Immunogenicity and safety of vaccination against seasonal 2012 influenza virus among patients with psoriatic arthritis and psoriasis

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Abstract

Objective

We aimed to assess the immunogenicity and safety of vaccination against seasonal influenza in psoriatic arthritis (PsA) and psoriasis (Pso) patients.

Methods

Patients with PsA or Pso and healthy controls were vaccinated with the Sanofi Pasteur vaccine recommended by the WHO in 2012. Clinical and laboratory assessments were performed on the day of the vaccination and 4–6 weeks later. The immunogenicity of the vaccine was evaluated by haemagglutination inhibition assay.

Results

The study included 63 consecutive PsA patients and 4 Pso patients (mean age 50.1, 37 females, 30 males, 55.2% treated with tumour necrosis factor alpha blockers [TNF-α], 31.3% on disease-modifying anti-rheumatic drugs [DMARDs]) and 30 healthy controls. The geometric mean titers increased significantly in all participants for each of the subtypes tested. A substantial and similar proportion of patients in both groups responded to the vaccine. The response rate was not affected by parameters such as age, gender, disease activity or the use of TNF-α blockers or DMARDs. There were no significant changes in the patients' 68 tender and 66 swollen joint counts, dactylitis, PASI, global evaluation of the patient and physician and ESR, while there was a rise in CRP levels.

Conclusion

Vaccination against seasonal influenza is safe and induces an appropriate response in patients with PsA, similar to healthy controls.

Key words

influenza vaccine psoriasis arthritis

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Received on June 4, 2014; accepted in revised form on October 17, 2014.

Competing interests: none declared.

Introduction

Influenza infection is a common disease that usually has a self-limiting course. However, in several populations, particularly in children, the elderly and immunosuppressed patients, severe complications can occur, such as viral pneumonia, secondary bacterial pneumonia or even death (1, 2). The last A/H1N1 pandemic in 2009 confirmed the vulnerability of these populations (1, 3, 4). Rheumatic patients are prone to develop influenza and its complications due to an impaired immune system inherent to their immune disease or secondary to the use of immunosuppressive drugs, including biologics (5-9). Therefore, various health organisations, such as the Center for Disease Control and Prevention as well as the European League against Rheumatism, recommend vaccinating these groups against seasonal influenza (10, 11). The efficacy and safety of the influenza vaccine was tested in several groups of rheumatic patients, including those suffering from rheumatoid arthritis and lupus (12-15). Those studies demonstrated the efficacy and safety of the vaccine, although the humoral response to the vaccine seemed to be lower compared to healthy controls.

Psoriatic arthritis (PsA) and psoriasis (Pso) are two inflammatory diseases that are often being treated with immunosuppressive drugs, such as disease-modifying drugs (DMARDs) and biologic agents. Several studies showed the general propensity of these patients to infections, particularly by viral upper respiratory disease (16-19).

The response of PsA patients to vaccination has been studied for the pneumococcal vaccine and the pandemic H1N1 virus (13, 20, 21). Mease *et al*. reported the effect of etanercept on vaccination against pneumococcus (20), while the studies on H1N1 included varied groups of inflammatory arthritis patients, with a relatively small proportion of PsA patients. All these studies showed a good efficacy and safety profile.

The response of patients with Pso and PsA to vaccination against influenza is not known. The aim of the present study was to evaluate the immunogenicity and safety of vaccination against seasonal influenza virus in patients with these two conditions.

Methods

Study population

All the patients who were consecutively recruited into this study were being routinely treated at the Rheumatology Unit of the Tel Aviv Medical Center. The first group included 63 patients diagnosed according to the Classification Criteria for Psoriatic Arthritis (CASPAR) as having PsA and 4 patients diagnosed clinically by a dermatologist as having Pso. The control group included 30 apparently healthy hospital personnel.

Vaccination

The study participants were vaccinated with the Sanofi Pasteur vaccine recommended by the WHO in 2012, which included 3 serotypes (A/California/7/2009, A/Victoria/361/2011 and B/Wisconsin/1/2010 influenza virus, *i.e*. H1N1, H3N2 and B).

