

# Response to Pneumococcal Vaccine in Patients with Early Rheumatoid Arthritis Receiving Infliximab plus Methotrexate or Methotrexate Alone

SUDHA VISVANATHAN, GREGORY F. KEENAN, DANIEL G. BAKER, ARNOLD I. LEVINSON,  
and CARRIE L. WAGNER

**ABSTRACT.** *Objective.* We assessed whether the addition of anti-tumor necrosis factor (TNF) agent to methotrexate (MTX) therapy might alter the response of patients with rheumatoid arthritis (RA) to pneumococcal vaccination.

*Methods.* Seventy patients with early RA (n = 20, 36, and 14 in the infliximab 3 mg/kg plus MTX, infliximab 6 mg/kg plus MTX, and placebo plus MTX groups, respectively) were included in an analysis of patients enrolled in an ASPIRE substudy. Patients received 0.5 ml pneumococcal vaccine (Pneumovax®) 34 weeks after initiation of study treatment; patient sera were collected 4 weeks later (week 38). Antibody responses were tested using enzyme immunoassay methods for reactivity to a panel of 12 serotypes of the pneumococcal vaccine.

*Results.* No significant difference in response to Pneumovax was observed between the infliximab plus MTX and placebo plus MTX groups. Roughly 80%–85% of patients responded to at least one serotype; however, only 20%–25% of patients in the different treatment groups responded to at least 6 different serotypes. Comparable proportions of patients in the 3 treatment groups responded to an increasing number ( $\geq 1$  to  $\geq 6$ ) of different serotypes. Patients < 45 years of age and those receiving oral corticosteroids generally appeared to respond better than those age 45 to 65 years and those not receiving oral corticosteroids.

*Conclusion.* All treatment groups in this study had lower responses to vaccine than would be expected in the normal population. However, the addition of the anti-TNF agent infliximab to MTX therapy did not appear to affect the response of patients with RA to pneumococcal vaccination. (First Release April 15 2007; J Rheumatol 2007;34:952–7)

## Key Indexing Terms:

TUMOR NECROSIS FACTOR INHIBITORS  
RHEUMATOID ARTHRITIS

INFLIXIMAB  
PNEUMOCOCCAL VACCINE

Patients with rheumatoid arthritis (RA) are at increased risk for pneumonia and other serious infections. The leading cause of mortality in patients with RA is bacterial infections, and 15%–25% of these deaths are caused by pneumonia<sup>1</sup>. It is generally accepted that treatment of RA with immunomodulators accounts for part of the increased susceptibility to infection; however, the underlying disease may also impair the

immune system of these patients. Current guidelines recommend vaccination with pneumococcal polysaccharide for persons 2 to 64 years of age with chronic illnesses that place them at higher risk for pneumococcal disease and for all persons 65 years of age or older<sup>2,3</sup>. The Pneumovax® 23 vaccine (Merck & Co., Inc., Whitehouse Station, NJ, USA) contains 23 different capsular polysaccharides from the cell walls of common serotypes of *Streptococcus pneumoniae*. Bacterial cell wall antigens activate the humoral response of the immune system by activating B lymphocytes independent of T cell antibody response<sup>4</sup>. The ability to respond to these capsular antigens can be useful for immunological assessment of patients with recurrent infections. It is generally agreed that healthy individuals would be expected to generate a response to at least half of the evaluated serotypes following vaccination.

Chronically ill individuals or those with impaired immunity are reported to have reduced immunoprotection or immune system responses compared with that associated with protection in healthy hosts<sup>5,6</sup>. A substantial proportion of patients with RA have been reported to not raise a significant response

---

From Clinical Pharmacology and Experimental Medicine, Medical Affairs, and Immunology, Centocor Research and Development, Inc., Malvern, Pennsylvania; and University of Pennsylvania School of Medicine and Philadelphia Veterans Administration Medical Center, Philadelphia, Pennsylvania, USA.

