Joining Forces: A Call for Greater Collaboration to Study New Medicines in Children and Adolescents With Type 2 Diabetes

Janina Karres,[1] Valerie Pratt,[2] Jean-Marc Guettier,[2] Jean Temeck,[3] William V. Tamborlane,[4] David Dunger,[5] Cristina Bejnariu,[1] Carine De Beaufort,[6] and Paolo Tomasi[1]

Diabetes Care 2014;37:2665–2667 | DOI: 10.2337/dc14-0494

The number of individuals with type 2 diabetes (T2D) is increasing worldwide and is projected to rise further over the next decades (1). The prevalence of T2D diabetes in the pediatric population is also rising and in the U.S. one in three new cases of diabetes mellitus diagnosed in patients younger than 18 years of age is T2D (2,3). In contrast, the prevalence of T2D in the European pediatric population remains relatively low (4–7).

Diabetes complications in children and adolescents may be evident as early as 2 years after diagnosis (8). Data from the Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study suggest almost half of children and adolescents with T2D in the U.S. have suboptimal glycemic control after 4–5 years of treatment with metformin monotherapy (9) and that hypertension, dyslipidemia, and early microvascular complications (e.g., nephropathy and retinopathy) are highly prevalent in these patients (10–12). There is therefore a need to make additional safe and effective treatment options available to youths with T2D.

Therapeutic options to treat pediatric T2D in the U.S. are limited, as only 2 of the 12 classes of glucose-lowering agents with an approved adult T2D indication have a pediatric indication. The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) enforce legislation that requires pharmaceutical companies to define how they will establish the safety and efficacy of new therapeutic products for use in children and adolescents, age less than 18 years (13–15). Under current U.S. and European (EU) laws, new therapeutic products with the potential to benefit children are required to be studied unless a waiver is granted.

Although FDA and EMA pediatric processes differ, pharmaceutical companies use a single pediatric drug development program to satisfy both EU and U.S. statutory requirements. Pediatric clinical development plans for T2D usually include two major components: a pharmacokinetic and pharmacodynamic (PK/PD) study or substudy to support dosing and administration recommendations for each relevant pediatric subpopulation, and one confirmatory pivotal clinical trial designed to establish the product's safety and efficacy in children and adolescents (7,16). If sponsors perform and complete the agreed-upon pediatric program, they may be eligible to retain exclusive marketing control of the product for an additional 6-month period. In the U.S. and Europe, this incentive is independent of the outcome (i.e., success or failure) of the pivotal pediatric trial.

As of April 2014, agreements on pediatric development plans have been reached between the EMA and 11 companies for 17 products for the treatment of T2D (6 GLP-1 analogs, 5 dipeptidyl peptidase-4 inhibitors, 3 sodium-glucose cotransporter 2 inhibitors, 1 G-protein–coupled receptor 40 agonist, 1 glucagon receptor antagonist, and 1 dopamine agonist). Of these products, 8 are already marketed for use in adults in the EU. As of April 2014, 10 single entity products and 4 fixed-dose combination products approved for use in adults in the U.S. have a postmarketing requirement with FDA to evaluate efficacy and safety in pediatric patients with T2D.

In spite of the rising prevalence of T2D in children, most pivotal clinical pediatric trials that have been launched to date are finding it difficult to enroll pediatric patients with T2D, despite global recruitment efforts. The reasons

[1]*Paediatric Medicines, European Medicines Agency, London, U.K.*
[2]*Division of Metabolism and Endocrinology Products, U.S. Food and Drug Administration, Silver Spring, MD*
[3]*Office of Pediatric Therapeutics, U.S. Food and Drug Administration, Silver Spring, MD*
[4]*Center for Clinical Investigation, Yale School of Medicine, New Haven, CT*
[5]*Department of Paediatrics, University of Cambridge, Cambridge, U.K.*
[6]*Centre for Systems Biomedicine, University of Luxembourg, Esch-sur-Alzette, Luxembourg*

Corresponding author: Janina Karres, janina.karres@ema.europa.eu.

