Alternate Approaches for Pediatric Type 1 Diabetes Drug Development and Potential Regulatory Approval: A Perspective

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The incidence and prevalence of pediatric type 1 diabetes are increasing globally, including in the U.S. While the increasing number of cases of pediatric diabetes makes expeditious availability of new medical products and therapies for diabetes care essential, there have been many barriers encountered in bringing some drugs and devices to pediatric patients who may benefit. Newer insulins have been studied and approved for use in children. However, hurdles exist in the inclusion of children in studies of therapies aimed at preventing β-cell loss in those with new-onset diabetes and those at risk for type 1 diabetes. This Perspective focuses on potential solutions to the challenges experienced in bringing new drugs for pediatric type 1 diabetes to marketing approval. Given their central importance as the users of medical products, patient perspectives are included along with scientific and regulatory considerations.

The development and approval of drugs for pediatric patients present particular challenges. Diseases that occur in both children and adults, such as type 1 diabetes, may have unique features such as increased hypoglycemia rates in young children and difficulty with meeting the demands of daily diabetes care in adolescents. Pediatric patients may have differences in drug metabolism and unique potential side effects such as impact on growth or pubertal development. The need to study drugs that will be used in children during drug development is widely recognized and is supported by legislation in many countries around the world. Despite this legislation, many challenges continue to exist in pediatric drug development.

The incidence and prevalence of pediatric type 1 diabetes are increasing, and this trajectory "may double the burden of disease in our youngest by 2020" (1). In the U.S., prevalence of pediatric type 1 diabetes has increased from an estimated 1.48 to 1.93 per 1,000 from 2001 to 2009; when adjusted for completeness of ascertainment, these figures represent a 21.1% increase (2). These increasing numbers, coupled with particular difficulties in care of children with diabetes, including the difficulties many adolescents face in managing the demands of diabetes care and dependence of younger children on others for aspects of care, make expeditious availability of new therapies for diabetes care essential.

However, many candidate drugs are not reaching children who may benefit. Barriers to drug development for pediatric type 2 diabetes have recently been discussed (3–5), including a need for greater collaboration to study new medicines in pediatric populations with type 2 diabetes (6). This Perspective extends the discussion into the domain of type 1 diabetes.

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CONSIDERATIONS IN TYPE 1 DIABETES

Over the past 20 years, new insulins and devices have been developed, tested, and approved for use in children. Despite these promising tools, however, the current reality is that most children and adolescents do not reach the targets for metabolic control set by the American Diabetes Association and the International Society for Pediatric and Adolescent Diabetes (7,8). Large studies from many countries, including the U.S. and countries in Europe, have found that mean HbA_{1c} in the pediatric age group ranges from 8.2 to 8.8% (9,10), with limited impact of the use of more frequent injections or insulin pump therapy (11). Continuous subcutaneous glucose monitoring offers great promise but is persistently used by very small numbers of pediatric patients, even in the setting of a clinical trial (12). Furthermore, both hypoglycemia and diabetic ketoacidosis remain as significant short-term complications of diabetes (12). In addition, young children experience unique cognitive effects of diabetes (13). These realities drive the need for new or improved drugs and devices for those with type 1 diabetes.

Scientific Considerations

Increased understanding of the pathogenesis of type 1 diabetes, the advent of new drugs with potential impact on the process of β-cell loss, and the ongoing recognition of the challenges of maintenance of excellent glycemic control in many patients have led to an active study of the prevention of β-cell loss in those at risk for type 1 diabetes and preservation of insulin secretion in those recently diagnosed. The goal of these studies is to arrest or reverse the autoimmune process to preserve β-cell function to reduce or eliminate dependence on exogenous insulin and to ameliorate severe hypo- and hyperglycemia. In this context, numerous immunologic interventions have been tried, ranging from nonspecific immunosuppression to use of autoantigens, such as GAD peptide and insulin itself, with some agents showing impact on the reduction of the rate of loss of insulin production. However, these efforts have had limited success and, to date, no therapies have been able to induce prolonged remission of the disease (14,15). Autologous nonmyeloablative hematopoietic stem cell transplantation in subjects with newly diagnosed type 1 diabetes also has been attempted with some success (16), but this procedure's safety profile in the target population is questionable, if not ethically unacceptable (17).

