may be markers of the rapidly progressive form of ILD in JDM. BAFF and APRIL were also positively correlated with KL-6 and IL-18 in the JDM patients with ILD. KL-6 is produced by type II alveolar epithelial cells and is known as a useful circulating biomarker for the clinical diagnosis of ILD and evaluation of disease severity[28,29,30,31]. Meanwhile, high levels of IL-18 have been observed in RP-ILD patients with adult-onset DM and JDM[5,32]. Gono, *et al* also suspected that macrophage activation in the lung tissue based on high levels of IL-18 could be a prognostic marker of RP-ILD[32]. In addition, we found that patients with high anti-MDA5 had higher BAFF and APRIL titers than those with lower values of anti-MDA5. In a previous study, we reported that a high titer of anti-MDA5 (> 200 U) was a possible disease marker of RP-ILD in patients with JDM[5]. The current results therefore support that BAFF and APRIL titers are correlated to ILD disease severity in JDM.

Krystufkova, *et al* described a relationship between BAFF and anti-Jo1 in IIM and implicated BAFF with anti-Jo1 production in IIM positive for anti-Jo1[6]. There is increasing evidence supporting a critical association between unique MSA profiles and distinct clinical phenotypes not only in adult-onset DM, but also in JDM[27,33]. We observed positive results for anti-MDA5 in 78% of patients with ILD and only a low frequency of anti-Jo1, suggesting that anti-MDA5 was the MSA related most to Japanese ILD patients having JDM. Additionally, several roles of BAFF and APRIL in the production of autoantibodies have been reported[6,15,16,17,18,34,35]. The elevated levels of BAFF and APRIL in the RP-ILD group possessing high anti-MDA5 further indicated a role of B cells and these cytokines in the production of autoantibodies and disease phenotypes in this subset of JDM.

Our study revealed that the RP-ILD group alone had significantly high serum levels of APRIL, while both RP-ILD and non-ILD groups exhibited elevated BAFF. In previous reports, serum APRIL and APRIL mRNA in peripheral blood mononuclear cells were not raised in IIM[6,21], but those studies did not include patients with RP-ILD. On the other hand, increased level of APRIL has been described in patients with other autoimmune diseases accompanying ILD[36,37]. We speculate that APRIL is more important in the pathogenesis of RP-ILD than in that of C-ILD. APRIL may be more directly involved than BAFF in the disease mechanisms of RP-ILD and more useful as a detection marker for JDM with RP-ILD.

BAFF levels were also significantly higher in the non-ILD group than in healthy controls. Gunawardena, *et al* reported that anti-transcriptional intermediary factor 1-γ protein, antinuclear matrix protein, and anti-Mi2 were the most common MSA in JDM (23–29%, 13–23%, and 2–13%, respectively) and described a low frequency of ILD among patients with those antibodies[27]. Accordingly, we cannot exclude the possibility that the high titers of BAFF in the non-ILD group may have been associated with other clinical phenotypes dependent on separate MSA.

Krystufkova, *et al* reported an association between BAFF and CK in IIM and speculated that BAFF levels are in close relation to local muscle involvement[6]. However, we found no relationship between circulating BAFF and CK levels in ILD accompanying JDM. Most of our patients with ILD had positive titers of anti-MDA5. Similarly to adult-onset DM, anti-MDA5–positive JDM appears to be a milder myositis phenotype and has normal levels of CK[38]. Our data also revealed that CK in the ILD group was within normal levels and lower in comparison with the non-ILD group. One possible explanation for this discrepancy is a difference in the analyzed subsets of clinical phenotypes. Another possibility is that CK is a low sensitivity indicator of muscle damage in JDM[39]. We observed an association of BAFF/APRIL with aldolase and AST in the ILD group. Aldolase and AST leak into the systemic circulation from damaged muscle and have been reported to more closely monitor disease activity than CK[39]. Several core sets have been proposed to assess myositis disease activity[40], which will be important in the future evaluation of associations between BAFF/APRIL and myositis. We were unable to compare BAFF/APRIL levels with activity scores in the present study owing to a lack of standardized measurements of disease activity among the collaborating institutes.

