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Mini Review

Thoughts on Pneumococcal Vaccination for the Adult Individuals with Autoimmune Diseases

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Abstract: *Streptococcus pneumoniae* is an important pathogenic bacteria causing pneumonia and invasive pneumococcal diseases, and the vaccination for pneumococcal vaccination is recommended in patients with RA and other autoimmune disorders. Compared with the immunocompetent individuals, frequency and the mortality rate were higher in the RA patients. The effect of pneumococcal vaccination may not be weakened in people using corticosteroid and biological disease-modifying anti-rheumatic drug (DMARD) currently being used, but mild to relatively inhibition of immunogenicity was suggested in patients using either methotrexate or rituximab. Administration of 13-valent pneumococcal conjugate vaccine (PCV13), rather than 23-valent Pneumococcal polysaccharide vaccine (PPSV23) may be desirable in preventing pneumonia in people with autoimmune disease and sequential administration of PCV13 in people aged ≤64 years and PPSV23 from age ≥65 years may be useful for preventing pneumonia in people with autoimmune disease according to the insurance system. In addition, PCV15 and PCV 20 will be available soon and expected for more clinical efficiency rather than current PCV13 and PPSV23.

Keywords: Biological disease-modifying anti-rheumatic drug (DMARD), Invasive pneumococcal disease (IPD), Rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE), *Streptcoccus pneumoniae*, pneumococcal conjugate vaccine (PCV), Pneumococcal polysaccharide vaccine (PPSV)

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1. Introduction

With rheumatoid arthritis (RA), for example, pneumococcus is an important pathogenic bacteria causing pneumonia and has the highest detection rate, similar to that in the average person [1]. There are not thought to be major differences in pathogenic bacteria between RA patients and non-RA patients. The possibility has been suggested that only *Pseudomonas aeruginosa* is involved in the development of pneumonia in RA patients at a slightly higher rate, perhaps because it becomes established more easily in the presence of bronchiectasis, which is common in RA patients [2]. Therefore, with pneumococcal infection in mind, taking steps to deal with pneumonia first is recommended in patients with RA and other autoimmune disorders. Prospective, active, population-based pneumococcus pneumonia surveillance study of adults in Japan revealed health-related quality of life (HRQoL) scores had not returned to prediagnosis levels at 1 year postdiagnosis, and cumulative losses of HRQoL scores were comparable to those in US adults with chronic heart failure, stroke, or renal failure [3].

In this review, we are going to show the thoughts on pneumococcal vaccination for the individuals with autoimmune diseases, especially focused on under 65 years of age and adults [4].

2. Review

We have done a systematic review of the literature those indexed in databases such as MEDLINE, Embase, Cinahl, SocIndex, Scopus, or Web of Science according tto the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline[5]. The key words, including autoimmune diseases, rheumatoid arthritis, *Streptococcus pneumoniae,* and pneumococcal vaccines were selected, and assessed the evidence on the efficacy/effectiveness of pneumococcal vaccines against clinical endpoints in the adult patients with autoimmune diseases, including RA.

2.1. Incidence of pneumococcal infection in the adult autoimmune disease patients

RA patients are known to have a higher incidence of pneumonia than the average persons, nearly two times higher (range 1.25–1.9 times higher)[1, 4, 6]. In one investigation of 149 RA patients in Japan, the breakdown of respiratory tract infections was reported to be pneumonia in 46 people (30.9%), lung abscess in 9 (6.0%), bronchiectasis exacerbation in 7 (4.7%), and empyema in 4 (2.7%), plus other mycoses and mycobacteriosis[7]. Serious infections have also been suggested to increase with the administration of TNF-α inhibitors[1]. Recent systemic literature review informing the 2019 update of the European Alliance of Associations for Rheumatology (EULAR) recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases (AIIRD) revealed that an increased incidence of influenza and pneumococcal disease was reported in patients with AIIRD versus general population[8]. Patients with SLE, including young patients, are particularly at increased risk for pneumococcal disease, with a more complicated course[9].

In Japan, the rate of pneumonia in RA patients who do not receive biological disease-modifying anti-rheumatic drug (DMARD) is 12.1%, but it increases to 21.1% in those who do receive DMARD[10, 11]. Compared with the general population, the standardized mortality ratio is 4.19. Thus, the administration of DMARD may not only increases the frequency of pneumonia, but it may also be a significant cause of death. Administration of the JAK kinase inhibitor tofacitinib, however, increases the frequency of herpes zoster, but there is not thought to be any difference in the risk of pneumococcal and other infections compared with patients who do not receive tofacitinib[12].

Risk factors for lung infections in RA patients include advanced age, lung comorbidities, concurrent use of corticosteroids, and Steinbrocker classification Stage III or higher[1]. In patients who use biological preparations, the risk factors with infliximab are male sex, advanced age, Steinbrocker classification Stage III or higher, and pre-existing disease. With etanercept, they are male sex, advanced age, pre-existing disease, concurrent non-serious infection, and concurrent corticosteroid use. With adalimumab, they are age ≥65 years/pre-existing disease and Steinbrocker classification Stage III or higher. Risk factors for serious respiratory tract infections with tocilizumab are male sex, weight <40 kg, disease duration ≥10 years, and pre-existing disease.

