide substantial cardiovascular benefit as well. It is increasingly clear that an A1C of <7.0% is the minimum acceptable standard for care and that for many patients an even lower goal is ideal. In early 2002, the American Association of Clinical Endocrinologists (AACE) was the first major organization to recommend an A1C target of ≤6.5%. This was followed by the CADRE recommendation that A1C levels be targeted as low as possible, adjusting as needed for unacceptable side effects. CADRE further specified that prompt action should be undertaken as soon as A1C levels exceed 7.0%. Most recently in 2006, the American Diabetes Association reaffirmed its A1C target of <7.0% but also indicated that for individual

patients A1C targets should be as close to normal as possible (ie, 4.0% to 6.0%) without incurring substantial hypoglycemia.

Recommendations

We now understand that the degree to which most agents control hyperglycemia is dependent upon the patient's initial A1C level. A 2006 meta-regression by Bloomgarden and colleagues evaluated 61 studies to identify the glucose-lowering efficacy of available oral agents among patients with varying baseline A1C levels. The majority (46) of these 61 studies used single-agent therapy. As shown in Table 3, a patient with an A1C of 8.0% to 8.9% could expect a mean reduction of about 0.6% with most agents. Thus it follows that such a patient could not expect to achieve an A1C of <7.0% using a single agent.

Although similar data are not available for combination therapy, it is reasonable to extrapolate this analysis to patients with A1C levels >9.5% and to surmise that they are unlikely to achieve glycemic

control even when 2 antihyperglycemic agents are used initially. Such patients might instead start with a combination of 2 oral agents (usually a secretagogue and a sensitizer) plus basal insulin. The early use of basal insulin will reduce FPG levels and can rapidly reduce glucotoxicity. In many instances, patients can be weaned off insulin once an acceptable A1C level is achieved and then managed for some time on a combination of oral agents.

To make these decisions, AACE, in conjunction with the American College of Endocrinology (ACE), developed a useful tool—the Road Map for the Prevention and Treatment of Type 2 Diabetes. Specifically, the Road Map recommends the “continuous titration” of new medications over a 2- to 3-month period until goal is achieved, with specific interventions guided by the patient's presenting A1C level. Road Maps for patients with T2DM who are naïve to antihyperglycemic drug therapy and for patients already receiving drug treatment can be downloaded from www.aace.com.

Two treatment options that might be useful include 70/30 premixed insulin aspart and the incretin therapies (glucagon-like peptide-1 [GLP-1] receptor agonists and dipeptidyl peptidase-4 [DPP-4] inhibitors). A 2005 trial of insulin-naïve patients with T2DM, A1C levels ≥8.0%, and inadequately managed with 1 or more oral therapies compared the efficacy and safety of initiating insulin with basal glargine once daily or twice daily 70/30 premixed insulin. Similar efficacy was observed in

Continued

Table 3. Observed Relationship Between Baseline A1C and A1C Reductions Following Monotherapy Initiation

Baseline A1C (%)	Change in A1C (%)
6.0-6.9	-0.2
7.0-7.9	-0.1
8.0-8.9	-0.6
9.0-9.9	-1.0
10.0-11.8	-1.2

Adapted from Bloomgarden ZT, et al. *Diabetes Care*. 2006;29(9):2137-2139.

patients with A1C levels $\leq 8.5\%$; however, in patients with A1C levels $>8.5\%$, 70/30 premixed insulin was superior. Patients receiving this insulin preparation did gain more weight and experienced greater rates of hypoglycemia compared with patients receiving insulin glargine.

The GLP-1 receptor agonist, exenatide, and DPP-4 inhibitors (which increase endogenous GLP-1 levels) lower A1C levels by about 0.7% in patients with initial A1C levels of 8.0%. This is similar to other available agents (see Table 3). Exenatide needs to be injected twice daily and is not approved for monotherapy. Sitagliptin, the only DPP-4 inhibitor currently approved for use in the US, is an oral medication that can be used once daily either as monotherapy or in combination with metformin or a thiazolidinedione. This topic is addressed further in Dr. Jens Juul Holst's article, which follows.

