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Development Process for Drugs for Pediatric Patients Suffering from T2DM

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Introduction

Despite the large increase in the number of cases of T2DM in children and adolescents over the last 15 to 20 years, this metabolic disorder remains relatively rare. The National Institutes of Health (NIH) estimates that there are around 40,000–50,000 children and adolescents with T2DM in the US currently [1]. A number that is far lower than the maximum number of 200,000 to be considered an orphan disease by the US FDA (http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm). This number is also a lot lesser compared to the more than 18 million adults with T2DM in the US. Furthermore, the annual incidence of T2DM in children and adolescent has been estimated by the SEARCH for Diabetes in Youth Study to be approximately 3700 in the US but not much as 5000 new cases per year [2].

Nonetheless, these numbers are still much less than the estimate of 15,000 new cases of childhood T1DM or the more than 1 million new cases of T2DM among adults each year [3]. Unlike in the adult population, undiagnosed T2DM is rare in high-risk obese adolescents [4], with less than 0.5 % of at-risk obese minority of children and adolescents being identified with T2DM via screening of FPG, OGTT, or HbA1c. Therefore, almost all children/adolescents with T2DM are identified clinically, and the registry-based estimates of diagnosed cases of T2DM in the US and Canada most likely reflect the total number of individuals under 18 years-old with the disease. Thus, potential clinical trials are very limited as they begin with a small pool from which to draw participants [5]. In the following article, we will discuss the factors that further limit eligibility of clinical trial participants as well as possible solutions to overcome these limitations.

Barriers to clinical trial participation

Pediatric T2DM represents a disorder with substantial risk for long-term metabolic, CVD, and renal morbidity and mortality. It is also an important individual and societal burden. Growing literature suggests that the disorder may have unique biological features, including accelerated loss of β-cell function relative to adults with T2DM, as well as a high risk of development of micro- and macrovascular complications. However, despite the availability of many novel oral anti-diabetic drugs (OADs) for the treatment of T2DM in adults, little information is available regarding the efficacy and safety of these OADs in the pediatric population [5]. Few results from pediatric studies have been reported, and approved treatment options remain limited to metformin and insulin. Furthermore, the results of the TODAY study demonstrated a high level of treatment failure with the use of metformin alone or in combination with LSI. Similarly, with the development of T2DM patients may have to switch or add other OADs to the initial regimen to better control their T2DM. Therefore, there is a high need in pediatric patients suffering from T2DM to have access to new OADs with higher efficacy and safety. A number of demographic, economic, and social challenges have limited the recruitment and the retention in pediatric T2DM clinical trials [5]. In the following sections we will discussed some limitations that could have an impact on the eligibility for clinical trials of pediatric patients with T2DM.

Early initiation of therapy

Despite the rise in prevalence of T2DM among children and adolescents, T1DM still remains more common, and an adolescent presenting with new-onset diabetes is still more likely to have T1DM [3]. Considering that many pediatric patients with T1DM will also present with obesity it becomes very difficult to reliably distinguish individuals with T2DM on the clinical basis alone since most of the T2DM pediatric patients are also obese. Therefore, even among those children and adolescent at highest risk i.e., obese patients, certain minorities and those in the middle of their puberty, the possibility of T1DM is high enough that many clinicians will decide to initiate insulin therapy until the diagnosis has been formally determined through antibody testing [6]. In addition, in regular clinical practice, if there is any doubt about the diagnosis of T2DM, then it is much safer to commence insulin treatment and revise the diagnosis later in order to avoid possible metabolic decompensation. However, once insulin is initiated, a certain degree of glycemic control is often achieved which means that the individual no longer meets the HbA1c criteria for clinical trial participation. Furthermore, insulin is often used as glycemic treatment in clinical studies of OADs and previous exposure to insulin limits the interpretation of results. Thus, the pool of naïve patients eligible for clinical trials is small, and identifying such patients requires careful coordination among HCPs and the research teams [7-8].