The serum levels of BAFF and APRIL in most of our JDM patients with ILD were markedly decreased by immunosuppressive therapy, suggesting that BAFF/APRIL production was sensitive to this form of treatment. Further, posttreatment levels of the 2 cytokines in treatment responders returned to almost normal levels. In contrast, nonresponders persistently had increased BAFF/APRIL values, even after more intensive therapy, in comparison with responders. In spite of the limited cohort size, our results indicate that sustained abnormal levels of BAFF and APRIL may contribute to a poor response to treatment and that analysis of these cytokine levels after treatment may be useful for evaluating treatment progress in patients with ILD-JDM.

Our findings on BAFF and APRIL levels in ILD-JDM support the notion that these cytokines may be disease markers of RP-ILD that can be used to assess treatment response in ILD associated with JDM. The efficacy of B cell depletion therapy using rituximab has been reported in patients with refractory anti-ARS–positive DM complicated with chronic ILD as well as on the mucocutaneous lesions of patients with anti-MDA5-positive DM[41,42,43,44]. Anti-BAFF antibodies have shown favorable results in SLE patients with joint and skin disease[8,19,20]. Our data also indicate that BAFF and APRIL might constitute potential therapeutic targets for RP-ILD accompanying JDM.

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ONLINE SUPPLEMENT

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REVIEW ARTICLE

Pediatric Rheumatology Association of Japan recommendation for vaccination in pediatric rheumatic diseases

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Abstract

Pediatric Rheumatology Association of Japan has developed evidence-based guideline of vaccination in pediatric rheumatic diseases (PRDs) as a part of Guideline of Vaccination for Pediatric Immunocompromised Hosts. Available articles on vaccination in both adult rheumatic diseases and PRDs were analyzed. Non-live vaccines are generally safe and effective in patients with PRDs on corticosteroid, immunosuppressant, and/or biologics, although efficacy may be attenuated under high dose of the drugs. On the other hand, efficacy and safety of live-attenuated vaccine for the patients on such medication have not been established. Thus, live-attenuated vaccines should be withheld and, if indicated, may be considered as a clinical trial under the approval by Institutional Review Board. All patients with PRDs anticipating treatment with immunosuppressants or biologics should be screened for infection of hepatitis B and C and tuberculosis before the commencement of medication. Varicella vaccine should be considered in sensitive patients ideally 3 weeks or longer before the commencement of immunosuppressants, corticosteroids, or biologics. Bacille Calmette-Guérin should be withheld at least for 6 months after birth, if their mothers have received anti-tumor necrosis factor-α antibodies during the second or third trimester of pregnancy.

Keywords

Immunosuppression, Pediatric, Rheumatic disease, Vaccine

History

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Abbreviations

HBV: hepatitis B virus; VZV: varicella–zoster virus; PRD: pediatric rheumatic disease; EULAR: The European League Against Rheumatism; PRAJ: Pediatric Rheumatology Association of Japan; Minds: Medical Information Network Distribution Service; DMARD: disease-modifying anti-rheumatic disease; ACIP: Advisory Committee on Immunization Practice; GMT: geometric mean titer; DPT, diphtheria–pertussis–tetanus; TT: tetanus toxoid; MTX: methotrexate; AZA: azathioprine; CYC: cyclophosphamide; MMF: mycophenolate mofetil; CSA: cyclosporine A; RTX: rituximab; Hib: *Haemophilus influenza type b*; PPV: pneumococcal polysaccharide vaccine; PCV: pneumococcal conjugate vaccine; TNF: tumor necrosis factor; SASP: salazosulfapyridine; HAV: hepatitis A virus; HPV: human papillomavirus; CRPS: complex regional pain syndrome; MMR: mumps–measles–rubella; MR: measles–rubella; BCG: Bacille Calmette–Guérin; MHLW: Ministry of Health, Labour, and Wealth

Introduction

Patients with rheumatic disease are at high risk for infection due to the disease itself or immunosuppressive treatment. Indeed, infectious complications have been the major causes of death in SLE regardless of immunosuppressive treatment [1–5]. Both rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) are also at increased risk for infections with *Pneumococcus*, *Haemophilus influenza*, and *meningococcus* [6–8]. In addition, infections with hepatitis B virus (HBV), measles virus, varicella–zoster virus (VZV) and *Mycobacterium tuberculosis* cause serious outcome in patients with rheumatic disease under immunosuppressive treatment [9–24]. On the other hand, it is reported that some viruses such as Epstein–Barr virus, human parvovirus B-19, and rubella virus trigger onset or deterioration of rheumatic diseases [25–32]. Thus, prevention of the infectious diseases by vaccinations in, particularly, pediatric rheumatic diseases (PRDs) is an urgent issue. Recently, The European League Against Rheumatism (EULAR) has published recommendations for vaccination

