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ABOUT CADRE

CADRE (the Council for the Advancement of Diabetes Research and Education) is a nonprofit organization committed to reducing the burden of diabetes by providing health care professionals with scientific information and educational initiatives designed to translate research into effective clinical practice.

This issue of *CADRE's Current Diabetes Practice* reviews selected presentations on promising new pharmaceutical developments for type 2 diabetes mellitus (T2DM) treatment from the 68th Annual Scientific Sessions of the American Diabetes Association (ADA), as well as information presented at the 2008 European Association for the Study of Diabetes Annual Meeting and the 2008 Canadian Diabetes Association Annual Meeting. As the burden of T2DM continues to grow, choosing between treatment options will become more complex,

and increasing patient adherence will continue to be a significant challenge. Therefore, in addition to providing information on new treatments under investigation, this issue also explores barriers to medication-taking and offers strategies that may increase adherence to treatment regimens.

We hope you will find the articles in this issue of *CADRE's Current Diabetes Practice* informative and useful.

▲ Melissa Miles, Executive Director

EDUCATOR'S PERSPECTIVE

TAKING MEDICATIONS: UNDERSTANDING THE BARRIERS AND SEEKING SOLUTIONS

Melinda D Maryniuk, MEd, RD, FADA, CDE

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In the last decade, many new medications, as well as new formulations of existing medications, have been added to the list of drugs available for treating hyperglycemia. Every year, new treatment options are anticipated as research results are discussed at major scientific meetings—and it was no exception at the American Diabetes Association 2008 Scientific Sessions. However, despite all the research on efficacy and the various algorithms for treatment choice, there is still a gap between what is prescribed and what is actually taken by the patient. When considering medication options, one way to increase a patient's adherence to a medication regimen is to include the patient in the decision-making process, and work together to select the drugs best suited to his/her needs. This article discusses the importance of acknowledging the barriers to medication taking and pro-

poses solutions to increase adherence through collaborative counseling.

Taking diabetes medicines can range from a fairly straightforward prescription of one pill a day to complex regimens involving multiple pills and several injections—and that is only for glycemic control. It is not uncommon for an adult with type 2 diabetes mellitus (T2DM) to be taking upward of a dozen different daily medicines. It is no wonder then that research on patients with T2DM has reported long-term adherence to oral glucose-lowering agents as ranging from 36% to 93%, and with

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insulin regimens as ranging from 62% to 80%. As expected, poor adherence is correlated with worsened glycemia.

How a medication is delivered may also affect the willingness of both the physician to prescribe and the patient to use; a case in point is the rather cumbersome unit for inhaled insulin (now off the market). Down the road, it will be critical to once-weekly exenatide LAR's acceptance for it to be provided in an easy-to-use injection device. It is important to keep in mind that patients who have physical limitations or trouble following multiple-step directions may not be suited for certain medications with complex delivery systems.

Awareness of warning signs for those at risk for poor adherence is the first step to resolving the issue. These warning signs include

- **Medication dosing frequency** – the more doses to be taken, and the more complex the regimen, the poorer the follow-through

- **Age** – both elders and adolescents exhibit poorer follow-through with medication plans
- **Socioeconomic status / medication cost** – a recent survey reported that 19% of adults with diabetes decreased medication use due to cost; 28% went without food and other essentials to afford medication
- **Lapses in medication refills** – these can often be noted by the pharmacist

Strategies to improve medication use include collaborative counseling to ensure patient participation and choice in the medication regimen, and a review of tools that can be used to aid administration. Establishing a trusting relationship where the patient feels able to participate in treatment choices is important to regimen adherence. The provider can discuss the pros and cons of different medications and ensure that the patient fully understands dosing recommendations, delivery methods, and side effects, with a goal of choosing medicine the patient believes he/she can take consistently and correctly. The provider also needs to discuss the expected benefits of the drug and take time to understand if the patient has reservations, concerns, or questions about the medicine that might get in the way of achieving optimal adherence.

In terms of medication taking, one study found that 80% of adults with diabetes use at least one form of adherence aid, such as a pill box (used by 50% of patients), medication alarm, calendar, or insulin injection aid. But patients often do not know about these options unless they are discussed by the physician. For example, pens can make insulin delivery easier and likely lead to improved follow-through with medication use. Yet in a recent survey of insulin users who were not using an insulin pen, 82% said their physician never discussed pen use while only a few (3%) said their physician encouraged pen use.

So as we consider existing pharmacologic treatment options and look down the pike at soon-to-be-available drugs, we should not only pay attention to data on efficacy and side effects. We must also think about how likely the patient

will be to actually follow the instructions and take the medicine. Having the patient participate in medication selection, as well as considering adherence and delivery aids, will increase the likelihood that the medication will actually be taken as prescribed.

