Can we get it right for youth with type 2 diabetes?

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The prevalence and magnitude of childhood obesity are increasing dramatically. Until two decades ago, symptomatic children and adolescents were automatically diagnosed with type 1 diabetes. In the 1990s, type 2 diabetes in children and adolescents emerged in association with the epidemic of childhood obesity, disproportionately affecting disadvantaged minority children. Between 1995 and 2007, the annual incidence of type 2 diabetes in children younger than 15 years increased five-fold.\(^1\) Tragically, type 2 diabetes in children is associated with comorbidities that increase 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.\(^2\)

Metformin has long been recognised as the preferred first line treatment for paediatric type 2 diabetes, and it is the only drug for which efficacy and safety have been established in a completed randomised clinical trial in children and adolescents with type 2 diabetes.\(^3\) However, the results of the TODAY study suggest that type 2 diabetes in youth may have a more aggressive course than in adults, since adequate glycaemic control could be maintained on metformin monotherapy in only \(~50\%\) of subjects during the trial.\(^4\) Insulin
is the other class of drugs that is approved for use in youth with type 2 diabetes but this approval was based on extrapolation of efficacy and safety from studies in youth with type 1 and adults with type 2 diabetes. Even more importantly, baseline data from the Pediatric Diabetes Consortium (PDC) T2D Clinic Registry indicate glycaemic control remains poor in patients with metformin treatment failure, despite the addition of insulin.\(^5\)

The limited treatment options available to clinicians treating adolescents with type 2 diabetes are in stark contrast to the plethora of new treatment modalities that are available for adults with the same disease.

The main reasons why virtually all of the current randomised clinical trials of new drugs for the treatment of youth with type 2 diabetes are failing are that there are too many trials for too few patients. According to www.clinicaltrials.gov, there are approximately eighteen paediatric trials with ten different agents for type 2 diabetes and recruitment for these studies has been ongoing for as long as seven years. While these studies would require at least 3800 subjects to complete, it is estimated that there are only 25-35,000 youth with type 2 diabetes in the US and far fewer in Europe. As illustrated by recent data from the 500 youth with type 2 diabetes enrolled in the PDC T2D Registry\(^5\) the large majority of youth with type 2 diabetes are obese, minority girls from low-income families. Difficulties in recruiting these youngsters are compounded by the frequency of depression and other psychiatric problems in this population.

Additionally, eligibility criteria mandated by regulatory authorities have made recruitment of an adequate number of subjects for these randomised trials virtually impossible. As will be illustrated by the two examples below, inclusion and exclusion criteria required by the FDA and EMA simply have not reflected the clinical characteristics of the relatively small pool of patients who are available for participation in these studies.

**Trials of experimental drugs versus metformin as initial monotherapy of type 2 diabetes**

In these early paediatric type 2 diabetes trials, subjects were eligible only if they were drug naïve and had an HbA\(_{1c}\) >7.0%. In the PDC cohort, only 4.8% were both drug naïve and had an elevated HbA\(_{1c}\) level.\(^5\)

**Trials of experimental drugs as add-on therapy in metformin failures**

To be eligible for these studies, HbA\(_{1c}\) had to be >7.0% on treatment with metformin alone. While 35% of the PDC cohort was treated with metformin alone at enrolment, only 8% of the total cohort had an elevated HbA\(_{1c}\) level while on metformin...
monotherapy; 50% of the cohort was excluded because of use of insulin.\textsuperscript{5}

Other obstacles to enrolment include the exclusion of subjects 18 to 25 years of age even though few of these emerging young adults have been enrolled in adult type 2 diabetes trials. Each individual trial requires a separate control group, and the EMA requires 30\% of subjects be European despite the very small number of youth with type 2 diabetes in Europe. Any and all restrictions on inclusion/exclusion criteria unless absolutely needed for specific safety purposes only serve to encumber already difficult recruitment, and potentially can have a negative impact on clinical trial retention of this typically difficult to engage population.

An obvious conclusion from the above is that metformin and insulin are likely to remain the only drugs approved for youth with type 2 diabetes in the foreseeable future in the absence of broader eligibility criteria and new study designs. New inclusion criteria would increase the pool of subjects by:
- Increasing the age of eligibility to 25 years.
- Making insulin-treated subjects eligible.
- Implementing early combination therapy trials (like the TODAY study) in patients who are well-controlled on metformin alone.

In addition, the number of subjects required for these trials could be substantially decreased by use of a multi-agent design where each experimental arm would be compared to a single control group. One example of a possible study that includes many of these components is shown in the Figure. Ideally, these multi-agent studies would feature collaboration between academic medical centre investigators, industry sponsors and regulatory agencies. National and international consortia of paediatric diabetes centres are also needed to provide the infrastructure to carry out future clinical trials in paediatric type 2 diabetes.

References