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in both adult rheumatic diseases and PRDs [33,34]. However, they are not necessarily applicable to Japanese patients because of several differences in the situations such as national vaccination programs and epidemics. The present report provides a guideline of vaccination for patients with PRD developed by Pediatric Rheumatology Association of Japan (PRAJ) in collaboration with Japanese Society for Pediatric Infectious Diseases.

Methods

English articles on the vaccination in rheumatic diseases were searched by two pediatric rheumatologists (IK and MM) in MEDLINE, EMBASE, and PubMed using search terms "vaccine, vaccination, immunization, arthritis, autoimmune, lupus, connective tissue disease, rheumatic disease, vasculitis, influenza, *Pneumococcus*, *Haemophilus*, tetanus, diphtheria, pertussis, hepatitis, human papillomavirus (HPV), measles, rubella, mumps, polio, Japanese encephalitis, varicella, Bacillus Calmette–Guérin or tuberculosis", hand-searching and the secondary articles of review articles.

Levels of evidences and recommendations were graded according to the level of evidence by Medical Information Network Distribution Service (Minds) 2007 (Tables 1 and 2). Interim draft was reviewed and commented by eight experts of PRDs, members of the Steering Committee of PRAJ. Final recommendations were Delphi voted by the members to determine the level of agreement with the recommendation ranging from 0 (no agreement) to 10 (maximal agreement).

High-dose corticosteroid, disease-modifying anti-rheumatic drugs (DMARDs), and immunosuppressants are defined according to the recommendations by Advisory Committee on Immunization Practice (ACIP) and EULAR (Table 3) [35].

Results

A total of 125 articles were appraised for review by the authors. Although only one report demonstrated clinical efficacy of seasonal influenza vaccines, other studies assessed the efficacy by antibody responses against vaccines such as preventive titers, geometric mean titers (GMT), or significant rise of titers. Safety was assessed by clinical flare of the underlying PRDs, development of the diseases by vaccine strains, and other adverse events.

Non-live composite vaccine

Diphtheria, pertussis, and/or tetanus toxoid (DPT/DT/TT) vaccine

Although diphtheria, pertussis, and tetanus are often fatal and cause morbidity, there is no evidence on whether they cause more serious in patients with PRDs than healthy individuals. As well, to our knowledge, there is no study on the flare of PRDs by natural infection of these agents.

Before the introduction of methotrexate (MTX) to the treatment, patients with JIA (formerly designated as juvenile rheumatoid arthritis) have shown comparable levels of antibody responses to healthy individuals [36]. Antibody responses to DT in patients with adult RA, adult SLE, and JIA under the treatment with corticosteroid alone or combined with immunosuppressant such as chlorambucil, azathioprine (AZA), cyclophosphamide (CYC), mycophenolate mofetil (MMF), or cyclosporine A (CSA) are comparable to [37,38] or lower than healthy control [39]. Pediatric patients with SLE who had received DPT vaccine before the onset of the disease show lower antibody titer than healthy individuals [40].

The influences of biologics on antibody responses to TT have been studied only in adults. Rituximab (RTX) has no influence on antibody responses to TT in patients with RA receiving weekly MTX [41]. Healthy volunteers who had administered with a single dose of abatacept before TT vaccination showed significant antibody responses but lower GMT than those who have not received abatacept [42].

Together, although DT/TT is generally effective and safe in patients with rheumatic diseases on corticosteroids, immunosuppressants, and biologics, some report demonstrated lower antibody responses in these settings. Thus, anti-tetanus immunoglobulin should be considered in patients with PRDs on high-dose corticosteroid, immunosuppressants, or biologics.

Pneumococcus *and* Haemophilus influenza B (Hib) *vaccine*

Patients with PRDs are at high risk for infection with *Pneumococcus* and *Haemophilus* [1,8]. Although the effect and safety of 23-valent pneumococcal polysaccharide vaccine (PPV23) have been extensively studied in adult patients, studies on 7-valent pneumococcal conjugate vaccine (PCV7) are limited.

