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SARS-CoV-2 vaccination in Primary Antibody Deficiencies: an overview on efficacy, immunogenicity, durability of immune response and safety

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Abstract

Purpose of review:
This review aims to summarize the current best knowledge on the efficacy of COVID-19 vaccination in vulnerable patients affected by Primary Antibody Deficiencies (PADs), both in patients previously infected and vaccine-immunized, focusing also on the durability, on the need for multiple booster doses and on the safety of anti-SARS-CoV-2 vaccines.

Recent findings:
Patients vaccinated for SARS-CoV2 have variable humoral response, still showing a tendency towards an increase in antibody titers, with factors such as booster doses, previous infections, age and specific genetic mutations influencing the outcome. Long-lasting cellular responses to SARS-CoV-2 vaccination instead, mostly of the T-cell type, have been observed. Overall the duration of protection given by vaccinations is sufficient and increased upon further simulations. Furthermore the safety profile in PID patients is excellent, with most adverse events being transient and mild and no major AE reported

Summary:
Several studies have emphasized the benefit of vaccinating patients with PADs against the SARS-CoV-2 virus and the necessity of administering booster doses. This review, by gathering the most recent and significant data from the scientific literature, could be helpful in clinical practice in the management of disease prevention in patients affected by primary immunodeficiency and also serve as inspiration for further in-depth clinical research.

Keywords: Sars-Cov2 vaccination; Covid; Vaccination; Antibody deficiency; Efficacy; Safety; Humoral and Cellular response; Inborn Errors of Immunity.

Keypoints:

- During the pandemic several questions have emerged on real efficacy of the vaccination in patients affected by Primary Antibody Deficiencies
- Despite a huge variability in individual response, COVID-19 vaccination in PAD was safe and able to elicit both humoral and cellular immune responses with an improvement in enhancing immunity after booster doses
- These findings underscore the importance of tailored vaccination strategies and ongoing monitoring for this vulnerable population.

Introduction

During the COVID-19 pandemic, vaccination against SARS-CoV-2 has played a pivotal role in the reduction of the severity of disease, occurrence of complications, burden of hospitalization and in the control of viral diffusion. While efforts in vaccination have been enormous, concerns have emerged regarding the efficacy and safety, particularly among individuals with Primary Immunodeficiencies (PIDs).

This review aims to summarize the latest knowledge regarding efficacy, disease burden reduction and safety in PID patients and in particular in those with Primary Antibody Deficiencies (PADs), the most common primary immunodeficiencies.

PIDs encompass a heterogeneous group of genetic disorders ranging from those affecting the cellular component of the innate and adaptive immune system, passing to those with primary antibody defects and finally the combined forms in which both cellular and humoral components are affected together.

Patients with immunodeficiencies have increased susceptibility to infections and their immune response to vaccination may show significant differences with respect to the healthy population.

PADs can be further subdivided into the following groups: X-linked Bruton's agammaglobulinemia (XLA) characterized by severe reduction in all serum immunoglobulin isotypes with profoundly decreased or absent B cells; Common variable immunodeficiency (CVID) in which there is reduction in at least 2 serum immunoglobulin isotypes with normal or low number of B cells; hyper IgM syndrome, in which both IgG and IgA are severely reduced but with normal/elevated IgM and normal numbers of B cells; specific antibody deficiency, in which patients, despite normal immunoglobulins and B cells, do not mount an immune response to specific antigens, such as pneumococcal vaccine, and transient hypogammaglobulinemia of the infancy, a transient immunodeficiency characterized by reduction in the IgG isotype levels. [1]

