Influenza vaccine with adjuvant on disease activity in psoriatic arthritis patients under anti-TNF-α therapy

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Abstract

Objective

To evaluate the effects on disease activity of seasonal influenza vaccination with adjuvant in psoriatic arthritis (PsA) patients in stable disease activity on anti-TNF-α drugs as compared to not vaccinated PsA patients adequately matched.

Methods

An observational study was conducted on a cohort of PsA patients in stable disease activity who underwent administration of an adjuvanted vaccine for seasonal influenza. Cases (Group 1) were matched for age, sex, disease activity and therapy with not vaccinated PsA patients (Group 2). Analysis included patients data before vaccination (T0), and one month (T1) and three months (T3) after administration of the vaccination for Group 1 and at correspondent intervals for Group 2. Assessment of disease activity parameters was performed at each visit.

Results

Twenty-five vaccinated and 25 not vaccinated patients were included in the study. As a first approach, we analysed the data within groups. At T1, as compared to baseline, the group of vaccinated patients had a statistically significant increase in TJC (tender joint count) and ESR (erythrocyte sedimentation rate). At T3, a statistically significant difference from baseline characteristics was found only for the TJC. In Group 2, all the observed variables showed no significant differences when comparing baseline to T1 and T3. Analysis of the data between groups at T1, Group 1, as compared to Group 2, showed a significant increase of TJC, ESR, HAQ (Health Assessment Questionnaire), PtGA (patient global assessment) and PhGA (physician global assessment). These findings were also confirmed when comparing the two groups at T3 for ESR and PtGA, while they were not confirmed for TJC, HAQ and PhGA.

Conclusion

Influenza vaccination is clinically efficacious in PsA patients under anti-TNF-α therapy, but it could trigger a short-lasting exacerbation of the disease.

Key words

psoriatic arthritis, influenza vaccination, adjuvant, disease activity, anti-TNF-α therapy

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Introduction

Vaccination consists in the administration of preparations capable of inducing in the organism the development of an immune response, generally of humoral type, which gives a specific resistance against an infectious microorganism (viral, bacterial, protozoal). It is one of the most effective and safe Public Health strategies for the primary prevention of infectious diseases (1). Influenza infection involves 10–20% of the general population and can be associated with severe course, especially in patients with conditions predisposing to immunosuppression (2). The incidence in patients with rheumatic diseases is unknown, but the use of immunosuppressive therapies may represent a predisposing factor. In a recent study, the authors reported a higher incidence of influenza in rheumatoid arthritis (RA) patients than in controls and a 2.75-fold increase in incidence of complications (3).

In Italy, the Ministry of Health, in line with the World Health Organisation (WHO) recommends influenza vaccination for specific categories of subjects, including "children and adults up to 65 years age suffering from conditions that increase their risk of complications from influenza" which include, among others, "congenital and acquired diseases involving defective antibody production, immunosuppression induced by drugs or Human Immunodeficiency Virus (HIV)" (4).

Over the years, the effectiveness and safety of vaccines in patients with autoimmune disease receiving immunosuppressive therapy has been largely discussed, but many questions remains open (5-12). The inhibition of the immune response induced by immunosuppressants can be caused by various factors, including: the presence of an inadequate population of T and memory B cell, which requires a smaller quantity of antigen; the type of immunosuppressive therapy; the use of adjuvanted vaccines (13).

According to the 2011 EULAR guidelines, all patients with rheumatic diseases should receive influenza vaccination during stable disease, due to the increased risk of complications (14). Its effectiveness has been demonstrated in all rheumatic diseases and adverse effects are quite comparable to those found in the general population (15-18). Regardless of therapy with disease-modifying anti-rheumatic drugs (DMARDs) and/or inhibitors of tumour necrosis factor (TNF)-α, a recent study showed a different immunogenic profile in patients with Spondyloarthritis (SpA), RA and healthy subjects vaccinated for influenza A/H1N1 (19). Unlike RA patients where no significant differences were found, in SpA patients anti-TNF-α therapy was associated with a lower immune response as compared to patients on methotrexate. Despite this, vaccination was effective in all subjects (19).

