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Original article

Evaluation of the immunogenicity of the 13-valent conjugated pneumococcal vaccine in rheumatoid arthritis patients treated with etanercept

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ABSTRACT

Objectives: To prospectively evaluate the immunogenicity of a 13-valent conjugated pneumococcal vaccine (PCV13) in rheumatoid arthritis (RA) patients undergoing etanercept therapy.
Methods: Twenty-two RA patients treated with etanercept (ETA) in combination with methotrexate (MTX) ($n=15$) or monotherapy ($n=7$) for at least one year were included. Altogether 24 osteoarthritis patients not receiving biological or MTX therapy, treating only NSAIDs or analgesics served as controls. All subjects were vaccinated with a single dose (0.5 ml) of the PCV13. Pneumococcal antibody levels at baseline, 4 and 8 weeks were assessed by a VaccZyme™ Anti-PCP IgG Enzyme Immunoassay Kit. Based on recommendations of the American Academy of Allergy, Asthma & Immunology, an at least two-fold increase in antibody level, as the protective antibody response (pAR) was an indicator of responsiveness (i.e., ratio of postvaccination and prevaccination antibody levels). The antibody levels and their ratios were analysed in a variety of different ways, vaccine safety parameters (fever, infections, changes in regular antirheumatic treatments) were assessed at baseline, 4 and 8 weeks after vaccination.
Results: Four weeks after vaccination, the anti-pneumococcal antibody levels significantly increased in both groups. At week 8, antibody levels somewhat decreased in both groups, however, still remained significantly higher compared to baseline. Compared with postvaccination levels at 4 and 8 weeks between two groups, the mean protective antibody levels were higher in control group (1st month $P=0.016$; 2nd month: $P=0.039$). Possible predictors of pAR were analysed by logistic regression model. In RA, increases of antibody levels at week 8 compared to baseline exerted a negative correlation with age, (Spearman's $R=-0{,}431$; $P=0.045$). There were no clinically significant side effects or reaction after administration of vaccine observed in any of these patients after the 2-month follow-up period, all patients medical condition were stable.
Conclusions: In RA patients treated with ETA, vaccination with PCV13 is effective and safe, resulting in pAR one and two months after vaccination. Higher age at vaccination was identified as predictors of impaired pAR. The efficacy of vaccination may be more pronounced in younger RA patients. The vaccine is safe in RA patients on ETA.

1. Introduction

In 2012, lower respiratory tract infections affected 3.1 million people and thus became the 4th most common cause of death. The deaths due to pneumonia are 2–5-times more common in RA patients than in the general population [1,2]. *Streptococcus pneumoniae* (*S. pneumoniae*) is the most common cause of pneumonia in the community, as well as in hospital inpatients. The most important virulence factors of *S. pneumoniae* are capsular serotypes [3]. From the known 90 serotypes globally only 20 serotypes are responsible for more than 80% of invasive pneumococcal diseases in all age groups [4]. These serotypes causing invasive diseases differ from country to country. The role of these serotypes and their follow-up are essential for development of the new generation of conjugate vaccines [5]. A 23-valent pneumococcal polysaccharide vaccine (PPV23) licensed in 1983 [6] is less immunogenic,

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than newly developed conjugated vaccines (PCV7, PCV10, PCV13). These new vaccines due to T-cell dependent immune responses induce high level of memory B-cells to trigger the creation of an immunological memory [7]. Two conjugated vaccines, a 7-valent and a 10-valent one were approved by FDA in 2000 and 2009, respectively, to be applied only to infants and children [4,8]. Infections caused by Gram-positive bacteria, *S. pneumoniae* are vaccine-preventable diseases, but the efficacy of vaccination may be problematic in immunocompromised patients, in particular in autoimmune rheumatological disease (AIRD) and elderly patients [9–14]. There is association between anti-pneumococcal antibody levels before versus after vaccination and subsequent infection in arthritis patients [13,14]. In addition, the use of immunosuppressive drugs, such as anti-TNF biologics, as well as rituximab and abatacept may mildly-moderately impair the host response to various vaccines against pneumococcal, influenza and other infections [9,11,12,15–18]. On the other hand, in multiple studies, the IL-6 receptor inhibitor tocilizumab did not impair antibody response to pneumococcal vaccine [17,19].

Kapatenovic et al. [8,16] investigated the 7-valent conjugated pneumococcal vaccine in adult RA patients treated with ETA. These studies have shown protective immune response using PCV7 vaccine. Only 20.5% of patients exerted decreased antibody levels after 1.5 years follow-up period. PCV7 vaccine has been approved for only children but its use has never been recommended in adult populations, and there is no clinical evidence for use in adults. The other 10-valent PCV vaccine has never been licensed and investigated in adults.

