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Authors

Russell, William E
Bundy, Brian N
Anderson, Mark S
et al.

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Abatacept for Delay of Type 1 Diabetes Progression in Stage 1 Relatives at Risk: A Randomized, Double-Masked, Controlled Trial

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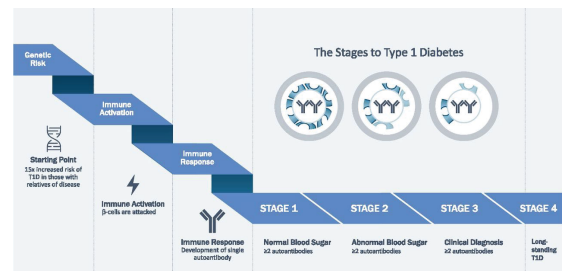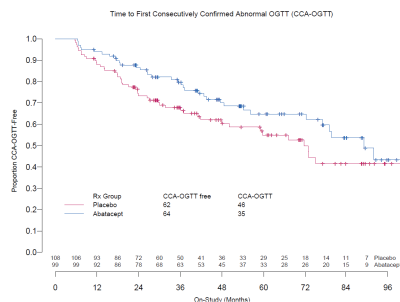
Abatacept for delay of type 1 diabetes progression in relatives at risk

Treg, regulatory T cell

Individuals with stage 1 type 1 diabetes (T1D) from the TrialNet pathway to prevention study were randomized to abatacept or placebo over 12 months. The endpoint was confirmed abnormal glucose tolerance (AGT, stage 2) or clinical diabetes (stage 3).
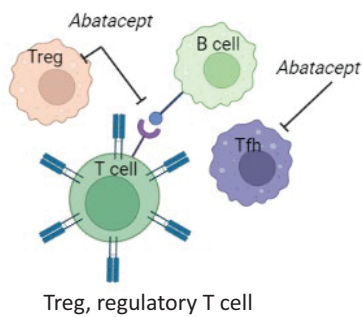
12 months of abatacept treatment in stage 1 changed immune cells and improved C-peptide as previously shown in stage 3 but did not achieve the pre-set criteria for the delay of stage 2 diabetes in individuals at stage 1. Costimulation blockade may modify the progression of type 1 diabetes

ARTICLE HIGHLIGHTS

- Abatacept blocks the activation of T cells and slows β-cell loss in new-onset type 1 diabetes.
- We tested whether it would be effective earlier in the autoimmune process before glucose levels are impacted.
- We treated individuals with stage 1 diabetes with abatacept or placebo for 1 year and followed them.
- Although abatacept increased the C-peptide response and induced the immunological changes that we expected, it did not significantly delay the progression to abnormal glucose tolerance to the degree we anticipated.
- The signals are promising, however, that abatacept may modify the progression of type 1 diabetes.

Abatacept for Delay of Type 1 Diabetes Progression in Stage 1 Relatives at Risk: A Randomized, Double-Masked, Controlled Trial

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William E. Russell,[1] Brian N. Bundy,[2] Mark S. Anderson,[3,4] Laura A. Cooney,[4] Stephen E. Gitelman,[5] Robin S. Goland,[6] Peter A. Gottlieb,[7] Carla J. Greenbaum,[8] Michael J. Haller,[9] Jeffrey P. Krischer,[2] Ingrid M. Libman,[10] Peter S. Linsley,[8] S. Alice Long,[8] Sandra M. Lord,[8] Daniel J. Moore,[11] Wayne V. Moore,[12] Antoinette M. Moran,[13] Andrew B. Muir,[14] Philip Raskin,[15] Jay S. Skyler,[16] John M. Wentworth,[17] Diane K. Wherrett,[18] Darrell M. Wilson,[19] Anette-Gabriele Ziegler,[20,21] Kevan C. Herold,[22] and the Type 1 Diabetes TrialNet Study Group*

OBJECTIVE

Previous studies showed that inhibiting lymphocyte costimulation reduces declining β-cell function in individuals newly diagnosed with type 1 diabetes. We tested whether abatacept would delay or prevent progression of type 1 diabetes from normal glucose tolerance (NGT) to abnormal glucose tolerance (AGT) or to diabetes and the effects of treatment on immune and metabolic responses.

RESEARCH DESIGN AND METHODS

We conducted a phase 2, randomized, placebo-controlled, double-masked trial of abatacept in antibody-positive participants with NGT who received monthly abatacept/placebo infusions for 12 months. The end point was AGT or diabetes, assessed by oral glucose tolerance tests.

RESULTS

A total of 101 participants received abatacept and 111 placebo. Of these, 81 (35 abatacept and 46 placebo) met the end point of AGT or type 1 diabetes diagnosis (hazard ratio 0.702; 95% CI 0.452, 1.09; P = 0.11) The C-peptide responses to oral glucose tolerance tests were higher in the abatacept arm ($P <$ 0.03). Abatacept reduced the frequency of inducible T-cell costimulatory (ICOS)$^+$ PD1$^+$ T-follicular helper (Tfh) cells during treatment ($P <$ 0.0001), increased naive CD4$^+$ T cells, and also reduced the frequency of CD4$^+$ regulatory T cells (Tregs) from the baseline (P = 0.0067). Twelve months after treatment, the frequency of ICOS$^+$ Tfh, naive CD4$^+$ T cells, and Tregs returned to baseline.

CONCLUSIONS

Although abatacept treatment for 1 year did not significantly delay progression to glucose intolerance in at-risk individuals, it impacted immune cell subsets and preserved insulin secretion, suggesting that costimulation blockade may modify progression of type 1 diabetes.

