



Costimulation Modulation With Abatacept in Patients With Recent-Onset Type 1 Diabetes: Follow-up 1 Year After Cessation of Treatment

Tihamer Orban,¹ Brian Bundy,² Dorothy J. Becker,³ Linda A. DiMeglio,⁴ Stephen E. Gitelman,⁵ Robin Goland,⁶ Peter A. Gottlieb,⁷ Carla J. Greenbaum,⁸ Jennifer B. Marks,⁹ Roshanak Monzavi,¹⁰ Antoinette Moran,¹¹ Mark Peakman,¹² Philip Raskin,¹³ William E. Russell,¹⁴ Desmond Schatz,¹⁵ Diane K. Wherrett,¹⁶ Darrell M. Wilson,¹⁷ Jeffrey P. Krischer,² Jay S. Skyler,⁹ and the Type 1 Diabetes TrialNet Abatacept Study Group

OBJECTIVE

We previously reported that 2 years of costimulation modulation with abatacept slowed decline of β -cell function in recent-onset type 1 diabetes (T1D). Subsequently, abatacept was discontinued and subjects were followed to determine whether there was persistence of effect.

RESEARCH DESIGN AND METHODS

Of 112 subjects (ages 6–36 years) with T1D, 77 received abatacept and 35 received placebo infusions intravenously for 27 infusions over 2 years. The primary outcome—baseline-adjusted geometric mean 2-h area under the curve (AUC) serum C-peptide during a mixed-meal tolerance test (MMTT) at 2 years—showed higher C-peptide with abatacept versus placebo. Subjects were followed an additional year, off treatment, with MMTTs performed at 30 and 36 months.

RESULTS

C-peptide AUC means, adjusted for age and baseline C-peptide, at 36 months were 0.217 nmol/L (95% CI 0.168–0.268) and 0.141 nmol/L (95% CI 0.071–0.215) for abatacept and placebo groups, respectively ($P = 0.046$). The C-peptide decline from baseline remained parallel with an estimated 9.5 months' delay with abatacept. Moreover, HbA_{1c} levels remained lower in the abatacept group than in the placebo group. The slightly lower (nonsignificant) mean total insulin dose among the abatacept group reported at 2 years was the same as the placebo group by 3 years.

CONCLUSIONS

Costimulation modulation with abatacept slowed decline of β -cell function and improved HbA_{1c} in recent-onset T1D. The beneficial effect was sustained for at least 1 year after cessation of abatacept infusions or 3 years from T1D diagnosis.

Diabetes Care 2014;37:1069–1075 | DOI: 10.2337/dc13-0604

Type 1 diabetes (T1D) is an immune-mediated disease in which insulin-producing β -cells are destroyed (1). A number of studies have used various forms of immune intervention in recent-onset T1D, usually initiated within 3 months of diagnosis, in an attempt to preserve residual β -cell function. We previously reported that costimulation modulation with abatacept administered for 2 years slowed decline of

¹Joslin Diabetes Center, Boston, MA

²University of South Florida, Tampa, FL

³University of Pittsburgh, Pittsburgh, PA

⁴Indiana University School of Medicine, Indianapolis, IN

⁵University of California, San Francisco, San Francisco, CA

⁶Columbia University, New York, NY

⁷University of Colorado Barbara Davis Center for Childhood Diabetes, Aurora, CO

⁸Benaroya Research Institute, Seattle, WA

⁹University of Miami Diabetes Research Institute, Miami, FL

¹⁰Children's Hospital Los Angeles, Los Angeles, CA

¹¹University of Minnesota, Minneapolis, MN

¹²King's College London, London, U.K.

¹³University of Texas Southwestern Medical School, Dallas, TX

¹⁴Vanderbilt University, Nashville, TN

¹⁵University of Florida, Gainesville, FL

¹⁶Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

¹⁷Stanford University, Stanford, CA

Corresponding author: Jay S. Skyler, jskyler@miami.edu.

Received 11 March 2013 and accepted 22 November 2013.

Clinical trial reg. no. NCT00505375, clinicaltrials.gov.

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc13-0604/-/DC1>.

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health, Juvenile Diabetes Research Foundation International, or American Diabetes Association.

