CLINICAL AND VACCINE IMMUNOLOGY, Apr. 2010, p. 524–528 Vol. 17, No. 4
1556-6811/10/$12.00 doi:10.1128/CVI.00389-09
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Serum Bactericidal Antibody Response 1 Year after Meningococcal Polysaccharide Vaccination of Patients with Common Variable Immunodeficiency▽

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Received 30 September 2009/Returned for modification 28 December 2009/Accepted 18 January 2010

Some patients with common variable immunodeficiency (CVID) can generate an antibody response following vaccination with *Neisseria meningitidis* polysaccharide, but the duration of this protection is unknown. In this study, serum bactericidal antibody (SBA) responses to serogroup C *N. meningitidis* of 23 patients with CVID and 23 sex- and age-matched controls were measured 1 year after vaccination with the plain A/C meningococcal polysaccharide vaccine. The fold rise in serum bactericidal antibody geometric mean titers of the control group from prevaccination to 1 year postvaccination was significantly higher than that of the patient group (5.41- versus 2.96-fold, $P = 0.009$). Of 23 CVID patients, 8 had a poor response to vaccine (<4-fold rise) 3 weeks after vaccination, and low titers remained when measured 1 year later. Of the 15 CVID patients who had a normal response to vaccine (≥4-fold rise) 3 weeks after vaccination, 6 cases failed to maintain protective SBA titers, whereas the remaining 9 had protective titers 1 year after vaccination. Only one of the 23 controls, who developed protective SBA titers after 3 weeks, lost the protective titers after 1 year. Among the patients, the presence of bronchiectasis and/or splenomegaly at enrollment was associated with poor SBA response to vaccine at 3 weeks and/or failure to maintain protective levels at 1 year. The results of this study demonstrate that a number of CVID patients can produce protective antibody titers that can persist for 1 year after vaccination, which lends strong support to the inclusion of polysaccharide vaccine in the immunization program for CVID patients.

Common variable immunodeficiency (CVID) is the commonest symptomatic primary immunodeficiency disease and is a heterogeneous group of disorders, characterized by severe reduction of serum levels of IgG and IgA, with normal or low numbers of B cells in the absence of any recognized genetic abnormality (2, 11, 16, 30). Patients with CVID usually experience recurrent bacterial infections (1, 14) and carry an increased risk of autoimmunity (12, 28) and malignancies (4, 24). Various defects of B cells, T cells, and dendritic cells have been reported for CVID (26, 29, 34–36); however, the exact pathophysiology of the disease is still unclear (3, 15).

Deployment of polysaccharide and protein vaccines in CVID is a subject of active debate. Although it is intuitive that CVID patients should have poor antibody responses to vaccine, it is apparent that some patients can produce normal antibody titers (5, 18, 21, 32, 33). We have reported that a protective antibody response was achieved 3 weeks following vaccination with polysaccharide meningococcal vaccine of a group of CVID patients (32, 33). In the current study, we measured serum bactericidal antibody (SBA) titers (7) of the same cohort of patients 1 year after the initial vaccination.

MATERIALS AND METHODS

Patients and controls. Twenty-three patients with CVID (17 male and 6 female; mean age, 20.4 ± 12.7 years) and 23 healthy volunteers (17 male and 6 female; mean age, 22.4 ± 10.3 years), who had been vaccinated with meningococcal polysaccharide vaccine A + C (Aventis Pasteur, Lyon, France) 1 year prior (32), were enrolled in this study. This study was approved by the Ethics Committee on Human Research of Tehran University of Medical Sciences and Health Services. The diagnosis of CVID for this patient group was made according to standard criteria (25), including reduction of at least two serum immunoglobulin levels (serum IgG, IgA, and IgM) by two standard deviations from normal mean values for age and genetic exclusion of other well-defined single-gene defects (2, 11). Only patients with well-established CVID who had been included in our previous study of meningococcal vaccination were included in this study. Agammaglobulinemia with absent B cells, including X-linked (Btk deficiency) and autosomal recessive forms, hyper-IgM syndromes, and other primary antibody deficiencies, were excluded by molecular studies. Patients less than 2 years of age were excluded because of the possibility of transient hypogammaglobulinemia. Two CVID

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▽ Published ahead of print on 27 January 2010.

