SAFETY AND EFFICIENCY OF INFLUENZA VACCINATION IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

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Abstract

Introduction: Systemic lupus erythematosus (SLE) patients have a higher infection rate than the general population. The role of influenza vaccination in SLE patients has been a matter of discussion due to the risk of disease exacerbation and to the influence of the disease and its treatment on vaccine efficacy.
Objective: To study safety and efficiency of influenza vaccination in SLE patients.
Methods: We studied 47 SLE patients and 27 healthy controls for influenza hemagglutinin titers before and 6 weeks after immunization. SLE patients were scored for disease activity by SLEDAI before and after receiving the vaccine. We also studied antibody titers in SLE patients according to the use of glucocorticoid, methotrexate and azathioprine.
Results: Seroprotection after vaccination was equal in SLE patients and healthy controls although seroconvertion was lower in SLE patients for one of the three antigens tested. No significant increase in SLEDAI was observed. Medications such as methotrexate and azathioprine did not change the mean titers of antibody response but glucocorticoids did affect the response to one of the antigens.
Conclusions: Although immune response to influenza vaccine in SLE patients may be diminished it is safe and effective.

Keywords: Immunization; Influenza; Systemic Lupus Erythematosus; Vaccination.

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Introduction

Patients with systemic lupus erythematosus (SLE) have a higher infection rate than the general population. At least 50% of them will have one severe infectious episode caused by common or opportunistic microorganisms during the course of the disease.[1,2] Among the predisposing factors for increased rate of infection are low complement levels, functional alterations of phagocytic cells, impaired cellular immunity with lymphopenia and decreased cytokine production, reduced immunoglobulin production, low capacity of microorganism elimination by reticulo-endothelial system and use of immunosupressant drugs.[1,2]

Vaccination is a cheap and efficient way to avoid some infections. Live vaccines are contraindicated in imunossupressed patients and in those using more than 20 mg of prednisone per day or equivalent but there is some evidence that inactivated and component vaccines are safe in SLE.[3] Even though vaccination of SLE patients has been largely debated; rheumatologists are reluctant to indicate it.[4] There are, at least, two good reasons to explain this. The first is that SLE is an autoimmune disease of unknown etiology in which infectious epitopes are candidates for inducing or exacerbating the disease.[5,6] There are some reports that vaccination flared the disease even causing patient's death.[3] The second is that the protective response of SLE patients may be low making the vaccine ineffective.[3,7]

Vaccination against influenza is recommended for immunocompromised people with high chances of infection similar to those of SLE.[8]

Previous studies have shown that vaccination against influenza in lupus patients is quite safe. Abu-Shakra et al[7] however, studying serum of patients 6 weeks after influenza vaccination, found that autoantibodies such as anticardiolipin, anti-Ro, anti-La, anti-RNP but not anti-DNA were increased. The titers fell in the subsequent 12 weeks

and no patient had clinical manifestation of disease flare. Stojanovich,[5] on the other side, found that this vaccine is well tolerated by SLE and rheumatoid arthritis patients.

Concerning protective response, Mercado[8] studying 18 patients with SLE and 18 controls found an adequate level of protective antibodies in 61 to 72% of patients (the variations being caused by different studied antigens). Abu-Shakra et al,[9] in 24 patients, found lower titers in SLE patients that in healthy controls and those titers were even lower in patients over the age of 50 or using azathioprine or prednisone in doses higher than 10 mg per day. Another study showed that influenza vaccination generated as good antibody response in children with SLE as in control children and that the response was not affected by immunosuppressant therapy.[10] Vaccination response may vary according to immunogenicity and previous vaccinations.[7]

Considering the discrepant results in the literature we proposed to analyze the response of local SLE population to influenza vaccination as well as its potentially deleterious effects on clinical activity of disease.

Material and methods

The study was approved by the local Research Ethical Committee and all participants gave a written consent.

We included SLE patients with at least four American College of Rheumatology classification criteria for this disease,[11] older than 18 years that agreed to participate in the study from April to May 2007. None of them could be using cyclophosphamide or have active renal disease, central nervous manifestations or severe hematological manifestations. For control we invited healthy hospital workers and medical students.