Overall, the role of vaccination in PADs is multipurpose: it is recognized as diagnostic,

prognostic, therapeutic and may even be used in patients with residual B-cell function to provide humoral immunity to specific infective agents. [2]
While mRNA vaccines, based on their mechanism of action, can be administered safely in PAD, live attenuated vaccines are not recommended in patients with major antibody deficiencies. [3]
This last statement was further confirmed on December 2020 by the European Medicines Agency (EMA), with the approval of vaccines against COVID-19 infection, and the recommendation by the European Society for Immunodeficiencies (ESID) to vaccinate PAD patients using mRNA vaccines, but not live attenuated ones. [4]
The rationale to use mRNA vaccinations in PAD patients, who might expectedly mount a partial or poor immune response due to their defective immune system, came from previous studies in which it was demonstrated that the use of the flu vaccine was able to induce robust T cell responses (cellular response) even in the absence of a complete humoral response [5].
From the beginning of the pandemic, several studies have been conducted to evaluate the humoral and cellular immune responses, as well as the safety and protection durability of the SARS-CoV-2 vaccination in PAD patients.

Humoral response

The humoral response to COVID-19 vaccination in PADs patients has been a subject of extensive research, with studies spanning from the start of the pandemic up to now with the majority revealing consistent findings, but also some contrasting results.

All studies have primarily focused on seroconversion and production of antibodies against the spike protein of the SARS-CoV-2 virus, with a minority also focusing on the neutralizing or blocking activity of these antibodies to their specific targets(e.g. anti trimeric S-protein and/or anti-RBD antibodies). Notably, Salinas et al. and Quinti et al. demonstrated that only 20% of CVID patients seroconverted to Pfizer-BioNTech vaccination after the initial course of 2 doses, also highlighting the reduced production of specific serum IgAs after vaccination. [6, 7]

Subsequent studies reported conflicting results. In particular, Bergman et al. [8] reported that 73% of patients with Inborn Errors of Immunity (IEI), including CVID, XLA, Combined Immunodeficiency (CID), and monogenic defects, seroconverted after the primary vaccination cycle with BNT162b2. Similar findings were observed by Helo et al. [9], where 65% of CVID patients demonstrated seroconversion and by Hagin et al. [10] where 69% of the IEI patients responded to the Pfizer-BioNTech vaccine. In this last study an age-dependent vaccine response was observed with older patients exhibiting lower antibody titers. Also Amodio et al. [11] revealed an even higher percentage (86%) of specific anti-spike antibodies in CVID and XLA patients vaccinated with BNT162b2, albeit at much lower levels compared to healthy controls (HC).

The analysis of responses to different vaccine types, conducted by Romano et al. [12], found that 80% of CVID patients had a humoral response to either BNT162b2 or mRNA-1273

vaccines, with most patients developing neutralizing antibodies and with similar results obtained also by. Delmonte et al. [13] who observed detectable anti-S antibodies in 85% of IEI patients after vaccination.

Other recent studies confirmed the immunogenicity of COVID-19 vaccines in IEI patients with a humoral response in about 75% of them [13, 15]. In detail, Sauerwein et al. [15] showed that 44% of enrolled patients were CVID, and 48% of CVID patients developed sufficiently relevant antibodies. Interestingly, anti-S antibody avidity was reduced in CVID after 3 doses but not after the primary cycle in the context of an impaired cTFH (Circulating T follicular helper) response [16]
In 2022, Fernandez-Salinas et al. [17] reported that in a cohort of 33 CVID patients, 33% responded to vaccination with sufficient antibody titers whereas a strong difficulty in generating RBD-specific memory B cells (MBCs) was reported after the primary vaccination cycle.
Pham et al. obtained similar results with 48% of 33 patients producing RBD-specific IgGs, but only 6% exhibiting ACE2 receptor blocking activity higher than 50%, indicating a suboptimal neutralization activity in CVID patients, despite the ability to produce antibodies directed against viral antigens. [18]