Whereas PCV7 did not cover for some most important serotypes (serotypes 1, 5 and 6A), thus it has not been used since March 2010 and has been broadly replaced by higher valency conjugate vaccine (PCV13) as World Health Organization recommended [20]. In 2011, FDA licensed the 13-valent pneumococcal conjugate vaccine (PCV13) for prevention of pneumonia and invasive diseases in adults aged ≥ 50 years [21], than 2012 the ACIP recommended the routine use of PCV13 for adults with immunocompromised conditions [22]. In a recently published randomized, double-blind, placebo-controlled trial including 84,496 adults (65 years of age or older), the efficacy of PCV13 in preventing vaccine-type pneumococcal, bacteremic, and nonbacteremic community-acquired pneumonia and vaccine-type invasive pneumococcal disease was confirmed [23].

There has been no available information with respect to the efficacy and safety of the PCV13 vaccine in immunocompromised patients in particularly anti-TNF-treated RA patients. The primary objective of our investigation was to compare immunologic responses for PCV13 between RA patients treated with ETA and patients suffering from osteoarthritis served as control group. Based on recommendations of the American Academy of Allergy, Asthma & Immunology [24], an at least two-fold increase in antibody level was an indicator of protective anitibody responsiveness (i.e., ratio of postvaccination and prevaccination antibody levels). The secondary objective was to show the safety of this vaccine in this group.

2. Methods

Altogether 22 RA patients (17 females, 5 males, mean age 55.1 ± 10.4 years) undergoing current treatment with the recombinant TNF-α receptor fusion protein ETA at the University of Debrecen, Faculty of Medicine, Department of Rheumatology were included into this prospective observational study. All RA patients had been treated with 50 mg ETA administered SC once a week for at least one year. Out of these 22 patients, 15 patients received combination therapy of ETA + MTX (the mean MTX dose was 12.3 ± 4.5 mg/week), while 7 patients received ETA monotherapy only. Five patients received corticosteroids in RA group (4 patients in the ETA + MTX combined group) at a mean dose of 2.8 ± 1.1 mg/day. There were no other type of DMARDs therapy administered to the patients. Mean DAS28 (CRP) indicated low disease activity in most of patients (2.78 ± 0.62) at baseline, before vaccination.

Table 1
Epidemiological data of patients.

	RA group	Control group	*P*
All patients (n)	22	24	1.00
Male	5	6	
Female	17	18	
Mean age (year)	55.1 ± 10.4	63.9 ± 9.8	0.005
Male	52.0 ± 11.1	61.3 ± 12.5	0.226
Female	56.1 ± 10.3	64.8 ± 8.9	0.011
Co-morbidities (n)			
Cardiovascular	12 (55%)	20 (83%)	0.034
Metabolic	6 (27%)	9 (36%)	0.460
Gastrointestinal	8 (36%)	6 (25%)	0.403
Treatment (n)			
Etanercept + MTX	15 (68%)	0	–
Etanercept + MTX + steroids	4 (18%)	0	
Etanercept monotherapy	7 (32%)	0	–
Etanercept + steroids	1 (5%)	0	
Immunserological tests			
Rheumatoid factor positive	13 (59%)	0	–
ACPA positive	11 (50%)	0	–
Disease activity			–
DAS 28 (CRP)	2.78 ± 0.62	–	–

A control group of 24 patients with osteoarthritis (OA) (18 females, 6 males; mean age 63.9 ± 9.7 years) was also established. Control subjects did not receive any immunosuppressive agents, they were only NSAIDs and analgetics. The clinical data of RA and OA patients are included in Table 1. All patients in the study groups were pneumococcal vaccine naïve (never vaccinated with any pneumococcal vaccines). Exclusion criterias included primary immunodeficiency, as well as other chronic autoimmune-rheumatic diseases and diabetes mellitus, chronic hepatitis, malignancy, bronchial asthma, alcoholism, splenectomy in order to exclude the most common causes of other secondary immunodeficiency that may influence of antibody response for vaccination in RA or control group. All patient of both groups has immunoglobulin levels (IgA, IgG and IgM) in a normal ranges. Control patients more frequently had cardiovascular disease (coronary heart disease, hypertension) than RA patients (Table 1); metabolic (hyperlipidaemia, obesity) and gastrointestinal (duodenal ulcer, gastro-esophageal reflux) co-morbidities did not differ significantly in the two groups. PCV13 vaccination was performed in all RA patients 5 days before administering the next dose of ETA. The vaccination was performed in written consent of patients and contraindication checklist.

All subjects were vaccinated with a single dose (0.5 ml) of the PC13 vaccine (Prevenar 13, Pfizer) IM into the upper arm. Total anti-PPV23 antibody levels produced against the various serotypes were measured. Prevaccination anti-PPV23 levels were compared to those 4 weeks and 8 weeks after vaccination. Pneumococcal antibody levels were assessed by a VaccZyme™ Anti-PCP IgG Enzyme Immunoassay Kit. According to recommendations of the American Academy of Allergy, Asthma & Immunology, an at least two-fold increase in antibody level was an indicator of good responsiveness [24]. An Institutional Review Board approval had been obtained before the initiation of the study.

Statistical analysis was performed using the SPSS 20 software. Data are presented as mean values and standard deviation