Effectiveness of Early Intensive Therapy on β-Cell Preservation in Type 1 Diabetes

Bruce Buckingham, MD[1]
Roy W. Beck, MD, PHD[2]
Katrina J. Ruedy, MSPH[2]
Peiyao Cheng, MPH[2]
Craig Kollman, PHD[2]
Stuart A. Weinzimer, MD[3]
Linda A. DiMeglio, MD, MPH[4]
Andrew A. Bremer, MD, PHD[5]
Robert Slover, MD[6]
William V. Tamborlane, MD[3]
Diabetes Research in Children Network (DirecNet) and Type 1 Diabetes TrialNet Study Groups*

OBJECTIVE—To assess effectiveness of inpatient hybrid closed-loop control (HCLC) followed by outpatient sensor-augmented pump (SAP) therapy initiated within 7 days of diagnosis of type 1 diabetes on the preservation of β-cell function at 1 year.

RESEARCH DESIGN AND METHODS—Sixty-eight individuals (mean age 13.3 ± 5.7 years; 35% female, 92% Caucasian) were randomized to HCLC followed by SAP therapy (intensive group; $N = 48$) or to the usual-care group treated with multiple daily injections or insulin pump therapy ($N = 20$). Primary outcome was C-peptide concentrations during mixed-meal tolerance tests at 12 months.

RESULTS—Intensive-group participants initiated HCLC a median of 6 days after diagnosis for a median duration of 71.3 h, during which median participant mean glucose concentration was 140 mg/dL (interquartile range 134–153 mg/dL). During outpatient SAP, continuous glucose monitor (CGM) use decreased over time, and at 12 months, only 33% of intensive participants averaged sensor use ≥6 days/week. In the usual-care group, insulin pump and CGM use were initiated prior to 12 months by 15 and 5 participants, respectively. Mean HbA_{1c} levels were similar in both groups throughout the study. At 12 months, the geometric mean (95% CI) of C-peptide area under the curve was 0.43 (0.34–0.52) pmol/mL in the intensive group and 0.52 (0.32–0.75) pmol/mL in the usual-care group ($P = 0.49$). Thirty-seven (79%) intensive and 16 (80%) usual-care participants had a peak C-peptide concentration ≥0.2 pmol/mL ($P = 0.30$).

CONCLUSIONS—In new-onset type 1 diabetes, HCLC followed by SAP therapy did not provide benefit in preserving β-cell function compared with current standards of care.

Diabetes Care 36:4030–4035, 2013

Retention of islet cell function in patients with type 1 diabetes has been associated with lower HbA_{1c} levels and reductions in short- and long-term complications (1,2). Several therapeutic approaches have been tried to preserve residual β-cell function in such patients. One approach, based on animal and human studies, is to optimize glycemic control as soon as possible after diagnosis. In vitro, resting β-cells are less immunogenic and more resistant to autoimmune damage than active β-cells (3). Tight metabolic control at the onset of type 1 diabetes can protect against insulitis in the BB rat (4–6) and insulin therapy in the NOD mouse has immunologic and metabolic effects (7). In humans, β-cell rest induced by closed-loop therapy shortly after the diagnosis of type 1 diabetes was reported to preserve β-cell function as assessed by C-peptide levels 1 year after diagnosis (8). The Diabetes Control and Complications Trial found that assignment to the well-controlled, intensively managed group slowed the rate of decline of stimulated C-peptide levels compared with that in the poorly controlled, conventionally treated group even when intensive metabolic control was initiated between 1 and 5 years after diagnosis (2).

With current technology, it may be possible to optimize glycemic control quickly after diagnosis with in-patient closed-loop control followed by home use of sensor-augmented pump (SAP) therapy. To test the hypothesis that use of advanced diabetes technologies within 7 days of onset of type 1 diabetes can preserve endogenous insulin production to a greater extent than current standard care of new-onset type 1 diabetes, we conducted a randomized trial comparing hybrid closed-loop control (HCLC) followed by home use of SAP therapy versus conventional management; the primary outcome was stimulated C-peptide levels 1 year after diagnosis.

