PATIENT WITH NEW-ONSET TYPE 2 DIABETES MELLITUS

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BACKGROUND

Patient AC presents with increasing fatigue, frequent urination, and excessive thirst. Her fasting blood glucose (FBG) level is 250 g/dL, glycosylated hemoglobin (A_{1c}) is 9.6%, blood pressure (BP) is 145/88 mm Hg, and low-density lipoprotein cholesterol (LDL-C) is 187 mg/dL. AC is 5′3″ and weighs 180 lbs; her body mass index is 31.9. She is a 43-year-old African American divorced administrative assistant who denies alcohol or tobacco use and leads a fairly sedentary lifestyle. The patient had gestational diabetes with her second and third pregnancies. Diabetes mellitus (DM) was present in her mother and maternal grandmother. Her father died suddenly of a myocardial infarction at age 49, and her mother died of a massive stroke at age 76.

COURSE OF THERAPY

AC was initially encouraged to take part in lifestyle interventions and was given patient education about the disease, its treatment, and complications. Because lifestyle interventions alone rarely achieve or maintain metabolic goals, AC also was started on metformin 500 mg twice a day because of its favorable effects on weight loss and dyslipidemia. After 3 months, the patient returned to the clinic with improved glycemic control (FBG is 160 mg/dL, A_{1c} is 8.6%), but no significant change in weight, lipid profile, or BP. At this time, she was given lisinopril 20 mg/day for hypertension and simvastatin 40 mg/day for hyperlipidemia. She was told to continue her current metformin regimen and was encouraged to make more lifestyle modifications to reduce her weight. She was maintained on her current medications for a year, with improvements seen in BP and lipid profile, but increasingly poor glycemic control (FBG in the range of 180 mg/dL–200 mg/dL and A_{1c} >8%). She admits to frequently missing doses because of her busy schedule, forgetfulness, and occasional gastrointestinal (GI) disturbances. Her regimen was recently changed to a newer, extended-release metformin 1500 mg/day and glimepiride 4 mg/day to increase adherence to medication and improve glycemic control. After undergoing intense counseling on the importance of compliance with her drug therapy, AC returned to the clinic after 3 months with acceptable BP (130 mm Hg), lipid (LDL-C 100 mg/dL), and FBG (130 mg/dL) values.

DISCUSSION

Ideally, treatment of hypertension and dyslipidemia should be initiated simultaneously with diabetes therapy to control cardiometabolic risk factors. According to Joint National Committee 7 guidelines, the BP goal for patients with DM is less than 130/80 mm Hg.[1] Lisinopril was chosen for hypertension because angiotensin-converting enzyme (ACE) inhibitors reduce BP without adversely affecting glucose, insulin, and lipid levels. ACE inhibitors also have been shown in numerous studies to favorably affect the progression of diabetic nephropathy and, therefore, hold a "compelling indication" for patients with DM and hypertension.[2] For patients, such as AC, who have DM and 2 or more coronary heart disease risk factors (hypertension and family history of premature coronary artery disease), the latest cholesterol guidelines recommend targeting LDL-C less than 100 mg/dL (potentially <70 mg/dL) and high-density lipoprotein cholesterol greater than 45 mg/dL. Simvastatin was chosen for hyperlipidemia because 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors are considered the most effective drugs for reducing LDL-C concentrations and have been shown to reduce the risk of coronary events.[2] Additionally, this patient's age,

hypertension, and family history mandate the use of aspirin 81 mg daily to further decrease coronary risk.

According to the American Diabetes Association diagnosis and classification system, the diagnosis of DM is made with a fasting plasma glucose (FPG) of at least 126 mg/dL (typically useful for type 2 DM) or a random plasma glucose of at least 200 mg/dL in the presence of classical symptoms (eg, polyuria, polydipsia, and polyphagia).[3] Patient characteristics typical of type 2 DM in AC include obesity (present in 80%–90% of patients), family history of DM, history of gestational DM (increases the risk of developing overt DM), hyperglycemia with symptoms, hypertension, and hyperlipidemia. Therapeutic goals include achievement and maintenance of glycemic control, avoidance of future episodes of acute hyperglycemia and hypoglycemia, and prevention of microvascular and macrovascular complications. In combination with lifestyle interventions, sulfonylureas and metformin are reasonable options for first-line therapy, reducing FPG by 70 mg/dL and A_{1c} by 1.5% to 2%. Metformin's beneficial effects on reducing body weight and dyslipidemia make it an especially appealing choice for initial monotherapy in this patient. However, metformin dosing in this patient never reached the therapeutic target dose of 2000 mg/day, contributing to the patient's poor glycemic control over the first year of therapy. Central obesity, as seen in AC, has been strongly associated with insulin resistance, a defect that is reduced with metformin. Sulfonylureas primarily augment pancreatic insulin release and are preferred in lean patients who are more likely to have a significant pancreatic insulin deficiency defect.

Because AC failed to maintain glycemic goals with metformin monotherapy, combination therapy was instituted. Simply switching to a different oral agent provides little benefit, and a single agent will not reverse all of the defects of DM. Successful oral combination therapy will address different aspects of the disease and may also delay the need for insulin therapy. Because of AC's elevated A_{1c} of 9.5% at diagnosis, combination therapy could have been considered, indeed, for the initial management of this case. The combination of metformin and the sulfonylurea glimepiride was the logical next step, because this combination produces additive hypoglycemic effects, resulting in additional reduction of approximately 60 mg/dL to 70 mg/dL in FPG and 1.5% to 2% in A_{1c}. If the patient is willing to consider subcutaneous injections, another logical addition to metformin might have been exenatide, which would improve postprandial hyperglycemia and also contribute to further weight loss.

Pharmacy Considerations

In educating AC on DM, it is important to focus on target (normal) ranges of blood glucose levels, using glucose monitoring devices, and recognizing symptoms of hypoglycemia (eg, nervousness, restlessness, shakiness, rapid pulse, sweating, hunger, unusual weakness, and confusion). She also should be counseled on her other comorbidities, including hypertension and hyperlipidemia. If the patient does not respond adequately to maximum recommended doses of lisinopril (African Americans are also less responsive to ACE inhibitors), it would be reasonable to suggest that her physician add a low dose of a diuretic (eg, hydrochlorothiazide 12.5 mg/day) or switch to a nondihydropyridine calcium channel blocker. In counseling AC on drug therapy for DM, it is important to explain to her that taking metformin with meals can help reduce the GI discomfort that she is experiencing. Because metformin has the potential to cause lactic acidosis, AC should be told to contact her doctor immediately if she experiences extreme weakness or dizziness, unusual muscle pain, trouble breathing, or an irregular heartbeat. Severe vomiting, diarrhea, or dehydration also should be reported to AC's physician. Although metformin usually does not cause hypoglycemia on its own, the combination of metformin with a sulfo-nylurea may cause hypoglycemia. Because sulfonylureas have a tendency to cause weight gain, weight reduction techniques should be emphasized to AC, because she is already considered obese. With this concern in mind, glimepiride was chosen because it has been reported to be weight neutral. In patients with problems adhering to frequent dosing schedules, as seen with AC, using extended-release formulations with once-daily dosing may optimize medication compliance.

REFERENCES

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