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Review

Vaccine use in primary immunodeficiency disorders

Q1 Nicola Principi*, Susanna Esposito

Pediatric Highly Intensive Care Unit, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

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ABSTRACT

Primary immunodeficiency disorders (PIDs) are a heterogeneous group of rare, congenital and genetically determined conditions caused by one or more defects of innate and/or adaptive immunity. In subjects suffering from PIDs, an unusually increased susceptibility to infections is demonstrated. As infections condition the final prognosis of most PIDs, clearly defined prophylactic practices are essential. In most cases, intravenously or subcutaneously administered immunoglobulin remains the mainstay of treatment, although antibiotics and antifungals can be added under some conditions, particularly when the infections are highly recurrent despite immunoglobulin replacement. Vaccines could also play a role, but their administration leads to different results depending on the type of PID: in some cases, immune response is not impaired, and vaccines can evoke the same protection as that usually induced in healthy subjects; in others, the immunodeficiency significantly interferes with antigen stimulation of the immune system and, depending on the type and degree of impairment, little or no protection is evoked. Moreover, particularly when live vaccines are given, significant vaccine-related adverse events can occur, including the emergence of disease from vaccine strains. The main aim of this paper is to discuss what is currently known about how and when vaccines can be used in patients with PIDs in order to facilitate physician choices and assure the best possible patient protection.

1. Introduction

Primary immunodeficiency disorders (PIDs) are a heterogeneous group of rare, congenital and genetically determined conditions caused by one or more defects of innate and/or adaptive immunity. In addition to a predisposition to autoimmunity and malignancies, they are characterised by an unusually increased susceptibility to infections [1]. As infections play a major role in conditioning the final prognosis of most PIDs, clearly defined prophylactic practices are essential. In most cases, intravenously or subcutaneously administered immunoglobulin remains the mainstay of treatment [2], although antibiotics and antifungals can be added under some conditions, particularly when infections recur frequently despite immunoglobulin replacement [3]. Vaccines could also play a role in preventing infections with vaccine-preventable diseases, but they have different results depending on the type of PID: in some cases, the immunodeficiency does not significantly interfere with the immune response to the vaccine and the vaccine can evoke the same protection as that usually induced in healthy subjects; in others, the immune response to vaccine antigens is impaired and, depending on the type and degree of impairment, little or no protection is evoked. Moreover, particularly when live vaccines are given, significant vaccine-related adverse events can occur, including the emergence of disease from vaccine strains [4].

These premises lead to the conclusion that the use of vaccines in patients with PIDs should be precisely defined in order to assure the greatest protection when possible, and to avoid the risks of adverse events in patients who cannot receive one or more vaccines. Unfortunately, much of the published information concerning the safety, tolerability, immunogenicity and efficacy of the individual vaccines in patients with different PIDs is insufficient or inaccurate. Most PIDs are very rare and some of them have only recently been identified [5] or have been excluded from prelicensure studies: these are *per se* important limitations when evaluating the impact of a vaccine. Moreover, the generalisability of study findings are further limited by the fact that the type and degree of immune deficiency can significantly vary within the same category of PIDs. Consequently, the use of vaccines in PID patients is not clearly defined

* Corresponding author at: Pediatric Highly Intensive Care Unit, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Commenda 9, 20122 Milano, Italy. Tel.: +39 02 55032203; fax: +39 02 50320206.
E-mail address: nicola.principi@unimi.it (N. Principi).

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even in high-quality reviews of PID treatment [6–8], and is poorly defined in most of the guidelines prepared to provide primary care and specialty clinicians with recommendations for the active vaccination of immunocompromised hosts [4,9,10].

The main aim of this paper is to discuss what is currently known about how and when vaccines can be used in patients with PIDs in order to facilitate physician choices and assure the best possible patient protection.

2. Primary immunodeficiency diseases

PIDs are classified on the basis of the component of the immune system that is primarily involved [3]. Defects of innate immunity include disorders of phagocytes, Toll-like receptor (TLR)-mediated signalling, and complement, whereas defects in adaptive immunity include B and T lymphocyte deficiencies. The first of these subgroups includes antibody deficiency syndromes and combined immunodeficiencies (CIDs); the second includes severe combined immunodeficiency disease and T cell immunodeficiencies caused by thymus defects (of which DiGeorge syndrome is the most important). All of these forms are generally characterised by an increased and distinctive susceptibility to various types of pathogens depending on the nature of the immune defect. In addition, some forms of PID only involve immune dysregulation, whereas others (the immunodeficiency syndromes) have a more complex phenotype in which immunodeficiency is only one of many components. The most widely studied in this last group are Chediak-Higashi syndrome (CHS), Wiskott–Aldrich syndrome (WAS), ataxia-telangiectasia (AT), hyper-IgE syndrome (HIES), and Shwachman-Bodian-Diamond syndrome.