RESEARCH DESIGN AND METHODS

—The study protocol, listed on www.clinicaltrials.gov (NCT00760526), was approved by institutional review boards at the five clinical centers. Written informed consent was obtained from adult patients and parents/guardians of minor patients, who themselves also provided written assent. Major eligibility criteria included age 6 to <46 years, clinical diagnosis of type 1 diabetes, and initiation of insulin therapy within the prior 7 days. Eligible participants were randomized to the intensive group or usual-care group in a 2:1 ratio, stratified by clinical center and the presence of diabetic ketoacidosis (DKA) (9). GAD, islet-cell antigen-512, insulin, and zinc transporter 8 antibodies were measured at baseline, and if these were negative islet cell antibodies, they

From [1]Pediatric Endocrinology, Stanford University, Stanford, California; the [2]Jaeb Center for Health Research, Tampa, Florida; [3]Pediatric Endocrinology, Yale University, New Haven, Connecticut; the [4]Department of Pediatrics, Section of Pediatric Endocrinology/Diabetology, Indiana University, Riley Hospital for Children, Indianapolis, Indiana; the [5]Division of Pediatric Endocrinology, Vanderbilt University Medical Center, Nashville, Tennessee; and [6]Pediatrics, Barbara Davis Center for Childhood Diabetes, University of Colorado School of Medicine, Aurora, Colorado.
Corresponding author: Katrina J. Ruedy, direcnet@jaeb.org.
Received 6 May 2013 and accepted 24 July 2013.
DOI: 10.2337/dc13-1074. Clinical trial reg. no. NCT00760526, clinicaltrials.gov.
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc13-1074/-/DC1.
A slide set summarizing this article is available online.
*A complete list of the writing committee and members of the Diabetes Research in Children Network (DirecNet) and Type 1 Diabetes TrialNet Study Groups can be found in the Supplementary Data online.

were measured by indirect immunofluorescence at the core TrialNet laboratories (Universities of Colorado and Florida, respectively). Since autoantibody results were not available at the time of randomization, it was decided a priori that only participants who were antibody-positive would be included in the primary analysis.

Intensive-treatment group

The intensive group received HCLC using the Medtronic MiniMed system (Medtronic) (10,11) as inpatients with a goal of achieving at least 72 h of HCLC, with a maximum of 96 h. The system consists of a subcutaneous glucose sensor and insulin pump which communicate wirelessly with a bedside computer running a proportional-integral-derivative algorithm. The proportional-integral-derivative algorithm has been previously described (10–12) but was modified to incorporate insulin feedback (13–15). The glucose set point was 110 to 120 mg/dL. Up to 20 min prior to each meal and snack, carbohydrates were counted, and a premeal bolus was given to cover ~75–80% of the meal based on the participant's carbohydrate-to-insulin ratio. Participants could choose their meals and snacks. The full details and results of this therapy have been previously published (16).

During the hospitalization, intensive group participants were instructed on use of the Medtronic MiniMed Paradigm or Revel insulin pump, MiniLink transmitter, and Sof-sensor continuous glucose monitor (CGM) (all from Medtronic MiniMed, Inc.) to be used as an outpatient following discharge. Glucose meters and strips were provided to both treatment groups. Following hospitalization, intensively treated participants were expected to use the pump and CGM daily. CGM data were reviewed by clinical staff at 1, 2, 4, 6, and 8 weeks and then monthly, with additional data reviews as needed and treatment adjusted according to Diabetes Research in Children Network (DirecNet) study group guidelines (17).

Usual-care group

Participants in the usual-care group received standard diabetes management as practiced at the participating diabetes treatment centers, including frequent telephone contacts to adjust the treatment regimen following discharge from the hospital by clinicians not involved in the management of participants in the intensive-treatment group. As in the intensive group, standard-care patients were seen as outpatients 2, 6, and 13 weeks after diagnosis and every 3 months thereafter. The aim of therapy was to achieve HbA_{1c} and blood glucose levels as close to normal as possible. There was no prohibition on use of an insulin pump or CGM if the physician believed that either or both would benefit from the participant's diabetes management.

Study procedures

Both groups had a 90-min mixed-meal tolerance test (MMTT) at baseline once DKA, if present, was resolved; 2-h MMTTs were performed at 2 and 6 weeks and at 3, 6, 9, and 12 months. HbA_{1c} was measured at 3, 6, 9, and 12 months at a central laboratory. HbA_{1c} was also measured locally at 6 weeks and at 3, 6, 9, and 12 months. For the intensive-treatment group, the CGM, insulin pump, and home glucose meter were downloaded at each visit. For the usual-care group, glucose meters were downloaded at each visit, and a blinded Medtronic Guardian CGM (Medtronic MiniMed, Inc.) was worn for 3 days after each visit. Investigators were masked to the MMTT results.

Statistical methods

Primary outcome measure was the area under the stimulated C-peptide curve (AUC) of the 12-month MMTT. AUC was computed using a trapezoidal rule, which is a weighted sum of the C-peptide values over the 120 min. Sample size was computed for the number of antibody-positive participants required for the study. Log(mean C-peptide + 1) and root mean square error in the standard-treatment group were assumed to be 0.315 and 0.167, respectively, based on 90% CIs from prior studies (18). The corresponding geometric-like mean C-peptide value of 0.370 pmol/mL was calculated using the inverse transformation exponential (0.315) − 1. The expected geometric-like mean C-peptide value in the treatment arm was 0.370 * 1.50 = 0.555 pmol/mL. With these estimates, a sample size of 63 was calculated to provide 85% power with a 5% one-sided type 1 error rate and a 2:1 treatment group allocation to detect a treatment group difference assuming the true relative difference between groups was 50%. Sample size was increased to 72 to account for antibody-negative individuals who would not be included in the primary analysis, incomplete follow-up, and anticipated noncompliance with the treatment regimen in the intensive group.