Ms. Maryniuk serves on an advisory board for Eli Lilly.

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CONFERENCE REPORTER I

INHIBITION OF SGLT2: A NOVEL WAY TO LOWER PLASMA GLUCOSE AND TREAT DIABETES

Derek LeRoith, MD, PhD, FACP

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Information on sodium-glucose cotransporters (SGLTs), in particular SGLT2, was presented at the 2008 American Diabetes Association 68th Scientific Sessions. Because SGLT2 plays a critical role in glucose reabsorption from the kidney (inhibition of SGLT2 activity increases renal glucose excretion and thus decreases plasma glucose levels), it is a potential new therapeutic target for the treatment of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).

A healthy kidney constantly filters waste products from the bloodstream for excretion as urine. Glucose is prevented from being excreted with regular waste products primarily due to the action of SGLT2, which actively transports filtered glucose from the kidney back into the bloodstream. Therefore, partial inhibition of SGLT2 activity, leading to increased urine glucose excretion, provides the rationale for developing and testing these compounds. Further impetus to their development is *familial renal glucosuria*, a condition in which a genetic SGLT2 mutation results in impaired glucose reabsorption by SGLT2 and thus lifelong glucosuria; this glucosuria appears to be asymptomatic, a benign rather than a morbid condition.

Results were presented from a 12-week, double-blind, dose-ranging trial that randomized 389 treatment-naive T2DM patients to one of five once-daily doses (2.5, 5, 10, 20, or 50 mg) of oral dapagliflozin, metformin, or placebo. All dapagliflozin treatment groups showed statistically significant mean A1C reductions from baseline compared with placebo (−0.55% to −0.9% versus −0.18%, respectively; $P < 0.01$). In addition,

the dapagliflozin treatment groups had greater mean weight loss from baseline (2.5% to 3.4%) compared with placebo (1.2%). The most common adverse events in dapagliflozin-treated patients were urinary tract infection, nausea, dizziness, back pain, headache, fatigue, and nasopharyngitis; the rate of reported hypoglycemic events was higher compared with placebo but similar to the metformin-treated group.

Targeting inhibition of SGLT2 may offer advantages in the treatment of diabetes. However, although not fully characterized in the limited clinical trials to date, the action of these inhibitor compounds suggests potential side effects as well. Table 1 lists some of these potential advantages and side effects.

COMMENTARY

Vivian Fonseca, MD

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Glucose in the urine is a hallmark of the diagnosis of diabetes mellitus; further, diabetologists have long recognized the concept of a *renal threshold*, in which glucose is allowed into the urine only when the plasma glucose concentration rises above a certain level (widely recognized as ~180 mg/dL). Indeed, the cardinal symptom of diabetes, polyuria, depends on excretion of excess glucose

in the urine and the osmotic effect of that glucose to increase water excretion.

Advances in physiology research have demonstrated that absorption of filtered glucose from the renal proximal tubule into the blood is mediated by a number of cell surface transporters on both surfaces of the tubule—SGLTs, of which SGLT2 is probably the most important. We have also recognized that the phenomenon of renal glucosuria that occurs at lower levels of plasma glucose is due to *tubular defects*—mutations of SGLT2.

Can we exploit this knowledge to inhibit these transporters, induce renal glucosuria, and thereby lower plasma glucose levels? The concept was tested previously with nonspecific inhibitors that affected glucose transporters in other organs, such as the gut; these induced undesirable side effects. However, the recent development of inhibitors that act only on the kidneys raises the possibility of a new diabetes treatment target.

Several drugs are currently in various phases of development and preliminary data look promising. These drugs increase glucosuria at a lower glycemic threshold and thus do not allow blood glucose levels to rise too high. Since diabetes complications are glycemia related, this approach may lower the risk of these complications. These new agents should be a good adjunct

Continued

Table 1. Potential advantages and side effects of SGLT2 inhibition in the treatment of diabetes

Potential advantages	Potential side effects
<ul style="list-style-type: none"> Decreased glycemia-related complications while improving glucose control Novel mechanism of action independent of the degree of insulin secretion or insulin resistance Potential use in T1DM and T2DM Potential for weight loss or weight maintenance due to the calories associated with excreted glucose Lack of direct stimulation of insulin secretion lowers risk of hypoglycemia 	<ul style="list-style-type: none"> Polyuria, due to the osmotic effect of increased glucose in the urine Recurrent urinary tract infections, due to increased glucose in the urinary tract Vulvovaginitis in women Salt-wasting, dehydration, and electrolyte imbalances associated with polyuria

to other therapies, as the mechanism involved is activated only if other therapies fail (eg, following a large meal or missing a medication or injection dose).

