

Review

Vaccination of children and adolescents with rheumatic diseases

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Abstract

Children with rheumatic diseases (RDs) are at greater risk of infection because of their aberrant immunity and frequent use of immunosuppressive drugs. However, the use of vaccinations in such children is debated by many experts who think that the patients' immune response is insufficient to assure protection; some of them are also afraid that vaccines could trigger a persistent autoimmune response and lead to severe clinical problems including a relapse of the RD. This review describes the available data regarding the risks of vaccine administration, and the immunogenicity, efficacy and tolerability of the vaccines usually recommended for children with RDs. The data not only show that the schedule suggested for otherwise healthy children should be followed, but also that pneumococcal and influenza vaccinations should be strongly recommended because of the known risk of severe infections in patients with RD. However, there are areas in which further research is urgently required.

Key words: Immunology, Infection, Paediatric rheumatology, Prevention, Vaccination, Vaccines.

Introduction

Children with rheumatic diseases (RDs) are at greater risk of infection than age- and gender-matched subjects without RD because of their aberrant immunity and frequent use of immunosuppressive drugs [1]. They are also significantly more likely to experience infections requiring hospitalization, including septicaemia and pneumonia [2].

The recent introduction of anti-TNF treatments has contributed to changing the pattern of infections in RD patients. It has been reported that common infections, such as upper respiratory tract infections, are frequent adverse events and reasons for withdrawal of anti-TNF therapy in clinical trials and observational studies [3, 4]. There have also been case reports of serious infections due to *Streptococcus pneumoniae* during therapy, including pneumonia, severe pneumonia, necrotizing fasciitis and fatal septicaemia [3, 4]. The use of anti-TNF therapy has also been identified as a risk factor for tuberculosis and opportunistic infections associated with a dysregulated

Th1 response [5, 6]. Moreover, escalating treatment regimens mean that many patients are on their second or third consecutive biological treatment for RD, and this could modify immune defence (i.e. suppression of T and B cells) and lead to increased risks of infectious diseases [7, 8]. Finally, a number of children with RD also have other risk factors for infection, such as central lines [2].

The possibility of preventing various infectious diseases by administering the vaccines routinely given to normal children should, therefore, lead to the systematic vaccination of subjects with RD. However, this is questioned by many experts on the grounds that the patients' immune response is impaired by immunosuppressive drugs and does not induce seroprotective antibodies; some of them are also afraid that vaccines could trigger a persistent autoimmune response and lead to severe clinical problems including a relapse of RD [9, 10]. Consequently, many children with RD do not receive the vaccinations usually recommended by health authorities for healthy children [11].

This review describes the available data regarding the risks of vaccine administration and the immunogenicity, efficacy and tolerability of the vaccines usually recommended for children with RDs. Its main aims are to verify whether these patients are really exposed to a substantial risk of autoimmune disease when vaccinated in the same way as healthy children, whether they can be considered protected after vaccination and whether a special vaccination schedule should be used.

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Vaccine-related risk of autoimmune reactions

As vaccines are usually intended for healthy children, their adverse effects are less well accepted than those of drugs administered to the sick. Consequently, even rare adverse reactions to vaccines are greatly magnified and can significantly modify acceptance by physicians and parents. In the case of the development of autoimmunity and autoimmune disease, the manifestations are rare, may be non-specific, and are often so mild that they are not reported [10]. Furthermore, the time between vaccination and the occurrence of autoimmunity can vary from days to even years, and may be further extended by the fact that some vaccines require multiple administrations [10]. It is therefore difficult to define a causal relationship, although one has been supposed in some cases [11].

The vaccines with the largest number of reports of RD induction are the HBV, influenza and measles, mumps and rubella (MMR) vaccines. There are reports of > 10 patients developing RA, ReA and vasculitis after HBV vaccination, and a small number have described the exacerbation of SLE, SS, cryoglobulinaemia, polyarthralgia and myalgia [12–23]. Only a few of these case reports involved young children [12, 18–22]. Given the millions of doses of HBV vaccine given to children, the number of autoimmune diseases associated with HBV vaccine is very small. However, all of the case-control studies that have analysed the safety of HBV vaccine in large groups of subjects have found no increase in the incidence of autoimmune manifestations after its administration [21, 22]. Furthermore, no differences have been found between the autoantibody profiles of 6-year-old children who had received HBV vaccine at birth and unvaccinated controls [23]. These data fully justify the conclusion of various experts (including those of the World Health Organization) that the risk of HBV vaccine-induced autoimmune reactions is no more than theoretical [24].