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TABLE 1. Characteristics of the CVID patients who enrolled in this study

Patient no.[a]	Sex	Diagnosis age (mo)	Study age (yr)	Serum immunoglobulin (mg/dl)			Lymphocyte surface marker (%)				Serum bactericidal antibody titer (before and after vaccination)		
				IgG	IgM	IgA	CD19	CD3	CD4	CD8	Before	3 wk after	1 yr after
1	Male	516	49	20	26	<5	11.0	54.0	31.0	22.5	1	16	2
2	Male	488	51	50	10	<5	7.0	70.4	24.0	40.1	4	32	16
3	Male	421	51	125	<10	<5	6.0	79.6	25.1	64.6	2	16	4
4	Male	228	28	50	<10	<5	12.0	85.0	57.0	52.0	1	2	2
5	Female	181	30	50	10	<5	11.2	79.3	40.4	35.2	1	16	16
6	Male	160	18	20	140	6	17.2	71.0	36.1	24.7	4	32	16
7	Female	150	20	100	<10	<5	8.3	85.3	23.4	50.0	1	1	1
8	Male	124	16	270	35	27	10.0	63.0	29.0	23.0	1	1	1
9	Female	110	16	410	20	10	15.1	78.1	38.3	35.1	1	16	16
10*	Male	108	24	50	10	5	10.0	65.0	35.0	32.0	1	2	2
11	Female	97	15	20	10	5	24.9	66.4	35.2	31.3	1	16	8
12	Male	86	15	470	10	5	7.5	80.9	43.1	34.6	4	32	16
13	Male	81	24	100	<10	<5	8.5	62.2	24.7	35.4	1	8	8
14	Male	59	12	50	10	5	5.2	65.1	43.9	32.0	4	32	4
15	Male	47	18	100	29	10	31.4	65.0	31.7	34.2	1	1	2
16	Male	42	19	360	42	10	2.2	62.7	6.8	50.4	1	1	2
17	Male	42	11	320	10	5	16.6	74.1	41.2	33.1	1	32	16
18	Female	42	9	213	<10	11	19.9	71.6	17.1	51.0	1	8	8
19	Female	33	26	100	10	5	2.1	88.6	66.2	19.0	4	16	4
20	Male	30	12	140	20	5	12.0	77.0	31.0	25.0	2	4	4
21	Male	29	11	200	20	<5	2.5	54.0	12.0	38.0	1	1	2
22	Male	27	14	310	48	10	21.9	66.7	37.4	26.4	2	8	2
23	Male	26	7	170	13	67	10.0	49.0	4.5	23.0	1	8	2

[a] *, the patient with history of bacterial meningitis.

patients and two controls who were enrolled in our previous study were unavailable and therefore not included in this study.

Serum sampling. After informed consent was given, blood samples were collected from the subjects 1 year after vaccination. As all patients were on regular intravenous immunoglobulin treatment (every 3 or 4 weeks), sampling was performed at least 3 weeks after immunoglobulin replacement therapy, just before the next immunoglobulin replacement therapy. Serum was separated, heat inactivated, and then stored at −70°C until the time of the SBA assay.

Measurement of SBA. The method of the SBA assay was previously described (33). Briefly, 50-μl heat-inactivated serum samples were serially diluted 2-fold in assay buffer. Then, 12.5 μl bacterial suspension and 12.5 μl pooled baby rabbit complement were added. The cell culture plates were incubated for 60 min at 37°C, and a 7-μl aliquot from each well was spotted onto a GC agar plate. The GC agar plate was incubated overnight at 37°C in a 5% CO_2 atmosphere, and then the CFU were counted. The serum bactericidal titer was reported as the reciprocal of the highest serum dilution yielding more than 50% bacterial killing, compared to the number of CFU present before incubation with serum and complement (32, 33).

