Emerging Treatments for Type 2 Diabetes

Focus on Incretin Therapies

ASHP ADVANTAGE eNEWSLETTER APRIL 2014

Ask the Experts: Controversies in Type 2 Diabetes Care

A live webinar about controversies in the care of patients with type 2 diabetes mellitus was conducted in early 2014, concluding an educational series designed to provide health care professionals with timely education and resources on new and emerging treatment options for type 2 diabetes, including incretin-based therapies. An archived version of the webinar is available and provides 1 hour of continuing education. Highlights of the webinar are summarized in this e-Newsletter, which is the final issue in a series of four issues. Other components of the initiative include:

On-demand CE Activities

- **New and Emerging Treatment Options** in Type 2 Diabetes
- **Clinical Case Studies** in the Management of Type 2 Diabetes: Interventions for Achieving Positive Patient Outcomes
- **Ask the Experts:** A Controversial Dialogue in Diabetes
- ***A Guide to Emerging Treatments for Type 2 Diabetes: Focus on Incretin Therapies***, a monograph that can be downloaded as a PDF or eBook and covers all aspects of incretin-based therapy, including rationale for development of the drugs and their pharmacology, dosing, adverse effects, and place in evidence-based treatment guidelines. One hour of CE credit is provided for successful completion of an online assessment test.

Visit **www.leadingdiabetescare.org** for a complete listing of activities and resources and to sign up for email updates about learning opportunities.

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Ongoing Sulfonylurea Safety Concerns

The cardiovascular safety of sulfonylureas has been questioned for more than a decade in part because of concerns that these agents may inhibit myocardial ischemic preconditioning, which ordinarily serves a protective function for the heart.[1] Sulfonylureas increase insulin secretion by acting on ATP-sensitive potassium channels in pancreatic β-cells, and the effects of the drugs on these channels in myocardial cells may interfere with the physiologic mechanisms used to cope with stress.

A meta-analysis recently was conducted of 115 randomized clinical trials comparing sulfonylureas with non-sulfonylurea antidiabetic therapy for at least 6 months in patients with type 2 diabetes, including 62 trials in which information on major adverse cardiovascular events (MACE) was reported and 30 trials in which at least one event was reported.[2] The use of sulfonylureas was associated with an increased risk for stroke and higher mortality than non-sulfonylurea therapy, but no difference was detected between sulfonylurea therapy and non-sulfonylurea therapy in the incidence of MACE. Questions about the cardiovascular safety of sulfonylureas remain unresolved. Additional long-term clinical trials using cardiovascular outcomes are needed to answer these questions.

Metformin in Renal Insufficiency

Metformin is considered first-line therapy for type 2 diabetes unless the drug is contraindicated or not tolerated.[3] Metformin provides glycemic control with a weight-neutral effect and a low risk for hypoglycemia, and it may reduce cardiovascular morbidity and mortality.

In patients with renal impairment, the plasma half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.[4] In healthy elderly subjects, the peak plasma metformin concentration is increased, total plasma clearance of the drug is decreased, and the half-life is prolonged compared with healthy young subjects. Alterations in metformin pharmacokinetics with advanced age are attributed primarily to changes in renal function. Renal function should be assessed before initiating metformin in patients 80 years of age or older.[4]

In the prescribing information for metformin approved by the Food and Drug Administration (FDA), renal insufficiency with a serum creatinine (SCr) concentration of 1.5 mg/dL or higher in men and 1.4 mg/dL or higher in women is a contraindication to use of the drug ostensibly because of the risk for lactic acidosis, a rare but potentially fatal condition reported primarily in patients with diabetes and substantial renal insufficiency.[4] The risk for lactic acidosis also is increased by acute congestive heart failure requiring pharmacologic management, alcohol abuse, liver failure, hypoxic states (e.g., sepsis), and advanced age. Whether the SCr cutoff values needlessly deny access to the drug for patients who could derive benefit without undue risk has been controversial.[5]

An analysis of pooled data from 347 prospective comparative trials and observational cohort studies of patients with type 2 diabetes who took metformin for at least 1 month found no cases of fatal or nonfatal lactic acidosis in 70,490 patient-years of metformin use or 55,451 patient-years of nonuse.[6] There was no difference between metformin users and nonusers in the mean serum lactate concentration during treatment or the net change from baseline in serum lactate concentration.

Because patients with chronic kidney disease stage 1, 2, or 3 can have an SCr value of 1.3 mg/dL or lower permitting use of metformin based on SCr alone, the glomerular filtration rate (GFR) is used instead of or in addition to SCr to guide metformin therapy for patients with renal impairment in some clinical guidelines from outside the United States.[5] A metformin dosage reduction by 50% for patients with

Table 1. Example of Metformin Use in Patients with Renal Insufficiency[5]

eGFR (mL/min per 1.73 m^2)	Action	Monitoring Frequency
60 or higher	No renal contraindication to use	12 months
45–59	Continue use	3–6 months
30–44	Prescribe with caution/do not start in new patient Use a low dose (e.g., 50% or half of maximum dose)	3 months
<30	Stop metformin therapy	NA

eGFR = estimated glomerular filtration rate; NA = not applicable

a GFR of 60–90 mL/min, further dosage reduction by another 50% for a GFR of 30–60 mL/min, and discontinuation of the drug for a GFR less than 30 mL/min have been advocated by some clinicians, although others suggest discontinuing metformin if the GFR falls below 50 mL/min.[7] Table 1 illustrates a similar approach published by Lipska and colleagues, with recommendations for increases in the frequency of renal function monitoring with decreases in GFR.[5] Guidelines for metformin use in patients with renal impairment from various sources around the world generally are consistent, although the recommendations may be expressed differently. The FDA-approved prescribing information for metformin does not provide specific recommendations for metformin dosage reduction or renal function monitoring frequency in patients with renal insufficiency.

