American Diabetes Association Treatment Algorithm for Type 2 Diabetes

Diagnosis of type 2 diabetes

Counsel patients regarding lifestyle modification (weight loss, exercise)
(expected decrease in HbA1c 1-2%)

and

initiate metformin [Glucophage, others] 500 mg once or twice daily,
titrating to 850 mg to 1000 mg twice daily (expected decrease in HbA1c 1.5%)

HbA1c 7% or greater
three months later

Add

rosiglitazone [Avandia] or pioglitazone [Actos] (expected decrease in HbA1c 0.5-1.4%)
or

sulfonylurea (expected decrease in HbA1c 1.5%)
or

basal insulin (bedtime intermediate-acting insulin or bedtime or morning long-acting insulin)
(expected decrease in HbA1c 1.5-2.5%)

HbA1c 7% or greater
three months later

Add

additional agent (glitazone or sulfonylurea or insulin)
or

intensify insulin for those on insulin*

HbA1c 7% or greater
three months later

In patients not yet receiving insulin, add basal insulin or intensify insulin in those already receiving insulin*

HbA1c 7% or greater
three months later

Metformin + intensive insulin with/without glitazone

*When prandial rapid or very-rapid acting insulin is added, insulin secretagogues such as the sulfonylureas or the glinides (repaglinide, nateglinide) should be discontinued.

- Consider insulin as initial therapy (with lifestyle modification) in patients with fasting glucose greater than 250 mg/dL or HbA1c greater than 10% or those with ketonuria or symptoms of hyperglycemia.
- When initiating insulin, start with a bedtime dose of an intermediate-acting insulin or once-daily long-acting insulin. Initiate with 10 units or 0.2 units per kg. Check fasting glucose concentrations and increase by approximately 2 units (4 units if fasting glucose is greater than 180 mg/dL) every 3 days, until fasting glucose is less than 130 mg/dL. If HbA1c continues to be 7% or greater after 2 to 3 months, with well-controlled fasting glucose concentrations, consider checking pre-meal glucose concentrations.
- The algorithm does not include pramlintide [Symlin], exenatide [Byetta], alpha-glucosidase inhibitors [Precose, Glyset], glinides [Prandin, Starlix], or sitagliptin [Januvia] due to generally lower overall affect on HbA1c, limited information, and/or cost. However, these agents may be appropriate for certain patients.
Treatment of Type 2 Diabetes Mellitus

Introduction

The incidence of diabetes is growing and is now considered an epidemic. A number of studies have demonstrated that control of blood glucose can reduce the morbidity associated with diabetes. The recent development of a number of new medications to control blood glucose has enlarged the armamentarium of agents used to treat this disease. However, the role of these newer agents has been unclear. The American Diabetes Association and European Association for the Study of Diabetes recently released a consensus algorithm for the initiation and adjustment of therapy in patients with type 2 diabetes.1

The goal of therapy is to maintain a HbA1c level of less than 7%. This goal was selected because of the practicality and potential for reduction in complications. According to the new guidelines, a HbA1c of 7% or higher should be “a call to action to initiate or change therapy with the goal of achieving an A1c level as close to the nondiabetic range as possible or at a minimum, decreasing the A1c to less than 7%.” In addition, careful attention to controlling blood pressure and cholesterol has been shown to reduce morbidity associated with diabetes.

Selecting an Initial Agent

Following lifestyle modification, the selection of the initial agent to treat patients with diabetes should be based on effectiveness, safety, tolerability, and cost. Other than the effects on glucose and HbA1c, there is very little information on the long-term benefits and risks of the agents. Consequently, decisions must be made based on their glucose and HbA1c effects.

