Advances in Diabetes Therapies

Jeff Unger, MD

As newer agents in development are approved, and as oral agents are combined with injectable therapies, many more therapeutic options will become available for patients with type 2 diabetes.

Although successful achievement of glycemic targets remains elusive for many patients and physicians, the prevalence of microvascular complications attributed to diabetes (retinopathy and nephropathy) is on the decline. Since 90% of all patients with diabetes are managed within the primary care setting, improvement in diabetes outcomes may be attributed to improved pharmacotherapeutic options as well as customized care for patients based on their metabolic profile.

Diabetes is a polygenic, chronic, progressive disorder with a complex pathogenesis. Physicians must provide patients with a solid foundation of healthy lifestyle interventions on which an array of oral and injectable medications may be added in a timely manner. The goal of diabetes therapy is to intensively manage patients who have been diagnosed with hyperglycemia as soon as possible, for as long as possible, as rationally as possible, and as safely as possible. Agents in development such as new formulations of insulin, sodium glucose co-transporter-2 (SGLT-2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors, offer additional therapeutic interventions that may further improve glycemic control in patients. These agents are advantageous in that they offer dosing flexibility, reduced risk of hypoglycemia, and less likelihood of clinically significant weight gain. As these new agents have been submitted to the FDA for approval, primary care physicians should be aware of how they may be useful in managing patients with type 2 diabetes.

DEVELOPMENT OF TYPE 2 DIABETES

Although the “core defects” of type 2 diabetes are pancreatic β-cell failure and insulin resistance, other systems play unique and contributory roles in disease progression. Genetic and environmental factors certainly increase the likelihood of developing type 2 diabetes. In addition, abnormalities in adipocytes (accelerated lipolysis), neuroprotective mechanisms (resulting in excessive appetite), incretin resistance in the gastrointestinal (GI) tract, and excessive hepatic glucose production despite a 3-fold increase in β-cell secretion of insulin, all contribute to chronic hyperglycemia, oxidative stress, and long-term complications. Whether a patient remains euglycemic or advances toward the hyperglycemic pathway is ultimately determined by the ability of his or her pancreatic β-cells to produce and secrete enough insulin to maintain normoglycemia.

Hyperglucagonemia is another primary feature of both prediabetes and diabetes. Under normal conditions, a postprandial increase in glucose concentration is associated with a corresponding reduction in glucagon. As plasma glucose levels decrease, glucagon levels increase, resulting in a 60% increase in hepatic glucose production and output through gluconeogenesis. Glucagon secretion is regulated, in part, by endogenous insulin secretion. Insulin action results in the storage of glycogen within hepatocytes. Insulin resistance, insulinopenia, or an increase in glucagon output, signals the liver to depolymerize glycogen, resulting in a rise in plasma glucose concentration. Glucagon secretion is substantially elevated in the fasting state and is not suppressed during the postabsorptive phase in patients with both prediabetes and clinically apparent diabetes. Drugs that inhibit glucagon secretion or antagonize the glucagon receptor, such as GLP-1 receptor agonists and DPP-4 inhibitors, are effective in treating patients with type 2 diabetes.

The role of the kidneys in maintaining normoglycemia, through the filtration and reabsorption of glucose, as well as gluconeogenesis, is well established. Euglycemic persons filter approximately 180 L of plasma and 180 g of glucose through the kidneys daily. Under normal conditions the ability of the kid-
ney to reabsorb glucose from the glomerular filtrate is extremely effective with <0.5 g per day of the filtered glucose appearing in the urine. However, in patients with hyperglycemia, the amount of filtered glucose reabsorbed increases in proportion to the plasma glucose concentration until the resorptive capacity of the proximal convoluted tubules of the glomerulus is exceeded. At this point, the excess glucose is excreted into the urine and is detected as glycosuria.

Drugs that are able to normalize plasma glucose levels by antagonizing the action of proximal tubule protein transporters seem to be an attractive pharmacologic target for patients with diabetes.

**DISEASE PROGRESSION INEVITABLE**

The inevitable worsening of diabetes has implications beyond glycemic control. The disease leads to significant medical complications; however, many studies have supported the positive effects of therapeutic intervention on long-term medical results. A 10-year, post-interventional follow-up of the United Kingdom Prospective Diabetes Study (UKPDS) survivor cohort by Holman et al showed continued microvascular benefit from earlier improved glucose control. In a study from the Diabetes Control and Complications Trial (DCCT) Research Group, investigators found that intensive therapy delayed the onset and slowed the progression of diabetic retinopathy, nephropathy, and neuropathy in 1441 patients with type 1 diabetes.