Antibody responses to PPV23 are attenuated in the patients with SLE regardless of the treatment [43], whereas two studies have demonstrated no influence of non-high-dose corticosteroid on the antibody responses to PPV14/23 in patients with SLE or RA [44,45]. On the other hand, MTX affects antibody responses to PCV7 and PPV23 in the patients with RA, inflammatory bowel diseases, and psoriasis [28,42,46–52]. In the patients with scleroderma, 83% of the patients acquired significant antibodies after PPV23 vaccination even under the treatment with 5 mg/day or lower dose of prednisolone in combination with intravenous CYC [53].

Table 1. Levels of evidence by Medical Information Network Distribution Service (Minds).

I	Systematic review/meta-analysis
II	At least one randomized controlled clinical trial
III	Non-randomized controlled clinical studies
IVa	Analytical epidemiologic study (cohort study)
IVb	Analytical epidemiologic study (case–control study, cross-sectional study)
V	Descriptive study (case report or case series)
VI	Opinion of an expert committee or individual specialist, not based on patient data

Table 2. Grade of recommendation by Medical Information Network Distribution Service (Minds).

Grades	Type of recommendation
A	Strongly recommended based on strong evidence
B	Recommended based on evidence
C1	May be under evaluation although there is no evidence
C2	Not recommended because there is no evidence
D	Not recommended because there is evidence showing ineffectiveness or harm

Table 3. Definition of high-dose corticosteroid, DMARDs and immunosuppressants.

Classification	Drugs	Doses
Corticosteroid	Prednisolone, betamethasone, dexamethasone, etc.	≥2 mg/kg/day or ≥20 mg/day of prednisolone equivalent for 2 weeks or longer
DMARDs	Salazosulfapyridine	>40 mg/kg/day
	Leflunomide*	>0.25–0.5 mg/kg/day
Immunosuppressants	Methotrexate	>15 mg/m^2/week
	Cyclosporine A	>2.5 mg/kg/day
	Azathioprine	>1–3 mg/kg/day
	Oral cyclophosphamide	>0.5–2 mg/kg/day
	6-Mercaptopurine	>1.5 mg/kg/day

*Leflunomide is not indicated for children in Japan.

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The influences of abatacept on antibody responses in healthy individuals have been assessed, which demonstrated that both TT and PPV23 induce lower GMT but significant antibody responses even after the administration of abatacept [42]. Most reports have shown that both tumor necrosis factor (TNF) inhibitors and abatacept have no influences on the antibody responses to PPV23 in adult RA patients [48–50,54], whereas others indicated that TNF inhibitors affect the responses in patients with ankylosing spondylitis [55]. In JIA patients, GMT to serotypes 4, 14, 29 and antibody response rate (>4-fold increase in HI titers to at least five serotypes) after vaccination of PCV7 are lower in patients receiving TNF inhibitors than those receiving DMARDs alone [56]. Although RTX affects antibody responses to PPV23 in RA patients, vaccinations on 6 days before the administration of RTX induce the responses comparable to those in patients receiving MTX alone [41,57]. Protective titers to Hib vaccine were acquired in 88% of adult SLE patients receiving non-high-dose corticosteroids and/or immunosuppressants [39].

There was no flare of the underlying disease or serious adverse events in the reports described above.

Although MTX attenuates antibody responses to PPV23 or PCV7, there are generally no influences of non-high-dose corticosteroids and immunosuppressants on these vaccines. However, vaccine should be inoculated more than 6 days before the commencement of RTX.

Seasonal or pandemic influenza vaccine

A large cohort study has demonstrated that seasonal influenza vaccination clinically reduces the prevalence of viral airway infection and secondary bacterial infection in adult patients with RA and SLE [58]. In other studies, responses to vaccine are assessed by GMT or acquisition of preventive titers of antibodies. Although 12 studies have demonstrated no influences of a low dose of corticosteroids (less than 10 mg of prednisolone/day) and immunosuppressants on antibody responses in patients with RA, SLE, systemic sclerosis (SSc), and granulomatosis with polyangitis [37,58–68], the other 6 studies have shown that 10 mg/day or more of prednisolone or immunosuppressants affect antibody responses in patients with RA or SLE [69–74]. Patients with SSc show good antibody responses to flu vaccine even under the treatment with corticosteroid or immunosuppressants [75,76].