Definition of vaccination responses. As is conventional, protective titers were defined as a value for SBA with rabbit complement (rSBA) of ≥8 (7). For the purpose of conservatively comparing responses in this study, in which patients were receiving regular doses of immunoglobulin, patients were subclassified into three groups: nonresponders (group I, <4-fold SBA titer rise from pre- to postvaccination [3 weeks and 1 year]), transient responders (group II, ≥4-fold SBA titer rise 3 weeks after vaccination and <4-fold SBA titer rise 1 year after vaccination), and long-term responders (group III, ≥4-fold SBA titer rise 1 year after vaccination).

Statistics. Statistical analysis was performed using the SPSS statistical software package (version 14.0). Geometric mean titers (GMTs) were calculated, and an SBA titer fold rise of ≥4 following vaccination was considered protective for each subject (6, 23). Clinical parameters were compared between groups using the chi square test. The Mann-Whitney U test was performed to compare GMTs between patient and control groups. The Kruskal-Wallis test was performed to compare GMTs among the groups, and the Wilcoxon signed-rank test was done to compare GMTs before and after vaccination in each group. A P value of less than 0.05 was considered significant.

RESULTS

Patients' characteristics. Twenty-three patients with CVID, all of whom were symptomatic as a result of recurrent infection, were investigated in this study (Table 1). There was a history of upper and/or lower respiratory tract infections in all patients, and 18 patients also experienced gastrointestinal manifestations. The most common manifestations were pneumonia (22 cases), diarrhea (18 cases), sinusitis (18 cases), and otitis media (15 cases), followed by eczema, conjunctivitis, septic arthritis, mucocutaneous candidiasis, superficial abscesses, pyelonephritis, and bacterial meningitis. Twelve patients had radiologically proven bronchiectasis. Splenomegaly and hepatomegaly were confirmed by ultrasound examination in 10 and 7 cases, respectively, and lymphadenopathy was found in 9 patients by clinical examination. Although none of these patients had autoimmunity and malignancies at the time of diagnosis, autoimmune diseases developed in six patients during the course of follow-up. Three other patients had malignancies, which were treated before enrollment in this study.

Serum bactericidal GMTs. Serum bactericidal GMTs are shown in Table 2. One year after vaccination, the SBA GMT of the patient group was significantly lower than that of the control group ($P = 0.045$). However, the serum bactericidal GMTs 1 year after vaccination were significantly higher than the prevaccination levels for both the patient group (4.38 versus 1.48,

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TABLE 2. SBA titers for patient and control groups

Time point or range	SBA GMTs or change		*P* value
	CVID patients (n = 23)	Controls (n = 23)	
Prevaccination	1.48	1.39	0.939
3 wk after vaccination	6.88	12.20	0.315
Prevaccination to 3 wk postvaccination	4.65-fold rise	8.76-fold rise	0.041
1 yr after vaccination	4.38	7.53	0.045
Prevaccination to 1 yr postvaccination	2.96-fold rise	5.41-fold rise	0.009
3 wk to 1 yr postvaccination	0.64-fold decrease	0.62-fold decrease	0.799

$P < 0.001$) and the control group (7.53 versus 1.39, $P < 0.001$). Small fold decreases in SBA titers in the period between 3 weeks and 1 year postvaccination were observed with both patients and controls. The fold rise in GMT from prevaccination to 1 year postvaccination in the control group was significantly higher than that in the patient group (5.41- versus 2.96-fold, $P = 0.009$). Among the patients, none had SBA titers ≥8 at the onset of the study, whereas 15/23 and 9/23 had such protective titers at 3 weeks and 1 year postvaccination, respectively (Table 1). In each case, a titer rise of at least 4-fold was exhibited from baseline. Among the controls, none had prevaccination SBA titers ≥8, whereas 22/23 and 16/23 had such protective titers at 3 weeks and 1 year postvaccination, respectively. Although 7 of the controls had SBA titers <8 at 1 year, only one control subject failed to have SBA titers ≥4-fold higher than those at the prevaccination level.