Study protocol

The study was approved by the research ethics committee of the medical centre. Appropriate informed consent was obtained from all the participants, and the clinical research was conducted in accordance with the guidelines for human experimentation specified by the Tel Aviv Medical Center. Between October 2012 and January 2013 (3.5 months during mid-autumn to the beginning of winter), all the consecutive subjects received one dose of the vaccination by intramuscular injection in the deltoid muscle. Exclusion criteria were a history of vaccination allergy, a known allergy to egg products, and any other vaccination within the previous 3 weeks before receiving the study vaccination. In addition, patients who refuse to be vaccinated or those who already received it at a community clinic were not included in the study. The patients were evaluated clinically, and blood was drawn for serologic and acute phase reactants on the day of vaccination and 4-6 weeks later.

Clinical assessment

A medical history, including the use of medications, was taken and a physical

examination was carried out for each patient before the vaccination was administered. The following clinical and laboratory parameters were assessed at baseline and 4–6 weeks later for all participants (or only for patients as appropriate): 68 tender and 66 swollen joint counts, number of dactylitis, psoriasis area severity index (PASI), patient visual analogue scale (VAS) for pain, physician VAS for pain, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level.

Immunogenicity of the vaccine

The vaccine immunogenicity was evaluated by the haemagglutination inhibition (HI) test. The pre- and postimmunisation HI antibodies were performed at the Central Virology Laboratory of the Israeli Ministry of Health using the HI according to a standard WHO procedure (22). Sera were separated, code labelled and stored at -20º C until tested. The material was treated with receptor-destroying enzyme cholera filtrate to remove non-specific inhibitors, and with turkey red blood cells to remove non-specific agglutinins. The treated sera were tested by an HI test against the 3 serotypes H1N1, H3N2 and B. The working dilution (test dose) of each antigen contained 4 units of antigen in phosphate buffered saline and added to the serial dilution of the antiserum. The HI titer was determined as the highest dilution of serum that completely inhibited haemagglutination of red blood cells. The titer of an antiserum that did not show any inhibition was recorded as 0. Humeral response was recorded as a 4-fold or greater rise in titer, or as a rise from non-protective baseline levels of <1:40 to ≥1:40 in HI antibodies at 4-6 weeks after vaccination. Advanced laboratory techniques were used for diagnosing influenza (23, 24). A titer above 1:40 was defined as being "protective". Geometric mean titers were calculated to assess the immunity for each group.

Statistical analysis

Non-parametric tests were used for analysis since most parameters were not normally distributed (based on the Kolomogorov-Smirnoff test). In addition, parametric tests were performed for the log transformation of the parameters. Associations between the response to vaccination and patient group and medication use were examined using the χ^2 and the Fisher's exact tests. The Mann–Whitney U-test and the *t*-tests for independent samples were used to compare patients who had a humeral response to vaccination to non-responders with respect to clinical parameters, including the use of medications at baseline, change in disease indices, disease duration and activity, ESRs and CRP levels. A binomial logistic regression model was constructed to assess the importance of the different variables relative to the immunogenicity response. Statistical analyses were carried out using the SPSS system for Windows, release 20.0. A *p*-value <0.05 was regarded as statistically significant.

Results

Characteristics of participants

Tables I and II summarise the demographic and clinical characteristics of the patients and controls. The distributions of males and females was similar, while the mean age of the patient group was significantly higher compared to the control group (p=0.03) (Table I). More than 30% of the patients were being treated with DMARDs (mainly methotrexate [MTX], 27%), and more than 50% were being treated with tumour necrosis factor alpha (TNF-α) blockers (Table III). The high proportion of patients treated with TNF-α blockers probably reflect the population treated in a tertiary centre.

Immunogenicity of the vaccine

At 4–6 weeks after being vaccinated, both the patient and control groups achieved significant increases in their geometric mean titers of the HI antibody against the 3 vaccination serotypes:

1. A/California/7/2009 (H1N1v) rose from 40.9 to 285.6 (p<0.01) for the patient group and from 75.3 to 219.5 (p<0.01) for the control group;
2. A/Victoria/361/2011 (H3N2v) rose from 24.1 to 217.5 (p<0.01) in the patient group and from 49.3 to 266 (p<0.01) in the control group;
3. B/Wisconsin/1/2010 (B) rose from 46.1 to 200.9 (p<0.01) in the patient group and from 57.9 to 139.3 (p<0.01) in the control group (Fig. 1). In addition, there were no significant differences in the geometric titers before and after vaccination between the patient and control groups (p=0.35).

Table I. Demographic characteristics of patients and healthy controls*.