© 2014 by the American Diabetes Association. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

β -cell function over this period in patients with recent-onset T1D (2). Longer-term, chronic therapy designed to alter the immune response may carry untoward effects that outweigh the benefits of therapy. Moreover, the therapeutic window for effect of such approaches may be limited to the peri-diagnosis period. In addition, transient alteration of the rate of β -cell dysfunction early in diagnosis may have long-term clinical benefits (3,4). Thus, this trial was designed for 2 years of therapy, with continued follow-up to evaluate risks and benefits after the prespecified primary study outcome at 2 years. Herein, we report the effect of abatacept in T1D 1 year after discontinuation of the study drug.

RESEARCH DESIGN AND METHODS

In our earlier report (2), we described the study design and patient characteristics. Figure 1 depicts the CONSORT diagram, showing randomization/enrollment and retention of subjects during the study through 36 months of follow-up. The baseline characteristics of the two groups are summarized in Supplementary Table 1. A total of 112

patients were enrolled in a double-masked parallel-group design and were randomized in a 2:1 ratio, with 77 subjects receiving abatacept and 35 subjects receiving placebo. Abatacept (CTLA4-Ig, Oncia; Bristol-Myers Squibb) was given as a 30-min intravenous infusion at a dose of 10 mg/kg (maximum 1,000 mg/dose) in 100 mL 0.9% sodium chloride on days 1, 14, and 28 and then every 28 days, with the last dose on day 700 (total 27 doses). Normal saline infusion was used as placebo. Patients did not receive any premedication. β -Cell function was evaluated by stimulated C-peptide secretion. The prespecified primary outcome of this trial was a comparison of the area under the curve (AUC) of stimulated C-peptide response over the first 2 h of a 4-h mixed-meal tolerance test (MMTT) conducted at the 24-month visit. Four-hour MMTTs were performed at baseline and at 24 months; 2-h MMTTs were performed at 3, 6, 12, and 18 months. After completion of the 2-year treatment phase, subjects entered a follow-up phase to continue to assess safety and efficacy, including the performance of 2-h MMTTs at 30 and 36 months.

The study protocol is available at the Type 1 Diabetes TrialNet public Web site: www.diabetestrialnet.org.

Statistical Analyses

Details of the statistical plan are included in our earlier report (2). In summary, all analyses were based on the prespecified intention-to-treat (ITT) cohort with known measurements. Missing values were assumed to be missing at random. The *P* values associated with the ITT treatment comparisons of the primary and secondary end points are one-sided. The prespecified analysis method for C-peptide mean AUC, HbA_{1c}, and total daily insulin dose was an ANCOVA model adjusting for baseline age, sex, baseline value of the dependent variable, and treatment assignment. In the protocol design, a normalizing transformation of

$$\log(x_{\text{C-peptide}} + 1)$$

was prespecified for C-peptide AUC mean, and normal plots of the residuals indicated that it was adequate transformation in order to fulfill the assumptions of the linear model used in the analysis. The C-peptide mean AUC

