Longterm Efficacy of an Antipneumococcal Polysaccharide Vaccine among Patients with Autoimmune Inflammatory Rheumatic Diseases

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ABSTRACT. ***Objective.*** To estimate the longterm humoral response of an antipneumococcal polysaccharide vaccine (PPSV23) in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), or inflammatory bowel disease (IBD)-associated spondyloarthropathy (SpA), and the effect of demographic and clinical factors and treatment on the longterm efficacy of the vaccine.

Methods. A total of 145 consecutive patients treated with biologics [tumor necrosis factor-α (TNF-α) or interleukin 6 (IL-6) receptor inhibitors] or methotrexate (MTX) participated in this study. Fifteen were excluded because of absent information regarding their vaccination status (n = 9) or because of technical problems in obtaining their serum sample (n = 6). They were diagnosed with RA (n = 63, 48.5%), PsA (n = 29, 22.3%), AS (n = 28, 21.5%), or IBD-associated SpA (n = 3, 2.3%). Their mean age was 54.6 years, and 61.5% were women. Data were collected on the timing of vaccination, demographic and clinical characteristics, and treatment, and patients' serum antipneumococcal antibody levels were tested.

Results. Two-thirds of the patients (67.7%) had received PPSV23 45 months (mean) earlier. Treatment included TNF-α inhibitors (73.9%), IL-6 receptor inhibitors (13.1%), or MTX without a biological treatment (13%). The uptake of vaccination was significantly higher in the older population (> 65 yrs). Vaccinated patients had significantly higher antibody levels compared with vaccine-naive patients. The antibody levels had been preserved after 10 years. MTX use, but not biologics, was associated with significantly lower antibody levels.

Conclusion. The longterm efficacy of the PPSV23 vaccination seems to be preserved among patients with RA, PsA, AS, and IBD-associated SpA for at least 10 years. Efficacy is slightly impaired by MTX, but it is not affected by biologics. These findings suggest that revaccination after 5 years might not be needed for all, and testing the antibody titers should be considered to identify those who may benefit from revaccination. (First Release January 15, 2016; J Rheumatol 2016;43:267–72; doi:10.3899/jrheum.150397)

Key Indexing Terms:
PNEUMOCOCCAL VACCINE AUTOIMMUNE EFFICACY RHEUMATOID ARTHRITIS

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Patients with autoimmune inflammatory rheumatic diseases (AIIRD) are at increased risk of contracting infections, especially when they are receiving immunomodulatory medications[1–9,10,11]. The high prevalence of multiple antibiotic-resistant strains and the considerable morbidity and mortality associated with invasive infections highlight the importance of prophylaxis with vaccination, particularly in patients at increased risk[12]. In the general population, fatal cases attributable to *Streptococcus pneumoniae* infections are usually associated with invasive infections[13,14,15]. Vaccination has been shown to prevent those infections and is recommended for individuals older than 65 years[1]. Vaccination against *S. pneumoniae* is strongly recommended for patients with AIIRD in whom the short-term humoral response to the pneumococcal vaccine has been well established[16]. Methotrexate (MTX) and tumor necrosis factor-α (TNF-α) blockers were reported to mildly reduce the humoral

response[17,18,19,20], while abatacept and rituximab were shown to severely impair it[21].

The longterm effect of vaccination is not well delineated. Antibody titers among immunocompetent patients decrease by 9 years postvaccination, although clinical protection seems to persist[22,23]. However, most of the earlier trials that assessed vaccine efficacy had a mean followup period of only 3 years (short-term)[24]. Based on those scarce data, the current recommendation is to revaccinate people over 65 years of age and immunocompromised patients of all ages after 5 years[25].