The primary analysis compared the difference between groups in the 2-h C-peptide using the log(AUC+1) transform in an ANCOVA model adjusting for sex, age, and baseline log(AUC+1) (19). Results are presented as the geometric-like mean, which was taken as the inverse transform noted above ($x = \exp(y) - 1$) of the mean $y = \log(x + 1)$ transformed C-peptide values and their corresponding confidence limits (18). This was done for both AUC and peak C-peptide. One participant without 12-month MMTT data was not included in the primary analysis.

For tabulating CGM usage from sensor downloads, CGM was considered to be used when there was at least one sensor glucose value for the day. CGM indices (mean glucose, percent readings in target range, percent readings in hypoglycemic range, and coefficient of variation) were calculated giving equal weight to each of the 24 h of the day (20). At least 24 h of CGM data were required for calculating CGM indices. SAS 9.3 (SAS Institute) was used for analyses.

RESULTS—Between May 2009 and October 2011, the trial enrolled 71 individuals with type 1 diabetes; 68 had positive autoantibodies and were included in the primary analysis, with 48 assigned to the intensive group and 20 to the usual-care group. Analyzed participants ranged in age from 7.8 to 45.7 years, with all but three <18 years old; 65% were male and 92% were white. For 72%, highest parental education was Bachelor's degree or higher (Supplementary Table 1). DKA was present at diagnosis in 20 (29%) participants. Enrollment occurred within 6 days of diagnosis in all participants (mean 2.9 ± 1.6 days).

Visit completion

The 12-month primary outcome visit was completed by all 68 participants (1 in the intensive group did not complete the MMTT). Visit completion for the six protocol-specified follow-up visits was 100% in the intensive group and 89% in the usual-care group (Supplementary Fig. 1).

Intensive-treatment group

HCLC was initiated 2–7 days after diagnosis of type 1 diabetes (mean 5.7 ± 1.2 days). Median duration of HCLC therapy was 71.3 h (interquartile range [IQR] 70.3–72.1 h; range 29.9–93.2 h). On

initiation of HCLC, the mean glucose concentration was 240 ± 100 mg/dL. During the first day of HCLC, the median participant mean glucose concentration fell rapidly to 146 mg/dL (IQR 135–166) and was 138 and 139 mg/dL on days 2 and 3, respectively. By day 3, the median percentage of glucose values >250 mg/dL and median percentage of glucose values <60 mg/dL were <1%. During the first 2 weeks of insulin pump and CGM use at home, the median participant mean sensor glucose level was 126 mg/dL (IQR 117–137), and the median percentage of values between 71 and 180 mg/dL was 85% (IQR 80–90%).

All but one participant in the intensive group used the insulin pump throughout the 12 months. Use of CGM gradually decreased over the 12 months (Supplementary Fig. 2), with 6 of 48 participants discontinuing CGM altogether before 12 months. At 12 months, median CGM hours per week were 76 (IQR 24–120), with 33% of participants averaging ≥6 days per week and 50% averaging ≥5 days per week.

Usual-care group

In the usual-care group, prior to 12 months, 15 of the 20 participants initiated insulin pump use, primarily after 6 months. Five used real-time CGM, although only two were still using CGM at 12 months.

C-peptide results

In the primary analysis of the 12-month MMTT results, the geometric mean (95% CI) of C-peptide AUC was 0.43 (0.34–0.52) pmol/mL in the intensive-treatment group and 0.52 (0.32–0.75) pmol/mL in the usual-care group (P = 0.49; Table 1 and Fig. 1). Geometric means of peak C-peptide concentrations were 0.53 (0.42–0.65) and 0.65 (0.40–0.95) pmol/dL, respectively; peak C-peptide concentrations were ≥0.2 pmol/dL in 37 (79%) and 16 (80%) in the intensive and usual-care groups, respectively. As seen in Fig. 1 and Supplementary Table 2, C-peptide results were similar between the two groups at all time points. A per-protocol analysis limited to the 22 participants in the intensive group using CGM at least 5 days/week and the 15 participants in the standard treatment group not using CGM at 12 months produced results similar to the intent-to-treat primary analysis, as did subgroup analyses based on participant characteristics (Supplementary Table 3).