Shields and Van Leeuwen obtained similar seroconversion proportions in their cohorts. In particular, Shields et al. found that 52.2% of CVID patients had detectable antibodies, but only 37% showed a viral neutralizing activity > 50%, compared to 100% of HC. [6]
Interestingly, Van Leeuwen et al. demonstrated a higher percentage of seroconversion among patients vaccinated with BNT162b2 in comparison to the ChAdOx1 nCoV-19 vaccine (65.7% vs. 48.0%) and that patients with mild antibody deficiencies had seroconversion rates comparable to HC with lower levels of neutralizing antibodies. [19]
Other authors reported that in CVID patients vaccinated with various COVID-19 vaccines (BNT162B2, mRNA-1273 or ChAdOx), a much higher anti SARS-CoV-2 specific antibody in comparison to previous studies ranging from 71.4 to 83% even if the magnitude was approximately 50% compared to HC. [20,21]

Several studies have highlighted the importance of booster doses in IEI patients, which significantly increased antibody levels, especially in those receiving mRNA vaccines compared to non mRNA vaccines. [7] Further analysis done by Barmettler [22], Erra [23] and Ponsford et al [24] found that a booster dose improved humoral responses among PAD patients and higher post-vaccination titers were observed in patients vaccinated with BNT162b2 Pfizer, a mRNA vaccine.
In line, Zimmerman et al. [25] showed that mRNA vaccine booster was able not only to produce a higher titer of serum neutralizing antibodies in PAD patients, but also a higher neutralizing activity against the Omicron variant.

Overall, the third dose increased the rate of responders (seroconverters) among CVID, albeit achieving a lower titer of anti-S and neutralizing antibodies against the Wuhan strain when compared to healthy subjects. [23,26]

Several papers analyzed whether or not a prior SARS-CoV-2 infection enhanced both the quantity and quality of the humoral response in vaccinated patients. Pulvirenti et al. [27] and Erra et al. [23] revealed that convalescent CVID patients exhibited a higher percentage of detectable anti SARS-CoV-2 antibodies compared to immunized COVID19-naive patients. Furthermore, natural infection primed different B cell responses, leading to more efficient memory B cells (MBCs) responses when boosted by vaccines, while BNT162B2 vaccination alone, shifted the immune response more towards atypical memory B cells (ATMs) generation with a lower binding capacity of anti-spike IgG.

Among patients with CVID, there is a difference in the production of MBCs and in antibodies. Based on this evidence, a study released by Piano Mortari et al done on 47 CVID patients identified the possibility to subclassify them in 4 different groups based on their ability to generate MBCs and Abs in response to the vaccination: Group 1 patients having both IgM and switched MBCs, group 2 with IgM MBCs present in normal numbers but switched MBCs severely reduced, group 3 with all MBCs missing and group 4 having low numbers of total B cells and with a significant reduction of mature-naive B cells and the absence of MBCs. Notably, patients of group 1 with IgM MBCs showed less severe disease, while those lacking IgM MBCs had worse outcomes. [28]

Similar results were obtained also by Salinas et al [29] with patients having a tendency towards higher anti-S antibodies after being naturally infected and then vaccinated.
Other studies reported contrasting results [6,24,29] showing that vaccination in post-infected patients was not associated with significant differences in antibody titers.

However it is important to underline the great variability in all the mentioned studies concerning the methods and cut-offs used to define seroconversion or presence of neutralizing antibodies (nAbs) and the specific timepoints in which sampling after vaccine doses was done.

Cellular response

Based on studies conducted regarding the immune response to flu vaccinations in patients with PAD, where a robust cellular response was observed despite a limited humoral one, several authors studied the cellular response of these patients after SARS-CoV-2 vaccination.
Cellular response to SARS-CoV-2 is one of the key determinants of severe disease protection, especially months after viral and/or vaccine exposure in the context of a naturally declining, or even absent, humoral immunity [30]. Beside antibodies and memory B cells, T cells contribute to protection upon exposure to the virus. T cells have also been shown to be less affected by VOC's (variants of concern) ability to overcome the protective effect of neutralizing antibodies produced as a result of natural infection and/or vaccination [31]. This may also be important in a context such as CVID where B-cell pool and differentiation and memory B-cells and T follicular helper (Tfh) responses are impaired, potentially leading to