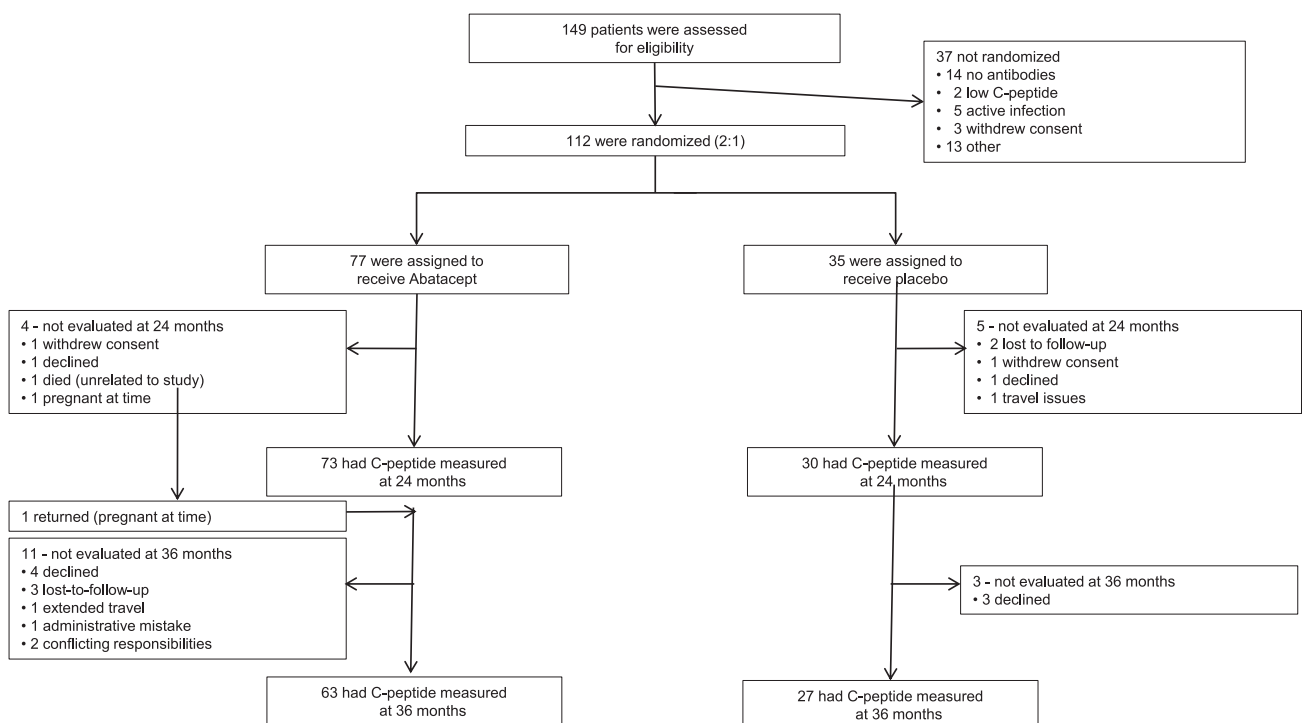


Figure 1—Enrollment, randomization, and follow-up of study participants.

equals the AUC divided by the 2-h interval (i.e., AUC/120). The AUC was computed using the trapezoidal rule from the timed measurements of C-peptide during the MMTT. Means that are calculated on this normalizing scale and then inverse transformed back are referred to as geometric-like means. The time to peak C-peptide falling to <0.2 nmol/L was analyzed using the Cox proportional hazards model, which assumes a constant hazard ratio for treatment group. The data would suggest that this ratio is not constant, and the estimate provides an approximate average over the follow-up period. Note that 95% CIs are more akin to two-sided tests while all *P* values reported are one-sided in accordance with the design, which is based on a one-sided hypothesis test.

RESULTS

In the primary analysis at 2 years, those subjects assigned to abatacept had a population mean stimulated C-peptide 2-h AUC, adjusted for age, sex, and baseline C-peptide, of 0.378 nmol/L (95% CI 0.328–0.431) vs. 0.238 nmol/L (95% CI 0.167–0.312) for those assigned to placebo (*P* = 0.0014). At 3 years, 1 year after discontinuation of treatment, population mean stimulated C-peptide 2-h AUC, adjusted for age, sex, and baseline C-peptide, was 0.217 nmol/L (95% CI 0.168–0.268) in the abatacept group vs. 0.141 nmol/L (95% CI 0.071–0.215) in the placebo group (*P* = 0.046). Figure 2A displays the adjusted population C-peptide mean 2-h AUC over 3 years. Subjects who received abatacept had a significantly higher mean AUC of 28%, 30%, 38%, 59%, 48%, and 54% compared with placebo subjects at 6, 12, 18, 24, 30, and 36 months, respectively. The geometric-like means of the unadjusted values for mean stimulated C-peptide 2-h AUC at 2 years were 0.375 nmol/L in the abatacept group and 0.266 nmol/L in the placebo group and at 3 years were 0.214 nmol/L in the abatacept group and 0.156 nmol/L in the placebo group. The predicted population mean of C-peptide AUC by treatment group over time was calculated to display the impact of treatment on delaying the decline of C-peptide (Fig. 2B). Considering the entire 3-year

observation period, the estimated lag time in the means of the abatacept group to drop to the same level as the placebo group is 9.5 months (95% CI 3.44–15.7), *P* = 0.0011. At 2 years, this was 9.6 months, indicating a consistent parallel separation when including the third-year data.

After the 36-month assessment, 35% of subjects in the abatacept group continued to have a peak stimulated C-peptide >0.2 nmol/L compared with 30% among placebo subjects (Fig. 2C); the difference (5%) is considerably smaller than 13% observed at 2 years. Thus, the rate of the peak C-peptide falling to <0.2 nmol/L for the abatacept group was initially less but increased after year 2 and is close to that in the placebo group. However, the adjusted relative risk estimate of the peak C-peptide falling to <0.2 nmol/L (based on proportional hazards model and adjustment for age, sex, and baseline C-peptide) was 0.60 (abatacept to placebo group; 95% CI 0.34–1.1; *P* = 0.043).

