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Original article

TNF blockers show distinct patterns of immune response to the pandemic influenza A H1N1 vaccine in inflammatory arthritis patients

Ivan Leonardo Avelino França[1], Ana Cristina Medeiros Ribeiro[2], Nádia Emi Aikawa[2,3], Carla Gonçalves Schain Saad[2], Julio Cesar Bertacine Moraes[2], Cláudia Goldstein-Schainberg[2], Ieda Maria Magalhães Laurindo[2], Alexander Roberto Precioso[4], Maria Akiko Ishida[5], Ana Marli Christovam Sartori[1], Clovis Artur Silva[2,3] and Eloisa Bonfa[2]

Abstract

Objective. To evaluate the immunogenicity of the anti-influenza A H1N1/2009 vaccine in RA and spondyloarthritis (SpA) patients receiving distinct classes of anti-TNF agents compared with patients receiving DMARDs and healthy controls.

Methods. One hundred and twenty patients (RA, $n = 41$; AS, $n = 57$; PsA, $n = 22$) on anti-TNF agents (monoclonal, $n = 94$; soluble receptor, $n = 26$) were compared with 116 inflammatory arthritis patients under DMARDs and 117 healthy controls. Seroprotection, seroconversion (SC), geometric mean titre, factor increase in geometric mean titre and adverse events were evaluated 21 days after vaccination.

Results. After immunization, SC rates (58.2% *vs* 74.3%, $P = 0.017$) were significantly lower in SpA patients receiving anti-TNF therapy, whereas no difference was observed in RA patients receiving this therapy compared with healthy controls ($P = 0.067$). SpA patients receiving mAbs (infliximab/adalimumab) had a significantly lower SC rate compared with healthy controls (51.6% *vs* 74.3%, $P = 0.002$) or those on DMARDs (51.6% *vs* 74.7%, $P = 0.005$), whereas no difference was observed for patients on etanercept (86.7% *vs* 74.3%, $P = 0.091$). Further analysis of non-seroconverting and seroconverting SpA patients revealed that the former group had a higher mean age ($P = 0.003$), a higher frequency of anti-TNF ($P = 0.031$) and mAbs ($P = 0.001$) and a lower frequency of MTX ($P = 0.028$). In multivariate logistic regression, only older age ($P = 0.015$) and mAb treatment ($P = 0.023$) remained significant factors for non-SC in SpA patients.

Conclusion. This study revealed a distinct disease pattern of immune response to the pandemic influenza vaccine in inflammatory arthritis patients receiving anti-TNF agents, illustrated by a reduced immunogenicity solely in SpA patients using mAbs.

Trial Registration: ClinicalTrials.gov, www.clinicaltrials.gov, NCT01151644.

Key words: vaccine, safety, immunogenicity, pandemic influenza A (H1N1), biologic agents, rheumatic disease, TNF blockers.

CLINICAL SCIENCE

[1]Division of Infectious Disease, [2]Division of Rheumatology, [3]Pediatric Rheumatology Unit, [4]Instituto Butantan, and [5]Instituto Adolfo Lutz, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

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Correspondence to: Eloisa Bonfá, Disciplina de Reumatologia, Faculdade de Medicina da Universidade de São Paulo, Av. Dr. Arnaldo, n° 455, 3° andar, sala 3190, Cerqueira César São Paulo, 05403-010, São Paulo, Brazil. E-mail: ebonfa@lim17.fm.usp.br

*Clovis Artur Silva and Eloisa Bonfa contributed equally to this study.

Introduction

People suffering with autoimmune rheumatic diseases (ARDs) who are treated with DMARDs [1–3] and biologic agents are recognized to be at increased risk of infection [4]. This insight was particularly relevant for the recent 2009 influenza A H1N1 pandemic, which led to a high frequency of hospitalization and death in this particular group of patients [5].

After the H1N1 A/California/7/2009 influenza pandemic, the vaccine was largely produced through immunization programs [5, 6], and both the European League Against Rheumatism [4] and the Centers for Disease Control and Prevention [5] strongly recommended that inactivated pandemic influenza vaccination should be indicated for ARD patients.

