ORIGINAL ARTICLE

Heptavalent pneumococcal conjugate vaccine elicits similar antibody response as standard 23-valent polysaccharide vaccine in adult patients with RA treated with immunomodulating drugs

Meliha Crnkic Kapetanovic · Carmen Roseman · Göran Jönsson · Lennart Truedsson

Abstract The objectives of the study were to compare antibody response in immunosuppressed patients with rheumatoid arthritis (RA) after vaccination with heptavalent pneumococcal conjugate vaccine (PCV7) to that of RA patients and healthy controls vaccinated with 23-valent polysaccharide vaccine (PPV23) and to study the impact of disease and/or treatment characteristics and type of vaccine on antibody response following pneumococcal vaccination in patients with RA. In total, 253 RA patients treated with methotrexate (MTX), anti-TNF blockers as monotherapy or anti-TNF+MTX were vaccinated with a single dose (0.5 ml) of PCV7. In addition, 149 RA patients receiving corresponding treatments and 47 healthy controls were vaccinated with a single dose (0.5 ml) of PPV23. Serotype-specific IgG to 23F and 6B were measured at vaccination and 4–6 weeks after vaccination using ELISA. Antibody response ratio (ARR), i.e. ratio between post-/prevaccination antibody levels, was compared between corresponding treatment groups. Differences in ARR were analysed using analysis of variance. Positive antibody response (posAR) was defined as equal to or greater than twofold increase in prevaccination antibody levels. Possible predictors of posAR were analysed using logistic regression model. Corresponding RA treatment groups showed similar ARR and posAR for both serotypes regardless of vaccine type. Higher age at vaccination and concomitant MTX were identified as predictors of impaired posAR for both serotypes tested, whereas type of vaccine did not influence posAR significantly. PCV7 elicits similar antibody response as PPV23 in patients with RA receiving immunosuppressive treatment. In RA patients, higher age and MTX treatment but not type of vaccine predicted impaired posAR.

Keywords Antibody response · Pneumococcal vaccination · Rheumatoid arthritis · 7-Valent pneumococcal conjugate vaccine · 23-Valent pneumococcal polysaccharide vaccine

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Introduction

Pneumococcal vaccination using 23-valent polysaccharide vaccine (PPV23) is currently recommended to all individuals age 65 years or older and those receiving immunosuppressive drugs regardless of age [1, 2]. Bacterial infections, including those caused by pneumococci, are major causes of morbidity and mortality in patients with rheumatic diseases. Pneumococcal vaccination should therefore be considered in the majority of patients with inflammatory rheumatic diseases [3, 4]. In Sweden, 23-valent pneumococcal conjugate vaccine (Pneumovax®) is licensed for use in adults. However, clinical trials and meta-analysis of controlled clinical trials studying the efficacy of this unconjugated pneumococcal

polysaccharide vaccine have shown conflicting results. The results from Cochrane meta-analysis of randomised clinical trials support the use of PPV23 for protection against invasive pneumococcal diseases in otherwise healthy adults, but the evidence of effectiveness in patients with chronic disease was less strong [5]. Another recently published meta-analysis of controlled clinical trials found little evidence for the effectiveness of PPV23 in reducing risk of all-cause pneumonia in older, chronically ill patients [6]. Furthermore, the immunogenicity of PPV23 is debated [7, 8]. Primary vaccination with PPV23 in generally healthy individuals has been shown to induce significant increase in antibody levels remaining higher compared with vaccine-naïve persons over a period of 5 years [7]. However, decreased antibody response has been reported in some target groups such as older or immunocompromised individuals [8, 9]. Our group previously studied antibody response following vaccination with PPV23 in patients with rheumatoid arthritis (RA) treated with different anti-inflammatory remedies. Antibody response was significantly reduced in RA patients receiving methotrexate (MTX) compared to those receiving anti-TNF remedies or healthy controls. We also found that less than 50% of patients developed positive immune response defined as a double increase in antibody levels [9]. Since PPV23 contains only free polysaccharide antigens, this vaccination mainly induces T cell-independent antibody response. It has been shown that in children, conjugation of these poorly immunogenic polysaccharide antigens to carrier protein gives rise to B cell stimulation resulting in antibody production or development into memory cells [10, 11]. Heptavalent pneumococcal conjugate vaccine (PCV7) was licensed for use in Sweden in 2009 and is included in the national vaccination programme for children but is not approved for immunization of adults. PCV7 has been shown to reduce not only the incidence of invasive pneumococcal disease by >90% in vaccinated children but also decrease the incidence of these infections in non-vaccinated children and adults due to "herd effect" [11, 12]. Data on potential advantage of PCV7 over the 23-valent polysaccharide vaccine in adults and particularly in patients with inflammatory rheumatic disease are sparse and inconclusive. Recently, our group reported antibody response following pneumococcal vaccination using heptavalent conjugate vaccine in patients with established RA and spondylarthropathy receiving different immunosuppressive treatments [13].

