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The Pediatric Diabetes Consortium: Improving Care of Children with Type 1 Diabetes Through Collaborative Research

The Pediatric Diabetes Consortium

Abstract

Although there are some interactions between the major pediatric diabetes programs in the United States, there has been no formal, independent structure for collaboration, the sharing of information, and the development of joint research projects that utilize common outcome measures. To fill this unmet clinical and research need, a consortium of seven pediatric diabetes centers in the United States has formed the Pediatric Diabetes Consortium (PDC) through an unrestricted grant from Novo Nordisk, Inc. (Princeton, NJ). This article describes the organizational structure of the PDC and the design of a study of important clinical outcomes in children and adolescents with new-onset, type 1 diabetes mellitus (T1DM). The outcomes study will describe the changes in A1c levels, the frequency of adverse events (diabetic ketoacidosis/severe hypoglycemia), and the frequency and timing of the "honeymoon" phase in newly diagnosed patients with T1DM over the first 12–24 months of the disease and examine the relationship between these clinical outcomes and demographic, socioeconomic, and treatment factors. This project will also allow the Consortium to develop a cohort of youth with T1DM whose clinical course has been well characterized and who wish to participate in future clinical trials and/or contribute to a repository of biological samples.

Introduction

Although there are some interactions between the major pediatric diabetes programs in the United States, there has been no formal, independent structure for collaboration, the sharing of information, and the development of joint research projects that utilize common outcome measures. To fill this unmet clinical and research need, a consortium of pediatric diabetes centers in the United States, the Pediatric Diabetes Consortium (PDC), was established. The long-term objective of the PDC is to improve the care of children with diabetes through sharing of best practices, collecting outcomes data with a common database, and collectively advocating for improvements in pediatric diabetes care focused on evidence-based education.

The PDC was established in January 2009 and supported by an unrestricted grant from Novo Nordisk, Inc. (Princeton, NJ). The grant was divided into two phases: a 6-month organization and protocol development phase and a 2-year study phase. The protocol that was developed during phase 1 is the first investigator-initiated study describing how diabetes is treated in children and adolescents with new-onset type 1 diabetes mellitus (T1DM) at leading pediatric diabetes centers in the United States. Information regarding rates of severe hypoglycemia, diabetic ketoacidosis (DKA), and other serious adverse events will be garnered. The study also will result in the acquisition of a large and geographically diverse cohort of youth with T1DM whose clinical course has been carefully characterized from onset of the disease and who can be recruited for participation in future studies.

The Steering Committee of the PDC consists of investigators at each of the seven Clinical Centers and the Director of the Coordinating Center. The seven participating clinical centers are located at the Barbara Davis Center at the University of Colorado, Baylor College of Medicine, Childrens Hospital of Los Angeles, Stanford University, University of Florida, University of Michigan, and Yale University. The Jaeb Center for Health Research is the primary contractor of the unrestricted grant from Novo Nordisk, Inc., and each of the clinical centers are subcontractors. The Jaeb Center is a nonprofit freestanding coordinating center for clinical trials and epidemiologic research that is based in Tampa, FL that also serves as the coordinating center for the Diabetes Research in Children Network (DirecNet), the Juvenile Diabetes Research Foundation (JDRF) Continuous Glucose Monitoring Trials, Diabetic Retinopathy Clinical Research Network (DRCRnet), Pediatric Eye Disease Investigator Group (PEDIG), and the JDRF Artificial Pancreas Project. The seven clinical centers

Members of the Consortium are given in the Appendix.

were selected to participate in the Consortium based on the quality of their multidisciplinary treatment teams and to provide as much geographical, racial, and ethnic diversity as possible.

During Phase 1 of the project (January 1, 2009–June 30, 2009), clinical centers were recruited, the study protocol was developed, case report forms were written, data acquisition and management plans were developed, Institution Review Board approvals were obtained, and center staff were trained and certified with regard to data collection methods. All of these milestones were accomplished on schedule, and the first subject was enrolled in the study in July 2009. During Phase 2 (July 1, 2009–June 30, 2011), clinical centers are collecting outcome data on all newly diagnosed T1DM patients who agree to participate in the study; the Jaeb Center is responsible for financial and data management, and the Steering Committee meets monthly by teleconference to review progress and approve protocol and operational changes.