Glycemic Control

Most newly diagnosed patients initially respond well to treatment, and measures of glycaemia, including FPG and HbA1c, rapidly

decrease. For instance, in the TODAY study, 90 % of participants were able to achieve a median HbA1c of 5.9 % after a median of 10 weeks on metformin [9]. Therefore, individuals who have been treated for more than a few weeks may no longer be suitable for clinical trials, since the main primary study objectives generally call for enrollment of participants with limited exposure to insulin or metformin and with inadequate glycemic control at baseline in order to demonstrate efficacy through reductions in HbA1c. To complicate matters further, the withdrawal of insulin or metformin in stably treated patients in order for them to qualify for placebo-controlled clinical trials is not ethically acceptable in this vulnerable population. Thus, randomised clinical trials with new OAD for the treatment of pediatric patients with T2DM are limited to the small pool of potential participants consisting of patients identified before treatment is initiated, including patients responding poorly to treatment, or those in whom insulin or metformin is discontinued on clinical grounds but who maintain HbA1c within the inclusion range after discontinuation [5].

Inclusion and exclusion criteria

Common additional inclusion/exclusion criteria further limit the number of eligible patients. For instance, there is a high prevalence of NAFLD in children and adolescents with T2DM [10], with up to one third having ALT values greater than three times the upper limit of normal. This is representative of common exclusion criteria in clinical trials of OADs [5]. In several studies of adolescents with T2DM a large percentage of screened patients do not meet eligibility criteria due to the high prevalence of obesity-related comorbidities, such as HTN, hyperlipidemia, menstrual irregularities, and obstructive sleep apnea, which result in failure to most patients to meet the minimal inclusion and/or exclusion criteria. In addition, exposure to atypical antipsychotics or oral corticosteroids for asthma is prevalent in this population of T2DM and both are often exclusions for study participation due to the potential diabetogenic properties of these compounds [11]. The combination of the upper age limit of 17 for pediatric studies and the median age at diagnosis of 14 means that the average duration of potential eligibility for a pediatric T2DM study is only 3–5 years [12]. Considering, all these exclusion criteria, the pool of candidate for clinical trial in pediatric T2DM is rather small [5]. Therefore, there is a need to find solution to overcome these barriers in order to be able to develop new OAD molecules for the unmet of this population of pediatric patients.

Loss of Compliance

The investigators of the TODAY trial reported that it was difficult to recruit patients with T2DM for duration beyond 6 months [12], as patients on oral therapy alone often begin to routinely miss clinic appointments for their diabetes care. This suggests that beyond the initial few months after diagnosis, enthusiasm of patients to participate in clinical trials, or to receive clinical care for their T2DM, decreases. Secondly, the mean HbA1c of 3 months prior to loss of glycemic control in TODAY study was 6.8 % suggesting that loss of glycemic control in children and adolescents with T2DM is significant and the time during which individuals on oral monotherapy will remain in the HbA1c window for inclusion into a clinical trial will be limited. Thirdly, TODAY results indicate that patients who fail metformin monotherapy have lower β-cell function than other individuals, thus, may be different from those responding to metformin monotherapy, potentially limiting the generalizability of a trial including too many of these patients [13-14]. Finally, given the potential for rapid metabolic deterioration of individuals failing metformin monotherapy, clinicians and investigators are cautious about enrolling such children and adolescents in placebo-controlled trials and will rather opt to initiate insulin therapy rapidly [5]. Adolescents as a group are generally less adherent than younger pediatric and adult cohorts to oral treatment regimens and study visits. Self-reported reasons for non-compliance included: forgetfulness, jobs busy schedules, less developed concepts of illness, less perceived vulnerability, higher levels of denial, and less cohesive future orientation [5]. Many adolescents may also leave home to attend college or live independently while others may have parents who are absent or poorly concerned about their child's condition [5]. Patients report that major facilitators to research participation are positive peer and family influences, program incentives including money and school credit, spending time with friends, commitment, and personal gain.