Vasculitis, HSP and, very rarely, ReA and cryoglobulinaemia have been described after the administration of influenza vaccine [25–32]. Case reports suggest that influenza vaccination can induce autoimmune disease, as in the case of two patients with HSP in whom aPLs appeared [25, 26]. However, the possible relationship between influenza vaccine and the recurrence of vasculitis was specifically addressed in a retrospective study of inactivated influenza vaccine in 230 adolescents and adults with ANCA-associated vasculitis [27], which found no increase in the relapse rate of patients vaccinated during the preceding year in comparison with unvaccinated patients. Furthermore, controlled studies of children with active arthritis receiving influenza vaccine have shown that vaccination does not worsen the clinical situation, and that the few cases of increased joint involvement can be attributed to expected fluctuations in disease activity [28]. Finally, Guillain-Barré syndrome occurred with one swine influenza vaccine in 1976, but this association has not been observed since then [29–32].

MMR vaccines contain live viruses that can trigger an immune-mediated disease, such as subacute sclerosing panencephalitis (SSPE), although this is much less common than after actual infection [33]. However, autoimmune complications after the administration of measles vaccines have been reported very rarely [34]. Arthralgia and acute transient arthritis have been described in ~10–25% of children receiving MMR vaccines: these have been associated with the rubella component as joint involvement is common after rubella infection [35]. However, chronic arthritis seems very rare and studies of adult women have clearly shown that those who have received rubella vaccine are at no risk of developing it [36, 37].

There are very few data concerning the other vaccines. Koshcheeva *et al.* [38] and Kashef *et al.* [39] have, respectively, studied diphtheria and tetanus vaccines and found that they do not interfere with the activity of the underlying disease. It has also been shown that the administration of meningococcal C or meningococcal B vaccine does not aggravate the disease activity of JIA or increase relapse frequency [40–42]. Similarly, no worsening in clinical parameters, and no disease flares or changes in the doses of medications have been observed after the administration of hepatitis A [43] or varicella vaccine [44].

Global evaluations of suspected autoimmune manifestations (including RD) after vaccination indicate that those that are really related to the vaccine are extremely rare in the healthy population, and generally have a short course, a spontaneous resolution and benign prognosis. Moreover, children with RDs are at no significantly increased risk of the reactivation or recurrence of their underlying disease. All the characteristics of the autoimmune problems theoretically related to vaccination suggest that their pathogenesis is due to transient mechanisms. Although the risk factors for these reactions have not yet been identified, there is the possibility that autoimmune diseases may recur when a patient is given a booster dose of the same vaccine. Some experts would suggest that a vaccine should be avoided if it has previously caused a disease relapse.

Immunogenicity, efficacy and tolerability of vaccines in children with RDs

Inactivated and recombinant vaccines

Diphtheria vaccine

The only published study of diphtheria vaccine in paediatric RD [38] is in 55 children aged 6–15 years, who were in clinical and laboratory remission, including some who were still receiving NSAIDs or immunosuppressive maintenance therapy. The results showed that diphtheria vaccination was immunogenic and safe in 95% of the children. Protective antibody levels were maintained for a long time, and simultaneous maintenance of immunosuppressive therapy at average age-related doses did not inhibit the production of protective antibodies [38].

Tetanus vaccine

The only available data concerning paediatric RD was obtained from 40 children with SLE in whom immunosuppressive therapy did not seem to interfere with the development of immunity [39]. However, it has been suggested that immunosuppressive drugs given to mothers with a systemic autoimmune disease during pregnancy can affect the vaccination response of 17% of infants, although there does not seem to be any clear relationship between specific drug exposure and antibody response [45].

Acellular pertussis vaccine

The only study of the presence of antibodies against pertussis in paediatric RD involved 72 Russian children with RD and no history of pertussis [46], 94.4% of whom were receiving immunosuppressive therapy. Immunoglobulin G (IgG) against pertussis toxin and the other antigens of an acellular pertussis vaccine were detected in, respectively, 98.6 and 100% of the children by means of ELISA [46]. The same authors also studied the vaccination history of 134 children with RD, and found that the incidence of pertussis was 116.3 per 1000 in 43 unvaccinated children and 62.5 per 1000 in 16 children with incomplete vaccinations; no clinically distinct pertussis was diagnosed in the 75 patients who received the entire vaccination and revaccination series [46].

