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Review Article

Vaccination for Patients with Rheumatic Diseases in the Era of Biologics

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A large proportion of patients with rheumatic disease have an immunocompromised status resulting from disease pathogenesis itself and/or several immunosuppressive drugs including biologics. These conditions are closely related to a higher risk of a variety of infectious diseases. Therefore, a few vaccinations for vaccine-preventable pathogens should be considered in patients with rheumatic disease at the appropriate time. The quadrivalent inactivated influenza and pneumococcal vaccinations, including both 13-valent conjugate and 23-valent polysaccharide vaccines, are strongly recommended in all patients with rheumatic disease. The immunogenicity of influenza and pneumococcal vaccination have generally been demonstrated in patients with rheumatic disease on biologics except for rituximab and abatacept. Vaccines can be administered during therapy with tumor necrosis factor-α antagonists but may be more ideal during a stable or remission status without immunosuppressive therapy. In particular, vaccination should be done at least 6 months after an injection of rituximab as a B-lymphocyte-depleting biologic. Basically, all live-attenuated vaccines should be avoided in highly immunocompromised rheumatic disease patients. The vaccination for herpes zoster (HZ) can be taken carefully according to degree of immunosuppression because the currently available vaccine is only live-attenuated. The newly developed subunit HZ vaccine is promising in immunocompromised patients with rheumatic disease. **(J Rheum Dis 2018;25:100-107)**

Key Words. Vaccination, Rheumatic disease, Biologic Agents, Influenza, Pneumococcal infections, Herpes zoster

INTRODUCTION

In general, patients with rheumatic disease including ankylosing spondylitis (AS), rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are more vulnerable to a wide array of infectious diseases than in the healthy general population, because immunosenescence or immune exhaustion by long-term persistent immune activating conditions in rheumatic disease could lead to impaired immune defense system against various pathogens and/or they are frequently exposed to several immunomodulating or immunosuppressive drugs [1-7]. In particular, the biologic agents becoming widespread in the past decade, which are directly targeting specific pro-inflammatory markers and signal pathways of innate or adaptive immune system, could apparently skew the immune function against certain microbes [7-12].

Some causative pathogens of infectious complications with high risk in patients with rheumatic disease can be prevented by active immunization. Therefore, several vaccination, which are essential in other immunocompromied patients including transplant recipients and chronic medical diseases such as diabetes mellitus or chronic pulmonary/renal diseases or solid cancers, are necessary to be applied in patients with rheumatic disease [13,14]. Importantly, physicians may take notice of two distinctive features for vaccination in patients with rheumatic disease. First, the defective immune functions by various causes could decrease the efficiency and/or immunogenicity of humoral or cellular immunity from vaccination. Consequently, the adequate preventable responses could not be arisen in spite of immunization [15-17]. Second,

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extrinsic further antigenic stimulation of vaccination might trigger a nonspecific immune response, potentially resulting in increased activity of rheumatic disease called rheumatic complications. Therefore, we need to pay attention to short and/or long-term side effects by vaccination [1,18].

In addition, we may apply to different vaccination strategies for mildly or highly immunocompromised rheumatic disease patients because of careful consideration for efficiency of vaccination and contraindication of a few live attenuated vaccines [1]. The mildly immunocompromised rheumatic disease patients are considered to those treated with (1) ≤2 weeks of corticosteroid, (2) low to moderate doses of corticosteroids (<20 mg/day of prednisone), (3) local injection of corticosteroids, (4) long-term treatment with low to moderate doses of short-acting corticosteroids, (5) methotrexate (<0.4 mg/kg/week, e.g., 25 mg/week), or (6) azathioprine (<3.0 mg/kg/day). Otherwise, the highly immunocompromised rheumatic disease patients are considered to those treated with tumor necrosis factor (TNF)-α antagonists, nonbiologic disease-modifying antirheumatic drugs (DMARDs), particularly cyclophosphamide or azathioprine, and corticosteroids with high amount exceeding above mild conditions [14].

In this review, we will address a few vaccines including seasonal influenza, *Streptococcus pneumoniae*, and herpes zoster (HZ), which are necessary to be taken into account to adult patients with rheumatic disease, especially focusing on those receiving with biologics.

