Immune Responses Following Administration of Influenza and Pneumococcal Vaccines to Patients with Rheumatoid Arthritis Receiving Adalimumab

JEFFREY L. KAINE, ALAN J. KIVITZ, CHARLES BIRBARA, and ALLISON Y. LUO

ABSTRACT. ***Objective.*** This study compared the immunogenicity of influenza and pneumococcal vaccines in adult patients with rheumatoid arthritis (RA) receiving adalimumab or placebo.

Methods. In this double-blind, randomized, multicenter study, patients received adalimumab or placebo on Days 1, 15, and 29. Pneumococcal and influenza vaccines were administered on Day 8 (vaccine baseline). Vaccine response (≥ 2-fold titer increase from baseline in ≥ 3 of 5 pneumococcal antigens and ≥ 4-fold titer increase from baseline in ≥ 2 of 3 influenza antigens) and protective antibody titers (≥ 1.6 μg/ml pneumococcal antibody concentration to ≥ 3 of 5 antigens and ≥ 1:40 influenza antibody titer to ≥ 2 of 3 antigens) were analyzed 4 weeks' postvaccination.

Results. Following pneumococcal vaccination, percentages of patients achieving a vaccine response were similar in the adalimumab and placebo groups [37.4% and 40.4%, respectively; 95% CI (confidence interval) –16.2%, 10.3%]. Percentages of patients with protective antibody titers were similar in both treatment groups (adalimumab: 85.9%, placebo: 81.7%). Following influenza vaccination, percentages of patients achieving a vaccine response were lower with adalimumab than placebo (51.5% and 63.3%, respectively; 95% CI –25.2%, 1.6%) — a result explained by the subgroup of patients with preexisting protective antibody titers at baseline. For patients without protective antibody titers at baseline, response rates were similar in the 2 groups (adalimumab: 73.3%, placebo: 73.9%). Percentages of patients with protective antibody titers were similar in both treatment groups (adalimumab: 98%, placebo: 94.5%).

Conclusion. Patients with RA treated with adalimumab can be effectively and safely immunized with pneumococcal and influenza vaccines. (J Rheumatol 2007;34:272–9)

Key Indexing Terms:
ADALIMUMAB INFLUENZA VACCINE PNEUMOCOCCAL VACCINE
RHEUMATOID ARTHRITIS IMMUNE RESPONSE

Adalimumab administered alone or in combination with methotrexate (MTX) has demonstrated efficacy and safety in patients with rheumatoid arthritis (RA) and has become an important therapy for the disease[1-6]. Adalimumab is a fully human, anti–tumor necrosis factor (anti-TNF) monoclonal antibody, indistinguishable from IgG1. Developed using phage-display techniques, adalimumab neutralizes the effects of TNF by inhibiting its interaction with TNF-RI/II cell-surface TNF receptors[7]. Although TNF inhibition is well tolerated and provides long-lasting clinical benefit, including the inhibition of structural joint damage in patients with RA[8,9], its effect on vaccine immunogenicity in RA patients receiving concomitant immunosuppressive therapy requires further investigation.

Patients with RA have an increased standard and proportionate mortality due to infection and respiratory disease. Immunosuppressive agents and corticosteroids used to treat the disease may pose additional risk. Therefore, patients with RA are potential candidates for pneumococcal and influenza vaccinations. These patients have demonstrated equivocal results in their abilities to mount an antibody response to influenza vaccine[10-12]. Variables that affect the response to the influenza vaccine in RA patients include advanced age, comorbid disease (e.g., diabetes, asthma), concomitant immunosuppressive therapy, and history of influenza vaccination and infection[13-15]. A recent study showed that administration of the 23-valent pneumococcal vaccine in RA patients was not associated with significant worsening of clinical or laboratory variables of RA disease activity. The vaccine induced significant increases in geometric mean titers (GMT) of T cell–independent capsule pneumococcal polysaccharide-specific antibodies similar to age-matched healthy control

From the Sarasota Arthritis Research Center, Sarasota, Florida; the Altoona Center for Clinical Research, Duncansville, Pennsylvania; the Clinical Pharmacology Study Group, Worcester, Massachusetts; and Abbott Laboratories, Parsippany, New Jersey, USA.