However, even if the effectiveness of vaccines administered in patients with rheumatic diseases under immunosuppressants is widely recognised, few data are available on the incidence of flares in rheumatic condition after vaccine administration (20-22). In particular, these data are scarce in patients with psoriatic arthritis (PsA) (16, 23).

The objective of this study was to evaluate the effects on disease activity of seasonal influenza vaccination with adjuvant in PsA patients in stable disease activity on anti-TNF-α drugs as compared to not vaccinated PsA patients adequately matched.

Patients and methods

Study population

An observational study was conducted on a cohort of PsA patients, classified on the basis of the CASPAR criteria (24, 25), consecutively attending the Psoriatic Arthritis Clinic at the University Federico II of Naples and at University of Padova.

Inclusion criteria were represented by: age ≥18 years; subjects who underwent administration of an adjuvanted vaccine for seasonal influenza, from October to December 2014, in conformity with specifications/recommendations provided by the National Plan for Prevention vaccine 2012-2014 of the Italian Ministry of Health (26); monotherapy with an anti-TNF-α agent; stable disease activity in the six months before the study recruitment.

Exclusion criteria were represented by: pregnancy; combination therapy with traditional DMARDs or systemic steroids; autoantibodies positivity; overlapping history and first-degree familial cases of autoimmune diseases; a history of vaccination allergy; a known allergy to egg products; previous dose of any influenza vaccine in the last 12 months. Cases (Group 1) were matched for age, sex, disease activity and therapy with not vaccinated PsA patients consecutively recruited in the outpatients clinic (Group 2).

Analysis included patients data before vaccination (T0), and one month (T1) and three months (T3) after administration of the vaccination for Group 1 and at correspondent intervals for Group 2.

In detail, at T0, the following data were recorded for each PsA patient: age, gender, vital signs, detailed family and personal medical history, previous and/or actual treatments, disease duration, anti-TNF-α use, DMARD use, steroid use and current comorbidities.

Assessment of disease activity parameters was performed at each visit, including: tender joint count (68 tender joints; TJC), swollen joint count (66 swollen joints; SJC); Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); Bath Ankylosing Spondylitis Functional Index (BASFI); number of digits with dactylitis; Maastricht Ankylosing Spondylitis Enthesis Score (MASES); Psoriasis Area and Severity Index (PASI); Health Assessment Questionnaire (HAQ), patient global assessment (PtGA) and physician global assessment (PhGA), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

At time of enrollment, all patients received a clinical diary to record systemic symptoms including: fever (>37.5°C), fatigue, chills, malaise, asthenia, headache, arthritis, arthralgia, myalgia, and muscle weakness.

Statistical analysis

Statistical analysis was performed using SPSS software (SPSS inc., Chicago, Il, USA). Descriptive statistics included mean values and standard deviation (SD) of the continuous variables and percentages and proportions for the categorical variables.

Table I. Demographic, clinical and laboratory characteristics at baseline of both groups at T0.

Variables	Group 1	Group 2	*p*-value
Patients (n)	25	25	-
Age (years)	57.96 ± 7.31	56.48 ± 7.95	0.644
Male, n (%)	15 (60%)	14 (56%)	0.774
PsA duration (months)	145.68 ± 60.83	152 ± 67.84	0.730
Anti-TNF-α therapy duration (months)	70.04 ± 26.57	59.72 ± 31.76	0.219
TJC	1.64 ± 1.93	1.48 ± 1.44	0.742
SJC	0.12 ± 0.33	0.20 ± 0.58	0.551
BASDAI	3.18 ± 1.08	3.30 ± 1.37	0.745
BASFI	2.30 ± 1.69	2.74 ± 1.55	0.579
MASES	1.12 ± 1.79	1.20 ± 1.66	0.870
PASI	1.67 ± 2.20	1.96 ± 2.85	0.691
HAQ	1.18 ± 2.06	0.58 ± 0.39	0.153
PtGA	41.20 ± 25.55	31.80 ± 17.43	0.135
PhGA	19.60 ± 10.60	16.00 ± 13.99	0.310
ESR (mm/h)	8.64 ± 3.94	8.04 ± 4.62	0.623
CRP (mg/dl)	0.27 ± 0.12	0.27 ± 0.17	0.901

Data expressed as mean±standard deviation, unless otherwise indicated.
TJC: tender joint count; SJC: swollen joint count; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; MASES: Maastricht Ankylosing Spondylitis Enthesis Score; PASI: Psoriasis Area and Severity Index; HAQ: Health Assessment Questionnaire; PtGA: patient global assessment; PhGA: physician global assessment; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table II. Clinical and laboratory characteristics of vaccinated patients (Group 1) at different times of the study.

