Pneumococcal Vaccine Response in Psoriatic Arthritis Patients During Treatment with Etanercept

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ABSTRACT. ***Objective.*** Therapeutics used to treat inflammatory diseases, including psoriatic arthritis (PsA), may potentially interfere with normal immune system function. Immune system function can be assessed by evaluating response to vaccination. We assessed the ability of patients with PsA treated with etanercept to produce antibodies in response to pneumococcal antigen challenge.

Methods. Patients with PsA (n = 205) were stratified by methotrexate (MTX) use and randomly assigned to receive either placebo or etanercept 25 mg twice weekly by subcutaneous injection. After 4 weeks of treatment with study drug, a 23-valent pneumococcal vaccination was administered. Antibody levels to 5 antigens (9V, 14, 18C, 19F, and 23F) were measured by ELISA before and 4 weeks after vaccination in 184 patients. The proportion (%) of patients with 2- and 4-fold increases in antibody titers was analyzed.

Results. Patients treated with etanercept or placebo had similar responses to the vaccine. A 2-fold increase in titer to at least 2 antigens was achieved by 67% of patients, and a 4-fold increase to at least 2 antigens was achieved by 47% of patients. Approximately 20% of patients in each group failed to show a 2-fold response to any antigens. Logistic regression analysis showed MTX use and age were predictors of a poor response.

Conclusions. Patients with PsA treated with etanercept were able to produce antibodies in response to pneumococcal vaccination. Patients receiving MTX had lower mean antibody levels in response to the vaccine. There was no increased risk of poor response with etanercept treatment given alone or with MTX. (J Rheumatol 2004;31:1356–61)

Key Indexing Terms:
ETANERCEPT
RHEUMATOID ARTHRITIS
PNEUMOCOCCAL VACCINE
METHOTREXATE

Etanercept has become an important treatment for inflammatory diseases such as rheumatoid arthritis (RA), juvenile RA, ankylosing spondylitis, and psoriatic arthritis (PsA)[1-7]. Etanercept is a soluble tumor necrosis factor (TNF) receptor protein that acts by competitively inhibiting TNF, a proinflammatory cytokine that plays an important role in both the pathophysiology of rheumatic disease and the immune response. Receptors for TNF are found on many types of cells that modify the immune system and TNF causes a wide spectrum of biologic actions on many types of immune and nonimmune target cells[8].

The effect of etanercept on the immune system is not fully understood. Immune system function in patients with RA has been studied both *in vivo* and *in vitro* as part of a randomized placebo-controlled clinical trial[9]. No major alterations were seen in neutrophil function, phagocytosis, T cell proliferative responses, leukocyte surface antigen phenotypes, immunoglobulin levels, or delayed-type hypersensitivity reactions in patients who were treated with etanercept compared with placebo. An important question has not yet been answered: can patients treated with etanercept respond appropriately to antigens?

Pneumococcal vaccination can be used to assess the immune response to antigens. Pneumococcal vaccine consists of a mixture of capsular polysaccharides from the cell walls of common serotypes of *Streptococcus pneumoniae*. Bacterial cell wall antigens activate the humoral response of the immune system via activation of B lymphocytes, independent of T cell antibody response[10]. TNF enhances antibody function and promotes B cell proliferation[8], and anti-TNF therapy theoretically could affect these responses.

Previous studies of antigenic responses to pneumococcal

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vaccinations found a high degree of variation between patients and patient populations[11]. We examined the response to pneumococcal vaccination in a subgroup of patients with PsA participating in a randomized, placebo-controlled clinical trial designed to examine the efficacy of etanercept (25 mg twice weekly)[7]. Our study design was ideal for examining antigenic response because comparisons could be made between patients receiving etanercept and patients receiving placebo in the same patient population.

Our objective was to determine if treatment with etanercept affects the ability of patients with PsA to respond to a pneumococcal vaccination and to examine the factors affecting the antigenic response. An appropriate antibody response would provide evidence to support the competency of the humoral immune system in patients receiving etanercept therapy.

MATERIALS AND METHODS

Patients. Patients with active PsA and an inadequate response to their current therapy were eligible. Patients were required to be aged 18 to 70 years and have at least 3 swollen and 3 tender joints at screening. Patients were required to have at least one of the following forms of PsA: distal interphalangeal involvement, polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis), arthritis mutilans, asymmetric peripheral arthritis, or ankylosing spondylitis-like PsA.