Supported by Centocor, Inc., Malvern, PA. Dr. Levinson has served as a consultant for Centocor, Inc. in the past year and has received honoraria.

S. Visvanathan, PhD; C.L. Wagner, PhD, Clinical Pharmacology and Experimental Medicine; G.F. Keenan, MD, Medical Affairs; D.G. Baker, MD, Immunology, Centocor Research and Development, Inc.; A.I. Levinson, MD, University of Pennsylvania School of Medicine and Philadelphia Veterans Administration Medical Center.

Address reprint requests to C.L. Wagner, Clinical Pharmacology, Centocor Research and Development, Inc., 200 Great Valley Parkway, RA-2-1, Malvern, PA 19355. E-mail: cwagner@centus.jnj.com

Accepted for publication January 22, 2007.

---

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2007. All rights reserved.

to pneumococcal vaccination<sup>1</sup>. Also, patients with psoriatic arthritis receiving methotrexate (MTX) were shown to have a lower response to pneumococcal vaccination than patients not receiving MTX<sup>7</sup>. In addition, given that tumor necrosis factor (TNF) enhances antibody function and promotes B cell proliferation<sup>8</sup>, there has been concern whether the addition of an anti-TNF agent to MTX therapy might further reduce the response of patients with RA to pneumococcal vaccination. We assessed patients with early RA who were enrolled in a substudy of the ASPIRE trial<sup>9</sup> for their ability to respond to pneumococcal vaccine when receiving MTX or a combination treatment of MTX plus the anti-TNF antagonist infliximab.

## MATERIALS AND METHODS

The ASPIRE protocol was approved by an institutional review board at each study center and was carried out in accord with the Helsinki Declaration and all subsequent revisions. Details of the ASPIRE study have been reported<sup>9</sup>. Briefly, 1049 patients with active RA who had no prior treatment with MTX or a TNF- $\alpha$  inhibitor were randomly assigned in a 4:5:5 ratio to 3 treatment groups: placebo plus MTX, infliximab 3 mg/kg plus MTX, and infliximab 6 mg/kg plus MTX.

Infliximab (Remicade; Centocor, Malvern, PA, USA) was supplied in 20-ml vials containing 100 mg of lyophilized concentrate; placebo was identical except that it did not contain infliximab. Patients could not have received more than 3 doses of MTX prior to study enrollment. Oral MTX was started at 7.5 mg/week at study entry and escalated in a graduated manner to 15 mg/week by Week 4 and to 20 mg/week by Week 8, with administration of at least 5 mg/week of folic acid. The MTX dose could be tapered only for toxicity. Patients using oral corticosteroids must have been taking a stable dose equivalent to  $\leq$  10 mg prednisone per day for at least 4 weeks prior to screening and were to continue taking stable doses during the study. Patients who were not currently using corticosteroids were to have received no corticosteroid for at least 4 weeks prior to screening. Infliximab or placebo infusions were given at Weeks 0, 2, and 6, and every 8 weeks thereafter through Week 46.

A subset of 90 participants from the ASPIRE trial were enrolled in a vaccine substudy at 25 selected study sites. All patients who completed Week 30 of the main protocol at these sites were invited to participate in the substudy. Patients who had received pneumococcal vaccination within 5 years prior to study randomization and those who had an active infection at the time of entry to the substudy were not eligible. Patients received 0.5 ml of the pneumococcal vaccine (Pneumovax<sup>®</sup> 23) intramuscularly at 34 weeks after initiation of study treatment, and their sera were collected prior to vaccine administration and 4 weeks later (Week 38) for antibody analysis. A patient was considered evaluable for vaccine response if pneumococcal polyvalent serotype data were available at both baseline (Week 34) and 4 weeks postbaseline (Week 38) for at least 6 of the 12 assessed serotypes. Seventy patients met the evaluability criteria and were included in the analyses: 20 patients in the infliximab 3 mg/kg plus MTX group, 36 patients in the infliximab 6 mg/kg plus MTX group, and 14 patients in the placebo plus MTX group.