The most recent recommendations from the American Diabetes Association recognize that lifestyle changes alone are often ineffective for long-term control of blood glucose because of failure to lose weight, the high rate of weight regain, and progression of the disease. Consequently, it is recommended that metformin be started at the time of diagnosis, along with lifestyle modification. Metformin is usually well tolerated, especially if the dose is gradually titrated to the effective dose. Patients should be started on a low-dose (i.e., 500 mg) once or twice daily with breakfast and/or dinner. If gastrointestinal adverse effects have not occurred, the dose can be increased to 850 to 1,000 mg with breakfast and dinner. The maximum effective dose is 850 mg twice daily (AWP for one month supply of generic immediate-release 850 mg twice daily is $71.43),2 with only modest improvements of blood glucose up to three grams daily.2 Although the guidelines from the American Diabetes Association suggest that the maximum dose of regular-release metformin is three grams daily, the U.S. prescribing information states that the maximum daily dose is 2,550 mg in adults and 2,000 mg in adolescents ten to sixteen years of age.3 The expected reduction in HbA1c is approximately 1.5%. Advantages of metformin include lack of weight gain and lower cost, while the major disadvantages are GI adverse effects and the rare potential for lactic acidosis. Preliminary evidence from the United Kingdom Prospective Diabetes Study (UKPDS) indicates that metformin may have a beneficial effect on cardiovascular disease outcomes, but more research is needed.

If glucose control is not achieved with lifestyle modification and the maximal dose of metformin tolerated by the patient within two to three months, a second medication should be added. Second-line medications include sulfonylureas, a thiazolidinedione, or insulin. The decision of which agent to use should depend on the degree of necessary A1c lowering. In patients with an A1c of greater than 8.5% or those who are symptomatic, insulin should be considered. Advantages of insulin include lack of maximum dose, improvement in cholesterol profile, and cost. Disadvantages of insulin include the need for injections and close monitoring of blood glucose concentrations, and the potential for weight gain and hypoglycemic reactions.

While most sulfonylureas are available generically and are therefore less expensive (for example, 20 mg of generic, extended-release glipizide daily has an AWP of $48.32 per month)2 than the newer agents for patients with type 2 diabetes; weight gain of about 2 kg and hypoglycemia may limit their use. The longer-acting sulfonylurea agents such as chlorpropamide (Diabinese, others), glyburide (Micronase, others), and sustained-release glipizide (Glucotrol XL, others) are more likely to cause
hypoglycemia. Additionally, elderly patients are at higher risk for hypoglycemia than younger patients.

Though the thiazolidinediones, pioglitazone (Actos) and rosiglitazone (Avandia) are less effective than insulin or the sulfonylureas in reducing HbA1c (0.5% to 1.4% compared with 1.5% to 2.5% for insulin and 1.5% for the sulfonylureas), they have been shown to have a beneficial effect on serum lipid profiles. Disadvantages include the potential for fluid retention, weight gain, and expense (AWP for one month supply of maximal dose of 45 mg once daily for Actos is $195.77 and 8 mg once daily for Avandia is $188.93).2 Due to the risk of fluid retention leading to an acute exacerbation of congestive heart failure, it is recommended that these agents not be used in patients with New York Heart Association Class 3 or 4 heart failure.5

In patients who continue to experience hyperglycemia despite lifestyle modification, metformin and either a sulfonylurea, glitazone or insulin, a third pharmacological agent (either a sulfonylurea or a thiazolidinedione) can be started. Another oral agent should be added only in patients where the HbA1c is close to the target goal. In patients with an HbA1c of 8% or greater, consideration should be given to adding insulin in those who are not receiving it, or intensifying insulin in those who are already receiving insulin. Intensifying insulin usually involves adding injections of short-acting or rapid-acting insulin prior to selected meals. When mealtime insulin is added, insulin secretagogues such as the sulfonylureas or the glinides (repaglinide [Prandin], nateglinide [Starlix]) should be discontinued since these agents do not act synergistically with insulin.

Other Agents

In addition to the agents included in the algorithm, there are a number of other agents for diabetes which are generally less effective in lowering the HbA1c, have limited clinical data, or are more expensive than other agents. In general, these agents should be considered for patients who are close to their HbA1c goal, yet continue to experience postprandial hyperglycemia.