Type 1 diabetes is a chronic autoimmune disease that occurs in individuals with genetic risk factors but in whom acquired events activate an immunologic assault on insulin-producing β-cells (1). The disease occurs at any age, but the highest incidence is in childhood where incidence rates have been increasing across the

^{1}Departments of Pediatrics and Cell & Developmental Biology, Vanderbilt University Medical Center, Nashville, TN
^{2}Health Informatics Institute, University of South Florida, Tampa, FL
^{3}Department of Medicine, University of California, San Francisco, San Francisco, CA
^{4}Immune Tolerance Network, Seattle, WA
^{5}Diabetes Center, University of California, San Francisco, San Francisco, CA
^{6}Departments of Medicine and Pediatrics, Columbia University, New York, NY
^{7}Barbara Davis Diabetes Center, University of Colorado, Anschutz, CO
^{8}Benaroya Research Institute, Seattle, WA
^{9}Department of Pediatrics, University of Florida, Gainesville, FL
^{10}University of Pittsburgh, Pittsburgh, PA
^{11}Departments of Pediatrics and Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, TN
^{12}Children's Mercy Hospital, Kansas City, MO
^{13}Department of Pediatrics, University of Minnesota, Minneapolis, MN
^{14}Emory University, Atlanta, GA
^{15}University of Texas Southwestern, Dallas, TX
^{16}Department of Medicine, University of Miami, Miami, FL
^{17}Royal Melbourne Hospital and The Walter and Eliza Hall Institute of Medical Research, Melbourne, Victoria, Australia
^{18}Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

world (2). Technologies to improve replacement of insulin and metabolic control have advanced in the past decades, but the proportion of patients at any age who meet accepted standards of care is small (3). The need for treatments that could delay or prevent type 1 diabetes is underscored by the reduced life expectancy for people with the disease (4).

Type 1 diabetes begins with the appearance of two or more autoantibodies and progresses, over months to years, through active β-cell loss until metabolic demands cannot be met and glycemic decompensation occurs (5,6). Multiple studies led to the characterization of the stages of type 1 diabetes, beginning with the finding of two or more biochemical autoantibodies with normal glucose responses to an oral glucose challenge (stage 1), followed by abnormal glucose tolerance (AGT) (stage 2), and finally, diagnosis with clinical disease (stage 3) (5).

Data from preclinical and human studies indicate that T cells are the major drivers of β-cell destruction (7). Abatacept, cytotoxic T-lymphocyte associated protein Ig (CTLA4Ig), blocks T-cell costimulatory signals delivered through the CD80/86 axis, thereby preventing T-cell activation. In prediabetic NOD mice, CTLA4Ig prevented autoimmune diabetes when given prior to the onset of hyperglycemia, but its effects were stage dependent (8,9). There are also costimulatory signals other than CD80/86 that may be involved in autoimmune diabetes and would not be affected by CTLA4Ig (10). In addition, CD80 and CD86 blockade may have other effects since regulatory T cells (Tregs) express CD28 and some express CTLA-4 (9,11,12).

In a previous clinical trial, we found that abatacept, administered monthly for 2 years, delayed the decline of C-peptide in individuals with stage 3 type 1 diabetes (13,14). Even 3 years after diagnosis, there was still improvement in

provoked C-peptide responses compared with placebo-treated participants, although the C-peptide responses declined in both groups. Studies of peripheral blood samples from the participants showed that abatacept reduced the frequencies of inducible T-cell costimulatory (ICOS)$^{+}$ T-follicular helper (Tfh) cells (15). These studies suggested that reducing Tfh cells may interrupt progression of autoimmunity and β-cell loss after T-cell activation (7–9,11,12).

Several factors, including the stage of disease, the participating cells, the inflammatory milieu, and others, may change the effects of abatacept in type 1 diabetes. While our previous clinical study indicated that stage 3 type 1 diabetes was sensitive to abatacept, the effects of CTLA4Ig at earlier stages are not known in humans. In addition to its effectiveness in those with clinical new-onset type 1 diabetes, abatacept has proven to be effective for the treatment of some other autoimmune conditions—juvenile idiopathic arthritis, rheumatoid arthritis, and psoriatic arthritis—but not others—lupus nephritis or relapsing-remitting multiple sclerosis (12). Therefore, we performed a randomized placebo-controlled trial of abatacept in participants with stage 1 diabetes to determine whether drug treatment would prevent progression to stage 2 or stage 3 diabetes and to obtain mechanistic insight on the process of diabetes progression.

RESEARCH DESIGN AND METHODS
Trial Participants
The trial was conducted April 2013–December 2021 at 33 sites in the U.S. and Canada and at 18 sites in Australia, U.K., Germany, Finland, Sweden, and Italy (Supplementary Table 1). Institutional Review Board approval was obtained at each participating site.

The participants, their parents, or both, provided written informed consent or assent before trial entry. Eligible participants

were relatives without diabetes of patients with type 1 diabetes between the ages of 6 and 45 at the time of screening for autoantibodies that occurred in the TrialNet Pathway to Prevention program (16).

