New Agents in the Management of Type 2 Diabetes: Do They Provide an Opportunity for a Shift in the Treatment Paradigm?

Connie A. Valdez, PharmD, MSED

According to the Centers for Disease Control and Prevention (CDC), approximately 20.8 million Americans were living with diagnosed (14.6 million) or undiagnosed (6.2 million) diabetes in 2005, and 41 million were considered to be in a prediabetic state and at high risk of developing diabetes.¹ Worldwide, the International Diabetes Federation estimates that 246 million people currently have diabetes, and by 2025, this number is expected to increase to 380 million.² Even with access to medical counseling and various treatment modalities, only about 50% of patients reach the glycosylated hemoglobin (A1c) target set by the American Diabetes Association (ADA) of less than 7%.³ In an attempt to manage type 2 diabetes more rigorously and successfully, the ADA has provided recommendations using a treatment algorithm. Based on this treatment algorithm, metformin, sulfonylureas, thiazolidinediones, and insulin are recommended as preferred agents.⁴ Newer agents in 3 therapeutic classes known as glucagon-like peptide-1 (GLP-1) analogs (e.g., exenatide), amylin analogs (e.g., pramlintide), and dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin) do not have a clear place in therapy and are only briefly mentioned or not addressed at all in the guidelines.

In the May 2008 issue of *JMCP*, VanDeKoppel et al. reviewed the pathophysiology of type 2 diabetes and summarized the existing data for 3 new agents “to help the clinician identify clinical situations in which the new agents should be considered in the treatment algorithm.”⁵ This review provides valuable information for clinicians, and VanDeKoppel et al. should be congratulated on their efforts. VanDeKoppel et al.’s assertion of weak or absent treatment recommendations for exenatide, pramlintide, and sitagliptin is supported by the discussion of these agents in the ADA Standard of Medical Care in Diabetes (2008): “Other medications such as pramlintide, exenatide, alpha-glucosidase inhibitors, the glinides, and dipeptidyl peptidase IV inhibitors were not included in the consensus algorithm, owing to less glucose-lowering effectiveness, limited clinical data, and/or relative expense. However, they may be appropriate choices in individual patients to achieve glycemic goals.”⁶ The American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus have yet to define a place in therapy for these new agents.⁷ Yet, there is rapid uptake of the 3 new agents, as demonstrated by sitagliptin’s market share of 14% of new prescriptions for diabetes treatment during the first 6 weeks following its approval.⁵ This discrepancy highlights how

the market uptake of new agents for diabetes can diverge from the clinical guidelines of respected organizations.

Within their review of diabetes treatment and pathophysiology, VanDeKoppel et al. did recognize that these 3 new agents may have a positive or neutral effect on weight loss but added that only a modest reduction in A1c is achieved when compared with other agents recommended by the ADA (metformin, sulfonylureas, insulin, etc.). While weight loss may occur with exenatide and pramlintide, clinical trials have not demonstrated that this weight loss is clinically relevant or results in improved health outcomes. In addition, evidence related to the safety and efficacy of these 2 agents for weight reduction is lacking.^{8,9}

The authors also note that decline in beta-cell function is common in individuals with type 2 diabetes. When beta-cell apoptosis exceeds the rate of replication, beta-cell failure ensues, resulting in worsened diabetes. Excessive apoptosis is thought to be secondary to glucotoxicity, lipotoxicity, and pro-inflammatory cytokines and leptin.¹⁰ This hypothesized causal relationship is important to consider when linking the pathophysiology with possible treatment options, since type 2 diabetes is associated with hyperglycemia and dyslipidemia characterized by elevated triglycerides and free fatty acids. As diabetes worsens, this related glucotoxicity and lipotoxicity promotes further decline of beta-cell function. This cycle of worsening diabetes and loss of beta-cell function continues until beta-cell exhaustion occurs. At recent meetings of the Metropolitan Diabetes Society (2007) and the ADA (2008), diabetes researcher Ralph DeFronzo advanced the idea that appropriate treatment would include not only reversing insulin resistance but also improving beta-cell function. Bloomgarden’s summary of the presentations suggested the implications of DeFronzo’s idea: The ideal agent would additionally “correct the pathophysiologic disturbances responsible for type 2 diabetes.”¹¹ While VanDeKoppel et al. note that exenatide may promote beta-cell proliferation and synthesis, and that sitagliptin may improve beta-cell function, the importance of this concept may have been overlooked by these authors when considering the potential role of these agents.