Take-Home Messages

- In drug-naïve patients, determine an initial treatment approach (monotherapy, combination therapy) based on the patient's presenting A1C level:
 - If $\leq 7.5\%$, apply monotherapy.
 - If $>7.5\%$ to $\leq 8.5\%$, apply combination therapy.
 - If $>8.5\%$, apply combination therapy plus basal insulin.
- In patients already on monotherapy with an A1C level $>8.5\%$, the addition of a second oral agent will probably not be sufficient to lower A1C to $<7.0\%$. These patients will likely need a second oral agent plus basal insulin.
- Glycemic control should be reassessed within 3 months of starting a new therapy; as needed, regimens should be adjusted promptly.

Dr. Gerich serves as a consultant to, is on the speakers' bureau for, and/or conducts research sponsored by Boehringer Ingelheim, Bristol-Myers Squibb, Centocor, Eisai, GlaxoSmithKline, Johnson&Johnson, Kowa, LifeScan, Merck, Novartis, Novo Nordisk, Pfizer, sanofi-aventis, Sankyo, and Takeda.

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LITERATURE CORNER

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GLP-1: WHERE ARE WE TODAY?

Editor's Note: CADRE is pleased to present this article on the future of GLP-1 receptor agonist development. Dr. Holst is a leading researcher in gut and pancreatic hormone physiology and was one of the pioneers in demonstrating the therapeutic value of the incretin GLP-1.

Introduction

Glucagon-like peptide-1 (GLP-1) has attracted the attention of clinicians and drug developers alike as a potent treatment target for type 2 diabetes mellitus (T2DM). This intestinal polypeptide is one of the incretin hormones that stimulates insulin secretion in a glucose-dependent manner. Along with glucose-dependent insulinotropic polypeptide (GIP), GLP-1 is responsible for 70% of postprandial insulin secretion in healthy individuals; however, individuals with T2DM have an impaired or even absent incretin response.

Both incretin hormones initially appeared promising for diabetes treatment: both are strongly insulinotropic and, being glucose dependent, do not appear independently capable of causing profound hypoglycemia. Attempts to stimulate insulin secretion with GIP, however, were not successful; in contrast, intravenous GLP-1 infusion increased insulin release and normalized fasting plasma glucose (FPG) levels, even in patients with T2DM of long duration. Exogenous GLP-1 was also found to inhibit glucagon secretion and exert a powerful effect on gastrointestinal motility, which in turn delayed gastric emptying and blunted postprandial glucose excursions. GLP-1 administration was also associated with decreased appetite and food intake. Finally, animal and in vitro data indicated that GLP-1 prevents β -cell apoptosis and promotes β -cell proliferation.

The challenge for drug development was that GLP-1 undergoes rapid enzymatic degradation by dipeptidylpeptidase-4 (DPP-4). Early experiments with GLP-1 treatment required continuous intravenous or subcutaneous infusion. While this provided proof of concept for GLP-1–based therapy, the need for ongoing delivery inhibited its clinical applicability. To address the problem, 2 discovery approaches were undertaken: (1) to identify GLP-1 receptor (GLP-1R) agonists with DPP-4 resistance, and (2) to develop DPP-4 inhibitors. Exenatide is currently the only GLP-1R agonist commercially available, although several more are in development. The DPP-4 inhibitor sitagliptin was recently approved by the FDA, while vildagliptin is currently under review.

DPP-4 inhibitors gradually increase both fasting and postprandial endogenous GLP-1 levels. This enhances β -cell function and lowers plasma glucagon levels through action on the α -cell, resulting in improved glucose regulation. DPP-4 inhibitors achieve glycemic control comparable to GLP-1R agonists, with a lower risk of gastrointestinal side effects, but do not reduce appetite or induce weight loss. While the actions and clinical effects of the various DPP-4 inhibitors are essentially similar,

Continued

the mechanism and side effects of the various GLP-1R agonists differ considerably; this appears to be due primarily to differences in their pharmacokinetic profiles.