At 2 years, the adjusted mean HbA_{1c} was lower in the abatacept group (7.21 [95% CI 6.96–7.46]) than in the placebo group (7.87 [95% CI 7.48–8.26]). During the extended follow-up, the abatacept group continued to have a lower adjusted mean HbA_{1c} than the placebo group, with the values at 3 years being 7.64 (95% CI 7.28–7.99) in the abatacept group and 8.55 (95% CI 8.00–9.11) in the placebo group (Fig. 3A). Noteworthy for HbA_{1c} is that the significance levels are <0.005 for all 6-month interval group differences. However, insulin doses in the two groups were nearly the same at 3 years (difference: 1%), with a nonsignificant difference of 4% at 2 years and only significantly less use in the abatacept group at 6 and 12 months (Fig. 3B).

Further analyses of the predefined subgroups are shown in Fig. 4. The homogeneity test of treatment effect was significant for DR3 allele status (*P* = 0.025) and race (*P* < 0.001). The significance level of the qualitative interaction between DR3 allele and treatment was adjusted for multiple comparisons and remained significant (*P* = 0.014). The significance level of the

homogeneity test for race may be spurious, stemming from the small sample nonwhites assigned placebo (*N* = 3) and the potential lack of normally distributed C-peptide values required for a valid model-based test.

No new safety issues emerged during the extended follow-up (Supplementary Table 1).

CONCLUSIONS

We previously reported the primary outcome of this clinical trial (2). Those results demonstrated that 2 years of costimulation modulation with abatacept slows the decline of β -cell function, measured by C-peptide as an index of endogenous insulin production, in recent-onset T1D. The current report, which extended follow-up of subjects for an additional year without further abatacept therapy, shows that the difference between the abatacept and placebo groups is maintained, with the delay in decline of β -cell function estimated to be 9.5 months—virtually identical to the estimated delay of 9.6 months seen after 2 years of abatacept therapy. Thus, it would appear that postcessation, the autoimmune response did not rebound to a more aggressive state, but rather, the subjects previously treated with abatacept experienced a gradual and continued loss of β -cell function at a rate similar to that seen in the placebo group. These data suggest that costimulation blockade initiated within 3 months of diabetes onset transiently alters the natural history of disease progression. At the time of onset of diabetes, when there is an ongoing autoimmune response, costimulation blockade appears to arrest or diminish T-cell-mediated effects on β -cell function. Subsequent, monthly treatment may maintain this effect but does not appear to extend or amplify it. At a mechanistic level, such an outcome could be ascribed to modulation of costimulation-dependent autoreactive T-cells that are specifically recruited in the peri-diagnosis period, perhaps as a component of epitope spreading. There is evidence to indicate that at the doses used in the current study, abatacept is highly effective in limiting priming of T-cell and B-cell responses to newly