Responders and nonresponders among CVID patients. All 23 controls that were evaluated in this study exhibited a ≥4-fold rise in SBA titer (responder) from prevaccination to 3 weeks after vaccination. In the CVID group, 8 of 23 patients (34.8%) had a <4-fold rise in SBA titer from prevaccination to 3 weeks after vaccination; all of them remained nonresponders 1 year after vaccination (group I, nonresponders; Table 1). Among 15 patients who had a ≥4-fold rise of SBA titer at 3 weeks, 6 cases (26.1%) failed to maintain protective SBA titers 1 year after vaccination (group II, transient responders; Table 1), whereas the remaining 9 patients (39.1%) retained an SBA titer at 1 year that was ≥4-fold higher than the prevaccination level (group III, long-term responders). The difference between the proportions of patients and controls who were responders was significant ($P < 0.01$).

Comparison of GMTs among CVID groups. The GMT 1 year after vaccination in group III (long-term responders) of the CVID patients was 12.69, which was significantly higher than those of group I (nonresponders) (1.83) and group II (transient responders) (2.8) ($P < 0.001$). The prevaccination titers of the 3 groups were not significantly different ($P = 0.13$). The GMTs 3 weeks after vaccination and the fold rise in the GMTs of groups II and III were significantly higher than those for group I (rises of 7.13-fold in group II and 10.89-fold in group III versus 1.29-fold in group I, $P < 0.001$). The GMTs 1 year after vaccination and the fold rise in SBA titer in group III were significantly higher than those of groups I and II (rise of 8.00-fold in group III versus 1.68-fold in group I and 1.41-fold in group II, $P < 0.001$). Comparison of the responses of groups II and III revealed that while GMTs 3 weeks after vaccination for both groups increased significantly from prevaccination levels (group III, 17.28 versus 1.59, $P = 0.007$; group II, 14.25 versus 2.00, $P = 0.028$), the rise in the GMT 1 year after vaccination compared to prevaccination was significant only for group III (group III, 10.89 versus 1.59, $P = 0.007$; group II, 7.13 versus 2.00, $P = 0.102$).

Clinical characteristics of nonresponders among CVID patients. The clinical and laboratory characteristics of the patients were compared among the groups. The age at first presentation and diagnosis lag of group III patients (medians of 25 and 84 months, respectively) were higher than those for group I (medians of 5 and 44 months, respectively) and group II (medians of 11.5 and 15 months, respectively) patients, but these differences were not significant ($P \geq 0.1$). There was no significant difference in serum immunoglobulin levels or lymphocyte subpopulations between members of these groups. Recurrent infections, especially in the respiratory and gastrointestinal tracts, were common to all groups. However, there was a significantly increased rate of splenomegaly ($P = 0.020$) in group I (6 of 8 patients, 75%) compared to groups II and III (0% and 44.4%, respectively). Moreover, 7 patients in group I had bronchiectasis (87.5%), which was significantly more frequent ($P = 0.020$) than for groups II (50%) and III (22.2%). Bronchiectasis in both groups I and II was significantly more common than in group III (71.4% versus 22.2%, $P = 0.036$). Splenomegaly was a prominent finding for group I in comparison with the remaining 15 patients in groups II and III (75% versus 26.7%, $P = 0.039$).

DISCUSSION

This study has shown that a substantial proportion of patients with a diagnosis of CVID are able to generate serum bactericidal antibodies following vaccination with plain meningococcal polysaccharide vaccine and that protective bactericidal antibody titers will persist for at least 1 year in the majority of responding patients.

In the study by Goldacker et al., a positive vaccination response was detected with 23% of CVID patients against polypeptide vaccines and with 18% against polysaccharide antigens (18). The study by Ko et al. also suggested that some CVID patients could also respond to certain polysaccharide vaccines (21). While almost all previous reports evaluated the quantity of antibody responses to certain vaccines, particularly pneumococcal polysaccharide vaccine, we used the SBA assay, an antibody-mediated complement-dependent method, to evaluate the function of antibody responses to meningococcal polysaccharide vaccine (7). The presence of bactericidal activity by SBA assay indicates production of specific antibodies, and the rise in SBA titer is correlated with protection (23). The patients were subclassified into three groups based on short and long-lasting responses to meningococcal polysaccharide vaccine.

