Efficacy and safety of vaccination in pediatric patients with systemic inflammatory rheumatic diseases: a systematic review of the literature

Sousa S[1], Duarte AC[1], Cordeiro I[1], Ferreira J[2], Gonçalves MJ[3], Meirinhos T[4], Rocha TM[5], Romão VC[3], Santos MJ[1]

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ABSTRACT

Introduction: Children and adolescents with systemic rheumatic diseases have an increased risk of infections. Although some infections are vaccine-preventable, immunization among patients with juvenile rheumatic diseases is suboptimal, partly due to some doubts that still persist regarding its efficacy and safety in this patient population.

Objectives: To review the available evidence regarding the immunological response and the safety of vaccination in children and adolescents with systemic inflammatory rheumatic diseases (SIRD).

Methods: A systematic review of the current literature until December 2014 using MEDLINE, EMBASE and abstracts from the American College of Rheumatology and European League Against Rheumatism congresses (2011-2014), complemented by hand search was performed. Eligible studies were identified and efficacy (seroprotection and/or seroconversion) and safety (reactions to vaccine and relapse of rheumatic disease) outcomes were extracted and summarized according to the type of vaccine.

Results: Twenty-eight articles concerning vaccination in pediatric patients with SIRDs were found, that included almost 2100 children and adolescents, comprising nearly all standard vaccinations of the recommended immunization schedule. Children with SIRDs generally achieved seroprotection and seroconversion; nevertheless, the antibody levels were often lower when compared with healthy children. Glucocorticoids and conventional disease-modifying anti-rheumatic drugs do not seem to significantly hamper the immune responses, whereas TNF inhibitors may reduce antibody production, particularly in response to pneumococcal conjugate, influenza, meningococcal C and hepatitis A vaccine. There were no serious adverse events, nor evidence of a relevant worsening of the underlying rheumatic disease. Concerning live attenuated vaccines, the evidence is scarce, but no episodes of overt disease were reported, even in patients under biological therapy.

Conclusions: Existing literature demonstrates that vaccines are generally well tolerated and effective in stable SIRD patients, yet antibody titers are frequently lower than in healthy controls. There is some evidence that biological therapy could hamper the immune response. Data on safety of live attenuated vaccines is limited. Although the available literature covers most vaccines included in the national immunization plan, there is a need for more information regarding new vaccines and new anti-rheumatic therapies.

Keywords: Pediatric population; Vaccination; Systemic rheumatic diseases.

INTRODUCTION

The progress in the diagnosis and management of pediatric rheumatic diseases resulted in improved long-term outcomes and survival. However, infection remains one of the leading causes of morbidity and mortality among children with systemic inflammatory rheumatic diseases (SIRDs). Although bacterial infections are the most common, any organism can potentially be a causative agent[1]. Children with SIRDs are at greater risk of infection than age- and gender-matched subjects without SIRDs, not only because of the use of immune-modulating medications, but mainly due to

1. Reumatologia, Hospital Garcia de Orta
2. Reumatologia, Centro Hospitalar e Universitário de Coimbra
3. Reumatologia, Hospital de Santa Maria, Centro Hospitalar Lisboa Norte
4. Reumatologia, Hospital Infante D. Pedro, Centro Hospitalar do Baixo Vouga
5. Reumatologia, Hospital de São João, Centro Hospitalar de São João

the underlying immune dysfunction associated with their disease[1,2,3].

Two recent observational retrospective cohort studies by Beukelman *et al*[4,5] demonstrated that juvenile idiopathic arthritis (JIA) subjects had twofold increased rates of hospitalization due to moderate and severe bacterial infections, as well as increased risk of opportunistic infections in comparison to children without rheumatic diseases. Conversely, severe infection rates in JIA subjects were not significantly higher during treatment with methotrexate (MTX) or tumor necrosis factor (TNF) inhibitors[4,6]. No difference in mild infection rates between JIA subjects treated with or without TNF inhibitors was also recently reported by Walters *et al*[7]. Additionally, JIA disease activity may have contributed to infection risk in this cohort, irrespective of immunosuppressive therapy[7]. Taken together, these observations suggest that JIA patients have a higher rate of infections even before treatment with immunosuppressive therapy, possibly due to underlying immune dysfunction. Nevertheless, the potential contribution of uncontrolled disease activity to this risk has not been fully elucidated.