Participants were required to fulfill the definition of stage 1 type 1 diabetes, defined as two or more diabetes-related autoantibodies, excluding anti-insulin antibodies (IAA), detected in two serum samples obtained within 6 months before randomization without dysglycemia, defined as fasting glucose 110–126 mg/dL (6.1–7 mmol/L), 2-h postprandial glucose >140 mg/dL (<7.8 mmol/L) but <200 mg/dL, or a glucose at 30, 60, or 90 min as >200 mg/dL (11.1 mmol/L) on two occasions with 52 days of randomization. IAA^{+} individuals were excluded to prevent overlapping eligibility with an ongoing prevention trial with oral insulin (Oral Insulin for Prevention of Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus [TN07]) (17). Individuals with other clinically relevant medical histories, abnormal laboratory chemistry values, or abnormal blood counts were excluded.

Trial Design and Intervention
Participants were randomly assigned in a 1:1 ratio to receive abatacept or placebo using random-size blocks and stratified according to TrialNet site and age: <18 years (n = 134) or ≥18 years (n = 78). Of these, 47% of the pediatric group and 49% of the adults received abatacept. Participants received 14 intravenous infusions of abatacept or placebo at 0, 2, and 4 weeks following randomization and then every 28 ± 7 days thereafter for 12 months. The dose of abatacept at each infusion was 10 mg/kg to a maximum of 1,000 mg. Participants underwent frequent assessments of their glucose tolerance status, insulin production, immunologic status, and overall health. Treatment assignments were

[19]*Stanford University, Stanford, CA*
[20]*Forschergruppe Diabetes, Technical University Munich at Klinikum rechts der Isar, Munich, Germany*
[21]*Institute for Diabetes Research, Helmholtz Munich, German Center for Environmental Health, Munich, Germany*
[22]*Yale University, New Haven, CT*

Corresponding author: William E. Russell, bill. russell@vumc.org

generated using PROC PLAN in SAS software and stored in a secure file

End Points and Assessments

The primary end point was the elapsed time from randomization to either a consecutively confirmed abnormal glucose tolerance test (AGT) result or to stage 3 type 1 diabetes. Participants and study sites remained masked to the diagnosis of AGT. Masking was maintained for a confirmatory oral glucose tolerance test (OGTT) by the inclusion of random requests for repeat OGTTs for quality control. The diagnosis of stage 3 diabetes was defined using American Diabetes Association criteria (18). Scheduled OGTTs were performed every 6 months after randomization. Random screening glucose levels were evaluated at 3-month intervals, and an OGTT was performed if the random glucose level was >200 mg/dL (11.1 mmol/L) with symptoms of diabetes. Study infusions were terminated in participants who confirmed a diabetic OGTT. The time to diagnosis was from the date of randomization to the first of the two diagnostic tests. Outcomes were reviewed by the TrialNet Eligibility and Events Committee, the members of which were unaware of the treatment group assignments.

Mechanistic and Metabolic Studies

Complete blood counts with differentials and chemistries were measured in local laboratories. Glucose and C-peptide levels were measured in a central laboratory, the latter using the Tosoh assay. Samples were immediately cooled and centrifuged within 1 h, per protocol (Supplementary Table 2). Autoantibodies were measured by radio binding assay at the Barbara Davis Diabetes Center. Peripheral blood mononuclear cells were used from a subset of the participants based on availability of samples at all time points to 24 months (n = 46 abatacept and n = 48 placebo). Flow cytometry was done at the Benaroya Research Institute. Cryopreserved peripheral blood mononuclear cells were thawed and stained with a single multicolor flow cytometry panel of 31 markers (Supplementary Table 3) developed to define both T-cell and B-cell subsets of interest, and acquired on a BD Symphony cytometer. Compensation and analysis were performed using BD FlowJo 10 (Supplementary Fig. 1). The C-peptide

areas under the curve (AUCs) were compared with ANCOVA, regressing on baseline level and age. The means are adjusted for age and baseline constituents using the predicted value from the fitted model substituting the average age and baseline value but expressing the treatment group effect. C-peptide was transformed using $\ln(AUC/120 + 1)$; for all other figures, the square root transformation was used.

Statistical Design and Analysis

The efficacy end point was the cumulative incidence of AGT over time after randomization within each group and was estimated using the Kaplan-Meier method, applying the intention-to-treat principle. The difference between treatment groups was estimated by the hazard ratio (HR) and hypothesis tests used the likelihood ratio test based on the Cox proportional hazards model (19,20). Time-to-AGT was discretized to 6-month times in keeping with the OGTT schedule. In planning, we predicted that 33% of participants would reach AGT during a 2-year period based on historic TrialNet data. The study was designed to provide 80% power to detect a 44% risk reduction (HR 0.56) in the rate of AGT using a two-sided test at the 0.05 level, which required the observation of 95 subjects with AGT (21). In the 7th year, with concurrence of the Data Safety Monitoring Board (DSMB), the study plan was revised as the number of events was lower than expected and was aimed to follow participants until at least 67 events occurred. This report includes 74 AGT events, with an associated detectable HR of 0.52 at 80% power. The 95% CIs of the mean are reported for each group, and significance levels are from the Wald test. All P values reported are two-sided.

Adverse events (Common Terminology Criteria for Adverse Events [CTCAE] version 4) of grade $\geq$2 were reported. Data on safety and efficacy were evaluated twice yearly by an independent DSMB. Lan-DeMets stopping rules were used for the primary end point, with a type I spending function patterned after the O'Brien-Fleming method (22). A single interim analysis was conducted when 72% of the required minimum number of events occurred, as set by the design. This interim assessment has a negligible effect on the threshold of significance for the final analysis (i.e., P = 0.0494);

consequently, fixed sample significance levels are reported (23). Statistical analyses were performed using TIBCO Spotfire S+ 8.2 Workbench or SAS 9.4 software.

