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IMMUNE DEFICIENCY AND DYSREGULATION (DP HUSTON AND C KUO, SECTION EDITORS)

Influenza Vaccination in Patients with Common Variable Immunodeficiency (CVID)

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Abstract
Purpose of Review Vaccination against influenza in patients with primary antibody deficiency is recommended. Common variable immunodeficiency (CVID) is the most frequent and clinically relevant antibody deficiency disease and is by definition characterized by an impaired vaccination response. The purpose of this review is to present the current knowledge of humoral and cellular vaccine response to influenza in CVID patients.
Recent Findings Studies conducted in CVID patients demonstrated an impaired humoral response upon influenza vaccination. Data on cellular immune response are in part conflicting, with two out of three studies showing responses similar to healthy controls.
Summary Available data suggest a benefit from influenza vaccination in CVID patients. Therefore, annual influenza vaccination in patients and their close household contacts is recommended.

Keywords Common variable immunodeficiency · Primary antibody deficiency · Influenza · Vaccination

Introduction

Common variable immunodeficiency (CVID) is the most frequent, clinically relevant antibody deficiency disorder affecting one in 25.000 to 50.000 individuals [1]. According to the criteria of the European Society for Immunodeficiencies (ESID) [2], secondary causes of hypogammaglobulinemia have to be excluded and based on reduced immunoglobulin isotypes (low IgG + low IgA +/− low IgM); vaccine response and percentage of switched memory B cell CVID patients are further differentiated from other forms of primary antibody deficiency (see Fig. 1).

The term CVID refers to a group of heterogeneous conditions. Patients suffer from an increased susceptibility

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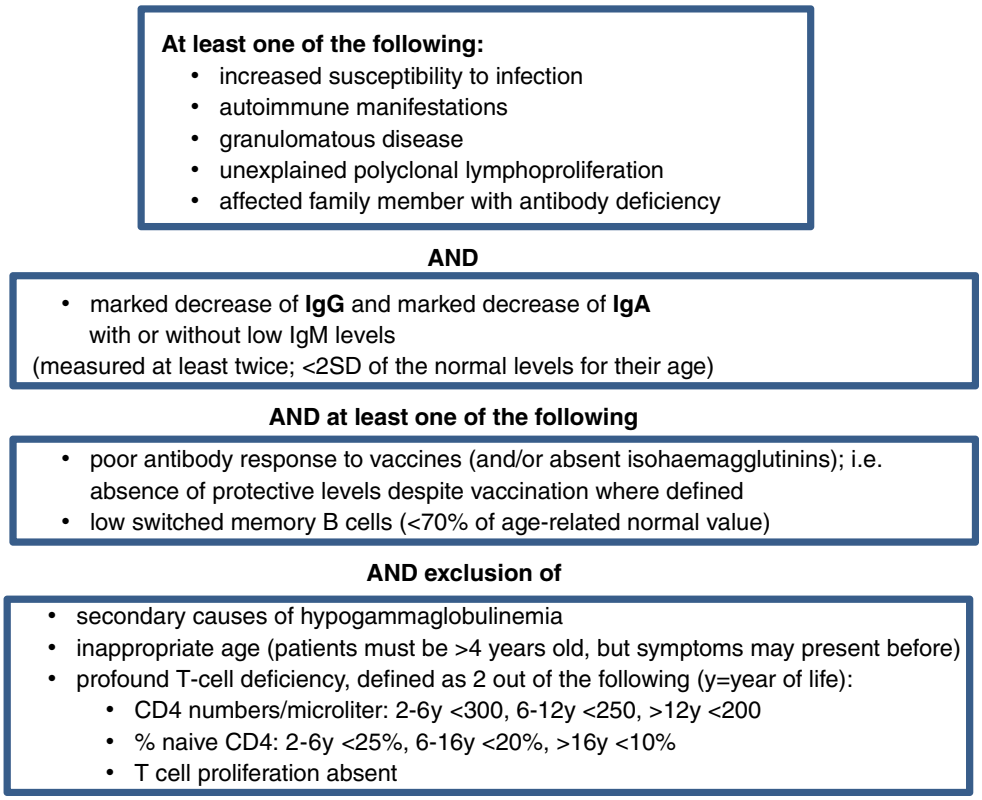

Fig. 1 Common variable immunodeficiency (CVID) according to ESID Registry—working definitions for clinical diagnosis of PID (2016)

to infections and in addition, about two thirds of the patients develop non-infectious complications, such as chronic inflammatory disorders, polyclonal lymphoproliferation, autoimmune syndromes, and malignancies. Frequent pulmonary complications include bronchiectasis and granulomatous lymphocytic interstitial lung disease (GLILD) occurring in approximately 25% of CVID patients [3••]. These structural lung changes contribute even further to the increased risk of pulmonary infections [4]. Associated comorbidities reduce the expectancy and quality of life of the CVID patients [3••, 5].