J.K. and V.P. contributed equally to the work.

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or the U.S. Food and Drug Administration or one of their committees or working parties.

for recruitment difficulties are multifactorial and potential reasons cited include the low number of children with T2D inadequately controlled on metformin (17), the fact that T2D disproportionally affects children difficult to recruit or unwilling to participate in clinical research studies (18) or who may lack access to trained pediatric endocrinologists (3), and the lack of an adequately developed pediatric clinical research infrastructure (19). Another complicating reason is an issue of timing. Many new drugs have been approved for T2D in adults in the last decade and companies compete for a limited number of available trial participants to fulfill pediatric requirements.

EMA estimates that up to 3,800 pediatric patients may be needed to conduct all of the individual studies agreed upon with EMA to date. This represents a large number of pediatric subjects given the low prevalence of the disease, especially in Europe. It appears possible, in light of current recruitment difficulties, that several of these treatment options will not become available for children and adolescents with T2D within the agreed timelines. The issue calls for innovative solutions to ensure timely availability of quality pediatric efficacy and safety data. Any solution to improving the efficiency of T2D pediatric drug development will require a collaborative effort on the part of stakeholders to optimize limited patient, infrastructure, and financial resources. Possible solutions to this problem that have been discussed in recent articles (20,21) and further possibilities are detailed in this article.

MULTIARM EFFICACY AND SAFETY STUDY IN PEDIATRIC SUBJECTS NOT OPTIMALLY CONTROLLED ON METFORMIN/INSULIN TREATMENT

The current paradigm to establish the efficacy and safety of new agents for the treatment of pediatric T2D is inefficient as each new agent is tested one by one in separate controlled clinical trials. The use of a multiarm trial was proposed as an attractive potential solution to the current problem. In such a paradigm, the efficacy and safety of multiple new agents (i.e., multiple arms) added to the standard of care (metformin alone, insulin alone, or both agents used in combination) would be evaluated against a shared control simultaneously in a single trial. A multiagent trial, sharing a single control arm, has the advantage of reducing the total pediatric patients required compared with a paradigm relying on individually run controlled trials (i.e., smaller sample size due to elimination of redundant control arms). If the control is placebo, a multiarm trial also has the added advantage of increasing the likelihood a patient will be randomized to an active agent, which may be more attractive to potential participants and facilitate recruitment efforts. Last but not least, efficiencies would be gained by the sharing of operational know-how and resources within and/or between companies as a single, established, clinical research infrastructure would be used to meet the needs of many.

The details of such a trial still need to be defined, but flexibility exists in how a multiarm trial would ultimately be structured and implemented. For example, the trial could be used to evaluate multiple products from the same pharmaceutical company or multiple products across different companies; similarly, a multiarm trial could be used to evaluate products within the same pharmaceutical class or across different classes depending on the need. As with current trials, efficacy would be assessed after at least 13, but preferably at 26, weeks of treatment, and safety data would be obtained based on 12 months of exposure to the agent. To satisfy regulatory requirements, the primary analysis in such a trial would be restricted to the comparison of the new agent to the control (i.e., currently placebo). The trial would not be designed, structured, or powered to compare efficacy between experimental agents because that is not the regulatory standard for a pediatric indication in either the U.S. or the EU.

Partial extrapolation of efficacy was proposed as a way to further reduce the number of patients needed in a multiagent pediatric study. EMA and the FDA have criteria that define when extrapolation of efficacy from adults to the pediatric population is appropriate (22,23). Generally, to permit extrapolation both the course of the disease and the drug's effects have to be sufficiently similar in the pediatric and adult populations.