An additional benefit of this drug class may relate to the loss of calories in the urine, which may, in turn, lead to weight loss. Associated with polyuria, however, is a risk of dehydration; additionally, increased glucose in the lower urinary tract may increase the risk of urinary tract infections.

Clearly, long-term clinical trials are needed to establish utility and safety for these drugs, and some have been initiated. Interestingly, this mechanism of action has potential in treating both T1DM and T2DM.

Dr. Fonseca receives grant/research support (to Tulane) from Astra-Zeneca, Pfizer, Inc.

and/or is a consultant and/or speaker for Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Novartis, Novo Nordisk, sanofi-aventis, and Takeda.

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CONFERENCE REPORTER II

HEART2D

A report on the Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus (HEART2D) study was presented at the 68th Scientific Sessions of the American Diabetes Association held in June 2008.

According to the article reporting its design, HEART2D was conceived as a 3-year, open-label, multicenter study testing whether a strategy targeting control of postprandial hyperglycemia was more effective in reducing cardiovascular (CV) events than one targeting fasting glucose. Planned enrollment was approximately 1355 patients with type 2 diabetes mellitus (T2DM) and recent acute myocardial infarction (MI). Participants were randomized to either prandial insulin (insulin lispro before each meal with a goal of 2-hour postprandial blood glucose levels of <135 mg/dL) or basal insulin (twice-a-day NPH insulin

or once-a-day insulin glargine with a fasting blood glucose target of <121 mg/dL) for a period of 1.5 to 3.5 years. All prior oral antihyperglycemic therapy was stopped and, to keep A1C levels below 8.0%, a bedtime injection of NPH insulin could be added to prandial treatment or the basal regimen could be converted to twice-daily premixed human 70% NPH/30% regular insulin.

The primary study endpoint was the difference between glucose-lowering treatment strategies (prandial versus basal) in length of time until the first recurrent event (death from a CV event, non-fatal MI or stroke, hospitalization for acute coronary syndromes, or coronary revascularization procedures).

Itamar Raz, MD, reported the study had been stopped earlier than planned due to finding no trend toward difference in CV benefit between the two groups: by study's end, 174 patients (of 558, or 31.2%) in the basal group had progressed to the first recurrent event, compared with 181 patients (of 557, or 32.5%) in the prandial group (hazard ratio, 0.98). The rate of drop-out was 38% from basal treatment and 39% from prandial treatment. There was no difference in mean A1C between

groups (~7.6% for each group, $P=0.48$), and approximately half the patients in each treatment group achieved an A1C <7.0%. Smaller 2-hour postprandial blood glucose excursions, however, were seen in the prandial treatment group compared with the basal group. Participants in the prandial group required more insulin, and gained more weight, than those in the basal group. Further data analysis is planned, particularly regarding any potential relationship between length of diabetes and CV events and the effect of hypoglycemia on CV events.

COMMENTARY

Matthew C Riddle, MD

Oregon Health & Science University
Portland, Oregon

The preliminary, verbal presentation from the ADA, as well as an editorial regarding the study outcomes, were published in the March 2009 issue of *Diabetes Care*; see the Suggested Reading section that follows for information on the articles by Itamar Raz, MD and Antonio Ceriello, MD, respectively. This study deserves comment because it addressed a topic of great interest.

Continued

A variety of findings have led to the controversial hypothesis that poor metabolic control after meals is an important risk factor for both CV and microvascular complications and that efforts to improve postprandial control may reduce CV events. These findings include an epidemiologic association between hyperglycemia after a meal or an oral glucose challenge and the risk of CV events in large populations, associations between increments of glucose and markers of tissue inflammation and oxidative stress in small physiologic studies, and the observation that basal-bolus treatment of patients with type 1 diabetes mellitus in the Diabetes Control and Complications Trial may have resulted in fewer complications than a less physiologic treatment regimen, even in patients with similar A1C levels. The HEART2D study tested this hypothesis by comparing the effects of one or two injections of basal insulin with injections of rapid-acting insulin before each meal in patients with T2DM.

The investigators encountered some difficulties in performing the study. Fewer participants were enrolled than planned (1115 versus 1355), and nearly 40% of those in each treatment group withdrew before completing the protocol. However, the equivalent A1C levels achieved in both treatment groups, together with definite reductions of postprandial glycemic increments in the prandial insulin group, allowed conclusions to be reached regarding the hypothesis. The lack of any trend toward reduced CV risk with prandial insulin treatment, compared with basal insulin treatment, failed to support the view that improving postprandial metabolic control will have unique medical benefits.