The objective of this study was to compare antibody response after vaccination with PCV7 vaccine among RA patients treated with immunomodulating drugs including MTX and anti-TNF remedies participating in our recent study [13] to that of RA patients receiving corresponding immunosuppressive treatment and healthy controls vaccinated with PPV23 [9]. In addition, we aimed to investigate whether disease or treatment characteristics and type of vaccine had an impact on antibody response following pneumococcal vaccination in patients with established RA.

Patients and methods

In total, 449 individuals participated in the study. Of these, 253 were patients with RA vaccinated with a single dose (0.5 ml) of 7-valent pneumococcal conjugate vaccine (Prevenar® intramuscularly) as previously described [13]. Additional 149 patients with RA and 47 healthy controls received a single dose of PPV23 (0.5 ml Pneumovax® intramuscularly) as previously reported [9]. Both PPV23 and PCV7 vaccinated RA patients were divided to three predefined corresponding treatment groups: RA on MTX alone and in some cases in combination with other disease modifying antirheumatic drugs (DMARDs) (n=122), RA on anti-TNF treatment as monotherapy (n=141) and RA on anti-TNF treatment combined with MTX (n=139). The number of individuals in different treatment groups and for each vaccine separately is shown in Table 1. Ongoing anti-TNF treatments at vaccination were etanercept (n=156), infliximab (n=102) and adalimumab (n=22). Levels of serotype specific IgG against pneumococcal polysaccharide serotypes 23F and 6B were measured at vaccination and 4–6 weeks after vaccination using standard ELISA according to the WHO protocol [14]. Antibody response ratio (ARR) was defined as ratio between post- and prevaccination antibody levels. Differences in immune responses between vaccines were compared for each serotype and between corresponding treatment groups. Positive antibody response (posAR) was defined as at least twofold increase in prevaccination antibody levels.

The ethical approval for this study was obtained from the Ethical Review Board at Lund University (file number 97/2007). Informed written consent was signed by each participant before the vaccination.

Statistical calculations

Differences in disease and treatment characteristics at vaccination between the groups were analysed using the χ^2 test and the Mann–Whitney U test when appropriate. Differences between post- and prevaccination antibody levels were compared using paired samples t test. Univariate analysis of variance (ANOVA) adjusted for age, gender, prevaccination antibody levels for each serotype, concomitant MTX and prednisolone treatment was used to compare ARR between the corresponding treatment groups. The impact of disease and treatment characteristics at vaccination and type of vaccine on posAR for both serotypes was performed using univariate binary logistic

Table 1 Demographics and disease characteristics of patients and controls at vaccination