Background nonsteroidal antiinflammatory drug (NSAID) and corticosteroids (≤ 10 mg/day prednisone or equivalent) were permitted as long as the doses were stable. Patients receiving concomitant methotrexate (MTX) were eligible if they had inadequate disease control and had been receiving a stable dose of MTX (≤ 25 mg/wk) for at least 2 months. These patients were required to continue taking a stable dose of MTX during the study. Other disease-modifying antirheumatic drugs (DMARD) were discontinued at least 4 weeks before the study start. Patients discontinuing an immunomodulatory drug were required to undergo a washout period of 2 to 4 weeks before screening.

Study design. This randomized, placebo-controlled study was conducted at 17 sites in the United States. Eligible patients were stratified according to whether or not they were receiving MTX and were randomly assigned to 1 of 2 dosage arms: etanercept or placebo. Patients received 25 mg etanercept or an indistinguishable placebo twice weekly by subcutaneous injection. Study drug was given for 4 weeks before vaccination to ensure that steady state levels were achieved. After 4 weeks of study drug treatment, a 23-valent pneumococcal vaccine (Pneumovax® 23) was administered. Serum samples were collected at week 4 (before vaccination) and week 8. Antibody concentrations to 5 antigens (9V, 14, 18C, 19F, and 23F) were measured.

Antibody assay. Pneumococcal enzyme-linked immunosorbent assay (ELISA) was used to measure IgG antibodies to pneumococcal polysaccharides. Type-specific *S. pneumoniae* polysaccharides were bound to microtiter plate wells. Dilutions of human serum were adsorbed with cell wall polysaccharides (C-polysaccharides) and then added to the microtiter wells. Danish type 22F pneumococcal antigen was added to the neutralizing buffer of test sera and to the reference standard to increase the specific binding of the antibodies being tested. Type-specific IgG antibodies in human serum were bound to the plate-bound pneumococcal polysaccharides. A mouse anti-human monoclonal antibody horseradish peroxidase (HRP) enzyme-labeled conjugate was added to the microtiter wells and allowed to bind to the polysaccharide-bound human serum antibodies. O-Phenylenediamine dihydrochloride was dissolved in phosphate citrate buffer with urea hydrogen peroxide and added to the microtiter wells as substrate. The substrate was catalyzed to a soluble colored end product by HRP. The reaction was stopped and the optical density of the soluble end product was read and compared with a human standard reference serum.

Antigens used in the testing were purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA). Antigens tested were Danish type 9V (lot #2046913), Danish type 14 (lot #1901392), Danish type 18C (lot #2047520), Danish type 19F (lot #2033178), and Danish type 23F (lot #2048448). The pneumococcal antigen used in the assay to increase specific binding, 22F (lot #2045906), was also purchased from the ATCC. Human reference serum (lot #89SF2) used in the assay was provided by Carl Frasch, Center for Biologics Evaluation and Review, Food and Drug Administration, Bethesda, Maryland.

Analysis. The criterion for antigenic response was based on the findings of a meta-analysis of studies evaluating pneumococcal antibody responses to vaccine in normal patients[11]. These authors state that a 2-fold increase in titer is seen most commonly in response to pneumococcal vaccination, and 3-fold and 4-fold increases are seen far less often. We calculated the number (%) of patients with 2-fold and 4-fold increases in pneumococcal antibodies 4 weeks after vaccination. Covariates that might influence the antigenic response were examined, including age, sex, comorbidities (diabetes and prior existing pulmonary disease including chronic obstructive pulmonary disease and asthma), C-reactive protein (CRP), concomitant RA therapy (etanercept, MTX, and corticosteroids), and duration of PsA.

To examine the factors affecting the antigenic response, a dichotomous variable was defined using the median number of antigens to which patients had produced a 2-fold increase in antibodies. Good responders were patients who responded with at least a 2-fold increase to more than 3 of the 5 antigens (the median number of antigens), and poor responders were patients who responded with a 2-fold increase to 3 or fewer antigens. Univariate analysis was conducted to assess the risk factors for poor response using the Mantel-Haenszel chi-square test and estimate of the relative risk.