Of course, this one study does not entirely disprove the hypothesis. For example, the 24-hour glucose profiles presented show greater reduction of postprandial increments of glucose with the prandial regimen, but these curves show *averages* rather than *patterns* for individual participants, and the overnight patterns are not shown. Patients taking prandial insulin may have had more fluctuation of glucose with meals than these curves imply, and overnight

fluctuations may have been significant. Postprandial increments of glucose are rarely prevented entirely by prandial insulin injections, and a more completely effective treatment might be needed to obtain the desired benefit. Alternatively, favorable CV effects of prandial insulin may have been neutralized by undesired ones, notably weight gain and hypoglycemia. Recent studies comparing prandial-only versus basal-only insulin regimens in T2DM have shown that equivalent and quite good control of A1C is possible with either method, but more weight gain and hypoglycemia accompany the prandial regimen. Yet another possibility is that both prandial and basal insulin regimens have protective effects on CV outcomes when equivalently applied, albeit by different mechanisms.

Targeting postprandial hyperglycemia using insulin with the aim of reducing CV risk is not yet justified by objective evidence.

The practical implications of this study are simple: the postprandial hypothesis remains a hypothesis. Targeting postprandial hyperglycemia using insulin with the aim of reducing CV risk is not yet justified by objective evidence. This is especially true given that prandial insulin treatment requires more frequent injections, glucose testing, and decisions by the patient and is more likely to cause hypoglycemia and/or weight gain than basal insulin treatment. Also, we must study other ways to control postprandial hyperglycemia in T2DM—methods less likely to cause hypoglycemia and weight gain. These include the stepwise addition of prandial insulin (rather than immediate use of three or more injections) or the use of α -glucosidase inhibitors, amylin agonists (pramlintide), glucagon-like peptide-1 receptor agonists (eg, exenatide), or perhaps sodium-glucose cotransporter 2 agents (also reviewed in this issue of *CADRE's Current Diabetes Practice*).

Dr. Riddle receives grant/research support from Amylin, Eli Lilly, and sanofi-aventis, and serves as a consultant and/or speaker

for Amylin, Eli Lilly, Pfizer, Inc., sanofi-aventis, and Valeritas.

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CONFERENCE REPORTER III

INCRETIN-BASED THERAPIES

To provide clinical perspective on what lies ahead in the growing field of glucagon-like peptide-1 receptor (GLP-1R) agonist replacement therapies, this article reviews selected abstracts on randomized controlled studies of GLP-1R agonists presented at the 2008 American Diabetes Association 68th Scientific Sessions.

Information from the ADA was complemented by similar and additional reports

presented at the 2008 annual meetings of the Canadian Diabetes Association (CDA) and the European Association for the Study of Diabetes (EASD).

For additional information on incretin-based therapies, see *CADRE's Current Diabetes Practice*, Vol 6, Issue 1.

Liraglutide

A number of reports from the Liraglutide Effect and Action in Diabetes (LEAD) studies were presented. This expansive series enrolled >4,000 patients; most studies included 2 to 3 doses of liraglutide (LIR), a once-daily GLP-1R agonist with 97% homology to human GLP-1, compared with placebo and/or active comparator. LIR is currently being

assessed for approval by the U.S. Food and Drug Administration.

Table 1 lists highlights from the LEAD 1 to LEAD 6 studies. Except for LEAD 6 (A1C 7% to 11%), for which patients remained on previous sulfonylurea and/or metformin, all participants had previous oral antidiabetic (OAD) therapy modified. Baseline A1C for LEAD 1 to 5 was also $\geq 7.0\%$, but the upper limit was $\leq 11.0\%$ for patients entering drug naïve or on one OAD, and $\leq 10.0\%$ for those entering on two OADs. Other mean baseline characteristics were:

- Age, 53 to 58 years
- A1C, 8.1% to 8.5%
- BMI, 30 to 33.5 kg/m²
- Diabetes duration, 5.4 to 9.4 years

