

Pneumococcal Vaccination in Rheumatic Diseases

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Introduction

The burden of rheumatic diseases in India is staggering. The prevalence of rheumatoid arthritis (RA) alone is 0.2-0.75%, translating into an adult patient population of 2.37-4.66 million patients with RA in India.¹ Based on global scenario, a similar or higher prevalence rate is expected for all spondyloarthropathies put together, Primary Sjogren's syndrome and all the remaining connective tissue diseases including lupus as a combined group. Patients with rheumatic diseases are also more prone to infections including pneumonia. The near universal use of immunomodulators, immunosuppressants and corticosteroids compounds this problem. Immunisation in patients with rheumatic diseases has emerged as a topic of contemporary interest which is rapidly evolving in the light of new knowledge and information explosion. *Streptococcus pneumoniae* being the most common cause of community-acquired pneumonia, pneumococcal vaccination assumes importance in patients with rheumatic diseases. While, number of vaccines are available, only a handful are relevant to patients with rheumatic diseases.² This write up outlines the current thinking about pneumococcal vaccination in rheumatic diseases.

Rationale for Vaccination: Infection Risk in Rheumatoid Arthritis

Patients with Rheumatoid arthritis (RA) have increased susceptibility to infectious diseases and related morbidity and mortality. RA may have up to twice the risk of acquiring a severe infection than the general population with

1.5- to 2-fold higher risk of being hospitalized for infection. Even the risk of death from infective complications is greater in RA as compared to patients with non-RA ailments of similar age.³ While autoimmunity itself can impart this risk, immune-modulatory / immunosuppressive therapy used in RA is additional contributory factors. The respiratory tract, joints, bone, skin and soft tissue are sites that are frequently involved in infectious processes in patients with RA.^{4,5} Apart from dose-dependent increase in infection with long-term prednisone use in irrational, high dosage and formulations, some studies suggest increased risk even at a dose as low as 5 mg/day.⁶ The addition of biologics to DMARDs may also amplify the immunosuppressive effects of traditional DMARDs. Moreover, lymphopenia as a result of RA treatment is postulated to be another risk factor for infection.⁷

Infectious complications in patients with Rheumatic Diseases

Apart from RA, the risk of infectious complications in patients suffering from several other autoimmune rheumatic diseases (ARD), namely systemic lupus erythematosus (SLE) and vasculitides is also twice as common as the healthy population.⁵ In one study, the incidence of pneumonia was 17 per 1,000 patient-years (95% CI 16.4–19.1) for all patients, 19.2 per 1,000 patient-years for men

(95% CI 16.3–22.5), and 17.3 per 1,000 patient-years for women (95% CI 15.8–18.9) with RA.⁸ With every 10-year increase in age, there was a 30% increase in pneumonia risk. As mentioned earlier, infections is also a major contributor of mortality in RA. In lupus, infections can account for as many as 25% of deaths with *Streptococcus pneumoniae* and *Haemophilus influenzae* as the major pathogens.^{9,10} With more aggressive line of current management including the use of biologics in patients with ARD, this trend may move upwards, especially in developing nations like India. Widely prevalent co-morbidities like chronic obstructive airways disease and diabetes mellitus, and occasional renal transplantations amongst ARD patients with end stage renal disease increase the risks further by manyfolds. The role of preventive vaccination is, thus, clinically pertinent in patients with ARD.

Safety and Immunogenicity of Pneumococcal vaccines in patients with Rheumatic Diseases

There have been concerns about the safety of vaccines in patients with ARD in the past. However, several studies have confirmed the safety of pneumococcal vaccination in RA and SLE.¹¹⁻¹³ Vaccination was not associated with an appreciable deterioration in any clinical, laboratory or immunologic measures of disease activity. According to a study,

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beneficial immune response to the vaccine was either not elicited at all or it was only against 1 of the 7 polysaccharides in as many as 33.3% of patients with RA and 20.8% of patients with SLE, thereby suggesting that a subset of patients may remain unprotected by the polysaccharide vaccine.¹¹ Age, sex, duration of disease, measures of disease activity, and the use of other immunosuppressive agents including corticosteroids, azathioprine, sulfasalazine, and antimalarial agents, were not significant determinants of antibody response in this study. Vaccination should, however, be avoided during periods of active disease and live virus vaccines are contraindicated for immunosuppressed patients.¹⁴