Antibody responses were tested using enzyme immunoassay (EIA) methods developed by the Nichols Institute of Quest Diagnostics (Van Nuys, CA, USA) laboratory for reactivity to a panel of 12 serotypes of the pneumococcal vaccine: serotypes 1, 3, 4, 6B, 7F, 8, 9N, 12F, 14, 19F, 23F, and 18C. Assay plates were coated with the 12 individual serotypes; the patient serum was added to each of the serotype wells and incubated 2 hours. Bound antibodies were detected with a conjugated probe, followed by substrate addition. To minimize the amount of anti-cell-wall polysaccharide antibody reactivity present in patient sera, an absorption/dilution step for the patient sera was performed prior to the analysis. The concentration of each specific antibody was calculated relative to the amount of color development.

The change from pre- to postvaccination antibody levels for each of the 12 serotypes was determined. A patient was considered to have responded to

the vaccine if postvaccination antibody levels met the threshold value used by Quest Diagnostics, or if there was at least a 2-fold increase in pre- to postvaccination antibody levels in at least 6 of the 12 serotypes.

## RESULTS

*Patient characteristics.* Baseline characteristics were generally similar between patients enrolled into each treatment group as well as between patients in the overall ASPIRE study and those considered evaluable in the vaccine substudy (Table 1A). The median tender joint count in the placebo plus MTX group (43) was higher than in the infliximab 3 mg/kg plus MTX group (30;  $p = 0.025$ ) and the infliximab 6 mg/kg plus MTX group (32;  $p = 0.092$ ). There was also a slightly higher proportion of women in the placebo plus MTX treatment group in the vaccine substudy (not statistically significant). Although the median pneumococcal antibody titers prior to vaccination at Week 34 were generally slightly higher in the placebo treatment group relative to the infliximab treatment groups, the results were not statistically different for the majority of serotypes (Table 1B).

*Individual serotype reactivity.* The proportions of patients in each treatment group that responded to each of the 12 serotypes are shown in Figure 1. Variable responses were observed across the individual serotypes, with no consistent pattern of high or low response to the 12 serotypes for the placebo plus MTX treatment group relative to the infliximab 3 mg/kg or 6 mg/kg plus MTX treatment groups. In general, the highest responses were observed for serotypes 9N and 18C.

*Number of serotypes to which patients reacted.* As shown in Figure 2, more than 80% of patients in the 3 treatment groups responded to at least one serotype, and 20%–25% of patients responded to at least 6 different serotypes. The proportions of patients responding to higher numbers of different serotypes decreased in a linear manner. There were no differences between the treatment groups in the proportion of patients who responded to an increased number ( $\geq 1$  to  $\geq 6$ ) of different serotypes.

A comparison of the proportion of patients with response according to different baseline characteristics is provided in Table 2. There were no significant differences in response to pneumococcal vaccination between the placebo plus MTX and the combined infliximab plus MTX treatment groups for the subsets that had sufficient numbers of patients for evaluation, i.e., female patients; age < 45 years; age  $\geq$  45 years; the use or absence of oral corticosteroids; patients who did or did not achieve MTX dosages of 20 mg/week; disease duration < 1 year; and tender/swollen joint counts above or below the study median. There were, however, differences in response within the combined infliximab group, with a trend toward a higher proportion of patients < 45 years of age (6/14, 43%;  $p = 0.067$ ) and significantly more patients receiving oral corticosteroids (11/26, 42.3%,  $p = 0.003$ ) responding to the vaccine compared with patients  $\geq$  45 years of age (7/42, 17%) and those not receiving oral corticosteroids (2/30, 6.7%),

Table 1A. Baseline characteristics at the time of enrollment into the ASPIRE study.