Other results

HbA_{1c} levels were similar in both treatment groups throughout the study, reaching nadir values <6.5% (<48 mmol/mol) at 3 months and increasing gradually thereafter (Fig. 2 and Supplementary Table 2). At 12 months, the mean HbA_{1c} was 7.4 ± 1.2% (57 ± 13 mmol/mol) in the intensive group and 7.3 ± 1.1% (57 ± 12 mmol/mol) in the usual-care group (P = 0.40). CGM-measured glucose indices were also similar in the two groups (Table 1, Supplementary Table 2, and Supplementary Fig. 3), as was mean total daily insulin doses (Fig. 3). Median BMI percentile at 12 months was 58 (IQR 39–81) in the intensive-treatment group and 62 (IQR 40–72) in the usual-care group.

Adverse events

Severe hypoglycemia, defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions due to altered consciousness, occurred in one participant (two events, at 6 months while CGM was being used and 12 months after CGM had been discontinued) in the intensive group and in no participants in the usual-care group. There were no cases of DKA. During inpatient HCLC therapy, one subject had an anaphylactic reaction following his first dinner, presumably resulting from a peanut allergy, and received intravenous steroids. There were two cases of venous thrombosis related to the intravenous line that resolved without consequence. During follow-up, in the intensive group, one participant fainted following the 3-month MMTT, one had a skin infection related to the CGM sensor insertion, and one with a prior history of depression developed suicidal ideation. In the usual-care group, one participant was hospitalized for gastroenteritis and two developed depression and anxiety.

Table 1—*Outcome data at 12 months*

	Intensive	Standard
n	47	20
C-peptide AUC (pmol/mL), geometric mean (95% CI)[a]	0.43 (0.34–0.52)	0.52 (0.32–0.75)
	N = 48	*N* = 20
HbA_{1c} (%)[b], mean ± SD	7.4 ± 1.2	7.3 ± 1.1
HbA_{1c} (mmol/mol), mean ± SD	57 ± 13	57 ± 12
CGM data median	*N* = 31	*N* = 15
Mean glucose (mg/dL)	150	152
71–180	69%	70%
<70	2.5%	0.7%
>180	27%	22%
CV (%)	35	35
	N = 48	*N* = 20
TDI (units/kg/day)	0.6 ± 0.2	0.6 ± 0.3
	N = 46	*N* = 19
BMI percentile[c]	58	62

CV, coefficient of variation (SD/mean, expressed as a percentage); TDI, total daily insulin. [a]Geometric mean (95% CI) calculated from an inverse transformation as described in RESEARCH DESIGN AND METHODS. [b]HbA_{1c} not measured at 2 weeks. The 6-week value is based on a local HbA_{1c} measurement; other times are central laboratory results. [c]BMI percentile was calculated for subjects <18 years of age based on 2000 Centers for Disease Control and Prevention pediatric growth chart data (29) and adjusted for age and sex. Three participants ≥18 years old were excluded: two were in the intensive group (one with BMI 24.9 kg/m^2 and one with BMI 18.8 kg/m^2), and one was in the control group (BMI 25.7 kg/m^2).

CONCLUSIONS—This study was undertaken to test the hypothesis that using advanced diabetes technologies to achieve tight glycemic control shortly after the diagnosis of type 1 diabetes would be beneficial in preserving β-cell function compared with current standards of care of new-onset type 1 diabetes as currently practiced at pediatric and adult diabetes treatment centers. The most important finding of the study was that the intensively treated participants who were randomized within the first week of diagnosis of type 1 diabetes to inpatient HCLC followed by outpatient SAP therapy did not have higher C-peptide levels at any time in the study when compared with a usual-care control group, even 2 weeks following closed-loop control. In evaluating the results, it is important to recognize that although the eligibility

