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Safety and Efficacy of Vaccinations In Pediatric Rheumatic Diseases.

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ABSTRACT

Rheumatic diseases in pediatric patients effect the immune system in a such a way that their immune response to fight infections reduces to a certain extent. Vaccinations are very important in all pediatric age groups, according to the respective immunization schedule. But with a reduce host immune response, how safe is it to administer vaccines in pediatric patients with rheumatic diseases is something a pediatrician should think about. With the regular assessment of the protective antibody titres, it has been proved that all vaccines, except BCG, are safe and recommended to be administered in pediatric patients with rheumatic diseases, according to the EULAR recommendations, with the necessary booster doses. In this article, all vaccines to be administered in children and their safety in patients with rheumatic diseases as well as those on the different immunosuppressive drugs, has been discussed in detail, with references of the various studies and trials already performed and available in the world literature.

Keywords: Pediatric rheumatic diseases, vaccines, seroprotection.

INTRODUCTION

Rheumatic diseases in children increase the risk of infections which worsens the morbidity of the disease and contributes to mortality.[1-3] In order to prevent a number of such infections, effective and safe vaccination is a key.

Immunogenicity of a vaccine is measured by geometric mean antibody titres (GMT) or geometric mean antibody concentrations (GMC), specific for the vaccine. The immunogenicity of a vaccine in children with rheumatic diseases is different from the healthy population because of the disease itself or due to the immunosuprressive treatment of the disease. The GMT or GMC differs for every vaccine as the cellular and humoral immune response for every pathogen differs.[4-6]

It is important for the protective immunologic memory to 'persist' besides the short term immune response induced by the vaccines.[7,8] But the long term effects of many vaccines is still unknown.

The rates of adverse effects of a vaccine compared to the healthy groups, vaccination induced increased activity of disease and infections caused by live attenuated vaccines, particularly in patients who are on high doses of immunosuppressive drugs and whether these vaccines can cause autoimmune diseases are some major issues of vaccine safety and efficacy in children with rheumatic diseases.

Vaccination in rheumatic conditions has created awareness over recent years. The European League Against Rheumatism (EULAR) in 2011, has published recommendations for vaccination of adult and pediatric patients with rheumatic diseases. In 2012, the Brazilian Society of Rheumatology also published recommendations for vaccination of patients with rheumatic diseases.[9-11] From these recommendations, it was concluded that non-live vaccines are adequately safe and immunogenic. Live- attenuated vaccines need to be avoided in patients who are on high dose immunosuppressive drugs or biologicals, but can otherwise be administered to children with rheumatic diseases.

The safety and efficacy of vaccination in rheumatic disease patients still remains to be of concern because not all vaccines have been studied in such patients and the studies are limited. A periodical overview in order to assure the safety and efficacy of vaccination in this vulnerable group of patients, is necessary, as advised by the EULAR recommendations.[12]

In this review, we provide an update of the effects of immunosuppressive drugs and biologicals on the safety, efficacy and immunogenicity of non-live and live-attenuated vaccines. We also provide information on adjuvants and their association with adverse effects.

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Immunogenicity Of Vaccines In Children With Rheumatic Diseases And Immunosuppressive Drugs

1. **Glucocrticoids**
Children who are on low dose glucocorticoids show lower rates of seroconversion or GMT but protective antibody titres are still achieved.[13] Many studies showed that a higher dose of glucocorticoids or immunosuppressive drugs used concomitantly showed lower responses but still protective levels were achieved. According to a study, The persistence of antibodies specific for vaccines like MMR- measles, mumps, rubella ; TD -tetanus diphtheria; was not affected by the use of glucocorticoids.[14] Thus, it can be concluded that low dose glucocorticoids have no general detrimental effects on the vaccine immunogenicity or antibody titres.

2. **METHOTREXATE**
From the various studies on Methotrexate, it has been concluded that this drug did not have any effect on the short-term immunogenicity of vaccines or on the antibody titres over time.[14-22]

3. **BIOLOGICALS**
Tumor necrosis factor -alpha has been the most commonly studied biological drug and for its effects on vaccine immunogenicity.[23,24] Studies have shown that majority of patients on biologicals achieved the protective antibody titres but the actual antibody concentrations in such patients was lower than those who were not on biologicals.[16,25-36] In addition, it was found that the levels of antibody rapidly declined over time in patients who were on biologicals.[16,36] A faster decrease in seroprotection rate is caused in such cases due to an initial lower GMT and rapidly declining antibody titres. In order to ensure protection in these patients, it is necessary to monitor the GMT regularly and additional booster vaccinations need to be considered. It would be a better choice to administer specific vaccines prior to starting biological drugs.

Non-live composite vaccines

1. Human Papillomavirus (HPV) Vaccine- Two types of HPV vaccines are currently available- the bivalent vaccine against HPV 16 and 18, and the quadrivalent vaccine against HPV 6,11,16 and 18. In a study it was concluded that the bivalent vaccine in patients with juvenile idiopathic arthritis showed seropositivity for up to 12 months. Though the GMCs in these patients were lower than in the controls, there was no statistical significant difference in the GMC over a period of time.[37]
In patients with Systemic Lupus Erythematosus (SLE), there is a higher risk of persistent HPV infections.[38,39] A number of studies showed that a majority of SLE patients seroconverted but the antibody titres were lower than that in healthy groups.[40] This concludes that the long term protection in SLE patients against HPV is unclear and hence, more studies are needed to assess the immunogenicity of HPV vaccine in SLE patients.

