ABSTRACT

Type 2 diabetes mellitus (T2DM) is a condition in which multiple organs are broken and multiple drugs are needed to fix multiple problems. Although new pharmacologic agents regulate blood glucose concentrations by targeting different organs, the Holy Grail for therapeutic intervention remains β-cell dysfunction. At diagnosis, most people have already had T2DM for 9 to 12 years and as much as 50% to 80% of β-cell function is already lost. Drugs that act on the incretin system improve glycemic control by acting on several key hormones and organs involved in the maintenance of glucose homeostasis. Included in these mechanisms are β-cell effects responsible for the enhancement of glucose-dependent insulin secretion and restoration of first-phase insulin response.

Type 2 diabetes mellitus (T2DM) is a function of deficits at multiple organ sites. It is characterized by insulin resistance in muscle tissue, impaired insulin, amylin, and glucagon secretion from the pancreas, and unrestrained glucose production in the liver. All of these deficits are augmented by defective insulin action in fat. Collectively, they contribute to the progression of hyperglycemia. In recent years, a plethora of new pharmacologic agents have become available, with mechanisms of action that work to regulate blood glucose concentrations by targeting different organs involved in this complex disease process. The Holy Grail for therapeutic intervention, however, remains chronic β-cell dysfunction. One study showed that the frequency of β-cell apoptosis was increased 10-fold in lean and 3-fold in obese cases of T2DM compared with their respective nondiabetic control group (P <.05).

At diagnosis, most people have already had T2DM for 9 to 12 years and as much as 50% to 80% of β-cell function is already lost (Figure). How can we save β-cell functionality in people with T2DM? That is the ultimate challenge we face in pharmacotherapy management of T2DM. Clearly, early diagnosis and aggressive management from the start are key to therapeutic success and disease management.

Drugs that act on the incretin system improve glycemic control by acting on several key hormones and organs involved in the maintenance of glucose homeostasis. Included in these mechanisms are β-cell effects responsible for the enhancement of glucose-dependent insulin secretion and restoration of first-phase insulin response. The insulin secretory response is known to be impaired in people with T2DM. The focus of this article is on pharmacologic strategies for enhancing incretin activity in patients with T2DM.

Patterns of Glucose, Insulin, and Glucagon in T2DM

Increased systemic glucose delivery, due primarily to unrestrained endogenous hepatic glucose output and, to a lesser extent, reduced visceral glucose sequestration, is thought to be the predominant factor...
responsible for postprandial hyperglycemia in T2DM. Early in the development of diabetes, there is a loss of the first-phase insulin secretion following food ingestion. Deficiencies in first-phase insulin secretion postprandially have been attributed to what is sometimes called the incretin effect. Briefly stated, glucagon-like peptide-1 (GLP-1) is secreted from intestinal L cells when food is ingested and is thought to contribute to insulin and amylin secretion and glucagon suppression. People with T2DM have a decreased GLP-1 response and an association between this deficiency and increased glucagon and reduced insulin secretion is likely.

ENHANCING INCRETIN ACTIVITY
Pharmacologic strategies to augment incretin activity fall into 2 broad categories. Incretin mimetics activate GLP-1 receptors. Drugs in this class are the GLP-1 analogs exenatide, which is currently available, and liraglutide, which is not yet approved in the United States. Dipeptidyl peptidase-4 (DPP-4) inhibitors, on the other hand, work to block the degradation of endogenous GLP-1 by inhibiting the DPP-4 enzyme. The only drugs currently available in this class are sitagliptin and saxagliptin; vildagliptin and alogliptin are currently undergoing US Food and Drug Administration (FDA) review.

A comparison of key attributes of these 2 classes is shown in Table 1. An important differentiating feature is that GLP-1 mimetics or analogs (exenatide and liraglutide) must be injected, whereas DPP-4 inhibitors, also known as gliptins (sitagliptin, vildagliptin, saxagliptin, and alogliptin) are taken orally. In both classes, reductions in glycosylated hemoglobin (A1c) are glucose dependent, so that higher A1c levels result in greater reductions. GLP-1 analogs are associated with weight loss and DPP-4 inhibitors are generally weight neutral, with minimal hypoglycemia when used as monotherapy. The following sections summarize key safety and efficacy data for drugs in these classes.

GLP-1 ANALOGS
Because incretins primarily target postprandial glucose, use in combination therapy with agents that impact fasting glucose makes good clinical sense. When used in combination with sulfonylureas or metformin, exenatide achieved A1c reductions of 0.46 to 0.86 and 0.4% to 0.78%, respectively. The triple combination of exenatide and sulfonylurea plus metformin achieved similar reductions in A1c (0.6%–0.8%).