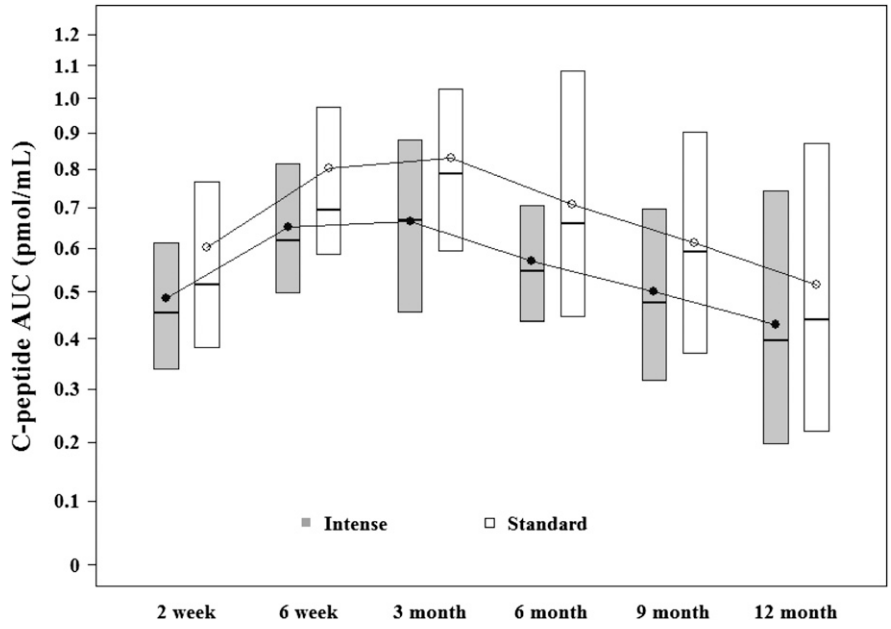

Figure 1—*Box plots for 2-h stimulated C-peptide AUC at each follow-up visit. The bottom and top of each box denote the 25th and 75th percentiles, respectively; the line inside the box denotes the median, and the dot is the geometric mean. The vertical axis is on a log(x + 1) scale.*

age range was 6 to <46 years old, all but three of the participants were <18 years old, and participants' parents were generally well-educated. The sample size was too small for a meaningful assessment as to whether there was suggestion of benefit in any subgroup.

Our inability to demonstrate any differences in C-peptide preservation between the two groups may be related to the similar achievement of good glycemic control in both groups over the course of the 12 months, with the few days of HCLC shortly after the diagnosis of type 1 diabetes not producing an additive effect. It is important to note that patients in the usual-care group also sought to achieve and maintain optimal control of diabetes and that insulin pump and CGM use were not prohibited in this group if the physician and patient/parent decided on that course of management. Indeed, in the control group, 75% were using an insulin pump by 12 months, and 33% used CGM during the 12 months. In the intensive group, CGM use progressively decreased as the study progressed, and by 12 months, only 33% of the intensive group was using CGM ≥6 days per week. Thus, it is not surprising that the intensive group participants did not achieve any better glycemic control than the standard-care group as measured by HbA_{1c} or CGM-measured glucose indices.

It is noteworthy that C-peptide results in both groups appeared similar to control group data from prior TrialNet trials (21) as seen in Supplementary Fig. 4. These data suggest that the lack of a treatment group effect was not due to the control group in this study having better than expected C-peptide results. Our results are similar to the results seen in the Onset study, which also did not find a difference in HbA_{1c} or C-peptide levels after 1 year. In the Onset study, SAP therapy was compared with pump therapy alone in children and adolescents enrolled within 4 weeks from diagnosis of diabetes (22). As in our study, both groups similarly achieved good glycemic control, and there was no difference in C-peptide levels between groups after 1 year. Other previously reported smaller randomized trials of intensive insulin therapy at the onset of diabetes also did not show an improvement in C-peptide levels at 1 year (23–28).

Although HCLC therapy in the intensive group was successful in quickly overcoming initial hyperglycemia, it did not achieve the same level of glucose control within the first 2 weeks that was achieved in the study of Shah et al. (8), in which intravenous insulin was delivered using the Biostator for 2 weeks. We arbitrarily selected 3 days of hospitalization for closed-loop control rather than the 2 weeks as was previously done by Shah et al. (8), because we wanted to evaluate a therapy that could be practically implemented if we were successful. In the study by Shah et al. (8), the Biostator used blood (instead of subcutaneous) glucose measurements and intravenous (instead of subcutaneous) insulin, allowing them to have their subjects at a target glucose of 60–80 mg/dL (8), a target too low for us to safely achieve with current subcutaneous closed-loop therapy. Thus,