Trial Oversight

Type 1 Diabetes TrialNet/National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) was the study sponsor. TrialNet investigators designed the trial. An independent medical monitor (who was unaware of the treatment group assignments) reviewed all safety data. Bristol-Myers Squibb (BMS), Lawrenceville, NJ, provided abatacept and the matching placebo and reviewed the manuscript before submission but was not involved in the conduct of the trial or in data analysis. Representatives from the NIDDK participated in the design and conduct of the trial, interpretation of the data, preparation, review, and approval of the manuscript for submission, and the decision to submit the manuscript for publication. The authors wrote the manuscript and reviewed the data.

RESULTS

Participants

From a potential pool of 1,285 participants, 324 (25.4%) were screened for eligibility, and 212 were randomized (Fig. 1). Of these, 101 were assigned to receive abatacept and 111 were assigned to receive placebo. Two in the treatment group and three in the placebo group withdrew before the follow-up assessment. Table 1 shows the demographics of the study groups—there were no significant differences between them. More than 50% were the siblings of individuals with type 1 diabetes. Most participants were positive for GAD antibody (GADA$^+$). Participants with IAA were excluded at screening, but six participants had converted to positive at randomization.

The dose of abatacept at each infusion was 10 mg/kg to a maximum of 1,000 mg. All 14 of the prescribed infusions were received over 12 months by 58.4% of participants in the abatacept group and by 44.7% of those in the placebo group. The median total dose of abatacept administered was 8,082 mg, with a range of 1,260 to 14,000 mg. All 14 infusions were received by 58% percent of the abatacept group, and 84% received $\geq$10 of the 14 infusions.
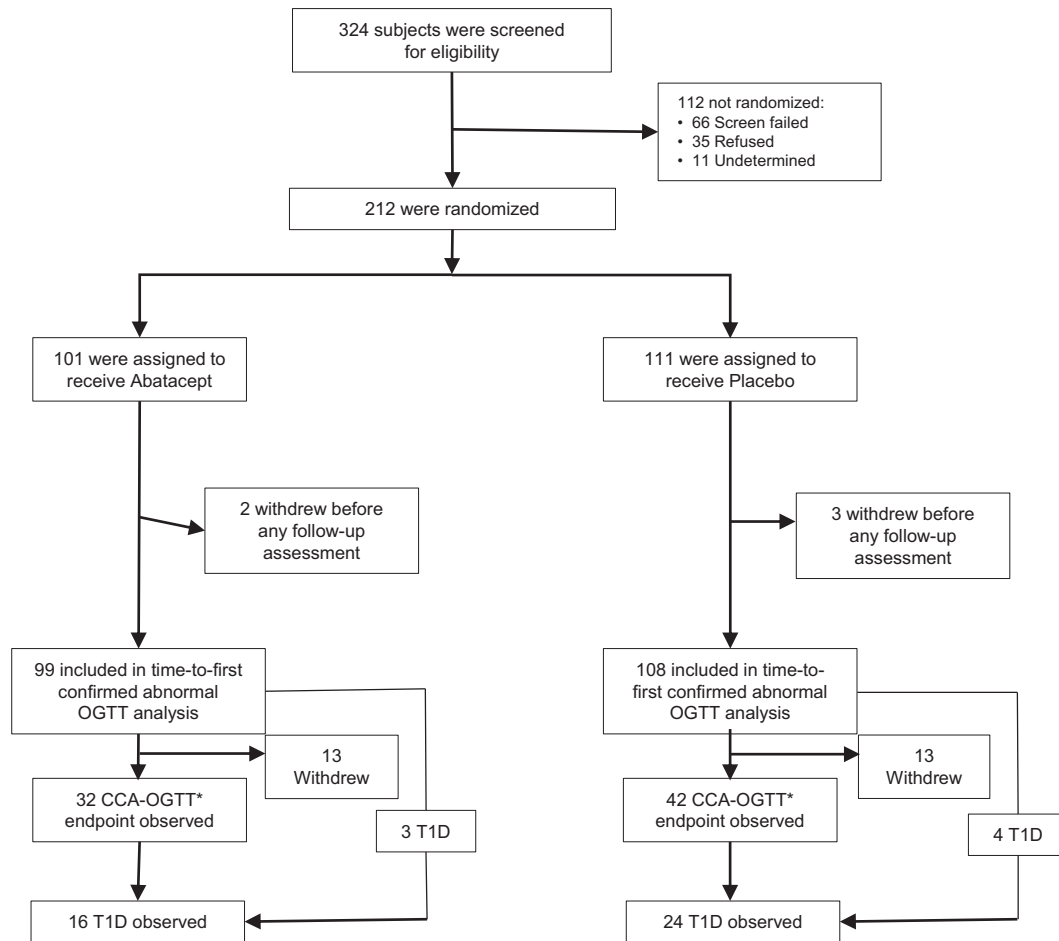
Figure 1—Consolidated Standards of Reporting Trials diagram. T1D, type 1 diabetes. *Consecutive confirmed abnormal OGTT.

Efficacy

The study participants were followed for a median of 36.9 months for confirmed consecutive abnormal OGTTs and a median of 47.6 months for development of stage 3 type 1 diabetes. A total of 81 participants (38%) met a study end point: 74 developed AGT and 7 were diagnosed with stage 3 type 1 diabetes. (In two participants, the confirmation OGTT after AGT was diabetic.) Figure 2A shows the Kaplan-Meier analysis of the time to the primary end point. Of the 81 events, 35 were in the abatacept group and 46 were in the placebo group (HR 0.702; 95% CI 0.452, 1.09; P = 0.11). The median time to the development of AGT was 89.2 and 71.6 months for the abatacept and placebo groups, respectively. The cumulative HR was lowest at 12 months on study, coinciding with the last prescribed abatacept infusion, although the ratio was not statistically significant (Supplementary Table 4).