Vaccine	7-Valent pneumococcal conjugate vaccine (n=253)			23-Valent pneumococcal polysaccharide vaccine (n=196)			Healthy controls (n=47)
Treatment groups	RA on MTX (n=85)	RA on anti-TNF monotherapy (n=79)	RA on anti-TNF+ MTX (n=89)	RA on MTX (n=37)	RA on anti-TNF monotherapy (n=62)	RA on anti-TNF+ MTX (n=50)	
Female (%)	79	87	78	68	76	70	74
Age (years, range)	61.5 (24–85)	59.8 (24–86)*	60.1 (31–81)**	61.3 (21–81)	53.7 (15–85)	52.8 (21–81)	30.3 (19–60)***
Disease duration (years, range)	11.4 (0–40)	20.6 (1–48)	16.2 (1–48)	7.0 (1–47)	20.8 (2–56)	10.8 (2–40)	–
HAQ (mean±SD)	0.7±0.6	1.2±0.7	0.9±0.69	–	–	–	–
Ongoing prednisolone (%)	31	43	28	51	50	52	–
Prednisolone dosage (mg/week)	14	14	8.8	17.5	17.5	6.5	–
DAS28/low/intermediate/high (%)	34/57/9	27/65/8	42/50/8	53/35/12	49/41/10	50/44/6	–
RF positive (%)	56##	61	72	86	61	65	–
Pneumococcal vaccination previously (%)[a]	10.6	16.5	18	–	–	–	–

DAS disease activity score, low DAS <3.2, intermediate DAS between 3.2 and 5.1, high DAS >5.1 using the 3 variables: 28 joint swollen joint count (SJC), 28 joint tender joint count (TJC) and CRP in mg/l where DAS=[sqrt(TJC)×0.56+sqrt(SJC)×0.28+0.36×ln(CRP+1)]×1.1+1.15

*p<0.001 compared to RA on anti-TNF monotherapy vaccinated with 23-valent polysaccharide vaccine; **p<0.001 compared to RA on anti-TNF+MTX vaccinated with 23-valent polysaccharide vaccine; ***p<0.001 compared to all RA treatment groups

##p=0.004 compared to RA on MTX vaccinated with 23-valent polysaccharide vaccine

[a] Previous vaccination using 23-valent pneumococcal polysaccharide vaccine >5 years prior the inclusion in the current study

Table 2 Antibody response ratio following vaccination with 7-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine in patients with establish RA and healthy controls

Vaccine	7-Valent pneumococcal conjugate vaccine ($n=253$)			23-Valent pneumococcal polysaccharide vaccine ($n=196$)			
Treatment groups	RA on MTX ($n=85$)	RA on anti-TNF monotherapy ($n=79$)	RA anti-TNF+ MTX ($n=89$)	RA on MTX ($n=37$)	RA on anti-TNF monotherapy ($n=62$)	RA on anti-TNF+ MTX ($n=50$)	Healthy controls ($n=47$)
Antibody response ratio 6B (median; min–max)	1.4 (0.4–100)	1.8 (0.5–58)	1.3 (0.4–75)	1.6 (0.8–20)	3.4 (0.8–280)	1.8 (0.9–44)	2.2 (0.4–75)
Antibody response ratio 23F (median; min–max)	1.9 (0.7–740)	2.5 (0.7–181)	1.5 (0.5–77)	1.4 (0.3–15)	2.8 (0.9–68)	2.0 (0.7–36)	2.3 (0.2–91)

regression analysis. In order to study the possible predictors of posAR, a multivariate regression model with adjustment for baseline characteristics was created. A p value of <0.05 was considered significant.

Results

There were some differences in demographic and disease characteristics between corresponding treatment groups. At vaccination, RA patients treated with TNF blockers as monotherapy or those treated with TNF blockers+MTX vaccinated with PCV7 were older compared to equivalent treatment groups receiving PPV23. Healthy controls were significantly younger than RA patients regardless of treatment or type of vaccine. Disease and treatment characteristics at vaccination are shown in Table 1.

Both vaccinations resulted in significant increase in antibody levels for both serotypes compared to prevacci-

nation antibody levels in each treatment group (p value between <0.001 and 0.035). ARR (median, range) in different groups and percentage of patients with posAR for each serotype separately and both serotypes are summarized in Table 2. Figures 1 and 2 show box plots of ARR between standard 23-valent polysaccharide vaccine and 7-valent conjugate vaccine. There were no statistical significant differences in ARR between corresponding treatment groups for neither 23F nor 6B serotype (p value between 0.079 and 0.946; ANOVA, adjusted for differences in age, gender and prevaccination antibody levels). No significant differences between corresponding treatment groups were found when posAR was used as outcome measure in the analysis.