**TREATMENT WITH INSULIN**

Encouraging physicians to take a more active role in becoming early adopters of insulin therapy would allow more patients with type 2 diabetes to minimize their “glycemic burden” and reduce the risk of activating long-term complication pathways. Insulin initiation is often delayed because patients are misinformed about the role insulin plays in mitigating disease progression. Barriers to insulin treatment, such as injection phobia, and concerns about side effects or the negative social stigma of taking insulin, have been observed in patients with type 2 diabetes. Clinicians should strive to provide clear communication regarding the importance of insulin treatment, including patient self-management, to improve adherence.

Practice guidelines, such as the consensus panel statement of the American Association of Clinical Endocrinologists (AACE), suggest that insulin therapy should be considered in patients with type 2 diabetes when A1C is >9%. In symptomatic patients, initiation of insulin therapy is appropriate, either with or without additional oral agents. Abundant evidence supports the early initiation of insulin therapy as insulin acts to significantly lower plasma glucose levels while minimizing the long-term complications associated with chronic hyperglycemia.

Medication regimens can be complex for patients with diabetes who are taking multiple agents and, consequently, adherence becomes a significant problem. The suggestion to either initiate insulin or modify their current intensive regimen may seem overwhelming to many patients. Therefore, clinicians should attempt to customize the treatment protocol using insulin by considering patients’ lifestyles and encouraging them to successfully and safely achieve their desired glycemic targets.

Patients with type 2 diabetes may achieve their customized glycemic targets by using basal insulin plus oral agents, basal-bolus insulin, or premixed insulin analogs. The initial use of basal insulin plus oral agents using patient-driven dose titration regimens has proven to be very successful in allowing patients to achieve the American Diabetes Association (ADA)-targeted glycemic goal of <7%.

Two long-acting insulin analogs are currently commercially available: insulin glargine (IGlar) and insulin detemir. While these analogs differ markedly in molecular structure and pharmacology, they demonstrate improved pharmacodynamic characteristics, lower levels of fasting glucose, reduced risk for nocturnal
hypo glycemia, and reduced intrasubject variability compared with human NPH insulin.9 The prolonged absorption of insulin glargine is due to the slow dissolution of the insulin microprecipitate that forms within the skin’s neutral pH.9 Insulin detemir’s prolonged action is accomplished by attaching a 14-carbon fatty acid chain (myristic acid) to the lysine residue at position B29. The side chain contributes to enhanced self-association of insulin detemir and reversible albumin binding in the subcutaneous depot and circulation. Insulin detemir is highly albumin bound once injected into the subcutaneous tissue. The insulin complex bound to albumin does not easily traverse capillary membranes. Thus, the plasma concentration of detemir is relatively constant and independent of capillary flow rate, which explains the insulin’s decreased variability in absorption compared with glargine and NPH.10

Armed with a wish list, investigators are now attempting to improve the safety, efficacy, and pharmacologic properties of novel basal insulin formulations. The attributes of what some might consider to be the properties of an “ideal basal insulin” are outlined below (see Table 1).

Insulin degludec (IDeg) is an ultra-long-acting basal insulin analog that was developed to achieve optimal glycemic control but with a lower risk of hypoglycemia and greater flexibility in dosing than currently available basal insulins.12 Insulin degludec is a new type of basal insulin, characterized by a unique mechanism of action: a continuous and sustained release of monomers into the circulation from a depot of soluble multihexamers that form after subcutaneous injection.13

In a double-blind, 2-period, crossover trial, Nosek et al14 assessed the dose-response relationship of 3 doses of IDeg (0.4, 0.6, and 0.8 U/kg) at steady state in 49 subjects with type 2 diabetes. After stopping all oral antidiabetic medications, the participants were given IDeg once daily for 6 days. Following dosing on Day 6, patients underwent a euglycemic glucose clamp; pharmacokinetic samples were taken up to 120 hours after the last IDeg injection. Regardless of dose, mean 24-hour glucose profiles were flat and unvarying; IDeg lowered glucose uniformly for all doses. Clinically, the study demonstrated that IDeg has a half-life (t1/2) of more than 25 hours, which is twice as long as insulin glargine.