The participants were followed after the diagnosis of stage 2, and 33 of the 74 who met the primary end point of AGT were diagnosed with stage 3 diabetes (Fig. 2B). The difference in the time to type 1 diabetes was not statistically significant between the treatment groups (HR 0.710; 95% CI 0.377, 1.34). Abatacept treatment improved β-cell function. There was a statistically significant difference in the C-peptide AUC at month 12 (P = 0.03) (Fig. 2C).

Safety

The abatacept infusions were well-tolerated. The frequency or severity of adverse events was not significantly different in the two treatment arms, except for skin and connective tissue disorders, which were higher with abatacept (Supplementary Tables 5 and 6A). Two participants in the abatacept group were diagnosed with cancers (breast and thyroid) during the observation period. Five serious adverse events were reported: two in the abatacept and three in the placebo arms (Supplementary Table 6B).

Effects of Abatacept on Immune Markers

Abatacept blocks T-cell activation by CD28 by binding to CD80 and CD86 on antigen-presenting cells and affects Tfh and T peripheral (Tph) helper CD4$^+$ T cells, thought to be involved in autoimmune diseases, including type 1 diabetes (15,24). We examined these and other cell subpopulations in prespecified and exploratory analyses. The absolute counts of CD4$^+$ or CD8$^+$ T cells were not significantly different with treatment. Abatacept treatment did not reduce the overall frequency of memory Tfh (Supplementary Fig. 2). However, there was a marked decline in the frequency of activated ICOS$^+$ Tfh cells (P < 0.0001) at months 3, 6, and 12 (Fig. 3A). Tph cells, which do not express CXCR5, were also reduced at these times (Fig. 3D) (25). The levels of ICOS$^+$ Tfh were lower in adults versus children at study entry (P < 0.0001) (Fig. 3B and C). At month 24, 12 months after cessation of treatment, the frequency of these cells

Table 1—Baseline characteristics of participants

Characteristics and descriptive statistics*	Abatacept (n = 101)	Placebo (n = 111)
Age, years	16.3 (11.9–27.5)	14.9 (11.4–22.0)
Range	6.8–52.8	7.2–53.7
<18 years	63 (62.4)	71 (64.0)
Male sex	51 (50.5)	54 (48.6)
Race/ethnicity		
White	91 (95.8)	102 (94.4)
African American	3 (3.2)	3 (2.8)
American Indian/Alaska Native	1 (1.1)	1 (0.9)
Hispanic	11 (10.9)	10 (9.0)
Other	0 (0.0)	2 (1.9)
Not reported	6 (5.9)	3 (2.7)
Relationship to index case		
Sibling(s)	53 (52.5)	56 (50.5)
Identical twin	1 (1.0)	2 (1.8)
Offspring	21 (20.8)	14 (12.6)
Parent(s)	14 (13.9)	23 (20.7)
Sibling and another first degree	6 (5.9)	9 (8.1)
Second degree	4 (4.0)	6 (5.4)
Third degree	2 (2.0)	1 (0.9)
Autoantibodies positive		
GADA	94 (93.1)	104 (93.7)
micro-IAA†	4 (4.0)	2 (1.8)
Insulinoma-associated protein-2 antibodies	49 (48.5)	61 (55.0)
ICA	76 (75.2)	79 (71.2)
Zinc transporter 8 autoantibody	47 (46.5)	65 (58.6)
Autoantibodies titer		
GADA	317 (91–683)	375 (100–707)
micro-IAA	0.002 (0.001–0.003)	0.002 (0.001–0.004)
Islet antigen 2 antibodies	2 (0–225)	23 (0–186)
ICA	40 (10–160)	40 (5–160)
Zinc transporter 8 autoantibody	0.013 (0.001–0.168)	0.041 (0.002–0.170)
HbA$_{1c}$ (%)	5.1 (4.9–5.3)	5.1 (4.9–5.25)
BMI (kg/m^2)	22.7 (18.5–27.3)	21.6 (17.6–25.6)
BMI Z-score	0.668 (−0.129 to 1.29)	0.582 (−0.213 to 1.25)
C-peptide, mean OGTT AUC (nmol/L)	2.16 (1.61–2.50)	2.07 (1.51–2.74)
HLA alleles present (%)		
DR3	47 (47.0)	60 (54.5)
DR4	60 (60.0)	63 (57.3)
Missing	1 (1.1)	1 (0.9)

*Data are presented as the median (1st and 3rd quartiles) or as N (%), unless indicated otherwise. †All micro-IAA were negative when screened for eligibility but six converted prior to randomization.

returned to pretreatment levels in children and adults.

Abatacept may also affect CD4$^+$ Tregs since they express CD28 and may express CTLA-4 (12). The frequency of Tregs was reduced from the baseline by abatacept treatment (P = 0.0067), and their frequency was significantly lower in the abatacept versus placebo group at months 3, 6, and 12, but returned to baseline 1 year after treatment (Fig. 3E).