Little is known about the longterm efficacy of the antipneumococcal vaccine pneumococcal polysaccharide vaccine 23 (PPSV23) in patients with AIIRD and whether revaccination every 5 years is necessary in this population. Coulson, *et al* studied the longterm efficacy of PPSV23 in MTX-treated patients with rheumatoid arthritis (RA) and did not find a significant decrease in immunization, although they did note a statistic tendency toward decreased immunity after 7 years[26]. To the best of our knowledge, no studies have addressed the longterm effect of biologic therapy on PPSV23 efficacy. The aims of our study were to estimate the longterm efficacy of PPSV23 in patients with RA, psoriatic arthritis (PsA), ankylosing spondylitis (AS), and inflammatory bowel disease (IBD)-associated spondyloarthropathy (SpA) being treated with biologics, and to evaluate the effect of clinical and demographic factors as well as treatment on the longterm efficacy of the vaccine.

MATERIALS AND METHODS

Study participants. The study was conducted between July and November 2012 at the Department of Rheumatology, Tel Aviv Medical Center. All consecutive patients who fulfilled the following inclusion criteria were eligible for study entry: diagnosed as having RA, AS, PsA, or IBD-associated SpA [RA according to the 1987 American Rheumatism Association criteria[27], PsA according to the CASPAR (ClASsification for Psoriatic ARthritis) criteria[28], AS according to the New York criteria[29], and IBD-associated arthritis] currently treated with biologic therapy consisting of TNF-α or interleukin 6 (IL-6) receptor inhibitors or treated with these regimens after receiving the antipneumococcal vaccine. The control group was composed of patients with the same inflammatory rheumatoid diagnoses, and currently receiving MTX. All candidates needed to be ≥ 18 years of age and able to provide informed consent. Patients who had human immunodeficiency virus (HIV)/AIDS, malignancy, or who were receiving rituximab or steroids at a dose > 20 mg/day were excluded.

The demographic and clinical data obtained for the study participants included age, clinical diagnosis, time since diagnosis, current and past medical treatment, and the date of vaccination with PPSV23. Data were collected during a patient interview by 1 of the authors (AB) and from the clinical files. The exact vaccination date was confirmed by the patient's general practitioner registrations in most cases. We found a 95% positive correlation between the reported data and the registered ones, and therefore assumed reliability of our patient's reports in all cases. Vaccinated patients for whom we did not have the vaccination date information were excluded. Eighty-eight patients (67.7%) of our study population had been vaccinated; time since vaccination was 0–5 years in 66 patients, 5–10 years in 19 patients, and more than 10 years in 3 patients.

Samples. Blood samples were collected, and serum was stored at –20ºC. Levels of antipneumococcal antibodies were determined with a standard ELISA kit that uses the PPSV23 vaccine as an antigen in microliter plates [MK012 anti-pneumococcal capsular polysaccharide (PCP) immunoglobulin G (IgG) enzyme immunoassay commercial kit; Binding Site Ltd]. The assay was conducted according to the manufacturer's instructions. Samples were drawn by venipuncture, put into tubes until clotting, and then centrifuged for serum separation. Serum was stored at –20ºC. The kit included microliter wells coated with PCP antigens of the different serotypes included in the PPSV23 vaccine (i.e., 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F). To neutralize the nonspecific C–PCP, antibody's controls and calibrators were adsorbed with C-polysaccharide, and samples were diluted (1:100) in a C-polysaccharide-containing solute. The calibrators, controls, and diluted samples were put into wells for a 30-min incubation. The wells were washed and then incubated with rabbit anti-human IgG. After another wash, the wells were incubated with conjugate attached to peroxidase (100 μl per well). After the third wash, the substrate (3,3′,5,5′ tetramethylbenzidine), which reacted with the conjugate, was added to give it a blue color. A phosphoric acid was then added to stop the reaction and a yellow color appeared. The color was inspected at a 450 nm wavelength. Optical density was transformed to antibody concentration according to calibration charts. Serum samples were assessed in duplicates and the result was the mean value. In cases of a high coefficient of variation (> 15%) between duplicates, we tested the serum a second time.