Socioeconomic Challenges

The enrolment of potential study participants into any clinical trial requires a thorough understanding of the basic demographic characteristics of potential subjects [15]. Children and adolescents in the US with T2DM are obese; two thirds are female and are almost always pubertal. They are socio-economically disadvantaged i.e., 41.5 % are from a household having a total annual income of <$25,000; they are predominantly living in a single-parent home, and they are overrepresented in most ethnic minority groups [5]. They are poorly educated i.e., their highest level of education attained by a parent/guardian in the household is less than a high school graduate in 26.3 %, and they are almost all have a strong family history of T2DM. In Europe, most of the reported cases have been among immigrant groups in the UK and Germany [17]. In China and in India, like in the USA, most new cases were in individuals who were pubertal and obese i.e., with a BMI above the 95th percentile [17-18]. Overall, these characteristics present particular challenges in designing and implementing clinical trials for pediatric patients with T2DM. There are other barriers inherent to the adolescent population, including changing housing and unstable home environments, unreliable transportation for travel to and from appointments, difficult communication between participant and research team because of suboptimal parental support for research participation, high rates of missed medical visits, poor adherence to medical therapy in part due to large financial burdens related to the costs of present-day diabetes care, and others [19].

Sponsor and Regulatory Challenges

In Canada, to have a medication authorised and marketed, pharmaceutical companies have the obligations to systematically demonstrate the safety and efficacy of their products and the risk/benefice ratio should be favorable. Pediatric patients should be given medicines that have been appropriately evaluated for their use. Their product should be safe and effective for pediatric patients and their

approval requires the timely development of information on the proper use of medicinal products in pediatric patients of various ages and, often, the development of pediatric formulations of those products [5]. Obtaining knowledge of the effects of medicinal products in the pediatric patients is an important goal. However, this should be done without compromising the well-being of pediatric patients participating in clinical studies [5]. This responsibility is shared by companies, regulatory authorities, health professionals, and society as a whole (http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/e11-eng.pdf).

In USA, the establishment of the Pediatric Review Committee (PeRC) under the Pediatric Research Equity Act (PREA) and the FDA Amendment Act in 2007 further permitted the FDA to specifically require assessment of the safety and effectiveness of a product in pediatric patients in all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration unless this requirement is waived, deferred, or inapplicable [5, 20-22]. PeRC reviews the requested pediatric plans and provides assessment and recommendations to FDA as a part of the New Drug Application (NDA) approval process and reviews all requests for deferral and waiver. In general, deferral is granted so that the approval for use in the adult population is not delayed.

In Europe, similar regulations have been established to govern requirement for pediatric investigation during the drug approval process by the Pediatric Committee of the European Medicines Agency (EMA) [23-24]. Despite the incentive of patent exclusivity or the statutory requirement from the EMA, it has remained challenging to initiate, conduct, and complete studies in the pediatric T2DM population for the reasons discussed above [5]. In addition, from the sponsor point of view, clinical research in the pediatric population has other barriers to overcome including the lack of financial incentive to conduct clinical trials in T2DM pediatric populations considering the limited market and the recruitment difficulties [5]. In the past few years, a number of new OADs with novel mechanism of action have emerged, and many studies in the pediatric T2DM population have been required by the FDA, the EMA and Health Canada. The success of novel OAD development has inadvertently made the challenges of conducting pediatric T2DM studies even more difficult because of the continually increasing competition for the limited number of eligible study patients. Currently, clinical safety and efficacy studies and PK studies for DPP-4 inhibitors and insulin Determir have been completed within the last 2 years. However, clinical trials for GLP-1 analogues, SGLT2 inhibitors, insulin glargine, and others, seeking to randomize a total of over 1000 new study subjects remind us that recruitment issues remain a limiting factor in pediatric T2DM drug development [25].

To make the situation worse, more clinical safety and efficacy studies have already been committed to as a condition of new drug approval and will need to be initiated in the near future, and more studies will be required for applications that are either under regulatory review or to be submitted in the near future. These pediatric studies will evaluate not only novel active ingredients but also new dosage forms and dosing regimens including extended-release formulations, oral suspension, and fixed-dose combination of approved agents. Unfortunately, new OAD development against pediatric T2DM seems to be a necessity since data from the TODAY study suggests that metformin monotherapy failure rates to be higher in children than adult population [26].

