Safety and efficacy of influenza vaccination in systemic lupus erythematosus patients with quiescent disease

Holvast A. ¹, Huckriede A. ², Wilschut J. ², Horst G. ¹, De Vries J.J.C. ³, Benne C.A. ³, Kallenberg C.G.M. ¹, Bijl M. ¹

¹Department of Clinical Immunology, University Medical Center Groningen, University of Groningen, The Netherlands
²Department of Medical Microbiology, Molecular Virology Section, University Medical Center Groningen, University of Groningen, The Netherlands
³Laboratory for Infectious Diseases, Groningen, The Netherlands

Category submitted: extended report

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd to permit this article (if accepted) to be published in ARD and any other BMJPL products and sublicences such use and exploit all subsidiary rights, as set out in our licence (http://ard.bmjjournals.com/misc/ifora/licenceform.shtml).

Corresponding author:

Bert Holvast
Department of Internal Medicine
Division of Clinical Immunology
University Medical Center Groningen, University of Groningen

PO Box 30.001, 9700 RB Groningen, The Netherlands
E-mail: B.Holvast@int.umcg.nl
Abstract

**Objectives:** to assess safety and efficacy of influenza vaccination in systemic lupus erythematosus patients, and to evaluate the influence of immunosuppressive drugs on the immune response.

**Methods:** SLE patients (n = 56) and healthy controls (n = 18) were included. All patients had quiescent disease (SLEDAI ≤ 5). Based on use of medication, four patient groups were constituted: (1) patients without medication, (2) patients on hydroxychloroquine, (3) patients on azathioprine, and (4) patients on prednisone, respectively. Participants received trivalent influenza subunit vaccine during October – November 2003. Disease activity scores and side-effects were recorded. Antibody titres against influenza virus were measured before and 30 days after vaccination using the haemagglutination inhibition assay.

**Results:** Influenza vaccination did not result in changes in disease activity and was well tolerated. SLE patients developed less seroconversions or 4-fold titre rises for A/H1N1 (p < 0.001) and A/H3N2 (p < 0.001) than healthy controls, for B/Hong Kong the difference tended to be significant (p = 0.051). With regard to immunosuppressive treatment, fewer SLE patients using azathioprine developed 4-fold titre rises against A/H3N2 (p = 0.041), and fewer achieved titres ≥40 against A/H3N2 (p = 0.030) compared to the other patient groups.

**Conclusions:** Influenza vaccination in SLE patients with quiescent disease is safe but is less effective than in controls. Use of azathioprine was associated with a trend towards decreased vaccination efficacy.

**Key Words:** SLE, influenza vaccination, safety, efficacy
**Introduction**

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterised by relapsing and remitting disease activity. Immunosuppressive drugs are often needed to control disease activity rendering patients more susceptible for infections. Immuno-compromised patients have an increased risk of morbidity and mortality following influenza infection (1). Therefore, influenza vaccination should be considered in SLE patients. It is, however, still questionable whether vaccination might induce disease activity in patients with established autoimmune disease. A limited number of studies have been performed to establish whether influenza vaccination is safe in SLE patients (2-9). These studies have their limitations, as most dealt with small numbers of SLE patients (3;4;6;8;9) and included patients irrespective of their level of disease activity (4;5;7-9).

Furthermore, it is unclear whether vaccination is effective in SLE patients as they are assumed to have decreased primary and secondary immune responses (10). In addition, use of immunosuppressive drugs may further decrease the immune response following vaccination. In some studies it has been demonstrated that SLE patients display a reduced antibody response after vaccination compared to healthy adults (4;7;11). In contrast, other studies suggested a normal vaccination efficacy (2;3;5;6). Although it has been shown in transplantation patients that the use of drugs like corticosteroids, azathioprine, and cyclosporin decreases the antibody response after vaccination (12-16), influence of immunosuppressive drugs on efficacy of influenza vaccination in SLE patients has not been well examined.