Continued

Table 1. Summary of Liraglutide Effect and Action in Diabetes (LEAD) studies

LEAD Study	Doses	Added to	Previous Treatment			Study Design		N	Results			Completed	
			Drug-Naïve	1 OAD	2 OAD	Lead-In	Duration		Δ A1C	Final A1C	Body Weight		
1	LIR 0.6 mg/d	GLIM 4 mg/d		30%	70%	2 – 6 wks	26 wks	1041	-0.6%	7.8%	+0.7 kg	86%	
	LIR 1.2 mg/d								-1.1%	7.5%	+0.3 kg		
	LIR 1.8 mg/d		Stop previous OAD during lead-in							-1.1%	7.5%		-0.2 kg ^a
	ROSI 4mg/d		Switch to/adjust GLIM							-0.4%	8.0%		+2.1 kg
	Placebo									+0.2%	8.7%		-0.1 kg
2	LIR 0.6 mg/d	MET 2000 mg/d		35%	65%	3 – 6 wks	26 wks	1091	-0.7%	7.8%	-1.8 kg	81%	
	LIR 1.2 mg/d								-1.0%	7.5%	-2.6 kg		
	LIR 1.8 mg/d		Stop previous OAD during lead-in							-1.0%	7.5%		+0.9 kg
	GLIM 4 mg/d		Switch to/adjust MET							+0.1%	8.6%		-1.5 kg
	Placebo												
3	LIR 1.2 mg/d		36%	64%		None	52 wks	746	-0.8% ^b	7.5%	-2.0 kg	65%	
	LIR 1.8 mg/d		Stop previous OAD at randomization							-1.1% ^b	7.2%		-2.4 kg
	GLIM 8 mg/d									-0.5% ^c	7.8%		+1.1 kg
4	LIR 1.2 mg/d	MET 2000 mg/d + ROSI 8 mg/d		16%	84%	9 wks	26 wks	533	-1.5%	7.0%	-1.0 kg	76%	
	LIR 1.8 mg/d		Stop previous OAD during lead-in							-1.5%	7.1%		-2.0 kg
	Placebo		Switch to/adjust MET and ROSI							-0.5%	7.9%		+0.6 kg
5	LIR 1.8 mg/d	MET 2000 mg/d + GLIM 2-4 mg/d		6%	94%	6 wks	26 wks	581	-1.3%	7.0%	-1.8 kg	90%	
	INS Glargine		Stop previous OAD during lead-in							-1.1% ^d	7.2%		+1.6 kg
	Placebo		Switch to/adjust MET and GLIM							-0.2%	8.1%		-0.4 kg
6	LIR 1.8 mg/d	Previous OAD(s)		37%	63%		26 wks	464	-1.1%	7.1%	-3.2 kg	86%(LIR) 81%(EX)	
	EX 10 μ g BID		Previous OAD unchanged (MET and/or SU)							-0.8%	7.3%		-2.9 kg

OAD=oral antidiabetic agent; LIR=liraglutide; ROSI=rosiglitazone; GLIM=glimepiride; MET=metformin; INS=insulin; EX=exenatide; SU=sulfonylurea

^a The lack of meaningful weight loss may be due to the effect of the sulfonylurea and the withdrawal of metformin in 2/3 of patients at study entry.

^b Of note, A1C reductions were greater in the drug-naïve subpopulation than the 1 OAD subpopulation.

^c This reduction was uncharacteristically low and may reflect the influence of washout from monotherapy.

^d IG titrated to fasting plasma glucose <100 mg/dL using a patient-driven algorithm; average final IG dose 24 IU/d.

Mild and transient nausea was the main adverse event with LIR in all studies, with incidence decreasing with time on medication, and with apparently less persistence than exenatide. Minor hypoglycemic events (<56 mg/dL) were reported by <10% of LIR patients in LEAD 1 to 4. For LEAD 5, 27% of LIR patients reported minor events (compared with 29% for

insulin glargine and 17% for placebo), while 5 major hypoglycemic events were reported with LIR and none in the other groups. In LEAD 6, LIR patients averaged 1.9 minor hypoglycemic events versus 2.6 events with exenatide.

Additionally, a fat distribution substudy of 160 LEAD 2 patients used dual-

energy X-ray absorptionmetry (DEXA) and computerized tomography (CT) scans to assess the effect of LIR on body composition. It demonstrated that adding LIR to metformin provided greater reductions in percentage of body fat, central adiposity, and possibly hepatic steatosis, versus add-on glipepride to metformin.

Exenatide

▲ **Effects of Maximized Exenatide versus Insulin Glargine on Beta Cell Function**

The primary purpose of this study was to compare the effects of maximized therapy with exenatide (EX) versus insulin glargine (IG) on β -cell function, and secondarily the impact on glycemic control and body weight (BW), and the adverse events profile, over a 1-year period in patients with type 2 diabetes mellitus (T2DM) previously treated with metformin for >6 weeks.

- **Study Design:**

Randomized, open-label study of intensive add-on therapy of either EX (maximum dose of 20 μ g TID [above label-approved dose] to achieve A1C \leq 7.0%) or IG (insulin titration to fasting plasma glucose [FPG] <100 mg/dL) over a 52-week period followed by a 12-week washout for repeated assessments off study drugs.

- **Baseline Demographics:**

N=69 randomized (EX=36; IG=33); age 58 years; A1C 7.5%; BMI 31 kg/m².

- **Key Findings:**

At 52 weeks, EX and IG reduced A1C similarly (-0.8% and -0.7%, respectively) but BW was different between groups (-3.6 versus +1 kg, respectively). EX significantly improved β -cell function versus IG as measured by arginine stimulation during hyperglycemic clamp and first- and second-phase glucose-stimulated C-peptide secretion, but all results in both groups reverted to pretreatment values 4 weeks after washout. Moreover, any A1C and BW changes also trended toward pretreatment levels after 12 weeks off therapy.