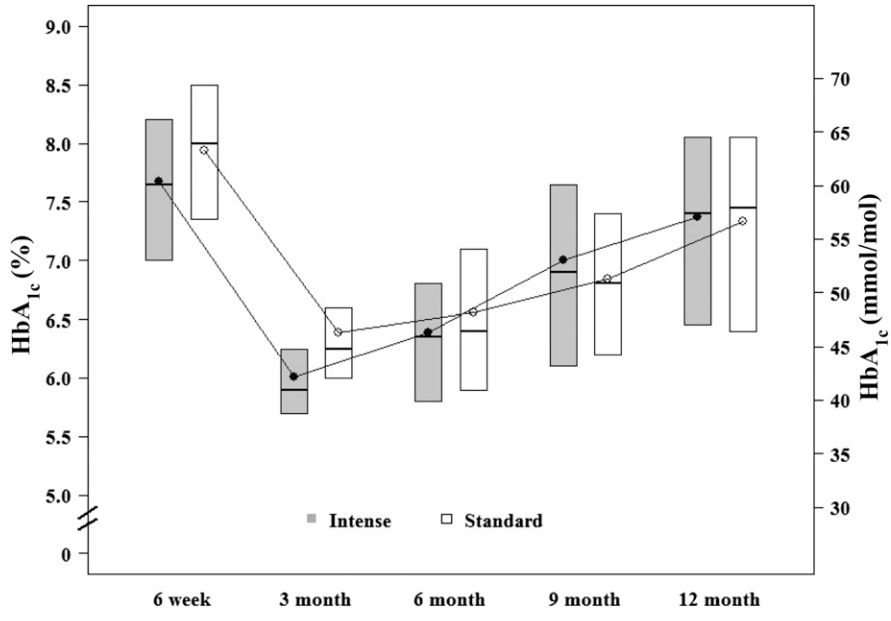

Figure 2—*HbA_{1c} results. The bottom and top of each box denote the 25th and 75th percentiles, respectively; the line inside the box denotes the median, and the dot is the mean. The 6-week value is a local HbA_{1c} measurement; others are from the central laboratory.*

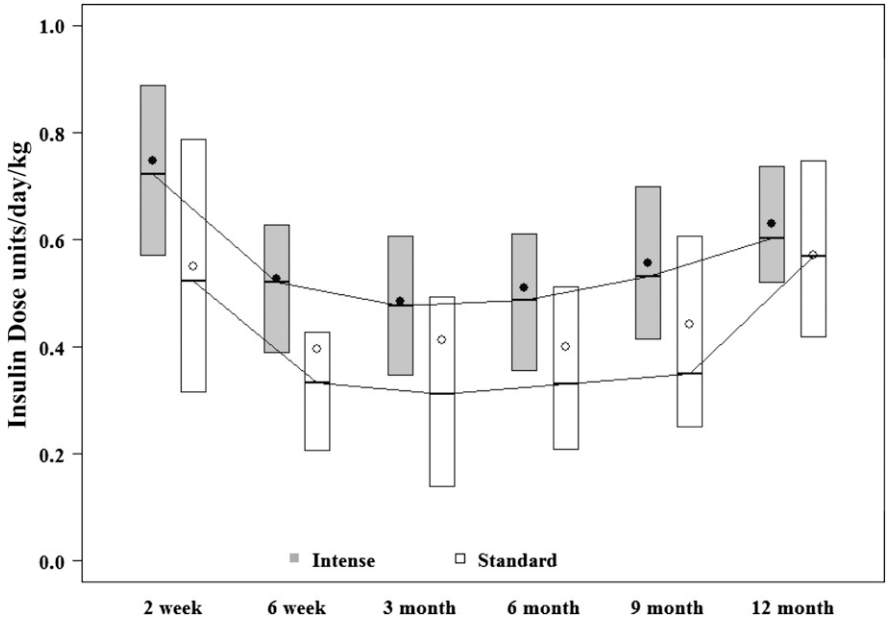

Figure 3—*Insulin doses at each follow-up visit. The bottom and top of each box denote the 25th and 75th percentiles, respectively; the line inside the box denotes the median, and the dot is the mean.*

it is possible that stricter glycemic control and/or longer duration of intensive therapy at diagnosis would show differences in preservation of C-peptide, but such a degree of glycemic control is not feasible with the technology used in this study. In addition, advances in insulin therapy and glucose monitoring since the time of the Shah et al. (8) study have made it much more difficult to achieve a separation in glycemic control between intensively treated and usual-care groups. Therefore, our study results do not necessarily refute the hypothesis that optimized glucose control from the time of diagnosis of type 1 diabetes can protect against β-cell destruction.

In summary, we did not find a benefit of HCLC therapy followed by SAP therapy in preserving β-cell function when initiated soon after the diagnosis of type 1 diabetes.

Acknowledgments—This research was supported by National Institutes of Health (NIH)/Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) grants for the Diabetes Research in Children Network (DirecNet) Study Group: HD-41890-10, HD-41906-10, and HD-41908-10 and by grants for the Type 1 Diabetes TrialNet Study Group: U01-DK-085509, U01-DK-06104211, 5U01-DK-085466-05, U01-DK-085505-02, and 5U01-DK-085465-04. Type 1 Diabetes TrialNet is a clinical trials network funded by the NIH through the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Allergy and Infectious Diseases, the NICHD, the National Center for Research Resources (NCRR), the Juvenile Diabetes Research Foundation International, and the American Diabetes Association. This research was supported in part by the Barbara Davis Center for Childhood Diabetes, the University of Colorado School of Medicine: CTRC grant number 1UL1 RR025780; the Division of Pediatric Endocrinology and Diabetes, Stanford University: Clinical and Translational Science Award SUL1 RR025744 for the Stanford Center for Clinical and Translational Education and Research (Spectrum) from the NCRR, NIH; the Department of Pediatrics, Yale University School of Medicine: grant UL1-RR-024139 from the NCRR, a component of the NIH, and the NIH Roadmap for Medical Research (the contents are solely the responsibility of the authors and do not necessarily represent the official view of the NCRR or NIH, and information on Re-engineering the Clinical Research Enterprise can be obtained from http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp); the Department of Pediatrics, Indiana University School of Medicine: Indiana Clinical and Translational Sciences Institute, CTSA grant UL1-RR-25761 from the NCRR, NIH; and the Division of Pediatric Endocrinology, Vanderbilt University Medical Center: CTSA grant UL1TR000445 from the National Center for Advancing Translational Sciences (the contents are solely the responsibility of the authors and do not necessarily represent official views of the National Center for Advancing Translational Sciences or the NIH).