SLE patients and controls should have blood drawn before and six weeks after influenza vaccination. Lupus activity was measured by SLE Disease Activity Index (SLEDAI). SLEDAI is a list of signs, symptoms and laboratorial findings to which are given values. A variation of 3 SLEDAI units is considered a disease flare.[12]

We included 47 lupus patients and 27 controls. None of them had received previous influenza vaccination.

SLE patient's age varied from 20 to 59 years old (mean 40.57±9.9) with one male and 46 female. Duration of disease varied from 24 to 336 months (mean 103.3± 65.9). Ten patients had had glomerulonephritis (class II, one patient; class III, four patients; class IV, four patients and class VI, one patient who was on hemodialysis). None of them had active renal disease. Twenty three patients used prednisone (mean dose 10.8 ±5.9 mg/day); eight were using methotrexate (mean dose 17.8± 5.8mg/week); nine were using azathioprine (mean dose 133.3±25mg/day) and one was using mycophenolate mofetil (1,5 g/day). Control persons were aged between 22 and 57 years (mean 34.7±12.0) and there were four male and 23 female.

Vaccine used had influenza virus hemagglutinin (HI) for the following antigens: A/NewCaledonian/20/99 (H1N1), A/Wisconsin/67/2005 (H3N2) and B/Malaysia/ 2506/ 2004. Seroconvertion was considered as a fourfold rise in the previous titer. Titers equal or over 1:40 were defined as protective against infection with influenza virus.[7]

Pre and post immunization hemagglutinin inhibition antibodies were tested according to a standard World Health Organization procedure.[13] Sera were treated with a receptor destroying enzyme (V. cholera neuraminidase) to remove non specific inhibitors. Treated sera were tested against A/New Caledonian/20/99 (H1N1), A/Wisconsin/67/2005 (H3N2) and B/Malaysia/2506/2004. Four hemagglutinin units in 25µL diluted in buffered saline and a 1% suspension of guinea pig erythrocytes were added to serial dilution of the sera (1:20 to 1:2560). Titer was determined as the last dilution of the serum that inhibited hemagglutinin. This procedure was repeated separately for each tested antigen.

Data obtained were studied through contingency and frequency tables. Fisher and chi squared tests were used for nominal variables and Mann-Whitney was used for numerical ones with the help of the software Graph Pad Prism 4.0. The adopted significance was 5%.

Results

Antibody level: The mean antibody level for lupus patients and controls before and after vaccination is showed in Table I. With all three tested antigens the mean value before and after immunization were lower in SLE patients. After immunization mean values for A/Wiscosin/67/2005 strain was 900.2±1012 µg/ml; for A/New Caledonian/20/99

strain 856±970 µg/ml and for M/Malaysia/2506/ /2004 strain 508.9±682.1 µg/ml in SLE patient against 1888± 108.3 µg/ml; 1994±1019 µg/ml and 1383±1059 µg/ml for the same antigens in healthy controls (Table I).

Seroprotection by vaccination: This study was repeated for each of the used antigens. Twenty five lupus patients (53.2%) and 23 controls (85.2%) already had seroprotection against influenza for the three antigens before vaccination. In SLE patients this protection raised to 68% for A/Wisconsin/67/2005; 76.6% for A/NewCaledonian/20/99 and to 63.9% for B/Malaysia/2506/2004 antigens. Comparative data on seroprotection levels obtained by lupus patients and controls after vaccination is seen in Figure 1.

When considering only patients and controls without previous seroprotection no difference was found in the number that became protected after vaccination (p=0.54 for A/NewCaledonian/20/99; p=0.10 for A/Wisconsin/67/2005 and p=0.53 for B/Malaysia/2506/2004 strains).

Seroconvertion by influenza vaccine: Seroconvertion was studied for each antigen isolated and is summarized in Table II. As observed, the number of SLE patients that achieved seroconvertion was lower than healthy controls (61% vs. 81.4% for A/Wisconsin/67/2005 strain; 57.4% vs. 81.4% for A/NewCaledonian/20/99 and 51.1% vs. 62.9% for B Malaysia/2506/2004 strain). This difference reached statistical significance only for A/ NewCaledonian/20/99 (Table II).

Lupus activity before and after immunization: There was no statistical difference between the values of SLEDAI before (mean 1.19 ±2.0) and 6 weeks after vaccination (mean 1.6± 2.6) (p=0.14, t test).