In the efforts to prevent diabetes and develop early treatment to preserve remaining insulin production, it is increasingly recognized that there is a spectrum of autoimmune intensity, in general ranging from rapid and aggressive in young children to more indolent in adults (18). This difference in biology makes extrapolation of data from the study of adults with recent-onset diabetes to children challenging. Outcomes data collected in adults with new-onset disease may not be completely relevant to children who have distinct differences in autoimmunity that are reflected in generally more rapid loss of β-cell function (19).

These considerations contribute to one of the largest challenges in the development of type 1 diabetes therapies; namely, modern insulin therapy and supportive technologies have made type 1 diabetes more manageable during recent years. This has been evidenced by the continued declines in the rates of complications and early death from diabetes (20). As such, the benefits and risks of every candidate therapy have to be compared with the alternative of no immune intervention and lifelong dependence on insulin therapy. This alternative still imposes a huge patient burden and carries its own risks of hypoglycemia and diabetes complications but narrows the field of treatments that could be appropriate in otherwise healthy patients with new-onset diabetes.

Regulatory Considerations

The U.S. Food and Drug Administration (FDA) has published a number of regulations and guidances aimed at encouraging the study of pediatric populations in drug development (21), including the Pediatric Research Equity Act, which mandates that sponsors must study relevant pediatric populations when submitting an application for approval of a new drug (21).

The FDA has held that some level of safety and efficacy should be established in adults before testing a therapy for diabetes in children:

> In the case of new molecular entities, particularly for new classes of therapeutic products with novel mechanisms of action, the early studies should enroll adult subjects only, reserving pediatric exposure until the metabolism, pharmacodynamics, and safety of the agent are reasonably well-defined. The same precaution can be applied to already approved agents with known toxicities in nondiabetic populations, such as immunosuppressive or immune modulatory products. Because many of the general aspects of the clinical pharmacology and safety profiles of an approved therapeutic are better understood, it may be appropriate to dose pediatric patients earlier in the development programs of approved versus unapproved investigational products. (22)

While this is a prudent policy, especially for drugs that have not been tested in pediatric populations previously, the challenge arises when deciding how much adult data are sufficient before children can be tested. For some novel therapeutics, especially those that have been tested (and approved) for other indications in children and have good safety records, it may be appropriate to include both children (particularly adolescents) and adults in phase 2 studies. Currently, the FDA recognizes the need to involve children with type 1 diabetes relatively early in new-onset therapeutic development. However, for immunomodulatory agents, it has recently only allowed inclusion of younger children within a phase 2 protocol after a cohort of adults has been evaluated.

An additional challenge is demonstration of efficacy in new-onset diabetes. In contrast to the case for glucose-lowering therapies, which generally show almost immediate efficacy, new-onset therapies aimed to preserve β-cells are judged by preservation of endogenous insulin secretion over the first year after diagnosis, as reflected by stimulated C-peptide levels. Improved metabolic control is not a viable efficacy end point in the setting of new-onset disease because good glycemic control is typical in the first months following diagnosis with insulin therapy. The well-known "honeymoon period" in which insulin dependence is reduced or even

temporarily eliminated underscores the lack of usefulness of HbA_{1c} as a primary efficacy end point in this setting (23). The high variability of glycemic control and C-peptide levels during the new-onset period adds to the challenge of showing treatment effects in these patients (24), whether the intent is to preserve β-cell function or to improve glycemic control. Accordingly, when an agent is aimed at directly improving glycemic control in patients with type 1 diabetes, which is now the case for sodium–glucose cotransporter 2 inhibitors (25), it is advisable to exclude new-onset patients.

Baseline and stimulated C-peptide as the primary efficacy end point has been explained (26) and accepted by the FDA (22). However, for clinical and biostatistical reasons, measurement of a reliable change in group mean C-peptide levels in a small group of participants in less than 6 months is extremely difficult even if the underlying efficacy is high (27). Additionally, if all other factors were equal, efficacy would be easier to measure in children because, due to generally more intense autoimmunity, their C-peptide decline is more rapid than those of adults (25). Currently, 2 years of treatment and/or follow-up in two phase 3 trials is expected by regulatory authorities when submitting a new drug application for drugs to prevent diabetes or to preserve β-cell function (22). However, despite great interest and investigation of alternative markers of β-cell failure, including markers of β-cell stress (29), currently no other valid potential primary outcome measures (particularly short-term measures) have been identified. Moreover, combinations of immunomodulatory agents are likely necessary to achieve complete clinical responses. Without some progress in approving type 1 diabetes monotherapies, the prospects for the study of robust combination approaches are poor.