The lowest proportion of patients with posAR was found in RA patients treated with MTX alone or MTX combined with anti-TNF drugs for both serotypes regardless of vaccination type (Fig. 3). Other differences in the antibody response as measured here between the two vaccination
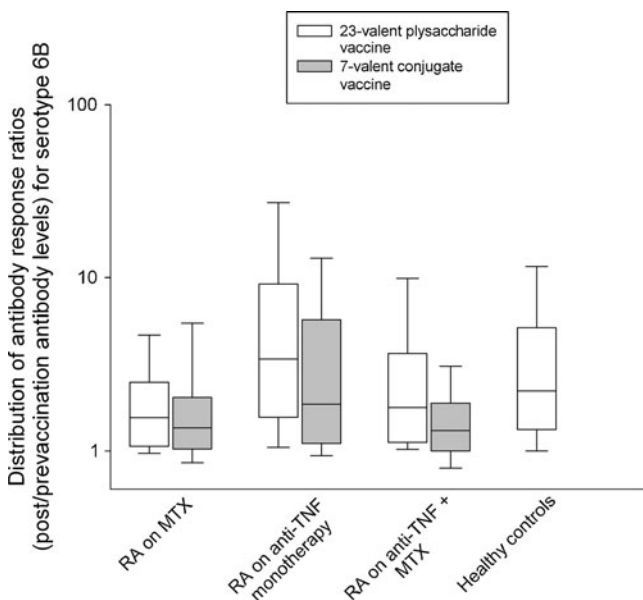

Fig. 1 Antibody response ratio (post/prevaccination antibody levels) following vaccination with 23-valent pneumococcal polysaccharide vaccine and 7-valent pneumococcal conjugate vaccine for serotype 6B in different groups of patients with RA and healthy controls
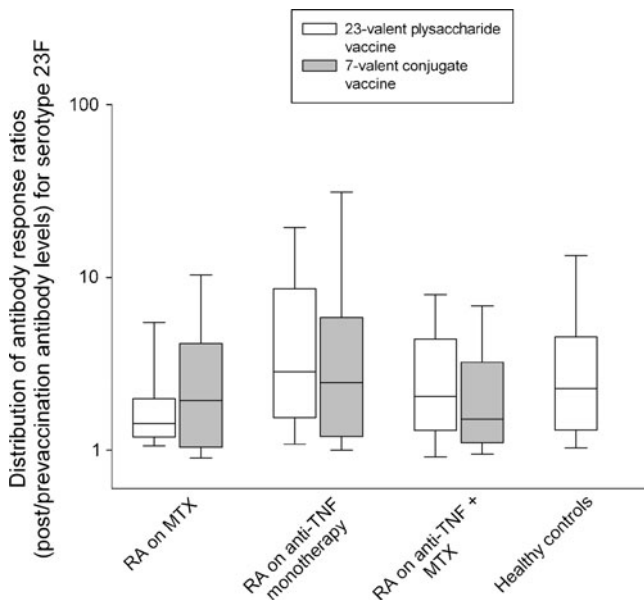