PDC Clinical Outcomes in Newly Diagnosed T1DM Study: Design and Methods

Specific aim

The goal is to develop and utilize a common data repository to evaluate treatment approaches for children and youth with new-onset T1DM.

Background

With the advent of insulin analogs, development of new and improved insulin pumps and advances in glucose monitoring,[1] a variety of treatment regimens are being used by pediatric endocrinologists to initiate insulin therapy in children and youth with new-onset T1DM. These regimens range from two insulin injections per day[2] to multiple daily insulin injections[3]; few if any centers in the United States start insulin pump therapy at the time of diagnosis. In addition, some centers initiate insulin therapy exclusively in hospitalized patients, whereas others utilize the outpatient setting to begin therapy in those patients who do not have a metabolic requirement for hospitalization. Within centers, clinicians may have different practices as to what regimen will be used and where insulin initiation will occur. Some centers allow patients/families to have a significant role in decision-making versus the center making the decisions based on a formal or informal assessment of family capability, family resources and support, and patient and family response to the diagnosis of diabetes, as well as the realities of school and child care. Despite wide variations in approaches to treatment, there is little current evidence as to which approaches are superior in terms of the time required to attain metabolic control, the duration of the remission phase of diabetes, and the risk of acute complications such as DKA and severe hypoglycemia.

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study has demonstrated that intensive therapy aimed at lowering hemoglobin A1c levels as close to normal as possible and as early in the course of the disease as possible has a durable effect on intermediate and long-term outcomes.[4,5] Nevertheless, the extent of data describing clinical outcomes and rates of serious adverse events in leading pediatric diabetes centers is quite limited. Therefore, it is imperative to determine how best to initiate insulin treatment in children at the time of diabetes diagnosis, as well as to describe the risks and benefits of intensive treatment as it is currently practiced.

Research design and methods

The design is a longitudinal, prospective, observational, clinical outcomes study in which children and adolescents <19 years of age are eligible if diagnosed with new-onset T1DM after July 1, 2008 and if cared for by the consortium centers from the time of diagnosis. Patients with a clinical diagnosis of type 2 or other types of diabetes are excluded. Written informed consent is obtained from all subjects who are 18 years of age and from parents of children <18 years of age. Written assent is also obtained from youth 8–17 years of age.

Case report forms were developed by the investigators to capture key clinical data at the time of diagnosis and during all subsequent follow-up visits:

- Baseline data include demographic, socioeconomic, and psychosocial data; presence or absence of DKA and degree of metabolic abnormalities on presentation; initial insulin regimens utilized; and site of initiation of insulin therapy (in- or outpatient).
- Follow-up clinical outcome data obtained at each clinic visit include: hemoglobin A1c levels (measured at each center by the DCA Vantage [Siemens USA, New York, NY]); 14-day mean plasma glucose from a home glucose meter; summary data from continuous glucose monitoring (if used); number of severe hypoglycemic events since last visit; other serious adverse advents such as DKA, emergency room visits, or hospitalizations for any cause; results of screening for associated autoimmune diseases, hypertension, microalbuminuria, and dyslipidemia; fasting C-peptide level at 1 year post-diagnosis; and data regarding insulin regimens and daily insulin doses.
- Centers also collect resource utilization data such as time spent by professional staff during clinic visits, answering phone calls, providing diabetes education classes, and dealing with school-related issues.