Variables	T_0 (n=25)	T_1(n=25)	T_3(n=25)	*p*-value (comparison between T0 and T3)
Patients (n)	25	25	25	-
TJC	1.64 ± 1.93	3.92 ± 3.74*	2.36 ± 2.34	**0.010**
SJC	0.12 ± 0.33	0.16 ± 0.37	0.12 ± 0.33	0.895
BASDAI	3.18 ± 1.08	3.53 ± 1.62	3.43 ± 1.60	0.679
BASFI	2.99 ± 1.67	3.10 ± 1.99	3.35 ± 2.19	0.808
MASES	1.12 ± 1.78	0.96 ± 1.67	0.80 ± 1.04	0.763
PASI	1.67 ± 2.20	2.58 ± 4.03	1.90 ± 2.99	0.578
HAQ	1.18 ± 2.07	0.82 ± 0.55	0.85 ± 0.59	0.541
PtGA	41.20 ± 25.54	46.60 ± 24.48	42.00 ± 21.50	0.691
PhGA	19.60 ± 10.60	24.80 ± 14.68	22.60 ± 14.79	0.398
ESR (mm/h)	8.64 ± 3.94	11.64 ± 6.18*	11.36 ± 6.99	0.142
CRP (mg/dl)	0.27 ± 0.11	0.31 ± 0.21	0.42 ± 0.41	0.146

Data expressed as mean±standard deviation. *$p<0.05$ in the comparison T_0-T_1.
See Table I for legend.

The comparison between the two groups was performed using the Pearson contingency test for categorical variables and analysis of variance (ANOVA) for continuous variables.

Results

On the basis of inclusion and exclusion criteria, in a period of three months, 25 vaccinated and 25 not vaccinated patients were included into the study. Demographic, clinical and laboratory characteristics at T0 of both groups are reported in Table I. Both groups were similar in age, sex, disease duration. All patients of Group 1 had been vaccinated with an adjuvanted vaccine (Fluad®).

All patients had been treated with anti-TNF-α agents for a similar period of time, and in the absence of concomitant administration of traditional DMARDs and/or systemic steroids. Each patient was allowed to use NSAIDs on demand and their use did not significantly changed in the two groups during the entire period of observation.

At T0, no patient showed dactylitis. For all parameters of disease activity, the mean values were comparable between the two groups.

With regard to comorbidities, in Group

1, one patient showed Chronic Obstructive Pulmonary Disease (COPD) and diabetes, and two patients ischemic and valvular heart disease, respectively; in Group 2, four patients showed, respectively, COPD, diabetes, chronic renal failure and ischaemic heart disease.

As first approach, we analysed data within groups. At T1, as compared to baseline, the group of vaccinated patients had a statistically significant increase in TJC (p=0.009) and ESR (p=0.046) (Table II). At T3, a statistically significant difference from baseline characteristics was found only for the TJC (p=0.01). The other clinical and laboratory parameters were stable both at T1 and T3 when compared with T0 (Table II).

In the Group 2 all the observed variables showed no significant differences when comparing baseline to T1 and T3 (Table III).

As second step, we analysed data between groups. At T1, Group 1, as compared to subjects in Group 2, showed a significant increase of TJC (p=0.004), ESR (p=0.007), HAQ (p=0.023), PtGA (p=0.013) and PhGA (p=0.026) (Table IV). These findings were also confirmed when comparing the two groups at T3 for ESR (p=0.006) and PtGA (p=0.017), while they were not confirmed for TJC (p=0.650), HAQ (p=0.055) and PhGA (p=0.062) (Table V). The remaining variables did not show significant differences in the comparison at T1 and T3.

With regard to local and systemic symptoms, in the Group 1, a total of 3 patients (12%) reported a mild local reaction with redness at the injection site of the vaccine, which regressed in 24-48 hours with the application of topical corticosteroids.