Fig. 2 Antibody response ratio (post/prevaccination antibody levels) following vaccination with 23-valent pneumococcal polysaccharide vaccine and 7-valent pneumococcal conjugate vaccine for serotype 23F in different groups of patients with RA and healthy controls
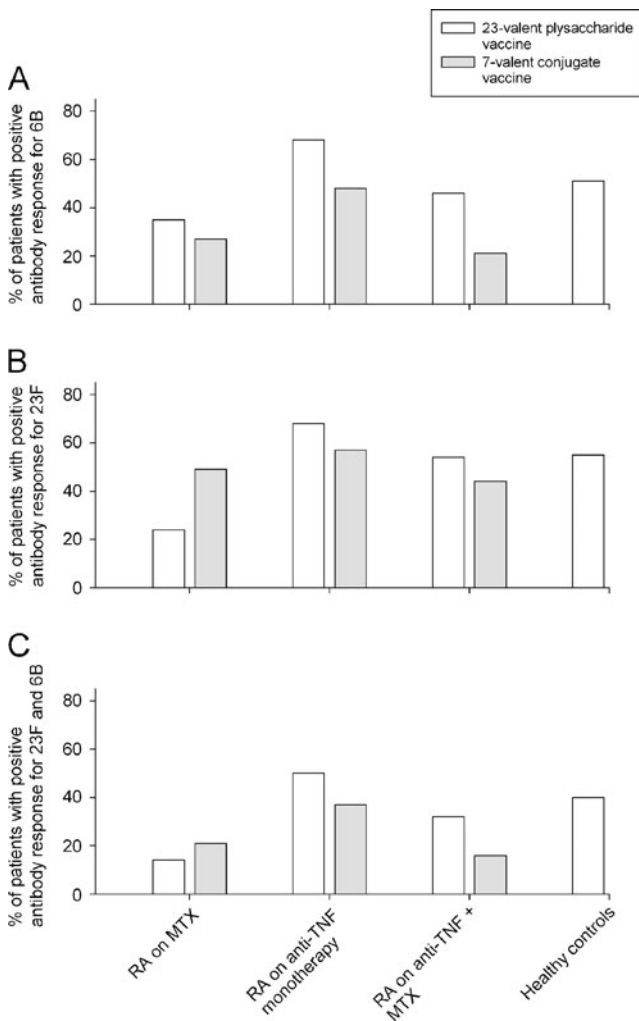
Fig. 3 Proportion (in percent) of patients with positive antibody response (posAR) following vaccination with 23-valent pneumococcal polysaccharide vaccine and 7-valent pneumococcal conjugate vaccine for serotype 6B (**a**), 23F (**b**) and both 23F and 6B (**c**) in different groups of patients with RA and healthy controls

Table 3 Predictors of positive antibody response for both 6B and 23F among RA patients

	p value	OR	95% CI	
			Lower	Upper
Age (years)	0.008	0.974	0.955	0.993
Disease duration (years)	0.873	0.998	0.975	1.022
Sex (male/female)	0.245	1.396	0.795	2.453
Heptavalent pneumococcal conjugate vaccine vs 23-valent polysaccharide vaccine (1/0)	0.977	1.007	0.607	1.673
Ongoing methotrexate (yes/no)	0.000	0.361	0.206	0.633
Ongoing anti-TNF treatment (yes/no)	0.811	1.081	0.570	2.050
Ongoing prednisolone orally (yes/no)	0.018	1.807	1.107	2.949
Prevaccination antibody levels for 23F (mg/l)	0.062	0.784	0.608	1.012
Prevaccination antibody levels for 6B (mg/l)	0.185	0.942	0.861	1.029

types were small and not statistically significant for any treatment group.

Possible predictors of posAR for both serotypes among all RA patients regardless of vaccine type were analysed using logistic regression model. In total, 402 RA of 449 vaccinated individuals were included in the analysis. Using univariate regression model, higher age ($p=0.030$) and ongoing MTX treatment ($p<0.001$) predicted impaired posAR for both serotypes whereas concomitant prednisolone ($p=0.002$) and anti-TNF treatment ($p=0.006$) predicted better posAR. Disease duration ($p=0.250$), gender ($p=0.651$) and RF status ($p=0.887$) did not predict significantly posAR for any of the serotypes tested. After adjustment for demographics and baseline disease characteristics and antibody levels for both 23F and 6B in multivariate logistic regression model, higher age and MTX treatment remained predictors of impaired antibody response (Table 3). As shown in the table, patients

with ongoing MTX treatment had only 36% chance to achieve positive antibody response compared to those not receiving MTX. Concomitant prednisolone treatment was a predictor of better posAR, while vaccine type (PCV7 compared to PPV23) and ongoing anti-TNF treatment had no significant impact on posAR for any of the serotypes.

Discussion

The present study reports of a comparison between immunogenicity of 7-valent pneumococcal conjugate vaccine and standard 23-valent pneumococcal polysaccharide vaccine in patients with RA treated with immunosuppressive drugs. The main finding in the study is that PCV7 and PPV23 elicits similar antibody response for two serotypes common for both vaccines (6B and 23F) among RA patients treated with MTX, anti-TNF drugs as monotherapy or combination of these remedies as corresponding treatment groups of RA patients vaccinated with PPV23.

