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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 (TIIV) administered during 2 consecutive seasons and to tetanus toxoid (TT) vaccine administered after 24 months of treatment in115 early onset T1D subjects randomly assigned to 24 months of Abatacept (N=71) or placebo (N=34). Anti-influenza titers before TIIV 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.

Keywords

Abatacept; type 1 diabetes mellitus; tetanus vaccine; influenza vaccine

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.

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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[1-3].

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 (TIIV) in T1D subjects enrolled in the phase 2 Abatacept trial.

Participants and Methods

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) or placebo infusions intravenously on days 1, 14, 28, and monthly for a total of 27 infusions over 2 years. Subjects received TIIV 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.

Hemagglutination Inhibition Assays (HAI)

Antibody responses to each influenza serotype in the TIIV 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 ≥1:40, which are associated with 50% decrease in the incidence of symptomatic disease, defined protection.

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 μg/ml defined protection.

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.

Results

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.

Antibody Responses to TIIV

Anti-influenza titers were similar in Abatacept and Placebo recipients in the first year of the study before the administration of TIIV 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 TIIV administration significantly increased the HAI titers against all 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 ≥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, ≥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, ≥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 TIIV to determine if they had a different pattern compared with the responses to repeat serotypes. Fifty-eight subjects received their first dose of TIIV in 2008/2009. The remaining 28 subjects received their first dose in 2009/2010. All 3 serotypes in TIIV 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 TIIV 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 TIIV vs. serotypes to which subjects had been exposed in the previous year (study vaccines only) showed similar trends (data not shown).

Antibody responses to tetanus toxoid boost

At baseline, the anti-tetanus toxoid antibody concentrations were similar between treatment groups (Table 4). Both groups had significant antibody titer increases after vaccination. However, the antibody increases tended to be less robust in Abatacept compared with placebo recipients (p=0.06).

At baseline, 92% and 89% of Abatacept and placebo recipients, respectively, had antibody concentrations 0.1 μg/ml, which are considered protective against tetanus disease. After vaccination, all subjects in both treatment groups had protective antibody concentrations.

Discussion

Our data show that Abatacept tended to decrease the magnitude of the antibody responses to influenza and tetanus toxoid vaccines. Even though the antibody titers after TIIV administrations were lower in absolute values in the Abatacept group, the responses were robust enough to provide similar proportions of subject protection against influenza in the Abatacept and placebo groups. Our results are consistent with previous studies in patients with rheumatoid arthritis [5, 6], a condition for which Abatacept currently has a therapeutic indication [7, 8].

The magnitude of the antibody responses to tetanus toxoid boost was marginally decreased by Abatacept administration. However, the decreased response to the re-challenge did not affect the proportion of subjects with protective antibody titers. In contrast to our results, antibody responses to tetanus toxoid were not affected by a single dose of Abatacept administered to otherwise healthy adults [9]. The main difference is that in our study the tetanus toxoid boost was administered after 2 years of Abatacept treatment, suggesting a cumulative immunosuppressive effect of Abatacept with respect to humoral immune responses.

Our data indicate that Abatacept decreases recall responses to TIIV and tetanus. If it also affects primary responses it is more difficult to derive from our data. All subjects were previously vaccinated against tetanus. For influenza, subjects were vaccinated in 2008/2009, 2009/2010 and 2010/2011. Considering all the serotype changes in the vaccine, we could not detect an association pattern of attenuated antibody responses to TIIV with repeat or de novo immunization in the Abatacept group. However, antibody responses to serotypes introduced for the first time in TIIV typically draw both on naïve and memory B cells generated by exposure to related serotypes. Therefore, changes in TIIV serotypes may not provide a true primary antigenic challenge.

The mechanism used by Abatacept to decrease antibody responses to vaccines has not been extensively studied. Abatacept is well recognized as a regulator of T cell responses, particularly of Th1 responses [10]. Since both TIIV and tetanus toxoid are T-cell dependent vaccines, it is possible that the regulatory effect of Abatacept on T cells played an important role in decreasing the B-cell antibody production. However, B cells also express CD80 and CD86 [11] and Abatacept may have a direct effect on B cell activation and function both as antigen presenters and antibody producers.