Wang et al. demonstrated in an animal model that glucose intolerance, secondary to age-dependent beta-cell function decline, was reversed with a constant infusion of GLP-1.¹² In another animal model, Fineman et al. demonstrated that beta-cell function was increased by 50%-100% at days 14 and 28 for all GLP-1 agonist arms compared with no change with placebo. Specifically, the homeostasis model assessment of B-cell function

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(HOMA-B) cell index was used to measure beta-cell function, with a higher number representative of more beta-cell function. The HOMA-B was approximately 43 on day 1, 68 on day 14, and 92 on day 28 for the twice daily (breakfast/dinner) GLP-1 agonist arm; approximately 43 on day 1, 78 on day 14, and 68 on day 28 for the twice daily (breakfast/bedtime) GLP-1 agonist arm; and approximately 55 on day 1, 96 on day 14, and 90 on day 28 for the thrice daily (breakfast/dinner/bedtime) GLP-1 agonist arm, compared with the placebo arm which decreased from day 1 to day 28 (approximately 58 on day 1, 57 on day 14, and 51 on day 28).¹³ The practical implication of using HOMA-B as a measurement of beta-cell function in humans was demonstrated with the United Kingdom Prospective Diabetes Study (UKPDS) findings. Sixty-two percent of patients receiving a sulfonylurea as monotherapy with HOMA-B below 27% required additional therapy to maintain glycemic goals compared with 28% of patients with HOMA-B above 55% who required additional treatment.¹⁴ Salehi et al. reviewed 14 studies using animal models and concluded that incretin-based drugs (GLP-1 agonists and DPP-4 inhibitors) have the potential to improve glucose tolerance by a favorable effect on beta-cell physiology and maintaining or possibly expanding beta-cell mass.¹⁵ Additional animal model studies support that these agents preserve beta-cell function and mass, providing a basis to evaluate their effects on beta-cell function, mass, and preservation in humans.¹⁶⁻³⁷

There are few studies of the effects of GLP-1 agonists and DPP-4 inhibitors in human cells. Farilla et al. found that within 5 days, GLP-1 preserved beta-cells through inhibiting apoptosis, preserving morphology and potentiating glucose-dependent insulin secretion in human islet cells. Specifically, at day 5, (a) approximately 45% of the control islet cells lost morphology compared with 15% in the GLP-1 treated islets; (b) apoptosis occurred in 18.9% of the control islet cells compared with 8.9% in the GLP-1 treated islets; and (c) the glucose-dependent secretion of insulin was greater in the GLP-1 treated islets.²⁹ Buteau et al. also evaluated GLP-1 in human islet cells and found that GLP-1 prevented apoptosis.³⁰ Although these data do not represent clinical practice, and the practical value of these effects has not yet been demonstrated, there seems to be sufficient basis for conducting further research to evaluate the effects of using these agents in an attempt to preserve beta-cell function in a clinical practice setting.

The results of several studies have led to the hypothesis that these agents may alter the course of diabetes or possibly prevent diabetes. Mu et al. concluded that these agents may offer “long-lasting efficacy in the treatment of type 2 diabetes by modifying the courses of the disease.”²⁶ Farilla et al. stated that “because GLP-1 is being considered for the treatment of type 2 diabetes, the identification of its antiapoptotic properties may better define the indication for its use in subjects at early stages of the disease when restoration of a normal islet mass delays or perhaps prevents the onset of diabetes.”²⁹ Turrel et al. concluded that “GLP-1 rep-

resents a unique tool because of its beta-cell replenishing effect” and that GLP-1 “may prove to be an invaluable agent for the prevention of human type 2 diabetes.”³⁷ Although these results appear promising, a test of the clinical significance of medications on beta-cell function in humans is needed. Unfortunately, in clinical practice, no method exists to directly measure beta-cell function. However, results of the ADOPT (A Diabetes Outcome Progression Trial) study suggest that it may be possible to evaluate preservation of beta-cell function from GLP-1 agonists and DPP-4 antagonists in a clinical practice setting.³⁸