B.B. received payment from Sanofi, Glysense, and Roche for serving on Medical Advisory Boards, consulted for BD Biosciences, received payment for a lecture (symposium at European Association for the Study of Diabetes) from DexCom, received payment from Medtronic for serving on the Data and Safety Monitoring Board for Sensor-Augmented Pump Therapy for A1C Reduction trial, and received institutional payment from Medtronic for other principal investigator–initiated studies and sponsored research. C.K. has consulted with Diabetes Technology Management. S.A.W. consulted for Johnson & Johnson and BD Biosciences and received payment for lectures including service on speaker bureaus from Eli Lilly, stock/stock options from Insuline Medical, and in-kind support for research from Medtronic. L.A.D. reports payment to her institution from Medtronic for an investigator-initiated grant. A.A.B. consults for the American Humane Society on projects regarding animal-assisted therapy for pediatric patients and has received payment for lectures from Pfizer. R.S. serves on the medical advisory board for Medtronic. W.V.T. works as a consultant for Medtronic Diabetes, LifeScan/Animas, Novo Nordisk, and UnoMedical. Medtronic MiniMed, Inc. (Northridge, CA) loaned the insulin pumps and provided the reservoirs and infusion sets for the pumps at a discounted cost. The company also provided technical support on using the Control Tool software, and Martin Cantwell from the company trained the staff at each clinical center on how to use this system. Medtronic MiniMed, Inc. also provided the MiniLink transmitters and UltraLink meters at no cost and provided the Sof-sensors at a discounted cost. This research was conducted with support from the Investigator-Initiated Study Program of LifeScan, Inc. (Milpitas, CA), and they provided the One Touch Ultra2 meters, test strips, and control solution at no cost. No other potential conflicts of interest relevant to this article were reported.

B.B., R.W.B., K.J.R., and W.V.T. researched data, contributed to discussion, wrote the manuscript, and reviewed and edited the manuscript. P.C. researched data and reviewed and edited the manuscript. C.K., S.A.W., L.A.D., A.A.B., and R.S. researched data, contributed to discussion, and reviewed and edited the manuscript. R.W.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The manuscript was reviewed and approved by the Steering Committee for the study and the TrialNet Publications Committee.

Data from this study were presented at the 6th International Conference on Advanced Technologies & Treatments for Diabetes, Paris, France, 27 February–2 March 2013.

The authors thank the families who made a decision to participate in this study, a decision that was made within days of diagnosis, at a time of significant stress.