In an analysis of the clinical picture of 897 adults with invasive pneumococcal disease (IPD), it was reported that the median age was 71 years, males accounted for 61% of patients, and people aged ≥65 years accounted for 69%[13]. Comorbidities were seen in 75%, and immunodeficiency was seen in 31% of all patients. Looking at the type of IPD, pneumonia associated with bacteremia (pneumonia) was the most common, at 60%, cerebral meningitis was seen in 15%, and bacteremia without focal symptoms was seen in 16%. Other types (arthritis associated with bacteremia, phlegmon, spondylitis, empyema and endocarditis) were seen in 8%. In these IPD patients, 11% had a history of PPSV23 vaccination within the past five years, and 19% had died as of the time of the report. Ultimately, 202 (72%) of the 281 patients who were the subjects of the analysis had comorbidities, including 33 (12%) with autoimmune disease and 26 (9%) who used corticosteroids, totaling 59 patients (21%). It is possible that approximately more than 20% of IPD cases are patients with autoimmune disorders or related diseases.

2.2. Immunogenicity of pneumococcal vaccines

In autoimmune disease patients, although immunogenicity is slightly decreased in RA patients receiving biological preparations and methotrexate (MTX), it has been confirmed that much of the rise in the antibody titer with pneumococcal vaccines is normal.

The immunogenicity of 23-valent Pneumococcal polysaccharide vaccine (PPSV23) has been investigated with and without the concurrent use of TNF-α inhibitors (infliximab, etanercept) and MTX[14]. Elevated antibody titers were seen in all groups, but the rise in antibody titer was reported to be higher in the TNF-α inhibitors only group than in the MTX only group and the combined MTX + TNF-α inhibitors group. This was nearly the same in patients using tacrolimus. The elevations in antibody titer and opsonin activity were not inhibited in patients using tacrolimus only, but antibody production and opsonin activity in the MTX group and the MTX + tacrolimus group tended to be weaker than in patients using tacrolimus alone[15]. With the IL-6 receptor antibody tocilizumab, the elevated antibody titer is thought to be unaffected by PPSV23 vaccination[16].

For conjugate vaccines, with 7-valent pneumococcal conjugate vaccine (PCV7), there was, not surprisingly, no effect on the rise in antibody titer in the TNF-α inhibitors only group compared with the control group (NSAID use), but a decrease was seen in the antibody titer in the MTX only group and the MTX + TNF-α inhibitors group[17]. With tocilizumab, elevation of the antibody titer is not inhibited, but the antibody titer elevation is known to be clearly suppressed in RA patients who have received B cell depletion therapy with rituximab. In patients scheduled to use rituximab, it is thought to be better to perform pneumococcal vaccination prior to the start of therapy[18].

With 13-valent pneumococcal conjugate vaccine (PCV13), a phase 3, multicenter, single-arm, open-label study in Japanese participants aged 6-64 years who are considered to be at increased risk of pneumococcal disease, including autoimmune diseases revealed that circulating antibody levels for all 13 serotypes , opsonophagocytic activity (OPA) and anticapsular immunoglobulin G (IgG) geometric mean concentrations (GMCs) were increased postvaccination[19]. Furthermore, antibody titer elevation and opsonin activity are well induced in patients using the JAK inhibitor baricitinib, and there was not thought to be any effect depending on whether corticosteroids were also used with PCV13[20].

2.3. Prophylactic effect of vaccines

With PPSV, it was reported from a meta-analysis of randomized, controlled trials (RCTs) in a Cochrane review that (1) IPD, one of the primary outcomes, was inhibited by 74%[21]. In contrast, among (2) all pneumonia and (3) pneumococcal infections, a significant prophylactic effect was seen in all aggregate results for the inhibition of the non-invasive type of pneumococcal pneumonia that is seen with the highest frequency. However, there was a high level of heterogeneity between the individual studies, suggesting that this should perhaps be viewed with some skepticism. Another RCT of PPSV23 was conducted in 1,323 people infected with human immunodeficiency virus (HIV), and efficacy against pneumococcal infections in these immunocompromised patients was not shown[22]. In an RCT conducted with 900 RA patients in Japan, PPSV23 was not shown to be effective in inhibiting pneumonia[23]. In RA, as mentioned above, bronchiectasis findings and interstitial pneumonia already exist at a high rate, suggesting that a clinical prophylactic effect from pneumococcus vaccination may be less likely in lung infections.

With PCV, a large-scale RCT of PCV13 in 84,496 health elderly people in the Netherlands confirmed that it effectively inhibited pneumonia in adults[24], and in an RCT with PCV7 in 496 people, PCV was reported to have a significant prophylactic effect in immunocompromised patients, although this was in HIV patients[25]. The same group reported an RCT with PPSV and PCV in HIV patients, and with pneumonia in mind,

PCV13 inoculation may be preferable in immune-deficient patients, especially encapsulated types of pneumococcal infection covered by the vaccine.