Although the total number of CD4$^+$ and CD8$^+$ T cells did not change, the reduced ICOS$^+$ CD4$^+$ T cells suggested that costimulation blockade may have prevented T-cell activation generally. Indeed, there was a marked increase in the frequency of naive CD4$^+$ and CD8$^+$ T cells (Fig. 3F and G), and proliferating, Ki67$^+$ CD4$^+$ T cells were reduced (Fig. 3H).

The participants in this trial were selected for expression of at least two or more autoantibodies other than IAA. We did not find an effect of abatacept treatment on the development of new IAA (Supplementary Fig. 3) or other autoantibodies (GADA or islet cell antibody [ICA], not shown).

Subgroup Analysis of Response to Abatacept

In a prespecified analysis, we determined whether baseline characteristics of the participants would identify individuals with responses to abatacept (Supplementary Fig. 4). There was a delay in the time to AGT in those with ICA titers ≤30 (P = 0.04), but we did not find a significant difference in the drug effect when participants were distinguished on the basis of biochemical autoantibodies, sex, age, BMI, or baseline C-peptide responses.
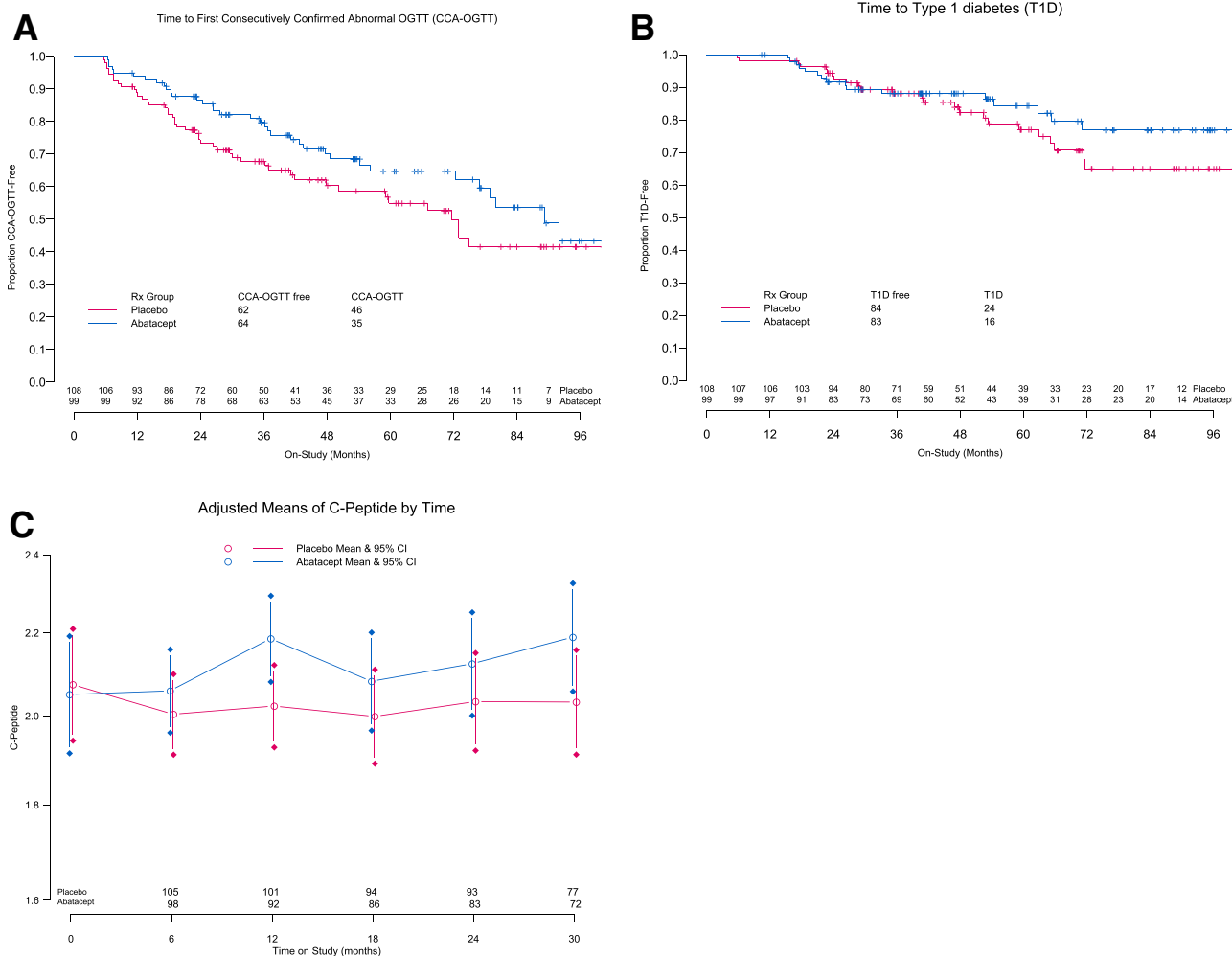
Figure 2—Effects of abatacept on study outcomes. *A*: Effect of abatacept on the development of the primary end point of AGT/diabetes (HR 0.702; 95% CI 0.452, 1.09; *P* = 0.11). *B*: Effect of abatacept on the progression from AGT to type 1 diabetes (T1D) (HR 0.710; 95% CI 0.377, 1.34). *C*: C-peptide levels were higher in the abatacept-treated group at month 12 (*P* = 0.03). Rx, prescription.