Influence of treatment on seroconvertion: Influence of glucocorticoid, azathioprine and methotrexate use on mean antibody titers is summarized in Table III. Glucocorticoid use was important only with regards to the formation of antibodies against B/ Malaysia/2506/2004 strain (Table III).

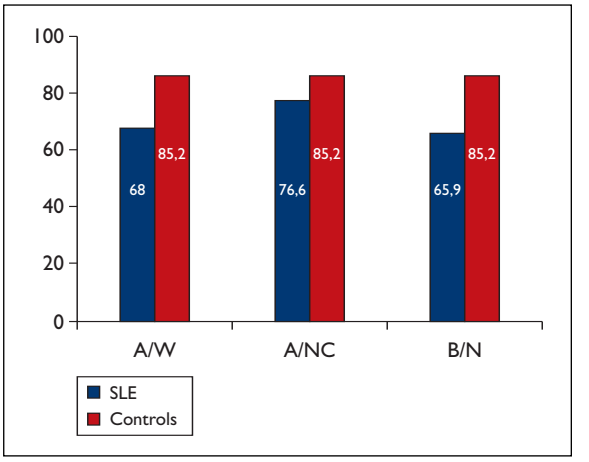

Figure 1. Seroprotection after influenza vaccination (%)
A/W - A/Wisconsin strain/67/2005
A/NC - A/New Caledonian/20/99 strain
B/M - B/ Malaysia/2506/2004 strain
*Fisher test

Discussion

Even though SLE patients have lower influenza antibody levels than controls before and after immunization, we found that influenza vaccination in a stable SLE population can offer protection against the infection. Younger age of control persons may also have contributed to the observed difference. Seroconvertion is slightly lower (although statistically significant only for one of the antigens). Nevertheless it is necessary to pay attention to the fact that influenza A causes more severe disease than influenza B and that in most seasons the prevalence of influenza A is higher than influenza B. Sufficient protection against influenza A is clinically more re-

Table I. Mean antibodies titer (µg/ml) in patients and controls before and 6 weeks after vaccination

	A/W		A/NC		B/M	
	Pre	Post	Pre	Post	Pre	Post
Lupus n=47	159±239	900.2±1,012	138.8±220	856±970	139±174.6	508.9±682.1
Controls n=27	1,059±1,114	1,888±1,083	1,305±1,120	1,994±1,019	980±1,409	1,383±1,059

A/W – A/Wisconsin strain/67/2005
A/NC – A/New Caledonian/20/99 strain
B/M– B/ Malaysia/2506/2004 strain

Table II. Seroconvertion (fourfold rise on previous titers) in lupus erythematosus patients and controls six weeks after immunization

	A/W	A/NC	B/M
Lupus patients (n=47)	n=29 (61.7%)	n=27 (57.4%)	n=24 51.1%)
Controls (n=27)	n=22 (81.4%)	n=22 (81.4%)	n=17 (62.9%)
P	0.11 (Fisher)	0.04 (Fisher)	0.32 (chi-squared)

A/W -A/Wisconsin/67/2005 strain
A/NC -A/New Caledonian/20/99 strain
B/M- B/ Malaysia/2506/2004 strain

levant than protection against influenza B. On the other hand it is reported that subtype H3N2 (which had a lower seroconvertion rate in our study) causes more severe disease than H1N1.[14]

Immunosuppressive drugs such as methotrexate and azathioprine did not change the level of produced antibodies. Glucocorticoids altered only antibody production for B/M antigen. It is important to notice that the mean prednisone dose was quite low and this cannot be extrapolated to larger doses. Also, it is necessary to note that the patient sample size is quite small and may be statistically underpowered. In the same way as in our SLE study, Fomin et al analyzing rheumatoid arthritis patients showed that DMARDs, including methotrexate, did not affect response to influenza vaccination.[15] In the present study we do not confirm the findings of Holvast et al[14] that azathioprine is associated with decreased efficacy of the vaccination.

With regards to safety we found in our study that influenza vaccination is safe and that lupus clinical activity did not rise as measured by SLEDAI before and 6 weeks after immunization.

We conclude that in stable disease, influenza vaccination is safe and effective and that SLE patients should be advised to receive it.

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Acknowledgements
The authors wish to thank the Municipal Department of Health of Curitiba for donation of vaccines used for this study.