MAIN SUBJECTS

Risk of vaccine-preventable infectious diseases in patients with rheumatic disease

Although the incidence varies between a wide range of types and disease activities of rheumatic disease as well as characteristics of immunosuppressive and disease-modifying agents, some vaccine-preventable infections including influenza, pneumococcal diseases including pneumonia and invasive pneumococcal disease (IPD) such as bacteremia or meningitis, HZ and human papillomavirus infection all occur more frequently in patients with rheumatic disease [1,2,19].

1) Seasonal influenza

The risk of admission for influenza is higher in elderly patients of ≥65 year-old with rheumatic disease, compared with elder individuals with no underlying medical condition [20,21]. The increased risk of influenza and its complications such as pneumonia in patients with RA was revealed by a large retrospective cohort study which were conducted with the matched healthy individuals [22]. The incidence of influenza and its complications was higher in patients with RA than in the healthy controls (409.33 vs. 306.12 cases/100,000 patient-years and 2.75-fold higher, respectively) [22].

2) Herpes zoster

Several studies showed patients with rheumatic disease were vulnerable to develop HZ. HZ could result in long-term morbidities including recurrence of skin lesion or postherpetic neuralgia (PHN) [2,23-28]. RA was an independent risk factor for occurrence of HZ (hazard ratio 1.65 to 1.91, compared with healthy individuals) with a wide range in incidence (0.55~12.1 cases/1,000 patient-years) in patients with rheumatic disease [23]. A systematic review indicated an increased risk of HZ in patients with RA treated with TNF-α antagonists, compared with patients treated with nonbiologic DMARDs [29,30]. The immunosuppressive drugs, combined use of rituximab and steroids, could affect risk of HZ development [31-33].

3) *Streptococcus pneumoniae*

Retrospective cohort studies have shown that patients with rheumatic disease were more likely than the healthy individuals to be admitted for pneumococcal disease [34]. Relative risk were 5.0 for systemic lupus erythematosus, 4.2 for scleroderma, 3.2 for Sjögren syndrome and 2.47 for RA [35-37].

Characteristics of recommending vaccines in patients with rheumatic disease and effect of biologics on vaccine efficiency or immunogenicity

Previous vaccination history should be thoroughly assessed in initial evaluation of patients with rheumatic disease, especially before starting treatment with biologic agent. In particular, timing of vaccination should be carefully considered in patients who are already taking biologic therapy, because some agents such as rituximab and abatacept could significantly decrease the efficacy of vaccines. Therefore, vaccine should ideally be administered to patients with rheumatic disease during stable disease without severe immunocompromised status,

even though all recommended vaccines generally can be administered during TNF-α antagonists and tocilizumab therapy.

Evaluating the efficacy of vaccination should use clinical endpoints which indicate the significant decline of incidence or prevalence for the infectious disease with follow-up during certain period. However, there were a little studies using clinical endpoints and almost of studies have investigated the efficiency of vaccines by immunogenicity measuring humoral (antibody [Ab] titer) or cell-mediated immune responses in patients with rheumatic disease [38-40]. In spite of lacking of definite evidence for disease prevention, the vaccination for quadrivalent inactivated seasonal influenza, *S. pneumoniae* and tetanus-diphtheria-pertussis are generally and strongly recommended in all patients with rheumatic disease. Table 1 is summarized some remarkable characteristics of recommend vaccines in patients with rheumatic disease.

1) Seasonal influenza

The annual vaccination of inactivated seasonal influenza should be strongly recommended in all patients with rheumatic disease [14,41]. Currently, there is two types of trivalent and quadrivalent in killed inactivated influen-

Table 1. The remarkable characteristics of the vaccines considering in patients with rheumatic disease [14]

Vaccines	General consideration	Precautions
Seasonal influenza	• Strongly recommended in all patients with rheumatic disease every year	• Encouragement of vaccination in people who are closely contact with patients (e.g., family members)
Inactivated	• IM or ID injection • Quadrivalent vaccine will be more proper than trivalent • Can be administered during therapy with TNF-α antagonist, tocilizumab, and abatacept • Formulation including adjuvant can be used	• Rituximab can significantly reduce the efficacy • Should be vaccinated at least 6 months after the start and 4 weeks before the next injection of rituximab
Live-attenuated	• Nasal application • Should be avoid in highly immunocompromised status	
Streptococcus pneumoniae	• Strongly recommended in all patients with rheumatic disease • Can be administered during therapy with TNF-α antagonist, tocilizumab, and abatacept	• Important to strictly comply the guideline for time interval between PCV13 and PPSV23 as well as time of boosting of PPSV23 • PCV13 and PPSV23 should not be co-administrated • Should be separated at least 8 weeks between two vaccination
PCV-13	• With preventive effect for non-bacteremic pneumonia as well as IPD • Induce humoral and cellular immunity	
PPSV-23	• Without preventive effect for non-bacteremic pneumonia • Induce only humoral immunity	
Herpes zoster		• Need to be considered for maintenance of long-term effectiveness, especially at old age of >80-year-old • Can prevent PHN as well as recurrence of HZ
Live-attenuated	• Has been used in general population • Should be avoid in highly immunocompromised status	
Subunit	• Inactivated vaccine • Not approved, not available	