Inactivated poliovirus vaccine

No data are available concerning children with RD.

Haemophilus influenzae Type b vaccine

No data are available concerning children with RD.

Hepatitis B vaccine

The only published study of the immunogenicity and tolerability of HBV vaccination in paediatric RD patients [47] enrolled 39 children with JIA (all in remission and serologically negative for hepatitis B surface antigen) and 41 healthy controls. All the study population except for one subject with systemic JIA developed a significant antibody response (antibody titres >10 mIU/ml), although the antibody levels in the children with JIA were significantly lower than those in the healthy controls [47]. Vaccine responsiveness was not affected by either MTX or prednisolone treatment [47]. The authors acknowledged that the study had some limitations, particularly its small sample size and the fact that the clinical investigators were not blinded to the patients' clinical status.

Hepatitis A vaccine

No data are available concerning children with RD.

Pneumococcal vaccines

Although RD patients are more prone to respiratory infections than healthy controls [2, 7, 8], and there is evidence that pneumococcal infections can be particularly severe during treatment with anti-TNF agents [3–5], only a small number of studies have evaluated the immunogenicity,

safety and tolerability of pneumococcal vaccines in subjects with these clinical problems. The only paediatric study used the heptavalent pneumococcal conjugate vaccine (PCV-7), which was administered to children with JIA and a mean age of 12.9 years, who were being treated with anti-TNF drugs plus conventional DMARDs or DMARDs alone [48]. After a single vaccine dose, geometric mean titres (GMTs) significantly increased above the level of 0.35 µg/ml, which was considered protective against invasive pneumococcal infections for all the serotypes included in the vaccine, regardless of anti-TNF treatment, disease type and duration and baseline titres [48]. However, ~50% of the children receiving anti-TNF drugs and 25% of those treated with conventional DMARDs did not develop a 4-fold increase in their baseline antibody titres against at least five serotypes [48]. These findings seem to suggest that children being treated for RD and vaccinated with PCV-7 can be protected from invasive pneumococcal infections regardless of the type of therapy, but this protection is less efficient than in otherwise healthy children, particularly when anti-TNF drugs are used. Obviously, other studies of larger numbers of patients with different RDs receiving different treatments are needed to confirm these results.

Some information regarding the protection offered by the 23-valent pneumococcal polysaccharide vaccine to older children can be drawn from studies of adult patients. Elkayam *et al.* [49] showed that average antibody titres in patients receiving conventional immunosuppressive agents and/or CSs between 1 month and 1 year after vaccination were the same as, or slightly lower than, those observed in control subjects. In a more detailed investigation, Elkayam *et al.* [50] found similar post-vaccination GMTs among the patients, regardless of treatment, but 33% of those with RA and 21% of those with SLE showed only minimal responses. Elkayam *et al.* [51] also compared antibody responses 1 month after pneumococcal polysaccharide vaccination in 16 patients treated with MTX plus etanercept or infliximab, and 17 matched patients treated with MTX alone. The patients receiving TNF antagonists showed a trend towards lower antibody responses to most of the tested antigens; 31% were poor responders compared with 18% of those receiving MTX alone [51]. In contrast, Kapetanovic *et al.* [52] compared responses to the 23F and 6B pneumococcal antigens in patients with RA receiving MTX alone or combined with TNF antagonists, and found that the former had significantly lower antibody responses. Mease *et al.* [53] investigated immune responses to 5 of the 23 antigens in the polysaccharide vaccine in 184 patients with PsA treated with MTX alone or combined with etanercept, and found that ~20% of the patients in both groups did not show a ≥2-fold increase in antibody titre against any of the antigens. Logistic regression analysis identified MTX therapy and older age (but not treatment with etanercept) as independent factors leading to the attenuated responses [53]. On the other hand, Visvanathan *et al.* [54] did not find any difference in antibody responses between patients with RA receiving MTX alone or combined with infliximab, but

the responses of both groups were lower than those of healthy controls.

None of these studies [49–54] reported any safety problems, and the tolerability of both the PCV-7 and polysaccharide vaccine was always good in both children and adults with RD, and no different from that observed in healthy controls or subjects suffering from different diseases. No efficacy data are available for any of the pneumococcal vaccines, and it is not known how long protective titres last after vaccination in patients receiving immunosuppressive therapy, or when such patients should be revaccinated.