CONCLUSIONS

In this randomized placebo-controlled trial of participants with stage 1 type 1 diabetes, costimulation blockade with abatacept did not result in a statistically significant delay in the progression to stage 2 or stage 3 type 1 diabetes in participants with stage 1 disease. We found that abatacept altered immune cell subsets and improved insulin secretion in the participants. Our study was well powered based on our previous experience in type 1 diabetes prevention trials and the results in abatacept-treated individuals with new-onset diabetes (13,14). However, the observed effect of abatacept in this trial of stage 1 participants treated for 1 year was less than had been hypothesized based on these experiences.

The effects of abatacept on immune cells were as predicted (12,15,26–31).

There were declines in activated Tfh and Tph cells and Tregs and an increase in the proportion of naive T cells, likely reflecting blockade of activation signals. Despite these immunologic effects, there were not detectable changes in the titers of existing autoantibodies or in the time to acquisition of new antibodies, indicating that after acquisition of two autoantibodies, the titers and further autoantibody development is not sensitive to blockade of CD80/CD86 costimulation or to the reduced frequency of circulating activated Tfh and Tph cells.

Interestingly, there was an increase in the frequency of naive CD4$^+$ T cells in the abatacept treatment arm that was significantly different from the placebo-treated participants at month 12. Our data overall would suggest that the accumulation of naive cells is due to reduced

activation of T cells and memory cell development since the proportions of ICOS$^+$ CD4$^+$ T cells, which reflects activation of Tfh cells, and overall Ki67$^+$ T cells were reduced. We also found that the frequency of Tregs was reduced. The significance of this finding is not clear, but the reduction in these immune-modulating cells may have mitigated beneficial effects of abatacept.

There are several important differences between this trial in participants at risk with stage 1 diabetes and the trial in individuals with new-onset stage 3 diabetes that may account for these findings. First, abatacept treatment in this trial was given for 1 year while it was given for 2 years in individuals at diagnosis (13,14). The presumed mechanism of abatacept, involving blockade of costimulation, requires the continuous presence of the drug. In the stage 3 trial,
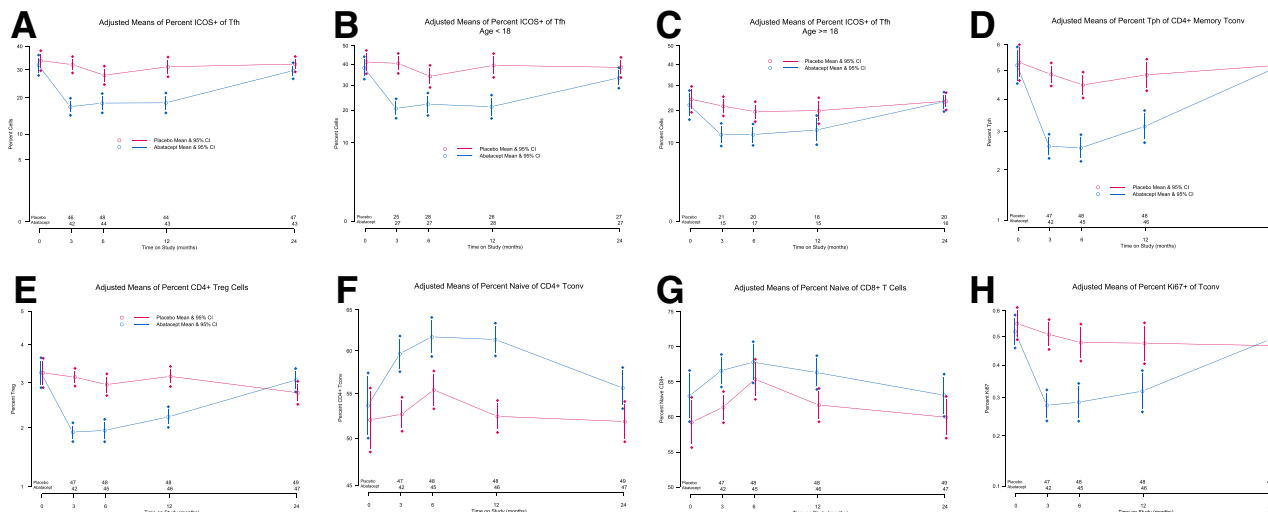
Figure 3—Immune cell subsets in the treatment groups and effects of abatacept on T-cell phenotypes and proliferation. The frequency of ICOS$^+$ of the total Tfh cells (*A*), ICOS$^+$ Tfh cells in children (3, 6, 12, and 24 months: $P = 0.0005$, $P = 0.003$, $P = 0.05$, and $P = 0.15$, respectively) (*B*), and in adults (3, 6, 12, and 24 months: $P < 0.0001$, $P < 0.0001$, $P = 0.008$, and $P = 0.93$, respectively) (*C*). The baseline levels of ICOS$^+$ Tfh cells was higher at the baseline in children ($P < 0.0001$), but there were similar effects of abatacept treatment in children and adults. *D*: Tph of CD4$^+$ memory cells were reduced with abatacept treatment vs. control (3, 6, 12, and 24 months: $P < 0.0001$, $P < 0.0001$, $P < 0.0001$, and $P = 0.67$, respectively). Tconv, conventional T cell. *E*: CD4$^+$ Tregs were also reduced (3, 6, 12, and 24 months: $P < 0.0001$, $P < 0.0001$, $P < 0.0001$, and $P = 0.13$, respectively). Gating strategy is shown in Supplementary Fig. 1. Naive CD4$^+$ (3, 6, 12, and 24 months: $P = 0.002$, $P = 0.25$, $P = 0.008$, and $P = 0.02$, respectively) (*F*) and CD8$^+$ T cells (3, 6,12, and 24 months: $P < 0.0001$, $P < 0.0001$, $P < 0.0001$, and $P = 0.15$, respectively) (*G*) in participants treated with abatacept or placebo. *H*: The percentage of Ki67$^+$CD4$^+$ T cells was reduced in participants treated with abatacept vs. placebo (3, 6, 12, and 24 months: $P < 0.0001$, $P < 0.0001$, $P < 0.0001$, and $P = 0.95$, respectively).