IM: intramuscular, ID: intradermal, TNF: tumor necrosis factor, PCV: pneumococcal conjugate vaccine, PPSV: pneumococcal polysaccharide vaccine, IPD: invasive pneumococcal disease, PHN: postherpetic neuralgia, HZ: herpes zoster.

za vaccine. The quadrivalent vaccine is composed of four strains for each two influenza A (H1N1 and H3N2) and B (Yamagata and Victoria lineage). The trivalent vaccine is same with quadrivalent except one strain of type B.

The attack rate of lower respiratory tract infection by influenza virus was significantly lower in influenza-vaccinated patients with RA compared than those without vaccination (relative risk 0.83, $p<0.01$) [39,42]. The haemagglutinin inhibition (HI) titers for each influenza antigen of ≥1:40 is considered seroprotective in patients with rheumatic disease like as in the general population, even though seroprotection levels may be not identical with clinical efficiency of influenza protection. On the basis of achievement of seroprotection, the efficacy of influenza vaccination of patients with RA and healthy individuals has been shown to be similar. In spite of some previous conflicting reports, most studies revealed neither TNF-α antagonists (adalimumab, certolizumab, etanercept, and infliximab) nor tocilizumab (monoclonal antibody [mAb] against interleukin-6 receptor) hampered humoral immune responses to influenza vaccination [15,42-52].

The time interval between biologics administration and vaccination need to be considered. When patients with RA were vaccinated 3 weeks after administration of infliximab, a trend towards a lower humoral immune response measured by HI titers was observed as compared with those vaccinated on the day of infliximab administration [49].

In contrast to DMARDs and TNF-α antagonists, many studies reported that rituximab of mAb against CD20 severely and abatacept of cytotoxic T-lymphocyte-associated protein (CTLA)-4 inhibitor significantly decreased HI titers and seroconversion/seroprotection rates after influenza vaccination [53-58]. Patients who were vaccinated influenza 6～10 months after rituximab had a better seroprotective response that those vaccinated 4～8 weeks after rituximab [53-55]. Therefore, it will be more appropriate to vaccinate the patients before starting rituximab, or, if not possible, at least 6 months after the start and 4 weeks before the next therapy [18].

The CD8+ cytotoxic T cell immune responses of patients with rheumatic disease to influenza vaccination may be decreased, which might be associated with inappropriate clearance of influenza in spite of enough seroprotection level [59,60]. However, the boosting of additional dose at 3～4 weeks after initial vaccination is not recommended.

2) *Streptococcus pneumoniae*

The vaccination for *S. pneumoniae* is strongly recommended in immunocompromised patients with rheumatic disease treating biologic agents irrespective of age [14,41,61]. The pneumococcal vaccine are divided into two different formulations, polysaccharide or protein conjugate. The 23-valent pneumococcal polysaccharide vaccine (PPSV23) has been widely used in adults to provide protection against 23 among ≥90 serotypes of *S. pneumoniae*, which can prevent IPD including sepsis and/or meningitis with or without pneumonia rather than non-bacteremic pneumococcal pneumonia alone [62,63]. The 13-valent pneumococcal conjugate vaccine (PCV13) typically induce more robust humoral and cellular immune responses than do polysaccharide vaccines that elicit Ab-producing humoral immunity alone [63,64]. The long-term large cohort study showed that PCV13 has a good protective effect for community-acquired pneumococcal pneumonia as well as IPD [65].