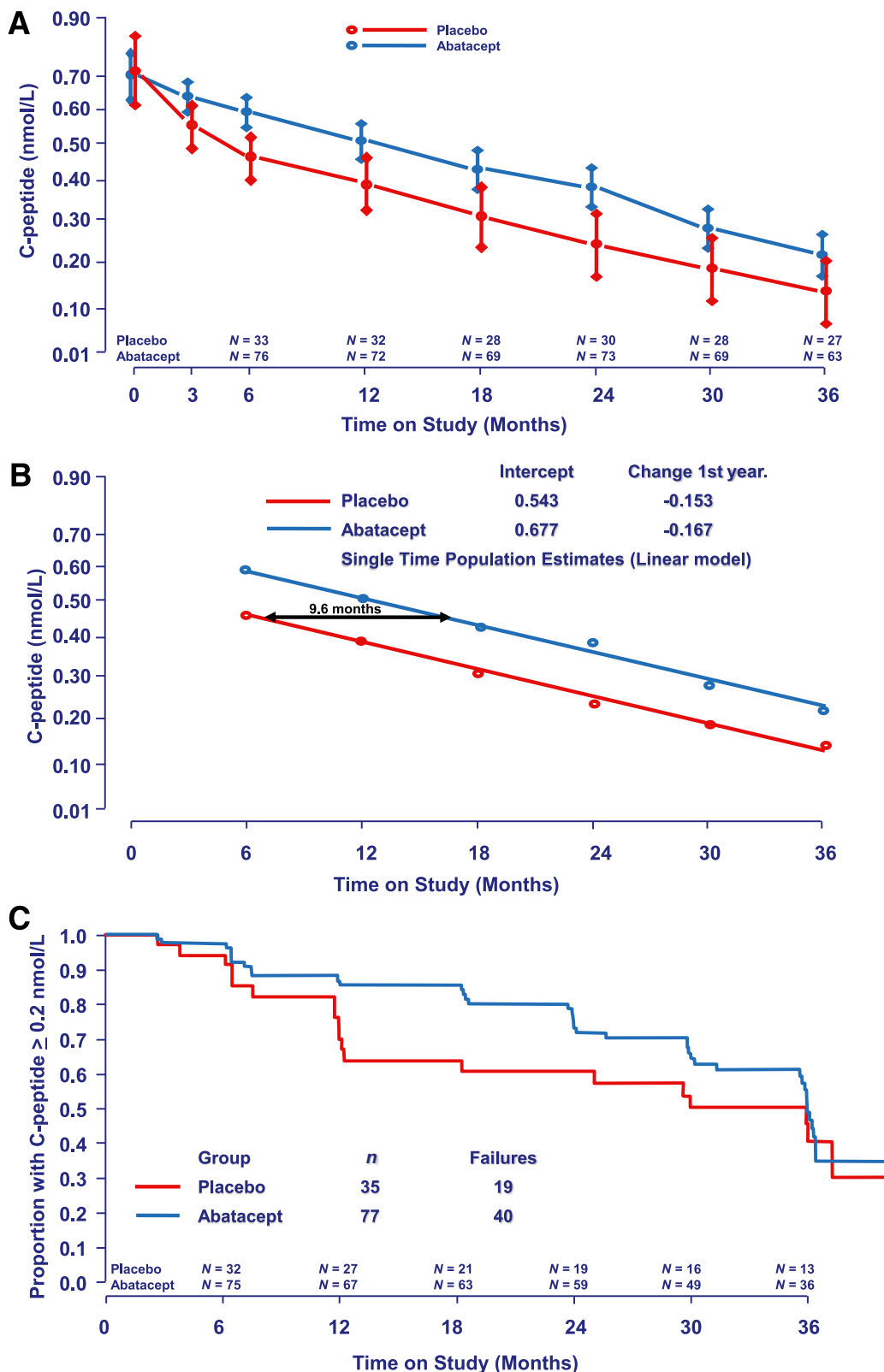


Figure 2—A: Population mean of stimulated C-peptide 2-h AUC mean over time for each treatment group. The estimates are from the ANCOVA model adjusting for age, sex, baseline value of C-peptide, and treatment assignment. y-Axis is on a $\log(y + 1)$ scale. The significance level at 36 months is 0.046. Error bars show 95% CI. B: Predicted population mean of stimulated C-peptide 2-h AUC mean over time for each treatment group. Estimates are from the analysis of mixed-effects model adjusting for age, sex, baseline value of C-peptide, and treatment assignment and including a fixed effect for time as a linear line on the $\log(y + 1)$ scale. The significance level of the difference between the two parallel lines is 0.0011. C: The proportion of participants with 2-h peak C-peptide remaining ≥ 0.2 nmol/L over time for each treatment group.