In recent years, our understanding on the genetic background in CVID has increased considerably. However, in contrast to many other primary immunodeficiencies (PID), monogenic forms probably account for only 10–25% of patients with CVID [6]. Genes currently implicated in monogenic CVID include ICOS, TNFRSF13B (TACI), TNFRSF13C (BAFF-R), TNFSF12 (TWEAK), CD19, CD81, CR2 (CD21), MS4A1 (CD20), TNFRSF7 (CD27), IL-21, IL-21R, LRBA, CTLA4, PRKCD, PLCG2, NFKB1, NFKB2, PIK3CD, PIK3R1, VAV1, RAC2, BLK, IKZF1 (IKAROS), and IRF2BP2 [7]. With an increasing number of disease genes identified, CVID is considered more and more as an "umbrella diagnosis," and it became evident that many of these genetic defects cause distinct disease entities. At least a subgroup of patients with CVID is suspected to have an oligogenic rather than a monogenic inheritance [7].

General Treatment in CVID

Treatment options in CVID include antibiotics, immunosuppressive drugs, vaccinations, and immunoglobulin (Ig) replacement therapy [3••]. To increase the diversity of immunoglobulins, treatment products are originated and pooled from > 1000 healthy donors, thereby transferring and replenishing missing IgG antibodies in patients. Naturally, immunoglobulin treatment cannot transfer protection against every infection. Particularly, antibody concentrations against diseases with low vaccine coverage in the general population (e.g., tick-borne encephalitis) [8] or diseases with a low prevalence (e.g., meningococcal meningitis) [9, 10] are variable or insufficient. Further, immunoglobulin replacement therapy would not be expected to protect recipients from currently circulating influenza strains, since antibodies to the current influenza strains are absent from the plasma donor pool from which the immunoglobulins had been purified at that time.

Vaccination in CVID

With regard to the humoral responses, the effectiveness of many common vaccines in patients with CVID has not been formally evaluated. Specific antibodies against many vaccine-preventable diseases are present in high amounts in therapeutic polyclonal IgG and for instance booster vaccinations against tetanus or diphtheria toxoids are not necessary for

individuals receiving IgG replacement therapy, meanwhile vaccination for instance against meningococcal disease (serogroups A, B, C, W, and Y) is recommended [11, 12•]. There is no theoretical reason that intravenous Ig (IVIg) should reduce effectiveness of inactivated vaccines.

Immunization remains the only possibility of transferring protection against seasonal influenza in these patients; despite the fact that, by definition, many CVID patients have a missing or impaired response to vaccinations [13]. Cellular immunity is thought to be mainly intact in the majority of patients with CVID; however, cell-mediated immune response is still a poorly understood effect of vaccination [14, 15]. Due to technical limitations and a missing clear correlate of protection [16], currently, cellular immune responses to vaccination cannot be conducted as part of routine diagnostics.

When using live attenuated vaccines in patients who are receiving immunoglobulins, the efficacy is reduced due to vaccine neutralization by pre-existing antibodies. Thus, it is recommended to postpone live attenuated vaccination until a minimum of three months after the last immunoglobulin infusion [12•, 17]. In patients receiving subcutaneous immunoglobulin therapy, vaccines should be administered at a different anatomical site [17]. Because of negligibly low concentrations of specific antibodies, immunoglobulin treatment does not interfere with yellow fever vaccine [18].

There are no safety concerns with the use of inactivated vaccines [12•]. Live attenuated vaccines are generally contraindicated in patients with PID and especially patients with impaired cellular immune response are considered to be at high risk for developing vaccine-related diseases [12•]. Viral live attenuated vaccination against MMR (mumps, measles, and rubella) and varicella (but not quadrivalent MMRV) is considered to be safe in patients with > 200/μl or > 25% of CD4+ cells and normal mitogen response [19, 20].