Characteristic	Controls (n=30)	Patients (n=67)	*p*-value
Age, y (mean ± SD)	43.3 ± 13	50 ± 14.2	0.03
Males:Females	1:1.7	1:1.2	0.51
Previous year vaccination, n (%)	17 (56.6%)	34 (50.7%)	0.66
Disease duration median, y (range)			
Psoriasis		14.5 (1-60)	
Psoriatic arthritis		8 (1-40)	

Table II. Clinical characteristics of the study patients.

Characteristic	Baseline	After 4–6 weeks	*p*-value
68 tender joint count	5.1 ± 11	4.5 ± 9	0.29
66 swollen joint count	1.1 ± 3.9	2.2 ± 9.5	0.42
Dactylitis	0.2 ± 1	0.2 ± 1	0.65
PASI	4.2 ± 6.6	3.9 ± 6.1	0.61
Patients VAS for pain	19.8 ± 26.2	29.8 ± 26.1	0.63
Physician VAS for pain	19.8 ± 15.6	19.1 ± 17.2	0.93
CRP level	6.5 ± 7.8	9.9 ± 13.5	0.04
ESR	21.8 ± 11.8	23.5 ± 13.6	0.89

All values are given mean ± SD. PASI: psoriatic area severity index; VAS: visual analogue scale; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Table III. Medications used by the 67 study patients.

Medication	Patients n. (%)
DMARDs	21 (31.3)
Methotrexate	18 (27)
Salazopyrin	2 (0.03)
Leflunomide	1 (0.02)
Prednisone	2 (0.03)
Acitretin	2 (0.03)
TNF-α blockers	37 (55.2)
Infliximab	14 (20.1)
Adalimumab	13 (19.4)
Etanercept	9 (13.4)
Golimumab	1 (0.02)

DMARDs: disease-modifying anti-rheumatic drugs; TNF-α: tumour necrosis factor alpha.

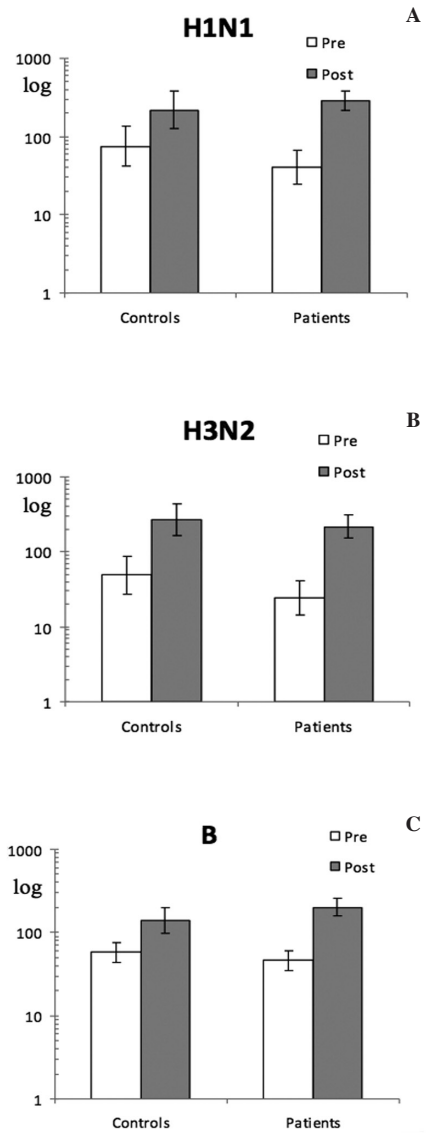
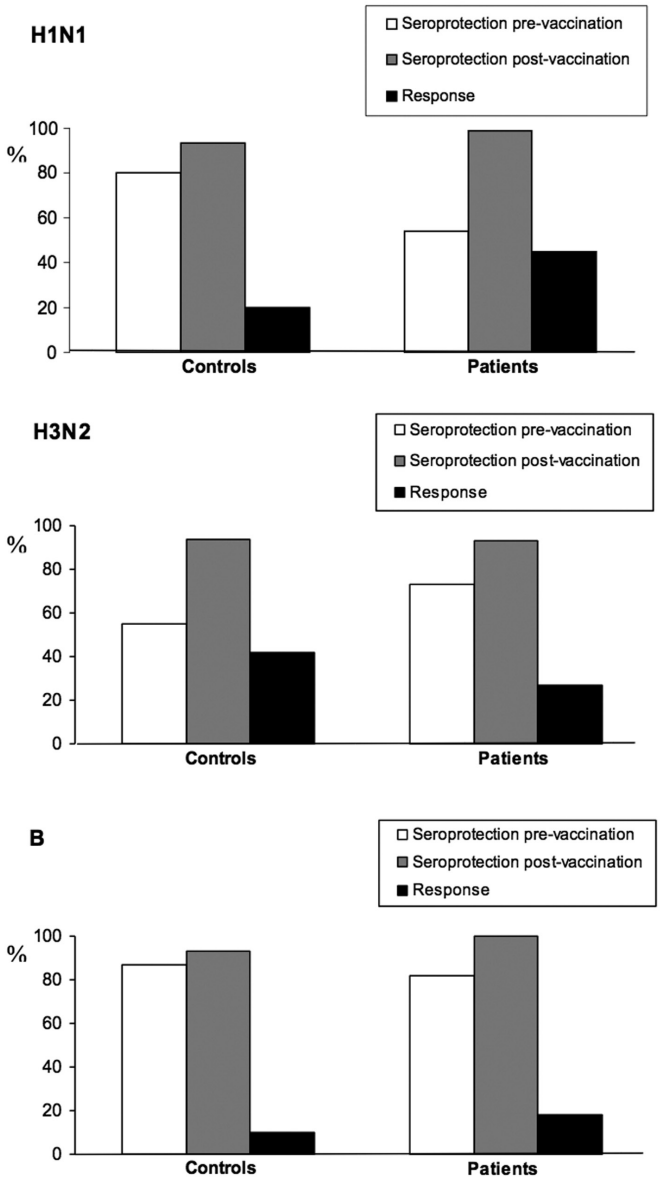