In pediatric age group, three reports involving 153 patients with JIA, childhood SLE, or JDM, who are receiving PSL, DMARDs, immunosuppressants, or combination of them, have demonstrated good antibody responses to flu vaccine at comparable levels with healthy controls [77–79]. Two reports involving 197 patients with inflammatory bowel diseases have shown no influences of corticosteroid, tacrolimus, AZA, MTX, or 6-mercaptopurine on antibody responses [80,81].

In adult patients with RA, TNF inhibitors or RTX affects antibody responses to flu vaccine [82–88]. In addition, 6–10 months are necessary to retrieve the responsibility to vaccine after cessation of RTX [57,85–87]. TNF inhibitors also affect antibody responses to flu vaccine in patients with JIA [88]. In contrast, patients with systemic JIA receiving tocilizumab show normal antibody response to flu vaccine [89].

None of the studies described above and vaccination to pandemic H1N1 virus has demonstrated serious adverse events or flare of the underlying disease [90–92]. However, a single case report has shown the flare of systemic JIA following flu vaccination [93]. Thus, close observations of patients with PRDs are necessary after vaccination.

Hepatitis B vaccine

Several reports have suggested association of HBV vaccine with immunological disorders such as multiple sclerosis, Guillain–Barre syndrome, idiopathic thrombocytopenic purpura, vasculitis, and SLE [94–96]. On the other hand, use of high-dose immunosuppressants or biologics increases the risk of HBV reactivation which occasionally causes liver failure and death in patients with malignancy and rheumatic diseases [11,12]. Thus, all the patients with PRDs should be screened for current or past HBV infection by HBs antigen, anti-HBs antibodies, and anti-HBc antibodies before the commencement of immunosuppressants or biologics according to the Guideline of HBV screening by Japanese College of Rheumatology and Japanese Society of Hepatology (http://www.ryumachi-jp.com/info/news110926_gl.pdf).

Sixty-eight percent of adult patients with RA acquired significant antibody to HBV vaccination during the treatment with low-dose corticosteroid, MTX, anti-malarials, AZA, gold salt, or salazosulfapyridine (SASP) [97]. Antibody response rate was not affected by MTX or low-dose corticosteroid in patients with JIA, autoimmune hepatitis, Behçet disease, or adult SLE [98–100]. In patients with childhood SLE, antibody response rate was not affected by corticosteroid, AZA, or anti-malarials, although GMT was lower than healthy control [101,102]. There were no serious adverse events or flare of the underlying diseases in these reports.

Together, HBV vaccine is safe and mostly effective in the patients with PRDs even under the treatment with corticosteroids and/or immunosuppressants. Although HBV vaccine is administered only to the offspring of HBV carriers and healthcare providers in Japan, it should be considered in patients with PRDs particularly with high risk for HBV infection.

Hepatitis A vaccine

Antibody response rate in patients with JIA or autoimmune hepatitis receiving corticosteroids, MTX, or SASP were comparable to that of general population [99,103]. However, all the four non-responders were patients with systemic JIA receiving TNF-α inhibitor. None of these studies reported serious adverse effects of hepatitis A virus (HAV) vaccine or flare of the underlying diseases. Given that HAV is not endemic in Japan, HAV vaccine is recommended to the patients with PRDs who are scheduled to visit endemic regions.

HPV vaccine

Female patients with SLE are at increased risk of HPV-associated cervical squamous intraepithelial lesion, infection of high-risk serotypes, and multiple infections in Hong Kong [104]. In addition, a report from UK demonstrated that female patients with SLE within 5 years from onset carried high levels of HPV load [105]. In female patients with SLE, antibody responses to quadrivalent HPV vaccine are comparable to those of healthy control [106]. Although flare rate of SLE following vaccination was comparable to that of unvaccinated group in this study, another report described flare of SLE within 3 months after HPV vaccination [107]. Antibody responses to bivalent HPV vaccine in female patients with JIA were present although they were non-significantly lower than healthy control [108]. MTX has no effect on the antibody responses [108]. Disease activity did not worsened after the vaccination. Although serious adverse events were more frequently observed in JIA patients, they were judged to be unrelated with the vaccination [108].