We recently studied the immunogenicity and safety of a non-adjuvanted pandemic 2009 influenza A H1N1 vaccine in 1664 ARD patients and 234 healthy controls, showing an overall reduced immune response [7]. We also observed reduced seroconversion (SC) rates in RA patients linked to MTX therapy and unrelated to disease activity [8]. Simultaneously, two studies with an adjuvanted pandemic 2009 influenza A H1N1 vaccine were published: one associated increasing age with DMARD therapy but not with anti-TNF blockers, which were associated with a low antibody response in ARD patients [9]; the second study found reduced immunogenicity in patients with RA or PsA and those on infliximab or LEF [10].

However, the limited number of subjects receiving different TNF blockers and the inclusion of diverse diseases may hamper the interpretation of these study findings because vaccine antibody response varies among the rheumatic diseases [7]. Moreover, the discrimination of the possible deleterious effects of biologic therapy on the vaccine immune response requires an evaluation of patients solely on DMARDs due to the widespread concomitant use of these drugs with biologic therapy [11].

Therefore the objective of the present study was to evaluate the immunogenicity and short-term safety of the anti-pandemic 2009 influenza A H1N1 vaccine in RA and spondyloarthritis (SpA) receiving distinct classes of anti-TNF agents compared with patients receiving DMARDs and healthy controls.

Methods

This study included 120 inflammatory arthritis patients receiving anti-TNF therapy and 116 patients on DMARDs in a large ($n = 1668$), prospective, rheumatic disease cohort conducted at a single site in São Paulo, Brazil (Rheumatology Division, Hospital das Clínicas da Universidade de São Paulo), between March 2010 and April 2010, described in detail elsewhere [7]. The study was approved by the local Institutional Review Board (Comissão de Pesquisa e Ética do Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo), and all participants signed the informed consent. The trial was registered at clinicaltrials.gov under NCT01151644.

Patients

All patients fulfilled their respective disease classification criteria for RA [12], AS [13] or PsA [14]. Patients were initially invited by letter to participate in the public health influenza A H1N1/2009 vaccine campaign at the immunization centre of our hospital. Blood samples were obtained from each participant immediately before and 21 days after vaccination.

The anti-TNF group included 41 RA and 79 SpA patients (57 AS and 22 PsA). The anti-TNF agents and dosage at vaccination were as follows: 54 infliximab (3–5 mg/kg body weight at 2 and 6 weeks and thereafter as recommended, every 6–8 weeks), 40 adalimumab (40 mg every other week) and 26 etanercept (50 mg/week). In addition, 116 inflammatory arthritis (41 RA, 75 SpA, 53 AS and 22 PsA) patients on traditional DMARD therapy (MTX, LEF, chloroquine or SSZ) with similar disease distribution ($P > 0.05$) were randomly selected from the 462 inflammatory arthritis group patients of the large study [7].

Exclusion criteria were: previous known infection with pandemic 2009 influenza A H1N1, anaphylactic response to vaccine components or to eggs, acute infection resulting in a fever $>38^{\circ}$C at the time of vaccination, history of Guillain–Barré syndrome or other demyelination syndromes, previous vaccination with any live vaccine 4 weeks before the study or any inactivated vaccine 2 weeks before the study, previous vaccination with a 2010 seasonal influenza vaccine, a blood transfusion within the past 6 months, less than 8 weeks of anti-TNF therapy, hospitalization or failure to complete the protocol.

Healthy controls

One hundred and seventeen healthy subjects who came to this centre seeking vaccination in response to a Public Health National Campaign were invited to participate under the same exclusion criteria; these subjects were randomly selected from 234 healthy controls from the large study [7].

Vaccine

The H1N1 vaccine, a novel, monovalent, non-adjuvanted, inactivated, split-virus vaccine was produced by Butantan Institute/Sanofi Pasteur (São Paulo, Brazil). The active substance is a split, inactivated influenza virus containing antigens equivalent to the A/California/7/2009 (H1N1) virus-like strain (NYMCx-179 A), one of the candidate reassortant vaccine viruses recommended by the World Health Organization. The vaccine was prepared in embryonated chicken eggs with the same standard techniques that are used for the production of seasonal trivalent inactivated vaccines, and it was presented in 5-ml multi-dose vials, with thimerosal added as a preservative (45 μg/0.5 ml dose).

Study procedures

All subjects were vaccinated with the pandemic 2009 influenza vaccine (A/California/7/2009/Butantan Institute/Sanofi Pasteur). A single i.m. dose (0.5 ml) of 15-μg haemagglutinin antigen, specific for the H1N1 A/California/7/2009-like virus, was administered [7, 8].