	Evaluable Patients* in Vaccine Substudy			All Patients in ASPIRE		
	Placebo + MTX	3 mg/kg + MTX	6 mg/kg + MTX	Placebo + MTX	3 mg/kg + MTX	6 mg/kg + MTX
Patients randomized, no.	14	20	36	298	373	378
Median age, IQR	50 (37, 54)	52 (45, 57)	50 (42, 56)	51 (41, 60)	52 (43, 59)	49 (41, 59)
% Female	78.6	65.0	66.7	74.8	71.6	67.7
Median no. tender joints (IQR)	43 (30, 52)	30** (20, 38)	32 (23, 45)	33 (22, 44)	29 (21, 42)	30 (22, 44)
Median no. swollen joints (IQR)	27 (12, 36)	20 (13, 25)	17 (12, 27)	19 (14, 27)	18 (14, 25)	19 (13, 27)
Median CRP, mg/dl (IQR)	0.90 (0.5, 5.0)	0.90 (0.4, 3.4)	1.05 (0.4, 2.2)	1.3 (0.5, 4.0)	1.6 (0.4, 4.3)	1.5 (0.5, 4.3)
% receiving oral corticosteroids	42.9	50.0	44.4	36.9	36.2	39.2
% RF-positive	71.4	60.0	69.4	70.9	71.0	72.7

IQR: interquartile ranges, CRP: C-reactive protein, RF: rheumatoid factor. \* A patient was considered evaluable for vaccine response if pneumococcal polyvalent serotype data were available at baseline (Week 34) and postbaseline (Week 38) for at least 6 of the 12 assessed serotypes. \*\*  $p < 0.05$  vs placebo + MTX.

Table 1B. Summary of pneumococcal antibody titers prior to vaccination at Week 34.

No. Serotype	Vaccine Substudy		
	Placebo + MTX	3 mg/kg + MTX	6 mg/kg + MTX
	Median Pneumococcal Antibody Titer at Week 34 (IQR)		
	14	20	36
1	2.40 (1.00, 3.30)	1.15 (1.70, 2.05)	1.30 (0.60, 4.30)
3	2.90 (1.40, 5.30)	1.55 (1.15, 3.90)	1.50 (0.90, 2.90)
4	2.45 (0.70, 4.70)	1.40 (0.55, 3.20)	1.10 (0.70, 2.30)
6B	2.05 (0.90, 2.90)	1.40 (1.00, 2.20)	1.65 (0.90, 5.05)
7F	6.75 (3.00, 8.20)	2.80* (1.25, 5.40)	3.10 (1.65, 4.95)
8	4.20 (3.00, 6.10)	1.70 (0.90, 4.80)	1.95 (1.20, 4.15)
9N	2.20 (1.10, 3.50)	1.20 (0.60, 3.15)	1.40 (0.60, 4.15)
12F	3.05 (1.50, 3.70)	1.50 (0.90, 3.40)	1.85 (0.90, 3.65)
14	9.00 (4.20, 12.50)	4.15 (2.25, 7.70)	3.75* (1.65, 8.10)
18C	4.25 (3.00, 6.80)	2.40 (1.05, 6.65)	2.95 (1.35, 5.15)
19F	3.15 (1.70, 5.90)	2.15 (1.30, 2.90)	1.75 (1.10, 3.75)
23F	3.85 (1.80, 4.60)	1.45* (0.95, 3.50)	3.60 (1.10, 5.55)

\*  $p < 0.05$  vs placebo plus MTX group.

respectively. Similar trends were observed in the placebo group. It is difficult to compare responses for patients with disease duration  $> 1$  year given the limited numbers of patients in this category.