A report described that six previously healthy individuals presented with SLE or SLE-like disease following quadrivalent HPV vaccine [109]. On the other hand, a recent report has demonstrated

that there is no evidence of an increase in the risk of autoimmune diseases [110]. Other serious adverse events of HPV vaccine in healthy individuals reported to date include complex regional pain syndrome (CRPS), venous thrombosis, and fatal intracranial vasculitis [111,112]. Although causal relationship with HPV vaccine has not been clear, such adverse events should be carefully monitored after vaccination.

Other non-live vaccine

There has been no study on the efficacy or safety of inactivated polio vaccine or Japanese encephalitis vaccine.

Live-attenuated vaccine

Measles/Mumps/Rubella (MMR) or Measles/Rubella (MR) vaccine

Natural infection of measles virus causes encephalitis and fatal pneumonia particularly in immunocompromised host. Infection of rubella virus in pregnant women causes congenital rubella syndrome of the fetus. Because most of the rheumatic diseases are prevalent in females of childbearing ages, protection from rubella infection is an urgent issue to prevent congenital rubella syndrome. Although arthralgia or arthritis following rubella vaccination has been reported, wild rubella infection is associated with a higher incidence, increased severity, and more prolonged duration of joint manifestations than rubella vaccination in adult populations [28–32].

In patients with SLE who have taken measles vaccine before the onset, titer of antibody is not affected by corticosteroid in combination with or without immunosuppressants such as AZA, CSA, CYC, or MMF [113]. In JIA patients, booster MMR vaccination induces normal antibody and T cell responses regardless of treatment with MTX or MTX + TNF inhibitors [114]. Although relapse of systemic JIA after rubella vaccination has been reported [115], there was no exacerbation of underlying disease or activation of vaccine strains of mumps, measles, and rubella viruses after MMR vaccination in 314 patients with JIA [116]. The efficacy and safety of booster MMR vaccination in JIA patients receiving MTX and/or biologics have recently further confirmed by randomized control study [117].

VZV vaccine

Serious VZV infections are the matters of concern in immunocompromised hosts particularly under the treatment with corticosteroid, TNF inhibitors, MTX, or calcineurin inhibitors [13–16]). Thus, all the patients with PRDs should be screened for susceptibility to the virus before the commencement of such medications. VZV vaccine should be considered in sensitive patients and, if possible, given at least 3 weeks before the commencement of immunosuppressants or corticosteroids [118]. It is recommended to inoculate varicella vaccine to family members of patients with PRD to prevent nosohusial infections [119].

Although ACIP has recommended single vaccination to patients with RA who is taking small dose of MTX (0.4 mg/kg/week or less) or non-high dose of corticosteroid (20 mg/day or less of prednisolone), it is an expert opinion and does not certificate the safety [120]. In a study of pediatric age group, preventive antibody following VZV vaccine is acquired in 50% of JIA patients on MTX in combination with corticosteroid or DMARDs, which is significantly lower than 72.2% in healthy control [121]. However, there was no increase in disease activity or varicella-like lesions following vaccination, suggesting safety of the primary vaccination of varicella.

Bacille Calmette–Guérin (BCG)

Patients receiving immunosuppressants are at increased risk for tuberculosis [18–27]. Indeed, reaction to purified protein derivative is attenuated in patients with JIA or SLE who are receiving low-dose immunosuppressants [122,123]. Thus, all the patients anticipating the treatment with immunosuppressants, corticosteroid, MTX, or biologics should be screened for tuberculosis by specific tests such as Quantiferon or its equivalents before the commencement of the drugs. Meta-analyses indicate that BCG is effective in the prevention of serious tuberculosis such as meningitis and disseminated tuberculosis in the early childhood [124]. The effect of BCG against early childhood tuberculosis has also been confirmed in Japan [125]. On the other hand, the effect of BCG in older children is still controversial. The effect and safety of BCG have not been examined in the patients with rheumatic diseases. Two reports have recommended BCG vaccination to young children with PRDs before the commencement of corticosteroids or biologics [126,127]. However, because live bacilli exist at the site of inoculation at least for 6 months, PRAJ does not positively recommend BCG vaccination for patients with PRDs anticipating the treatment with corticosteroids, immunosuppressants, or biologics. On the other hand, BCG is included in the national vaccination program. Furthermore, there is no evidence indicating that the inoculated bacillus caused serious infection following the commencement of immunosuppressive therapy. Thus, in the cases of PRD that developed within 6 months after BCG vaccination, treatment of PRD should not be delayed. Young infant with acute phase Kawasaki disease shows injection of BCG site [128,129]. Thus, BCG should be avoided in patients with Kawasaki disease in acute phase.