Safety assessments

A 21-day diary card was given to each participant at entry with 13 (Yes or No) established reactions. This card included local reactions (pain, redness, swelling and itching) and systemic adverse events, such as arthralgia, fever, headache, myalgia, sore throat, cough, diarrhoea, rhinorrhoea and nasal congestion. Participants were required to return their diary cards at the end of the follow-up period (21 days after vaccination). All local reactions were considered to be related to the H1N1 vaccine. Recorded symptoms were checked by the investigators to determine the causality of solicited systemic adverse events, and unsolicited adverse events were also assessed. Severe side effects were defined as those requiring hospitalization or leading to death.

Laboratory assays

Blood samples were collected at baseline and 3 weeks after vaccination, and sera were stored at -70°C. The two samples from each patient or control were tested in parallel in the same plate for all laboratory determinations. The immunogenicity of the H1N1 A/California/7/2009-like virus vaccine was evaluated with the use of a haemagglutination inhibition assay (HIA) at the Adolfo Lutz Institute.

HIA

The influenza virus antigen used in this study was the H1N1 A/California/7/2009, supplied by the Butantan Institute. Virus concentrations were determined by haemagglutinin antigen titration, and the HIA test was performed after removing naturally occurring, non-specific inhibitors from the sera, as previously described [15]. The H1N1 vaccination immune response was evaluated by determining the levels of antibodies by HIA. Anti-H1N1 titre was determined by influenza HIA. The percentages of seroprotection (SP) (titre $\geqslant$1:40) and SC (pre-vaccination titre $<$1:10 and a post-vaccination HIA titre $\geqslant$1:40 or pre-vaccination titre $\geqslant$1:10 and a $\geqslant$4-fold increase post-vaccination), geometric mean titre (GMT) and the factor increase in GMT were calculated.

Statistical analysis

Selection of inflammatory arthritis patients on DMARDs and healthy controls was randomly carried out using SPSS Statistics v 15.0 (SPSS Inc., Armonk, NY, USA). Two-sided 95% CIs were calculated assuming binomial distributions for dichotomous variables and a log-normal distribution for HIA titres. Every subgroup had its HIA GMT calculated before vaccination and 21 days after vaccination. The factor increase in GMT (i.e. the ratio of the titre after vaccination to the titre before vaccination) was also obtained and log-transformed. Categorical variables were compared by Fisher's exact test or the chi-squared test. Normally or non-normally distributed variables were compared using the *t*-test or Wilcoxon rank-sum test, respectively. When comparisons of continuous variables were performed among more than two groups, one-way analysis of variance (ANOVA) or Kruskal–Wallis ANOVA was used. Multiple logistic regression modelling was applied to analyse the interaction between demographic characteristics, pre-vaccination status, medications and SC. All tests were two-sided, with a 0.05 significance level.

Results

Demographic data and current treatment

Inflammatory arthritis patients on anti-TNF therapy and healthy controls were of similar current age (45.1 ± 11.8 *vs* 44.3 ± 12.4 years, $P = 0.61$), a finding also observed for the comparison between inflammatory arthritis patients on anti-TNF and those on DMARDs (45.1 ± 11.8 *vs* 46.5 ± 10.6 years, $P = 0.44$). The frequency of female gender was significantly lower in anti-TNF compared with controls (50% *vs* 68%, $P = 0.0004$) and similar to DMARDs (50% *vs* 55.7%, $P = 0.43$). Mean disease duration was significantly higher in anti-TNF *vs* DMARD patients (18.4 ± 10.1 *vs* 15.6 ± 10.4, $P = 0.02$) (Table 1).

As expected, the frequencies of MTX (35.8% *vs* 53.4%, $P = 0.007$) and SSZ (15% *vs* 39.7%, $P = 0.0001$) use were significantly lower in patients under anti-TNF therapy compared with the DMARD group. No differences were observed in the frequencies and current doses of the other DMARDs, NSAIDs and immunosuppressive drugs in both groups ($P > 0.05$; Table 1).