the rates of C-peptide decline were comparable in the two groups after the first 12 months, suggesting the drug effectiveness was lost when it was discontinued (7). The changes in T cells with drug administration that we found only were seen when the drug was being given— the differences did not persist after drug discontinuation. It remains possible that cognate signals to T cells without costimulation may render them nonresponsive (32), but the data in this trial would suggest that priming of autoreactive cells had occurred prior to the intervention, that activation of the immune response at this stage is not sensitive to costimulation blockade, or that the slow progression of stage 1 type 1 diabetes evaded the 1 year of drug treatment. The rate of conversion to AGT was lower in this population than had been initially predicted, which may have limited the exposure to drug treatment during the active phase of disease progression in many participants. Our data concerning progression of autoantibodies suggest that priming had occurred before study entry. Timing may be important in the efficacy of abatacept since preclinical studies identified stage-dependent effects of CD80 and CD86 blockade on progression of diabetes in NOD mice. Human

CTLA4Ig did not prevent disease when given to mice 2–4 weeks of age, but its efficacy was restricted to after insulitis and before frank diabetes (12, 32,33).

Second, the study in early stage 3 individuals had as its primary end point the effect of abatacept on C-peptide responses, whereas in this trial, we evaluated the effects on glucose tolerance. In our other prevention trials, these outcomes were not equivalent, most likely because glucose tolerance is the net outcome of several factors, including quantitative and qualitative insulin secretion, and insulin sensitivity (33).

Third, the decline in C-peptide responses to oral glucose in the placebo group was minimal in this stage 1 study, whereas in individuals with stage 3 disease, 50% of the C-peptide response was lost after 1 year. Therefore, despite the immunologic effects, the slow progression of the natural disease in many participants with stage 1 type 1 diabetes would dilute our ability to identify any effect on the primary end point that may only be reached after there is much greater loss of C-peptide than was seen in the placebo group or with a larger sample size in which more events occurred during the year of treatment.

Finally, there were differences in the baseline characteristics in this trial and the study with stage 3 individuals, such as a younger age of the stage 3 participants, a greater number of autoantibodies (>50% had three or four positive autoantibodies), and even the presence of IAA (14). Curiously, in this trial, the levels of Tfh cells were higher in the children (age <18) than in adults, but the effect of the drug in both age categories was similar. There may be differences in the role of Tfh or other cells by age as well as disease stage that may necessitate selection of mechanistically directed therapies and dosing depending on these and other factors that define disease endotypes (34).

There are limitations to the interpretation of these clinical trial data. The study was completed during the coronavirus disease 2019 pandemic, which may have influenced the timing of the follow-up visits and the discovery of AGT. Missed doses of study drug and visits were comparable in both groups. Therefore, the timing of the primary end point would not be affected, but the exposure to the active drug may have been less than planned in the abatacept arm. A larger sample size may have had the power to detect a statistical difference in the progression to stage 2 type 1 diabetes.

Our decision regarding the study design involved several considerations, such as the acceptable time for continuous drug administration, our experience in individuals with stage 3 type 1 diabetes in which the greatest effect of abatacept on C-peptide was in the first year of the study. Some of the participants progressed directly to stage 3 diabetes, and while the drug effect on this end point was also not statistically significant, longer follow up may identify a persistent effect of treatment that was suggested by our studies in individuals with stage 3 type 1 diabetes.

Our mechanistic studies involved participants with complete sample collections, but this subgroup (n = 42 abatacept, 47 placebo) was not identical to the entire cohort in disease progression. Nonetheless, this is not likely to have affected the drug effects on immune cells in the two treatment arms.

Finally, our planning parameters assumed a constant rate of progression to stage 2 type 1 diabetes, but we found that the rate declined with longer duration in the trial (Supplementary Table 4). This may have been influenced by our restriction of IAA$^+$ individuals from randomizing. Excluding participants with IAA reduced the number of autoantibodies that may be positive, and the number of positive autoantibodies has been shown to correlate with the rate of disease progression (35). The relatively long time required for the IAA$^-$ participants to reach AGT may have adversely affected results that were seen in the early time periods.

In conclusion, this trial of 1-year treatment with abatacept in participants with stage 1 type 1 diabetes did not show a statistically significant effect on progression to stage 2 or stage 3 type 1 diabetes. The treatment caused the anticipated biologic changes in immune cells and an effect on metabolic function in these early-stage participants. Had there been higher rates of progression in the placebo group or a longer period of treatment, we may have seen a greater effect on metabolic function and a statistically significant effect on the primary outcome. However, it is also important to consider that costimulatory pathways that do not involve CD80/CD86 may be engaged at this early stage of the disease. Multiple cell types and events may be required for progression to clinical type 1 diabetes. Some or all of these may be affected by abatacept.

The contrast in findings from our previous study in stage 3 diabetes help to identify the mechanisms and timing of progression in stage 1 type 1 diabetes but identify limitations in testing agents in stage 3 disease for use in earlier stages. Thus, while the trial did not meet its primary outcome, results suggest that abatacept may have a role as a disease-modifying therapy in type 1 diabetes.

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access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

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