2.H1N1 Vaccine : From the various studies it has been concluded that the seroprotectivity against influenza virus was almost similar in patients and healthy control group,[26-28,30,31,36,41-46] but the antibody concentrations was lower in the patients. In patients with SLE, the sereoprotection rates, seroconversion rates, and GMT was found to be lower than in the healthy group. This may be due to the higher disease activity index in patients with SLE.[42]

3.Hepatitis A and Hepatitis B Vaccine
Adequate immunogenicity to Hepatitis A vaccine was found in patients who were not on anti TNF alpha drugs.[35,47,48]
Studies on the immunogenicity of Hepatitis B vaccine showed that majority of the patients achieved protective antibody levels as the healthy control group but the persistence of immunity against the Hepatitis B virus was found to reduce over time in children with pediatric rheumatic diseases.[17,25,47,49,50] This necessitates the need of booster vaccines for Hepatitis B virus.

4.Meningococcal Vaccine: Neisseria Meningitides C vaccine has been found to be safe and immunogenic in JIA patients.[16,51] The serum levels of MenC-IgG levels decreased over time in patients with JIA. Patients on biologicals showed an accelerated decline in the levels of antibody.[16]

5.Pneumococcal Vaccine: A review of a study showed that pediatric patients with JIA achieved a seroprotection rate to the 7-valent pneumococcal vaccine similar to that of the healthy controls. These patients were on Methotrexate (MTX) or Cyclosporine, with or without the concomitant use of Glucocorticoids. But those patients who were on anti TNF alpha achieved seroprotection but the concentrations of antibody were significantly lower.[34]

6.Diphtheria-Tetanus (DT) Vaccine : DT vaccine in pediatric patients with rheumatic diseases produced antibody levels similar to the control group but showed lower seroprotection rates and antibody concentrations over a follow-up of 7-16 years, compared to the healthy control group.[14,15,52,53]

7.Other Vaccines: No studies or articles could be found on other vaccines like Haemophilus influenza type B vaccine, Pertussis vaccine or poliovirus vaccine, vaccines against typhoid fever, tick-borne encephalitis, Japanese encephalitis, Rabies or Cholera.

Live Attenuated Vaccines:

1.Measles, Mumpd, Rubella (MMR) Vaccine : MMR vaccine administered to children with pediatric rheumatic diseases showed immune responses that was comparable to healthy groups.[29] A study also showed that all patients who were vaccinated with MMR vaccine had significant antibody concentrations and were seroprotected even after 1 year of being vaccinated.[24] While another study showed that after 10 years of the MMR booster vaccination, the protective levels of antibody in JIA patients was lower than that of the control group.[54]

2.Varicella Zoster Vaccine: Studies have showed that pediatric patients with rheumatic diseases responded with lower rates of immunity on being vaccinated with Varicella Zoster vaccine.[13] The risk of infections was found to be higher in patients on biological drugs as compared to those on disease modifying anti-rheumatic drugs (DMARDs).[55]

3.Bacillus Calmette-Guerin (BCG) Vaccine: BCG vaccine is known to cause inflammation at the site of vaccination in patients with Kawasaki disease, hence, it has been advised to with-hold this vaccine in active Kawasaki Disease patients.[11] It has also been suggested that due to the lower induration size of the tuberculin skin test, pediatric patients with JIA have low rates of protection after vaccination.[18,56]

4.Yellow Fever Vaccine: This vaccine has showed good immunogenicity in patients with rheumatic diseases but the response was found to be reduced in patients using anti -TNF alpha drugs.[57] According to the EULAR recommendations, booster dose can be given to patients who are on low dose corticosteroids and on Methotrexate dosage lower than 15mg/m^2.[12]

DISCUSSION

Vaccination holds its own importance in pediatric age group, whether normal children or diseased. In pediatric patients with rheumatic diseases, vaccines have been generally found to be immunogenic. For assessing the effect of a drug on the immunogenicity of a vaccine, a comparison needs to be done between patients who are not using the drugs and patients who are using the drugs. From the studies mentioned earlier in the text, it has been concluded that low dose corticosteroids (less than 20mg/day) and Methotrexate do not have a negative effect on the immune response, hence, vaccines have good immunogenicity in patients who are on these drugs. On the other hand, biological agents may have a slightly negative effect on the long term immunogenicity of vaccines. Sero-protection rates being usually adequate, antibody concentrations are lower in these patients. Vaccines, still, need to be administered in patients who are on biologicals but require booster doses of the same.

The protective antibody levels need to be persistent in order to ensure long term protection against vaccine-preventable infections. In pediatric patients with rheumatic diseases, the persistence of protective antibody levels is lower as compared with the healthy control group.[16,54] Biological agents not only lower the antibody concentrations induced by the vaccines but also accelerate the natural lowering of antibody levels. Thus, to ensure the long term protection in these patients, it is important to assess the antibody levels regularly and administer the booster doses of vaccines. Assessment of cellular memory may help in studying the long term protection against vaccine-preventable diseases in vaccinated pediatric rheumatic disease patients.

Vaccination in pediatric patients with rheumatic diseases are quite safe and do not cause any serious adverse events. Vaccination does not influence the disease activity in majority of patients.

Live attenuated vaccines have been found to not cause any vaccine-induced infections in pediatric patients with rheumatic diseases. Thus, booster doses can be administered even in patients on biological drugs. However, BCG vaccine should not be administered in patients who are on biological drugs or on high dose immunosuppressive drugs, as there is not much data on its safety. Larger controlled trials are necessary to study rare adverse events in patients on biologicals and high dose immunosuppressive drugs.

More studies and trials are needed to understand and prove the efficacy of vaccines in pediatric patients with rheumatic diseases, especially in those on biological drugs.

CONCLUSION

It is hence, advocated to administer vaccines in pediatric patients with rheumatic diseases with a regular assessment of protective antibody levels in order to decide the frequency of administration of booster doses, according to the EULAR recommendation.

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