



Effect of abatacept on immunogenicity of vaccines in individuals with type 1 diabetes



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ABSTRACT

Abatacept delayed progression of type 1 diabetes (T1D) when administered soon after diagnosis. Its use in T1D is expanding to prevention trials and, therefore, it is important to fully characterize its immunosuppressive effect. We compared antibody responses to trivalent inactivated influenza vaccine (TIV) administered during 2 consecutive seasons and to tetanus toxoid (TT) vaccine administered after 24 months of treatment in 115 early onset T1D subjects randomly assigned to 24 months of abatacept ($N = 71$) or placebo ($N = 34$). Anti-influenza titers before TIV were similar between the 2 treatment groups and both groups had significant increases after vaccination. Although the magnitude of antibody responses against some influenza serotypes was significantly lower ($p < 0.05$) in abatacept compared with placebo recipients, no differences were observed in the proportion of subjects with protective titers against influenza after vaccination. The magnitude of antibody responses against TT also tended to be lower ($p = 0.06$) in abatacept compared with placebo recipients, without affecting the proportion of subjects who achieved protective titers. We conclude that abatacept moderately decreases the magnitude of antibody responses to recall vaccination. Further studies are needed to assess its effect on primary immunization.

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1. Introduction

Type 1 diabetes mellitus (T1D) is an immune-mediated disease in which insulin-producing pancreatic beta-cells are destroyed, resulting in life-long dependence on exogenous insulin. The pathophysiology of T1D most likely requires the presentation of beta-cell antigens to T cells within lymph nodes. The antigen-reactive T cells then migrate to the pancreas where autoimmune destruction of the beta cells occurs. The use of immunosuppressive therapy for treatment of autoimmune diseases has been rapidly growing. This approach is widely utilized for rheumatoid arthritis, systemic lupus erythematosus and inflammatory bowel disease and is in the experimental stage for the treatment of T1D [1,2,3].

A recent double-blind placebo-controlled phase 2 study of abatacept in early onset T1D showed that the drug delayed beta-cell

destruction as measured by the serum C-peptide concentration after a mixed-meal tolerance test at 2 years' follow-up [1]. Abatacept, which is a formulation of CTLA4-Ig, is an immune modulatory agent that binds to CD80/CD86 receptors on antigen presenting cells and thereby inhibits their binding to the co-stimulatory molecule CD28 on T-cells. CD28 binding is essential for full T-cell activation. By blocking T cell activation, abatacept presumably prevents pancreatic beta-cell destruction. However, the interference with co-stimulatory pathways is not T1D-specific and may lead to undesired effects, such as opportunistic infections and impaired responses to vaccines.

The goal of this study was to characterize the antibody response to tetanus and seasonal trivalent inactivated influenza vaccines (TIV) in T1D subjects enrolled in the phase 2 abatacept trial.

2. Participants and methods

2.1. Clinical study design

This was a multicenter, double-blind, randomized, placebo-controlled trial that enrolled 112 individuals aged 6–45 years recently diagnosed with T1D. Subjects were randomly assigned (2:1) to receive abatacept (10 mg/kg, maximum 1000 mg per dose)

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or placebo infusions intravenously on days 1, 14, 28, and monthly for a total of 27 infusions over 2 years. Subjects received TIIIV yearly before the influenza seasons. Subjects also received a tetanus toxoid boost after 2 years of treatment with abatacept or placebo. Sera were collected before and 4 weeks after each immunization.

2.2. Hemagglutination inhibition assays (HAI)

Antibody responses to each influenza serotype in the TIIIV were measured by HAI as previously described [4]. Vaccine-matched antigens for each year's vaccine were obtained from the CDC. HAIs were performed on serial serum dilutions between 1:10 and 1:1280 using Turkey red blood cells (RBC). The titer was the last serum dilution that inhibited RBC agglutination. Antibody response was defined as ≥ 4 -fold increase in titer from baseline to post-vaccine. Titers $\geq 1:40$, which are associated with 50% decrease in the incidence of symptomatic disease, defined protection.

2.3. ELISA for antibodies to tetanus toxoid

The assay used the FDA-approved tetanus toxoid IgG ELISA (Immuno-Biological laboratories; cat. # IB79282) as per manufacturer's instructions for quantitative analysis. All samples were run in duplicate and averaged for the final result. Results were accepted if differences between replicates were < 2 -fold and all assay controls performed as expected. Antibody response was defined by a difference ≥ 2 -fold between baseline and post-vaccine antibody concentrations. Concentrations ≥ 0.1 $\mu\text{g/ml}$ defined protection.