However, there are potentials solutions to overcome these barriers and in the following paragraphs some of these solutions will be briefly discussed.

Possible Solutions

What can be done to improve clinical research in pediatric T2DM patients so as to provide meaningful clinical trial data to inform treatment decisions? To reduce the burden on performing clinical trials with the very limited patient pool, it would be useful to consider the patients' and the HCPs' point of view in setting the priorities for clinical research in pediatric T2DM. From this perspective, it can be argued that it is more logical to selectively assess the most promising OADs and treatment regimens, instead of testing each new OAD and having them evaluated and authorised by regulatory agencies [5].

Create a Consortium

One interesting approach is to create a consortium of clinical research experts, together with other key stakeholders, to identify and prioritize the development of OADs and strategies needed to improve T2DM management in pediatric patients. The Drug Safety and Efficacy Network (DSEN) is an example of such a consortium which works in collaboration with the Canadian Institute of Health Research (CIHR) and many other stakeholders to identify appropriate therapy for patients who have already failed initial treatment. They work to identify and prioritize the clinical trial hypotheses, to determine the most promising OADs to be tested, and to design and conduct the clinical studies, utilizing a network of clinical trial sites representing centers most commonly tertiary hospital centers with clinical and research expertise in pediatric T2DM to undertake and perform the designed trials. This consortium and others require collaboration rather than competition between the HCPs, the clinical research experts, the medical societies, the pharmaceutical sponsors, the regulatory agencies, and the patient group representatives [26].

Adaptive design

Over the past few years, the use of adaptive designs in clinical research and in drug development based on accumulated data has become very popular because of its flexibility and its efficacy [27]. Based on the adaptations applied to the initial clinical trial during the drug development, this can lead to a reduction in the duration and the number of patients in the adaptive study and indirectly limit the exposure of patients to ineffective placebo or active comparators with less efficacy and known adverse drug reactions. A study performed by Spann et al. demonstrated, using an adaptive design, the same conclusion regarding the effectiveness of a treatment by using 50% fewer patients when compared to the initial trial. The number of patients had been reduced from 311 to 156; exposure to the placebo was reduced from 54 to 30 and exposure to the active comparator, with known side effects, was reduced from 126 to 60, compared to what was initially planned [28]. However, it must be ensured that the actual

population of patients after the modifications does not deviate from the initial patient population, therefore avoiding a type I error i.e., to affirm the effectiveness of a drug by mistake while it is not effective, thus decreasing the possibility of arriving at inadequate conclusions or results difficult to interpret [29-30].

In addition, important adaptations to clinical trials and/or statistical procedures during development can make these clinical trials totally different from those initially designed and therefore these changes render us unable to adequately answer the scientific or medical issues raised initially. Traditionally, the clinical trial protocol must be carefully planned a priori and all clinical aspects related to this new protocol must be clearly documented and must comply with the requirements for clinical trials. Any significant changes in the design of the protocol, once started, must be authorized by a regulatory agency. In addition, changes made to the initial statistical procedures must be approved before their implementation, because these changes may represent a potential risk of bias, thus compromising the results of the clinical trial. In conclusion, the adaptive study plans allow a study protocol to be modified from its initial version based on new data from external sources or from an interim analysis of the data obtained from the ongoing clinical trial. However, any changes to the design or analysis of data from the study must be planned in advance and the situations where these changes will be introduced should also be previously specified.

While increased efficiency is an important goal in the development of drugs, this should not compromise the safety of the participants in clinical trials. The FDA says in its Guidance Document (www.fda.gov/downloads/Drugs/.../Guidances/ucm201790.pdf) that adaptive clinical trials may be suitable for the products with prior experience of known security or for products with adverse events with known pathophysiological mechanisms. The use of adaptive designs can certainly contribute to shortening the drug development timeframe by allowing the initiation of larger trials (Phase III) before smaller studies (Phase II) are fully completed and analyzed. However, the identification of adverse reactions may be inappropriately missed due to a reduced number of exposed patients combined with a reduction in duration of drug exposure. With this approach, the side effects associated with new drugs occurring in the long term can pass unnoticed, placing pressure on the development of prevention activities in post-approval phase.