Meningococcal vaccines

Among the meningococcal vaccines, the meningococcal serogroup C conjugate vaccine was evaluated in a multicentre cohort study of children with RD in order to determine whether their immune response may be hampered by immunosuppressive therapy [40]: 234 children and adolescents with JIA were vaccinated, and adequate antibody levels were observed even in those receiving highly immunosuppressive medication.

Inactivated influenza vaccine

Annual vaccinations against influenza are recommended throughout the world for children with impaired immune responses, including those with RD [55, 56]. Although no randomized controlled trial has studied influenza vaccinations in these patients, there are some small studies but as most of them were carried out before 2000, they do not consider the effects of biological drugs such as anti-TNF preparations on immune responses to influenza vaccine.

Data have been collected from patients treated with CSs and/or other DMARDs. In a study by Malleson *et al.* [28] involving 34 children with JIA and 13 healthy controls, at least 95% of the patients developed presumably protective antibody levels. Pre-immunization titres, sero-response rates and final titres against influenza antigens were similar in the patients and controls. Olson *et al.* [57] reported similar results from a small study of 14 subjects with JIA aged 5–20 years. The absence of any interference with antibody response to influenza vaccine by immunosuppressive drugs has also been demonstrated by Kanakoudi-Tsakalidou *et al.* [58], who found no difference between 70 children with chronic RDs aged 4–17 years and five healthy siblings despite the fact that some of the patients had been receiving prednisone and/or other anti-rheumatic drugs for a long time.

No data are available concerning the possible impact of cytotoxic or biological drugs (e.g. TNF antagonists, rituximab or abatacept) on the immune response of children with RD to influenza vaccination. However, some findings in adults (although not entirely transferable to children) do indicate that the responses of RD patients treated with these drugs may be similar to or only slightly lower than those observed in untreated patients or healthy subjects, depending on the prescribed drug and the characteristics of the patients [58–62]. It has been shown that the response of subjects receiving adalimumab is not different

from that of matched healthy controls [59], and that the serological responses of patients with RA treated with MTX without TNF antagonists are significantly better than those of patients receiving TNF antagonists alone or combined with MTX and/or other drugs [60], although the majority developed protective antibody levels after vaccination (from 52% against H1N1 to 94% against B antigen) [60]. Similarly, Gelinck *et al.* [61] found that 80% of patients with various autoimmune diseases receiving TNF antagonists developed protective antibody titres, a percentage that was slightly but not significantly lower than those of the patients receiving conventional drugs (82–93%) and healthy controls (89–94%). In contrast, van Assen *et al.* [62] found that rituximab reduced the humoral responses of RA patients to influenza vaccination, which slightly recovered 6–10 months later. As previous influenza vaccination in rituximab-treated patients increases pre- and post-vaccination titres, it is not possible to foresee the immune response of children who have to be treated with the more recent anti-rheumatic drugs, and so specific studies are required before they can be routinely prescribed influenza vaccine.

All the studies [58–62] found that the local and systemic tolerability of influenza vaccine in children with RD was no different from that observed in healthy paediatric subjects. Solicited and unsolicited reactions are equally frequent in patients and controls, and the total number of severe adverse events is very small in all groups [28, 38, 57]; only Malleson *et al.* [28] found that their JIA patients felt unwell for longer than the controls.

HPV vaccine

No data are available concerning children with RD.

Live attenuated vaccines

Oral poliovirus vaccine

Immunization coverage against poliomyelitis and the post-vaccination level of immunity have been assessed in 136 children with RD who had previously received oral poliovirus vaccine [63]. The proportion of children with RD who were seropositive to all three serotypes was 75.8% [63]. Although international guidelines state that live vaccines are contraindicated in patients receiving anti-TNF therapy, there is a report of one such patient who inadvertently received live polio vaccine without suffering from any infectious sequelae [64].

MMR vaccine

There are two published studies of MMR vaccine in paediatric RDs, both involving children with JIA. The first was a retrospective observational multicentre cohort study of 314 patients born between 1989 and 1996 [65]. Disease activity and medication use were compared during the 6 months before and 6 months after vaccination between patients vaccinated at the age of 8 and 9 years and those who had not been vaccinated by that age. In the second study, the effect of low-dose MTX therapy alone or combined with etanercept on the immunogenicity and tolerability of an MMR booster was evaluated in 15 children

[66]. Neither study observed any overt MMR or secondary severe infections. Borte *et al.* [66] also found that low-dose MTX therapy following MMR vaccination did not interfere with T-cell-mediated immunity *in vitro*, and that neither low-dose MTX nor etanercept given simultaneously with revaccination markedly interfered with the generation of long-lived virus-restricted T cells or protective levels of virus-specific IgG antibodies. Arthralgia and acute transient arthritis have been described in children receiving MMR vaccines (see above) [35–37].