## DISCUSSION

The approved pneumococcal vaccine, comprising purified capsular polysaccharide of 23 serotypes indicative of more than 90% of the invasive pneumococcal infections seen in the United States, induces adequate antipolysaccharide IgG antibody levels to most of the component polysaccharide antigens in immunocompetent adults. In our study of patients with early RA enrolled in the ASPIRE trial<sup>9</sup>, no significant difference in response to Pneumovax was observed between the infliximab plus MTX and placebo plus MTX treatment groups. In addition, comparable proportions of patients in both treatment groups responded to an increasing number

( $\geq 1$  to  $\geq 6$ ) of serotypes; however, only 20%–25% of patients in the different treatment groups responded to  $\geq 6$  different serotypes.

In an analysis of 205 patients with psoriatic arthritis, Mease, *et al*<sup>7</sup> found that MTX use was a predictor of poor response to pneumococcal antigen challenge. More recently, Kapetanovic, *et al*<sup>10</sup> reported that following pneumococcal vaccination, patients with RA given MTX alone had lower immune responses to the polysaccharides 23F and 6B than those RA patients receiving TNF blockers (etanercept or infliximab) with or without MTX. Together, these findings may indicate that the generally low response rate to the pneumococcal vaccine could be related to concomitant MTX administration. Of note, our analysis failed to detect a difference in vaccine response based on MTX doses achieved and maintained throughout the study.