While some obvious similarities exist between adult and pediatric T2D (i.e., basic pathophysiology of insulin resistance and progressive β-cell dysfunction), recent data related to disease complications suggest T2D course in the pediatric population may be more aggressive than in adults (10–12). Disease course difference is further supported by the observed higher than predicted failure rate of metformin therapy in children in the TODAY study and evidence from other failed T2D pediatric trials that were designed based on assumptions of PK/PD and disease similarities between adults and children (9,24).

These data raise questions regarding the usefulness of full extrapolation for pediatric T2D. However, partial extrapolation of efficacy can be used when uncertainty exists about the assumptions underlying full extrapolation. Partial extrapolation of efficacy can range from requiring a single adequate and well-controlled trial (i.e., as opposed to two, the regulatory standard for adults) to requiring only a PK/PD (exposure-response) study. In the latter, long-term efficacy would be predicted based on observed similarities in exposure-response between adult and pediatric patients using, most commonly, a short-term PD marker. Safety data would also need to be collected at the recommended dose(s) (22). Most if not all of the pediatric T2D programs agreed to date accept partial extrapolation of efficacy from adults by allowing a single pivotal trial in the pediatric population.

It remains to be determined whether the concept of partial extrapolation can be further extended to reduce the number of pediatric patients required in pediatric programs without compromising the adequacy of the pediatric efficacy assessment. This is mainly a clinical question, and the answer depends on the magnitude of the disease course difference between children and adults and on the ability to correctly identify the parameters that drive these differences for each product or product class. Certainly, if such partial extrapolation approaches are considered by applicants, the dialogue with regulatory agencies should start early in the planning of the pediatric studies.

DEVELOPING A T2D PEDIATRIC RESEARCH INFRASTRUCTURE

In concert with these novel approaches clinical research funding bodies, health care professionals and professional

societies will need to work together to develop a robust pediatric T2D clinical research infrastructure. Such efforts are already under way with the creation of the European Network of Pediatric Research at the EMA (Enpr-EMA) for diabetes and endocrinology (25) and with the expansion of the U.S. Pediatric Diabetes Consortium to include T2D (26) and should be encouraged. The aim of these consortia is to develop a large network of investigators and centers with pediatric T2D clinical research expertise across the EU and U.S. Funding bodies such as the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) through its Diabetes Working Group have also been involved in facilitating discussions among stakeholders to come up with innovative solutions, such as those described above, to tackle the problems facing pediatric T2D drug development.

SUMMARY

A collaborative effort will facilitate the collection of adequate and well-controlled pediatric efficacy and safety clinical trial data to inform pediatric use of new drugs to treat T2D. An approach relying on a multiarm trial is one particularly attractive approach that leverages efficiencies gained from use of a shared control group, with efficiencies gained from a shared research infrastructure. Success in pediatric drug development has often involved collaboration. Indeed, reliance on consortia-based approaches to evaluate novel therapies was successful for other relatively uncommon pediatric diseases (e.g., juvenile idiopathic arthritis and schizophrenia) and should be met with similar success in T2D.

Duality of Interest. W.V.T. is a consultant for Novo Nordisk, Sanofi, Janssen, Takeda, Bristol-Myers Squibb, and Boehringer Ingelheim. No other potential conflicts of interest relevant to this article were reported.