The alpha-glucosidase inhibitors, acarbose (Precose) and miglitol (Glyset), are considered less effective than other available agents with an expected reduction in HbA1c of approximately 0.5% to 0.8%. The major advantage of these agents is a lack of effect on weight. Disadvantages include the high incidence of GI adverse effects, especially gas and bloating. Adverse effects lead to discontinuation in up to 45% of patients. These agents are contraindicated in patients with intestinal or bowel disease, or intestinal obstruction. Additionally, these agents must be dosed three times daily with meals and are expensive (AWP for one month supply of maximal dose of Precose 100 mg three times daily is $89.38 and 100 mg three times daily of Glyset is $87.62).2

The glinides, repaglinide and nateglinide, are effective at lowering HbA1c (expected reduction in HbA1c of approximately 1.5% with repaglinide and approximately 1% with nateglinide), but each must be given three times daily and these are expensive (AWP for one month supply maximal dose of 4 mg three times daily of Prandin is $250.42 and 120 mg three times daily of Starlix is $124.86).2 As with the sulfonylureas, there is a risk of weight gain with the glinides.

Only one agent of the glucagon-like peptide (GLP)-1 agonists, exenatide (Byetta), is approved for use in the United States. There is less published clinical information on exenatide compared with other agents commonly used to treat type 2 diabetes. Exenatide is considered an “incretin mimetic.” It works by a number of mechanisms including stimulation of insulin production in response to high blood glucose levels, inhibition of the release of glucagon after meals, and slowing the rate of gastric emptying. It is thought that the expected reduction in HbA1c is approximately 0.5% to 1%, a value lower than that of the other recommended agents. An advantage of exenatide is the weight loss that is commonly noted in patients who take the medication. In clinical trials, patients typically lost 2 kg to 3 kg of weight, some of which may have been due to the GI adverse effects associated with the medication. Disadvantages include the need for twice daily injections, the high incidence of GI adverse effects such as nausea, vomiting or diarrhea, and cost (AWP for one month supply maximal dose of 10 mcg twice daily of Byetta is $219.42).2 It is currently only approved for use with metformin and/or a sulfonylurea.

Pramlintide (Symlin) is the only approved agent in the class of medications known as the...
amylin agonists. It is only indicated for use with insulin. The expected reduction in HbA1c is lower with pramlintide (approximately 0.5% to 0.7%) than other agents. It is given subcutaneously before meals. The most common adverse effect is nausea. Weight loss often occurs with this agent, but may be due to the gastrointestinal adverse effects. As with many of the newer agents, pramlintide is expensive, with the AWP of a 5 mL vial (containing 25 x 120 mcg doses) of $103.03.2 Patients with type 2 diabetes typically inject 60 mcg to 120 mcg with major meals. Preprandial rapid-acting or short-acting insulin doses must be reduced when initiating pramlintide in order to reduce the risk of hypoglycemia.

The newest class of medication for the treatment of type 2 diabetes is the dipeptidyl peptidase IV (DPP-4) inhibitors. Like exenatide, these agents work by enhancing the incretin system in the body. The incretin system is one of the mechanisms in the body which lowers blood glucose. When the body senses hyperglycemia, incretins stimulate the pancreas to release insulin and signal the liver to cease glucose production. DPP-4 inhibitors increase the active levels of incretin hormones in the body while exenatide is an “incretin mimetic” and works by stimulating the GLP-1 receptor. Sitagliptin (Januvia) is an orally active, once-daily DPP-4 inhibitor which has been approved by the FDA and vildagliptin (Galvus) is expected to be approved in the near future. The role in therapy for the DPP-4 inhibitors has not yet been determined. Like exenatide, the expected reduction in HbA1c is lower than other agents (approximately 0.6% to 0.8%). However, sitagliptin does not appear to cause weight loss or nausea commonly seen with exenatide. According to the manufacturer, a 30-day supply of 100 mg once daily will be about $145.80.4

Summary

The incidence of type 2 diabetes continues to grow. Because of the morbidity and mortality associated with the disease, aggressive therapy is required to rapidly achieve and maintain glycemic levels as close to normal as possible. The newest recommendations of the American Diabetes Association emphasize these principles and will assist the clinician in achieving these goals.

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References