Many infections are preventable through routine vaccination, but vaccination uptake in many JIA children is suboptimal[8]. Also, the impaired patients' immune response could raise the question whether patients can mount an adequate response to vaccines. On the other hand, there may be some concerns about the possibility of vaccines triggering a persistent autoimmune response and leading to severe clinical problems including a relapse of SIRDs[9,10].

This review describes the available evidence regarding the efficacy, safety and tolerability of vaccination in childhood SIRDs.

METHODS

This paper is part of a broad systematic literature review, addressing the safety and efficacy of vaccination in patients with systemic inflammatory rheumatic diseases, all ages included. We searched MEDLINE (until 31 October 2014) and EMBASE (until 14 December 2014) databases. Additionally, we searched the abstracts of the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) congresses (2011-2014) and performed a complementary hand search. Patients with any SIRD were included and all vaccines were considered. Any safety and efficacy outcomes were admitted. Studies that assessed the simultaneous administration of two or more vaccines (except commercially available combinations) were excluded.

In this review, we included articles pertaining to patients with SIRD and age ≤18 years; the intervention tested was any vaccine administered to children with SIRD; the comparator were vaccinated healthy children or children with SIRD that were randomly not vaccinated; the outcomes were the efficacy of the immunization defined as seroconversion (≥4-fold increase in post vaccination titer), seroprotection (antibody titers ≥10 mIU/ml in case of hepatitis B virus vaccine or ≥40 IU/ml after immunization in all other vaccines) or increase in the serum geometric mean titers (GMT) of antibodies[11]; and the safety and tolerability of vaccination estimated by flares of rheumatic disease, local and systemic adverse events related to the administration of vaccines and episodes of overt disease like varicella or rubella. All type of studies, except reviews, expert opinions, and single case reports, were included[12].

Title and abstract selection was performed by 8 independent reviewers. Eligible studies were submitted to detailed review (Figure 1). Translation was requested when needed. The quality of individual studies was appraised using a checklist of 13 items[13]. Risk of bias was assessed using the Cochrane Collaboration Tool[14]. Study and patient characteristics, the use of glucocorticoids and immunosuppressants (both synthetic and biologic), type of vaccine, as well as safety and efficacy outcomes, were independently extracted into piloted forms. Retrospective and prospective data from the pediatric population (≤18 years) were analyzed separately and subsequently pooled according to the type of vaccine and the SIRD considered. Subsequently, a descriptive analysis was performed.

RESULTS

We retrieved 14594 abstracts. After title and abstract selection, 123 papers met the inclusion criteria. Of these, 28 were studies pertained to pediatric population and were included in this detailed review (Figure 1). All the studies included have high quality (9/13), but also high risk of bias.

We obtained 11 papers on influenza vaccine[15-25], 4 on viral hepatitis vaccine[26-29], 3 on human papillomavirus (HPV) vaccine[30-32], 2 on meningococcus C vacci-