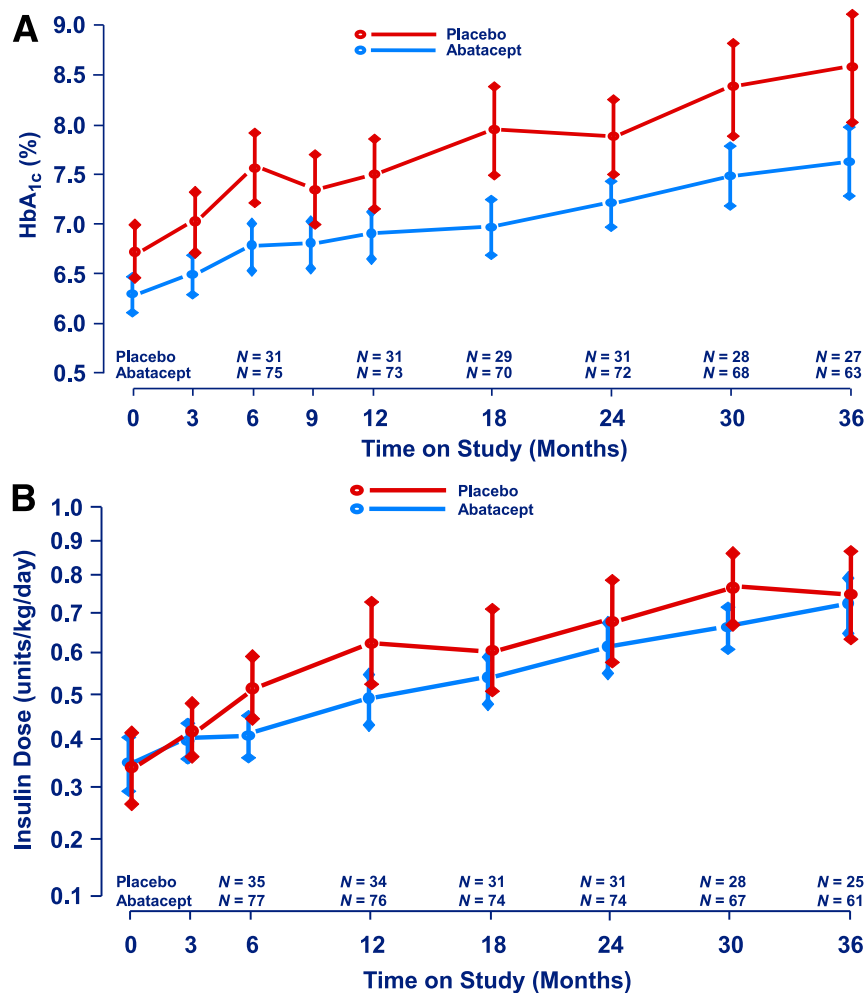


Figure 3—The population mean of HbA_{1c} (significance levels are <0.005 for all 6-month interval group differences) (A) and insulin use over time (B) for each treatment group (only statistical significance for less use in the abatacept group was at 6 and 12 months). The estimates are from the ANCOVA model adjusting for age, sex, baseline value of HbA_{1c}, and treatment assignment. Insulin use is per kilogram of body weight at 3-month intervals. Error bars show 95% CIs.

encountered antigens (5,6). However, after the initial postdiagnosis response abatacept treatment does not alter further the tempo of the underlying, progressive loss of β -cell function. This may imply that this later component of the autoimmune process is costimulation independent. This would also be consistent with the observation that cessation of costimulation blockade does not result in acceleration of decline in β -cell function.

It is not known how late after diagnosis abatacept treatment could be used. Also, an unanswerable question, from the current data alone, is whether a shorter treatment protocol would be sufficient to maintain the slowed decline of β -cell function. This is a particularly important issue, since

abatacept is a potential candidate to be tested in a trial for prevention of T1D in individuals determined to be at high risk for the disease. Abatacept also is a candidate to be a component of a combination therapy protocol in recent-onset T1D. The apparent lack of effect of abatacept in HLA-DR3–negative subjects needs further study. It is not related to age, as the mean age in HLA-DR3 positive subjects was 14.5 years and the mean age in HLA-DR3–negative subjects was 14.9 years, with no statistically significant shift in age distribution.

Four recent randomized trials with adequate sample size that have demonstrated some preservation of β -cell function in T1D as evidenced by stimulated C-peptide secretion,

including the earlier report from this trial using abatacept for costimulation modulation. The other trials have used anti-CD3 (7,8), and anti-CD20 (9). Interestingly, in all of these trials the treatment effect diminished with time, such that after an initial effect, C-peptide secretion subsequently declined parallel to the control group in all of these studies. Yet, continued effects on insulin dose were seen after 4 years in one of the anti-CD3 trials (10). Whether a transient change in the natural course of the disease will have long-term clinical benefit is unknown. In this regard, it is important to reflect upon the results from the Diabetes Control and Complications Trial (DCCT). In that trial, after the primary end point was met and all individuals were offered