2.4. Statistical analysis

Descriptive statistics, the Wilcoxon rank sum test, the Wilcoxon sign rank test, McNemar's test, analysis of covariance (with log transformations) and the Chi-Square test (or Fisher's exact test) were used to analyze the characteristics of the cohorts. An arbitrary value of 5 was assigned to HAI titers < 10 . The Anderson Darling statistic was used to assess normality, and, where appropriate, data were log transformed to achieve a normal distribution and apply a parametric test. Non-parametric tests were used when normal distributions were not achieved. *P*-value adjustments for multiple testing were not included. SAS software was used in all analyses.

3. Results

3.1. Characteristics of the study population

Of the 112 subjects enrolled in the parent study, 105 contributed data to the immune response analysis (Table 1). The average age was 14.4 years ($SD = 12.9$). There were 58% males, 96% white and 92% non-Hispanic. There were no significant demographic differences between the treatment groups.

3.2. Antibody responses to TIIIV

Anti-influenza titers were similar in abatacept and Placebo recipients in the first year of the study before the administration of TIIIV for all influenza serotypes (Table 2). After the first year vaccine administration, the geometric mean antibody titers (GMT) increased significantly in both treatment groups for all serotypes included in the vaccine. However, the GMT responses to H1N1 and H3N2 were significantly lower in abatacept compared with Placebo recipients ($p = 0.02$ for both) after adjusting for pre-vaccination titers. In year 2, baseline titers were similar between the 2 treatment groups for the serotypes included in the vaccine. Although TIIIV administration significantly increased the HAI titers against all

Table 1
Demographic characteristics.

	Abatacept (n = 71)	Placebo (n = 34)	Total (n = 105)
Age at baseline			
Mean (SD)	14.4 (6.6)	14.3 (5.3)	14.4 (6.2)
Median	12.3	14.4	12.9
Minimum	6.5	7.6	6.5
Maximum	35.0	34.2	35.0
Gender			
Male (%)	37 (52.1)	24 (70.6)	61 (58.1)
Female (%)	34 (47.9)	10 (29.4)	44 (41.9)
Race			
White (%)	65 (91.6)	31 (91.2)	96 (91.4)
Black (%)	2 (2.8)	1 (2.9)	3 (2.9)
Multiple races (%)	1 (1.4)	1 (2.9)	2 (1.9)
Other (%)	2 (2.8)	1 (2.9)	3 (2.9)
Unknown (%)	1 (1.4)	–	1 (1.0)
Ethnicity			
Hispanic (%)	9 (12.7)	4 (11.8)	13 (12.4)
Non-hispanic (%)	62 (87.3)	30 (88.2)	92 (87.6)

serotypes in both treatment groups, the GMT for influenza H1N1 and B were significantly or marginally lower ($p = 0.03$ and 0.06 , respectively) in abatacept compared with placebo recipients after adjusting for pre-vaccination titers.

The qualitative analysis of the proportions of subjects with titers $\geq 1:40$, which are considered 50% protective against symptomatic disease, did not show any differences between treatment groups for any influenza serotypes at baseline or subsequent time points (Table 3). There were significant increases in the proportion of seroprotected subjects in both treatment groups for H1N1 and H3N2 in years 1, but not in year 2. The proportion of subjects with seroprotection against influenza B significantly increased in the abatacept group in both years and marginally increased in the Placebo group in both years ($p = 0.06$ for both). In both groups, $\geq 70\%$ of the subjects achieved seroprotection against H1N1 and H3N2 after the year 1, but not after the year 2 vaccine. In the Placebo group, $\geq 70\%$ of the subjects achieved seroprotection against B in year 1, but not in year 2. In the abatacept group, the rate of seroprotection against B was $< 70\%$ in both years.

We performed individual analyses of the responses to serotypes newly introduced in the seasonal TIIIV to determine if they had a different pattern compared with the responses to repeat serotypes. Fifty-eight subjects received their first dose of TIIIV in 2008/2009. The remaining 28 subjects received their first dose in 2009/2010. All 3 serotypes in TIIIV were newly introduced in the vaccine in 2008/2009. The B serotype changed again from B/Florida/4/2006 in 2008/2009 to B/Brisbane/60/2008 in 2009/2010. Both A H1N1 and H3N2 serotypes in the vaccine changed between 2009/2010 and 2010/2011 (A/Brisbane/59/2007 and A/Brisbane/60/2008 to A/California/7/2009 and A/Perth/16/2009, respectively). Differences between treatment groups with respect to antibody responses to serotypes newly introduced in TIIIV were mixed: (1) there were significant differences between treatment groups in antibody responses against H1N1 and H3N2 after vaccination in 2008/2009, but not to the B serotype (Table 2); (2) there was a marginal difference between groups in antibody responses to B in year 2009/2010; (3) a combined analysis of the antibody responses to serotypes introduced for the first time in TIIIV vs. serotypes to which subjects had been exposed in the previous year (study vaccines only) showed similar trends (data not shown).

3.3. Antibody responses to tetanus toxoid boost

At baseline, the anti-tetanus toxoid antibody concentrations were similar between treatment groups (Table 4). Both groups had

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