In this study we assessed safety and efficacy of influenza vaccination and the effect of medication on vaccination efficacy in our (immuno-suppressed) cohort of systemic lupus erythematous (SLE) patients.

**Patients and methods**

**Patients**

Patients were eligible for the study when they fulfilled at least 4 of the American College of Rheumatology criteria for SLE (17) and had quiescent disease, defined as a SLE Disease Activity Index (SLEDAI) ≤ 5 (18). Based on predefined criteria concerning medication, patients were divided in 4 groups. Group A consisted of SLE patients who did not use immuno-suppressive drugs. Patients in group B used hydroxychloroquine ≥ 400 mg/day and patients in group C used azathioprine ≥ 50 mg/day. In both groups (B and C) a stable dose of prednisone less than 10 mg/day was allowed. Finally, group D consisted of patients who used a stable dose of prednisone ≥ 10 mg/day. Stable was defined as a constant dose, unaltered for at least a period of 2 months prior to vaccination. Patients were excluded when: (1) no informed consent was given, (2) in case of pregnancy, (3) other immuno-suppressive drugs than hydroxychloroquine, azathioprine, or prednisone were used , A total of 5 patients using MTX and 12 patients treated with a variety of other immunosuppressive drugs (cyclophosphamide, cyclosporine, mycophenolate mofetil) were excluded. Healthy volunteers, age and sex matched, were used as controls.

**Vaccines**

Influvac®, a trivalent influenza vaccine (2003-2004), was supplied by Solvay Pharmaceuticals (Weesp, Netherlands). The vaccine contained surface-antigens (haemagglutinin and neuramidase) of viruses bred on chicken eggs, of the following strains: A/Moscow/10/99-like (A/H3N2) (A/Panama/2007/99 RESVIR-17 reass.), A/New...
Caledonia/20/99-like (A/H1N1) (A/New Caledonia/20/99 IVR-116 reass.), B/Hong Kong/330/2001-like (B/Shangdong/797); 15 µg haemagglutinin per virus preparation.

Procedures
Patients and controls were vaccinated with Influvac®, a subunit vaccine, in October and November 2003. SLE patients were vaccinated at a regular outpatient visit. SLEDAI was recorded for measuring disease activity. After 30 ± 3 days patients and controls were seen again during which visit SLEDAI scores were once more recorded in the patients. In addition, patients were asked to fill in a Visual Analogue Score on a scale of 0-10 (patient VAS, disease activity as experienced by the patient) during both visits. In all participants information on previous influenza vaccination was obtained and adverse effects following vaccination were recorded. Adverse effects were classified into local (itching, pain, erythema, and induration at the site of vaccination), systemic (fever, tiredness, sweating, myalgia, chills, headache, arthralgia, diarrhoea, common cold like complaints), and other adverse effects.

At the time of vaccination and at the follow-up visit 10 ml blood was drawn. After sampling, serum was stored at –20° C till the end of the study.

Haemagglutination Inhibition Test (HAI test)
For quantitative detection of influenza antibodies the haemagglutination inhibition (HAI) test was used. HAI tests were performed with guinea pig erythrocytes following standard procedures (19) with slight modifications as described elsewhere (20). Sera were tested against all three vaccine strains. The antibody response was evaluated in three ways: by assessment of a ≥ 4-fold titre rise, by means of a titre rise to ≥ 40, and by the Geometric Mean Titres (GMTs). Four-fold titre rises and seroconversions are widely in use as parameters for efficacy of vaccination. Seroconversions were defined as those samples that tested negative (below 1:10) prior to vaccination, rising to at least 40 after vaccination. Titres ≥ 40 can be considered as protective in healthy adults (21), and a median titre of 28 protects 50% of healthy adult vaccinees (22).

Statistical analysis
Data were analysed using SPSS 11 (SPSS Inc). Mann-Whitney U test, Wilcoxon Signed-Rank test, Fisher’s exact test, and Kruskal-Wallis test were used where appropriate. A P-value < 0.05 was considered statistically significant.