2.1. Defects of innate immunity

2.1.1. Phagocytic cell defects

Phagocytic cells play a key role in defending against bacteria and fungi, and so patients with deficiencies in the number and/or function of cells experience recurrent and severe fungal infections (especially those due to *Candida* and *Aspergillus* species) and bacterial infections (mainly those due to *Staphylococcus aureus*, *Serratia marcescens*, *Nocardia* species and *Burkholderia cepacia*) [11]. Respiratory tract and cutaneous infections predominate, but deep-seated abscesses are also common. Recurrent oral stomatitis is present in most cases. Chronic granulomatous disease (CGD) is the prototype of this group of clinical conditions [12].

Although the pathogens mainly involved in causing infections in patients with phagocytic cell defects are not included in the currently available vaccines, vaccination remains a very important preventive measure. Consequently, vaccines should be administered whenever possible bearing in mind that the immune response to the vaccines, and their safety and tolerability, may vary widely from disease to disease and will depend on whether the vaccines are inactivated or live.

Although no controlled study has been published, inactivated vaccines can be considered effective, safe and well tolerated in PIDs caused by all phagocytic cell defects because there have never been any reports of severe clinical problems following their administration [4,9]. All of them (including pneumococcal and influenza vaccines) can therefore be recommended using the same schedules as those aged for healthy subjects of the same age [4,9].

The use of viral vaccines has to be carefully evaluated. The immune defects in patients with CGD and congenital or cyclical neutropenia do not alter the response to antigen stimulation and there should be no problem with live attenuated vaccines. However, they are contraindicated in patients with other phagocytic cell defects, including leucocyte adhesion deficiency and cytotoxic granule-release defects, because these can be associated with defective T cell and natural killer cell toxicity [13,14], which could cause an altered immune response to live viral vaccines and lead to the development of very severe disease associated with the vaccine strains. Chediak-Higashi syndrome is the best example of this [15].

Live attenuated bacterial vaccines give rise to the same problem. There is convincing documentation of an increased risk of developing disease due bacillus Calmette-Guérin (BCG) vaccine, and disseminated BCG infection has been described in patients with CGD even a long time after vaccination [16–18]. There are no published reports of complications following the administration of live typhoid vaccine; however, the fact that minor salmonella bacteremia is frequent in subjects with CGD [19] suggests little defence against these pathogens and a theoretical risk when live bacteria are given. All of these findings seem to indicate that, with the exception of live attenuated viral vaccines in the case of CGD and congenital or cyclic neutropenia, attenuated live viral and bacterial vaccines can be recommended for subjects with phagocytic cell defects when there is evidence of impaired antibody production.

2.1.2. Complement deficiencies

Deficiencies in the components of the early classical and lectin pathways are primarily accompanied by upper respiratory infections and acute otitis media together with lupus-like symptoms. Patients deficient in alternative pathway components and terminal pathway proteins are also susceptible to invasive infections due to encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* [20]. As all vaccines are generally safe and well tolerated in subjects with these clinical conditions, they should be administered in accordance with the normally recommended schedule but, given the clinical importance of infections due to encapsulated bacteria, conjugate vaccines against these pathogens should be systematically included. Influenza vaccine is also strongly recommended, mainly as a means of preventing bacterial complications [4].

Although the immunogenicity and safety of the vaccines has not been adequately evaluated in patients with deficiencies in the components of the early classical and lectin pathways, the absence of any reports indicating an increased risk of vaccine-related adverse events or vaccine failures after vaccination suggests that all of the vaccines are as immunogenic and safe as in healthy subjects.

There are a number of reports indicating that the vaccine response of some patients with deficiencies in alternative pathway components and terminal pathway proteins may be impaired, which may explain the greater susceptibility to some infections such as those due to encapsulated bacteria [21–23]. Despite this, most of the studies that have evaluated the immunogenicity of the tetravalent polysaccharide meningococcal vaccine (4PMV) in subjects with these deficiencies have found that, in comparison to healthy individuals, median values of serum bactericidal and opsonophagocytic activity were similar or only marginally reduced [24–28]. However, some patients remain at higher risk of meningococcal disease in the years following vaccination as demonstrated by the evidence that during the 3–5 years following immunisation breakthrough infections in vaccinated patients can occur. Moreover, analysis of the correlation between meningococcal disease occurrence and antibody levels evoked by vaccination has evidenced that infections are more common in patients with the lowest immune response [29,30]. As these findings were considered clear evidence that some subjects could remain unprotected, it was concluded that further efforts should be made to assure protection against infections due to encapsulated bacteria. It was therefore recommended that the post-vaccination immune response of all subjects with these kinds of PID should be monitored, and that those with inadequate levels of protection should

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