Patients who have difficulty adhering to strict dosing schedules may benefit from IDeg’s more flexible dosing regimen. An open-label, randomized trial conducted for 26 weeks in people with type 2 diabetes evaluated the noninferiority of IDeg with once-daily administration in a flexible regimen (IDeg Flex; a compulsory, rotating morning and evening schedule, creating 8- to 40-hour dosing intervals) compared with IGlar taken at the same time each day according to label.15 In patients on oral antidiabetic (OAD) therapy, insulin was added to their regimen. At 26 weeks, IDeg Flex and IGlar reduced A1C levels by 1.28% and 1.26%, respectively; the upper 95% confidence interval limit was < 0.4, confirming noninferiority. This trial demonstrated that IDeg can be administered anytime daily, and injection times can be changed daily, while maintaining a minimum of 8 hours between doses, without negatively affecting glycemic control or the risk of hypoglycemia. In comparison, the package insert states that IGlar must be administered at the same time each day.15,16 Both IDeg

<table>
<thead>
<tr>
<th>Table 1. Therapeutic Wish List for the “Ideal” Basal Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>With appropriate titration, patients may attain consistent and predictable fasting blood glucose control.</td>
</tr>
<tr>
<td>Patients using the basal insulin experience less confirmed and nocturnal hypoglycemia, especially once the target fasting glucose level has been achieved and changes in the patient’s daily dose are minimal.</td>
</tr>
<tr>
<td>The insulin allows for flexible daily dosing (ie, the insulin may be injected at any time of the day). This flexibility in dosing may improve patient adherence to the intensified regimen (33% of insulin-naïve patients never become ongoing users and fail to refill their prescriptions).11</td>
</tr>
<tr>
<td>Dosing delivery systems must be precise while allowing patients (who use pen devices) with greater daily insulin requirements to dose more than 80 units, the current maximum dose possible in pen devices, in a single injection.</td>
</tr>
<tr>
<td>Basal insulin may be coformulated with a rapid-acting analog that may be administered once daily.</td>
</tr>
<tr>
<td>Accurate dosing with minimal pain can be administered via a pen device.</td>
</tr>
</tbody>
</table>

Table provided courtesy of Jeff Unger, MD.
Flex and IGLar had similar rates of confirmed hypoglycemia, nocturnal confirmed hypoglycemia, and adverse events (AEs).15 Severe hypoglycemia was rarely noted in either group.

In a 1-year, open-label, treat-to-target study of 992 subjects, investigators compared the efficacy and safety of IDeG with IGLar. The investigational drugs were given once daily in basal-bolus treatment with mealtime insulin aspart (IASp) ± metformin ± pioglitazone in patients with type 2 diabetes.17 Both IDeG and IGLar improved glycemic control and reduced A1C levels by 1.2% and 1.3%, respectively, at the study’s conclusion. Rates of nocturnal confirmed hypoglycemia were 25% lower with IDeG compared with IGLar ($P = .04$). IDeG patients also exhibited an 18% lower rate ($P = .036$) of overall confirmed hypoglycemia compared with IGLar.

IDeg is also being studied as a coformulation with the rapid-acting prandial IAsp, resulting in a soluble product containing two different insulin analogs: IDeGAsp. A single injection of IDeGAsp consists of 70% long-acting basal insulin and 30% rapid-acting prandial insulin.18 Thus, IDeGAsp will permit patients to target both fasting and mealtime glycemic control in a single injection.

Insulin degludec seems to have advantages for many patients with type 2 diabetes. For patients with a history of hypoglycemia, this agent could be effective and reassuring; for patients who skip a dose, such as patients who travel frequently or have irregular work/sleep schedules, IDeG’s long-lasting effects are beneficial. For patients who need a basal-bolus insulin in a single injection, IDeGAsp may simplify their medication regimen as well as improve treatment adherence.

The 200 U/mL formulation of IDeG (IDeg U200) contains equal units of insulin in half the volume compared to the 100 U/mL (IDeg U100) formulation, and thus allows larger insulin doses to be administered in a single injection (up to 160 units) with a prefilled pen device. This insulin may provide a safe and effective means by which patients can self-administer between 2 and 160 units of concentrated basal insulin in a single prefilled pen-delivered dose. IDeg U200 would be an ideal insulin for patients who desire to use a pen device and require more than 80 units of basal insulin in a single injection. A double-blind, two-period, crossover trial by Korsatko et al19 found that IDeG U100 and IDeG U200 are bioequivalent, provide equal glucose-lowering effects, and may be used interchangeably.

OTHER ANTIDIABETES THERAPIES IN DEVELOPMENT

In the search for alternative, safe, effective, and durable therapeutic options, new agents with novel mechanisms of action are in various stages of development and include SGLT-2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors.