Results
Fifty-six SLE patients and 18 healthy controls were included. Forty-three (77%) of the SLE patients had received influenza vaccination in the past compared to 4 (22%) of the healthy controls (p < 0.001). In accordance, more patients (34 out of 56) than controls (1 out of 17) had received influenza vaccination the year before (2002-2003; p < 0.001), which consisted of the same viral antigens. Patients were divided into 4 groups, based on immunosuppressive medication (Table 1). Medians for these various drugs were 400 mg/day of hydroxychloroquine in group B, 100 mg/day of azathioprine in group C and 10 mg/day of prednisone in group D. Baseline characteristics were equally distributed among groups. Patient groups did not differ in duration of SLE, patient VAS and SLEDAI (Figure 1, p = 0.644) before vaccination. Within patient groups, the numbers of patients who had received influenza vaccination in the past were comparable (p = 0.231), however more patients in the azathioprine group had received a vaccination in the previous influenza season (2002-2003) compared to other patient groups (p = 0.026).
Table 1: Baseline characteristics of SLE patients and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>No medication</th>
<th>Hydroxychloroquine</th>
<th>Azathioprine</th>
<th>Prednisone</th>
<th>Healthy controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>12</td>
<td>17</td>
<td>13</td>
<td>14</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Age, Median (range)</td>
<td>45 (29 - 78)</td>
<td>42 (26 - 66)</td>
<td>47 (28 - 64)</td>
<td>46.5 (18 - 71)</td>
<td>40.5 (21 - 57)</td>
<td>0.518</td>
</tr>
<tr>
<td>Sex Male/ Female</td>
<td>4/8</td>
<td>1/16</td>
<td>1/12</td>
<td>0/14</td>
<td>4/14</td>
<td>0.068</td>
</tr>
<tr>
<td>Duration of disease (Yrs), Median (range)</td>
<td>8 (2 - 43)</td>
<td>9 (3 - 45)</td>
<td>10 (4 - 29)</td>
<td>5 (1 - 36)</td>
<td></td>
<td>0.730</td>
</tr>
<tr>
<td>Influenza vaccination in the past Yes/ No</td>
<td>8/4</td>
<td>1/6</td>
<td>12/1</td>
<td>2/2</td>
<td>4/14 #</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Influenza vaccination last season Yes/ No</td>
<td>6/6</td>
<td>7/10</td>
<td>12/1*</td>
<td>9/5</td>
<td>1/17 #</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Kruskal-Wallis test was used to compare all groups for age and duration of disease, Fisher’s exact tests were used to compare all groups for sex and for influenza vaccination in the past/ last season.

# p < 0.001 when SLE patients are compared to healthy controls
* p = 0.026 when patients on azathioprine are compared to other patient groups

Safety of vaccination
SLEDAI scores after vaccination did not differ significantly from scores before vaccination in any of the patient groups. However, in the azathioprine group patient VAS scores were significantly lower after vaccination. In the other patient groups no significant changes of patient VAS scores were observed (figure 1).

Concerning side effects, 3 SLE patients reported local adverse reactions, 19 reported systemic adverse reactions. One healthy control reported a local adverse reaction and 1 healthy control reported a systemic adverse reaction. The difference in systemic adverse reactions between SLE patients and controls was significant (p = 0.02). In particular tiredness, sweating and myalgia were reported. All adverse reactions were mild.