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J.L. Kaine, MD, Director, Sarasota Arthritis Research Center; A.J. Kivitz, MD, Director, Altoona Center for Clinical Research; C. Birbara, MD, Principal Investigator, Clinical Pharmacology Study Group; A.Y. Luo, MD, formerly Associate Medical Director, Abbott Laboratories.

Address reprint requests to Dr. J.L. Kaine, Sarasota Arthritis Research Center, 1945 Versailles Street, Suite 101, Sarasota, FL 34239. E-mail: jkainemd@gmail.com

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volunteers 1 month after vaccination. However, the vaccine was not uniformly immunogenic in RA patients; the immune response, defined as either a 2-fold increase in antibody concentration or an absolute change in specific antibody of 1 μg/ml, at 1 month varied from 35% to 71% among the different antigens. It was also demonstrated that 33% of RA patients responded to none or only 1 of 7 antigens tested. There was no association between poor antibody response and the use of immunosuppressive agents, varying demographic variables, and measures of RA disease activity[16].

The extent of antibody response to influenza and pneumococcal vaccination in RA patients treated with adalimumab has not been fully elucidated. A prior substudy in 64 patients with RA demonstrated that there was no difference in the number of adalimumab- and placebo-treated patients responding [i.e., a doubling in pneumococcal antibody titer to any of 4 pneumococcal vaccine antigens (3, 7F, 9N, and 14)]. Overall, 22.5% to 52.5% of adalimumab-treated patients and 7.7% to 46.2% of placebo-treated patients responded positively to pneumococcal vaccination at 4 weeks postvaccination (Abbott Laboratories, data on file).

Our randomized, double-blind, placebo-controlled study was conducted to compare the immunogenicity of the trivalent subvirion influenza virus vaccine and the 23-valent pneumococcal vaccine in adult patients with RA receiving adalimumab or placebo. A comparable antibody response and safety profile in the 2 treatment groups would support that these vaccines can be administered effectively and safely to adalimumab-treated patients with RA.

MATERIALS AND METHODS

Role of the funding source. An Advisory Committee, which consisted of the authors from academic institutions and Abbott Laboratories, was developed for the study. The Advisory Committee and members of the Abbott clinical trial team designed the study with input from several of the study investigators. This clinical trial was sponsored by Abbott Laboratories and conducted at 22 investigational sites in the United States. A central, Independent Ethics Committee/Institutional Review Board approved the study protocol, and all patients provided written informed consent. Clinical data were collected and analyzed by Abbott Laboratories. All authors reviewed and contributed to the manuscript during its development, agreed to submit the manuscript, and approved the content of the submitted manuscript.

Patients. Patients were considered eligible for the study if they were 20 years of age or older and had a documented history of RA as defined by American College of Rheumatology diagnosis criteria. Patients must have discontinued administration of any TNF antagonists, including adalimumab, at least 2 months prior to Day 1. Patients were excluded from the study if they (1) had a recent (3-month) history of any influenza or pneumococcal infection, (2) received any vaccine within 3 months prior to initial study drug administration, or (3) received an influenza vaccine within 6 months or a pneumococcal vaccine within 5 years. All patients underwent purified protein derivative testing for latent tuberculosis infection and chest radiographs at screening.

Patients were permitted to continue their prestudy dosages of nonbiologic antirheumatic therapy, including nonsteroidal antiinflammatory drugs, corticosteroids (prednisone equivalent of ≤ 10 mg/day), and conventional (nonbiologic) disease modifying antirheumatic drugs (DMARD); however, dosage changes were not permitted during the blinded phase of the study.

Study design. The study was a randomized, double-blind, placebo-controlled, multicenter, phase IV clinical trial. Patients were stratified by concomitant MTX use (yes/no) and randomized 1:1 to receive adalimumab (80 mg on Day 1 and 40 mg on Days 15 and 29) or matching placebo subcutaneously. Commercially available 2003–04 trivalent subvirion influenza virus vaccine (0.5 ml) and standard 23-valent pneumococcal vaccine (0.5 ml) were administered intramuscularly to all patients on Day 8 (vaccination baseline). Blood samples for influenza A (H1N1, H3N2) and B (Hong Kong) and pneumococcal (9V, 14, 18C, 19F, and 23F) antibody titers were collected on Day 8 (prevaccination) and Day 36 (4 weeks postvaccination). After Day 36, patients had the option to continue adalimumab treatment (40 mg every other week) in a 6-month open-label extension. Safety evaluations, including physical examinations, laboratory assessments, vital signs, and adverse event (AE) reports, were assessed throughout the study.