The ADOPT study enrolled and randomized drug-naïve patients who had been diagnosed with type 2 diabetes for less than 3 years to glyburide, metformin, or rosiglitazone (dose titrated to achieve ADA goals) for 4 years. The primary outcome was the time to monotherapy failure (defined as “fasting plasma glucose level, >180 mg per deciliter on consecutive testing after at least 6 weeks of treatment at the maximum-dictated or maximum-tolerated dose of the study drug”) with secondary outcomes of change in glycemic control, insulin sensitivity and beta-cell function from baseline. Rosiglitazone had the slowest decline in glycemic control (15% failure rate and annual beta-cell function decline of 2.0%), a finding consistent with the theory (based on small trials) that glitazones may have beta-cell preservation properties. Glyburide, which does not preserve beta-cell function or mass, had the most rapid decline in glycemic control (34% failure rate and annual beta-cell function decline of 6.1%). For decline of both glycemic control and beta-cell function, comparisons of rosiglitazone with glyburide were statistically significant ($P<0.001$).³⁸

Since the completion of the ADOPT trial, 2 clinical studies have evaluated the effect of the DPP-4 inhibitor sitagliptin on beta-cell function using HOMA-B measurements, but these studies were 24 weeks in duration. Aschner et al. performed a double-blind, placebo controlled study of 741 patients who were not on an oral antiglycemic agent for at least 8 weeks. The patients were randomized to sitagliptin 100 mg daily, sitagliptin 200 mg daily, or placebo for 24 weeks. The authors found that HOMA-B increased significantly from approximately 58 to 71 and 55 to 68, respectively, with sitagliptin 100 mg daily and 200 mg daily compared with no change (56 to 56) with placebo from baseline to 24 weeks.³⁹ Charbonnel et al. performed a randomized, placebo-controlled study of 701 patients with mild to moderate hyperglycemia (mean A1c 8.0%) receiving ongoing metformin (>1,500 mg per day). The patients were randomized to additionally receive sitagliptin 100 mg once-daily in a 1:2 ratio or placebo for 24 weeks. The authors found that HOMA-B increased significantly from approximately 46 to 65 with sitagliptin 100 mg daily compared with 45 to 48 with placebo.⁴⁰ Longer-term studies similar to ADOPT for both GLP-1 agonists and DPP-4 antagonists are needed. However, the available data suggest that if researchers look beyond A1c reduction as described by VanDeKoppel et al., and towards the opportunity of these 2 agents to preserve beta-

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cell function and mass, perhaps they will be encouraged to obtain funding in order to conduct clinical studies similar to ADOPT. These studies could evaluate whether using these agents in early stages of diabetes, including the prediabetes stage, will slow down and possibly prevent diabetes progression.

To further understand the possible role of exenatide and sitagliptin in treating type 2 diabetes, it is important to recognize that the initial phase of the diabetes continuum (the prediabetes phase) is when patients begin to present with impaired glucose homeostasis in the form of hyperglycemia, thus reflecting the initial decline in beta-cell function. Beta-cell function continues to decline as the disease progresses.⁴¹ In fact, based on the UKPDS findings, patients diagnosed with type 2 diabetes had already lost approximately 50% of their beta-cell function at the time of diagnosis followed by a linear reduction in beta-cell function. Specifically, subjects treated with diet therapy had lost 49% of their beta-cell function at the time of diagnosis and continued to lose beta-cell function during the study period, resulting in a 72% loss of beta-cell function after 6 years.¹⁴ As suggested by Farilla et al., if beta-cell preservation medications are introduced early in the disease course, then perhaps the evolution of diabetes can be altered.²⁹ Admittedly, this proposed mechanism is only speculative, and rigorous clinical trials are required to substantiate it and to establish a place in therapy for these medications. However, the hypothesized mechanism does set forth a reasonable therapeutic theory. Of course, any use of these new agents in the management of prediabetes would be considered experimental and currently off-label. Long-term efficacy and safety data are not available for the new agents, and this information is necessary to permit evaluation of their possible role in preservation of beta-cell function and not just A1c reduction.