SGLT2 Inhibitors

Glucose reabsorption is accomplished via the active high-capacity transport protein, SGLT-2, which is expressed predominantly in the kidney and is located in the brush border membrane of the S1 segment of the proximal tubule. The rest of the glucose is reabsorbed from the distal S3 segment of the proximal tubule by the SGLT-1.20

In patients with diabetes, the SGLT-2 transport mechanism is as potent as in euglycemic individuals. This mechanism seems to be an adaptive response by the kidney to conserve glucose, which is required for patients with a history of hypoglycemia, insulin degludec could be effective and reassuring; for patients who skip a dose, such as patients who travel frequently or have irregular work/sleep schedules, insulin degludec’s long-lasting effects are beneficial.

to meet the energy demands of the brain and cardiovascular system in the presence of severe insulin resistance. Thus, an individual with insulin resistance is incorrectly “marked” as developing intracellular starvation of nutrients. To correct this defect, the kidneys reabsorb excessive amounts of glucose to supply the metabolic requirements of the insulin-resistant brain, muscles, and cardiovascular system.
Renal tubular glucose reabsorption is mediated by SGLTs, and SGLT-2 is the isoform that seems to be a better target for therapy. Selective inhibition of SGLT-2 increases urinary glucose excretion by inhibiting renal glucose reabsorption.21

Dapagliflozin, in a single daily dose, has reduced A1C levels, fasting plasma glucose (FPG), postprandial PG (PPG), and weight compared with placebo when combined with metformin alone or as add-on therapy with insulin and with OADs.21 Although urinary tract infections (UTIs) were common AEs, these were comparable in all study groups, including placebo. However, patients taking 20 mg dapagliflozin experienced a greater rate of genital infections, chiefly vaginal thrush.21 In a 24-week, parallel-group, double-blind, placebo-controlled, phase 3 trial, 485 patients were randomly assigned to once-daily placebo or dapagliflozin 2.5 mg, 5 mg, or 10 mg. Patients had clinically meaningful decreases in A1C levels and FPG; they also had positive results for weight, blood pressure, and other metabolic parameters without major episodes of hypoglycemia.22 Signs and symptoms indicating UTIs and genital infections were more frequently reported in the dapagliflozin subjects.22,23

In July 2011, however, the FDA’s Endocrinologic and Metabolic Drugs Advisory Committee voted not to approve the agent (9 to 6) for use in patients with type 2 diabetes after finding 9 cases of bladder cancer in patients receiving dapagliflozin compared with 1 case in control groups in 11 randomized, controlled, phase 3, clinical trials.24,25 In January, 2012, the FDA declined approval of dapagliflozin, asking the developers (Bristol-Myers Squibb and AstraZeneca) to provide additional data in regard to the drug’s risk-benefit profile.

Canagliflozin has also been shown to improve glycemic control and decrease body weight in patients with type 2 diabetes. Compared with placebo or sitagliptin, canagliflozin was associated with a greater likelihood for *Candida* colonization or symptomatic vulvovaginal candidiasis without increasing the risk for bacteriuria or UTIs.26-28

Ipragliflozin has been shown to improve glycemic control and decrease body weight in a phase 3 study.29 In the double-blind, randomized study, the ipragliflozin group reported 1 case of hypoglycemia and 2 genital tract infections, whereas the placebo group reported 1 UTI.

The SGLT class offers clinicians and patients additional pharmacologic interventions by which hyperglycemia can be reduced.30 However, these drugs may not be effective in patients with renal insufficiency and have been associated with hepatotoxicity, hematuria, genital infections, and certain cancers.

Therapeutic interventions for patients with type 2 diabetes should be directed toward safe and efficacious glycemic control while minimizing the risk of cancer. No specific drug has been endorsed as being the “preferred antihyperglycemic agent” in high-risk cancer patients. Nevertheless, clinicians should be familiar with the defined risks and benefits of each therapeutic option in relation to minimizing cancer risk in patients with type 2 diabetes.

**GLP-1 Receptor Agonists**

Exenatide extended-release (ER) received FDA approval for once-weekly treatment of type 2 diabetes in January 2012. In the 24-week DURATION-5 head-to-head trial, patients taking once-weekly exenatide experienced a statistically superior reduction in A1C of 1.6% from baseline compared to a 0.9% decline for patients taking exenatide 10 mg twice daily.31 Weight loss was statistically significant for both cohorts, with a mean reduction of 5.1 lb for patients taking exenatide ER and 3 lb for individuals using twice-daily exenatide. The most common AE was nausea, which was noted in 14% of the ER patients vs 35% of those using daily exenatide. No major hypoglycemic events were reported.

Exenatide ER has been approved with a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the drug outweigh the risks of acute pancreatitis and medullary thyroid carcinoma. Exena-
tide ER may be used in combination with metformin, a sulfonylurea (SU), or a thiazolidinedione, but it is not recommended as first-line therapy in patients with type 2 diabetes.