References

1. Steffes MW, Sibley S, Jackson M, Thomas W. β-cell function and the development of diabetes-related complications in the diabetes control and complications trial. Diabetes Care 2003;26:832–836
2. The Diabetes Control and Complications Trial Research Group. Effect of intensive therapy on residual β-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. Ann Intern Med 1998;128:517–523
3. Mirouze J, Selam JL, Pham TC, Mendoza E, Orsetti A. Sustained insulin-induced remissions of juvenile diabetes by means of an external artificial pancreas. Diabetologia 1978;14:223–227
4. Like A. Insulin injections prevent diabetes (DB) in biobreeding/worcester (BB/Wor) rats. Diabetes 1986;35:74A
5. Appel MC, O'Neil JJ. Prevention of spontaneous diabetes in the bb/w rat by insulin treatment. Pancreas 1986;1:356–368
6. Gotfredsen CF, Buschard K, Frandsen EK. Reduction of diabetes incidence of BB Wistar rats by early prophylactic insulin treatment of diabetes-prone animals. Diabetologia 1985;28:933–935
7. Bowman MA, Campbell L, Darrow BL, Ellis TM, Suresh A, Atkinson MA. Immunological and metabolic effects of prophylactic insulin therapy in the NOD-scid/scid adoptive transfer model of IDDM. Diabetes 1996;45:205–208
8. Shah SC, Malone JI, Simpson NE. A randomized trial of intensive insulin therapy in newly diagnosed insulin-dependent diabetes mellitus. N Engl J Med 1989;320:550–554
9. The DCCT Research Group. The Diabetes Control and Complications Trial (DCCT). Design and methodologic considerations for the feasibility phase. Diabetes 1986;35:530–545
10. Weinzimer SA, Steil GM, Swan KL, Dziura J, Kurtz N, Tamborlane WV. Fully automated closed-loop insulin delivery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. Diabetes Care 2008;31:934–939
11. Steil GM, Rebrin K, Darwin C, Hariri F, Saad MF. Feasibility of automating insulin delivery for the treatment of type 1 diabetes. Diabetes 2006;55:3344–3350
12. Steil GM, Panteleon AE, Rebrin K. Closed-loop insulin delivery-the path to physiological glucose control. Adv Drug Deliv Rev 2004;56:125–144
13. Ruiz JL, Sherr JL, Cengiz E, et al. Effect of insulin feedback on closed-loop glucose control: a crossover study. J Diabetes Sci Tech 2012;6:1123–1130
14. Steil GM, Palerm CC, Kurtz N, et al. The effect of insulin feedback on closed loop glucose control. J Clin Endocrinol Metab 2011;96:1402–1408
15. Loutseiko M, Voskanyan G, Keenan DB, Steil GM. Closed-loop insulin delivery utilizing pole placement to compensate for delays in subcutaneous insulin delivery. J Diabetes Sci Tech 2011;5:1342–1351
16. Buckingham BA, Beck RW, Ruedy KJ, et al.; Diabetes Research in Children Network (DirecNet) Study Group; Type 1 Diabetes TrialNet Study Group. The effects of inpatient hybrid closed-loop therapy initiated within 1 week of type 1 diabetes diagnosis. Diabetes Technol Ther 2013;15:401–408
17. Buckingham B, Xing D, Weinzimer S, et al.; Diabetes Research In Children Network (DirecNet) Study Group. Use of the DirecNet Applied Treatment Algorithm (DATA) for diabetes management with a real-time continuous glucose monitor (the FreeStyle Navigator). Pediatr Diabetes 2008;9:142–147
18. Palmer J, Fleming G, Greenbaum C, et al. C-peptide Is the appropriate outcome measure for type 1 diabetes clinical trials to preserve β-cell function [published correction appears in Diabetes 2004;53:1934]. Diabetes 2004;53:250-264
19. Lachin JM, McGee PL, Greenbaum CJ, et al.; Type 1 Diabetes Trial Network. Sample size requirements for studies of treatment effects on beta-cell function in newly diagnosed type 1 diabetes. PLoS ONE 2011;6:e26471
20. Buckingham B, Beck RW, Tamborlane WV, et al.; Diabetes Research in Children Network (DirecNet) Study Group. Continuous glucose monitoring in children with type 1 diabetes. J Pediatr 2007;151:388–393, e1–e2
21. Greenbaum CJ, Beam CA, Boulware D, et al.; Type 1 Diabetes TrialNet Study Group. Fall in C-peptide during first 2 years from diagnosis: evidence of at least two distinct phases from composite Type 1 Diabetes TrialNet data. Diabetes 2012;61:2066–2073
22. Kordonouri O, Pankowska E, Rami B, et al. Sensor-augmented pump therapy from the diagnosis of childhood type 1 diabetes: results of the Paediatric Onset Study (ONSET) after 12 months of treatment. Diabetologia 2010;53:2487–2495
23. Schnell O, Eisfelder B, Standl E, Ziegler AG. High-dose intravenous insulin infusion versus intensive insulin treatment in newly diagnosed IDDM. Diabetes 1997;46:1607–1611
24. de Beaufort CE, Houtzagers CM, Bruining GJ, et al. Continuous subcutaneous insulin infusion (CSII) versus conventional injection therapy in newly diagnosed diabetic children: two-year follow-up of a randomized, prospective trial. Diabet Med 1989;6:766–771
25. Edelmann E, Walter H, Biermann E, Schleicher E, Bachmann W, Mehnert H. Sustained normoglycemia and remission phase in newly diagnosed type I diabetic subjects. Comparison between continuous subcutaneous insulin infusion and conventional therapy during a one year follow-up. Horm Metab Res 1987;19:419–421
26. Krarup T, Madsbad S. Effect of two periods with intensified insulin treatment on B-cell function during the first 18 months of type 1 (insulin-dependent) diabetes mellitus. Diabete Metab 1986;12:256–260
27. Perlman K, Ehrlich RM, Filler RM, Albisser AM. Sustained normoglycemia in newly diagnosed type I diabetic subjects. Short-term effects and one-year follow-up. Diabetes 1984;33:995–1001
28. Flores d'Arcais A, Morandi F, Beccaria L, Meschi F, Chiumello G. Metabolic control in newly diagnosed type 1 diabetic children. Effect of continuous subcutaneous infusion. Horm Res 1984;19:65–69
29. Ogden CL, Kuczmarski RJ, Flegal KM, et al. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. Pediatrics 2002;109:45–60