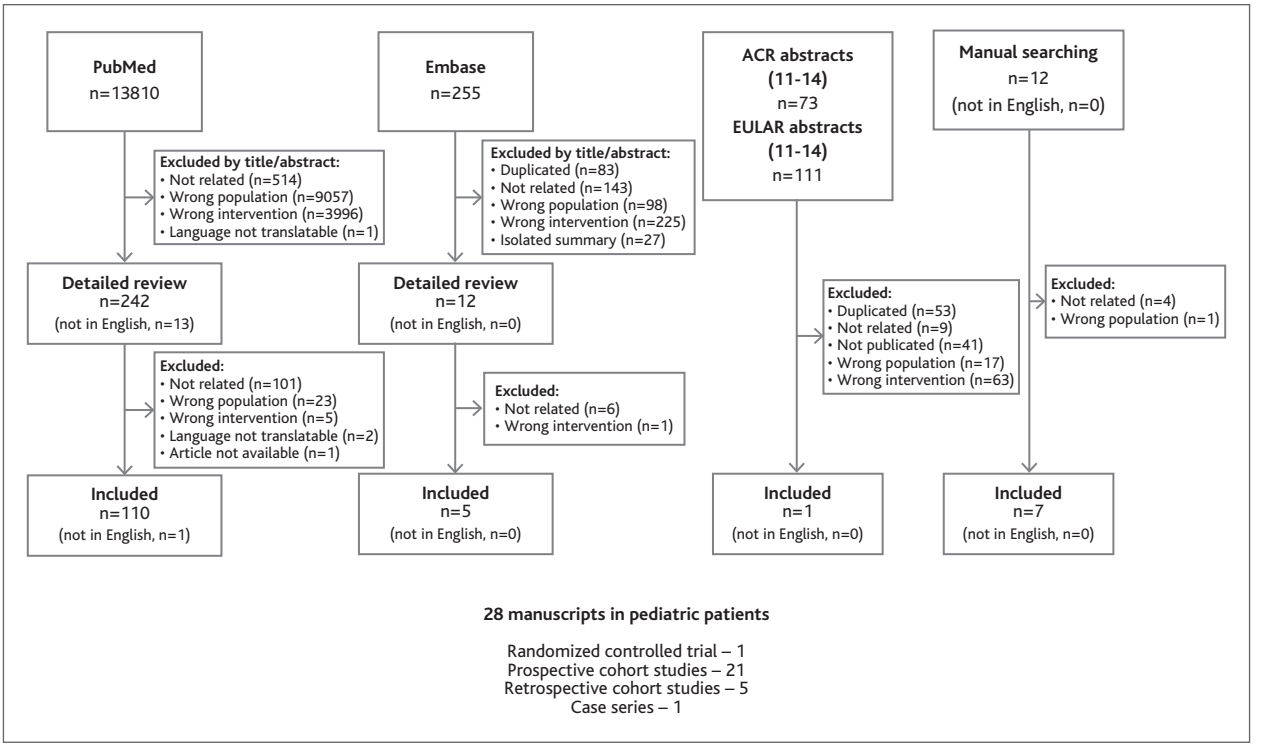

FIGURE 1. The search strategy for the systematic review

ne[33,34], 2 on diphtheria/tetanus (DT) vaccine[35,36], 1 on pneumococcal vaccine[37], 3 papers on measles/mumps/rubella (MMR) vaccine[38-40], and 2 on varicella virus vaccine[41,42]. Table I summarizes the distribution of included studies according to the disease and vaccine considered.

INACTIVATED AND RECOMBINANT VACCINES

Inactivated Influenza vaccine: In total, eleven articles concerned children with SIRD, aged 6 months-21 years, receiving immunosuppressive therapy were obtained. Except one that only assessed safety, all the

TABLE I. NUMBER OF PATIENTS INCLUDED IN THE STUDIES ACCORDING TO THE DIAGNOSIS AND VACCINES ASSESSED

Vaccine	JIA	jSLE	SSc	jPSV	jDM	jSIRD
Influenza[15-25]	172	118	–	–	30	428
Viral hepatitis A/B[26-29]	175	20	–	–	–	–
Human papillomavirus[30-32]	89	12	–	–	12	–
Meningococcus C[33,34]	361	–	–	–	–	–
DT/Tetanus[35,36]	–	82	59	13	17	–
Pneumococcal 7-valent conjugate[37]	63	–	–	–	–	–
Measles/mumps/rubella[38-40]	285	–	–	–	–	–
Varicella[41,42]	–	54	–	–	–	25

Some studies included vaccination in more than one SIRD. JIA – Juvenile idiopathic arthritis; jSLE – juvenile systemic lupus erythematosus; SSc – systemic sclerosis; jPSV – juvenile primary systemic vasculitis; jDM – juvenile dermatomyositis; jSIRD – juvenile systemic inflammatory rheumatic diseases that included SLE, DM, JIA, SSc, vasculites, mixed connective tissue disease and spondyloarthritis; DT – diphtheria/tetanus

studies evaluated both the efficacy and safety of vaccination. Antibody titers to influenza were measured before and 3-4 weeks after vaccination using hemagglutinin inhibition assay. Antibody titers ≥ 40 IU/ml were considered protective (seroprotection rate). A ≥ 4-fold increase in titer post vaccination (including changes from < 10/20 to 40) was considered a satisfactory response to vaccine antigens (seroconversion rate). Some studies considered also a fold increase in GMT titer after vaccination as a seroconversion factor. To examine the safety after vaccination, adverse events and flares of rheumatic disease were evaluated.