Our study was approved by the ethics committee of the medical center. Appropriate informed consent was obtained from all patients, and the clinical research was conducted in accordance with the guidelines for human experimentation specified by the Tel Aviv Medical Center.

Statistical analysis. The statistical analysis was performed with the IBM SPSS statistics system for Windows, release 20. We used nonparametric tests (Mann-Whitney U) because the antibody levels did not conform to a Gaussian distribution among our study population.

Although there is no acceptable level that confers immunity, we regarded a level of 35 mg/l as the protective level, as accepted in guidelines for revaccination of asplenic patients and in previous similar studies[26].

RESULTS

There were 145 patients who participated in our study. Fifteen were excluded, and statistical analyses included 130 patients who were previously diagnosed with RA (n = 67, 51.5%), PsA (n = 29, 22.3%), AS (n = 28, 21.5%), or IBD-associated SpA (n = 3, 2.3%); 3 (2.3%) had other inflammatory rheumatoid diseases (Behçet disease, Takayasu arteritis, juvenile rheumatoid arthritis). The 15 excluded patients lacked information on past vaccination date (n = 9) or a proper blood sample for ELISA (n = 5), or they had the hepatitis C virus (n = 1), leaving 130 patients who had complete data and proper blood samples and were included in the final analysis. Table 1 and Table 2 summarize their demographic and clinical characteristics. The mean age of the cohort was 54.6 years, and 80 (61.5%) were women. The patients were treated with biologic therapy (TNF-α or IL-6 receptor inhibitors) or MTX.

Characteristics of the patients who had been vaccinated. Eighty-eight of our patients (67.7%) had been vaccinated with PPSV23. The major reasons for not having received the vaccine were patient unawareness (n = 26, 61.9%) or unwillingness (n = 6, 14.3%). The uptake of vaccination was significantly higher in the older population (> 65 yrs, n = 34), among whom 97% (n = 33 of 34) had been vaccinated compared with the younger population (< 65 yrs, n = 55 of

Table 1. Demographic and clinical characteristics of the patients. Values are n (%) unless otherwise specified.

Characteristics	Values
Age, yrs, mean (range)	54.6 (20–88)
Females	80 (61.5)
AIIRD subtype	
RA	67 (51.5)
AS	28 (21.5)
PsA	29 (22.3)
IBD-associated SpA	3 (2.3)
Other*	3 (2.3)
Time since diagnosis, mos, mean (range)	169.7 (8–660)
Cardiopulmonary comorbidities**	
None	34 (26.2)
1–2	62 (47.6)
≥ 3	34 (26.2)

* Behçet disease (1 patient), juvenile RA (1 patient), Takayasu arteritis (1 patient). ** Congestive heart failure, ischemic heart disease, hypertension, diabetes mellitus, dyslipidemia, chronic occlusive pulmonary disease, and interstitial lung disease. AIIRD: autoimmune inflammatory rheumatic diseases; RA: rheumatoid arthritis; AS: ankylosing spondylitis; PsA: psoriatic arthritis; IBD: inflammatory bowel disease; SpA: spondyloarthropathy.

Table 2. Patients' vaccination status and biologic or DMARD treatment. Values are n (%) unless otherwise specified.

Characteristics	Values
Patients with a history of vaccination with PPSV23	88 (67.7)
Time since vaccination, mos, mean (range)	45 (0–180)
Biologic treatment	
Infliximab	59 (45.4)
Etanercept	21 (16.2)
Adalimumab	16 (12.3)
Tocilizumab	17 (13.1)
Duration of biologic treatment, mos, mean (range)	43.4 (1–192)
Methotrexate	54 (41.5)
Steroids	25 (19.4)
Steroid dose, mean (range)	7.3 (1–20)

DMARD: disease-modifying antirheumatic drug; PPSV23: pneumococcal polysaccharide vaccine 23.