Efficacy of vaccination
Geometric Mean Titres (GMT) in SLE patients and in controls are shown in Table 2A. As expected, since more SLE patients were vaccinated with the same vaccine the previous season, GMTs before vaccination were significantly higher in SLE patients compared to controls (p < 0.001 for A/H1N1, p = 0.036 for A/H3N2, and p < 0.001 for B/Hong Kong ). In patients as well as in controls GMT increased after vaccination and did not differ significantly between both groups. However, SLE patients had less seroconversions or 4-fold titre rises against A/H1N1 (p < 0.001) and A/H3N2 (p = 0.001) compared to controls, for B/Hong Kong this difference tended to be significant (p = 0.051; Table 2B). Seventy-five percent of SLE patients achieved a titre after vaccination of ≥40 for both influenza A strains together compared to 100 percent of healthy controls (p = 0.030). No significant differences were found in the percentage of patients who achieved a post-vaccination titre ≥40 for separate influenza strains compared to healthy controls, although a trend towards a lower percentage in patients could be seen.

Because more SLE patients than controls had an antibody titre ≥40 against influenza A/H1N1 and B/Hong Kong before vaccination (Table 2C), we assumed that this could reduce the number of patients reaching a seroconversion or 4-fold increase in titre. To exclude effects of an influenza vaccination the previous season, we examined those participants who did not receive an influenza vaccination in 2002 separately. SLE patients showed significant less seroconversions or 4-fold titre rises to A/H1N1 and A/H3N2 (Table 2D).
Table 2: Efficacy of influenza vaccination

2A. Geometric Mean Titres to influenza

<table>
<thead>
<tr>
<th></th>
<th>GMT to A/H1N1 before vaccination</th>
<th>GMT to A/H1N1 after vaccination</th>
<th>GMT to A/H3N2 before vaccination</th>
<th>GMT to A/H3N2 after vaccination</th>
<th>GMT to B/Hong Kong before vaccination</th>
<th>GMT to B/Hong Kong after vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE n = 56</td>
<td>32.4</td>
<td>142</td>
<td>50.0</td>
<td>183</td>
<td>16.2</td>
<td>64.0</td>
</tr>
<tr>
<td>Healthy Controls n = 17</td>
<td>6.93 **</td>
<td>130</td>
<td>21.7 *</td>
<td>272</td>
<td>5.65 **</td>
<td>49.0</td>
</tr>
</tbody>
</table>

Mann-Whitney U test was used for all variables.

* p < 0.05

** p < 0.001

2B. Seroconversions or 4-fold titre rises

<table>
<thead>
<tr>
<th></th>
<th>SLE n = 56</th>
<th>Healthy Controls n = 17</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/H1N1</td>
<td>24 (43%)</td>
<td>16 (94%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>22 (39%)</td>
<td>15 (88%)</td>
<td>0.001</td>
</tr>
<tr>
<td>B/Hong Kong</td>
<td>23 (41%)</td>
<td>12 (71%)</td>
<td>0.051</td>
</tr>
</tbody>
</table>

Fisher’s exact test was used for all variables.

2C. Titres ≥ 40 to influenza

<table>
<thead>
<tr>
<th></th>
<th>SLE patients n = 56</th>
<th>Healthy Controls n = 17</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/H1N1 ≥ 40 before vaccination</td>
<td>27 (48%)</td>
<td>1 (6%)</td>
<td>0.001</td>
</tr>
<tr>
<td>A/H1N1 ≥ 40 after vaccination</td>
<td>47 (84%)</td>
<td>17 (100%)</td>
<td>0.105</td>
</tr>
<tr>
<td>A/H3N2 ≥ 40 before vaccination</td>
<td>35 (63%)</td>
<td>7 (41%)</td>
<td>0.163</td>
</tr>
<tr>
<td>A/H3N2 ≥ 40 after vaccination</td>
<td>48 (86%)</td>
<td>17 (100%)</td>
<td>0.185</td>
</tr>
<tr>
<td>B/Hong Kong ≥ 40 before vaccination</td>
<td>14 (25%)</td>
<td>0 (0%)</td>
<td>0.030</td>
</tr>
<tr>
<td>B/Hong Kong ≥ 40 after vaccination</td>
<td>39 (70%)</td>
<td>12 (71%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Fisher’s exact test was used for all variables.
2D. Response of participants with no influenza vaccination in the previous year (2002)

