Management of Type 2 Diabetes

The case vignette illustrates a key therapeutic decision most physicians face when managing type 2 diabetes: namely, how to advance treatment in patients whose glycated hemoglobin levels remain above the target value despite dual oral antihyperglycemic therapy, such as with metformin and glipizide, as in this patient. Medications such as pioglitazone can delay the almost inevitable necessity of initiating the use of insulin in such patients. Furthermore, patients receiving a thiazolidinedione who later need insulin may have a better response to it than those not receiving a thiazolidinedione. However, there are no comparative data to determine what the optimal treatment should be when a patient does not have...
a response to dual oral therapy. I believe the addition of pioglitazone is a rational next step. Several short-term trials have examined the effects of thiazolidinedione treatment as an “add-on” therapy in patients with elevated glycated hemoglobin values who are already taking maximum doses of metformin and a sulfonylurea. Collectively, these studies demonstrate that the addition of a thiazolidinedione can lower the glycated hemoglobin level by as much as 2 percentage points. Three such studies compared the addition of a thiazolidinedione or insulin to the metformin–sulfonylurea treatment regimen of subjects with baseline glycated hemoglobin values of more than 9.0%. These studies showed that a thiazolidinedione had an efficacy similar to that of insulin in lowering glycated hemoglobin levels. Together, the studies suggest that, as compared with treatment with insulin, treatment with pioglitazone is associated with a lower incidence of hypoglycemia, a similar amount of weight gain, and an increase in the high-density lipoprotein (HDL) cholesterol level. The expenses associated with the triple oral therapies that include a thiazolidinedione are greater than those of either insulin (70% NPH insulin and 30% regular insulin) or insulin glargine added to metformin–sulfonylurea.

Pioglitazone is likely to have few side effects and can be taken once daily. The weight gain that typically accompanies its use (3–4 kg, on average) can be mitigated by intensifying medical nutrition therapy at the time of initiation. Since recent evidence suggests that the use of thiazolidinediones may reduce bone density, a bone-density scan may be appropriate, particularly for women who are already postmenopausal.

It is possible that the need for initiating insulin therapy is delayed by the addition of pioglitazone in patients whose diabetes is inadequately controlled with the use of metformin and sulfonylurea. One study, A Diabetes Outcome Progression Trial (ADOPT), showed that rosiglitazone, when used as initial monotherapy in patients with a recent diagnosis of type 2 diabetes, maintained glycemic targets for longer than did treatment with sulfonylurea or metformin and suggested that this might be due to a beneficial effect on beta-cell function. Though the addition of pioglitazone to a regimen of metformin and a sulfonylurea could be expected to have a durable effect on the maintenance of improved glycemic control, especially if administered soon after the glycated hemoglobin level begins to rise, longer-term studies are needed to evaluate the effectiveness of this approach.

In support of this strategy, the ratio of proinsulin to insulin, considered a marker of beta-cell function, improved when pioglitazone was added to metformin and sulfonylurea as treatment. Pioglitazone also mobilizes fat from the liver, an effect that is thought to be accompanied by sensitization of the liver to insulin. Fatty liver is common in patients with diabetes and is linked in selected patients to the development of steatohepatitis, which pioglitazone has been shown to ameliorate.

Finally, despite the findings in meta-analyses that rosiglitazone may increase the risk of ischemic events, a similar effect has not been demonstrated for pioglitazone. In fact, there is evidence that treatment with pioglitazone increases the HDL cholesterol level by 10 to 15%, lowers the systolic blood pressure by 4 to 5 mm Hg, and reduces the thickness of the carotid wall, as compared with a sulfonylurea. In addition, a marginally beneficial effect on ischemic events was found when pioglitazone was added to existing treatment in patients with type 2 diabetes in the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive), a randomized, double-blind, controlled clinical trial of a strategy that was considered cost-effective. In combination, these results support the possibility that pioglitazone may have cardioprotective effects; it would be my choice for this patient.