Varicella zoster virus vaccine

A number of reports show that complicated varicella and herpes zoster are very common in patients with RD [67–70]. However, varicella vaccination is contraindicated in patients taking glucocorticoids at prednisone-equivalent doses of 2 mg/kg/day or 20 mg/day for >14 days [71]. Consequently, Athreya and Lindsley [72] suggested measuring serum antibody levels and immunizing seronegative patients with varicella zoster virus (VZV) vaccine 3 weeks before starting the therapy. However, although this approach can be adopted in some cases, RD therapy is begun during the acute phase in the majority of situations and cannot be postponed until after the administration of VZV vaccine.

The immunogenicity and tolerability of VZV vaccine have been assessed in only one study of 25 susceptible children with juvenile RDs and 18 controls [44]. All the patients were receiving MTX, 13 were also receiving prednisone and five other DMARDs. Positive VZV IgG titres were detected in 50% of the seronegative patients and 72.2% of the controls 4–6 weeks after vaccination [44]. No episodes of overt varicella and no severe adverse reactions were observed during the follow-up [44].

Live influenza vaccine

No data are available concerning children with RD.

Vaccine recommendations for children with RD

Analysis of the international literature published during the past 15 years shows that there are only a few studies of immunization in children with RDs. Some vaccines have not been specifically studied at all; in other cases, the studies have involved small groups of patients with different clinical characteristics or therapies. No randomized, double-blind, controlled studies are available, and no clinical efficacy or effectiveness data relating to individual vaccines have been collected. The studies that are available show that conventional RD therapy generally has little effect on immune responses to vaccines, whereas the new biological drugs can reduce antibody production. However, this evidence is not very satisfactory because it does not make it possible to establish whether certain biological drugs reduce immune responses more than others, what doses can interfere with antibody responses or whether active disease (*per se* or because of the treatment it requires) justifies the deferral of vaccination. Moreover, although some case reports have suggested

possible associations between vaccinations and the induction or exacerbation of autoimmune reactions, few data relate to children and they have not been confirmed by prospective investigations or thorough case-control studies. In addition, the lack of specific guidelines for children with RDs leads to discordances in clinical practice [11] and explains why about one-third of them are incompletely vaccinated [73].

The current data and risk/benefit ratios of vaccinations are sufficient to encourage their use in children with stable RD. This recommendation applies to inactivated and recombinant vaccines, whatever the degree of immunosuppression, and all disease subgroups regardless of the treatments given. Vaccinations should be postponed only in the case of severe active RD (and then only until the child has stabilized) in order to avoid any misunderstandings related to safety issues (i.e. adverse events attributed to a vaccination but actually due to the underlying disease), and a vaccine should be avoided if it has previously caused a disease relapse. There are few data concerning the immunogenicity and safety of live attenuated vaccines in children with RD. The available evidence suggests that MMR vaccine is safe, whereas other live vaccines should not be administered in the presence of severe immunosuppression until further studies are available. Furthermore, pneumococcal and influenza vaccinations should be strongly recommended because of the increased risk of these infections associated with immunosuppressive therapy.

In conclusion, a number of areas should be covered by future research. First of all, there is an urgent need for studies of the immunogenicity, safety and efficacy of the new PCVs and adjuvanted influenza vaccines, including when they are co-administered. There is also a need for studies of HPV vaccines (usually administered after the onset of RD) as immunocompromised patients are at increased risk of HPV infection. It is essential to clarify how long vaccine-induced immunity lasts, and whether vaccinations actually protect RD patients against the respective infections. Finally, educational programmes are required for health-care workers, the patients and their families in order to guarantee adequate protection against infectious diseases in this high-risk category of subjects.

Rheumatology key messages

- The current data are sufficient to encourage vaccinations in children with RD.
- Vaccination recommendations for healthy children should continue to be followed after diagnosis of RD.
- Pneumococcal and influenza vaccinations should be strongly recommended for children with RD.

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