EFFICACY

In a study by Malleson *et al*[15] involving 34 children with chronic arthritis and 13 healthy controls, at least 95% of the patients developed protective antibody levels. Pre-immunization titers, seroresponse rates and final titers against influenza antigens were similar in patients and controls (Beijing 85% vs. 70%; Taiwan 39% vs. 60%; Panama 64% vs. 50%; % with significant titer rise). Ogimi *et al*[16] reported similar results from a study including 49 subjects with SIRD and mean age of 12 years. The absence of any interference with antibody response to influenza vaccine by immunosuppressive drugs (prednisolone, MTX, cyclosporine A and azathioprine) was also demonstrated by Kanakoudi-Tsakalidou *et al*[17] who found no difference between 70 children with chronic SIRDs aged 4–17 years and 5 healthy siblings, despite the fact that some of the patients had been receiving prednisone and/or other anti-rheumatic drugs for a long time. Aikawa *et al*[18] found a reduced but adequate immune response to monovalent H1N1 vaccine in 237 juvenile SIRD patients, and identified current glucocorticoid use as a major factor for decreased antibody production. Guissa *et al*[19] showed similar results in a cohort of 30 juvenile dermatomyositis (jDM) and 81 controls. A lower rate of seroconversion was observed in patients taking prednisolone>20mg/day and in those treated with a combination of prednisolone, MTX and cyclosporine. In a cohort of 118 children with juvenile systemic lupus erythematosus (jSLE) treated with glucocorticoids and conventional disease-modifying anti-rheumatic drugs (cDMARDs), Campos *et al*[20] showed that seroprotection, seroconversion, GMTs and factor increase in GMT 3 weeks after vaccination were all reduced, when compared to healthy children. Concerning biological treatment, Dell'era *et al*[21] evaluated immunogenicity of the seasonal influenza vaccine in 60 pediatric patients with JIA (30 treated with DMARDs and 30 with etanercept) and compared with 30 healthy controls. JIA patients treated with etanercept (ETN) showed significantly lower GMT against A/H1N1 strain, significant reduction in GMTs against the A/H1N1 and A/H3N2 strains 1 to 3 months after vaccination, and lower seroconversion and seroprotection rates than those observed in the others groups. These results indicate a reduced immune response to vaccine in JIA children treated with ETN in comparison with those treated with cDMARDs and healthy controls. In contrast, Aikawa *et al*[22,23] demonstrated that treatment with TNF inhibitors was not a factor influencing the immunogenic response. Shinoki *et al*[24] also showed that systemic JIA patients treated with tocilizumab could be effectively immunized with the influenza vaccine.

In total, 616 (82%) SIRD patients involved in these studies achieved seroprotection, although the antibody levels were lower compared to healthy controls. A single dose of flu vaccine was administrated in all, except in the study published by Ogimi *et al*[16] and Aikawa *et al*[20] where two doses of vaccine were administered in the same flu season. Table II summarizes the factors influencing the immunogenicity of the vaccine.

No data is available concerning differences between

TABLE II. FACTORS INFLUENCING THE IMMUNOGENICITY OF INFLUENZA VACCINE

	Glucocorticoids	cDMARDs	Biologics	Disease activity
JIA	↓	∅	↓/∅	∅
jSLE	↓	↓	ND	↓*
jDM	↓	↓	ND	∅
SSc	↓	∅	ND	∅
jPSV	↓	∅	ND	∅

JIA – Juvenile idiopathic arthritis; jSLE – juvenile systemic lupus erythematosus; jDM – juvenile dermatomyositis; SSc – systemic sclerosis; jPSV – juvenile primary systemic vasculitis; ↓ – reduces immunogenicity; ∅ – no effect on immunogenicity; ND – no data; *SLEDAI>8

age groups, or the impact of other cytotoxic and other biological drugs (e.g. anakinra, rituximab or abatacept) on the immune response of children with SIRD to influenza vaccination.

SAFETY

All studies[15-25] found that tolerability of influenza vaccine in children with SIRD was not different from that observed in healthy pediatric subjects. The follow-up period ranged from 3 weeks in most studies to 6 months in one single study[17]. Most studies have not documented disease flares. However, Ogimi *et al*[16] verified a flare of rheumatic disease in 2/49 children (JIA and Takayasu arteritis) within 2 weeks after vaccination that stabilized after increasing the dosage of prednisolone. Malleson *et al*[15] documented increase in joint count in 7/34 children, particularly those medicated with prednisolone. These differences are not statistically significant. Campos *et al*[20] found that jSLE patients experienced more local erythema, pruritus and arthralgia than healthy controls.