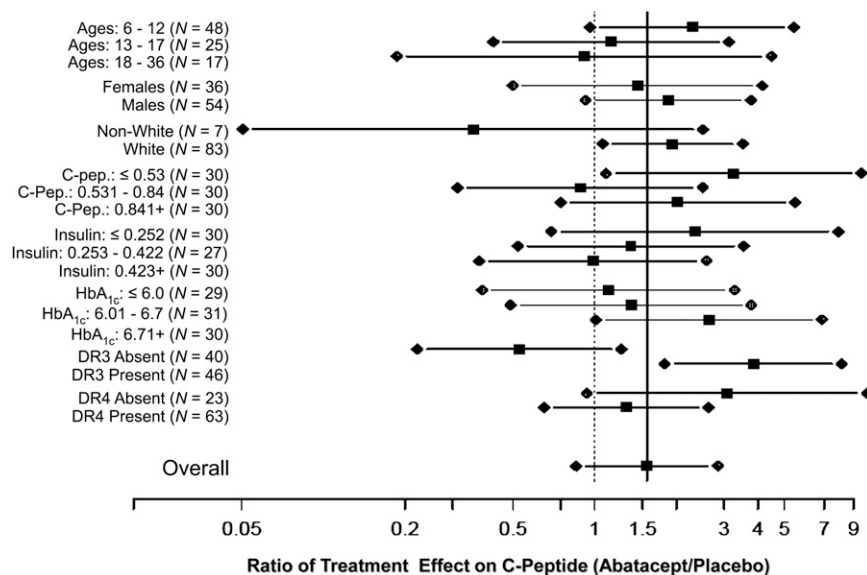


Figure 4—The ratio (abatacept to placebo) of treatment effect on 3-year stimulated C-peptide (C-Pep.) AUC mean within categories of prespecified baseline factors. The estimates are from the ANCOVA modeling log of C-peptide adjusting for age, sex, baseline value of C-peptide, the indicated categorized factor, treatment assignment, and treatment interaction terms. Error bars show 95% CI.

intensive therapy, there were no longer differences between the two groups with regard to HbA_{1c} (11–13). Yet, the previously intensively treated group had less retinopathy and nephropathy even after the HbA_{1c} levels converged (11,12) and less macrovascular disease >15 years later (13). These observations suggest that a short-term treatment close to diagnosis had a clinically important effect many years later (11–13). Remarkably, in our trial the significantly improved HbA_{1c} persisted in the abatacept-treated group even after discontinuation of the therapy. In the light of the DCCT trial results, this may translate into reduction of micro- and macrovascular complications at later stage.

In the current study, we demonstrate that treated subjects as a group maintain better HbA_{1c} and still have more insulin secretion 3 years after diagnosis than the placebo-treated subjects, although the number maintaining C-peptide >0.2 nmol/L diminished. Even if the eventual course of β -cell destruction in these individuals results in essentially absent β -cell function over time, this early preservation may, like the DCCT treatment, have long-term benefits. Continued long-term follow-up of these cohorts will be needed to address this

important question. Moreover, the optimal duration of treatment is unknown. Further studies are indicated to clarify the role of costimulation blockade in altering the course of recent-onset diabetes and in preventing the disease in individuals at risk thereof. To that end, a prevention study is currently under way (clinical trial reg. no. NCT01773707, clinicaltrials.gov).

Funding. The sponsor of the trial was the Type 1 Diabetes TrialNet Study Group. Type 1 Diabetes TrialNet Study Group is a clinical trials network funded by the National Institutes of Health through the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Allergy and Infectious Diseases, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development through the cooperative agreements U01-DK-061010, U01-DK-061016, U01-DK-061034, U01-DK-061036, U01-DK-061040, U01-DK-061041, U01-DK-061042, U01-DK-061055, U01-DK-061058, U01-DK-084565, U01-DK-085453, U01-DK-085461, U01-DK-085463, U01-DK-085466, U01-DK-085499, U01-DK-085505, and U01-DK-085509; contract HHSN267200800019C, the National Center for Research Resources, through Clinical and Translational Science Awards U11-RR-024131, U11-RR-024139, U11-RR-024153, U11-RR-024975, U11-RR-024982, U11-RR-025744, U11-RR-025761, U11-RR-025780, U11-RR-029890, and U11-RR-031986; and General Clinical Research Center Award M01-RR-00400, the Juvenile Diabetes Research Foundation International, and the American Diabetes

Association. Bristol-Myers Squibb (Princeton, NJ) provided abatacept (Orencia). LifeScan Division of Johnson & Johnson provided blood glucose monitoring meters and strips to research subjects.