It is also possible that the low response observed is related

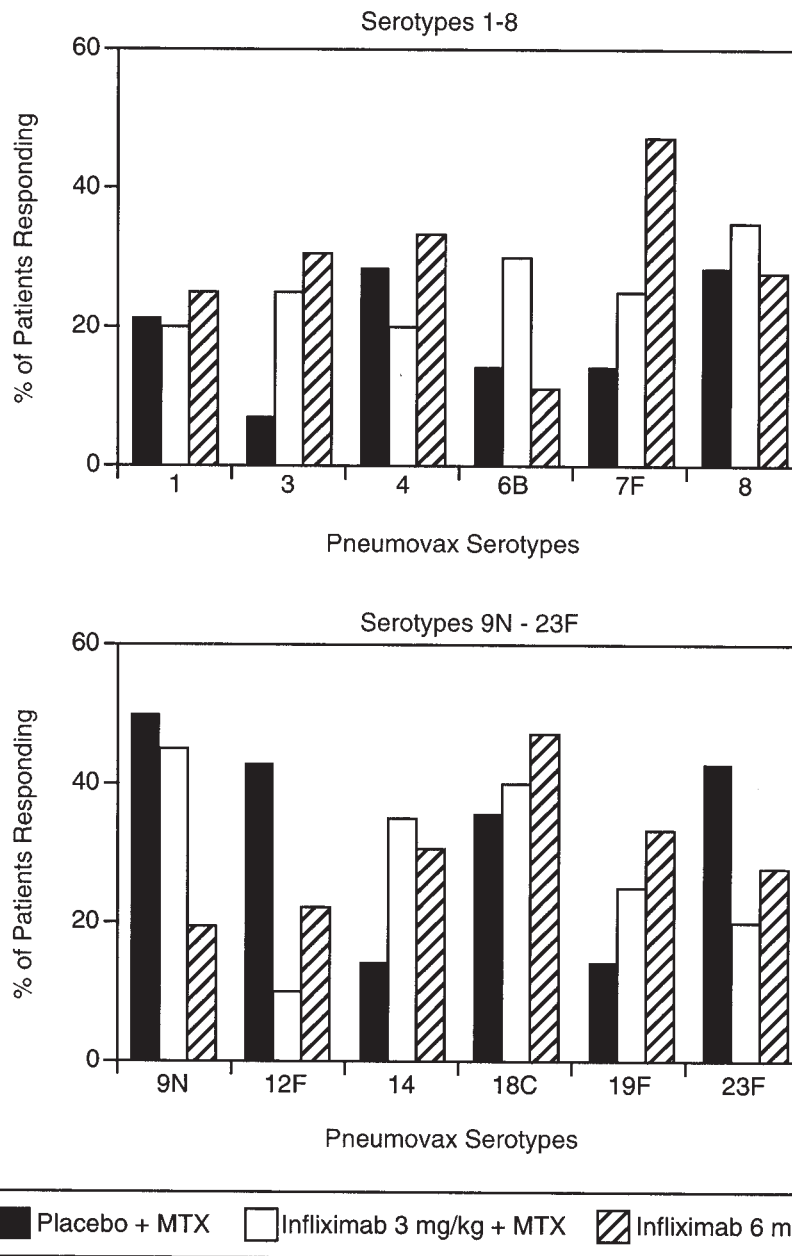


Figure 1. Proportions of patients responding to Pneumovax serotypes 1 to 8 (top panel) and 9N to 23F (bottom) by treatment group.

to the presence of RA. In an evaluation of the efficacy of influenza virus vaccine in 82 patients with RA and 30 healthy controls, Fomin, *et al*<sup>11</sup> observed a lower humoral response in RA patients than in the healthy controls. The response in that study did not appear to be affected by the use of prednisone, MTX, plaquenil, infliximab, or etanercept. Of note, an additional evaluation of 16 patients (11 with RA, 5 with ankylosing spondylitis), who received either infliximab or etanercept and were compared with 17 age-matched RA patients not receiving anti-TNF- $\alpha$  therapy, indicated that RA patients receiving anti-TNF- $\alpha$  therapy might not respond adequately to pneumococcal vaccination<sup>12</sup>. The smaller sample size,

fewer serotypes tested ( $n = 7$ ), and variable use of MTX (65% of patients) may account for the lack of consistent findings between this evaluation and our substudy of the ASPIRE trial that involved testing of 12 serotypes in 70 patients, all receiving concomitant MTX.

Some reports have suggested that elderly adults respond about equally well to vaccination compared to younger adults<sup>13,14</sup>, while other studies have shown suboptimal efficacy of the currently available 23-valent pneumococcal vaccine in adults > 65 years old<sup>15</sup>. In a study by Rubins, *et al*<sup>15</sup> a subset (roughly 20%) of elderly outpatients responded to fewer than 2 of 7 serotypes tested 1 and 3 months after immuniza-

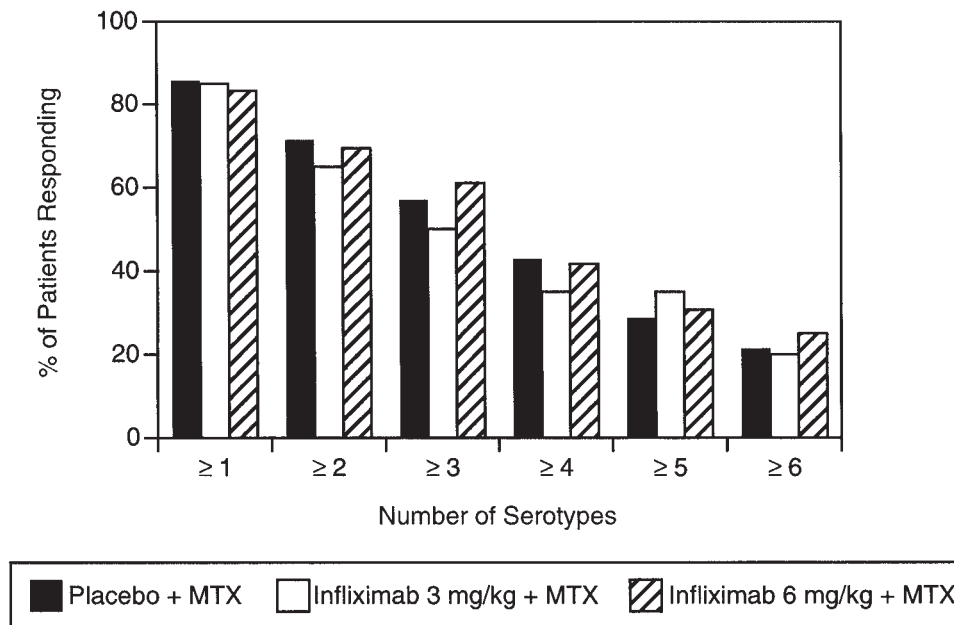


Figure 2. Proportions of patients responding to number of Pneumovax serotypes by treatment group.