Comments

Non-live composite vaccine is generally considered effective and safe and should be administered to patients with PRDs regardless of treatment. Although favorable antibody responses to vaccination are observed under treatment with low-dose corticosteroids (less than 0.5–2 mg/kg/day for children and less than 10 mg/day for adults) [45,54,63,65,74,77,79,82,98], 10 mg/day or more of prednisolone may reduce the responses in adult [71,72]. MTX tends to reduce antibody responses to polysaccharide vaccine such as PPV23 possibly because of their T cell independency [46,48,54,83]. TNF inhibitors do not affect the acquisition of protective levels of antibodies, although they may reduce the GMT after vaccination [47–50,54,56,65,80–83]. On the other hand, RTX affects antibody responses to non-live component vaccine and requires 6–10 month to retrieve the response [41,57,85–87]. However, favorable antibody response to PPV23 is observed, if it is given 6 days or longer prior to administration of RTX [41,57].

The prevalence of adverse events related to vaccination in general population reported to the Ministry of Health, Labour, and Welfare (MHLW) of Japan ranges from 6.4 in seasonal influenza vaccine to 245.1 in bivalent HPV vaccine per 1 million inoculations. Among them, serious adverse events range from 0.9 in seasonal influenza vaccine to 26.0 in Japanese encephalitis vaccine per 1 million inoculations (http://www.mhlw.go.jp/stf/shingi/2r98520000032bk8-att/2r98520000032br2.pdf). On the other hand, the annual incidence of PRDs is estimated to be about 1.6 per 100,000 children in Japan [130]. Given the rarity of both PRDs and serious adverse events of vaccines, it may be difficult to compare the safety of vaccines between patients with PRDs and general population.

HPV vaccine is currently of public concern in Japan because of adverse events such as CRPS after the vaccination. However, whether vaccination is the causal or precipitating factor of CRPS remains to be elucidated. Some reports have described serious adverse effects such as intracranial vasculitis, SLE, or SLE-like diseases following HPV vaccination [107,109,111,112]. Thus, it

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is necessary to compare the incidence of those diseases associated with HPV vaccine and the population-based incidence.

According to the medical package inserts, live-attenuated vaccines are contraindicated in the cases on corticosteroids or immunosuppressants. Although the safety and efficacy of booster MMR vaccine and primary or booster VZV vaccine have recently been reported in the patients with JIA on MTX [114,116,117,120], further evidences are necessary to recommend the live-attenuated vaccine to such patients. In addition, the safety and efficacy of primary MR vaccine have not been examined in patients with PRDs. Thus, it is advisable to consider booster MR vaccine or primary VZV vaccine, if indicated, as clinical trials with approval by the patients and/or parents and Institutional Review Board of each institute. Vaccination is the primary strategy to prevent the spread of vaccine-preventable disease in general population, which protects patients with PRDs from the infections. However, there have been several problems in Japan. MMR vaccine was withdrawn in 1993 because of mumps vaccine-related aseptic meningitis and transmission of vaccine strain to healthy individuals and has been switched to measles–rubella (MR) vaccine in 2006. Although MR vaccine is currently included in the national routine vaccine program, the coverage of primary vaccination is unfortunately still low (95.3% in 2011). MHLW of Japan has recently decided to include primary VZV vaccine to the routine vaccine program. However, booster VZV vaccination has not currently been included in the program despite strong recommendation by Japan Pediatric Society. Thus, nosohusial and nosocomial infection of wild-type viruses should be prevented by vaccination to the healthcare providers and family members of the rheumatic patients.

A 3-month-old baby who was born to a mother receiving infliximab for Crohn's disease during pregnancy died of disseminated infection of BCG [131]. Both infliximab and adalimumab are transplacentally transferred to the fetus [131,132]. Given a long half-life of these biologics in infants [131,133], BCG should be withheld at least for 6 months after birth, if their mothers have received anti-TNF-α antibodies during the second or third trimester of pregnancy [134]. There has been no evidence, to date, indicating the influences of other biologics on their offspring.