<table>
<thead>
<tr>
<th></th>
<th>SLE patients</th>
<th>Healthy Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 22</td>
<td>n = 16</td>
<td></td>
</tr>
<tr>
<td>A/H1N1 titre ≥ 40 after vaccination</td>
<td>18 (82%)</td>
<td>16 (100%)</td>
<td>0.124</td>
</tr>
<tr>
<td>A/H1N1 seroconversion or 4-fold titre rise</td>
<td>14 (64%)</td>
<td>16 (100%)</td>
<td>0.012</td>
</tr>
<tr>
<td>A/H3N2 titre ≥ 40 after vaccination</td>
<td>19 (86%)</td>
<td>16 (100%)</td>
<td>0.249</td>
</tr>
<tr>
<td>A/H3N2 seroconversion or 4-fold titre rise</td>
<td>10 (45%)</td>
<td>15 (94%)</td>
<td>0.002</td>
</tr>
<tr>
<td>B/Hong Kong titre ≥ 40 after vaccination</td>
<td>15 (68%)</td>
<td>12 (75%)</td>
<td>0.729</td>
</tr>
<tr>
<td>B/Hong Kong seroconversion or 4-fold titre rise</td>
<td>13 (59%)</td>
<td>12 (75%)</td>
<td>0.490</td>
</tr>
</tbody>
</table>

Fisher’s exact test was used for all variables.

Effect of medication on vaccination efficacy

To evaluate the influence of immunosuppressive medication on vaccination efficacy we compared the percentage of seroconversions or 4-fold titre rises and protective titres after vaccination in patients without medication with those in patients using immunosuppressives. For this purpose we combined patient groups B-D in which immunosuppressive medication was used. This analysis showed no difference between patients without medication compared to patients using immunosuppressives in the percentage of seroconversions or 4-fold titre rises (p = 0.325 for A/H1N1, p = 0.184 for A/H3N2) nor in achievement of titres ≥40 (p = 0.666 for A/H1N1, p = 0.180 for A/H3N2). Next, we conducted a sub-analysis in which all patient groups were compared to each other (Table 3). Concerning A/H1N1 and B/Hong Kong no difference was found in the percentage of seroconversions or 4-fold titre rises (p = 0.619 for A/H1N1, p = 0.316 for B/Hong Kong) nor in the achievement of titres ≥40 (p = 0.396 for A/H1N1, p = 0.226 for B/Hong Kong). However, concerning A/H3N2 SLE patients receiving azathioprine had less 4-fold titre rises than other patient groups (p = 0.041). Furthermore, a smaller proportion of the azathioprine group achieved titres ≥40 against A/H3N2 (p = 0.030) compared to the other patient groups.

Table 3: Influence of medication on vaccination efficacy

<table>
<thead>
<tr>
<th></th>
<th>No medication n = 12</th>
<th>Hydroxychloroquine n = 17</th>
<th>Azathioprine n = 13</th>
<th>Prednisone n = 14</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/H1N1</td>
<td>7 (58%)</td>
<td>7 (41%)</td>
<td>4 (31%)</td>
<td>6 (43%)</td>
<td>0.619</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>7 (58%)</td>
<td>8 (47%)</td>
<td>1 (8%)</td>
<td>6 (43%)</td>
<td>0.041</td>
</tr>
<tr>
<td>B/Hong Kong</td>
<td>7 (58%)</td>
<td>8 (47%)</td>
<td>3 (23%)</td>
<td>5 (36%)</td>
<td>0.316</td>
</tr>
</tbody>
</table>