Logistic regression was used to explore the relationship between the explanatory variables and poor response (≥ 2-fold increase in titer for ≤ 3 antigens). The explanatory variables were etanercept treatment, baseline MTX use, age, sex, corticosteroid use, history of pulmonary disease, diabetes, elevated CRP (greater than the upper limit of normal of 0.79 mg/dl), and duration of PsA. Both baseline MTX use (yes/no) and MTX dose (mg/wk) were examined. The analysis by MTX dose did not result in a significant improvement to the model over the binary measure (MTX use vs no MTX use). The presence of interaction between explanatory variables was examined using the residual chi-square test.

A logistic regression model for response was constructed. Stepwise selection with entry and elimination criteria level of $p < 0.05$ was used. Odds ratios (OR) and confidence intervals (CI) for OR from the logistic regression model were used to obtain approximate relative risks and CI for relative risks.

RESULTS

Patients. Of the 205 patients enrolled in the study, 184 had samples available for the pre-vaccine and 4-weeks post-vaccine time points and were included in this analysis (90 in the placebo group and 94 in the etanercept group). Baseline characteristics for the 184 patients are given in Table 1. Fifty-two percent of the patients were men. Both the mean and the median age were 47 years (range 18 to 76). Sixty-two percent of the patients had a CRP > 0.79 mg/dl (the upper limit of the normal range). Forty-five percent of patients were receiving MTX and 12% were receiving corticosteroids.

Antibody response. Mean pre-vaccination antibody titers ranged from 1.63 to 6.44 µg/ml for the 5 antigens tested (Table 2). Mean post-vaccination levels ranged from 4.55 to

Table 1. Baseline characteristics of patients.

	n = 184
Sex	
Male, n (%)	96 (52)
Female, n (%)	88 (48)
Age, yrs	
Mean (median)	47 (47)
Range	18 to 76
Disease duration, yrs	
Mean (median)	9 (8)
Range	0 to 41
CRP > 0.79*, mg/dl, n (%)	115 (62)
MTX use, n (%)	83 (45)
Corticosteroid use, n (%)	22 (12)
Pulmonary disease, n (%)	19 (10)
Diabetes, n (%)	12 (7)

* Upper limit of normal for CRP 0.79 mg/dl; MTX: methotrexate; CRP: C-reactive protein.

24.91 µg/ml. On average, titers increased from 3.0 fold (for antigen 19F) to 11.2 fold (for antigen 14).

The proportion of patients who had a 2-fold and 4-fold (or greater) increase in antibody titers for each of 5 antigens (9V, 14, 18C, 19F, and 23F), 4 weeks after vaccination, is presented in Table 3. Patients were grouped according to their use of etanercept or MTX. The proportion of patients who showed a 2-fold response was similar between the group receiving etanercept (in which the proportion of responders ranged from 35% to 62% across the 5 antigens) and the placebo group (in which the proportion of responders ranged from 40% to 62%). Fewer patients receiving MTX showed responses compared with patients not receiving MTX. For patients receiving MTX, the proportion of responders ranged from 27% to 42%, whereas for patients not receiving MTX, the range was 47% to 79%.

Fewer patients showed a 4-fold increase in titer to the presented antigens, but the pattern of response was similar to the 2-fold increases. The proportion of patients achieving a 4-fold increase who received MTX was less than that of the group not receiving MTX. Responses from the groups receiving or not receiving etanercept were similar.

For the whole group, 67% percent of patients achieved a 2-fold or greater rise in antibody titer to at least 2 of 5 antigens. Twenty-one percent of patients achieved a 2-fold or greater increase in titer to all 5 antigens. The same proportion of patients in each group failed to show a 2-fold increase to any antigens [20/90 in the placebo group (22%) and 19/94 in the etanercept group (20%)]. The mean number of antigens to which patients showed a 2-fold increase in titer was 2.7 (median 3.0).

Forty-seven percent of the patients achieved a 4-fold increase in titer to at least 2 antigens, and 35% of patients achieved a 4-fold increase to at least 3 antigens. Nine percent of patients achieved a 4-fold increase to all 5 antigens, and 35% failed to show a 4-fold increase to any antigens. The mean number of antigens to which patients showed a 4-fold increase in titer was 1.8 (median 1.0).

Table 2. Antibody titers before and after pneumococcal vaccination. Values shown for titer are geometric means for each antigen.

