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SHORT COMMUNICATION

Low level of seroconversion after a novel influenza A/H1N1/2009 vaccination in Japanese patients with rheumatoid arthritis in the 2009 season

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Abstract We examined change in the antibody titre against pandemic influenza A/H1N1/2009 before and after vaccination in Japanese patients with rheumatoid arthritis. This observational study was conducted with the participation of five hospitals in Japan. A total of 89 patients with rheumatoid arthritis were included in this study. The seroprotection and seroresponse rates to vaccination with the pandemic influenza A/H1N1/2009 vaccine were analysed. The seroprotection rates prior to the vaccination were 5.6% in the Japanese patients with rheumatoid arthritis. The seroprotection rates after subcutaneous vaccination were 55.1%. The seroresponse rate after subcutaneous vaccination was 50.6% in the patients with rheumatoid arthritis. Both the seroprotection and seroresponse rates obtained after the vaccination with the pandemic influenza A/H1N1/2009 vaccine were low in Japanese patients with rheumatoid arthritis. We should realise that a vaccination against this newly emerged influenza virus may protect only half of the Japanese patients with rheumatoid arthritis in a real world.

Keywords Influenza A/H1N1/2009 · Vaccination · Rheumatoid arthritis

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Introduction

A novel influenza A/H1N1/2009 of swine-origin emerged as a pandemic in Mexico, Canada and the US in April 2009 [1, 2]. A vaccine against this virus was manufactured, and its safety and efficacy were evaluated [3, 4]. Data from a clinical trial of a vaccine made available by a Japanese pharmaceutical company were published by the Ministry of Health, Labour and Welfare, Japan [5, 6]. In these data, a single subcutaneous dose of 15 μg of haemagglutinin antigen without adjuvant yielded a seroresponse rate of 73.5% [95% confidence interval (CI), 63.6–81.9] in healthy Japanese individuals.

It was reported that the seasonal influenza virus vaccine mounted a good humoral response in rheumatoid arthritis (RA) patients despite treatment with prednisone and/or other disease modifying anti-rheumatic drugs (DMARDs), including biologics; however, the response was weaker in patients receiving tumour necrosis factor (TNF) blockers than that in healthy controls or in those not receiving TNF blockers [7–9].

We conducted the observational study to survey the seroprotection and seroresponse rates to the new influenza A/H1N1/2009 virus among Japanese patients with RA.

Materials and methods

Subjects

A total of 89 patients with RA and 14 healthy volunteers were included in this study. These patients had been treated at Jichi Medical University, the Japanese Red Cross Society Koga Hospital, Shimotsuga General Hospital, Utsunomiya Social Insurance Hospital and Kawakami Hospital (Table 1). Vaccination with a pandemic influenza A/H1N1/2009 vaccine was performed between October 2009 and March 2010. RA was diagnosed according to the American College of Rheumatology 1987 criteria [10]. RA patients treated with immunosuppressants such as corticosteroids and methotrexate (MTX), and/or biologics were examined in this study. Thirty-six patients with RA were under treatment with biologics (infliximab, 3; etanercept, 18; adalimumab, 7; and tocilizumab, 8). The study protocol was approved by the ethics committee of each of the participating hospitals. The exclusion criteria from the study were severe allergic reaction to any of the content of the newly manufactured vaccine, active infectious disease or fever. Written informed consent was obtained from all the patients. This study was registered at UMIN000002754 in the UMIN Clinical Trials Registry, Japan.

The study participants received a subcutaneous injection of a commercially available inactivated monovalent vaccine containing 15 μg of haemagglutinin of the pandemic influenza (H1N1) 2009 virus in a manner approved by the Ministry of Health, Labour and Welfare, Japan. If antibody response was not observed to the first vaccination, the patients could receive a booster vaccination, if they wanted.

Table 1 Demographics of the patients

Characteristics	Value
Gender (male/female)	8/81
Median age (year) [range]	67 [29–90]
Median dose of prednisolone (mg/day) [range]	1.5 [0–12.5]
Median dose of methotrexate (mg/week) [range]	4 [0–10]
Drugs no. (%)	
Corticosteroid	54 (60.7)
Methotrexate	63 (70.8)
Leflunomide	2 (2.2)
Mizoribine	1 (1.1)
Tacrolimus	4 (4.5)
Biologics no. (%)	
Infliximab	3 (3.4)
Etanercept	18 (20.2)
Adalimumab	7 (7.9)
Tocilizumab	8 (9.0)

Laboratory examinations

Serum samples were collected before and 3–6 weeks after the vaccination and stored at −30°C until the assay. The haemagglutination inhibition (HI) assay was performed according to the standard World Health Organization procedure by one of the authors (M.I.). The sera were treated with receptor-destroying enzyme derived from cholera filtrate to remove non-specific inhibitors, and with chicken red blood cells to remove non-specific agglutinins. The inactivated pandemic influenza (H1N1) 2009 antigen for HI assays was obtained from the National Institute of Infectious Diseases (Tokyo, Japan). The working dilution contained 4 haemagglutinin units of pandemic influenza (H1N1) 2009 antigen in 25 μl of phosphate-buffered saline. The HI assay was performed using twofold dilutions of the serum, and the titre was expressed as the reciprocal value of the highest dilution of the serum at which complete inhibition of haemagglutination was achieved [7]. All the serum samples from each individual were tested simultaneously.

Statistical analysis

Seroprotection was defined as an HI titre of ≥40. Seroresponse (seroconversion) was defined as an increase in both an HI titre of ≥4-fold and an HI titre of ≥40 after vaccination. The differences in clinical characteristics between two groups were evaluated with the use of Mann–Whitney's *U* test for continuous variables, and Fisher's exact probability test and chi-square statistic for categorical variables. A statistical analysis of the confidence interval was performed using SAS version 9.2 (SAS Institute Inc., NC). A multiple logistic regression analysis was performed to survey the potential baseline predictors of seroresponse in patients with RA, including age, gender and use of biologics using SAS version 9.2 (SAS Institute Inc., NC).