Fisher’s exact test was used for all variables.
3B. Titres ≥40 to influenza

<table>
<thead>
<tr>
<th></th>
<th>No medication n = 12</th>
<th>Hydroxychloroquine n = 17</th>
<th>Azathioprine n = 13</th>
<th>Prednisone n = 14</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/H1N1 ≥40 before vaccination</td>
<td>6 (50%)</td>
<td>8 (47%)</td>
<td>7 (54%)</td>
<td>6 (43%)</td>
<td>0.982</td>
</tr>
<tr>
<td>A/H1N1 ≥40 after vaccination</td>
<td>11 (92%)</td>
<td>14 (82%)</td>
<td>9 (69%)</td>
<td>13 (93%)</td>
<td>0.396</td>
</tr>
<tr>
<td>A/H3N2 ≥40 before vaccination</td>
<td>8 (67%)</td>
<td>11 (65%)</td>
<td>7 (54%)</td>
<td>9 (64%)</td>
<td>0.929</td>
</tr>
<tr>
<td>A/H3N2 ≥40 after vaccination</td>
<td>12 (100%)</td>
<td>16 (94%)</td>
<td>8 (62%)</td>
<td>12 (86%)</td>
<td>0.030</td>
</tr>
<tr>
<td>B/Hong Kong ≥40 before vaccination</td>
<td>5 (42%)</td>
<td>2 (12%)</td>
<td>4 (31%)</td>
<td>3 (21%)</td>
<td>0.295</td>
</tr>
<tr>
<td>B/Hong Kong ≥40 after vaccination</td>
<td>11 (92%)</td>
<td>12 (71%)</td>
<td>8 (62%)</td>
<td>8 (57%)</td>
<td>0.226</td>
</tr>
</tbody>
</table>

Fisher’s exact test was used for all variables.

Discussion

The present study demonstrates that influenza vaccination is safe in SLE patients with quiescent disease but has decreased efficacy, in particular in patients using azathioprine. It can be argued that disease activity may increase after a longer time period than the follow-up used in this study. However, the immune response to influenza generates during the first weeks following vaccination. In case vaccination enhances established autoimmunity, this is expected to occur particularly in this period. Therefore we applied a second assessment of disease activity 4 weeks following vaccination.

We found no increase in SLE disease activity nor in patient perception of disease activity, as measured by patient VAS, 4 weeks after influenza vaccination. This corresponds with previous studies (2-9), in which clinical and laboratory-assessed lupus disease activity did not increase following vaccination. In one study, increased disease activity was reported, though infrequent and usually mild (2). Another study reported 1 patient (out of 11) with significant more disease activity following vaccination (6). Although SLE patients had more systemic side effects of influenza vaccination, these were all mild. Symptoms as tiredness, sweating and myalgia, which were considered as side effects, are common in SLE patients although these are not criteria for disease activity in SLEDAI. Whereas SLEDAI scores did not change, the symptoms mentioned above occurred in some patients following vaccination. This suggests, at the least, a temporal relationship. However, the higher frequency of side effects might be a result of a reporting bias in patients. It is known that many SLE patients with quiescent disease experience a decreased sense of well-being (23-25), which contributes to such a bias. We conclude that influenza vaccination in SLE patients appears to be safe.