Hepatitis B virus (HBV) vaccine: We found 3 articles concerning HBV vaccination, one of them without safety data.

EFFICACY

The published studies on the immunogenicity and safety of hepatitis B vaccination in JIA patients[26,27] enrolled 128 children (all in remission and serologically negative for hepatitis B surface antigen) and 130 healthy controls. In total, 68% of the JIA population developed significant antibody response (antibody titers >10 mIU/ml) versus 95% of the control group. The antibody levels in children with JIA were also significantly lower than those in controls. Response to vaccine was not affected either by MTX or prednisolone treatment[26]. Diagnosis of JIA was statistically significant risk factor associated with the absence of protective antibodies after vaccination[27]. Another study enrolled 20 non-immunized jSLE children and 20 healthy controls[28]. Sixteen (80%) jSLE patients and all of the healthy controls achieved seroconversion (antibody titers >10 mIU/ml), although mean antibodies titers were lower in jSLE. The response was not affected by prednisone, azathioprine or hydroxichloroquine.

It should be noted that the methodology used in the 3 studies was somewhat different. In 2 of them[26,28] three doses of vaccine were given at 0, 2 and 6 months in children between 4-19 years and the serum samples was collected 1 month after the last dose. In the other study[27] were included children between 1-13 years of age who had completed the vaccination schedule at 2, 4, and 6 months of life. The mean time from last vaccine dose to time to enrollment was 3 years.

SAFETY

Vaccinated patients were clinically evaluated at entry and one month after each vaccine dose. In all studies, no major adverse events or worsening of rheumatic disease activity were reported.

Hepatitis A virus (HAV) vaccine: Only one study that included children with JIA was found[29]. The study population consisted of 47 JIA children with mean age of 11 years and 67 healthy controls with mean age of 9 years. Both groups were vaccinated with two doses of hepatitis A vaccine at 6-month intervals.

EFFICACY

Anti-HAV IgG titers were evaluated in average 2 months after the second dose of vaccine. Anti-HAV IgG positivity was detected in all, except four cases. These four patients were boys with active systemic JIA who were under anti-TNF treatment.

SAFETY

None of the patients with JIA developed fever, clinical worsening, or disease activation within 2 months after vaccination.

Human papilloma virus (HPV) vaccine: Few data are available concerning HPV vaccine.

EFFICACY

One study enrolled 6 jSLE and 6 jDM girls and compared them with 49 healthy controls aged 15 years[30]. Participants received 3 doses of the HPV vaccine in a 0, 1 and 6 month schedule and the HPV16/18-specific IgG antibodies were measured before vaccination and at 3, 7, and 12 months afterwards. All participants, except one subject with jDM, developed significant antibody response (>9 Luminex U/ml HPV16 and 13 U/ml HPV18). Another 2 studies[31,32] included 89 JIA females, mean age of 14 years, that also received three doses of the bivalent vaccine in a 0, 1 and 6 month schedule. Immunogenicity was evaluated after 6 months (before the third vaccine dose), 7 and 12 months. All participants (100%) seroconverted for HPV16 and HPV18 at 7 months after vaccination. One patient became

seronegative after 12 months. Immunosuppressants and biological therapies did not seem to interfere with the immunogenic responses. In all studies, the antibody levels in children with SIRD were significantly lower than those in the healthy controls.

SAFETY

During 12 months of follow-up, non-serious adverse events were similar in patients and controls, transient and of short duration. Serious adverse events occurred more frequently in JIA patients than in healthy controls, but none were deemed related to HPV vaccination. Disease activity measured by the JADAS27 did not worsen after HPV vaccination.

Meningococcal C vaccine: Meningococcal serogroup C conjugate vaccine was evaluated in two studies[33,34] involving JIA patients in order to determine whether their immune response could be hampered by immunosuppressive therapy.

EFFICACY

Three hundred and sixty one JIA patients with mean age of 10 years (range 1-19 years) were vaccinated between June and December of 2002 in a Dutch catch-up campaign. In one study[33] the blood sampling was performed until 12 weeks post vaccination, and in the other[34] the serum samples were collected between 2002 and 2010. Adequate antibody levels (titres ≥8 g/ml, the accepted correlate of protection against MenC disease) were observed in all patients, even in those receiving highly immunosuppressive medication (MTX≥10mg/$/m^2$/week, infliximab, ETN, cyclosporin A or a combination of MTX and sulfasalazine). The concentration of antibodies was lower in patients under immunosuppression (sulfasalazine, MTX alone or in combination with ETN). Lower antibody titers persistence were observed in children treated with biologicals[33,34].