Dr. Goldberg reports receiving speaker’s honoraria from both Takeda and GlaxoSmithKline and consulting fees and grant support from Takeda. No other potential conflict of interest relevant to this article was reported.

From the Division of Endocrinology, Diabetes, and Metabolism, Diabetes Research Institute, University of Miami Miller School of Medicine, Miami.
formin and a sulfonylurea is all too familiar. It reflects the progressive nature of the condition, in which declining beta-cell function results in elevations in glycemia year after year unless antidiabetes medications are added or the doses of these medications are increased. In this obese patient who has no clinical evidence of complications from diabetes and whose cardiovascular risk factors are currently well managed, the immediate concern is the need to reduce the glycated hemoglobin level to below that recommended in the International Diabetes Federation 2005 guidelines (6.5%) to minimize the risk of future complications. Ideally, glycemic control should be handled in a proactive manner, according to the joint consensus algorithm for the management of hyperglycemia from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), which suggests that a glycated hemoglobin value of 7% or more should serve as “a call to action to initiate or change therapy, with the goal of achieving a glycated hemoglobin level as close to the nondiabetic range as possible.”

Adding a third oral agent is not recommended, given that the patient already has a glycated hemoglobin value of 8.1% and that this approach is relatively more expensive and potentially not as effective in reducing glycemia as adding insulin would be. Adding a basal insulin to existing oral therapy has been shown to be more effective in reducing glycated hemoglobin levels than adding a thiazolidinedione — especially at higher initial glycated hemoglobin values — with less weight gain, no edema, salutary lipid changes, and a lower cost. Indeed, the increased risk of edema, congestive heart failure, and fractures in women now recognized to be associated with thiazolidinediones and the uncertainty about their effects on the risk of cardiovascular disease have led to an updated recommendation by the ADA–EASD that greater caution should be exercised in their use. Adding exenatide in this patient would be unlikely to achieve the target glycated hemoglobin levels (<6.5% or <7.0%), given an expected absolute decrease in the level of only 0.5 to 1.0%, despite the potential weight loss, and would incur a risk of gastrointestinal side effects. Also, exenatide requires twice-daily injections, and despite its increasing use, there have been no large-scale trials to assess its efficacy or safety in the long term.

Insulin therapy can reduce absolute glycated hemoglobin values sufficiently — by 1.5 to 3.5% — to allow glycemic targets to be met. Adding an intermediate-acting insulin before bedtime is a relatively straightforward approach to increasing therapy for glycemia. It can be undertaken readily in a community-care–based setting and obviates the need to amend existing therapy. Some patients may be concerned about self-injection but can be reassured that with modern needles it is a virtually painless process and certainly much less onerous than their finger-stick capillary-glucose measurements. Maintaining existing sulfonylurea therapy when supplementing basal insulin requirements means that the required insulin dose is lower and the problem of offsetting sudden glycemic deterioration when a sulfonylurea is withdrawn can be avoided. The initiation of NPH insulin at bedtime involves a single injection at a time when patients will be undressed and does not require them to carry insulin-injection equipment during the day. Glycemic control can still be monitored, and the need for insulin-dose adjustments can be determined by continuing to measure mainly fasting glucose levels.