The GLP-1R Agonists

The first attempt to protect GLP-1 from DPP-4 degradation was accomplished by substituting the penultimate amino acid residue (Ala) with other short side chain amino acids. Because this substitution did not affect renal GLP-1 elimination, this process only extended GLP-1 half-life by a few minutes. It was then recognized that effective GLP-1R agonists needed to be both DPP-4 resistant and able to avoid renal clearance. Several receptor agonists that appear to meet these criteria are available or under development, including:

Exenatide. Exenatide is the most familiar GLP-1R agonist, having been approved in the United States in June 2005 for use in T2DM in combination with either metformin or a sulfonylurea. Exenatide is the synthetic form of exendin-4, a peptide found in the saliva of the desert lizard *Heloderma suspectum* (also known as the Gila monster). Exenatide is a full agonist for the GLP-1 receptor, is resistant to DPP-4, and is cleared renally via glomerular filtration. A 10- μ g dose injected subcutaneously is active for ~5 hours. The usual dosing schedule is twice daily; this provides adequate GLP-1 replacement for breakfast and dinner but not a substantial amount of midday postprandial coverage. Overnight GLP-1 coverage is also limited. This lack of a 24-hour effect likely explains why exenatide does not have a strong effect on FPG but still reduces A1C levels by up to 1.1%.

On the other hand, because exenatide is eliminated quickly from the circulation, patients do not appear to develop desensitization to its effects on delayed gastric emptying. The drug's effect on gastric motility appears to lead to sustained reductions in food intake and consequent weight loss. This benefit has made exenatide popular with practitioners and patients. Most recently, participants in the original 30-week exenatide phase 3 trials

were followed for an additional 52 weeks. Long-term exenatide use was associated with sustained reductions in A1C, FPG, and body weight.

Liraglutide. This long-acting injectable GLP-1R agonist avoids renal clearance and DPP-4-mediated degradation by binding to albumin. The resulting 12-hour half-life allows for once-daily dosing and adequate 24-hour coverage; this contributes to a more sustained effect on FPG than observed with exenatide. The results of a 14-week, placebo-controlled clinical trial of liraglutide were presented at the 2006 European Association for the Study of Diabetes (EASD) 42nd Annual Meeting. Patients with T2DM (n=165) receiving a daily dose of liraglutide 0.65, 1.25, or 1.9 mg showed significantly decreased A1C levels and dose-dependent weight loss with limited side effects. Phase 3 testing was initiated in February, 2006.

GSK-716155. Formerly known as albugon, GSK-716155 represents another approach to albumin utilization. Technology is used to fuse genes that express human albumin to genes that express therapeutically active proteins (in this instance, GLP-1)—resulting in GSK-716155. Preclinical data indicate that GSK-716155 stimulates insulin secretion and lowers blood glucose levels. Phase 1 and 2 human trials are expected to start in the near future.

CJC-1134-PC. Also known as PC-DAC: Exendin-4, this compound is similar in concept to GSK-716155. In this case, exendin-4 is modified to attach covalently to recombinant human albumin. A recent inpatient study of CJC-1134-PC demonstrated that a daily dose of 3 mg lowered mean plasma glucose readings by 13% after the first week of treatment. Weight loss was observed initially but weight returned to baseline levels at the end of 6 weeks. An additional phase 1/2 study is planned for early 2007.

Exenatide Long-Acting Release (LAR). A 15-week study of 45 patients presented at the 2006 EASD meeting compared once-weekly exenatide LAR 0.8 mg, 2.0 mg,

and placebo. The 0.8-mg dose had almost no effect on body weight, although the 2.0-mg dose produced weight loss similar to the 10- μ g twice-daily exenatide dose currently in use. Both the 0.8-mg and the 2.0-mg doses were associated with substantial A1C reductions (-1.4% and -1.7%, respectively) and decreased FPG (-42.7 mg/dL and -39.0 mg/dL, respectively), as well as lower rates of nausea (19% and 27%, respectively) than have been typically observed with exenatide administered twice daily. Exenatide LAR is currently in Phase 3 testing.