For this reason, PCV13 has been recommended in pneumococcal vaccine-naïve immunocompromised patients with rheumatic disease aged ≤64-year-old, followed by PPSV23 vaccination at least 8 weeks later or ideally 6～12 months later, with subsequent doses of PPSV23 at intervals of 5 years because of the decline of protective Abs over time [66]. The patients who previously received PPSV23 at age ≥65-year-old, vaccination of PCV13 is recommended at least 1 year later of PPSV23 administration [66]. The falling rate of Abs in patients with rheumatic disease would be more rapid than those without rheumatic disease [67]. However, there are no any consensus or clinical studies to support effectiveness of short-term boosting of PPSV23 in patients with rheumatic disease. Physicians should be careful of adequate time interval and sequence between PCV13 and PPSV23 vaccination as well as boosting time of PPSV23 according to previous vaccine history of PPSV23 [64,66]. Most important caution is that PPSV23 and PCV13 should not be simultaneously administrated, because of increased local reactogenicity [64,66].

Most of studies about effectiveness of PPSV23 or PCV13 in patients with rheumatic disease regardless of TNF-α antagonists or tocilizumab therapy showed no difference compared with controls [68-70]. Although PCV13 could reduce overall disease burden of *S. pneumoniae* than PPSV23, because PCV13 has potential effectiveness against non-bacteraemic pneumococcal pneumonia as well as IPD, there are no data regarding this issue in rheu-

matic disease patients treated with biologic [64,65].

3) Herpes zoster

The immunocompromised status in patients with rheumatic disease could cause the frequent recurrence of HZ and/or severe disseminated skin lesion along with more violent pain. This may be associated with agonizing and/or prolonged PHN especially at old age [71,72]. This clinical impacts generate continuous controversy and conduct clinical studies about the safety and effectiveness of HZ vaccine in rheumatic disease patients receiving certain biologic agent.

As the currently available HZ vaccine (Zostavax; Merck, Whitehouse Station, NJ, USA) contains live attenuated virus, its use should be avoided in patients with rheumatic disease in general, even though the balance between safety issue and protective effect are debating [1,18,73]. The Zostavax has relatively low effect for reduction of HZ risk compared than subunit vaccine and continuously decline of vaccine efficacy over time [74-76]. It is possible that the Zostavax was essentially no protective effect by about 10 year after vaccination, when the risk for occurrence of HZ and/or postherpetic neuralgia would be highest [74]. The newly developed, but not available adjuvanted recombinant Varicella-zoster virus subunit vaccine, that is not live vaccine, showed the better vaccine efficiency in all age group of ≥50 year-old [76,77]. However, the further study need to evaluate the sustained effectiveness over time especially at over 80-year-old. The advantage as inactivated vaccine raises the hope that subunit HZ vaccine can be used in severely immunocompromised rheumatic disease patients with guaranteed safety. The study will be warranted to evaluate the efficacy of subunit vaccine in rheumatic disease patients receiving several different biologics.

Vaccines which should be avoided or carefully administered in rheumatic disease patients receiving immunosuppressive biologic agents

All live attenuated vaccines are contraindicated for rheumatic disease patients receiving highly immunosuppressive biologic agents, because these vaccinations may be associated with poor safety profiles mainly caused by uncontrolled replication of bacteria or virus of essential ingredients for vaccine [13,78-80]. Vaccination itself could induce the critical disseminated infectious disease [13,78,80]. These include the followings; (1) nasal spray live attenuated trivalent influenza vaccine, (2) live attenuated HZ vaccine (Zostavax), (3) BCG (Bacillus Calmette–Guérin), (4) yellow fever, (5) measles, mumps and rubella (MMR), (6) rotavirus, (7) Ty21a oral typhoid.

If the live attenuated vaccine is inevitably necessary in special case, physicians must use these with great caution. Initiation of TNF-α antagonist therapy should be delayed at least 2～4 weeks after administration of live attenuated vaccine, especially HZ vaccine [81]. It is safe to wait a more than of 4 weeks between any live attenuated vaccination and highly immunosuppressive biologic agent therapy.

CONCLUSION

The patients with rheumatic disease can have vulnerability to several infectious diseases compared to the general population. Therefore, a couple of vaccination should be strongly considered with carefulness. In general, the quadrivalent seasonal influenza and pneumococcal vaccination (both PCV13 and PPSV23) need to be administered to all patients with rheumatic disease irrespective of their medication status, even if the vaccination before use of highly immunosuppressive drugs including biologic will be guaranteed to be more adequate immune response. The negative effect of rituximab on vaccine efficacy has been well known. Therefore, it should be taken into account of appropriate time interval between vaccination and rituximab injection. All live attenuated vaccines including currently available HZ vaccine (Zostervax) are generally contraindicated in severely immunosuppressive patients with rheumatic disease.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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