The Treat-to-Target trial showed that systematic titration of bedtime NPH insulin, used in addition to oral therapy, can safely achieve a 7% glycated hemoglobin value in a majority of overweight patients with type 2 diabetes who have glycated hemoglobin levels between 7.5% and 10.0% when receiving oral agents alone. The mean (±SE) weight gain was modest (2.8±0.2 kg) with a confirmed rate of hypoglycemic events of 5.1 per patient per year. The Treating to Target in Type 2 diabetes (4-T) trial showed that adding a basal insulin, instead of a biphasic insulin twice a day or a short-acting insulin three times a day, to metformin and sulfonylurea reduced the likelihood of hypoglycemia by half to three quarters, with a decrease in weight gain by half to two thirds. Insulin doses vary considerably among patients, but safe starting doses can be easily calculated, as shown in the 4-T trial. Patients can then adjust their doses, using a simple algorithm, as demonstrated in the Treat-to-Target trial. In the long term, this incremental approach to adding insulin therapy as a once-daily bedtime injection can ease the transition to a more complex insulin regimen in the face of continued hyperglycemic progression.
A recent meta-analysis of clinical trials involving incretin therapies concluded that the efficacy of these agents was generally similar to that of other antidiabetes therapies. Of direct relevance to the treatment of this patient, exenatide produces more potent control of postprandial glyceremia than NPH insulin or pioglitazone, probably because exenatide suppresses gastric emptying. This finding may be important, in view of data linking the control of postprandial glyceremia to cardiovascular risk in patients with diabetes. The opportunity to improve postprandial glucose control, while achieving weight loss, is appealing.

Although considerable preclinical data suggest that GLP-1–receptor agonists improve beta-cell function and are cardioprotective, such discussions may not be directly relevant for the care of this patient. The actions of GLP-1–receptor agonists on the stimulation of insulin and inhibition of glucagon secretion are glucose-dependent; hence, there is a very low risk of hypoglycemia in the absence of concomitant sulfonylurea therapy. The remarkable ability of GLP-1–receptor agonists to improve the glucose sensitivity of beta cells and potentiate insulin secretion rapidly suggests that discontinuation of the glipizide (or alternatively, the initial reduction of the dose by 50%), coincident with initiation of exenatide therapy, would be prudent.

The addition of exenatide to ongoing metformin and sulfonylurea therapy was associated with an absolute reduction of 0.8 to 1.0% in the glycated hemoglobin level, with 0.9 to 1.6 kg of weight loss, after 30 weeks of therapy in subjects with type 2 diabetes.\textsuperscript{12} There have been several head-to-head comparisons of regimens of insulin administration, as compared with twice-daily exenatide, in patients who did not have adequate glycemic control when they were taking metformin and a sulfonylurea.\textsuperscript{13,14} The use of exenatide and the use of insulin resulted in similar degrees of reduction in glycated hemoglobin and similar numbers of hypoglycemic events, but the resultant body weight was significantly higher at the end of the study in patients receiving insulin, often as much as 4 kg higher than in subjects taking exenatide.

What are the potential limitations associated with exenatide therapy? Gastrointestinal side effects, principally nausea, generally abate several weeks after the initiation of exenatide therapy.
Nausea and gastrointestinal upset may limit tolerability in 10 to 20% of patients, and pancreatitis has recently been described in subjects treated with exenatide, although the actual prevalence is low and the pathophysiological characteristics remain uncertain. Exenatide therapy is expensive, and its long-term durability and safety have not been defined. Since incretin drugs are new, they are comparatively more expensive than older agents, and we do not yet have outcome studies to determine the long-term effects of exenatide on beta-cell function or cardiovascular events. On the other hand, the use of exenatide reduces glycemia through multiple mechanisms of action, is simple to use, and provides superior control of postprandial glucose. Critically, unlike with existing diabetes therapies, many subjects will experience satiety and weight loss. These features make exenatide an appealing option for the treatment of patients in whom existing antidiabetic agents fail to achieve glycemic control.

Dr. Drucker reports receiving advisory or consulting fees from Amylin Pharmaceuticals, Arisaph Pharmaceuticals, Chugai, Conjugchem, Eli Lilly, Emisphere Technologies, Glaxo-SmithKline, Glenmark Pharmaceuticals, Isis Pharmaceuticals, Merck Research Laboratories, Novartis Pharmaceuticals, Novo Nordisk, NPS Pharmaceuticals, Phenomix, Takeda, and Transition Pharmaceuticals; and grant support from Eli Lilly, Merck, and Novo Nordisk. No other potential conflict of interest relevant to this article was reported.

From Banting and Best Diabetes Centre, University of Toronto, Mount Sinai Hospital, Toronto.


Copyright © 2008 Massachusetts Medical Society.