In a study of 311 Asian subjects with type 2 diabetes insufficiently controlled by basal insulin with or without a SU, the short-acting GLP-1 receptor agonist lixisenatide (not yet FDA approved in the US) once daily not only bettered glycemic control to an appreciable degree, but also demonstrated a significant FPG and PPG effect. More patients in the lixisenatide group experienced GI AEs, chiefly nausea. This trial is part of a program called GetGoal, in which lixisenatide, used as monotherapy and with antidiabetic agents, will be assessed for efficacy and safety. Endpoints of these randomized, controlled trials in >4500 patients will include cardiovascular outcomes and GI AEs. Initial phase 3 findings have demonstrated lixisenatide’s beneficial effect on glycemic control, and lessened, or complete absence of, risk of hypoglycemia and weight gain.

In pharmacokinetic studies, the long-acting GLP-1 analog, dulaglutide, demonstrated a t1/2 in humans of up to 90 hours, and clinical trials have shown a reduction in PPG. Two phase 2 trials demonstrated a dose-dependent reduction in A1C levels compared with placebo; AEs are largely GI related. Several phase 3 trials are ongoing.

Other GLP-1 receptor agonists, albiglutide and exenatide, are in phase 3 trials.

**DPP-4 Inhibitors**

Neither alogliptan nor vildagliptan have been approved by the FDA, which has asked for more safety data for vildagliptan and more data regarding cardiovascular outcomes for alogliptan; as a result, alogliptan is being studied in additional phase 3 trials.

Among the lixisenatide studies presented at the ADA 2011 Annual Meeting were the results from a large phase 3 program by Barnett et al demonstrating that the drug is associated with a very low risk of hypoglycemia. Data from 8 randomized, placebo-controlled, phase 3 clinical trials were pooled on 3572 patients with type 2 diabetes; AEs and investigator-defined hypoglycemia were evaluated. In addition, subgroup analyses were performed for elderly, obese, and renal impaired patients. A total of 2523 patients were given lixisenatide 5 mg once daily, and 1049 patients were given placebo. The incidence of both AEs and serious AEs with lixisenatide were similar to placebo; hypoglycemia occurred in 8.2% of patients taking lixisenatide and 5.1% taking placebo. Thirty-eight percent of patients taking an SU background therapy accounted for 96% of all hypoglycemic events with lixisenatide treatment. Similarly, 33% of patients taking an SU accounted for 87% of all hypoglycemic events while taking placebo. Patients (including those who were elderly, obese, and renally impaired) taking lixisenatide but not an SU reported a very low hypoglycemic rate (<1%).

**CONCLUSION**

As new therapies become available, and oral agents are combined with injectables, many more therapeutic options will become available. As always, treatment must fit each patient’s medical, personal, and economic needs. For some patients with type 2 diabetes, optimal sequencing may require the initiation of treatment with metformin and a GLP-1 receptor agonist as an add-on before starting basal insulin; starting metformin and proceeding to basal insulin; or starting immediately with an insulin formulation.

These increasingly complex decisions require educated health care professionals who are able to fully gauge their patients’ needs and assess the array of therapeutic options. Physicians should remember that safety and efficacy trumps cost when prescribing any form of therapy to patients with a chronic illness. Perhaps the most cost-effective and safe mode of treatment for patients with type 2 diabetes is lifestyle intervention. Metformin remains the time-tested initial pharmacologic option for most patients with type 2 diabetes is lifestyle intervention. Metformin remains the time-tested initial pharmacologic option for most patients with type 2 diabetes, assuming patients remain free of renal insufficiency. Patients who have had diabetes for many years are more likely to have evidence of ß-cell failure and are prone to hypoglycemia; avoidance of SUs is warranted in these patients. Although thiazolidinediones may prevent the progression from prediabetes to diabetes, patients who use pioglitazone may gain weight, experience edema, and, in women, have an increased risk of bone fractures. The newer agents in development offer safe, practical, and effective interventions for patients with type 2 diabetes based on rational disease pathogenesis.

**Author Disclosures**

Dr. Unger reports he is on the Advisory Board for Abbott Laboratories; Allergan, Inc.; Boehringer Ingelheim; Eli Lilly and Company; Hoffmann-La Roche Inc.; Novo Nordisk Inc.; sanofi US; and Takeda Pharmaceuticals North America, Inc.
Disaster
This article may discuss unlabeled or investigational use of certain drugs. Please review complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.

REFERENCES