Our study represents the first systematic evaluation of antibody responses in subjects treated with Abatacept for an autoimmune disorder. We found lower recall antibody responses in Abatacept recipients after TIIV and tetanus toxoid recall immunization. However, antibody responses need to be further evaluated in individuals with other underlying conditions and by studying antibody responses to primary immunization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Orban T, Bundy B, Becker DJ, DiMeglio LA, Gitelman SE, Goland R, et al. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. Lancet. 2011; 378:412–9. [PubMed: 21719096]
2. Herold KC, Pescovitz MD, McGee P, Krause-Steinrauf H, Spain LM, Bourcier K, et al. Increased T cell proliferative responses to islet antigens identify clinical responders to anti-CD20 monoclonal antibody (rituximab) therapy in type 1 diabetes. J Immunol. 187:1998–2005. [PubMed: 21775681]
3. Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, Becker DJ, Gitelman SE, Goland R, et al. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. N Engl J Med. 2009; 361:2143–52. [PubMed: 19940299]
4. Flynn PM, Nachman S, Muresan P, Fenton T, Spector SA, Cunningham CK, et al. Safety and Immunogenicity of 2009 Pandemic H1N1 Influenza Vaccination in Perinatally HIV-1-Infected Children, Adolescents, and Young Adults. The Journal of infectious diseases. 2012; 206:421–30. [PubMed: 22615311]
5. Ribeiro AC, Laurindo IM, Guedes LK, Saad CG, Moraes JC, Silva CA, et al. Abatacept and reduced immune response to pandemic 2009 influenza A/H1N1 vaccination in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2013; 65:476–80. [PubMed: 22949223]
6. Adler S, Krivine A, Weix J, Rozenberg F, Launay O, Huesler J, et al. Protective effect of A/H1N1 vaccination in immune-mediated disease--a prospectively controlled vaccination study. Rheumatology (Oxford). 2012; 51:695–700. [PubMed: 22171015]
7. Kremer JM, Russell AS, Emery P, Abud-Mendoza C, Szechinski J, Westhovens R, et al. Long-term safety, efficacy and inhibition of radiographic progression with abatacept treatment in patients with rheumatoid arthritis and an inadequate response to methotrexate: 3-year results from the AIM trial. Ann Rheum Dis. 2011; 70:1826–30. [PubMed: 21893583]
8. Abrams JR, Lebwohl MG, Guzzo CA, Jegasothy BV, Goldfarb MT, Goffe BS, et al. CTLA4Ig-mediated blockade of T-cell costimulation in patients with psoriasis vulgaris. J Clin Invest. 1999; 103:1243–52. [PubMed: 10225967]

9. Tay L, Leon F, Vratsanos G, Raymond R, Corbo M. Vaccination response to tetanus toxoid and 23-valent pneumococcal vaccines following administration of a single dose of abatacept: a randomized, open-label, parallel group study in healthy subjects. Arthritis Res Ther. 2007; 9:R38. [PubMed: 17425783]

10. Pilat N, Schwarz C, Wekerle T. Modulating T-cell costimulation as new immunosuppressive concept in organ transplantation. Curr Opin Organ Transplant. 2012; 17:368–75. [PubMed: 22790071]

11. Lim TS, Goh JK, Mortellaro A, Lim CT, Hammerling GJ, Ricciardi-Castagnoli P. CD80 and CD86 differentially regulate mechanical interactions of T-cells with antigen-presenting dendritic cells and B-cells. PLoS One. 2012; 7:e45185. [PubMed: 23024807]

- Antibody titers to flu vaccine were lower in CTLA4Ig than in placebo recipients
- However, there were no differences in the proportion of seroprotected individuals
- Same trends were observed after tetanus vaccination.