Studies concerning efficacy of influenza vaccination thus far are conflicting, as some indicate normal efficacy in SLE patients (2;3;5;6) whereas others conclude that vaccination efficacy is reduced (4;7;11). An overview is given in Table 4. In general, these studies contained less numbers of patients than our study, efficacy was partially analysed and effects of previous vaccinations were not mentioned. In addition, the effects of differences in drug use were often not sufficiently taken into account. Furthermore, previous influenza vaccinations were not recorded. In summary, conflicting data can be explained by methodological differences.
Table 4: studies dealing with efficacy of influenza vaccination in SLE patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>SLE patients</th>
<th>Controls; study design</th>
<th>Parameters</th>
<th>Humoral response of SLE patients</th>
<th>Influence of medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brodman et al. (5)</td>
<td>1978</td>
<td>46</td>
<td>58 healthy controls 23 patients on prednisone, mean 20mg/day 3 patients on azathioprine, 50mg/day 28 patients on hydroxychloroquine</td>
<td>GMTs GMTs Titres ≥40</td>
<td>similar/decreased</td>
<td>No significant effect of prednisone, azathioprine or hydroxychloroquine.</td>
</tr>
<tr>
<td>Louie et al. (6)</td>
<td>1978</td>
<td>11</td>
<td>8 healthy controls</td>
<td>4-fold rises GMTs</td>
<td>similar</td>
<td>-</td>
</tr>
<tr>
<td>Ristow et al. (4)</td>
<td>1978</td>
<td>29</td>
<td>29 healthy controls, matched for prevaccination antibody titre</td>
<td>4-fold rises GMTs Titres ≥40</td>
<td>decreased/similar (trend towards lower immunogenicity)</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Williams et al. (7)</td>
<td>1978</td>
<td>19</td>
<td>36 healthy controls Influenza vaccination in 19 patients and 18 controls, placebo vaccination in 21 patients and 18 controls, double blind. Controls were matched for prevaccination antibody titre.</td>
<td>4-fold rises GMTs Titres ≥40</td>
<td>decreased</td>
<td>Trend towards lower immunogenicity when using prednisone</td>
</tr>
<tr>
<td>Herron et al. (2)</td>
<td>1979</td>
<td>20</td>
<td>32 healthy controls, open label study</td>
<td>4-fold rises GMTs</td>
<td>similar</td>
<td>Trend towards lower immunogenicity when using prednisone</td>
</tr>
<tr>
<td>Kanakoudi-Tsakalidou et al. (3)</td>
<td>2001</td>
<td>11</td>
<td>Both patients and healthy controls (5) were children</td>
<td>4-fold rises GMTs Titres ≥40</td>
<td>similar</td>
<td>No significant effect</td>
</tr>
<tr>
<td>Abu-Shakra et al. (11)</td>
<td>2002</td>
<td>24</td>
<td>None, immunogenicity of vaccination was compared to expected immunogenicity</td>
<td>4-fold rises GMTs Titres ≥40</td>
<td>decreased</td>
<td>Trend towards lower immunogenicity in case of azathioprine or ≥10 mg prednisone/day</td>
</tr>
</tbody>
</table>

Therefore, we evaluated efficacy of influenza vaccination in SLE patients in several ways. With respect to the percentage of patients who reached a seroconversion or 4-fold titre rise we found that influenza vaccination is less effective for A/H1N1 and A/H3N2 in SLE patients. Accordingly, fewer SLE patients achieved a protective titre after vaccination for both influenza A strains together when compared to healthy controls, despite the fact that more patients than controls had received a vaccination consisting of the same viral antigens the year before. We suggest that the GMT in SLE patients after vaccination did not differ from controls because GMT before vaccination was higher in SLE patients which can well be accounted for by the higher rate of previous vaccination in SLE patients. The conclusion that SLE patients appear to have a decreased immune response compared to healthy controls is supported by the sub-analysis of those patients and healthy controls who did not receive an influenza vaccination the previous season. Also in these subgroups a significantly decreased humoral response to A/H1N1 and A/H3N2 in SLE patients as compared to healthy controls was found.

To evaluate whether our group of healthy controls was representative we compared the GMTs of this group with those of a healthy control group vaccinated in the course of a routine survey of the 2002-2003 Influvac vaccine (data kindly provided by Solvay Pharmaceuticals, Weesp, The Netherlands). The 2002-2003 vaccine was identical to the 2003-2004 vaccine, used in our study. A group of 17 healthy persons, age and sex matched, was compared to our group of controls. In the Solvay survey GMT of A/H1N1 increased from 7.5 to 221.4, of A/H3N2 from 16.0 to 247.2, and of B/Hong Kong from 8.2 to 90.0. The change in GMTs was not different compared to the results obtained in the controls included in the present study (Mann-Whitney U test). Why patients showed a decreased humoral
responses to both influenza A strains, but not to the B/Hong Kong strain is subject of discussion. As in our study healthy controls appeared to have a decreased response to the influenza B strain, a possible explanation is that the immunogenicity of the influenza B strain was lower than the immunogenicity of the included influenza A strains. This might have caused a smaller difference in response between patients and controls, in which case the power of our study could have been too low to detect such a difference.

