Type 2 Tx in Teens Starts With Metformin

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EXPERT ANALYSIS FROM A CONFERENCE ON MANAGEMENT OF DIABETES IN YOUTH

KEYSTONE, COLO. – Most pediatric endocrinologists rely on metformin as the linchpin in treating new-onset type 2 diabetes in adolescents, adding insulin in those who are in poor glycemic control.

"This isn't an evidence-based treatment algorithm. There aren't any studies in kids to guide us. But this is the current practice among most pediatric endocrinologists who treat a lot of youths with type 2 diabetes," Dr. Phil Zeitler said at the meeting, sponsored by the Children's Diabetes Foundation at Denver.

Dr. Zeitler is study chair for the Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY), a large, ongoing, multicenter, NIH-sponsored study.

For the new-onset type 2 diabetic teen who is nonketotic and in "reasonable" glycemic control, current practice among most specialists is to start metformin at 500 mg/day, along with initiating standard diabetes education with an added focus on the basics of lifestyle change and weight loss. The daily dose of metformin should be increased by no more than 500 mg a week to a target of 2,000 mg/day. It is crucial to titrate the drug slowly to minimize GI side effects.

"I tell my patients that I want them on 2,000 mg/day and I really don't care how long it takes to get there. If they're not feeling well after a week, they stay at that dose for the next week," said Dr. Zeitler, professor of pediatrics and clinical science at the University of Colorado, Denver, and medical director of the Children's Hospital Clinical Translational Research Center.

He stressed that what constitutes "rea-

sonable" glycemic control in a new-onset patient is an individual physician decision because there is no evidence to provide guidance. He often uses an HbA_{1c} of about 9% as a cutoff. Other pediatric endocrinologists use 10%, and still others use an HbA_{1c} closer to 8% as their threshold for turning to insulin, he noted.

Insulin isn't generally considered first-line therapy for type 2 diabetes in adults. However, teens have far fewer approved treatment options. Insulin is effective, it acts synergistically with oral metformin to reduce glucose toxicity, and it sends the adolescent a message that this is a disease to be taken seriously.

For these reasons, Dr. Zeitler recommended the following strategy for a new-onset type 2 diabetic adolescent in poor glycemic control who has no acidosis: Start metformin and diabetes education as previously described, along with 15-30 U of basal insulin given at night or whenever family supervision is most likely in order to ensure adherence. "These kids will not take that insulin on their own," he continued.

Once glucose control is attained – as signified by an HbA_{1c} below 6.5% – wean the patient off insulin.

"There is no evidence that weaning slowly is any more effective than weaning quickly in these patients. You might as well find out if the patient is going to be on metformin alone," said Dr. Zeitler.

In a new-onset patient with acidosis and in poor glycemic control, start the patient on metformin and use insulin as in a type 1 patient until the acidosis resolves, then wean the patient off insulin.

For patients who can't maintain an HbA_{1c} below 6.5% on full-dose metformin alone, he recommended adding once-daily insulin detemir or glargine, starting at 10-20 U/day. If the patient can't maintain the target HbA_{1c} despite long-acting insulin at a dose of 1 U/kg of body weight and there is evidence of postprandial hyperglycemia, consider adding short-acting insulin. But, there's a caveat.

"Keep in mind that this is going to substantially increase the burden on these children and therefore you may, in fact, not get any benefit because they won't do it. You need to have a good conversation with the family and figure out what's going to work," Dr. Zeitler said.

Metformin is the sole oral agent approved for use in pediatric type 2 diabetes. It is well studied in adults, safe, and now costs no more than generic oral sulfonylureas. Among its desirable qualities are that it induces weight loss, there is mild improvement in lipids, it improves hirsutism and menstrual irregularities, and it may improve hepatic steatosis. Lactic acidosis, once thought to be a serious problem with metformin, was absolved in a meta-analysis of 40,000 patients. Nonetheless, the drug shouldn't be used in adolescents who have substantial renal disease, are dehydrated, or are having a radiologic procedure.

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DR. ZEITLER

Sulfonylureas are rarely used in kids because they cause weight gain, and hypoglycemia is a much bigger problem than in adults.

"It may be [that] the balance of insulin resistance and beta-cell function is different in kids and adults. Kids actually have relatively well-maintained beta-cell function, so when you give them a secretagogue, they're able to produce large amounts of insulin, leading to substantial hypoglycemia. I have not been able to effectively use a sulfonylurea in a kid without substantial hypoglycemia," the physician continued.

The thiazolidinediones are well studied in adults, where they reduce HbA_{1c} by about 1% and might prolong beta-cell function, a highly desirable attribute in a teenager who may live with type 2 diabetes for another 50 years. But there are no published studies on thiazolidinediones for treatment of type 2 diabetes in youth, and the drugs have substantial side effects, especially weight gain.

The glucagon-like peptide-1 analogue exenatide (Byetta) is the subject of an ongoing clinical trial in pediatric type 2 diabetes. Exenatide slows gastric emptying, increases insulin secretion, and causes weight loss, but must be administered by twice-daily injections before meals.

The dipeptidylpeptidase-4 inhibitors sitagliptin (Januvia) and saxagliptin (Onglyza) have actions similar to exenatide, but without the weight-loss feature. However, they can be taken orally. Pediatric trials are in the design phase.

Dr. Zeitler serves as an advisor to numerous pharmaceutical companies. ■