Influenza

Influenza is a worldwide, highly infectious airborne disease affecting millions of individuals every year (reviewed in [21]). Influenza viruses are single-stranded RNA viruses belonging to the *Orthomyxoviridae* family. Three types of influenza viruses, influenza A, B, and C, affect humans and are capable of causing epidemics and pandemics. Influenza A is most prone to antigenic shifts and the most common circulating type causing significant illness. Influenza strains are named after their types of hemagglutinin (HA) and neuraminidase (NA) surface proteins, which are the primary target of the immune response to influenza.

The influenza virus infects all age groups but especially children and adults over the age of 65 are considered to be at high risk for severe influenza infections. Therefore, vaccination is strongly recommended for these age groups, and also for anyone with high-risk conditions for disease-associated complications such as patients with chronic medical conditions (metabolic, cardiac, pulmonary, or kidney diseases, as well as immunocompromised patients) [22, 23].

In patients with PID, influenza is a common viral infection [24]. A recent population-based study from Japan reported a high morbidity in pediatric PID patients suffering from influenza, with 90% requiring hospitalization [25].

Influenza Vaccines

The earliest attempts of developing vaccines against influenza date back to the 1930s when the first live attenuated virus vaccines were produced in chicken eggs [26]. Today, vaccine efficacy remains highly variable due to uncertain predictions concerning the main circulating strain, as occurred in the season 2014/15 with the CDC (Centers for Disease Control and Prevention) reporting an overall vaccine efficacy of only 23% [27]. However, when the annual prediction is well matched to circulating influenza strains, vaccine efficacy can reach up to 75% [28, 29].

The currently available seasonal influenza vaccines are either trivalent vaccines (TIVs), containing one strain of each of the two subtypes of influenza A virus (A/H1N1 and A/H3N2) and one of the two co-circulating B virus lineages (B/Victoria or B/Yamagata), or quadrivalent vaccines (QIVs), containing both influenza A subtypes (A/H1N1 and A/H3N2) and both influenza B co-circulating lineages (B/Victoria and B/Yamagata) [30]. Protective effects of inactivated influenza vaccines remain variable, particularly in vulnerable groups such as the elderly [31].

Oil-in-water adjuvants like MF59 and AS03 have been licensed and widely used, and shown efficacious in preventing influenza infections in the last pandemic. In young children, MF59-adjuvanted inactivated vaccine was more efficacious than non-adjuvanted vaccine in preventing influenza infections [32]. Furthermore, MF59-adjuvanted influenza vaccines reduced hospitalization following influenza infection in the elderly [48]. Other adjuvants are currently developed and some are already being tested in clinical trials (reviewed in [33]).

Universal influenza vaccines targeting conserved regions of the influenza virus including the HA stalk domain or the ectodomain of the M2 ion channel represent a promising approach. Universal influenza vaccine development is in its late preclinical and clinical stage [34].

The live attenuated influenza vaccine (LAIV) is available for large-scale use in the United States (US) since 2003 and in Europe since 2011. Recent data have revealed conflicting results concerning its effectiveness in children. LAIV appears to protect particularly poorly against currently circulating H1N1 viruses that are derived from the 2009 pandemic H1N1 viruses. This observation led to the decision of US authorities to not further advise the use of LAIV in 2016–17; however, other

countries, including the UK, Canada, and Finland, have continued to recommend the use of LAIV [35, 36].

In secondary immunodeficiencies such as HIV and solid organ transplanted patients, different vaccination schedules with intradermal administration or adjuvanted influenza vaccination have been examined, with variable results [37–39].

In PID patients, there are no comparative studies on alternative influenza vaccination protocols available. The use of live attenuated influenza vaccines is generally not recommended in PID patients [12•]. Some national recommendations favor the use of tetravalent influenza vaccines, expecting a broader coverage against two influenza A (H1N1 and H2N3) and two influenza B strains (Yamagata and Brisbane), which is a plausible procedure, although comparative studies between trivalent and tetravalent influenza vaccines are missing.

To further limit the risk of influenza infection, it is recommended that household contacts are vaccinated with the inactivated influenza vaccine [40].

In addition to active immunization, there is ongoing research on monoclonal antibodies for passive immunization against influenza. However, so far these products have only entered phase 2 clinical trial stage and their clinical benefit cannot be judged yet [41].