Efficacy analyses. Serum pneumococcal antibody titers were determined using the enzyme-linked immunosorbent assay, and serum influenza A and B antibody titers were determined using the hemagglutination inhibition antibody assay. All antibody titer analyses were conducted by ViroMed Laboratories, Minnetonka, MN, USA. The primary measure of response was the percentage of patients achieving a satisfactory humoral response as defined by ≥ 2-fold titer increase from vaccination baseline (Day 8) in ≥ 3 of 5 pneumococcal antigens (9V, 14, 18C, 19F, and 23F)[17] and a ≥ 4-fold titer increase from vaccination baseline (Day 8) in ≥ 2 of 3 influenza antigens (H1N1, H3N2, and Hong Kong)[18,19].

Secondary measures of response included (1) percentage of patients with protective antibody titers 4 weeks postvaccination (defined as antibody titer ≥ 1.6 μg/ml for ≥ 3 of 5 antigens for the pneumococcal vaccine[20,21] and antibody titer ≥ 1:40 for ≥ 2 of 3 antigens for the influenza vaccine[18,19]; (2) percentage of patients achieving a ≥ 2-fold increase in pneumococcal antibody titers and ≥ 4-fold increase in influenza titers from baseline by antigen; and (3) mean changes in antibody titers from baseline by antigen. Results are presented as the means of variables expressed in a $\log_2$ scale, transformed into GMT. Differences between means of variables expressed in a $\log_2$ scale were transformed into geometric mean ratios (GMR).

The primary analysis was performed in a "per-protocol" population[22]. The per-protocol analysis set for the pneumococcal/influenza vaccine was defined as all patients who were randomized; who received the pneumococcal/influenza vaccine on Day 8 (vaccination baseline); who received adalimumab or placebo on Day 1 and Day 15; and for whom a complete set of blood samples for pneumococcal/influenza antibody assay (from both Day 8 and Day 36) was collected and available for analysis. Patients who had missing data were classified as nonresponders. The treatment differences in the percentages were assessed using chi-square tests.

Covariates that might influence immunogenicity such as age, sex, comorbid conditions (diabetes and pulmonary disease), and concomitant RA medications (DMARD, corticosteroids, and MTX) were examined using logistic regression models.

RESULTS

Patient disposition. The trial was conducted at 22 sites across the USA from October 2003 through December 2004. Of the 226 patients randomized to receive treatment, 115 were assigned to the placebo group and 111 to the adalimumab group. A total of 220 patients completed the double-blind period of the study and participated in the open-label extension. Of the 226 patients enrolled in the study, 208 met the per-protocol definition and were included in the efficacy analyses.

Demographics and baseline characteristics. Baseline characteristics for the 208 patients were comparable between treatment groups and are presented in Table 1. Patients had a mean age of 51.7 years. Fifty-two percent (57/109) of placebo-treated patients and 53% (52/99) of adalimumab-treated patients

Table 1. Baseline characteristics.

Characteristic	Placebo (n = 109), n (%)	Adalimumab 40 mg eow (n = 99), n (%)	Total (N = 208), n (%)	p*
Age, yrs, mean ± SD	51.1 ± 11.46	52.2 ± 11.90	51.7 ± 11.66	0.504
Age category, yrs, n (%)				0.644
≤ 40	22 (20.2)	20 (20.2)	42 (20.2)	
> 40–65	78 (71.6)	67 (67.7)	145 (69.7)	
> 65	9 (8.3)	12 (12.1)	21 (10.1)	
Sex, n (%)				0.084
Male	27 (24.8)	15 (15.2)	42 (20.2)	
Female	82 (75.2)	84 (84.8)	166 (79.8)	
Disease				
Diabetes mellitus	4 (3.7)	6 (6.1)	10 (4.9)	0.421
Pulmonary disease	38 (34.9)	30 (30.3)	68 (32.6)	0.484
Concomitant medication				
MTX, n (%)	59 (54.1)	55 (55.6)	114 (54.9)	0.836
DMARD (not MTX)†, n (%)	32 (29.4)	17 (17.2)	49 (23.6)	0.039
Corticosteroids, n (%)	50 (45.9)	45 (45.5)	95 (45.7)	0.952
CRP status				
Normal	57 (52.3)	52 (52.5)	109 (52.4)	0.973
Elevated, > 0.8 mg/dl	52 (47.7)	47 (47.5)	99 (47.6)	