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)

Table 2

Anti-influenza antibody titers before and after immunization

Serotype and time	Abatacept			Placebo			P
	N	GMT (95% CI)	P*	N	GMT (95% CI)	P*	Abatacept vs. placebo
H1N1							
YEAR1 pre	65	33 (26.0, 42.0)	na	29	34.7 (23.2, 51.8)	na	0.95+
YEAR1 post	65	72.7 (55.4, 95.3)	**<0.0001**	29	129 (79.6, 209.3)	**0.0001**	**0.02#**
YEAR2 pre	34	53.2 (36.3, 78.0)	na	16	70.2 (35.7, 138.3)	na	0.52+
YEAR2 post	34	76.8 (51.1, 115.5)	**0.0003**	16	167.1 (78.4, 356.0)	**0.0002**	**0.03#**
H3N2							
YEAR1 pre	65	65.3 (47.1, 90.7)	na	29	66.1 (38.8, 112.4)	na	0.90+
YEAR1 post	65	146.9 (107.4,201.0)	**<0.0001**	29	240.2 (151.7,380.3)	**<0.0001**	**0.02#**
YEAR2 pre	34	69.4 (46.8, 102.8)	na	16	99.3 (48.2, 204.7)	na	0.39+
YEAR2 post	34	108.6 (73.1, 161.4)	**0.0002**	16	160 (80.4, 318.3)	**0.004**	0.66#
B							
YEAR1 pre	65	25.6 (20.4, 32.0)	na	29	27.9 (20.1, 38.8)	na	0.57+
YEAR1 post	65	41.7 (32.7, 53.2)	**<0.0001**	29	50.8 (34.2, 75.3)	**<0.0001**	0.44#
YEAR2 pre	34	13.0 (9.8, 17.3)	na	16	11.9 (8.4, 16.7)	na	0.82+
YEAR2 post	34	22.6 (16.9, 30.2)	**<0.0001**	16	33.6 (20.9, 54.2)	**0.008**	0.06#

Abbreviations: N=number of subjects with data; GMT = geometric mean titer; CI = confidence interval; na = not applicable.

Significant differences are underscored by bold facing.

* p value for GMT increase after vaccination, Wilcoxon Signed Rank Test.

+ p value, Wilcoxon Rank Sum Test.

p value adjusted for pre-immunization titer, Analysis of Covariance (log-transformed).

Table 3

Proportion of subjects protected against vaccine strains of influenza before and after immunization

Serotype and time of immunization	Abatacept			Placebo			P**
	N	% protected	P*	N	% protected	P*	Abatacept vs. placebo
H1N1							
YEAR1 pre	65	46.2	na	29	48.3	na	0.85
YEAR1 post	65	75.4	**<0.0001**	29	89.7	**0.0005**	0.16
YEAR2 pre	34	70.6	na	16	75	na	1.00
YEAR2 post	34	76.5	0.50	16	87.5	0.50	0.47
H3N2							
YEAR1 pre	65	69.2	na	29	62.1	Na	0.50
YEAR1 post	65	86.2	**0.0009**	29	93.1	**0.004**	0.49
YEAR2 pre	34	73.5	na	16	87.5	Na	0.47
YEAR2 post	34	85.3	0.12	16	93.8	1.00	0.65
B							
YEAR1 pre	65	44.7	na	29	55.2	Na	0.50
YEAR1 post	65	66.2	**0.0005**	29	72.4	0.06	0.55
YEAR2 pre	34	17.6	na	16	12.5	Na	1.00
YEAR2 post	34	41.2	**0.008**	16	43.8	0.06	0.86

Abbreviations: N=number of subjects with data; GMT = geometric mean titer; CI = confidence interval; na = not applicable

Significant differences are underscored by bold facing.

* p value for % increase after vaccination, McNemar's test.

** p value for abatacept vs placebo, Chi-Square test.

Table 4

Anti-tetanus toxoid antibody titers before and after immunization

Abatacept			Placebo			P
N	**GMC (95% CI)**	**P***	**N**	**GMC (95% CI)**	**P***	**Abatacept vs. placebo**
59	0.72 (0.47, 1.10)	na	25	0.68 (0.37, 1.28)	na	0.76+
59	10.5 (8.01, 13.77)	**<0.0001**	27	16.2 (10.04, 26.07)	**<0.0001**	0.06#

Abbreviations: N = number of subjects with data; GMC = geometric mean concentration; CI = confidence interval; na = not applicable

Significant differences are underscored by bold facing.

*p value for GMT increase after vaccination, Wilcoxon Signed Rank Test.

+p value, Wilcoxon Rank Sum Test.

#p value adjusted for pre-immunization titer, Analysis of Covariance (log-transformed).