Considering the results of this study and also other recent reports (18, 21), it is apparent that some patients with CVID can generate antibodies against protein or polysaccharide antigens. This observation is of practical importance for two reasons. First, it may help us to define clinical subgroups within this heterogeneous disease (18, 31). Second, it shows us that vaccination against encapsulated bacteria, such as *Streptococ-*

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cus pneumoniae, *Haemophilus influenzae*, and *Neisseria meningitidis*, is worthwhile for some CVID patients and probably should be recommended for routine care.

The plain meningococcal polysaccharide vaccine induces a T-cell-independent immune response, which stimulates B cells to produce specific antibodies against the capsular polysaccharides. These antibodies have an important role in defense against bacterial infections by opsonization of bacteria for phagocytosis by macrophages and for classical complement-mediated killing (10, 19, 20). However, as the polysaccharide cannot induce antibody avidity maturation or isotype switching, this polysaccharide vaccine generates relatively poor immunological memory for long-term protection (8, 13, 17, 20, 37). This is reflected in the significant fold decreases of SBAs that we observed with both groups of CVID patients and controls. Thus, while responses could decay over time in some cases, repeat vaccination could have some benefits, especially in the transient responder group. However, the immunological basis of long-term protection is still poorly understood (7) and further studies are needed to evaluate how CVID patients respond to repeat vaccination.

Comparison of some characteristics among the groups showed that bronchiectasis was significantly more common in groups I and II with poor vaccine response either 3 weeks after or 1 year after vaccination, while splenomegaly was a prominent finding for group I. It should be noted that discriminating between the complications that are part of the underlying immune dysregulation (such as splenomegaly) and those that are due to infections (such as bronchiectasis) is important (11). Recurrent respiratory infections can lead to long-term complications such as bronchiectasis, which was detected with half of our patients. Poor antibody response to polysaccharide antigens could explain the development of bronchiectasis in the nonresponder group, while normal antibody responses to polysaccharide antigens could protect patients from recurrent severe pneumonia and consequently bronchiectasis (31). A high rate of bronchiectasis in CVID patients with a paucity of switched memory B cells and poor antibody responses to polysaccharide vaccine have previously been shown (9, 21, 35). Although low numbers of IgM memory B cells and an absence of IgM antibodies against polysaccharide antigens could underlie the recurrent pneumonia in this group of CVID patients (9, 22), it has not been confirmed in a pediatric population (31). Splenomegaly also seems to be more common in the group of patients with low numbers of switched memory B cells (27).

Although the study was performed on a group of patients who were under immunoglobulin replacement therapy, the fact that all patients who had a <4-fold rise in SBA titer from prevaccination to 3 weeks after vaccination remained nonresponders 1 year after vaccination implies that immunoglobulin infusions did not confound the measurements of SBA. There are also some complexities regarding antibody responses in CVID, which warrant discussion. Although quantitative and qualitative assessment of a panel of antibodies could be done, it is not clear how many antigens should be tested and which conclusion could be drawn in the case of normal response to some antigens and defective response to others (31). The strength of our study is that it has used the widely accepted functional parameter of bactericidal activity and clinically relevant protective response.

In conclusion, this study has shown that some CVID patients can produce protective bactericidal antibody titers even 1 year after vaccination, similar to those of the normal population. Therefore, vaccination of CVID patients with certain vaccines should be strongly considered by clinical teams, while evaluation of antibody response could also show the T-cell-independent immune response of these patients. The responder patients, either transient or long term, may have a better prognosis than nonresponders.

ACKNOWLEDGMENTS

This research has been supported by the Immunology, Asthma, and Allergy Research Institute, Tehran University of Medical Sciences and Health Services.

We are very grateful for all colleagues in the Department of Bacterial Vaccine and Antigen Production, Pasteur Institute of Iran, for their kind help and advice in the laboratory and all the patients and their families for their kind collaboration in this study. We thank Mohsen Siavashi, Reza Khalili, and Shahnaz Faridani for their contribution in collecting the samples from the subjects and also Maryam Haftlang, Elham Reyhani, and Sepideh Shahkarami for their contribution in preparing the serum samples.

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