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

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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.
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 Clínicas 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°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-179A), 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).
Use of H1N1 vaccine in arthritis patients

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, rhinorrhea 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 >1:40) and SC (pre-vaccination titre <1:10 and a post-vaccination HIA titre >1:40 or pre-vaccination titre >1:10 and a >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

Immunization response pattern in SpA
Analysis of the immune response in SpA patients before immunization revealed that before immunization the SP rate and GMTs were comparable in SpA 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 RA
Analysis of the immune response in RA patients before immunization revealed comparable SP rates 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).
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 ≤ 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 therapies, revealing that anti-TNF and mAb therapies are associated with a reduced seroconversion rate in SpA patients compared with healthy controls and patients on traditional DMARDs.
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 2** Serological data before and after pandemic 2009 influenza A H1N1 vaccine in RA patients and healthy controls

| Variable | Pre-vaccination | Post-vaccination | FI | SC |
|----------|----------------|-----------------|----|----|
|          | GMT            | SP              |    |    |
| 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 (30.3, 112.3) | 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 | FI | SC |
|----------|----------------|-----------------|----|----|
|          | GMT            | SP              |    |    |
| 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) | 53.7 (41.5, 79.2) | 64.6 (53.9, 75.2) | 6.2 (4.6, 8.3) | 56.2 (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 MTX). FI: factor increase in GMT.
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

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**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).
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, 31, 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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References

1 Silva CA, Tererli MT, Aikawa NE et al. Vaccination practice in children with rheumatic disease. Rev Bras Reumatol 2010;50:351–61.

2 Rahier JF, Moutschen M, Van Gompel A et al. Vaccinations in patients with immune-mediated inflammatory diseases. Rheumatology 2010;49:1815–27.

3 Furst DE. The risk of infections with biologic therapies for rheumatoid arthritis. Semin Arthritis Rheum 2010;39:327–46.

4 Van Assen S, Agon-Levin N, Elkayam O et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2011;70:414–22.

5 Centers for Disease Control and Prevention (CDC). Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. http://www.cdc.gov/mmwr/preview/mmwrhtml/r59e0729a1.htm (19 March 2012, date last accessed).

6 Estratégia Nacional De Vacinação—Ministério Da Saúde—Brasil [National vaccination strategy—The Ministry of Health—Brazil]. http://portal.saude.gov.br/portal/arquivos/pdf/pt_gripe_final_com_faxa250210.pdf (19 March 2012, date last accessed).

7 Saad CG, Borba EF, Aikawa Ne et al. Immunogenicity and safety of the 2009 non-adjuvanted influenza A/H1N1 vaccine in a large cohort of autoimmune rheumatic diseases. Ann Rheum Dis 2011;70:1068–73.

8 Ribeiro AC, Guedes LK, Moraes JC et al. Reduced seroprotection after pandemic H1N1 influenza adjuvant-free vaccination in patients with rheumatoid arthritis: implications for clinical practice. Ann Rheum Dis 2011;70:2144–47.

9 Gabay C, Bel M, Combesure C et al. Impact of synthetic and biologic disease-modifying antirheumatic drugs on antibody responses to the AS03-adjuvanted pandemic influenza vaccine: a prospective, open-label, parallel-cohort, single-center study. Arthritis Rheum 2011;63:1486–96.

10 Elkayam O, Amir S, Mendelson E et al. Efficacy and safety of vaccination against pandemic 2009 influenza A (H1N1) virus among patients with rheumatic diseases. Arthritis Care Res (Hoboken) 2011;63:1062–7.

11 Haraoui B, Pope J. Treatment of early rheumatoid arthritis: concepts in management. Semin Arthritis Rheum 2011;40:371–88.

12 Arnett FC, Edworthy SM, Bloch DA et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.

13 van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361–8.

14 Taylor W, Gladman D, Helliwell P et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665–73.

15 Kendal AP, Pereira MS, Skehel JJ, eds., Concepts and procedures from laboratory-based influenza surveillance. Atlanta, GA: Centers for Disease Control and Prevention, 1982.