* Continuous comparisons from one-way analysis of variance model; discrete variables compared using the chi-square test. If 25% of cells had expected count < 5, Fisher's exact test was used. † The majority of the patients taking concomitant DMARD other than MTX took hydroxychloroquine (51%) and/or leflunomide (43%). CRP: C-reactive protein; DMARD: disease modifying antirheumatic drugs; eow: every other week; MTX: methotrexate.

had normal C-reactive protein (CRP) concentration status (< 0.8 mg/dl). No statistically significant differences were observed between treatment groups in the percentages of patients using MTX or corticosteroids; however, there was a significantly higher percentage of patients in the placebo group using concomitant DMARD other than MTX compared with the adalimumab group (29.4% vs 17.2%, respectively). All patients had negative purified protein derivative skin tests.

There was no significant difference between treatment groups in baseline antibody titer for the individual pneumococcal and influenza antigens, with the exception of antibody for pneumococcal antigen 14 (1.45 μg/ml in the placebo group; 2.22 μg/ml in the adalimumab group; p = 0.031) (Table 2). Both treatment groups had similar percentages of patients with baseline protective antibody titers.

Immune response to pneumococcal vaccine. The percentage of patients who received adalimumab and achieved a ≥ 2-fold increase in ≥ 3 of 5 pneumococcal antibody titers was similar to that in the placebo group [37.4% vs 40.4%, respectively; 95% confidence interval (CI) of difference between treatment groups –16.2, 10.3] (Table 3). Across both treatment groups, the percentage of patients who achieved ≥ 2-fold increase in ≥ 3 of 5 pneumococcal antibody titers was higher in the group without protective antibody titers at baseline (Table 3).

Univariate analyses of the primary measure of response demonstrated that concomitant MTX use (p < 0.0001), concomitant DMARD use (p < 0.044), and protective antibody titers at baseline (p < 0.0001) significantly reduced the response rate to pneumococcal vaccine, whereas elevated baseline CRP concentration significantly increased the response rate (p < 0.035; Table 4). Sex, age, race, weight, concomitant corticosteroid use, diabetes, and pulmonary disease did not affect the response rate.

Similarly high percentages of patients in both the placebo (81.7%) and adalimumab (85.9%) treatment groups achieved protective antibody titers (antibody titer ≥ 1.6 μg/ml in ≥ 3 of 5 antigens) 4 weeks postvaccination. A higher percentage of adalimumab-treated patients (66.7%) converted from unprotected to protected status in ≥ 3 of 5 antigens versus placebo-treated patients (57.4%). When shifts from unprotected to protected status were examined by MTX use, a greater percentage of patients converted from unprotected status to protected status in the absence of MTX use (76.5% vs 60.0% in the adalimumab treatment group and 72.7% vs 44.0% in the placebo treatment group).

Overall, the percentages of patients with a ≥ 2-fold increase in pneumococcal antibody titers from baseline at 4 weeks postvaccination were similar between treatment groups (Table 5). Antibody response was fairly uniform among antigens, with a similar range of response observed between the placebo and adalimumab treatment groups (36%–50% and 36%–47%, respectively).

Changes from baseline in antibody titers 4 weeks after pneumococcal vaccination were statistically significant for all 5 antigens tested and were similar between treatment groups, as demonstrated by lack of statistical significance between

Table 2. Mean pneumococcal and influenza antibody titers by antigen at prevaccination and postvaccination and change in pneumococcal and influenza antibody titers by antigen.