Extrapolation from adult studies

The FDA has put in place the following rule that could be beneficial for the development of new drug that could also be applicable in pediatric patients suffering from T2DM. "*Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults usually supplemented with other information obtained in pediatric patients, such as PK studies. Studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another.*" **[21 CFR 314.55(a); 21 CFR 601.27(a)].** This extrapolation is based on three evidence-based assumptions as follows: 1) the course of the disease is sufficiently similar between adults and children; 2) the response to treatment is sufficiently similar between adults and children; and 3) adults and children have a sufficiently similar exposure-response relationship. Considering that the drugs that require development in the pediatric population suffering from T2DM are mainly required in adolescents (mean age of 14) and that the response to treatment and the adverse drug reactions we are following are mainly the same as in adults, we can conclude that we meet the criteria for extrapolation from adult studies according to the FDA regulations. If needed, PK data to allow for the determination of an appropriate pediatric dosage and additional pediatric safety information can also be submitted using the 14 and above year-old group as mentioned above.

Health Canada has also put in place the following rule regarding the extrapolation from adult studies: *When a medicinal product is to be used in the pediatric population for the same indication(s) as those studied and approved in adults, the disease process is similar in adults and pediatric patients, and the outcome of therapy is likely to be comparable, extrapolation from adult efficacy data may be appropriate. In such cases, pharmacokinetic studies in all the age ranges of pediatric patients likely to receive the medicinal product, together with safety studies, may provide adequate information for use by allowing selection of pediatric doses that will produce blood levels similar to those observed in adults. If this approach is taken, adult pharmacokinetic data should be available to plan the pediatric studies as discussed above* (http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/e11-eng.pdf) .

Clinical trials combining adult and pediatric patients

Another interesting approach is to include a subgroup of pediatric patients within the adult's clinical trials and perform the statistical analysis by subgroup based on the age of patients. Considering, that the mean age that the pediatric patients that develops T2DM is around the mid-puberty, which is around 14 years-old, therefore, having a subgroup aged 13-17 years-old would be acceptable where compared to control group of the same age similar weight or body surface area. Obviously consideration should be given to extrapolation from adult studies as mentioned above. It is not the purpose of this paragraph to discuss the design and the statistical methods used for this combine clinical trial. Briefly, these clinical trials should follow the ICH-E6 Guideline for Good Clinical Practice (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf), the ICH-E9 on Statistical Principles for Clinical Trials (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf) and must be authorised on a case by case basis by a regulatory agency such as the FDA, the EMA or Health Canada.

Conclusions

Pediatric T2DM represents an emerging disorder with substantial risk for long-term metabolic complications, CVD, and renal morbidity and mortality, as well as individual and societal burden. A number of demographic, economic, and social barriers limit the recruitment and the retention of patients in pediatric T2DM clinical trials resulting in limited studies with limited population. We have also discussed a

certain number of potential solutions to overcome these barriers. These solutions could facilitate timely completion of the required clinical trials sponsored by pharmaceutical companies, and acknowledge the mandate of regulatory agencies to ensure the availability of safe and well-studied OADs for affected pediatric patients with T2DM. If successful, these potential solutions could also serve as a model for clinical trials in other rare and understudied pediatric disorders.

How might we improve recruitment and retention of pediatric patients in clinical trials? Studies outside the field of pediatric T2DM offer some promising strategies. Villarruel et al. [31] showed that a combination of incentives including money and school credit for participation, flexible program start times, continued contact with project staff including more frequent reminders, increasing the interactive components of follow-up, and recognizing the importance of potential mobility limitations among adolescents and their families contributed to a reduction in risky sexual behavior in Latino youth. Finally, we suggest that more should be done to find young patients in the places where they are most comfortable i.e., at their local clinics, in their neighborhoods, and at their schools. Rather than asking patients to come to us, perhaps we should consider that we, as HCPs and research investigators, go to them [32].

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