Immunization response pattern in RA

Analysis of the immune response in RA patients revealed that before immunization the SP rate and GMTs were comparable in RA patients receiving anti-TNF therapy, those receiving DMARDs and healthy controls ($P > 0.05$). After immunization, the GMTs were significantly lower in patients on DMARDs ($P = 0.011$) compared with controls. Those using MTX showed a significant reduction in GMT ($P = 0.006$), factor increase in GMT ($P = 0.047$) and SP ($P = 0.018$) compared with controls, whereas reduced SC did not reach statistical significance ($P = 0.066$; Table 2). No differences in any parameters were evidenced in patients on mAbs and etanercept compared with healthy controls or those on DMARDs ($P > 0.05$; Table 2).

Immunization response pattern in SpA

Analysis of the immune response in SpA patients before immunization revealed comparable SP rates and GMTs in patients receiving anti-TNF therapy, those receiving DMARDs and healthy controls ($P > 0.05$). After immunization, SC ($P = 0.018$), SP ($P = 0.03$), GMT ($P = 0.005$) and factor increase in GMT ($P = 0.001$) were significantly lower in patients receiving anti-TNF therapy compared with healthy controls. The comparison of SpA patients receiving anti-TNF with those receiving DMARDs also

TABLE 1 Demographic data, disease distribution and treatment in patients on anti-TNF therapy, patients on DMARDs and healthy controls before pandemic 2009 influenza A H1N1 vaccination

Variable	Anti-TNF ($n = 120$)	DMARDs ($n = 116$)	Healthy controls ($n = 117$)
Demographic data			
Female gender	60 (50)*	67 (55.7)**	79 (68)
Current age, years	45.1 ± 11.8	46.5 ± 10.6	44.3 ± 12.4
Disease duration, years	18.4 ± 10.1***	15.6 ± 10.4	–
Diseases			
RA	41 (34.2)	41 (35.3)	–
SpA	79 (63.8)	75 (64.7)	
AS	57 (47.5)	53 (45.7)	–
PsA	22 (18.3)	22 (19.0)	–
Treatment			
Anti-TNF			
mAbs	94 (78.3)	–	–
Infliximab	54 (45.0)	–	–
Adalimumab	40 (33.3)	–	–
Soluble receptor			
Etanercept	26 (21.7)	–	–
Glucocorticosteroid	49 (40.8)	45 (38.8)	–
Current dose, mg/day	7.3 ± 3.2	9.6 ± 5.4	–
DMARDs			
MTX	43 (35.8)***	62 (53.4)	–
Current dose, mg/week	18.4 ± 6.3	19.2 ± 5.1	–
SSZ	18 (15.0)***	46 (39.7)	–
LEF	16 (13.3)	18 (15.5)	–
Chloroquine	11 (9.2)	18 (15.5)	–
Other drugs			
AZA	3 (2.5)	5 (4.3)	–
Ciclosporin	1 (0.8)	2 (1.7)	–
MMF	0	2 (1.7)	–
NSAID	36 (30.1)	41 (35.3)	–

Data are expressed as *n* (%) or mean (S.D.). *$P < 0.05$ (anti-TNF compared with age-matched randomly selected healthy controls), **$P < 0.05$ (DMARDs compared with randomly selected healthy controls), ***$P < 0.05$ (anti-TNF compared with randomly selected patients on traditional DMARDs).

revealed reduced SC ($P = 0.031$), GMT ($P = 0.024$) and factor increase in GMT ($P < 0.001$) in the former group. In addition, SP was also reduced but did not reach statistical significance ($P = 0.053$; Table 3). After immunization, the SC ($P = 0.002$), SP ($P = 0.006$), GMT ($P = 0.002$) and factor increase in GMT ($P < 0.001$) were significantly lower in SpA patients on mAb therapies (adalimumab or infliximab) compared with healthy controls. These same parameters were also significantly lower compared with those of patients receiving DMARDs ($P = 0.005$; $P = 0.014$; $P = 0.009$; $P < 0.001$, respectively) (Table 3).

Demographic data, pre-vaccination parameters, diseases (AS and PsA) and treatment of non-seroconverted ($n = 52$) *vs* seroconverted ($n = 102$) patients are illustrated in Table 4. The mean current age was significantly higher in non-seroconverted SpA patients compared with those who seroconverted (45.0 ± 11.3 *vs* 41.5 ± 10.3 years, $P = 0.003$). The frequency of anti-TNF ($P = 0.031$) and mAbs ($P = 0.001$) was significantly higher in patients who did not seroconvert compared with those who seroconverted, whereas the frequency of MTX use was lower in patients who did not seroconvert compared with those who seroconverted ($P = 0.028$; Table 4).

