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COMMENTARY

Immunogenicity of pneumococcal vaccines in comorbid autoimmune and chronic respiratory diseases

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ABSTRACT

Streptococcus pneumoniae causes pneumonia, meningitis, otitis media, and bacteremia. The mortality and morbidity of invasive pneumococcal disease are high among adults aged >65 years or those with underlying chronic or immunosuppressive conditions. A recent systematic review showed that patients treated with immunosuppressive agents have impaired immune responses to pneumococcal conjugate vaccine (PCV) and pneumococcal polysaccharide vaccine compared with healthy subjects. A more favorable response is observed in patients treated with tumor necrosis factor-alpha-blocking agents compared with those treated with other immunosuppressive agents. Low systemic corticosteroid doses do not affect the responses to pneumococcal vaccines. Patients with human immunodeficiency virus and idiopathic pulmonary fibrosis receiving immunosuppressive therapy exhibit decreased immunogenicity to pneumococcal vaccines. The effects of T-cell-dependent PCV possibly depend on host memory B cells in some disease conditions. Several immunosuppressive therapy types and disease conditions may affect the responses to pneumococcal vaccines. Immunization should be administered before immunosuppressive medication initiation whenever possible.

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Introduction

Streptococcus pneumoniae infection is responsible for substantial mortality and morbidity among adults aged >65 years or those with underlying chronic or immunosuppressive conditions. In case of invasive pneumococcal disease (IPD), mortality rates range from 5% to 35%.[1] Patients with impaired immune responses are at a higher risk of IPD.[2]

The Centers for Disease Control and Prevention Advisory Committee on Immunization Practices recommend routine use of 23-valent pneumococcal polysaccharide vaccine (PPSV) and 13-valent pneumococcal conjugate vaccine (PCV) for invasive pneumococcal disease prevention in at-risk populations.[3] The guidelines also recommend the vaccination schedule of PCV, followed by administration of PPSV 2 months later. This vaccination schedule is based on the background that PCV is more immunogenic than PPSV because of its conjugation to the diphtheria toxoid CRM197, which evokes a robust T-cell-dependent immune response.

Although pneumococcal pneumonia-related mortality or a pneumococcal pneumonia event are the desirable primary end-points in clinical trials to evaluate the efficacy of vaccines, gathering large sample sizes with respect to costs and efforts is not feasible.[4] Therefore, surrogate markers are considered more realistic; however, the time point of antibody-level measurement after vaccination also remains controversial. In clinical trials of pneumococcal vaccines, serotype-specific immunoglobulin G and opsonophagocytic killing assay (OPA) are usually used as surrogate markers.

Immunosuppressive agents that influence the immunogenicity of PCV/PPSV

Pneumococcal vaccination has reduced the IPD risk in immunocompetent individuals.[5] Although some researchers suggest beneficial effects of PPSV in terms of post-vaccination immunogenicity in immunocompromised patients, their responses are weaker compared with those of the healthy individuals.[6] Immunocompromising conditions consist of different subgroups depending on the underlying immunologic deficits. A major subgroup comprises patients treated with immunosuppressive agents, which are most frequently used to treat autoimmune diseases.

A recent systematic review has shown that patients treated with immunosuppressive agents have impaired immune responses to PCV and PPSV compared with controls.[7] The responses observed in patients treated with tumor necrosis factor (TNF)-alpha-blocking agents are more favorable compared with those observed in patients treated with other immunosuppressive agents, such as methotrexate and rituximab. In children, rituximab or methotrexate treatment was predictive of an impaired antibody response to PCV; however, TNF-alpha-blocking agents, mycophenolate mofetil and cyclosporine A, did not affect the antibody responses.[8–10] Systemic corticosteroids also induce immunosuppression.[11] Low doses of systemic corticosteroid do not affect pneumococcal vaccine responses.[7,12,13] High doses of corticosteroids (>10 mg/day) may affect the immunogenicity of pneumococcal vaccines; however, no reliable systematic review has confirmed their effects in those undergoing a high-dose corticosteroid therapy .[7,11]

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Immunogenicity of co-morbid autoimmune and respiratory diseases