Duality of Interest. The authors provided Bristol-Myers Squibb a copy of the original manuscript prior to submission. T.O. reports serving on the Data Safety Monitoring Board for Osiris Therapeutics and being a founder of Orban Biotech LLC. B.B. reports receiving a grant from Diamyd. S.E.G. reports serving on an advisory board for Genentech. R.G. reports receiving grants from Diamyd and Tolerx. P.A.G. reports serving on advisory boards for Genentech, Eli Lilly, Sanofi, and Tolerx and reports receiving grants from Bayhill Therapeutics, Diamyd, MacroGenics, Omni BioTherapeutics, and Tolerx. C.J.G. reports receiving grants from Bayhill Therapeutics, Diamyd, and Tolerx. J.B.M. reports serving on an advisory board for Amgen. A.M. reports serving on an advisory board for Pfizer and receiving grants from Tolerx, Merck, and Osiris Therapeutics. P.R. reports serving on advisory boards for Amgen, AstraZeneca, MannKind, and Novo Nordisk; serving on speakers bureaus for Merck and Novo Nordisk; and receiving grants from Aegera, Andromeda Biotech, Bayhill Therapeutics, Biodel, Boehringer Ingelheim, Calibra, CPEX, Generex, Hoffmann-La Roche, MannKind, Novo Nordisk, Osiris Therapeutics, and Reata. D.S. reports serving on advisory boards for Eli Lilly and GlaxoSmithKline and receiving a grant from Diamyd. D.K.W. reports receiving lecture fees from Eli Lilly and Medtronic. D.M.W. reports serving on advisory boards for Dexcom and Genentech and receiving grants support from Genentech, Diamyd, and Osiris Therapeutics. J.S.S. reports serving on boards for Amylin Pharmaceuticals, Dexcom, Moerae Matrix, Sanofi Diabetes, and

Viacyte and reports receiving grants from Bayhill Therapeutics, Halozyme, Intuity, Mesoblast, and Osiris Therapeutics. No other potential conflicts of interest relevant to this article were reported.

Bristol-Myers Squibb had no involvement with study design, conduct, or management; data collection, analysis, or interpretation; or manuscript preparation. There are no agreements concerning confidentiality of the data between the sponsor and the authors or the institutions named in the credit lines.

Author Contributions. T.O. proposed the trial to TrialNet, served as study chair, was a member of the manuscript writing group, had full access to all data, and made the decision to publish the manuscript. B.B., C.J.G., M.P., J.P.K., and J.S.S. were members of the manuscript writing group, had full access to all data, and made the decision to publish the manuscript. D.J.B., L.A.D., S.E.G., R.G., P.A.G., J.B.M., R.M., A.M., P.R., W.E.R., D.S., D.K.W., and D.M.W. conducted the study, collected and reviewed study data, reviewed and commented on various versions of the manuscript, and suggested revisions. J.S.S. 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 analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 72nd Scientific Sessions of the American Diabetes Association, Philadelphia, PA, 8–12 June 2012.

References

- Bluestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. *Nature* 2010;464:1293–1300
- Orban T, Bundy B, Becker DJ, et al.; Type 1 Diabetes TrialNet Abatacept Study Group. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011;378:412–419
- The Diabetes Control and Complications Trial Research Group. Effect of intensive therapy on residual beta-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
- Steffes MW, Sibley S, Jackson M, Thomas W. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. *Diabetes Care* 2003;26:832–836
- Abrams JR, Lebwohl MG, Guzzo CA, et al. CTLA4lg-mediated blockade of T-cell costimulation in patients with psoriasis vulgaris. *J Clin Invest* 1999;103:1243–1252
- Ribeiro AC, Laurindo IM, Guedes LK, et al. Abatacept and reduced immune response to pandemic 2009 influenza A/H1N1 vaccination in patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2013; 65:476–480
- Herold KC, Hagopian W, Auger JA, et al. Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. *N Engl J Med* 2002;346:1692–1698
- Keymeulen B, Vandemeulebroucke E, Ziegler AG, et al. Insulin needs after CD3-antibody therapy in new-onset type 1 diabetes. *N Engl J Med* 2005;352:2598–2608
- Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, et al.; Type 1 Diabetes TrialNet Anti-CD20 Study Group. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. *N Engl J Med* 2009; 361:2143–2152
- Keymeulen B, Walter M, Mathieu C, et al. Four-year metabolic outcome of a randomised controlled CD3-antibody trial in recent-onset type 1 diabetic patients depends on their age and baseline residual beta cell mass. *Diabetologia* 2010;53:614–623
- The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med* 2000;342:381–389
- Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 2003; 290:2159–2167
- Nathan DM, Cleary PA, Backlund JY, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643–2653