Results

The seroprotection rates before vaccination with the pandemic influenza A/H1N1/2009 vaccine were 5.6% in the Japanese RA patients included in this study. The seroprotection and seroresponse rates after the vaccination were 55.1 and 50.6% in the RA patients (Table 2) and 71.4 and 64.3% in the healthy volunteers, respectively.

The seroprotection and seroresponse rates after the vaccination in patients without biologics were 60.4 and 58.5%, respectively. On the other hand, the seroprotection and seroresponse rates after vaccination in patients with biologics were 47.2 and 38.9%, respectively (Table 2). Multiple logistic regression analysis showed that the seroresponse rate in patients with biologics tended to be

Table 2 Seroprotection and seroresponse rates after vaccination

	Seroprotection rates	Seroresponse rates
Total patients ($n = 89$)% (95% CI)	55.1% (44.1–65.6)	50.6% (39.8–61.3)
Non-biologic users ($n = 53$)% (95% CI)	60.4% (46.0–73.6)	58.5% (44.1–71.9)
Biologic users ($n = 36$)% (95% CI)	47.2% (30.4–64.5)	38.9% (23.1–56.5)

CI confidence interval

Table 3 Seroresponse rates according to biologic use using the multiple logistic analysis

Parameter	Odds ratio	95% CI	*P* value
Age	0.98	0.96–1.01	0.28
Gender	0.71	0.18–2.84	0.63
Biologic use	0.46	0.20–1.06	0.07

CI confidence interval

lower compared to that in those without (odds ratio, 0.46; 95% CI, 0.20–1.06; $P = 0.07$). There was no association between the seroresponse rate and age or gender (Table 3). There was no association between the duration of biologic treatment and level of seroconversion after vaccination (data not shown). The median dose of prednisolone was 2.5 mg daily in patients without biologics and 0.5 mg daily with biologics. The median dose of MTX was 6 and 4 mg weekly in patients without and with biologics, respectively. Thus, the doses of prednisolone and MTX were higher in patients without biologics than those with biologics ($P = 0.010$ and 0.017, respectively).

A total of 9 patients liked to receive a booster vaccination because the first vaccine did not give the seroprotection level of antibody response. Three of 9 patients achieved seroprotection level of response after the booster. The seroresponse rate to the booster was 22.2% in these patients. One patient with infliximab and one without biologics showed seroresponse after the booster.

A case of facial palsy was reported in this study, probably related to influenza A/H1N1/2009 vaccine.

Discussion

Pandemic influenza A/H1N1/2009 appeared as an emerging infection in April 2009. In Japan, the first patient who contracted pandemic influenza A/H1N1/2009 was confirmed on May 16, 2009. Although the data are available for the seroprotection and seroresponse rates in healthy individuals, those are lacking in RA patients. Greenberg et al. [3] reported that antibody titres of 1:40 or more are observed in 95.0% of the 120 subjects, who received the 15 μg dose of inactivated, unadjuvanted, split-virus influenza A/H1N1/2009 vaccine intramuscularly, by day 21. Zhu et al. [4] also reported that antibody titres of 1:40 or more are observed in 97.1% of subjects between 18 and 60 years, who received the 15 μg dose of inactivated, unadjuvanted, split-virus influenza A/H1N1/2009 vaccine intramuscularly, by day 35. In Japan, vaccination with a single subcutaneous dose of 15 μg of haemagglutinin antigen without adjuvant yields a seroprotection rate of 78.6% and seroresponse rate of 73.5% (95% CI, 63.6–81.9) in healthy individuals by day 21 [6], which is consistent with the result from our healthy volunteers. The seroprotection rates in Japan are lower than that in other countries, one possible reason of which is an administration route (subcutaneously in Japan versus intramuscularly in other countries). In our present study, the seroprotection and seroresponse rates after the first vaccination were 55.1% (95% CI, 44.1–65.6) and 50.6% (95% CI, 39.8–61.3) for RA patients. The seroresponse rates were much lower in patients with RA than in healthy individuals in Japanese. Age in subjects may contribute to the lower seroprotection and seroresponse rates in our study, because the median age of subjects in our study was older than the healthy subjects in the Japanese study conducted by the Ministry of Health, Labour and Welfare, Japan. Zhu et al. [4] had reported younger subjects showed higher responses to the influenza vaccine than older subjects at day 21, but same responses at day 35.

Multiple logistic regression analyses disclosed the lower seroresponse rates, not reaching statistical significance, in RA patients with biologics than those without, even though those with biologics received smaller doses of corticosteroid/MTX. A previous report showed that anti-TNF therapy is not associated with a diminished humoral immune response to seasonal influenza vaccination in Japanese RA patients [8]. However, RA patients with MTX and without TNF blockers show significantly better serological response to seasonal influenza vaccination than those with TNF blockers alone or TNF blockers with MTX and/or other DMARDs [9]. A larger-scale trial is needed to determine whether biologics influence the antibody production after any vaccinations. A booster of influenza A/H1N1/2009 vaccine gave lower seroresponse rates than the first vaccination in patients in this study; a booster effect might appear in a small number of patients.

Only a half of the Japanese patients with RA mounted an antibody response to a level of potential protection after influenza A/H1N1/2009 subcutaneous vaccination in a real world and RA patients on biologics were even worse.

Meticulous attention should be paid to caring these patients in epidemic season and a whole year.

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Conflict of interest The authors have no conflicts of interest to declare.

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