- **Adverse Events:**

Nausea occurred in ~47% of EX patients; hypoglycemia was more frequent with IG.

- **Conclusion:**

β -cell improvements were not sustained after 1 year of supramaximum EX therapy. Longer exposure to EX may be necessary to demonstrate any lasting disease-modifying effects.

▲ **Exenatide BID versus Exenatide LAR QW on Glucose Control**

This study compared twice-daily EX (EX BID) to once-weekly EX (LAR QW) on glycemic control, BW, and adverse events in T2DM.

- **Study Design:**

Randomized, open-label, 30-week study of EX (10 μ g BID) vs LAR (2 mg QW).

- **Baseline Demographics:**

N=295 randomized (~15% drug naïve, ~45% treated with 1 OAD, ~40% on 2 OADs); A1C 8.3%; BW 102 kg; BMI 35 kg/m²; diabetes duration 6.7 years.

- **Key Findings:**

Significantly greater improvement with LAR QW versus EX BID was achieved in FPG (-42 versus -25 mg/dL) and A1C (-1.9% versus -1.5%) with 77% versus 61%, respectively, achieving target A1C \leq 7.0%. Both groups had ~4 kg BW reduction.

- **Adverse Events:**

Nausea occurred in 26% of LAR QW and 35% of EX BID patients, with vomiting in 11% and 19%, respectively; no major hypoglycemia was reported. Skin lesions were not reported except for pruritus in 18% of patients.

- **Conclusion:**

This open label, proof-of-concept study demonstrated the merits of continuous weekly vs intermittent twice daily GLP-1 replacement therapy.

Exenatide once-weekly demonstrated a greater A1C reduction (-1.9%) than twice-daily exenatide (-1.5%), with a similar 4 kg weight loss.

New GLP-1R Agonists

Daily dosing

▲ **AVE0010 Dose Study QD vs BID**

Reports on the dose-response effect of subcutaneous AVE0010, a new GLP-1R agonist with a close homology to exenatide, provided the results of a randomized, 13-week, double-blind, placebo-controlled, parallel group study in T2DM patients inadequately controlled with metformin monotherapy (A1C 7% to 9%). Multiple options were investigated (once- or twice-daily regimens of AVE0010 5, 10, 20, or 30 µg, QD or BID) to assess glycemic control, BW, and adverse events.

Patients (N=542; placebo, 109; each other group, 52 to 56; completed, ~90%) had mean baseline characteristics of: age, 56 years; A1C, 7.5%; BMI, 32 kg/m²; and diabetes duration, 6.6 years. Despite only mildly elevated baseline A1Cs, all once-daily AVE0010 doses showed significant A1C decreases (ranging from -0.5% to -0.8%), with similar A1C decreases with twice-daily AVE0010 (from -0.7% to -0.9%), versus placebo (-0.2%). Target A1C <7.0% at study end was achieved in 47% to 69% of patients on QD AVE0010, similar to BID (51% to 77%), versus 32%

on placebo. BW decreased from -2 to -3.9 kg with all AVE0010 groups versus -1.9 kg with placebo. Adverse events with AVE0010 included transient, dose-dependent nausea (7% to 33%) versus 5% with placebo; no severe hypoglycemia was reported.

A clear dose response, with similar efficacy, was shown in both the QD and BID regimens. The 20 µg QD dose appeared to be the dose with the most meaningful efficacy potential and the most favorable adverse events profile.

Weekly dosing

▲ **Taspoglutide Dose Finding Study QW vs Q2W**

This study was designed to assess the efficacy, safety, and tolerability of escalating doses of the long-acting, human GLP-1R agonist taspoglutide (TSP) when given weekly (QW) or biweekly (Q2W) in T2DM patients inadequately controlled with metformin (A1C 7% to 9.5%).

• **Study Design:**

Placebo-controlled, double-blind, parallel-group, 8-week study that randomized patients to add-on treatment with TSP QW (5, 10, or 20 mg) or Q2W (10 or 20 mg), or placebo.

• **Baseline Demographics:**

N=306 randomized; age 55 years; A1C 7.9%; BMI 33 kg/m²; diabetes duration 5 years.

• **Key Findings:**

All doses of TSP significantly reduced A1C from baseline versus placebo (-0.2%), with no clear differences between QW (-1.0%, -1.2%, and -1.2% for 5, 10, and 20 mg QW; respectively) and Q2W doses (-1.0% for both 10 and 20 mg Q2W). Target A1C <7.0% at study end was achieved in 59%, 79%, and 81% of patients on 5, 10, and 20 mg QW, respectively, and in 44% and 63% on Q2W 10 and 20 mg, respectively, versus 17% on placebo. BW decreased progressively and dose-dependently with TSP ~2 to 3 kg.