Multivariate logistic regressions were performed, including variables with $P \leqslant 0.2$ [current age, pre-vaccination GMT, MTX, LEF, disease (PsA or AS), mAbs and etanercept] and revealed that only older age ($P = 0.015$) and mAb treatment ($P = 0.023$) remained significant for non-SC.

Adverse events

Only mild systemic reactions were more often observed in patients on anti-TNF compared with healthy controls: fever (8.3% *vs* 0.9%, $P = 0.01$), arthralgia (12.5% *vs* 4.3%, $P = 0.03$) and nasal congestion (13.3% *vs* 4.3%, $P = 0.014$). No differences were observed in the frequency of adverse events in patients on anti-TNF compared with the DMARDs group ($P > 0.05$; Table 5). No severe adverse event was reported in any group after 3 weeks of follow-up.

Discussion

To our knowledge, this study was the largest analysis in inflammatory arthritis patients on distinct anti-TNF

Table 2 Serological data before and after pandemic 2009 influenza A H1N1 vaccine in RA patients and healthy controls

Variable	Pre-vaccination		Post-vaccination			
	GMT	SP	GMT	SP	FI	SC
Healthy controls ($n = 117$)	9.1 (7.8, 10.7)	11.1 (5.4, 16.8)	107.6 (83.6, 138.5)	78.6 (71.2, 86.1)	11.8 (9.3, 14.9)	74.3 (66.4, 82.3)
RA DMARD ($n = 41$)	6.8 (5.7, 8.1)	4.9 (1.7, 11.5)	56.1 (36.6, 86.0)*	63.4 (48.7, 78.2)	8.3 (5.4, 12.7)	61.9 (47.2, 76.6)
RA MTX ($n = 25$)	6.8 (5.5, 8.3)	0	43.5 (26.1, 72.5)*	56.0 (36.5, 75.5)*	6.4 (3.8, 10.8)*	56.0 (36.5, 75.5)
RA anti-TNF ($n = 41$)	7.4 (5.9, 9.2)	7.3 (0.6, 15.3)	66.4 (41.6, 106.1)	65.9 (51.3, 80.4)	9.0 (5.9, 13.7)	65.9 (51.3, 80.4)
mAbs ($n = 30$)	7.5 (5.7, 9.9)	6.7 (0, 15.6)	66.1 (36.1, 120.8)	66.7 (49.8, 83.5)	8.8 (5.1, 15.1)	66.7 (49.8, 83.5)
Etanercept ($n = 11$)	7.3 (5.1, 10.5)	9.1 (7.9, 26.1)	58.4 (30.1, 113.2)	63.6 (35.2, 92.1)	8.0 (4.6, 13.9)	63.6 (35.2, 92.1)

Data are expressed as percentage or value (95% CI). *$P < 0.05$ (RA DMARDs, RA MTX or RA anti-TNF compared with randomly selected healthy controls). FI: factor increase in GMT.

Table 3 Serological data before and after pandemic 2009 influenza A H1N1 vaccine in SpA patients and healthy controls

Variable	Pre-vaccination		Post-vaccination			
	GMT	SP	GMT	SP	FI	SC
Healthy controls ($n = 117$)	9.1 (7.8, 10.7)	11.1 (5.4, 16.8)	107.6 (83.6, 138.5)	78.6 (71.2, 86.1)	11.8 (9.3, 14.9)	74.3 (66.4, 82.3)
SpA DMARD ($n = 75$)	7.6 (6.4, 9.0)	6.7 (1.0, 12.4)	107.5 (74.3, 115.6)	78.7 (69.3, 88.0)	14.2 (10.1, 19.9)	74.7 (64.8, 84.6)
SpA MTX ($n = 35$)	8.2 (6.1, 11.1)	8.6 (0, 17.8)	176.7 (102.3, 305.1)	88.6 (78.0, 99.1)	21.5 (12.4, 37.4)	80.0 (66.7, 93.3)
SpA a-TNF ($n = 79$)	9.2 (7.5, 11.4)	11.4 (4.3, 18.4)	57.3 (41.5, 79.2)*,**,***	64.6 (53.9, 75.2)*,***	6.2 (4.6, 8.3)*,**,***	58.2 (47.3, 69.2)*,**,***
mAbs ($n = 64$)	9.0 (7.0, 11.5)	14.1 (5.5, 22.6)	50.2 (34.4, 73.4)*,**,***	59.4 (47.2, 71.5)*,**,***	5.6 (4.0, 7.8)*,**,***	51.6 (39.2, 63.9)*,**,***
Etanercept ($n = 15$)	10.5 (7.5, 14.7)	0	100.8 (64.1, 158.5)	86.7 (68.9, 100.0)	9.6 (6.9, 10.4)	86.7 (68.9, 100.0)

