Crisis in Care: Limited Treatment Options for Type 2 Diabetes in Adolescents and Youth

Until two decades ago, children and adolescents were automatically assumed to have insulin-dependent type 1 diabetes. However, type 2 diabetes emerged as a "new type" of childhood diabetes in the 1990s in association with the epidemic of childhood obesity. It quickly became apparent that this new pediatric disease disproportionally affected disadvantaged minority children and was associated with comorbidities that increased the risk of future cardiovascular disease.

After more than 20 years, the optimal approach to the treatment of childhood type 2 diabetes remains largely unknown. Besides insulin, metformin remains the only other antidiabetic medication that is approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for use in youth with type 2 diabetes. Glimepiride and rosiglitazone failed noninferiority tests versus metformin as initial monotherapy in company-sponsored clinical trials. While the primary study results of the randomized phase of the TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) study showed that combination therapy with metformin plus rosiglitazone was more effective than metformin plus intensive lifestyle intervention and metformin alone (1), rosiglitazone will not be used with any frequency in young patients with type 2 diabetes because of concerns about the cardiovascular and other adverse effects of this class of medications. Once again, pediatric diabetes practitioners are left with just metformin and insulin for adolescents with type 2 diabetes.

Why haven't glucagon-like peptide 1 (GLP-1) agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors that have been approved for use in adults with type 2 diabetes been approved for the treatment of adolescents with the same condition? What about newer agents in the pipeline, such as sodium glucose cotransport inhibitors? Isn't the basic pathophysiology of type 2 diabetes very similar in pediatric and adult populations with abnormal glucose metabolism the result of severe insulin resistance and progressive β-cell dysfunction? Aren't adolescents with type 2 diabetes just "big adults" who are physically mature and often more obese than adults with type 2 diabetes? Where is the sense of urgency in making newer medications available to treat this very challenging condition?

A number of major obstacles have severely limited the successful completion of randomized clinical trials designed to test the efficacy and safety of the newer classes of drugs for adolescents with type 2 diabetes. First and foremost, the epidemic of type 2 diabetes in adolescents is an epidemic in relative rather than absolute terms. Although type 2 diabetes is the most rapidly increasing type of diabetes in pediatrics, the absolute number of patients remains small compared with the prevalence of type 1 diabetes. Based on data collected in 2002, the SEARCH for Diabetes in Youth Study estimated that there would be between 20,000 and 23,000 patients with type 2 diabetes who were <20 years of age in 2010 (2). Even under the best of circumstances, finding qualified and compliant subjects for clinical trials among adolescents with diabetes is difficult. These challenges are heightened in the disadvantaged populations that are over-represented among adolescents with type 2 diabetes and by other confounding factors such as concomitant treatment with atypical antipsychotic drugs that are diabetogenic. In addition, teenaged girls, who are the most difficult and noncompliant patients with type 1 diabetes to treat (3), make up two-thirds of the type 2 diabetes population.

Many of the study requirements imposed by the FDA and the EMA have made the completion of pivotal labeling studies in children and adolescents with type 2 diabetes nearly impossible. For example, virtually all of the early clinical trials in pediatrics mandated a comparison of the experimental drug against metformin as initial monotherapy in drug-naïve patients with elevated A_{1c} levels. Since virtually all patients with type 2 diabetes and elevated A_{1c} levels are immediately treated with metformin or insulin (to rapidly clear glucotoxicity), subjects who met these criteria were few and far between. Moreover, treatment guidelines recently published by the American Academy of Pediatrics state that all youth with newly diagnosed type 2 diabetes should be treated immediately with metformin and/or insulin (4).

As a result of its low cost and efficacy in early type 2 diabetes, metformin is well-established as initial monotherapy in youth with type 2 diabetes. On the other hand, the efficacy of newer antidiabetic agents as add-on therapies in pediatric type 2 diabetes patients with elevated A_{1c} levels on metformin alone, metformin plus insulin, and other antidiabetic medications is an open question. The Pediatric Diabetes Consortium (5) has established a Type 2 Diabetes Clinic Registry, which has collected data that underscore the need for new second and third lines of treatments for type 2 diabetes in adolescents. Patients enrolled in the registry who were treated with insulin alone or insulin with metformin had mean HbA_{1c} levels of ~9.0%.

While the supply of appropriate pediatric type 2 diabetes patients for randomized clinical trials of the newer drug classes is limited, the regulatory agencies have exaggerated the problem by cutting the pool of potential subjects in half by excluding patients being treated with insulin or other drugs besides metformin. At the same time, the demand for subjects for pediatric type 2 diabetes trials has sharply increased. All of the companies with recently approved GLP-1 agonists and DPP-4 inhibitors are required to carry out studies of their medications in youth with type 2 diabetes as part of mandatory pediatric investigation plans. As a result, the number of subjects that are required for these studies may be greater than the total number of potentially eligible children and adolescents with type 2 diabetes in the U.S. and Europe combined. Immediate steps that could increase the pool of potential subjects for such add-on trials is to include patients who are being treated

with metformin and/or insulin and/or any other antidiabetic drug of a different class and to expand the age range of eligible subjects from 10–17 years to 10–21 years.

The EMA convened a group of pediatric diabetes clinicians and industry representatives in February 2013 in London, England, to discuss steps that could be taken to facilitate the approval of new drugs for the treatment of youth with type 2 diabetes. During these discussions, an exciting solution to the problems of carrying out many large-scale, long-term randomized clinical trials in adolescents with type 2 diabetes was suggested. Where the course of a disease and the effects of a drug are sufficiently similar in adults and pediatric patients, both the FDA and the EMA may conclude that pediatric effectiveness can be extrapolated from well-controlled studies in adults, even though the details of this process differ slightly between the two agencies. The acquisition of supplemented data, such as the results of pharmacokinetic studies, is usually requested. Postapproval safety studies would likely be required, and pediatric type 2 diabetes registries could be used for the collection of additional safety and effectiveness information. Another innovative suggestion was to combine the study of several new drugs into a single study with separate experimental drug arms and a single control group. Let's hope that the EMA and the FDA can use these and other suggestions to come up with a workable and mutually agreeable plan to break up the logjam of unapproved drugs for adolescents with type 2 diabetes. Otherwise, we will have to continue to strive to treat this condition with one or two hands tied behind our backs.

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