• **Adverse Events:**

The most frequent adverse event was dose-dependent, transient, mild-to-moderate nausea.

• **Conclusion:**

All doses of TSP consistently improved glycemic control and were associated with BW reduction; the slight loss of efficacy between Q2W doses suggests that TSP is more suitable for a QW regimen.

▲ **Taspoglutide Dose Finding Study QW**

A similar study assessed the safety, tolerability, and efficacy of escalating weekly doses of TSP in T2DM patients inadequately controlled with metformin (A1C 7% to 9.5%).

• **Study Design:**

Placebo-controlled, double-blind, parallel-group, 8-week study that randomized patients to 4 arms (1:1:1:1): TSP 20 mg once weekly (QW) or matching placebo for 4 weeks, followed by 4 weeks continued at 20 mg (20/20 QW), or titrated up to TSP 30 mg (20/30 QW) or to TSP 40 mg (20/40 QW), or placebo.

• **Baseline Demographics:**

N=133 randomized (completed 88%); age 57 years; A1C 7.9%; BMI 32 kg/m²; diabetes duration 7 years.

• **Key Findings:**

Target A1C ≤7.0% was reached in 72%, 53%, and 70% of patients with TSP 20/20, 20/30, and 20/40, respectively, versus 19% with placebo. Fasting plasma glucose (FPG) levels declined with TSP after the first dose, followed by a continued effect to -41, -29, and -40 mg/dL in the 20/20, 20/30, and 20/40 groups, respectively, versus -11 mg/dL with placebo by study end.

• **Adverse Events:**

Transient nausea was greatest after the first TSP injection and declined throughout study; 6% of 20/30 and 3% of 20/40 patients withdrew due to gastrointestinal side effects.

• **Conclusion:**

This limited, short-term study demonstrated that the maximum TSP pharmacodynamic effect associated with fewer gastrointestinal side effects was the 20 mg QW dose.

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Albiglutide Studies

Reports were presented from two studies of the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) profiles of subcutaneous albiglutide (ALB), a GLP-1R agonist formed by genetic fusion of a dipeptidyl peptidase-4-resistant GLP-1 dimer to human serum albumin.

A dose-escalation study evaluated ALB (9, 16, or 32 mg) versus placebo in patients with T2DM (n=54; age, 18 to 70 years, A1C 7.0% to 10.0%, FPG \leq 240 mg/dL, BMI 25 to 40 kg/m²; 49 patients completed all assessments). Patients were either drug-naïve or withdrawn from previous metformin and/or sulfonylurea treatment 2 weeks prior to the first study dose. ALB or placebo was administered on Days 1 and 8; FPG and 24-hr glucose profiles were obtained at baseline and on Days 2 and 9; PK sampling continued through day 56 or 63. Mean placebo-adjusted FPG for ALB doses is shown in Table 2; there was no change in FPG for placebo. The 95% CI of mean glucose-weighted AUC_(0-24h) was decreased from baseline for all ALB doses. Median T_{max} for ALB was reached 3 to 5 days after dosing, with no clear dose-dependent trend; mean half-life ranged from 6 to 7 days and was similar for all ALB doses. Adverse events with ALB were mild; the most common were headache, nausea, and vomiting, dizziness, and rash.

Table 2. Placebo-adjusted mean fasting plasma glucose (FPG, Δ from baseline)

FPG (mg/dL)	Albiglutide dose		
	9 mg	16 mg	32 mg
Day 2	-7.4	-22.9	-26.7
Day 9	-23.8	-32.5	-50.7

Next, an injection site study enrolled 46 patients with criteria similar to the dose escalation study, except for age (18 to 75 years), A1C (6.5% to 10.0%), and current treatment regimens of metformin or a thiazolidinedione that were continued throughout the study. A single ALB dose (16 or 64 mg) was administered to the arm, leg, or

abdomen on Day 1 of study following baseline assessments; periodic repeat assessments continued until Day 42. Mean FPG reductions on Day 3 were statistically significant in the 16 mg/abdomen and 16 mg/arm groups, as well as in all 64 mg groups. T_{max} was similar for all injection sites and doses, with a median of 3 to 4 days. Half-life ranged from 3.62 days (16 mg/leg) to 5.67 days (64 mg/arm).

In both studies, ALB improved FPG and postprandial glucose, although no consistent changes were observed in plasma glucagon, insulin, or C-peptide levels. The safety and tolerability of ALB was favorable in all doses tested, with a low risk of hypoglycemic events; no ALB-related adverse events were reported that led to discontinuation.