Statistical analyses

Clinical outcomes that will be analyzed include, but are not limited to, the following: changes in A1c levels, frequency of adverse events (DKA/severe hypoglycemia), and the frequency and timing of the "honeymoon" phase (defined as a total daily insulin dose $\leq$0.5 U/kg with A1c <7.0%) in newly diagnosed patients with T1DM over the first 12–24 months of the disease and examine the relationship between these clinical outcomes and:

- Age and gender
- Socioeconomic factors
- Clinical center
- Severity of metabolic decompensation at presentation (DKA vs. non-DKA)
- Inpatient versus outpatient treatment at diagnosis
- Insulin regimen utilized at onset and over time
- Time to switch to insulin pump therapy
- Number of self-monitoring of blood glucose tests per day

- Mean and SD of all glucose readings compared to fasting glucose readings
- Carbohydrate counting versus other dietary approaches
- Other

Visit data are entered into customized web-based electronic data collection forms. Data are maintained in a central, secure database at the Jaeb Center. The content of the forms was based on the information typically collected during office visits at the seven clinical centers. Details of the onset and diagnosis of type 1 diabetes are collected. During the course of the study, data are collected with respect to diabetes management, hypoglycemia, DKA, other medical conditions, medications, family history, socioeconomic status information, screening for other autoimmune diseases such as thyroid disease and celiac disease, and assessment for hyperlipidemia and microalbuminuria.

Discussion

The PDC was established in order to develop an independent group of centers comprising clinicians and clinical investigators who would collaborate together in clinical and translational research protocols. We hypothesized that such a group that was free of external encumbrances and whose primary concern was to promote better care of children and adolescents with diabetes would provide a novel and productive approach in developing studies with practical clinical relevance. Such a consortium would complement the research activities of the five-center National Institutes of Health-funded DirecNet, which has focused much of its attention on the application of continuous glucose monitoring in the treatment of children with T1DM.[6,7] An even larger European network of pediatric diabetes centers, called SWEET, has been established by grants from the European Union and industry and is working on standardizing guidelines for care of children diabetes in Europe (www.sweet-project.eu).

We anticipate that information gained from the PDC Clinical Outcomes in Newly Diagnosed T1DM Study described above will have a similar impact on the care of newly diagnosed T1DM, as the Hvidøre studies have had on the care of children and adolescents with established T1DM.[8,9] Moreover, the accomplishment of putting the Consortium together and developing and launching our first project in such a short time frame provides a proof of concept that the study group can work together rapidly and effectively.

While not included in the original proposal for support from Novo Nordisk, having a nonprofit freestanding coordinating center, like the Jaeb Center, serve as the primary contractor that coordinates the financial, administrative, and research aspects of the PDC has been crucial to our early success. A long-range goal of the coordinating center is to integrate PDC data collection with an electronic health record maintained by each clinical center and ultimately to have an electronic health record module for pediatric diabetes. The efficiencies of having a single point of contact for contracting purposes also has positive implications regarding potential collaborations with industry to promote future Phase 3 or 4 randomized clinical trials in pediatric diabetes and for seeking additional philanthropic support to build and sustain the Consortium. Clinical and basic scientists have expressed the need for a national database of patients with diabetes who wish to participate in clinical trials and/or contribute to a repository of biological samples, further underscoring the need to increase the number of centers in the PDC throughout the country in the future that would also provide a population of patients with racial and ethnic diversity that is representative of the United States as a whole.

Appendix

The following institutions and investigators constitute the PDC Research Group:

Coordinating Center

Jaeb Center for Health Research, Tampa, FL (R. Beck)

Clinical Centers

Barbara Davis Center, Aurora, CO (G. Klingensmith)
Baylor College of Medicine, Houston, TX (M. Haymond)
Childrens Hospital of Los Angeles, Los Angeles, CA (J. Wood)
Stanford University, Stanford, CA (B. Buckingham)
University of Florida, Miami, FL (D. Schatz and J. Silverstein)
University of Michigan, Ann Arbor, MI (J. Lee)
Yale University, New Haven, CT (E. Cengiz and W. Tamborlane)

Executive Committee

W. Tamborlane (Chair, Yale), G. Klingensmith (Co-Chair, Barbara Davis Center), and R. Beck (Director, Jaeb Center)

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Author Disclosure Statement

No competing financial interests related to the manuscript exist.

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