Data on the effect of biologic DMARDs is beginning to emerge. A recent study investigated the impact of rituximab, abatacept and tocilizumab on antibody response following pneumococcal vaccination using a 7-valent conjugate vaccine in 88 patients with established RA.¹⁵ Specific IgG antibodies against 23F and 6B serotypes were measured at vaccination and 4 to 6 weeks after vaccination using standardised ELISA. In total, 10.3% of patients on rituximab monotherapy and no patient on rituximab plus methotrexate combination had positive antibody response for both the serotypes. For abatacept and tocilizumab, the corresponding figures were 17.6% and 50% respectively, suggesting that treatment with rituximab and abatacept was associated with more pronounced blunting of beneficial antibody response. Does it mean that pneumococcal conjugate vaccine may be given even during ongoing tocilizumab therapy without losing sufficiently protective antibody response, while it should be administered at least 2 weeks prior to initiation of rituximab or abatacept therapy to allow the protective vaccine

response to establish itself before these biologics abort the immune response?¹⁵ According to the authors of this write up, therefore, a safer option is to adopt a policy of vaccinating 2 weeks prior to all biologics therapy for the maximum protection against pneumococcal infections, as it takes that much period for eliciting any meaningful and longlasting antibody response. Once this is achieved, biologics don't usually dampen the immune response, as memory B cells and more mature antibody producing cells are not affected by the biologics including Rituximab.

Recommendations for Pneumococcal vaccination in patients with Rheumatic Diseases

Pneumococcal vaccination in patients with rheumatic diseases has been recommended by various scientific societies including the American College of Rheumatology (ACR),¹⁶ European League Against Rheumatism (EULAR),¹⁷ and the Canadian Rheumatology Association¹⁸ among others. The Indian Rheumatology Association Consensus Statement proposed way back in 2008 has not addressed the issue of vaccination in RA.¹⁹ While almost all guidelines endorse the use of pneumococcal and influenza vaccines in rheumatic diseases, there is considerable difference of opinion regarding the type of pneumococcal vaccine to be used, namely pneumococcal conjugate vaccine (PCV13) or pneumococcal polysaccharide vaccine (PPV23).²⁰

The polysaccharide vaccine (PPSV-23) has been used in adults to provide protection against 23 serotypes of *S. pneumoniae*, while, the protein conjugate vaccines PCV-13 is the standard of care choice in children. Conjugate vaccines typically provide more robust immune responses than do polysaccharide vaccines. Accordingly, more recently, PCV13 has been recommended by the Advisory Committee on Immunization Practices (ACIP) for use in adults aged 65 years

and older.²¹ To date, however, there is a lack of data evaluating PCV-13 responses in patients on immunomodulatory drugs, and it is not yet clear if the conjugate vaccine provides a better response or protection.

The pneumococcal vaccine (PPSV-23) is recommended in immunosuppressed patients and should be repeated 5 years after the first vaccination. After this time point, the rationale for giving additional vaccinations is unclear, as diminished immune responses have been documented with additional vaccinations in some patients, for reasons that are unclear.²² Recent data suggest that more robust responses to the PPSV-23 vaccine might be observed if the vaccine is given after an initial vaccination with PCV-13.²³ This data forms the basis for the recent ACIP recommendations for pneumococcal vaccination in immunosuppressed adult populations.²⁵ These recommendations are relatively new, based upon limited data that did not include RA patients or patients on immunomodulatory drugs.

At present it is not clear if and when revaccination should take place.¹⁷ For patients commencing treatment with biologics, vaccination status should be assessed in all patients.¹⁰ Vaccination should be administered at least 2 weeks prior to therapy with Rituximab, anti-TNF agents, tocilizumab and abatacept. Influenza and pneumococcal vaccines have been strongly recommended in patients being planned to be put on biologics.¹⁰

Conclusions

Vaccination in rheumatic diseases is underutilized. Due to several gaps in the existing knowledge, consensus on the optimum vaccination strategy is not available. Conventional DMARDs such as methotrexate

do not seem to adversely impact vaccination efficacy. The available body of literature suggests that pneumococcal vaccination is safe and effective in patients with autoimmune rheumatic diseases.

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