96, 57.2%). Age and vaccination status were dependent variables according to the Pearson correlation chi-square test ($p < 0.001$). The mean age of the patients in the vaccinated group was ~59 years compared with ~46 years in the unvaccinated group ($p < 0.001$). Interestingly, there was a significant correlation between the uptake of PPSV23 and the uptake of influenza vaccine, the reasons for not receiving vaccination being similar.

Antibody concentrations among vaccinated patients. Vaccinated patients had significantly higher antibody levels compared with unvaccinated patients (214 mg/l vs 96 mg/l, respectively, $p = 0.001$).

Thirteen (29.1%) of the unvaccinated patients had non-protective levels (< 35 mg/l) compared with 9 (10.2%) of the vaccinated population ($p = 0.005$).

Longterm vaccine efficacy. The longterm efficacy of PPSV23 was analyzed in the 88 vaccinated patients by means of a consecutive timeline method. It was also analyzed in subgroups according to vaccination date (< 5 yrs, 5–10 yrs, and > 10 yrs earlier). Time since vaccination was 0–5 years in 66 patients (75%), 5–10 years in 19 patients (21%), and more than 10 years in 3 patients (4%). We used the parametric Student t test and the nonparametric Mann-Whitney U test for the grouped data. Both analyses revealed a preservation of the antibody concentration over time. There was a nonsignificant trend toward lower antibody levels among patients who were vaccinated > 5 years before study entry, but no significant decrease in the antibody concentration was observed in patients who had been vaccinated > 10 years earlier (Figure 1).

Factors affecting longterm vaccine efficacy. No association was found between longterm efficacy of the vaccine and the patient's age or the use of TNF-α blockers, tocilizumab, or low-dose prednisone. In contrast, the use of MTX was associated with significantly lower antibody levels (187 mg/l vs 289 mg/l for no MTX, $p = 0.037$). A higher but nonsignificant proportion of MTX users had non-protective levels of antibodies (13% vs 7% for non-treated patients). Female sex correlated significantly with higher antibody levels (Table 3).

DISCUSSION

The longterm efficacy of the pneumococcal vaccine is not well defined. The results of our current study demonstrated that the antibody levels are preserved over at least 10 years in RA, AS, PsA, and IBD-associated SpA in all ages treated with TNF-α blockers, tocilizumab, and low-dose prednisone. Treatment with MTX was associated with lower (but still protective) antibody levels, regardless of the time since vaccination. Vaccinated patients had significantly higher antibody levels as well as a significantly higher proportion of protective levels. Similar results were described by Coulson, *et al* among patients with RA treated with MTX[26]. Those authors found no significant decrease in antipneumococcal antibody concentration, although a tendency toward a decrease was noted after 7 years since vaccination[26]. Our data, taken together with theirs, suggest that revaccination after 5 years might not be needed.

The findings of our study show similar data regarding antibody levels among the unvaccinated population to what is known in the literature[30].

Data on the longterm efficacy of PPSV23 in the general population are limited. Musher, *et al* concluded that primary vaccination with PPSV23 induced antibody response that persisted during at least the 5 years of their observation period[31]. An exception was serotype 3 for which antibody levels had returned to baseline after 2 years. Manoff, *et al* found that primary vaccination of older adults (≥ 65 yrs)