Antigen	Antibody Titer, µg/ml Pre-vaccination	4 Weeks Post-vaccination	Fold Increase, Mean (median), n = 184
9V	1.64	5.14	6.2 (2.4)
14	6.44	24.91	11.2 (2.6)
18C	1.89	6.99	7.7 (3.2)
19F	6.37	12.95	3.0 (1.5)
23F	1.63	4.55	6.9 (2.2)

Table 3. Percent of patients showing 2-fold and 4-fold increases in titer 4 weeks after pneumococcal vaccination.

	2-Fold Increase in Titer				
	Etanercept		Methotrexate		Total
Pneumococcal antigen	No (n = 90)	Yes (n = 94)	No (n = 101)	Yes (n = 83)	(n = 184)
9V	59	50	72	33	54
14	62	59	79	37	60
18C	62	62	78	42	62
19F	40	35	47	27	37
23F	58	51	70	35	54
	4-Fold Increase in Titer				
9V	46	34	53	23	40
14	46	43	62	22	44
18C	47	40	59	24	43
19F	22	19	27	13	21
23F	34	27	41	18	30

Further analysis of the factors affecting the antigenic responses was conducted using the criteria for good and poor response. By these criteria, a poor response (≥ 2-fold increase in titer to ≤ 3 antigens) was seen in 55% of patients. The relative risk of a poor response was assessed using a univariate analysis for each of the covariates (Table 4). Concomitant use of MTX, advanced age (47 years or older), and female sex were associated with a significantly increased risk of poor response. Other factors assessed did not reach statistical significance.

Logistic regression analysis. Logistic regression was used to explore the relationship between the explanatory variables and poor response. The explanatory variables included etanercept treatment, MTX use, age, sex, corticosteroid use, comorbidities (pulmonary disease, diabetes), CRP, and duration of PsA. Results of the logistic regression analysis revealed no significant interactions ($p > 0.20$) between either etanercept treatment or MTX use and any other explanatory variable. In particular, there was no etanercept treatment by MTX use interaction ($p = 0.75$), indicating that there is no increased risk of poor response to pneumococcal vaccination when etanercept is administered concomitantly with MTX compared with MTX alone.

To construct the final logistic regression model, a stepwise selection procedure was used. The results of the final logistic regression model are presented in Table 5. This evaluation indicates that patients receiving MTX are less likely to respond to pneumococcal antigen challenge than those who were not. Older patients (47 years of age or older) were less likely to respond than were younger patients.

The candidate explanatory variables that were examined but not included in the final model were sex, corticosteroid use, history of pulmonary disease, diabetes, duration of PsA, and etanercept treatment. Given the relatively small sample sizes, there may not have been adequate power to assess the effects of some of these covariates.

Table 5. Logistic regression model: relative risk for poor response.

	RR	p	95% CI
MTX user	2.11	< 0.0001	1.73–2.37
Age ≥ 47 yrs	1.53	0.0053	1.16–1.83

DISCUSSION

Antibody responses to pneumococcal vaccinations have been reported as absolute levels of titer, the size of the increases in titer (fold increase), and number of antigens to which increased titers were produced. A meta-analysis of published studies was conducted by Go and Ballus[11], who compared responses to pneumococcal vaccinations in normal control groups. They found a wide variability in antibody responses whether the responses were expressed as absolute level of antibody, fold increase, or number of antigens with 2-, 3-, or 4-fold increases in titers. They observed that only 1 of 12 serotypes presented produced a consistent 3- or 4-fold increase in antibodies in all studies, and healthy subjects did not respond to all the serotypes with a 2-fold increase in antibody titer.

In our study, patients with PsA were able to mount an immune response to the pneumococcal vaccination challenge; a 2-fold increase in titer to 2 or more antigens was achieved by 67% of the patients, and a 4-fold increase to 2

Table 4. Univariate analysis: relative risk for poor response.

		Poor Response (%)	p*	RR	95% CI
MTX use	Yes	64/83 (77)	< 0.0001	2.10	1.59 to 2.79
	No	37/101 (37)			
Age, yrs	≥ 47	64/98 (65)	0.0025	1.52	1.14–2.01
	< 47	37/86 (43)			
Sex	Female	56/88 (64)	0.0228	1.36	1.04–1.77
	Male	45/96 (47)			
Duration of PsA, yrs	≥ 8	57/92 (62)	0.0548	1.30	0.99–1.69
	< 8	44/92 (48)			
Diabetes	Yes	9/12 (75)	0.1488	1.40	0.98–2.00
	No	92/172 (53)			
Corticosteroid use	Yes	9/22 (41)	0.1613	0.72	0.43–1.21
	No	92/162 (57)			
Etanercept	Yes	56/94 (60)	0.1932	1.19	0.91–1.55
	No	45/90 (50)			
Pulmonary disease	Yes	11/19 (58)	0.7817	1.06	0.71–1.60
	No	90/165 (55)			
C-reactive protein, mg/dl	> 0.79	63/115 (55)	0.9696	0.99	0.76–1.30
	≤ 0.79	38/69 (55)			

