Specific Antibody Response After Influenza Immunization in Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To determine the efficacy of influenza virus vaccine in patients with systemic lupus erythematosus (SLE).

Methods. The study population comprised 24 patients with SLE who received the split-virion, inactivated vaccine containing 15 μg hemagglutinin (HA)/dose of each of A/Beijing/262/95(H1N1), A/Sydney/05/97(H3N2), and B/Harbin/07/94. Hemagglutination inhibition (HI) antibodies were tested using the HI test according to a standard World Health Organization procedure. Immune response was defined as 4-fold or greater rise in HI antibodies 6 weeks after vaccination. Geometric mean titers (GMT) were calculated to assess the immunity of the whole group.

Results. All patients were women. Prior to vaccination, the percentage of SLE patients with protective levels of HI antibodies and the GMT of HI antibodies were similar to those of age matched healthy women. Six weeks after vaccination, 75% of the patients had immune response to at least one of the 3 antigens; 58.3% and 62.5% of the patients responded to A/Sydney/05/97(H3N2) and B/Harbin/07/94, respectively. However, only 37.5% of the patients responded to A/Beijing/262/95(H1N1).

Six weeks after immunization, the SLE patients generated immune response against a mean number of 1.5 of the 3 influenza vaccines. There was a trend toward a lower immune response in patients with age $\geq$ 50 years, prednisone dosage $\geq$ 10 mg daily, and who used azathioprine. However, methotrexate therapy was not associated with decreased response.

Conclusion. The immune response to influenza vaccine of patients with SLE is lower than that seen in adults in the general population, in particular among older patients and those treated with immunosuppressive therapy. (J Rheumatol 2002;29:2555–7)

Key Indexing Terms:
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Recently we have shown that influenza virus vaccination is safe for patients with systemic lupus erythematosus (SLE)[1]. However, it may trigger autoimmunity manifested by the generation of a wide range of autoantibodies including anti-Sm, anti-RNP, anti-Ro, and anti-La[2]. We examined the sera of patients with SLE who received the influenza vaccine for the presence of anti-influenza antibodies.

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MATERIALS AND METHODS

The study population comprised 24 patients with SLE who were vaccinated with 0.5 ml of split inactivated influenza virus vaccine (Vaxigrip, Pasteur Institute, Paris, France). All patients were seen at the time of enrollment into the study and 6 and 12 weeks after vaccination. Disease activity was assessed by SLE Disease Activity Index (SLEDAI)[3]. Sera at each assessment were separated from cells and stored at –70°C until tested for antibodies against the 3 components of influenza vaccine.

The hemagglutination inhibition test (HIT). The pre and postimmunization hemagglutination inhibition (HI) antibodies were tested at the Central Virology Laboratory, Ministry of Health (Tel-Hashomer, Israel), using the HIT according to a standard World Health Organization (WHO) procedure[4] and with the 1998-99 influenza reagent kit for identification of influenza isolates, produced and distributed by the WHO Collaborating Center for Reference and Research on Influenza (Atlanta, GA, USA). Sera were treated with receptor-destroying enzyme-cholera filtrate (No. C-8772, Sigma, Israel) to remove nonspecific inhibitors and with turkey red blood cells to remove nonspecific agglutinins. The treated sera were tested by HIT against the following influenza antigens: A/Sydney/05/97(H3N2), A/Beijing/262/95(H1N1), and B/Harbin/07/94. Four hemagglutinin units in 25 μl of each of the influenza antigens, diluted in phosphate buffered saline, were added to serial dilutions of the sera (1:20 to 1:2560).

The HI titer was determined as the last dilution of the serum that completely inhibited hemagglutinin. At least a 4-fold rise in the HI titer after immunization or seroconversion indicated an immune response to the vaccine. The HI antibody titers for each assessment for a whole group were

calculated as the geometric mean titers (GMT) of the group. HI titers ≥ 1:40 are defined as protective against infection with influenza virus[5].

HI antibodies in patients' sera prior to immunization were compared to those in sera from healthy adult female controls matched for age. None of those women had chronic diseases or had received chronic medications. All lived in southern Israel.

RESULTS

All patients were women. Their mean age at enrollment into the clinic was 46.1 years (range 20–74) and their mean disease duration was 9.1 years. The mean SLEDAI scores were 18 (4–59) at enrollment, 6.6 (0–36) at time of vaccination, 4.9 (0–28) at 6 weeks, and 5.1 (0–24) at 12 weeks after vaccination. The clinical and laboratory variables are published[1].

Seventeen patients had received oral steroids (mean dose 12 mg, range 2.5–40 mg), 9 patients were treated with 400 mg hydroxychloroquine, 3 patients were given 100 mg azathioprine, and 4 patients received methotrexate (MTX; mean dose 10 mg, range 7.5–12.5 mg). Six patients were taking only antimalarial therapy; their mean SLEDAI was 5 (range 3–8). The mean SLEDAI of patients treated with oral steroids/azathioprine or MTX was 7.6 (0–36).

Eighteen (75%) of the patients with SLE had a 4-fold or greater antibody response to at least one of the 3 influenza strains. Among them, 5 (20.8%) patients had antibody response to only a single influenza strain, 8 (33.4%) to 2 strains, and 5 (20.8%) patients had a 4-fold or greater immune response to all 3 influenza viruses (Table 1). Six (25%) patients did not respond to any of the 3 vaccine strains. Their mean age was 50.8 years (30–64) and their mean SLEDAI was 5.5 (0–14). All were taking oral steroid therapy (mean dose 15.8 mg, range 5–40), 2 patients were treated with azathioprine (100 mg each), and one patient received MTX (7.5 mg weekly).