Fig. 1. Geometric mean titers against (**A**) A/California/7/2009 (H1N1), (**B**) A/Victoria/361/2011 (H3N2) and (**C**) B/Wisconsin/1/2010 (B) serotypes. Pre: pre-vaccination; Post: post-vaccination.

Fig. 2. Rates of baseline seroprotective levels, post-vaccination seroprotective levels and rates of responders among the psoriatic arthritis patients, the psoriasis patients and the healthy controls according to serotype.



Individual responses to the vaccination

The proportion of baseline protective levels of antibodies (above 1:40) against the H3N2 and the B serotypes were similar between the patient and control groups (55.2% *vs*. 73.7%, p=0.12, and 82.1% *vs*. 86.7%, p=0.76, respectively), while the protection levels against the H1N1 serotype were significantly lower in the patient group (53.7% *vs*. 80% for the controls, p=0.02) (Fig. 2). The response rates to the H3N2 and B serotypes were similar in both the patient and control groups (41.8% *vs*. 26.7%, p=0.18, and 17.9% *vs*. 10%, p=0.38, respectively), while the response rate to the H1N1 serotype were substantially higher in the patient group (44.8% *vs*. 20% for the controls, p=0.02). The percentage of patients who attained protective levels of antibodies after vaccination was similarly high in both groups for each serotype: it was 93.3% for the controls and 98.5% for the patients against H1N1, 93.3% for the controls and 94% for the patients against H3N2, and 93.3% for the controls and 100% for the patients against B.

Predictors of response

No association was found between the humoral response to the H1N1 and B influenza serotypes and the parameters of age, gender, receiving vaccination during the previous year, duration of disease (skin and arthritis), disease activity (68 tender joint count, 66 swollen joint, number of dactylitis, PASI,

patients VAS for pain, physician VAS for pain, ESR and CRP level) or the use of DMARDs or TNF-α blockers. However, there was a positive association between the humoral response to the H3N2 serotype and a longer duration of PsA and Pso. The multivariate logistic regression did not identify any parameter as a predictor of response.

Safety of the vaccine

Most of the parameters of disease activity did not change significantly after vaccination, the exception being an increase of CRP levels (Table II). There was no significant group difference between the rates of adverse events to the vaccination (30% for the controls *vs*. 17.9% for the patients). The most common side effect was transient local inflammation at the vaccination site.