While the FDA has acknowledged the high unmet need of therapies for patients with type 1 diabetes, their Division of Metabolism and Endocrinology Products does not routinely grant pre-Investigational New Drug meetings (30) or use available provisions for expedited approval of drugs and biologics for serious conditions (Fast Track for drugs that address unmet medical needs for a serious or life-threatening disease, priority review, accelerated approval) to facilitate diabetes therapeutic development in general or in pediatric age-groups in particular (30). In fact, apparently no Fast Track designations have been awarded for a type 1 diabetes therapy to date. The FDA does not report a specific Fast Track or Breakthrough designation until the New Drug Application is approved. Sponsors typically announce that they have received one of these distinctions soon after they have been awarded. Because none has been announced, it is presumed that none has been awarded. In one instance of a new-onset therapy case, the justification provided by the FDA for denying a Fast Track designation was that clinical end points (diabetes complications, serious hypoglycemia rate reduction) were not being targeted (G.A.F., personal observation). New-onset type 1 diabetes has qualified for orphan status at the FDA, and a number of designations have been awarded (Table 1) (31).

One consequence of this regulatory environment is that no drugs indicated for type 1 diabetes have been approved for children outside of insulin products. Metformin has been approved for pediatric type 2 diabetes and is sometimes used in type 1 diabetes, although its efficacy has been small (32). Of note is that the FDA has been more willing to approve diabetes devices (e.g., continuous glucose monitors, insulin pumps) indicated for pediatric use. For example, in February 2014 it approved a pediatric indication for Dexcom's G4 Platinum that allowed the company to market a continuous glucose monitor to children 2–17 years old in the U.S. (it had previously been used for individuals aged 18 years and older) (33). With regard to pumps, there are a number of devices approved for use in children. We applaud FDA's practical thinking in the device space and believe that the growing burden of type 1 diabetes in children begs a similar need for approvals in the drug space.

Table 1—Drugs that have received orphan designation in type 1 diabetes

Generic name	Designation date	Orphan designation
CD40/CD80/CD86 modified autologous dendritic cell therapy	20 December 2013	Treatment of patients with type 1 diabetes with residual β-cell function
Abatacept	30 May 2013	Treatment of patients with type 1 diabetes with residual β-cell function
Ex vivo cultured adult human mesenchymal stem cells	30 April 2010	Treatment of patients with type 1 diabetes with residual β-cell function
α-1 Proteinase inhibitor (human)	28 July 2011	Treatment of patients with recent-onset (<15 years) type 1A diabetes with residual β-cell function
α-1 Proteinase inhibitor (human)	3 March 2015	Treatment of patients with type 1 diabetes with residual β-cell function
Human insulin β-chain peptide with incomplete Freund's adjuvant vaccine	11 February 2013	Treatment of patients with type 1 diabetes with residual β-cell function
Otelixizumab	6 February 2006	Treatment of new-onset type 1 diabetes
Ustekinumab	29 November 2010	Treatment of patients with type 1 diabetes with residual β-cell function
Recombinant human GAD65kDa isoform	22 March 2010	Treatment of patients with type 1 diabetes with residual β-cell function
Humanized anti-CD3 monoclonal antibody	29 September 2006	Treatment of recent-onset type 1 diabetes

Patient Considerations

Pediatric diabetes is a challenging, complicated, and frustrating disease for patients and their families, caregivers, and health care providers. Despite patients' obvious importance as the users of therapies and products, they have only recently been consulted as key stakeholders; rather, opinions and insights have predominantly been solicited from medical product companies, regulators, physicians, and payers. Pediatric patients and their families are also well placed to provide more input into the general drug development process than has traditionally been the case. Patients and their families and advocates are increasingly questioning whether the need to protect children in clinical research has resulted in children being underrepresented in such research and whether the balance of protection and potential harm from not being a larger part of this research is appropriate.

ACTIONABLE SUGGESTIONS FOR IMPROVING PEDIATRIC TYPE 1 DIABETES DRUG DEVELOPMENT

The scientific challenges in providing compelling evidence of the safety and efficacy of a drug to prevent β-cell loss, as just summarized, are considerable, and sponsors must unquestionably continue to address these in innovative and rigorous manners. In addition, modifications in regulatory and study design approaches, including greater considerations of patient perspectives, may prove of significant help in bringing drugs more efficiently to patients. As regulatory and study design approaches are intertwined (regulators need to consider study designs to be capable of providing compelling evidence of safety and of efficacy if it truly exists), a single list of 10 actionable suggestions is presented here.