SAFETY

Just one study reported safety issues[33]. The vaccine did not aggravate JIA disease activity or increased relapse frequency, even in patients receiving highly immunosuppressive medication until 6 months after vaccination.

Diphtheria-tetanus vaccine: The only published study on diphtheria-tetanus vaccine in pediatric SIRD is a retrospective evaluation of the intensity of post-vaccinal immunity at different time-points (less than five years versus more than five years) after the primary course of immunization against diphtheria and tetanus in 130 children with systemic connective tissue diseases[35].

EFFICACY

Protective levels of antibodies to diphtheria and tetanus toxoids were retained by children for 5 years and longer. Significantly lower titers of antibodies to diphtheria and tetanus toxoids were registered in children undergoing therapy with glucocorticoids and cytostatics at the time of the study.

No safety data were analyzed.

Tetanus vaccine: The only available data concerning pediatric SIRD were obtained from 40 children with jSLE (mean SLEDAI 4.9) and 60 age- and sex-matched healthy controls followed over a period of one year[36].

EFFICACY

The whole population (100%) achieved anti-tetanus antibody titer > 0.1 IU/ml. Immunosuppressive therapy did not seem to interfere with the development of immunity and there was no association between SLEDAI score and anti-tetanus response.

No safety data is available.

Pneumococcal vaccines: Although SIRD patients are more prone to respiratory infections than healthy controls, only a small number of studies evaluated the immunogenicity, safety and tolerability of pneumococcal vaccines in subjects with SIRD. The only pediatric study found used the heptavalent pneumococcal conjugate vaccine (PCV-7), which was administered in two doses with an interval 6-8-weeks to children with JIA, aged 12.9 years, treated with anti-TNF drugs (adalimumab or ETN) plus cDMARDs (n=31) or cDMARDs alone (n=32)[37]. Measurement of antibody titers was performed before the first dose, 41 days thereafter and immediately prior to the second dose.

EFFICACY

After a single vaccine dose, GMTs significantly increased for all vaccine serotypes in both groups and were found to be protective (>0.35 µg/ml) in 87-100% of children. Children receiving anti-TNF drugs achieved significantly lower GMTs against serotypes 4, 14 and 23F. Moreover, 50% of the children receiving anti-TNF drugs and 25% of those treated with cDMARDs did not develop a 4-fold increase in their baseline antibody titers against at least five serotypes.

SAFETY

No patient developed vaccine associated serious adverse events or disease flares until 6-8 months post-vaccination.

LIVE ATTENUATED VACCINES

Measles-Mumps-Rubella (MMR) vaccine: We found three studies on MMR booster vaccination in pediatric SIRD, all JIA patients. Two of them addressed efficacy and safety, and one addressed only safety issues[38-40].

EFFICACY

In a Dutch multicenter cohort study[38], 131 JIA patients, 4 to 9 years old were included, all with low disease activity. Sixty-three children with mean age at vaccination of 6.3 years received booster versus 68 JIA patients who did not. At 12 months, seroprotection rates were higher in revaccinated patients. MTX and biological therapy did not affect humoral responses. In another study[39], the effect of low-dose MTX (mean 9 mg/m^2/ /week) therapy alone or combined with ETN on the immunogenicity and tolerability of an MMR booster was evaluated in 15 children. Low-dose MTX therapy following MMR booster vaccination did not interfere with T-cell-mediated immunity *in vitro*, and neither low-dose MTX nor ETN given simultaneously with revaccination markedly interfered with the generation of long-lived virus-restricted T cells or protective levels of virus-specific IgG antibodies. Blood sampling was done at least 6 months after initiation of low-dose MTX therapy or 6 months following revaccination.

SAFETY

During the follow-up period, 6-12 months after revaccination, transient local injection site reactions, arthralgia, myalgia and acute transient arthritis were described in children receiving MMR booster vaccines. Vaccine did not seem to aggravate rheumatic disease activity. No study observed any overt MMR or secondary severe infections, including in JIA patients using ETN.