Table 2 shows the number of patients and controls who had protective titers of HI antibodies at the 3 assessments. The percentage of HI antibodies > 40 and the mean GMT in the sera of the patients prior to immunization was similar to that seen in the controls matched for age (mean age 54 yrs). The GMT of HI antibodies for H3N2, H1N1, and B/Harbin of the controls were 14.8, 13.5, and 45.7, respectively, compared with 15.8, 12.6, and 63.1 among the patients with SLE at vaccination.

Table 3 shows the number of patients who had protective antibodies to one, 2, or 3 influenza viruses. Prior to vaccination, patients had protective antibodies against a mean 0.96 of the 3 influenza vaccines. The vaccination resulted in doubling this number to 1.96 vaccines.

Mean number of immune responses. We stratified the mean number of immune responses to the 3 components of influenza vaccine (≥ 4-fold or seroconversion) for each patient by age, SLEDAI score, and the intake of prednisone, MTX or azathioprine. The range of this mean number is 0–3, where 0 indicates patients had no response to all 3 antigens and 3 indicates the patient responded to all 3 antigens.

At 6 weeks after vaccination, the mean number of immune responses for the whole group was 1.5. There was a trend (not statistically significant) suggesting a mean number of immune responses less than 1.5 among patients with age ≥ 50 years, (mean 1.33, compared with 1.6 for patients younger than 50 yrs), patients treated with ≥ 10 mg prednisone (mean 1.14 vs 1.65), and patients who received azathioprine (mean 1.33 vs 1.6). MTX therapy and SLEDAI were not associated with reduced response to influenza antigens. The mean number of immune responses for the 4 patients given MTX was 1.75.

DISCUSSION

We measured the titers of HI antibodies 6 weeks and 12 weeks after vaccination. Before vaccination, GMT indicated that the anti-influenza immunity of the whole group of patients with SLE was similar to that of the control group. This immunity is the result of previous infections or vaccinations. The presence of HI titers ≥ 1:40, unrelated to the type of immune response, was considered protective, with an estimated protection level of 56%[4-6].

The number of patients with SLE who responded to the influenza was lower than expected in the general population. The WHO report on influenza vaccine indicates that vaccine containing A/Sydney/5/97(H3N2) stimulates postimmunization HI antibodies at titers ≥ 40 in the sera of 72–100% of adults (mean 89%), A/(H1N1) stimulates HI antibodies in 40–87% (mean 66%), and vaccines containing B/Harbin/07/94 stimulated postimmunization protective antibodies in the sera of 94–100% (mean 97%) of adults[7].

Our data suggest that individual patients with SLE may

Table 1. Influenza immune response in the sera of patients with SLE.

Response	Influenza A/Syd/05/97 (H3N2), n (%)	Influenza A/Beij/262/95 (H1N1), n (%)	Influenza B/Harbin/07/94, n (%)
No response*	8 (33.4)	15 (62.5)	2 (8.3)
No rise in titer	2 (8.3)	0	7 (29.2)
≥ 4-fold rise or seroconversion	14 (58.3)	9 (37.5)	15 (62.5)

* Titers < 1:20.

Table 2. HI antibody titers ≥ 1:40 in SLE patients at 6 and 12 weeks post vaccination and in a control group of 30 healthy women.

Vaccine	At Vaccination, n (%)	6 Weeks, n (%)	12 Weeks, n (%)	Controls, n (%)
A/Sydney/05/97 (H3N2)	5 (20.8)	16 (66.7)	14 (58.3)	6 (20)
A/Beijing/262/95 (H1N1)	2 (8.3)	8 (33.3)	6 (25)	5 (16.7)
B/Harbin/07/94	16 (66.7)	22 (91.6)	18 (75)	19 (63.3)

Table 3. Number of SLE patients with protective antibodies against the influenza antigens at time of vaccination and 6 and 12 weeks later.

Number of Inflenza Antigens	At Vaccination, n (%)	6 Weeks, n (%)	12 Weeks, n (%)
0	8(33.3)	2 (8.3)	4 (16.7)
1	11 (45.8)	6 (25)	8 (33.3)
2	3 (12.5)	8 (33.3)	6 (25)
3	2 (8)	8 (33.3)	6 (25)
Mean no. for all patients	0.96	1.92	1.6

respond to influenza vaccines. However, a significant number of patients may not respond or they may have a decreased response.

The reason for the reduced immune response to influenza vaccines is not clear, and most likely it is multifactorial. We observed a trend suggesting a diminished immune response to influenza vaccines among patients age 50 or above, as well as among patients treated with azathioprine or ≥ 10 mg prednisone. However, MTX therapy was not associated with decreased antibody responsiveness to influenza vaccine. It has been reported that aging and chronic diseases were associated with a significant impairment of IgG1 antibody response to influenza vaccine and possibly a reduced number of memory and naive T cells[8].

Others have also shown diminished immune antibody response to vaccines. In 1976, patients with SLE at several centers were immunized with the A/New Jersey/76 HswINI (swine) strain[9-13]. Decreased anti-influenza titers were observed among patients with serologically active SLE disease and nephritis and patients with renal failure. Only 48% of 29 patients with SLE who were vaccinated with A/New Jersey/76 HswINI generated a 4-fold or greater increase in anti-influenza (HI) antibodies.

Our data indicate that patients with SLE had a decreased immune response against influenza vaccine, particularly against influenza A/Beijing/262/95(H1N1). Although the immune response to influenza antigens is impaired, patients with SLE should be encouraged to receive the influenza vaccine, since it is well tolerated and may be protective[1].

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