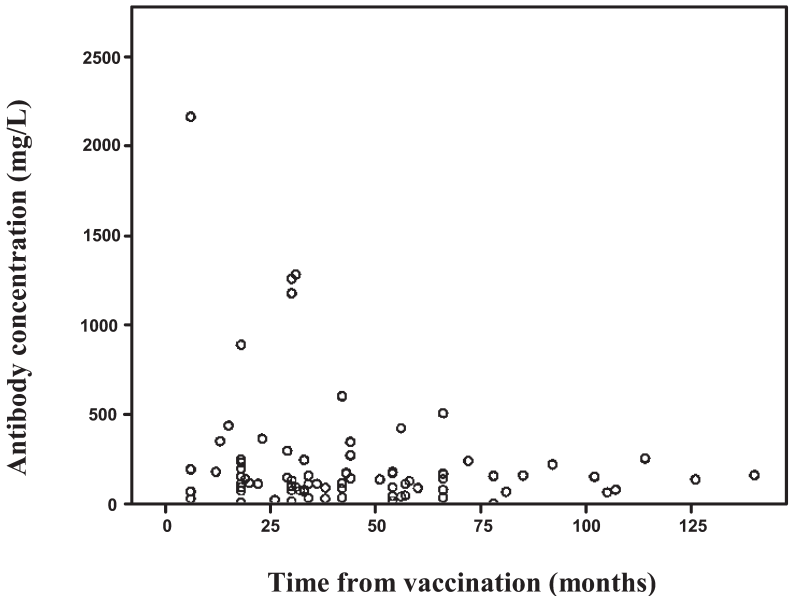

Figure 1. No correlation was found between antibody concentration and time since vaccination.

Table 3. Correlation of sex with antibody levels.

Characteristics	Antibody Concentration, mg/l	p
Females vs males	125 vs 89	0.024
MTX treatment vs no MTX	187 vs 289	0.037
Anti-TNF ± MTX vs MTX alone	175 vs 173	0.058
Steroids treatment vs no steroids	221 vs 213	0.900

MTX: methotrexate; TNF: tumor necrosis factor.

induced an elevated and persistent antibody response after 5 years[32].

Valenzuela, *et al* showed that titers remained high 2 years after the vaccination for the 10 serotypes studied in an elderly population[33]. Another study among the elderly showed that mean serotype-specific IgG concentrations decreased by 33% at 1 year after vaccination; however, they remained significantly higher than prior to vaccination[34]. Based on these results, a review of the longterm immunogenicity data for PPSV concluded that antibody levels persist above concentrations in unvaccinated patients for at least 5–10 years in most studies[35]. The few exceptions involved significant host factor issues, such as hospitalized patients with pneumonia (community-acquired) and immunocompromised patients (postrenal transplantation and patients with HIV)[35].

The longterm efficacy of PPSV23 might vary for different populations. Dransfield, *et al* observed no difference in antibody levels after 3 years among vaccinated and vaccine-naive patients with chronic obstructive pulmonary disease[36]. Likewise, the proportion of HIV-infected patients who maintained antibody responses to pneumococcal pneumonia vaccine declined significantly over a 5-year followup period (especially among those who had CD4 counts < 100 cells/μl at vaccination and who failed to achieve virologic suppression)[35]. One study on 149 splenectomized patients who received the pneumococcal polysaccharide vaccine reported that the mean antipneumococcal antibody concentration did not correlate with time since vaccination when estimated 0–10 years after vaccination[37]. Lindemann, *et al*'s report on patients with kidney transplants revealed a significant decrease in total antibody concentrations 15 months after vaccination, but it was only minor in younger patients, in women, in patients receiving cyclosporine A versus tacrolimus, and in patients with better kidney function[38]. Finally, the effect of biologic therapy on immunogenicity was assessed by Kaufman, *et al*, who found that patients with longstanding RA preserve longterm immunity to common viruses (polio, mumps, and measles) despite treatment with infliximab[39].

Our study has several limitations, including a retrospective design and a study population that included specific diagnoses only. We also measured the anti-PPSV23 antibodies instead of serotype-specific antibodies or opsonophagocytic (functional) antibody activity, which might correlate better with vaccine efficacy[40]. However, to our knowledge, this is the first attempt to address the longterm efficacy of PPSV23 in patients with AIIRD who are receiving biologic therapy. The results of our study suggest that the longterm vaccination of the pneumococcal vaccine is preserved in patients with RA, AS, PsA, and IBD-associated SpA, and that biologic treatment did not alter that response. These findings suggest that revaccination after 5 years might not be needed for all, and testing the antibody titers should be considered to detect those who may benefit from revaccination.

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