	n	Prevaccination GMT	Postvaccination GMT	Within-group Comparison (postvaccination: prevaccination) GMR (95% CI)*	Between-group Comparison (ADA:placebo) GMR (95% CI)*
Pneumococcal antigen treatment					
9V					
Placebo	109	2.65	6.23	2.34 (1.97, 2.79)	1.00 (0.77, 1.28)
Adalimumab	99	2.60	6.10	2.36 (1.96, 2.83)	
14					
Placebo	109	1.45†	4.40	3.03 (2.47, 3.73)	1.32 (0.98, 1.78)
Adalimumab	99	2.22†	5.09	2.30 (1.85, 2.86)	
18C					
Placebo	109	2.84	7.49	2.63 (2.18, 3.17)	1.08 (0.82, 1.41)
Adalimumab	99	2.90	7.05	2.44 (2.01, 2.97)	
19F					
Placebo	109	2.16	4.16	1.92 (1.61, 2.28)	0.95 (0.74, 1.22)
Adalimumab	99	1.96	3.96	2.03 (1.69, 2.43)	
23F					
Placebo	109	2.26	4.22	1.86 (1.57, 2.19)	0.85 (0.67, 1.08)
Adalimumab	99	1.84	4.01	2.19 (1.84, 2.60)	
Influenza antigen treatment					
H1N1					
Placebo	109	51.89	188.68	3.63 (2.92, 4.51)	1.05 (0.77, 1.44)
Adalimumab	99	47.16	162.64	3.46 (2.75, 4.34)	
H3N2					
Placebo	109	89.13	602.81	6.74 (5.04, 9.02)	1.51 (0.99, 2.30)
Adalimumab	99	105.86	472.25	4.48 (3.30, 6.08)	
B (Hong Kong)					
Placebo	109	22.71	92.94	4.08 (3.28, 5.08)	1.25 (0.91, 1.71)
Adalimumab	99	22.62	73.86	3.27 (2.60, 4.12)	

* Adjusted GMR are from analysis of covariance (ANCOVA) model: response = treatment group plus MTX use (yes/no), where response is the difference in the log-transformed values of Day 36 titer and Day 8 titer. The adjusted means (least-square means) were then transformed to GMR for the endpoint titers, and the differences in least-square means were transformed into GMR of titers in Adalimumab group with respect to titers in Placebo group. † $p = 0.031$; 95% CI 0.101, 2.133. Any pneumococcal antibody titer < 1.3 μg/ml (undetectable) is expressed as 0.65 μg/ml. For prevaccination and postvaccination, the GMT was used. For change from prevaccination, the GMR of postvaccination titer to prevaccination titer was used. ADA: adalimumab; GMT: geometric mean titer; GMR: geometric mean ratio.

group comparisons of GMR (Table 2). Similar trends were observed when the change from baseline at 4 weeks postvaccination was examined by MTX use; however, markedly larger increases in GMT were observed for both treatment groups in the absence of MTX use (data not shown).

Immune response to influenza vaccine. A smaller, although not statistically significant percentage of patients who received adalimumab achieved a ≥ 4-fold increase in ≥ 2 of 3 influenza antibody titers compared with patients who received placebo (51.5% vs 63.3%, 95% CI of difference between treatment groups –25.2, 1.6; Table 3). The lower percentage of response in the adalimumab group is explained by the subgroup of patients with preexisting protective antibody titers (≥ 1:40 antibody titer to ≥ 2 of 3 antigens) at baseline. In this subgroup, the percentage of patients who achieved a ≥ 4-fold increase in ≥ 2 of 3 influenza antibody titers was 36.2% in the adalimumab group and 55.6% in the placebo group. In the subgroup of patients without protective antibody titers at baseline, the percentage of patients who achieved ≥ 4-fold increase in ≥ 2 of 3 influenza antibody titers was similar in the adalimumab and placebo treatment groups (73.3% and 73.9%, respectively; Table 3).

Univariate analyses of the primary measure of response demonstrated that protective antibody titers at baseline significantly reduced response rates to influenza vaccine ($p < 0.001$). Although concomitant MTX use also reduced the response rate, the reduction was not statistically significant. Concomitant DMARD use, baseline CRP concentration, sex, age, concomitant corticosteroid use, diabetes, and pulmonary disease did not affect the response rate (Table 4).

Similarly high percentages of patients in the placebo and adalimumab treatment groups (94.5% and 98.0%, respective-

Table 3. Primary efficacy results for each coprimary endpoint; sensitivity analyses of the number (%) of patients with a ≥ 2-fold increase from baseline in ≥ 3 of 5 pneumococcal titers and a ≥ 4-fold increase from baseline at Day 36 in ≥ 2 of 3 influenza antibody titers.