16 Shoenfeld Y, Agmon-Levin N. ‘ASIA’ - autoimmune/inflammatory syndrome induced by adjuvants. J Autoimmun 2011;36:4–8.

17 Mathian A, Devilliers H, Krivine A et al. Factors influencing the efficacy of two injections of a pandemic 2009 influenza A (H1N1) nonadjuvanted vaccine in systemic lupus erythematosus. Arthritis Rheum 2011;63:3502–11.

18 Lu CC, Wang YC, Lai JH et al. A/H1N1 influenza vaccination in patients with systemic lupus erythematosus. safety and immunity. Vaccine 2011;29:444–50.
19 Urowitz MB, Anton A, Ibanez D, Gladman DD. Autoantibody response to adjuvant and nonadjuvant H1N1 vaccination in systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2011;63:1517–20.

20 Lertdumrongluk P, Changsirikulchai S, Limkunakul C et al. Safety and immunogenicity of a 2009 influenza A (H1N1) vaccine in hemodialysis patients. Vaccine 2012;30:1108–14.

21 Fomin I, Caspi D, Levy V et al. Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying drugs, including TNF alpha blockers. Ann Rheum Dis 2006;65:191–4.

22 Kubota T, Nii T, Nanki T et al. Anti-tumor necrosis factor therapy does not diminish the immune response to influenza vaccine in Japanese patients with rheumatoid arthritis. Mod Rheumatol 2007;17:531–3.

23 Elkayam O, Bashkin A, Mandelboim M et al. The effect of infliximab and timing of vaccination on the humoral response to influenza vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. Semin Arthritis Rheum 2010;39:442–7.

24 Kapetanovic MC, Saxne T, Nilsson JA, Geborek P. Influenza vaccination as model for testing immune modulation induced by anti-TNF and methotrexate therapy in rheumatoid arthritis patients. Rheumatology 2007;46:608–11.

25 Gelinck LB, Van Der Bijl AE, Beyer WE et al. The effect of anti-tumour necrosis factor alpha treatment on the antibody response to influenza vaccination. Ann Rheum Dis 2008;67:713–6.

26 Salemi S, Picchianti-Diamanti A, Germano V et al. Influenza vaccine administration in rheumatoid arthritis patients under treatment with TNF alpha blockers: safety and immunogenicity. Clin Immunol 2010;134:113–20.

27 Kaine JL, Kivitz AJ, Birbara C, Luo AY. Immune responses following administration of influenza and pneumococcal vaccines to patients with rheumatoid arthritis receiving adalimumab. J Rheumatol 2007;34:272–9.

28 Strangfeld A, Listing J, Herzer P et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. JAMA 2009;18(301):737–44.

29 Wallis RS. Tumour necrosis factor antagonists: structure, function, and tuberculosis risks. Lancet Infect Dis 2008;8:601–11.

30 Scallon B, Cai A, Solowski N et al. Binding and functional comparisons of two types of tumor necrosis factor antagonists. J Pharmacol Exp Ther 2002;301:418–26.

31 Young F, Marra F. A systematic review of intradermal influenza vaccines. Vaccine 2001;29:8788–801.

32 Borba EF, Saad CG, Pasoto SG et al. Antimalarials: a window of opportunity to improve the influenza A/H1N1 vaccine response in lupus patients under immunosuppressive agents. Rheumatology 2011;51:1061–9.

33 Aikawa NE, Campos LM, Silva CA et al. Glucocorticoid: major factor for reduced immunogenicity of 2009 influenza a (H1N1) vaccine in patients with juvenile autoimmune rheumatic disease. J Rheumatol 2012;39:167–73.

34 Rahier JF, Papay P, Salleron J et al. H1N1 vaccines in a large observational cohort of patients with inflammatory bowel disease treated with immunomodulators and biological therapy. Gut 2011;60:456–62.

35 Crowe SR, Merrill JT, Vista E S et al. Influenza vaccination responses in human systemic lupus erythematosus: impact of clinical and demographic features. Arthritis Rheum 2011;63:2396–406.

36 European Committee for Medicinal Products for Human Use. Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application. London: European Medicines Agency, 2004. Publication no. EMEA/CPMP/VEG/4717/2003-Rev.1. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003869.pdf (19 March 2012, date last accessed).

37 Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for industry: clinical data needed to support the licensure of pandemic influenza vaccines. May 2007. http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091985.pdf.