Combination Incretin-Based Therapy

Glucagon-like peptide (GLP)-1 receptor agonists increase pancreatic insulin secretion and suppress glucagon secretion in a glucose-dependent manner after meals, resulting in increased glucose uptake by peripheral tissues and reduced hepatic glucose production and blood glucose concentrations.[8] These drugs are administered subcutaneously and produce pharmacologic concentrations of GLP-1 receptor activity that are 6- to 10-fold higher than the postprandial physiologic levels in persons without diabetes.[9]

Dipeptidyl peptidase (DPP)-4 inhibitors interfere with enzymatic degradation of GLP-1, thereby increasing insulin secretion and suppressing glucagon secretion and blood glucose concentrations.[8] The DPP-4 inhibitors are administered orally and produce physiologic GLP-1 concentrations after meals in patients with type 2 diabetes that are similar to those in healthy individuals without diabetes.[10]

Increased satiety, reductions in caloric intake and gastric emptying, gastrointestinal (GI) adverse effects (i.e., nausea, vomiting), and weight loss are associated with GLP-1 receptor agonists but not DPP-4 inhibitors.[8,11,12] These differences are attributed to the higher pharmacologic GLP-1 receptor activity associated with GLP-1 receptor agonists.

Questions have arisen about whether DPP-4 inhibitors and GLP-1 receptor agonists should be used in combination to treat type 2 diabetes. In 255 patients with type 2 diabetes and inadequate glycemic control while receiving metformin plus the DPP-4 inhibitor sitagliptin, a randomized study was conducted to determine whether switching sitagliptin to the GLP-1 receptor agonist exenatide twice daily plus metformin (the SWITCH group) is non-inferior to adding exenatide twice daily to sitagliptin and metformin (the ADD group).[13] After 20 weeks of treatment, the reduction from baseline in A1c was significantly greater in the ADD group than in the SWITCH group (0.68% vs. 0.38%, p = 0.012). The incidence of nausea and vomiting was higher in the SWITCH group than in the ADD group. These findings support adding a GLP-1 receptor agonist to metformin plus DPP-4 inhibitor therapy instead of switching to metformin plus a GLP-1 receptor agonist in patients with an inadequate response to metformin plus a DPP-4 inhibitor.

Evidence-based guidelines from authoritative groups recommend incretin therapies in combination with metformin as a second-line therapeutic option after metformin plus lifestyle modifications (i.e., diet, exercise) have failed to provide adequate glycemic control in patients with type 2 diabetes.[3] Because multiple organ defects (e.g., pancreas, liver, GI tract, brain) are associated with type 2 diabetes, the use of antidiabetic therapies with complementary mechanisms of action to address these defects is recommended.[14] Although DPP-4 inhibitors and GLP-1 receptor agonists both increase insulin secretion and suppress glucagon release and hepatic glucose production, the DPP-4 inhibitors lack the GI adverse effects associated with GLP-1 receptor agonists. Thus, using the two types of drugs in combination with metformin might be considered rational if it minimizes GI adverse effects associated with use of GLP-1 receptor agonists.

Overcoming Barriers to Use of Injectable Therapies

Healthcare professionals may be reluctant to initiate insulin and other injectable therapies for type 2 diabetes for a variety of reasons, including the need for complex treatment regimens and associated monitoring and concerns about the risk of hypoglycemia and weight gain.[15,16] A lack of education, training, and the time, support personnel, and resources needed for patient education about injection preparation and administration techniques also may present a barrier to the use of injectable therapies.

The use of insulin may represent a last resort for healthcare professionals. The possibility of angering and alienating patients, resulting in nonadherence, may make healthcare professionals reluctant to broach the idea to patients of using insulin therapy.

Patients often are reluctant to initiate insulin and other injectable therapies for diabetes because of an aversion to the use of injections, concerns about hypoglycemia and weight gain, and the need for frequent monitoring, which can interfere with their daily routine. Many patients share healthcare professionals' view of insulin therapy as a last resort and consider the need to initiate insulin therapy a personal failure. Other patients fail to appreciate the importance of glycemic control in preventing diabetes complications in part because symptom severity is not an accurate reflection of disease severity (i.e., the disease may be more advanced than symptoms suggest).

Possible strategies for healthcare professionals to use in overcoming patient barriers to the use of injectable therapy for diabetes include avoiding the mention of insulin as a threat for failure to achieve glycemic control using noninsulin therapies and providing education about the disease and importance of glycemic control. Prescribing the smallest available needles and minimizing the frequency of injection can promote adherence to the treatment regimen. Healthcare professionals should use sample devices to demonstrate dose preparation and injection techniques and have the patient practice under supervision in an office or clinic setting. Printed and audiovisual educational materials on injection preparation and administration technique for use in the home setting should be provided. Patients who experience difficulty learning to use injectable therapies might be referred to a diabetes educator if one is available.

Explore Additional Opportunities for Learning

Visit the ASHP Advantage website to browse listings of convenient on-demand continuing education (CE) activities, as well as publications, podcasts, and live webinars. More than 30 hours of free on-demand CE programming are available.

Learn more and find a full listing of topics and activities at **www.ashpadvantage.com**.

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Planned and coordinated by ASHP Advantage.

This activity is supported by an independent educational grant from Boehringer Ingelheim Pharmaceuticals, Inc., which was made possible, in part, through collaboration with Eli Lilly, and an independent medical education grant from Bristol-Myers Squibb and AstraZeneca LP.