Looking at sequential administration in which PCV13 is administered first, subsequent PPSV23 inoculation in people aged ≥65 years has been accepted in the insurance system based on the publicly funded schedule for vaccination in the world, including Japan. This schedule has been expected the clinical effectiveness in people aged ≤64 years, especially those with autoimmune diseases such as RA. In the insurance system of the many countries, elderly persons were defined as 65 years and older, therefore, protection by the pneumococcal vaccination for immunocompromised patients of under 65 years started be recommended in Japan, too. However, when PPSV23 is administered first, attenuation of the B-cell-mediated response from subsequent inoculation with PCV13 has long been reported to be a risk[26]. Meanwhile, good elevations of antibody titers and opsonin activity were seen in an analysis of 24 RA patients first administered PCV13 and then PPSV23, but the effect was no longer seen beyond 24 months[27]. In the Korean younger subgroup (aged 65-74 years), sequential PCV13/PPSV23 vaccination showed the highest adjusted vaccine effectiveness (VE) of 80.3%, followed by single-dose PCV13 (adjusted VE, 66.4%) and PPSV23 (adjusted VE, 18.5%)[28]. In contrast, sequential PCV13 and PPSV23 achieved protective status for approximately two thirds of pediatric lupus patients[29], and 11 of 21 (52.4%) patients had no long-term protection with a seroconversion that never or only transiently occurred SLE patients received the sequential PCV13/PPSV23[30]. Cost-effectiveness of a sequential pneumococcal vaccination for adults were reported from Hong Kong, compared to single-dose vaccination strategy[31]. Further detailed examinations of the inoculation sequence or inoculation interval will probably be needed.

2.4. Pneumococcal vaccine efficacy/effectiveness and the next generation PCV15 and PCV20.

As we mentioned above, routine vaccination of elderly people against pneumococcal diseases is recommended in many countries, but national guidelines differ, recommending either the PPSV23, PCV13 or both. Falkenhorst G et al. performed the meta-analysis and it revealed significant vaccine effect of PPV23 against both IPD and pneumococcal pneumonia by any serotype in the elderly, comparable to the efficacy of PCV13 against vaccine-serotype disease in a recent clinical trial in elderly people[32]. Due to its broader serotype coverage and the decrease of PCV13 serotypes among adults resulting from routine infant immunization with PCV13, PPV23 continues to play an important role for protecting adults against IPD and pneumococcal pneumonia.

Furthermore, in January 2022, recommendations were made for the next generation PCV15 and PCV20[33]. Both of these vaccines were licensed by the Food and Drug Administration for adults aged ≥18 years, and antibody responses to two additional serotypes included in PCV15 were compared to corresponding responses after PCV13 vaccination, and antibody responses to seven additional serotypes included in PCV20 were compared with those to the PPSV23. PCV20 was well tolerated in adults 60 to 64 years of age, with a safety profile consistent with historical experience of PCVs in this age group, and substantial OPA responses were elicited against all serotypes[34].

On October 20, 2021, the Advisory Committee on Immunization Practices (ACIP) recommended use of either PCV20 alone or PCV15 in series with PPSV23 for all adults aged ≥65 years, and for adults aged 19-64 years with certain underlying medical conditions or other risk factors, including immunocompromising persons who have not previously received a PCV or whose previous vaccination history is unknown[35].

Although the some data showed the immunological and clinical safety of PCV15 and PCV20[36, 37], administration of PCV15 followed by PPSV23 was well tolerated and induced comparable antibody levels to PCV13 followed by PPSV23 in healthy adults aged ≥50 years[38]. More significant study results by PCV15 and PCV20 in both basic and

clinical fields will be expected especially for the prevention of pneumococcal diseases in these patients.

3. Conclusions

In conclusion, we found the frequency of pneumococcal infection in autoimmune diseases patients may be about two times that of the average person with pneumonia, and the mortality rate about four times higher than the immunocompetent persons. About 20% of IPD patients may have autoimmune disorders. For DMARD currently being used, the effect of pneumococcal vaccination may not be weakened in people using TNF-α inhibitors, IL-6 inhibitors, corticosteroids, or tacrolimus, but mild to relatively obvious inhibition of immunogenicity was suggested in people using either MTX or rituximab. There is slight skepticism about the effect of PPSV23 in preventing pneumonia in people with autoimmune disease, and administration of PSV13 may be desirable. There is a possibility that sequential administration with PCV13 in people aged ≤64 years and PPSV23 from age ≥65 years, similar to the cases <65 years may be potent from the perspective of inhibiting pneumonia in people with autoimmune disease, and the next generation PCV15 and PCV20 will be hopeful to prevent to IPD and pneumococcal pneumonia especially in the patients with autoimmune diseases, including RA. Careful and continuous investigation will be needed in the future.

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