Varicella Virus (VV) vaccine – Vaccine against varicella zoster virus was assessed in two studies[41,42] involving JIA, jSLE, jDM, SSc and jPSV patients in order to evaluate safety and immunogenicity of VV vaccine in susceptible children with rheumatic diseases receiving immunosuppressive therapy.

EFFICACY

The immunogenicity of VV vaccine was assessed in one study of 25 susceptible children with juvenile SIRDs aged 8 years (20 had negative pre-immunization titers of IgG anti–varicella-zoster virus antibodies) and 18 controls (pre-immunization seronegative healthy children)[41]. All patients were receiving MTX, 13 were also receiving prednisone (range 3-20mg/day) and 5 another cDMARDs. Positive VZV IgG titers were detected in 50% of the seronegative patients and 72.2% of the controls 4–6 weeks after vaccination. Another study with 54 jSLE aged 15 years previously exposed to varicella-zoster virus and 28 healthy controls were performed. Varicella antibodies were measured before immunization and at days 30, 180 and 360 afterwards. All subjects with protective levels before vaccination, achieved immunogenic response after revaccination (AntiVZV>0.1UI/ml), although a lower cellular response was observed in the jSLE group[42].

SAFETY

No episodes of overt varicella or herpes zoster and no severe adverse reactions were observed during the follow-up (1-2 years after vaccination). No worsening of clinical parameters and no flares of juvenile rheumatic diseases or changes in doses of medications used were detected after vaccination.

DISCUSSION

The analysis of the literature published over the last 20 years shows limited data on immunization in children with SIRDs. The interest in this area increased in the last years and most of the papers included in this review were actually published after 2009.

There are some quality issues in the literature concerning vaccines in pediatric SIRD. The majority of studies involved small number of patients with different diseases and therapies. Most studies show combined results from children with a wide range of ages, not allowing to infer potential differences in immunogenicity of the vaccine in different age groups. In addition, the information about the dose of glucocorticoids, provided as total daily dose and not taking into account the child's weight, is another point that limits the interpretation of the study results.

Also, vaccine efficacy has not been specifically studied. All studies used surrogate markers of efficacy, such as seroprotection and seroconversion rates as the

primary study outcome, and not the occurrence of infections. So, definite conclusions on the impact of vaccination on the infection rate is still lacking, although there is evidence that most children and adolescents with SIRDs achieve adequate antibody titers in response to inactivated as well as to live attenuated vaccines. Nevertheless, these titers are generally lower than in healthy controls. Regarding the durability of the protective antibody titles, long-term follow-up data are lacking. Additionally, cellular immunity was not evaluated in most studies and may be sufficient to prevent progression to severe infection. Antibody titles below the limit considered protective do not necessarily mean absence of effective humoral response after exposure to antigen. Medication may reduce antibody production, although this effect is apparently smaller with conventional DMARD therapy and glucocorticoids than with biological drugs, especially TNF blockers. This fact is particularly evident in some serotypes of the heptavalent pneumococcal conjugate, seasonal influenza, meningococcal C and hepatitis A vaccines. However, the numbers are small to draw definitive conclusions and to point out putative differences between the different biologic agents. Moreover, it is unclear whether the most determinant factor for antibody response is related to the anti-rheumatic medication or to the active disease (*per se*).

Vaccination did worsen rheumatic disease or induced new flares. However, there is no published safety data in patients with highly active disease.

Concerning live attenuated vaccines in children with SIRD, the little available evidence suggests that MMR booster vaccine and varicella virus vaccine may be safe. No data on other live attenuated vaccines is available.

In conclusion, all addressed vaccines are immunogenic and reasonably safe in stable SIRD patients. The current efficacy data together with the lack of serious adverse events reported in the literature are sufficient to encourage immunization in children with low activity disease.

For the future, it will be important to establish the long-term persistence of immunological memory and to assess the effectiveness of vaccines using infectious events rate in vaccinated patients. Additionally, studies on immunogenicity, safety and tolerability of the new vaccines and also efficacy and safety of existing vaccines using non-conventional vaccination schedules and in patients receiving new treatments are needed.

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CORRESPONDENCE TO

Sandra Sousa
Serviço de Reumatologia, Hospital Garcia de Orta
Av. Torrado da Silva, 2805 Almada, Portugal
E-mail: sandrainsousa@gmail.com

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