It is reported that the H3N2 subtype of influenza A causes more severe illness than A/H1N1 or influenza B (26), and in most seasons the prevalence of influenza A infections is higher than influenza B infections (27). So sufficient protection to influenza A (especially A/H3N2) is clinically more relevant than sufficient protection to influenza B.

Why SLE patients have a decreased response to influenza vaccination is not entirely clear. Ioannou et al. demonstrated that vaccinations in SLE patients generally tend to give rise to lowered immune responses (28). Another study showed that pneumococcal vaccination in SLE patients in general is immunogenic but that a subset of patients may remain unprotected by the currently available vaccine (29). It is conceivable that SLE patients have an intrinsic immunological defect that results in decreased responsiveness to vaccination. The assumption of an intrinsic immune defect is supported by studies reporting decreased cellular immune responses to influenza in SLE patients (30;31).

In addition, use of immunosuppressive medication may influence the efficacy of vaccination. To assess this effect, we included patients using hydroxychloroquine, azathioprine and/or prednisone and analysed data of these groups of patients separately, as there are considerable differences in pharmacological effects between these drugs. Patients using other immunosuppressives were excluded to prevent the formation of small heterogeneous subgroups. SLE patients receiving azathioprine showed a trend towards a decreased immune response against influenza A/H3N2 compared to the other patient groups. This is in concordance with the study of Abu-Shakra et al., in which a trend towards a decreased immune response to influenza vaccination was observed in SLE patients who received azathioprine (11). In renal transplant patients the use of azathioprine was reported to lower the antibody response to influenza vaccination compared to healthy controls (32) but this could not be confirmed by others (16). Although the number of patients included in this study is quite substantial, the subgroups (according to treatment) are quite small. Data on the effects of immunosuppressive drugs on the efficacy of the vaccination should therefore be interpreted with caution.

Twenty-five percent of SLE patients reached titres <40 against both influenza A strains together and are not expected to be protected from influenza A infection (22). Moreover one might expect that SLE patients experience less protection from influenza vaccination because cellular immunity also seems to be impaired after vaccination (30;31).

To improve the antibody response of immuno-suppressed patients several studies have been conducted in which a second vaccination was given. In general, in immune compromised patients an increased antibody response could not be achieved after a booster injection (33;34), although Soesman et al. did find an increased response in liver transplant patients (15). Recent studies have shown that virosomal vaccines generate better cellular immune responses, and they enhance the humoral immune response following vaccination as well (35-38). Regarding the hampered humoral and cellular immune response to influenza vaccination in SLE patients these new vaccines are of particular interest as one might expect them to improve efficacy of vaccination in SLE patients.

Acknowledgement: Solvay Pharmaceuticals, for the kind supply of vaccines and additional efficacy data of healthy controls.
Competing interest statement: the corresponding author declares no competing interests.

Figure 1. Influence of vaccination on disease activity in the different patient groups
Disease activity was measured by SLEDAI (A) and patient VAS (B) depicting patient perception of disease activity. Data are presented as mean + SEM. Left bars in each couple represent results before, right bars represent data 30 days after vaccination. * p < 0.05 (Wilcoxon Signed-Rank tests).

References

Safety and efficacy of influenza vaccination in systemic lupus erythematosus patients with quiescent disease
Bert Holvast, Anke L.W. Huckriede, Jan Wilschut, Gerda Horst, Jutte De Vries, René Benne, Cees Kallenber and Marc Bijl

Ann Rheum Dis published online December 1, 2005

Updated information and services can be found at:
http://ard.bmj.com/content/early/2005/12/01/ard.2005.043943.citation

Email alerting service
These include:
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
- Immunology (including allergy) (5144)
- Connective tissue disease (4253)
- Systemic lupus erythematosus (571)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/