Data are expressed as percentage or value (95% CI). *$P < 0.05$ (SpA DMARDs or SpA anti-TNF compared with randomly selected healthy controls), **$P < 0.05$ (SpA anti-TNF compared with randomly selected SpA patients on DMARDs), ***$P < 0.05$ (SpA anti-TNF compared with randomly selected SpA patients on MTX). FI: factor increase in GMT.

classes, and clearly showed reduced immunogenicity in SpA patients on mAb therapies.

The major strength of this study was the inclusion of two randomly selected control groups. The absence of these control groups, specifically for the anti-TNF group, in the two previous studies evaluating pandemic influenza vaccine immune response precludes a definitive conclusion about the possible influence of other DMARDs [9, 10]. In addition, the separate evaluation of RA and SpA was an essential parameter to define more precisely the influence of a biologic agent on the immune response because a diverse pandemic vaccine immunogenicity profile in distinct autoimmune rheumatic diseases has been reported [7]. Moreover, the use of non-adjuvant vaccine was chosen to avoid autoimmune disease [16–18], although recent studies have reinforced the safety of adjuvanted influenza vaccine in rheumatic diseases [19]. On the other hand, the short observation period of the present study is a limitation and does not exclude long-term adverse events [20]. Furthermore, the influence of disease activity was not evaluated herein and must be clarified in future studies.

Biologic drugs may affect antibody production and vaccine immunogenicity [1, 2]. There are, however, controversial results regarding the humoral immune response after seasonal influenza immunization in patients with autoimmune rheumatic disease with either unaffected [21–23] or reduced immunogenicity [24–27].

Concerning the pandemic influenza vaccine, we have shown for the first time a distinctive immune response not only among RA and SpA patients but also between different anti-TNF agents. We have confirmed a previous observation that MTX [8, 9, 27] but not TNF blockage [8] therapy had a deleterious effect on influenza vaccination in RA patients.

The separate evaluation of the SpA group allowed for a more accurate definition of the effects of anti-TNF mAbs on the vaccine response in these diseases. In fact, mAbs seem to incur a higher risk for herpes zoster virus infection and tuberculosis than do soluble receptor TNF blockers [28, 29]. Additional studies are necessary to determine whether reported structural and functional differences among TNF blockers regarding pharmacokinetics, ability to cross-link transmembrane TNF, binding avidity and

Table 4 Comparison of pandemic 2009 influenza A H1N1 vaccine non-seroconverter SpA patients and seroconverters

Variable	Non-seroconverters ($n = 52$)	Seroconverters ($n = 102$)
Demographic data		
Female gender	17 (32.7)	31 (30.4)
Current age, years	45.0 ± 11.3*	41.5 ± 10.3
Disease duration, years	20.8 ± 12.6	16.7 ± 9.4
Pre-vaccination parameters		
SP	6 (11.5)	8 (7.8)
GMT	8.0 (95% CI 6.0, 10.6)	8.6 (95% CI 7.4, 10.0)
Diseases		
AS	35 (67.3)	75 (73.5)
PsA	17 (32.7)	27 (26.5)
Treatment		
Anti-TNF	33 (63.4)*	46 (49.7)
mAbs	31 (59.6)*	33 (32.4)
Etanercept	2 (3.8)	13 (12.7)
Glucocorticosteroid	8 (15.4)	15 (14.7)
Current dose, mg/day	9.1 ± 5.0	7.8 ± 4.1
DMARDs		
MTX	13 (25.0)*	44 (43.1)
Current dose, mg/week	16.3 ± 3.6	18.3 ± 6.5
SSZ	17 (32.7)	42 (42.2)
LEF	4 (7.7)	2 (2.0)

Data are expressed as *n* (%) and mean (S.D.). *$P < 0.05$ (non-seroconverters compared with seroconverters).