Recommendation

Based on the evidences as described above, although their evidence grades are not high enough, PRAJ developed 15 recommendations for vaccination in patients with PRDs. Strength of recommendation and Delphi voting score are shown in parentheses.

1. It is recommended that non-live vaccines are administered to patients with PRDs according to the national vaccination guidelines ideally during the underlying diseases are stable (C1; Delphi, 10.0).
2. It is recommended to adhere to national vaccination guidelines for non-live vaccine against DPT/DT, PCV7/13, Hib, and Japanese encephalitis in patients with PRDs regardless of the treatment with corticosteroids, DMARDs, immunosuppressants, or biologics (B; Delphi, 9.9).
3. When indicated, it is advisable that non-live vaccines are administered ideally 1 week or longer prior to rituximab use (C1; Delphi, 9.6).
4. Administration of anti-tetanus immunoglobulin should be considered in PRD patients with contaminated wounds particularly under treatment with high-dose corticosteroid, immunosuppressants, and/or biologics (C1; Delphi, 9.4).
5. Seasonal influenza vaccine should be considered in all patients with PRDs (C1; Delphi, 10.0).
6. HPV vaccine should be considered in women with PRDs, particularly with SLE, because patients with SLE are at increased risk for multiple infections with high-risk strains of HPV. However, serious adverse events such as CRPS, venous thrombosis, intracranial vasculitis, and flare of SLE should be closely monitored after the vaccination (C1; Delphi, 9.3).
7. Non-live vaccines that are not included in the regular vaccination program such as HAV, meningococcus, typhoid fever, rabies, and cholera are recommended for patients with PRDs who are scheduled to visit endemic regions (C1; Delphi, 9.9).
8. All patients with PRDs anticipating treatment with immunosuppressants or biologics should be screened for HBV infection by HBs antigen, anti-HBs antibodies, and anti-HBc antibodies before the commencement of medication according to the Guideline of HBV screening by Japanese College of Rheumatology and Japanese Society of Hepatology. HBV vaccine should be considered in patients at increased risk for HBV infection (C1; Delphi, 10.0).
9. It is recommended to withhold any live-attenuated vaccine in patients with PRDs on high-dose immunosuppressants, high-dose corticosteroids, or biologics (C2; Delphi, 9.0).
10. It is recommended that all patients with PRDs should be screened for the sensitivity to VZA before the treatment. If possible, VZV vaccine should be considered in sensitive patients ideally 3 weeks or longer before the commencement of immunosuppressants, corticosteroids, or biologics (C1; Delphi 9.6).
11. Booster vaccination to measles–rubella and mumps and primary vaccination to VZV, if indicated, could be considered in patients with PRDs on low-dose immunosuppressants or low-dose corticosteroids as a clinical trial under the approval by Institutional Review Board (C2; Delphi, 8.9).
12. To prevent nosohusial and nosocomial infection of wild-type viruses, it is recommended to administer VZV vaccination to sensitive healthcare providers and family members of PRD patients (C1; 8.6).
13. It is recommended to withhold BCG vaccination in patients with PRDs on immunosuppressants, corticosteroids, or biologics (C2; Delphi, 9.3).
14. It is recommended to withhold BCG vaccination in patients with acute phase Kawasaki disease (C2; Delphi, 9.3).
15. BCG should be withheld at least for 6 months after birth, if their mothers have received anti-TNF-α antibodies during the second or third trimester of pregnancy (C2; 9.1).

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The Japanese version of this work is available in the homepage of Pediatric Rheumatology Association of Japan (http://www.kufm.kagoshima-u.ac.jp/~ped/praj/) and is published as a part of "Guideline of Vaccination for Pediatric Immunocompromised Hosts". A commentary on this work is published in the Journal of the Japanese Pediatric Society.

Conflict of interest

M. Mori has received lecture fees from Kitasato Daiichi Sankyo Vaccine Co., Ltd, Abbvie GK, MSD Japan, Astellas Pharma Inc, Sanofi-Pasteur Japan, Mitsubishi-Tanabe Pharma, Pfizer Japan, and Glaxo-Smith-Klein Japan.

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