The long half-life of the GLP-1R agonist ALB makes it suitable for weekly administration and may allow for less-frequent dosing.

COMMENTARY

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The field of incretin-related therapies based on glucagon-like peptide-1 receptor (GLP-1R) agonist replacement is rapidly expanding with several players on the horizon having promising data.

GLP-1 replacement therapy is a physiologically sound approach that benefits from the incretin effect of stimulating glucose-dependent insulin secretion and suppressing inappropriately elevated postmeal glucagon secretion. The combination of A1C and body weight reductions obtained with GLP-1R agonists makes this therapy particularly attractive.

Exenatide was the first GLP-1 mimetic to demonstrate significant clinical efficacy in combination with metformin and/or a sulfonylurea or glitazone, with A1C reductions in the 0.8% to 1.0% range and weight loss in the 1 to 2.5 kg range as demonstrated in properly

controlled studies. However, exenatide use has been limited by the need for a twice-daily subcutaneous administration and a relatively high frequency of gastrointestinal side effects that often lead to discontinuation.

The study comparing once-weekly exenatide with twice-a-day exenatide generated great interest in view of the robust -1.9% A1C reduction obtained with once-weekly exenatide, which was superior to twice-daily exenatide (-1.5%) and associated with a similar 4 kg weight loss. It appears that the gastrointestinal side-effect profile was better with once-weekly exenatide, but skin problems were more frequent—due perhaps to the viscous nature of the LAR compound. Some of the robustness of the effects achieved with both compounds, however, may be related in part to the *study effect* nature of an open-label trial, with high expectations existing for both physicians and patients.

The studies reviewed above also explored the efficacy and safety of new GLP-1R agonists with improved pharmacokinetic and pharmacodynamic profiles allowing for once-daily or once-weekly administration that should theoretically improve patient compliance and increase acceptance of these compounds.

The Liraglutide Effect and Action in Diabetes (LEAD) program, exploring several clinical scenarios for once-daily liraglutide as monotherapy or in different combination scenarios, is particularly robust with thoroughly designed controlled studies that included placebo and/or active comparators. This is particularly important to understanding the findings, as most of the LEAD studies discontinued previous OADs at study entry to start or adjust to a homogeneous background OAD. The efficacy of once-daily liraglutide was consistently demonstrated with A1C reductions in the 1% to 1.3% range and body weight loss in the ~2 to 3 kg range depending on the study design and patient population.

Although 3 doses of liraglutide were explored, most effects seen between

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the 1.2 and 1.8 mg/day doses were very similar. The study comparing liraglutide with insulin glargine showed a 0.2% greater A1C reduction with liraglutide, with the expected benefit on body weight changes. However, the dose of insulin glargine was low and clearly suboptimal—this has been a limitation in other studies comparing different insulin regimens to exenatide.

Of particular interest is LEAD 6, a liraglutide study press-released but not presented at the 2008 ADA meeting in June. This study was fully reported at the annual meeting of the Canadian Diabetes Association in October 2008. It provided a head-to-head comparison of liraglutide 1.8 mg once daily versus exenatide 10 µg twice a day in patients with type 2 diabetes mellitus (T2DM) on metformin and/or a sulfonylurea. LEAD 6 demonstrated significantly greater A1C reduction by liraglutide compared with exenatide (−1.1% versus −0.8%, respectively), from baseline A1Cs of 8.2% and 8.1%, respectively, with a tendency for liraglutide to have less gastrointestinal side effects and slightly more weight loss.

The dose-finding study with AVE0010 explored multiple options administered once or twice daily, and demonstrated similar effects for the 2 dosing regimens in patients with T2DM on metformin monotherapy. Of particular importance were the low baseline A1C levels (~7.5%) — resulting in a significant proportion of patients reaching A1C <7% — and the associated weight loss in the ~2 to 3 kg range.

Of note, the new long-acting soluble GLP-1R agonists also look promising. Taspoglutide dose-finding studies demonstrated significant A1C reduction and weight loss despite the short duration of the trials; the pharmacokinetic and pharmacodynamic profiles of albiglutide make it clearly suitable for weekly dosing, with the potential to explore bi-weekly administration.

Finally, several preclinical studies with incretin-related agents have previously demonstrated β-cell protection and regeneration properties. However, the

expectation that GLP-1 mimetics such as exenatide may modify the underlying defects in T2DM and thereby change the course of the disease was not demonstrated in the 1-year study discussed above, where exenatide was compared with insulin glargine. Most likely, any disease-modifying effect by GLP-1R agonists will require much longer-term, controlled studies, carefully designed to identify sustained near-normoglycemia.

Dr. Rosenstock has been actively involved with all GLP-1R agonists reported above, either as a scientific advisor and/or as a clinical investigator.

Suggested Reading

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