	Responders, n/N (%)		
	Placebo	Adalimumab, 40 mg eow	Difference Between Treatment Groups, % (95% CI)
Pneumococcal vaccine			
Per-protocol analysis set	44/109 (40.4)	37/99 (37.4)	–3.0 (–16.2, 10.3)
Presence of protective antibody concentration at baseline*	17/62 (27.4)	16/57 (28.1)	0.7 (–15.5, 16.8)
Absence of protective antibody concentration at baseline*	27/47 (57.4)	21/42 (50.0)	–7.4 (–28.1, 13.3)
Influenza vaccine			
Per-protocol analysis set	69/109 (63.3)	51/99 (51.5)	–11.8 (–25.2, 1.6)
Presence of protective antibody concentration at baseline†	35/63 (55.6)	21/58 (36.2)	–19.3 (–36.8, –1.9)
Absence of protective antibody concentration at baseline†	34/46 (73.9)	30/41 (73.2)	–0.7 (–19.3, 17.8)

* Protective antibody concentration in ≥ 3 of 5 pneumococcal titers at baseline. Any pneumococcal antibody titer < 1.3 μg/ml (undetectable) was expressed as 0.65 μg/ml; any influenza antibody titer < 1:20 (undetectable) was expressed as 1:10. † Protective antibody concentration in ≥ 2 of 3 influenza titers at baseline. eow: every other week.

Table 4. Number of patients achieving ≥ 2-fold increase in ≥ 3 of the 5 pneumococcal titers and number of patients achieving ≥ 4-fold increase in ≥ 2 of the 3 influenza titers by correlate.

Correlate	Pneumococcal Vaccine				Influenza Vaccine			
	Placebo n/N (%)	Adalimumab n/N (%)	OR* (95% CI)	p*	Placebo n/N (%)	Adalimumab n/N (%)	OR* (95% CI)	p*
Protective antibody concentration				< 0.001				< 0.001
Yes	17/62 (27.4)	16/57 (28.1)	0.33 (0.18, 0.58)		35/63 (55.6)	21/58 (36.2)	0.31 (0.17, 0.56)	
No	27/47 (57.4)	21/42 (50.0)			34/46 (73.9)	30/41 (73.2)		
MTX use†				< 0.001				0.288
Yes	17/59 (28.8)	10/55 (18.2)	0.23 (0.13, 0.41)		33/59 (55.9)	29/55 (52.7)	0.74 (0.42, 1.29)	
No	27/50 (54.0)	27/44 (61.4)			36/50 (72.0)	22/44 (50.0)		
MTX dose, mg/wk				0.321				0.052
> 0–10	3/16 (18.8)	3/17 (17.6)	1.12 (0.35, 3.80)		6/16 (37.5)	6/17 (35.3)	2.92 (1.14, 7.78)	
> 10–15	5/21 (23.8)	3/19 (15.8)	2.09 (0.72, 6.68)		5/21 (23.8)	3/19 (15.8)	2.73 (1.08, 7.22)	
> 15	9/22 (40.9)	4/19 (21.1)			14/22 (63.6)	11/19 (57.9)		
DMARD use (except MTX)				0.044				0.810
Yes	11/32 (34.4)	2/17 (11.8)	0.48 (0.23, 0.96)		18/32 (56.3)	11/17 (64.7)	1.08 (0.57, 2.10)	
No	33/77 (42.9)	35/82 (42.7)			51/77 (66.2)	40/82 (48.8)		
Corticosteroid use				0.776				0.369
Yes	19/50 (38.0)	17/45 (37.8)	0.92 (0.53, 1.61)		33/50 (66.0)	25/45 (55.6)	1.29 (0.74, 2.25)	
No	25/59 (42.4)	20/54 (37.0)			36/59 (61.0)	26/54 (48.1)		
CRP status				0.035				0.596
Normal	18/57 (31.6)	17/52 (32.7)	1.84 (1.05, 3.24)		35/57 (61.4)	26/52 (50.0)	1.16 (0.67, 2.02)	
Elevated (> 0.8 mg/dL)	26/52 (50.0)	20/47 (42.6)			34/52 (65.4)	25/47 (53.2)		

* Odds ratio and likelihood ratio CI and p values are from logistic regression models. † Concomitant medications at baseline. If patients were receiving DMARD at baseline, they may or may not have also been receiving MTX. Protective antibody concentrations in ≥ 3 of 5 pneumococcal titers for pneumococcal vaccine. Any pneumococcal antibody titer < 1.3 μg/ml (undetectable) was expressed as 0.65 μg/ml. The protective antibody concentration was defined as ≥ 1.6 μg/ml. Protective antibody concentration in ≥ 2 of 3 influenza titers for influenza vaccine. Any influenza antibody titer < 1:20 (undetectable) was expressed as 1:10. The protective antibody concentration was defined as ≥ 1:40.