tion, whereas none of the healthy young adults were such poor responders. Based on these findings, the authors concluded that, despite the adequate mean immune responses of the elderly as a group, a substantial proportion of elderly persons may have poor responses to the currently available pneumococcal vaccine<sup>15</sup>. These findings are consistent with those of our study, which showed patients < 45 years of age to generally respond better than those aged > 45 years. These findings are also consistent with those observed in the psoriatic arthritis study<sup>7</sup>.

Further, we observed that patients who received oral corticosteroids appeared to respond better than those who had not received such therapy, although the explanation for this finding is not clear. It may be that corticosteroid treatment aided in maintaining better control of the inflammatory processes, thereby promoting a more robust immune response to the vaccine.

Of note, our results, which indicated that the addition of infliximab to a MTX regimen does not appear to alter the response to pneumococcal vaccine, are consistent with findings recently reported for the TNF antagonist adalimumab. In a double-blind, placebo controlled study of 226 patients with active RA who received adalimumab or placebo, adalimumab treatment did not diminish the ability of RA patients to develop protective antibody concentrations from influenza and pneumococcal vaccines<sup>16</sup>.

The results of this exploratory analysis are limited by the low power and relatively small sample size of the ASPIRE substudy. In addition, there were disproportionately fewer patients in the placebo group, which was attributable to more discontinuations from the study in this group.

Results of this study suggest that patients with RA receiving MTX treatment may not be adequately protected from the risk of pneumonia by administration of the pneumococcal vaccination, especially those patients aged 45 years or older. The addition of infliximab to a MTX regimen does not appear to alter this response. These findings warrant additional studies to confirm the poor protection that pneumococcal vaccination provides for RA patients receiving MTX treatment.

#### ACKNOWLEDGMENT

The authors thank Timothy Gathany, MEd, Songkai Yan, PhD, and Michelle Perate, MS, of Centocor for their assistance in preparing this report. The authors also thank Roberta Weiss for her assistance with conduct of the study.

#### REFERENCES

1. Elkayam O, Paran D, Caspi D, et al. Immunogenicity and safety of pneumococcal vaccination in patients with rheumatoid arthritis or systemic lupus erythematosus. *Clin Infect Dis* 2002;34:147-53.
2. Centers for Disease Control and Prevention. Prevention of pneumococcal disease: recommendation of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mort Wkly Rep* 1997;46 (RR-80):1-24.
3. Whitney CG. Preventing pneumococcal disease. ACIP recommends pneumococcal polysaccharide vaccine for all adults age ≥ 65. *Geriatrics* 2003;58:20-2, 25.
4. DeFranco AL. B-lymphocyte activation. In: Paul WE, editor. *Fundamental immunology*. Philadelphia: Lippincott-Raven; 1999:225-61.
5. Pirofski L, Casadevall A. Use of licensed vaccines for active immunization of the immunocompromised host. *Clin Microbiol Rev* 1998;11:1-26.
6. Simberkoff MS, Cross AP, Al-Ibrahim M, et al. Efficacy of pneumococcal vaccine in high risk patients. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986;315:1318-27.
7. Mease P, Ritchlin C, Martin R, et al. Pneumococcal vaccine response

Table 2. Proportions of patients responding to Pneumovax® vaccine by baseline characteristics.