Pharmacoeconomic analyses of these new agents and their contribution to the costs of diabetes management are also needed. VanDeKoppel et al. provided information related to the direct drug cost of the new agents which ranged from \$171 per month for sitagliptin to approximately \$230 per month for exenatide.⁵ The authors note that these agents carry a higher financial burden in direct drug cost than conventional agents, and that cost should be a consideration prior to determining appropriate therapy. However, VanDeKoppel et al. did not consider the possible cost-savings that could result by changing the treatment paradigm, and using GLP-1 agonists or DPP-4 antagonists early in disease progression, which could ultimately lead to fewer cases of severe diabetes in the United States. Although Watkins et al. performed a pharmacoeconomic analysis of exenatide to estimate the incremental effect of exenatide over other available therapies, the authors did not assess the pharmacoeconomic impact of initiating exenatide early in treatment, as patients in the Watkins et al. analysis had an average duration of type 2 diabetes for 8 years.⁴²

Without clinical data to support the number needed to treat and/or harm, possible cost savings associated with early use of sitagliptin or exenatide cannot be determined. However, we do

know that the total direct and indirect costs of diabetes in the United States were estimated to be \$174 billion in 2007.⁴³ This figure included direct costs related to medical expenditures of \$116 billion (\$27 billion for diabetes care, \$58 billion for complications related to diabetes, \$31 billion for excess general medical expenses) and indirect costs of \$58 billion. The indirect costs were determined based on disease-related unemployment disability, reduced productivity, absenteeism, and loss of productive capacity from early mortality. Medical expenditures are approximately 2.3 times higher for patients with diabetes than for those without diabetes. Furthermore, the CDC estimates that 54 million Americans have prediabetes.¹ Most of these individuals will likely develop diabetes if the disease process is not altered. Imagine the economic impact of halting or at least slowing down the progression of prediabetes to diabetes with lifestyle modifications and drug therapy.

As concluded by VanDeKoppel et al., based on the current high direct drug cost and lack of long-term safety and efficacy data, these new agents should be reserved for individuals with either a contraindication or evidence of inadequate response to other recommended agents.⁵ These conclusions are consistent with the Cochrane Systematic Review, which reviewed 25 DPP-4 inhibitor studies of “good quality” and concluded that “DPP-4 inhibitors have some theoretical advantages over existing therapies with oral antidiabetic compounds but should currently be restricted to individual patients. Long-term data especially on cardiovascular outcomes and safety are urgently needed before widespread use of these new agents. More information on the benefit-risk ratio of DPP-4 inhibitor treatment is necessary especially analysing adverse effects on parameters of immune function. Also, long-term data are needed investigating patient-oriented parameters like health-related quality of life, diabetic complications and all-cause mortality.”⁴⁴ These conclusions are also consistent with some managed care organizations, such as the Regence Group, that have explicit clinical guidelines for the use of exenatide and sitagliptin.^{8,45} However, as suggested by Farilla et al., Mu et al., and Turrel et al., further studies are needed to determine if use of exenatide and sitagliptin early in the course of diabetes and/or during the prediabetes phase would preserve beta-cells (while the patient still has adequate numbers) to the extent that the clinical course of diabetes could be altered.^{26,29,37}

Author

CONNIE A. VALDEZ is Assistant Professor, Department of Clinical Pharmacy, School of Pharmacy, University of Colorado Denver.

AUTHOR CORRESPONDENCE: Connie A Valdez, PharmD, MEd, University of Colorado Denver, School of Pharmacy C238-L15, Academic Office 1, 12631 E. 17th Ave., Room L15-1221 P.O. Box 6511, Aurora, CO 80045. Tel.: 303.724.2630; Fax: 303.724.2627; Email: connie.valdez@uchsc.edu

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