- **Do not gate involvement of pediatric participants in type 1 diabetes research programs by demonstration of preliminary success in adult research programs.** Evidence strongly suggests that the current regulatory approach is to include only adults in initial studies with the end point of preservation of β-cell function in new-onset diabetes. A ClinicalTrials.gov search conducted on 7 May 2015 using the terms "type 1 diabetes" and "new onset" and including only those studies being carried out in the U.S. with preservation of endogenous insulin secretion as an end point revealed that all identified studies currently recruiting participants accepted only those ≥16 years of age, with the vast majority accepting only those ≥18 years of age. One study will include younger participants after 30 adults have been enrolled. This strategy delays the inclusion of children in appropriate clinical research and, importantly, potentially eliminates an intervention that shows little effect in the slower autoimmune process in adults but one that may have therapeutically beneficial impact on the more rapid autoimmune process in children. In contrast to the enormous logistical challenges of recruiting participants with type 2 diabetes (5), finding young subjects and their families willing to participate in type 1 diabetes trials has not been problematic; study start-up times would therefore be favorable.
- **Award Fast Track designations.** Despite diabetes being named as one of the conditions in FDA's description of qualifying diseases (34), the Division of Metabolism and Endocrinology Products has not awarded Fast Track status to any type 1 diabetes or type 2 diabetes therapy. Without the potential for Fast Track designation and a realistic pathway to approval, it is unlikely that any major sponsor will become involved in the field of type 1 diabetes autoimmunity.
- **Add diabetes to the list of indications for which the FDA intends to move toward a patient-centered regulatory process for drug development.** In 2013, the *Federal Register* announced the FDA's intent in this regard (35). Meetings for various therapeutic areas have already been held and others are scheduled for 2015 (36). However, diabetes is not included among the more than 20 indications listed on the relevant FDA Web site (36).
- **Use multiarm, multistage (MAMS) trials that use multiple novel treatments and one common control treatment as discussed by Karres et al. (6) in the context of drugs for pediatric type 2 diabetes.** MAMS trials can work very well for a single sponsor testing multiple novel therapies in a single trial. Going one step further, use of a precompetitive paradigm (sponsors working in a collaborative manner that aims to help all sponsors involved to move their drugs toward marketing acceptance more efficiently and hence to be available to patients as expeditiously as possible) would facilitate the creation of "a single, established, clinical research infrastructure that would be used to meet the needs" of multiple sponsors (6), helping each to bring new medicines to patients faster. Incorporating adult data could be used in pediatric MAMS trials, which would facilitate the use of Bayesian methods (37) that are certainly of considerable interest to the FDA (38).
- **Develop a provisional or adaptive approval system (39).** Such a system could reduce the time (including the time to the inclusion of relevant pediatric populations) and costs to market. This concept is increasingly being advocated (40,41).
- **Involve patients to a greater degree in the design and execution of clinical trials.** The Center for Information and Study on Clinical Research Participation, for example, has helped to incorporate patient advisory board panels into clinical trials; such panels can provide valuable input on study protocols, communications, and aspects of trial conduct (42). Organizations such as PatientsLikeMe (43) are creating new patient-driven research paradigms by conducting observational studies using voluntarily submitted patient data and sharing the results with health care and life sciences companies.
- **Include top diabetes drug leadership (as well as device leadership) at future meetings similar to the first FDA-Patient Dialogue on Unmet Needs in Diabetes held in November 2014 (44).**
- **Ensure that differences in pediatric and adult study populations are reflected in the design, timing, and execution of trials.** There are differences in clinical contexts and challenges for assessing risks, acceptability of devices, and ability to adhere to complex study protocols.
- **Provide more attention to sponsors early in the development process,**

such as in granting pre-Investigational New Drug meetings. Sponsors are often small companies, individual investigators, or academic consortia with limited experience and resources for whom early advice is particularly important.

- **Incorporate long-term follow-up in development programs.**

CONCLUDING COMMENTS

The need to protect children in clinical research is challenged by the increasing realization that physicians effectively have to conduct "*n* of 1" clinical research every time they treat a pediatric patient when there is no documented research addressing pediatric prescribing. Much work is needed to improve the biopharmaceutical armamentarium for children with type 1 diabetes. It is hoped that the suggestions herein will spark additional discussions that eventuate beneficial changes.

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