	Placebo + MTX, n = 14	Infliximab + MTX, n = 56	Odds Ratio*	p*
Patients with response, %	21.4 (3/14)	23.2 (13/56)	1.109	1.000
Sex, %				
Male	0.0 (0/3)	21.1 (4/19)	NA	NE
Female	27.3 (3/11)	24.3 (9/37)	0.857	1.000
Age, yrs, %				
< 45	40.0 (2/5)	42.9 (6/14)	1.125	1.000
≥ 45	11.1 (1/9)	13.2 (7/42)	1.212	1.000
p**	0.505	0.067		
Oral corticosteroid use***, %				
Yes	33.3 (2/6)	42.3 (11/26)	1.467	1.000
No	12.5 (1/8)	6.7 (2/30)	0.500	0.519
p**	0.538	0.003		
MTX dose progression, %				
Patients who achieved and maintained MTX 20 mg/wk	23.1 (3/13)	22.9 (8/35)	1.01	1.000
Patients who did not achieve or maintain MTX 20 mg/wk	0 (0/1)	23.8 (5/21)	NE	1.000
p**	1.000	1.000		
Disease duration, yrs, %				
< 1	30.0 (3/10)	27.5 (11/40)	0.885	1.000
≥ 1 to < 2	0.0 (0/2)	8.3 (1/12)	NA	NE
≥ 2	0.0 (0/2)	25.0 (1/4)	NA	NE
Tender joint count, %				
TJC ≥ 34.5 <sup>†</sup>	20.0 (2/10)	28.0 (7/25)	0.64	1.000
TJC < 34.5 <sup>†</sup>	25.0 (1/4)	19.4 (6/31)	1.39	1.000
p**	1.000	0.532		
Swollen joint count, %				
SJC ≥ 18 <sup>†</sup>	20.0 (2/10)	29.6 (8/27)	0.59	0.6941
SJC < 18 <sup>†</sup>	25.0 (1/4)	17.2 (5/29)	1.60	1.000
p**	1.000	0.349		

NA: not available, NE: not evaluable. \* For comparison of placebo plus MTX vs infliximab plus MTX groups; Fisher's exact 2-sided test. \*\* For comparison across age/medication/joint count categories within treatment group; Fisher's exact 2-sided test. \*\*\* Patients using oral corticosteroids must have been on a stable dose equivalent to ≤ 10 mg prednisone per day for at least 4 weeks prior to screening, and were to continue stable doses during the study. Patients who were not currently using corticosteroids were not to have received corticosteroids for at least 4 weeks prior to screening. Median value determined from the distribution among all patients in the vaccine substudy.

- in psoriatic arthritis patients during treatment with etanercept. *J Rheumatol* 2004;31:1356-61.
- Oppenheim JJ, Ruscetti FW, Faltynek C. Cytokines. In: Stites DP, Abba IT, editors. *Basic and clinical immunology*. Norwalk, CT: Appleton and Lange; 1991:78-100.
  - St. Clair EW, van der Heijde DMFM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis. *Arthritis Rheum* 2004;50:3432-43.
  - Kapetanovic MC, Saxne T, Sjöholm A, Truedsson L, Jönsson G, Geborek P. Influence of methotrexate, TNF blockers and prednisolone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. *Rheumatology Oxford* 2006;45:106-11.
  - 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.
  - Elkayam O, Caspi D, Reitblatt T, Charboneau D, Rubins JB. The effect of tumor necrosis factor blockade on the response to pneumococcal vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. *Semin Arthritis Rheum* 2004;33:283-8.
  - Mufson MA. Antibody response of pneumococcal vaccine: need for booster dosing? *Int J Antimicrob Agents* 2000;14:107-12.
  - World Health Organization. *Pneumococcal vaccines: World Health Organization position paper*. *Can Commun Dis Rep* 1999;25:150-1.
  - Rubins JB, Puri AK, Loch J, et al. Magnitude, duration, quality, and function of pneumococcal vaccine responses in elderly adults. *J Infect Dis* 1998;178:431-40.
  - Kaine J, Kivitz A, Birbara C, Luo AY. Effect of adalimumab (Humira®) on response to pneumococcal and influenza virus vaccines in patients with rheumatoid arthritis (RA). *Ann Rheum Dis* 2006;65 Suppl II:304.