References

1. Bouza E, Moya JGL, Munoz P. Infections in systemic

Table III. Antibodies mean titers in lupus erythematosus patients according to treatment used six weeks after immunization.

GLUCOCORTICOID (GC) USE (mean dose of 10.8±5.9 mg/day)			
	With GC (n=23)	**Without GC(n=24)**	**p (Mann Whitney)**
A/W	807.0±1010	989.6±1027	0.54
A/NC	320.0±640.0	640.0±1280	0.20
B/M	234.8±310.6	771.7±831.3	0.018
METHOTREXATE (MTX) USE (mean dose of 17.8± 5.80 mg/week)			
	With MTX(n=8)	**Without MTX(n=39)**	
A/W	587.5±899.4	964.4±1032	0.37
A/NC	458.4±800.3	926.3±990.2	0.18
B/M	227.5 ±262.7	566.7±728.3	0.33
AZATHIOPRINE (AZA) USE (mean dose133.3± 25 mg/day)			
	With AZA (n=9)	**Without AZA (n= 38)**	
A/W	540.0±498.1	985.6±1086	0.58
A/NC	1002 ±1185	822.4 ±926.9	1.0
B/M	398.9 ±408.4	541.1±743.0	0.81

A/W - A/Wisconsin strain
A/NC - A/New Caledonian strain
B/M - B/Malaysia strain

lupus erythematosus and rheumatoid arthritis. Infect Dis Clin N Am 2001; 15: 335-361.
2. Alarcón GS. Infections in Systemic connective tissue diseases: systemic lupus erythematosus, scleroderma, and polymyositis/dermatomyositis. Infect Dis Clin N Am 2006; 20: 849-875.
3. O'Neill SG, Isenberg DA. Immunizing patients with systemic lupus erythematosus: a review of effectiveness and safety. Lupus 2006; 15:778-73.
4. Mercado U. Why have rheumatologists been reluctant to vaccinate patients with systemic lupus erythematosus? J Rheumatol 2006; 33: 1469-1471.
5. Stojanovich L. Influenza vaccination of patients with systemic lupus eryhtematosus and rheumatoid arthritis. Clin Dev Immunol 2006; 13:373-375.
6. Shoenfeld Y, Aron-Maor A. Vaccination and autoimmunity-"vaccinosis': a dangerous liaison? J Autoimmun 2000; 14:1-10.
7. Abu-Shakra M, Press J, Varsano N, et al. Specific antibody response after influenza immunization in systemic lupus erythematosus. J Rheumatol 2002; 29:2555-2557.
8. Mercado U. Antibody response to influenza immunization in patients with systemic lupus erythematosus. J Rheumatol 2003; 19: 2295-2296.
9. Abu-Shakra M, Press J, Sukenik S, Buskila D. Influenza virus vaccination of patients with SLE: effects on generation of autoantibodies. Clin Rheumatol 2002; 369-372.
10. Kanakoudi-Tsakalidou F, Trachana M, Pratsidou-Gertsi P, Tsitsami S, Kyriasopoulou-Dalaina V. Influenza vaccination in children with chronic rheumatic disease and long term immunossupressive therapy. Clin Exp Rheumatol 2001; 19: 589-594.
11. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997; 40: 1725.
12. Bombardier C, Gladman DD, Urowits MB, Caron D, Chan CH. Derivations of SLEDAI. A disease activity index for lupus patients. Arthritis & Rheum 1992; 35:630-640.
13. WHO Manual on Animal Influenza Diagnosis and Surveillance, WHO/CDS/CSR/NCS/2002.5 Rev. 1 Available at: http://www.who.int/csr/resources/publications/influenza/whocdscsrncs20025rev.pdf
14. Holvast A, Huckriede A, Wilschut J, et al. Safety and efficacy of influenza vaccination in systemic lupus erythematosus patients with quiescent disease. Ann Rheum Dis 2006; 65:913-918.
15. Fomin I, Caspi D, Varsano N, et al. Vaccination against influenza in rheumatoid arthritis: The effect of disease modifying drugs, including TNFα blockers. Ann Rheum Dis 2006;65:191-194.

ACR/ARHP Annual Scientific Meeting

Filadelfia, Estados Unidos (EUA)
16 a 21 de Outubro de 2009