Table 5. Number (%) of patients with a ≥ 2-fold increase in pneumococcal antibody titers or a ≥ 4-fold increase in influenza antibody titers from baseline at Day 36 by antigen (per-protocol analysis set).

	Placebo, N = 109, n (%)	Adalimumab, N = 99, n (%)	OR (95% CI)*
Pneumococcal antigen			
9V	46 (42.2)	45 (45.5)	1.17 (0.66, 2.08)
14	54 (49.5)	41 (41.4)	0.72 (0.41, 1.26)
18C	53 (48.6)	46 (46.5)	0.92 (0.53, 1.61)
19F	39 (35.8)	36 (36.4)	1.04 (0.58, 1.87)
23F	41 (37.6)	44 (44.4)	1.40 (0.78, 2.54)
Influenza antigen			
H1N1	61 (56.0)	50 (50.5)	0.81 (0.46, 1.40)
H3N2	74 (67.9)	58 (58.6)	0.67 (0.38, 1.18)
B (Hong Kong)	66 (60.6)	48 (48.5)	0.61 (0.35, 1.07)

* Odds ratio and likelihood ratio CI are from a logistic regression model: model response = therapy MTX use. Any pneumococcal antibody titer < 1.3 μg/ml (undetectable) is expressed as 0.65 μg/ml. Any influenza antibody titer < 1:20 (undetectable) was expressed as 1:10.

ly) achieved protective antibody titers (≥ 1:40 antibody titer in ≥ 2 out of 3 antigens) at 4 weeks postvaccination. In addition, a greater percentage of adalimumab-treated versus placebo-treated patients experienced conversion to protected status in ≥ 2 of 3 antigens (97.6% vs 87.0%, respectively). When shifts from unprotected to protected status were examined by MTX use, a slightly greater percentage of patients converted from unprotected status to protected status in the absence of MTX use (100% vs 95.8% in the adalimumab treatment group and 92.3% vs 80.0% in the placebo treatment group).

Overall, at Day 36, the percentage of patients with ≥ 4-fold increase in influenza antibody titers from baseline by antigen was lower in the adalimumab treatment group versus the placebo treatment group, although the differences were not statistically significant (Table 5). Within each treatment group, the immunogenicity of the 3 antigens was similar (56%–68% in the placebo group and 49%–59% in the adalimumab group).

Changes from baseline in antibody titers 4 weeks after influenza vaccination were statistically significant for all 3 antigens tested in both treatment groups (GMR range from 3.3 to 6.7). The increase from baseline was greater in the placebo treatment group compared with the adalimumab group, although the difference was not statistically significant (Table 2). Significant increases in titers 4 weeks postvaccination were observed in groups with and without MTX use. However, larger increases in titers, although not significant, were observed for both treatment groups in the absence of MTX.

Safety. Adalimumab was generally well tolerated. During the blinded period of the study no deaths were reported, and one patient receiving placebo reported a serious AE. A slightly greater percentage of patients in the placebo group reported an AE than did patients in the adalimumab group [54.8% (63/115) vs 45.9% (51/111), respectively]. The most frequently reported treatment-emergent AE occurring during the blinded period of the study were upper respiratory tract infection and injection site reaction; both were reported more frequently by placebo-treated patients. There were no serious infectious AE, malignancies, or opportunistic infections, including tuberculosis, reported during the double-blind period. The rate of infectious AE was statistically significantly higher in the placebo treatment group [23.5% (27/115)] versus the adalimumab group [12.6% (14/111)] (p = 0.039). The percentages of patients reporting AE leading to discontinuation of study drug were similar between the 2 groups.

DISCUSSION

We have shown that adalimumab does not diminish humoral response to commercially available 23-valent pneumococcal polysaccharide and trivalent subvirion influenza virus vaccines in patients with RA, and that 4 weeks after vaccination, the majority of patients have protective antibody titers. Similarly high percentages of patients in both the placebo and adalimumab treatment groups achieved protective pneumococcal antibody titers (81.7% and 85.9%, respectively) as well as influenza antibody titers (94.5% and 98.0%, respectively) 4 weeks postvaccination, as defined by antibody titers ≥ 1.6 μg/ml in ≥ 3 of 5 antigens and ≥ 1:40 antibody titer in ≥ 2 of 3 antigens, respectively.