* Mantel-Haenszel chi-square test. MTX: methotrexate; PsA: psoriatic arthritis; RR: relative risk; CI: confidence interval.

or more antigens by 47% of patients. The assessment of risk factors for antigenic response was performed by defining a criterion for good response (a 2-fold increase to 4 or more antigens) that divided the patient group roughly in half (a good response was achieved by 45% of patients). MTX use and age were identified as risk factors for poor response. Patients receiving MTX were less likely to respond to antigen challenge than those not receiving MTX, and older patients were less likely to respond than younger patients. Etanercept treatment was not a significant predictor of poor response. Further, there was no evidence indicating that the addition of etanercept treatment to MTX further reduced the response.

Patients with chronic diseases often have decreased responses to vaccines[13]. Impaired response to pneumococcal vaccine was reported in patients with systemic lupus erythematosus compared with normal controls[14]. Antibody titers to pneumococcal antigens were reported in a small study by Elkayam, *et al*[15], who compared patients with RA and matched control patients who did not have RA. The geometric mean responses and the increases in titers to antigens 14 and 23F (the only antigens common to both the Elkayam and our study) were similar to responses seen in this study. The proportion of control patients who showed a 2-fold or greater response to antigens 14 and 23F in the Elkayam study was similar to the proportion of PsA patients who showed a response in our study. In the Elkayam study, 62% of the RA patients received MTX, but unlike our findings, MTX use was not predictive of a poor antigenic response (study size may have affected the ability to determine difference in the small study). In a preliminary report by O'Dell, *et al*[16], however, a decreased immune response to pneumococcal vaccine was noted in RA patients treated with MTX. This effect was greatest for patients older than 60 years. Perhaps administering pneumococcal vaccinations during times of cessation of MTX would result in a more robust antigenic response in patients with inflammatory disease.

The efficacy of a vaccine is related to many factors including the amount of antibody raised, the number of serotypes that antibodies were raised against, the specific serotype that elicited the response (a few pneumococcal serotypes account for most infections), and the serotypes of the *S. pneumoniae* pathogens encountered. Reports of the efficacy of pneumococcal vaccine show efficacy in some patient populations but not in others. In a study of middle-aged and elderly patients with a history of pneumonia, patients who responded to ≥ 4 antigens (1, 4, 14, 18C, 19F), or had a high post-vaccine antibody titer (> 12 mg/ml by radioimmunoassay), had a significantly lower risk for recurrent pneumonia than poor responders[17]. In a randomized study of chronically ill patients over 55 years of age who were vaccinated with 14-valent pneumococcal vaccine, no difference was seen in the rate of pneumococcal infections in vaccinated patients compared with unvaccinated patients[18].

Concerns have been raised about the ability of elderly patients to mount and sustain an antibody response to pneumococcal vaccine. Although differences occur in certain cohorts, most studies show that older adults have good responses to vaccinations[19]. A study comparing healthy young patients with healthy elderly patients showed equal responsiveness in biological response measures such as antibody avidity[20]. Older age appears to affect the risk of infection in some patient populations but not others, possibly reflecting the effects of other contributing factors such as concomitant disease. Although age may not be a factor in healthy patients, based on these results it may be a more important determinant of immune response in patients with PsA.

Direct comparison between antibody responses achieved in healthy patients, patients with PsA, and patients with PsA who are treated with TNF-inhibitors might elucidate the factors most important for predicting the status of immune function in patients with chronic inflammatory disease.

In summary, in a trial where pneumococcal vaccination was given to evaluate response to foreign antigen, two-thirds of patients with PsA achieved a 2-fold increase in antibodies, and about half achieved a 4-fold increase, to 2 or more of the 5 antigens measured. Patients who received MTX and older patients had a significantly reduced response to antigen challenge. Treatment with etanercept did not have a meaningful impact on antibody formation. Thus, it is rational to presume that patients treated with etanercept will, in general, have a normal humoral response to a T cell-independent antigen.

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