Recent research also reveals significant reductions in cardiovascular risk factors following long-term use of exenatide. Specifically, a 3.5-year study showed a reduction in triglycerides (-12%), total cholesterol (-5%), low-density lipoprotein cholesterol (-6%), as well as systolic/diastolic blood pressure (-2%/-4%). High-density lipoprotein cholesterol was increased by

Table 1. Key Attributes of GLP-1 Receptor Agonists and DPP-4 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>GLP-1 Agonists</th>
<th>DPP-4 Inhibitors (Gliptins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>Injection</td>
<td>Orally available</td>
</tr>
<tr>
<td>GLP-1 concentrations</td>
<td>Pharmacologic</td>
<td>Physiologic</td>
</tr>
<tr>
<td>A1c reduction</td>
<td>-0.5% to -1.1%</td>
<td>-0.8% to -1.8%</td>
</tr>
<tr>
<td>Insulin secretion</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Glucagon suppression</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Gastric emptying</td>
<td>Inhibited</td>
<td>+/-</td>
</tr>
<tr>
<td>Weight loss</td>
<td>-3 to -5 kg</td>
<td>± 0 kg</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Potential immunogenicity</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

A1c = glycosylated hemoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1. Data from Nauck et al.; Drucker et al.; Drucker and Nauck; and Moretto et al.
24%. Clinical trials of exenatide long-acting release, also known as once-weekly exenatide, are currently under FDA review and have shown reductions in A1c of 1.4% to 1.7% over 15 weeks.23

Although liraglutide has been delayed pending additional data review, its entry to market would make it the second GLP-1 agonist available. Also injectable, liraglutide requires a single daily injection whereas exenatide is injected twice daily. Studies of liraglutide as monotherapy resulted in A1c reductions of up to -1.41%.24 Used in combination with metformin and rosiglitazone, liraglutide achieved a -1.48 reduction in A1c.25 A recent meta-analysis of clinical trials of GLP-1 analogs26 revealed significantly greater incidence of nausea in studies of twice-daily exenatide (41.9%) than in studies of liraglutide (5.6%).

Acute pancreatitis is 3 to 4 times greater in patients with T2DM than in the overall population. The FDA has reported 30 cases of pancreatitis in patients using exenatide,27 and 6 cases of necrotizing or hemorrhagic pancreatitis.28 Based on these reports, the FDA recommends that clinicians consider therapies other than exenatide in patients with a history of, or risk factors for, pancreatitis.

MANAGING GLP-1-ANALOGS ADVERSE EVENTS
Nausea and vomiting

Although nausea and vomiting are transient side effects of the GLP-1 analogs, in my clinical experience these problems seem to be related to portion size and are modified by adjusting eating habits. Instruct patients to eat smaller meals, and to take these medications within 60 minutes of eating.

Injection site pain

Patients who complain of injection site pain may need a review of injection techniques. Patients should be advised to avoid reusing needles.

Pancreatitis

In patients with suspected pancreatitis, promptly discontinue exenatide and other potentially suspect drugs. Patients with confirmed pancreatitis should undergo appropriate treatment. Carefully monitor the patient until fully recovered. Exenatide should not be restarted.

Patient candidates for GLP-1 analogs

Appropriate patients for GLP-1 mimetics are those who:

• Are newly diagnosed to long-standing T2DM
• Do not have gastroparesis, are not pregnant, or do not plan to become pregnant
• Experience postprandial glucose elevations
• Require modest A1c lowering
• Will benefit from weight loss
• Are committed to making nutrition and lifestyle changes (portion size can influence side effects)
• Have had renal function assessed and whose medication profile has been reviewed to identify other agents that may affect renal function
• Have undergone education on the signs and symptoms of acute pancreatitis
• Understand and accept injectable administration of drugs

DPP-4 INHIBITORS (GLIPTINS)

A recent meta-analysis22 of 20 clinical trials of sitagliptin and vildagliptin reported an overall A1c reduction of -0.74%. Similar A1c effects were observed when these agents were used as monotherapy and as add-on therapy. Fasting plasma glucose reductions of -18 mg/dL were reported. Although the 2 agents have not been directly compared, clinical trials of saxagliptin have reported A1c reductions ranging from -0.62% to -0.73%, whereas alogliptin studies report reductions ranging from -0.56% to -0.59%.29-34

The most frequently reported adverse events for this drug class are nasopharyngitis (6.4%) and upper respiratory tract infection (6.3%) across trials.22 Other adverse events reported were headache (5.1%), influenza (4.1%), and diarrhea (3.8%).22 A list of key points to consider when selecting pharmacotherapy is provided in Table 2.

Table 2. Key Points to Consider When Selecting Pharmacotherapy

| • How long has the patient had diabetes? |
| • Which blood glucose level is being targeted (fasting, postprandial, or both)? |
| • How great of an A1c reduction is needed to achieve goal? |
| • What is the drug’s side-effect profile, and what is the patient’s tolerability for those side effects? |
| • What are the co-existing conditions? |
| • What is the patient preference for route of administration (eg, oral, inhaled, or injectable)? |

A1c = glycosylated hemoglobin.
CONCLUSIONS
Preservation of β-cell function is critical to curtailting progression of T2DM. Currently, this goal can only be accomplished with early diagnosis and aggressive patient management to achieve A1C target goals. Patients who are not at goal after 3 months should be re-evaluated and therapy adjusted accordingly, to include combination treatments as appropriate. Combination therapy should target different dysfunctional organs in order to treat glucose abnormalities from a variety of fronts. Although tracking and monitoring various numerical targets represents the cornerstone of diabetes management, as pharmacists it is important that we remember to treat the patient as well as the number.

REFERENCES