A metaanalysis conducted by Go and Ballas[17] evaluating pneumococcal vaccine response in healthy immunocompetent patients demonstrated that there is wide variability in antipneumococcal antibody response among healthy patients; moreover, not all patients will respond to all antigens with a ≥ 2-fold increase in antibody titer. Only 1 of 12 antigens presented produced a consistent 3- or 4-fold increase in antibodies in all studies, suggesting that increasing the number of antigens examined may not necessarily facilitate interpretation of antibody response to pneumococcal vaccination. Analysis of antibody response in studies using enzyme-linked

immunosorbent assay for antibody determination indicated that the percentage of studies in which patients developed a 2-fold increase in antibody to antigens 9, 14, 18, 19, and 23 was 100%, 100%, 75%, 80%, and 80%, respectively[17].

Studies have demonstrated that RA patients have reduced immunogenicity to pneumococcal vaccines compared with healthy control subjects[16]. A study by Elkayam and colleagues[16] assessed the effect of adalimumab therapy on the immunogenicity of pneumococcal and influenza vaccination in patients with RA. One-third of RA patients responded to none or only 1 of the 7 serotypes tested. None of the clinical and laboratory measures evaluated appeared to predict poor response to pneumococcal vaccination in these patients, suggesting that impaired antibody response may be related primarily to the disease itself. Immunomodulating therapy with TNF antagonists may potentiate the already-increased tendency of these patients to develop serious infectious complications.

Our data show that patients with RA were able to develop an effective antibody response to pneumococcal vaccine, and that concomitant adalimumab use did not appear to affect the response; ≥ 2-fold increase in ≥ 3 of 5 pneumococcal antibody titers was achieved by 37.4% of patients treated with adalimumab compared with 40.4% of placebo-treated patients. Patients receiving concomitant MTX or concomitant DMARD or with protective antibody titers at baseline were significantly less likely to respond to pneumococcal vaccination. It should be noted that 89 of 208 (43%) patients entering the study had protective pneumococcal antibody titer concentrations at baseline and this led to the appearance of a lower response rate than in other studies. In the patients without protective antibody titer concentrations at baseline, the response rates in the adalimumab and placebo groups were 50.0% and 57.4%, respectively. These results are similar to those in a study by Mease and colleagues[23] that examined the effect of etanercept on pneumococcal vaccine response in patients with psoriatic arthritis. Researchers found no increased risk of poor humoral response with TNF antagonist therapy, whereas MTX caused a reduced response. Similarly, Elkayam and colleagues[24] evaluated the immunogenicity of pneumococcal vaccination in patients with RA and ankylosing spondylitis receiving TNF antagonist therapy. In their study, treatment with etanercept or infliximab did not interfere with mean antibody responses to pneumococcal vaccination, although smaller percentages of patients treated with TNF antagonists responded adequately to the vaccine.

In our subgroup of patients with RA without protective antibody titers at baseline, antibody response to influenza vaccination (≥ 4-fold increase in ≥ 2 of 3 influenza antibody titers) was similar in the adalimumab and placebo treatment groups (73.3% and 73.9%, respectively). Protective antibody titers at baseline (found in 58% of patients) significantly reduced response rates to influenza vaccine, as did concomitant MTX use; however, the latter reduction was not statistically significant. Concomitant DMARD use did not affect the response rate to influenza vaccination. These results are in agreement with those from a recent study by Fomin and colleagues[11] demonstrating that the use of commonly administered DMARD (including MTX), infliximab, and etanercept does not affect the humoral response to influenza vaccination in RA patients. A study by Chalmers and colleagues[14] also demonstrated comparable antibody responses to influenza vaccination in patients with RA and healthy age-matched control subjects, with no correlation between the use and dosage of immunosuppressive medications/steroid ≥ 7.5 mg/day on the immunogenicity of the vaccine.

Pneumococcal and influenza vaccinations are important for the reduction of mortality and morbidity associated with these infections, particularly in RA patients who are at increased risk because of their immunocompromised status. However, concerns about the safety and reduced immunogenicity of these vaccines in patients with RA receiving immunomodulatory therapy with TNF antagonists have limited their uptake in this patient population[11]. In this study, treatment with adalimumab was well tolerated and did not appear to diminish antibody response to the antigens analyzed in patients with RA receiving pneumococcal and influenza vaccines. These results suggest that patients with RA treated with adalimumab can be effectively and safely vaccinated with pneumococcal and influenza vaccines.

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