The conjugation of polysaccharides antigens to a polypeptide is shown to elicit immune response and vaccination results in better protection against vaccine serotypes that caused invasive pneumococcal disease in children [10, 11, 15–17] but does not seem to induce stronger antibody response in adult patients [18, 19].

Our findings with similar antibody response in treatment stratified RA patients are in accordance with previously reported studies including elderly patients [18, 19]. In contrast, de Roux et al. demonstrated higher antibody levels following the initial dose of PCV7 compared to PPV23-vaccinated elderly vaccine-naïve adults not exposed to immunosuppressive drugs [20]. Superior antibody response to PVC7 versus

PPV23 was shown in patients with chronic obstructive pulmonary disease [21]. The vaccinated subjects were treated with glucocorticoids and no other immunosuppressive remedies which could be one possible explanation for these diverging results.

In the present study, we found that the proportion of patients with posAR for both serotypes was lowest in MTX-treated patients for both vaccines (21% and 14%, respectively). Maximal posAR for both serotypes tested (approximately 50% of patients) was found in RA patients on anti-TNF treatment as monotherapy. This is in line with previously reported experimental data showing that exposition to anti-TNF antibodies reverse the T cell activation caused by chronic exposition to TNF in RA [22]. Our analyses including all RA patients did not identify vaccine type or anti-TNF treatment as significant predictors of immune response, while MTX treatment and higher age remained predictors of impaired response for both serotypes also after adjustment for differences in demographic and disease characteristics at vaccination. The underlying mechanisms by which MTX influences antibody response may include both increased T cell apoptosis and impact on humoral response [23].

The association between higher age and diminished immune response previously also reported by others [18, 19] could at least in part be explained by age-related immune disturbance affecting both the innate and adaptive immune systems including decreased ability of B cells to produce antibodies [24].

Unexpectedly, concomitant treatment with glucocorticoids elicited superior antibody response after pneumococcal vaccination using conjugate vaccine but had no significant impact on antibody response to polysaccharide vaccine. The reasons for these diverging effects of steroids are not known. An improved antibody response to pneumococcal polysaccharide vaccine in RA patients receiving oral glucocorticoids has previously been observed [25].

There are some limitations to this study. RA patients not taking immunosuppressive drugs were not included in the study and therefore the influence of immunological disturbance as part of the RA disease on antibody response was not possible to investigate. The number of patients with RA not treated with DMARDs at our department is limited which precluded inclusion of such patients in the study. Since PCV7 vaccine is not approved for use in adults in Sweden, recruitment of population-based healthy controls would pose ethical, logistic and administrative problems.

We were not able to study the influence of previous pneumococcal vaccination on antibody response since these data were not collected at vaccination using PPV23. However, pneumococcal vaccination within the previous 5 years was one of the exclusion criteria for both vaccinations. Previous pneumococcal vaccination >5 years prior to vaccination with PCV7 had no significant impact on antibody response [13].

We measured antibody response to only two serotypes (23F and 6B). The reason for choosing these serotypes is that they are commonly associated with invasive pneumoccocal diseases in northern Europe [26]. Overall, we believe that immune response to these serotypes represents the pattern expected for all serotypes regarding the impact of disease and treatment, but individual serotypes may have variable immunogenicity. It must be remembered that antibody response is a surrogate measure of vaccine effectiveness, and a study of the true prevalence of invasive pneumococcal diseases following these vaccinations is needed.

Results from this study contribute to the knowledge about immunogenicity of currently available pneumococcal vaccines in this group of immunosuppressed patients with RA. Although individual serotypes might be more immunogenic and elicit better antibody response, in general, PCV7 does not appear to have convincing advantage over currently available PPV23 in this high-risk group of RA patients.

Key messages

Heptavalent conjugate pneumococcal vaccine elicits similar antibody response as polysaccharide vaccine in immunosuppressed RA patients. In RA, higher age and MTX treatment but not type of vaccine predicted impaired antibody response.

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