weak or no nAbs and short-term antibody production [29,32] and thus leading to defective components of layered defenses against SARS-CoV-2. [33]
Contrary to expectations, data concerning the cellular response after anti-SARS-CoV-2 vaccination have not yielded encouraging results. In fact, several studies have demonstrated that PAD patients exhibited a poor T-cell response compared to HC. [6,10,11,17,19,20]
A weaker cellular response has been observed not only after immunization but also following infection and vaccination after infection. [27]
This weak response observed after Covid-19 vaccination could be explained by insufficient stimulation given by the first contact with the SARS-CoV2 antigen; stronger responses are expected to occur after multiple exposures to this stimuli (second dose and boosters), as happened with Flu vaccination. [29]
Indeed, several studies have demonstrated an enhancement of the cellular response after additional vaccine doses, such as Arroyo-Sanchez et al, that demonstrated a response rate of 50% after the initial dose with an elevation to 83% after the second dose based on the response found with IFN-γ FluoroSpotTM plates. [21]
After the 3rd dose, the differences in IFN-gamma response were reported to be overall reduced compared to HC, as described in recent reports. [26,34,35]

Furthermore, different cellular responses have been observed among the subgroups of IEI patients. Specifically, CVID patients have shown reduced production of spike-specific T cells compared to XLA patients.
It has been hypothesized that CVID patients not only had a delayed response upon a first antigen exposure but also a defective cellular system underlying the poor T-cell response. Sauerwein et al divided CVID patients into two subgroups based on the humoral response to the vaccine: responders and no responders. The responders had defective activation of circulating T follicular helper cells but intact vaccine-specific activation of CXCR5-negative CD4+ memory T cells. The group of non-responders showed defective vaccine-specific activation of both CD4+T cell subsets: CXCR5-negative CD4+ memory T cells and T follicular helper cells. They also demonstrated that defective CD4+ T cells were present even when antigen-induced TNF alpha production was detected. [15]
Furthermore, in addition to having an alteration in CD4+ T lymphocytes, patients with CVID also appeared to have an alteration in the CD8+ T lymphocyte compartment. Gupta et al. evaluated SARS-CoV-2−specific tetramer-positive CD8+ T Cells and functional Cytotoxic T lymphocytes in CVID and XLA patients vaccinated with BNT162b2. They found that CVID patients had reduced SARS-CoV-2-specific CD8 T cells and functional cytotoxic T cells in both natural SARS-CoV-2 infection and in response to SARS-CoV-2 mRNA vaccine, whereas natural infection in XLA patients was associated with a robust SARS-CoV-2-specific CD8 and functional cytotoxic responses. [36]
A study published by Hurme et al. [37] showed a greater cellular response in CVID, compared to previously published data, which remained relatively long-lasting (evaluated up to a 3 month time span from the last injected vaccine) and further strengthened after the second and additional booster doses. The response also appeared to be effective against VOC.

Durability of immunity

Only a few studies have assessed the long-term response to vaccinations in immunocompromised patients. Despite having generally lower levels of antibodies, IEI patients did not show a rapid decline in antibody titers, which has been observed within 3-6 months after vaccination. [19,24,25]. This result was observed also in HC but with a different trend.

Zimmerman et al. [25] observed a decrease in anti-spike and anti-RBD levels after 90 days from both primary vaccination and booster dose and found differences between PAD patients who had previously experienced the infection and COVID-naive patients. Despite the decline, unlike COVID-naive patients with PAD, the antibody levels 90 days after vaccination were significantly higher than pre-vaccination levels in PAD patients with prior infection and in HC.

Conversely, Van Leeuven et al did not identify differences in the decline of antibody titers or cellular response between IEI patients and HC. [19]

Recently, Hurme et al. [37] investigated humoral and cellular response in PAD patients three weeks and three months after the third and fourth dose. Regarding T cellular response, they found an enhancement following the second dose which remained consistently high following additional booster vaccinations throughout the entire follow-up period with 60% to 86% of patients showing S-specific CD4+ T cells after the third dose and 69% to 78% of patients positive after the 4th dose (after 3 weeks and 3 months respectively).