Discussion

The results of the current study show that vaccination against seasonal influenza cause immunologic response and is safe in patients with PsA. Although the response to the H1N1 serotype has been previously studied in a small cohort of PsA patients, our study is the first to report the humeral effect and safety of seasonal influenza vaccine in this population of patients (13, 21). The study patients achieved a significant level of immunogenicity with a very high (>90%) proportion of seroprotection for each of the 3 serotypes, with no significant difference from the control group. This trend was also seen in the studies conducted on the H1N1 vaccine, although the proportion of patients who achieved seroprotection was significantly lower in the PsA group compared to the healthy control group (13, 21).

The baseline protective levels against the H3N2 and B serotypes in the patient group were relatively high (>50% and >80%, respectively) and similar to that of the control group, possibly pointing to prior exposure to the virus either by direct contamination or due to previous vaccination. The response rates against the H3N2 and B serotypes were similarly low in both the patient and control groups, possibly due to these high baseline levels. The baseline levels against the H1N1 serotype in the patient group were above 50%, while those in the control group were significantly higher (80%). This difference could be attributed to different exposure to this virus. However, the response rate against the H1N1 serotype in the patient group was significantly higher compared to the control group, emphasising the effective function of the patients' immune system. The higher response rate in the patient group could be due to their lower antibody baseline levels. These data are contrary to those from the aforementioned two studies that showed a significantly lower response in the PsA group compared to the healthy controls group (13, 21).

Elkayam *et al*. showed that PsA is a predictor of a significantly lower response to H1N1 vaccine, and that there was a negative association between the use of infliximab and leflunomide to a lower response rate in their entire mixed rheumatic diseases cohort (13). Mease *et al*. examined the efficacy and safety of pneumococcal vaccination in PsA and identified the parameters of MTX and age as predictors of a poor response (20). In contrast, our current study did not identify any predictor for a decreased response, including the use of DMARDs or biologics.

The safety issue, particularly the induction of inflammatory disease by vaccination, is a matter of considerable controversy. With regard to psoriasis, a few case reports described the occurrence of Pso following vaccination of BCG and tetanus-diphtheria (25-27). Pattison *et al*. showed a positive association between receiving rubella vaccination and the onset of inflammatory arthritis in Pso patients (28), while Eder *et al*. did not (29). Likewise, we found no significant changes in the different parameters of disease activity, such as 66/68 tender and swollen joints and PASI. Our current results confirm previous observations concerning the safety of vaccination against influenza in patients suffering from autoimmune inflammatory rheumatic diseases activity (13).

Despite the increased susceptibility to infection and the higher propensity for substantial complications among inflammatory rheumatic patients, the uptake of vaccination is surprisingly low. Curtis *et al.'s* findings in a large Medicare database, including 141,140 rheumatoid arthritis and 6300 PsA, showed that only one-third of them had received pneumococcal vaccination and that 18.7-21.6% received influenza vaccination each year during a 5-year follow-up (30). Similarly, another study that assessed the uptake of the 2009 monovalent H1N1 serotype in 1308 Pso patients showed that, overall, only 19% received this vaccination, with a higher proportion (33%) among those treated with biologics (31). The underestimation of the immunosuppressive state was reinforced by a study on rheumatic patients which examined factors that influenced vaccination rate (32). It showed that patients with other risk factors (*e.g*. metabolic, cardiovascular and age) had a substantially higher proportion of influenza and pneumococcal vaccination in comparison to those treated with a major immunosuppressant DMARDs (93% *vs*. 53% for the influenza and 64% *vs*. 28% for the pneumococcal, respectively).

We are aware that the relatively small number of patients and the short-term follow-up pose a limitation to this study. In addition, the control group was not optimal as it included younger healthy hospital personnel. Likewise, the response to vaccine was evaluated according to the surrogate parameters of humoral response. However, this is the first report that clearly demonstrates the immunogenicity and safety of vaccination against seasonal influenza in PsA patients.

In summary, this is the first study to demonstrate that vaccination against seasonal influenza is immunogenic and safe in patients diagnosed as having PsA. Our study further strengthens the recommendation of yearly vaccination of this population of patients against seasonal influenza.

The study was approved by the research ethics committee of the medical centre. Appropriate informed consent was obtained from all the participants prior to their inclusion in the study, and the clinical research was conducted in accordance with the guidelines for human experimentation specified by the Tel Aviv Medical Centre

Acknowledgement

Mrs Esther Eshkol is acknowledged for her editorial assistance

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