References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–1053
2. Dabelea D, Mayer-Davis EJ, Saydah S, et al.; SEARCH for Diabetes in Youth Study. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. JAMA 2014; 311:1778–1786
3. Springer SC, Silverstein J, Copeland K, et al.; American Academy of Pediatrics. Management of type 2 diabetes mellitus in children and adolescents. Pediatrics 2013;131:e648–e664
4. Ortega-Rodriguez E, Levy-Marchal C, Tubiana N, Czernichow P, Polak M. Emergence of type 2 diabetes in an hospital based cohort of children with diabetes mellitus. Diabetes Metab 2001;27:574–578
5. Feltbower RG, McKinney PA, Campbell FM, Stephenson CR, Bodansky HJ. Type 2 and other forms of diabetes in 0-30 year olds: a hospital based study in Leeds, UK. Arch Dis Child 2003; 88:676–679
6. Schober E, Waldhoer T, Rami B, Hofer S; Austrian Diabetes Incidence Study Group. Incidence and time trend of type 1 and type 2 diabetes in Austrian children 1999–2007. J Pediatr 2009; 155:190–193.e1
7. European Medicines Agency. European Medicines Agency (EMA) Report of the Paediatric Workshop on Paediatric Investigation Plans (PIP) in type 2 diabetes mellitus, 2013. Available from http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2013/01/event_detail_000695.jsp&mid=WC0b01ac058004d5c3. Accessed 1 February 2014
8. Copeland KC, Zeitler P, Geffner M, et al.; TODAY Study Group. Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline. J Clin Endocrinol Metab 2011;96:159–167
9. Zeitler P, Hirst K, Pyle L, et al.; TODAY Study Group. A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med 2012;366:2247–2256
10. TODAY Study Group. Rapid rise in hypertension and nephropathy in youth with type 2 diabetes: the TODAY clinical trial. Diabetes Care 2013;36:1735–1741
11. TODAY Study Group. Lipid and inflammatory cardiovascular risk worsens over 3 years in youth with type 2 diabetes: the TODAY clinical trial. Diabetes Care 2013;36:1758–1764
12. TODAY Study Group. Retinopathy in youth with type 2 diabetes participating in the TODAY clinical trial. Diabetes Care 2013;36: 1772–1774
13. *Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on Medicinal Products for Paediatric Use and Amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004*. Official Journal of the European Union, 2006, p. L 378/1
14. *Regulation (EC) No 1902/2006, of the European Parliament and of the Council of 20 December 2006 Amending Regulation 1901/2006 on Medicinal Products for Paediatric Use*. Official Journal of the European Union, 2006, p. L 378/20
15. U.S. Congress. Pediatric Research Equity Act of 2003. Available from www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077853.pdf. Accessed 26 March 2012
16. European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus, 2012. Available from www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129256.pdf. Accessed 1 February 2014
17. Nguyen TT, Jayadeva V, Cizza G, et al. Challenging recruitment of youth with type 2 diabetes into clinical trials. J Adolesc Health 2014;54: 247–254
18. Ortiz B, Guerrero S. Recruitment and Retention of Minority Populations in Clinical Trials. In *Pediatric Drug Development: Concepts and Applications*. Mulberg AE, Murphy D, Dunne J, Mathis LL, Eds. Chichester, U.K., John Wiley & Sons Ltd., 2013
19. Connor EM, Smoyer WE, Davis JM, et al. Meeting the demand for pediatric clinical trials. Sci Transl Med 2014;6:227fs11
20. Karres J, Tomasi P. New medicines for type 2 diabetes in adolescents: many products, few patients. Expert Rev Clin Pharmacol 2013;6: 227–229
21. Tamborlane WV, Klingensmith G. Crisis in care: limited treatment options for type 2 diabetes in adolescents and youth. Diabetes Care 2013;36:1777–1778
22. Dunne J, Rodriguez WJ, Murphy MD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. Pediatrics 2011;128:e1242–e1249
23. European Medicines Agency. Concept paper on extrapolation of efficacy and safety in medicine development, 2012. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC509285.pdf. Accessed 1 February 2014
24. Vaidyanathan J, Choe S, Sahajwalla CG. Type 2 diabetes in pediatrics and adults: thoughts from a clinical pharmacology perspective. J Pharm Sci 2012;101:1659–1671
25. European Medicines Agency. The European Network of Paediatric Research at the European Medicines Agency. Available from http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000303.jsp&mid=WC0b01ac05801df74a. Accessed 1 February 2014
26. Pediatric Diabetes Consortium. The Pediatric Diabetes Consortium: improving care of children with type 1 diabetes through collaborative research. Diabetes Technol Ther 2010;12:685–688