GLP-1 receptor agonists need to be both DPP-4 resistant and able to avoid renal clearance.

For both exenatide LAR and liraglutide, the low observed rates of nausea and gastrointestinal side effects are probably due to the stable drug concentration plateau obtained. This plateau may be associated with some desensitization of the mechanisms that result in nausea and inhibit food intake. On the other hand, the variable plasma concentrations following the administration of more rapidly metabolized receptor agonists (such as twice-daily exenatide) are associated with a higher rate of side effects but, conversely, may not cause desensitization.

The Future of GLP-1R Agonists

It is likely that exenatide LAR will become available at the same time as liraglutide. Competition will be fierce and we can expect scrutiny of the differences and potential problems associated with both products. As many as 40% of individuals produce antibodies to exendin-4 and this figure may be even higher for exenatide LAR. However, the presence of antibodies does not necessarily create adverse reactions. Nonetheless, liraglutide reportedly produces no antibodies at all and this may be an attractive characteristic.

Continued

Table 1. GLP-1 Receptor Agonists Available or in Development

Product	Developer/partners	Current development status
Exenatide	Amylin/Lilly	FDA approved
Exenatide LAR	Amylin/Lilly	Phase 3
Liraglutide	Novo Nordisk	Phase 3
GSK-716155	Human Genome Sciences/GlaxoSmithKline	Phase 1/2
CJC-1134-PC (PC-DAC™; Exendin-4)	ConjuChem	Phase 1/2

The blood-brain barrier is relatively impermeable to albumin, raising concerns for formulations where GLP-1 is bound covalently to albumin or other large molecules before administration. As satiety is regulated by GLP-1 receptors in the hypothalamus, the question is whether these drugs will influence appetite in a sustained manner. Peripheral sensory nerves may also transmit GLP-1 action, so satiety may be achieved without requiring direct central nervous system (CNS) GLP-1–receptor stimulation. Animal studies of albumin-bound investigational drugs have observed reduced activation of food intake regulating CNS nuclei, suggesting that these drugs may have fewer side effects and less gastrointestinal and appetite-regulating effects but a powerful effect on blood glucose levels. Should this occur with these agents, it would theoretically mean that the drug’s dose could be increased to potentially trigger a stronger pancreatic β -cell survival effect without the limitations of associated nausea.

Emerging Off-label Issues

With exenatide’s high efficacy and associated weight loss, it is reasonable to expect a certain level of off-label use. Some physicians have increased the dosage of exenatide to 3 injections per day. This makes sense given its short-acting effect and could lead to improved FPG control and even greater appetite control and weight loss. However, in the long run, it could also lead to desensitization.

Recent media reports have highlighted the use of off-label exenatide for weight control in patients without diabetes. In

such individuals, exenatide might be more likely to cause hypoglycemia related to meal intake. This hypoglycemia would probably not be severe or long-lasting, but could decrease the treatment’s attractiveness as a weight loss drug.

The successful off-label use of exenatide combined with basal insulin has been reported both in clinical practice and in a recent trial presented at the 66th Annual Scientific Sessions of the American Diabetes Association. This may prove to be the most powerful anti-diabetic combination available today; combining these 2 drugs may make it possible to treat patients to any desired A1C target with a decreased risk of hypoglycemia. The strength of this approach may also hold for the combination of DPP-4 inhibitors and basal insulin.

Conclusion

Based on what we know regarding the important role of early and intensive glycemic control, a new consensus is emerging that antihyperglycemic medication should be introduced earlier in the course of T2DM progression. Although data have yet to be produced, one powerful option might be to start patients on metformin plus a GLP-1R agonist or DPP-4 inhibitor. This approach would not only combine 2 antihyperglycemic drugs with complementary, additive properties, but would combine one that fails over time (metformin) with one (the incretin-based therapy) that may be more durable. In addition, this approach could also spare further β -cell and glycemic deterioration, thereby potentially slowing the progression of T2DM and its complications.

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Suggested Reading

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