Table 5 Adverse events of pandemic 2009 influenza A vaccine in inflammatory arthritis patients on anti-TNF therapy, patients on DMARDs and healthy controls

Variable	Anti-TNF ($n = 120$)	DMARDs ($n = 116$)	Healthy controls ($n = 117$)
Local reactions	8 (6.7)	12 (10.3)	16 (13.7
Pain	6 (5.0)	6 (7.9)	14 (12.0)
Redness	0 (0)	0 (0)	4 (3.4)
Swelling	2 (1.7)	2 (1.8)	6 (5.1)
Itching	1 (0.8)	2 (1.8)	1 (0.9)
Systemic reactions	43 (35.8)	33 (28.4)	32 (27.4)
Fever	10 (8.3)*	4 (3.5)	1 (0.9)
Tremor	10 (8.3)	9 (7.9)	3 (2.6)
Arthralgia	15 (12.5)*	9 (7.9)	5 (4.3)
Headache	19 (15.8)	18 (15.8)	17 (14.5)
Myalgia	14 (11.7)	19 (16.7)	14 (12)
Diarrhoea	5 (4.2)	6 (5.7)	10 (8.5)
Sore throat	8 (6.7)	11 (9.6)	10 (8.5)
Cough	12 (10)	12 (10.5)	5 (4.3)
Rhinorrhoea	15 (12.5)	11 (9.6)	7 (6)
Nasal congestion	16 (13.3)*	12 (10.5)	5 (4.3)

Data are expressed as *n* (%). *$P < 0.05$ (anti-TNF compared with randomly selected healthy controls).

inhibition of cell activation and cytokine expression could ultimately affect vaccine antibody response [28, 30]. Moreover, the lower SC rate in patients treated with mAbs was not related to higher doses because only patients with the recommended standard dosage and interval for each TNF antagonist were included.

The uniformly low pre-vaccine SP in all groups, and absence in SpA patients under etanercept, may reflect the chance of acquiring a natural immunization, since the vaccine was not available in the previous year. However, post-vaccination immunogenicity in SpA patients on etanercept was adequate. The persistence of this antibody response for the next year needs to be evaluated in further studies.

Despite the similar ages in the three groups (anti-TNF, DMARDs and healthy controls), further analysis of non-seroconverting and seroconverting SpA patients confirmed on multivariate analysis that age influenced the pandemic influenza vaccination immune response [9, 31]. However, the small difference observed in the present study within a restricted age bracket may have no clinical relevance, despite the statistical significance.

Glucocorticoid therapy did not seem to influence immunogenicity in inflammatory arthritis patients, as also evidenced in RA and AS [10] and in SLE patients [32] who received the pandemic influenza vaccine. In contrast, current glucocorticoid [33] use was the major factor associated with decreased antibody production in a paediatric rheumatic disease population. Remarkably, the use of

DMARDs was not a predictive factor for a reduced humoral response in SpA, a pattern different from that observed in RA patients.

Of note, the influenza A (H1N1) vaccine was safe in inflammatory arthritis patients on anti-TNF therapies with predominantly mild systemic reactions. No serious short-term adverse event was observed, a finding reported previously in autoimmune rheumatic patients who received the seasonal influenza [21–25, 27] and pandemic vaccines [8, 9, 17–19, 32, 34, 35].

The European Committee for Medicinal Products for Human Use has suggested that all three criteria for vaccine immunogenicity should be met for pandemic vaccines [36]: SP >70%, SC >40% and factor increase in GMT >2.5 [37]. Despite a lower SC rate in patients receiving anti-TNF drugs, the majority achieved an adequate response, supporting the recommendation of this vaccine. Nevertheless, the second pandemic influenza A vaccination injection increased the immunogenicity of the rheumatic diseases [9, 17], supporting the notion that a booster may improve vaccine response in SpA patients on anti-TNF mAb therapy. In conclusion, this study revealed a distinct disease pattern of immune response in inflammatory arthritis patients receiving anti-TNF agents, with reduced immunogenicity solely in SpA patients using mAbs.

Rheumatology key messages

- Older age and anti-TNF mAbs reduced immunogenicity to pandemic 2009 influenza A H1N1 vaccine in SpA patients.
- Short-term safety after pandemic influenza vaccination was observed in inflammatory arthritis patients on anti-TNF treatment.

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