In Group 1, the number of short lasting episodes of any among the following symptoms: malaise, headache, fatigue, low-grade fever, arthralgia and myalgia, in the absence of joint swelling, reported during the first month and the first three months of observation, was approximately doubled as compared to not vaccinated patients [5 (20%) *vs*. 2 (8%)] and [9 (36%) *vs*. 4 (16%)]. All episodes were reported lasting a few days and well-controlled by standard home therapy, without the need for antibiotics.

No other vaccine-related adverse event was recorded.

Table III. Clinical and laboratory characteristics of not vaccinated patients (Group 2) at different times of the study.

Variables	T_0 (n=25)	T_1(n=25) *	T_3(n=25)	p-value (comparison between T0 and T3)
Patients (n)	25	25	25	-
TJC	1.48 ± 1.44	1.44 ± 1.45	2.04 ± 2.61	0.467
SJC	0.20 ± 0.58	0.12 ± 0.33	0.12 ± 0.44	0.778
BASDAI	3.30 ± 1.37	3.20 ± 1.35	2.90 ± 1.21	0.536
BASFI	2.74 ± 1.55	2.53 ± 1.62	2.47 ± 1.66	0.827
MASES	1.20 ± 1.66	0.92 ± 1.32	0.96 ± 1.40	0.767
PASI	1.96 ± 2.85	2.19 ± 2.88	1.98 ± 2.78	0.952
HAQ	0.57 ± 0.39	0.50 ± 0.42	0.56 ± 0.47	0.793
PtGA	31.80 ± 17.43	31.20 ± 16.97	28.40 ± 17.24	0.758
PhGA	16.00 ± 13.99	15.40 ± 14.21	15.20 ± 12.46	0.977
ESR (mm/h)	8.04 ± 4.62	7.44 ± 4.15	6.88 ± 3.54	0.613
CRP (mg/dl)	0.27 ± 0.17	0.26 ± 0.20	0.37 ± 0.29	0.675

Data expressed as mean±standard deviation.
See Table I for legend.

Table IV. Comparison between the two groups at T1.

Variables	Group 1	Group 2	p-value
Patients (n)	25	25	-
TJC	3.92 ± 3.74	1.44 ± 1.44	**0.004**
SJC	0.16 ± 0.37	0.12 ± 0.33	0.691
BASDAI	3.53 ± 1.62	3.17 ± 1.35	0.428
BASFI	3.11 ± 1.99	2.53 ± 1.62	0.267
MASES	0.96 ± 1.67	0.92 ± 1.32	0.926
PASI	2.58 ± 4.03	2.19 ± 2.88	0.697
HAQ	0.82 ± 0.55	0.50 ± 0.42	**0.023**
PtGA	46.60 ± 24.48	31.20 ± 16.97	**0.013**
PhGA	24.80 ± 14.68	15.40 ± 14.21	**0.026**
ESR (mm/h)	11.64 ± 6.18	7.44 ± 4.15	**0.007**
CRP (mg/dl)	0.31 ± 0.22	0.26 ± 0.20	0.479

Data expressed as mean±standard deviation.
See Table I for legend.

Discussion

This paper reports our experience in PsA patients in therapy with anti-TNF-α undergoing influenza vaccination. Although data on vaccine and rheumatic diseases are increasing, they are substantially scarce in PsA patients.

The results of the study show that PsA patients under anti-TNF-α therapy, with a stable disease before receiving seasonal influenza vaccination, had a short-lasting worsening in TJC, HAQ, PtGA and PhGA after 1 month from vaccination as compared to not vaccinated PsA patients. After three months from vaccination, PtGA was the only variables that remained slightly increased.

Actually, also ESR, both after 1 month and after 3 months, was significantly increased, however its values remained within the normal range.

A limitation of the study was the relatively small sample size, but it was sufficient to document statistical significance of results. However, given the relevance of the study question, further studies with longer number of patients are needed.

Other study limitations were the lacking of measurement of anti-influenza antibody titers and anti-adjuvant specific antibody.