Safety

In addition to assessing vaccine immunogenicity, most studies have also investigated the safety of vaccines in immunocompromised patients.

Overall, a good safety profile of vaccines has been found, reporting no severe post-vaccination reactions [23,38]. In particular, our group has investigated adverse events (AEs) specifically in a cohort of 342 patients among which 286 with a CVID diagnosis. Overall AE were described as mild in 67% of 121 patients with local manifestations only and in 60% of 151 patients with local and systemic vaccine related reactions. In general AE had little impact on daily living. [38]

Females have been found to have AEs more frequently compared to men. Vaccinated PID patients showed fewer AEs and similar or reduced reactogenicity compared to HC, highlighting the good safety profile of the mRNA vaccines used.

No severe AEs such as myocarditis or anaphylaxis were reported and hypersensitivity reactions, including anaphylaxis, have never been reported.

Among all studies analyzed, only Van Leeuwen and Bergman have reported very few serious AEs (9 and 3 patients respectively). [8,19]

Conclusions

Based on reported studies, anti SARS-CoV-2 vaccination is protective also in patients affected by PADs, even if an elevated antibody titer is not always detectable, also due to a durable cellular response.

This mechanism is elicited by repeated stimulation, provided by previous natural infection and multiple booster vaccine doses, capable of stimulating memory T cells and of implementing B cells affinity maturation to high-affinity specific memory B cells accounting for recall responses.
In CVID and IEI patients the response to the first course of 3 vaccine doses (mostly done with mRNA vaccines), the availability of specific antiviral treatments and the current prevailing omicron lineage subvariants have led to an attenuated severity even in the context of pre-existent severe comorbidities. [39,40]

Regarding the humoral response, overall a variable but steadily increasing rate of seroconversion has been shown for many PAD patients, with some patients exhibiting a robust response to vaccination, while others having a weaker one with factors such as age, previous SARS-CoV-2 infection, specific genetic mutations and, most importantly, booster doses influencing the quality and quantity of the response.
On the other hand, long-lasting cellular responses to SARS-CoV-2 vaccination, mostly of the T-cell type, have been observed.
As the pandemic has evolved and various types of vaccines have become available, studies have included patients who received different vaccine types, allowing for comparisons of diverse vaccination schedules/combinations. Almost unanimously, the studies have indicated that mRNA vaccines have been shown to give a superior cellular response. [24]

Overall COVID-19 vaccines have exhibited a good safety profile in PID patients, with most adverse events being transient and mild and no major AE reported.

In conclusion, COVID-19 vaccination in IEI patients, especially in those with PAD has demonstrated overall safety and is able to elicit both humoral and cellular immune responses. Despite showing a huge variability in individual responses, booster doses have shown improvement in enhancing immunity. These findings underscore the importance of tailored vaccination strategies and ongoing monitoring for this vulnerable population. Additionally, previous SARS-CoV-2 infection appears to enhance vaccine-induced immunity in PID patients, underlining the importance of vaccinating at the right time point, also patients who already caught the infection.
A crucial concept for future evaluation of risk in IEI patients will be the one of hybrid immunity which refers to the combined protection obtained by both natural infection and vaccination against specific viruses (eg. Sars-Cov2). Those who have already received COVID-19 vaccination and later encountered the virus (or vice versa) will fit in this kind of category and might benefit from this risk-evaluation.

During the last year, studies about the evidence of neutralizing anti SARS-CoV-2 spike protein antibodies in intravenous and subcutaneous immunoglobulin commercial products have been completed.[41,42,43] Therefore patients in immunoglobulin replacement therapy can now also benefit from this “passive immunization”.
Further research, including the development of optimized vaccine strategies and a punctual booster programme, in association with replacement therapy with immunoglobulins may

provide a better protection for individuals with PAD, facilitating the ongoing endemization of SARS-CoV-2 virus, reducing the risk of severe infectious life-threatening clinical pictures and severe outcomes.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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