Many guidelines recommend pneumococcal vaccination in asplenic patients, cancer patients, human immunodeficiency virus (HIV) patients, inflammatory bowel diseases (IBD) patients, psoriasis patients, primary immunocompromised patients, and inflammatory rheumatic disease patients as well as in hematopoietic stem cell transplant recipients and solid organ transplant recipients.[14] Some general differences in vaccination responses are noted between rheumatologic conditions and IBD, which tend to utilize similar therapeutic classes.[15–17] Most studies on subjects with rheumatic diseases have shown a relatively normal vaccination response among those treated with immunosuppressive therapies. In contrast, studies on subjects with IBD have suggested impaired vaccination responses among those treated with immunosuppressive therapies. This discrepancy may be explained by the higher doses of immunosuppressants used in IBD because of rheumatic diseases. In patients with rheumatoid arthritis, the vaccination response is not influenced by the administration of corticosteroids, but is reduced by administration of methotrexate.[18] On the contrary, patients with systemic lupus erythematous have impaired vaccination responses not influenced by corticosteroid therapy.[19]

Respiratory diseases are a risk factor of pneumococcal diseases.[20] Immunization with pneumococcal vaccine has been recommended for patients with chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD).[21] However, systemic corticosteroids do not influence the vaccination response in patients with steroid-dependent asthma and COPD.[21–23]

Patients with interstitial lung disease, such as interstitial pneumonia associated to collagen vascular diseases, have shown normal pneumococcal vaccination responses.[12] However, the vaccination responses of patients with idiopathic pulmonary fibrosis (IPF) receiving immunosuppressive therapy are low. In the 2015 clinical practice guidelines of the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association, IPF treatment with corticosteroid and immunosuppressive agents is not recommended. This is different from the previous (2011) guidelines, where progressively worsened or acute exacerbation of IPF was reported to be treated with steroids.[24] Recent studies on acute exacerbation of IPF have shown that immunosuppressive therapy influences survival.[25] Furthermore, the occurrence of interstitial lung diseases has been associated with pneumonia in patients with rheumatoid arthritis.[26] Clinicians should be aware of the decreased immunogenicity of pneumococcal vaccines against patients with IPF undergoing corticosteroid and immunosuppressive therapy.

The difference between PCV and PPSV on at risk patients

PCV is thought to provoke a more robust immune response than PPSV because of its conjugation to the diphtheria toxoid; however, short-term immune responses to PCV are inferior to those to PPSV in immunosuppressive patients.[7,12] In contrast, responses to PPSV and PCV in controls are similar. A review on the effects of PCV versus PPSV administration in adults showed no clear advantage of the former over latter.[27] Another study on older adults has demonstrated that the OPA levels did not differ between the recipients of PCV and PPSV 1 year after vaccination.[28] However, after administering the second vaccination (PCV or PPSV) 4 years after the first vaccination, the PCV group had better immune responses compared with those who received PPSV as the first vaccination.[29] Long-term immunogenicity from pneumococcal vaccination in patients with autoimmune diseases has shown reduced antibody concentrations over time, which were lower than those in vaccinated healthy controls.[13,30] Therefore, protection intervals, as defined in the healthy population, do not apply on patients receiving immunosuppressive therapy. PCV is thought to be more important for the development of long-term immunity.

The response to PCV, a T-cell-dependent vaccine is reduced because of impaired T-cell-mediated immunity evoked by immunosuppressive medications, and the response to PPSV is less compromised because this response is T-cell independent.[31] Low concentrations of isotype-switched memory B cells were the strongest independent predictors of poor PCV responsiveness, emphasizing that disturbances to the B-cell subset are associated with poor vaccine responses among HIV-infected patients.[32,33] The distinct memory B-cell subsets, rather than $CD4^+$ T cells, may contribute to PCV responses in immunocompromised children.[34] Rituximab, a chimeric monoclonal antibody, is administered against the pan-B-cell marker CD20. The pathogenesis of IPF has been associated with abnormal B cells and B-lymphocyte-stimulating factors.[35] Several specific agents and diseases modulating the host B-cell characteristics may affect the immunogenicity of pneumococcal vaccines.

Conclusion

Several types of immunosuppressive therapies may prevent responses to pneumococcal vaccinations. Therefore, immunization should be administered prior to the initiation of immunosuppressive medications whenever possible.

Disclosure of potential conflicts of interest

There are no conflicts of interest for K. Kuronuma or H. Takahashi.

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