In literature, only one study had faced this question in PsA patients (23). The authors assessed the immunogenicity and safety of vaccination against seasonal influenza in 63 PsA and 4 psoriasis patients. Parameters of disease activity did not change after vaccination,

Table V. Comparison between the two groups at T3.

Variables	Group 1	Group 2	*p*-value
Patients (n)	25	25	=
TJC	2.36 ± 2.34	2.04 ± 2.61	0.650
SJC	0.12 ± 0.33	0.12 ± 0.44	1.000
BASDAI	3.44 ± 1.60	2.90 ± 1.21	0.185
BASFI	3.35 ± 2.19	2.47 ± 1.66	0.117
MASES	0.80 ± 1.04	0.96 ± 1.39	0.649
PASI	1.90 ± 2.99	1.98 ± 2.77	0.922
HAQ	0.85 ± 0.59	0.56 ± 0.47	0.055
PtGA	42.00 ± 21.50	28.40 ± 17.24	**0.017**
PhGA	22.60 ± 1480	15.20 ± 12.45	0.062
ESR (mm/h)	11.36 ± 7.00	6.88 ± 3.54	**0.006**
CRP (mg/dl)	0.42 ± 0.41	0.32 ± 0.29	0.326

Data expressed as mean±standard deviation.
See Table I for legend.

except for an increase of CRP levels, as compared to healthy controls. In this study the vaccine administered was not adjuvanted (23).

Another study reports on the efficacy and safety of non-adjuvanted vaccination against influenza virus among patients with several rheumatic diseases, including 17 PsA patients. Authors report as ancillary finding a stable disease activity of these patients after 4–6-weeks from vaccination using the 28-joint Disease Activity Score (DAS28), ESR and CRP (16).

Other studies investigated the effect of vaccination in other rheumatic diseases. In all of them main objective was always efficacy of vaccination and data on flares were reported among safety information, showing no significant increase of disease activity (20-22).

Our study addresses, primarily, the question of a potential effect on disease flare in PsA patients of the influenza vaccination with an adjuvanted product. We observed a short-lasting worsening involving mainly peripheral joints, with increased joint tenderness in the absence of arthritic signs, that could partially explain the consensual increase of PtGA and HAQ values. This finding was not associated with any clinical evidence of reduced efficacy of vaccination. The vaccinated patients only showed a higher frequency of episodes of any among the following symptoms: malaise, headache, fatigue, low-grade fever, arthralgia and myalgia, during the three months of observation as compared to not vaccinated patients (36% *vs*. 16%).

This effect could be in part explained by the presence of the adjuvant MF-59 in the vaccine. MF-59 is an oil-in-water emulsion that increases the uptake of antigens by the antigen presenting cells and promotes the innate immune response only locally, providing the critical immunologically competent micro-environment for productive generation of B and T cell immunity (27). Importantly, as said, MF59 does not activate the immune system systemically (27).

In 2011 Shoenfeld *et al*. outlined the possible effects of adjuvants, defining a new clinical entity, indicated by the acronym ASIA (Autoimmune / inflammatory Syndrome Induced by Adjuvants), in order to group together the set of symptoms that can develop after exposure to the adjuvants (chemical or infectious). It consists of a variety of symptoms, including fever, fatigue, arthromyalgia, muscle weakness, neurological disorders, sometimes associated with the development of anti-adjuvant or specific autoimmune diseases (28).

In addition, we should outline that PsA is a complex condition (29-33) in which environmental factors play an important role in disease susceptibility (34). In particular, in a recent study infections and lifting heavy loads were associated with the occurrence of arthritis in patients with psoriasis (35).

Similarly, we may hypothesise that (as vaccine contains antigens from infectious agents) the antigenic stimulation may induce a non-specific response, potentially resulting in a short-lasting reactivation of the underlining disease and patients might be more prone to develop transient reactions to vaccine administration as a sort of systemic Koebner-like reaction.

To our knowledge, this is the first study on influenza vaccine with adjuvant that has as primary objective the evaluation of disease flare in PsA patients.

In conclusion, influenza vaccination is clinically efficacious in PsA patients under anti-TNF-α therapy, but it could trigger a short lasting exacerbation of the disease.

The association could be coincidental, but the role of adjuvants and antigens from infectious agents in predisposed subjects with PsA needs to be better evaluated.

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