Correlate of Protection

Immunity induced by current vaccines is predominantly based on antibodies capable of neutralizing pathogens [42]. Knowledge of a correlate of protection is indispensable in each vaccine, but in the majority of vaccines it remains poorly defined. Humoral vaccination response to the seasonal influenza vaccine is commonly assessed by hemagglutination inhibition (HI) assay. Early studies by Hobson et al. [43] have established that HI antibody titers are correlated with protection against influenza infection with the definition of an HI antibody titer of 1:40 as 50% protective against influenza infection compared to an HI titer < 1:10. This cut-off is still applied by the European Medicines Agency (EMA) defining seroprotection at 1:40 [44]. According to the EMA, a positive vaccination response (seroconversion) is considered as an increase in HI titer pre- to post-vaccination ≥ fourfold or an HI titer of at least 1:40 with antibodies being absent before vaccination [44]. Despite this definition, higher HI titers have been shown to lead to a higher degree of protection especially in children and elderly patients [45, 46].

While regulatory agencies are focusing on the role of antibody response, effects of cell-mediated immunity are not assessed [47]. Even if cell-mediated immunity does not appear to contribute significantly to the prevention of the infection, data suggest that it plays an important role in viral clearance after influenza infection and that it may also be protective against disease-associated complications [49]. In particular, T lymphocytes play a crucial role in mediating the cellular immune response, by providing a helper antibody response and intervening directly in reducing viral replication [50].

T cell-mediated immunity against influenza appears to be less affected by the annually occurring epitope changes. Studies of viral evolution over the years indicate that while only 2.7% of epitopes recognized by antibodies are conserved, 15% of T cell epitopes remain unchanged [51]. This higher conservation of T cell epitopes correlates with the ability of T cells to target internal viral proteins, which are far less tolerant to selection pressure compared to external coat proteins [52–54]. This is also exemplified by the observation that the hemagglutinin (HA) and neuraminidase (NA) of the pandemic H1N1 strain have acquired mutations at a rate six to eight times faster than the internal nucleoprotein (NP) protein, in terms of amino acids substitutions per site per year [55].

During the 2009 pandemic waves in the UK, it was demonstrated that higher frequencies of pre-existing interferon (IFN)-γ+ T cells against conserved CD8+ epitopes were found in individuals, who developed less severe illness [56••]. In addition, recent influenza challenge studies have demonstrated a correlation between influenza A virus-specific CD4+ T cells and lower virus shedding with less severe illness in human volunteers following infection with non-virulent influenza A strains [57]. Data provided evidence that both influenza-specific CD4+ and CD8+ T cells confer cross-protective immunity towards various influenza subtypes. Ex vivo cellular immune responses to influenza were shown to correlate with protection in the elderly [58]. Cell-mediated immunity is characterized by stimulation of CD8+ cytotoxic lymphocytes that are critical in the defense against viral diseases. This stimulation is mediated, and maintained, to a large extent by CD4+ Th1 cells capable of IFN-γ, IL-2, or TNF-α cytokine production [59–62]. Preliminary studies of young children confirmed that the IFN-γ enzyme-linked immunospot (IFN-γ ELISPOT) was a more sensitive measure of influenza memory than serum antibody titers [63].

Antibody Responses to Seasonal Influenza Vaccine in CVID Patients

To our best knowledge, currently, only three studies have addressed the issue of influenza vaccination in CVID patients [64, 65•, 66]. An absent or insufficient antibody response was found in most but not all cases.

Van Assen et al. reported a significant increase of HI titers against all three strains included in the seasonal vaccine 2006/2007 (non-adjuvanted) in healthy controls but not in 17 CVID patients [64]. No seroconversion was reported for any patient against A/H1N1 or A/H3N2.

In line with this study, the majority of the patients described by Hanitsch et al. did not respond to the seasonal non-adjuvanted influenza vaccine 2013/2014 [65•]. Following

vaccination, increasing antibody titers were observed in the healthy control group; however, only one patient expressed a positive humoral response against both A strains. While fulfilling the ESID criteria for CVID, this patient was considered to suffer from a less severe form of CVID, as this patient had also shown a good vaccine response to pneumococcal vaccine and had higher concentrations of switched memory B cells compared to the other CVID patients.

Finally, Pedersen et al. studied effects of influenza vaccination in four cases with primary antibody deficiencies [66]. The study included one patient suffering from x-linked agammaglobulinemia (XLA) and three patients with CVID. Patients were vaccinated with the pandemic vaccine A/California/7/2009 (H1N1)-like split virus (X179a) adjuvanted with the oil-in-water emulsion AS03. Seroconversion was reported for two out of three CVID patients after two doses of the adjuvanted influenza vaccine. However, and in line with the results of the other studies, the vaccine-induced fold increase of HI titers of both responders was rather marginal compared to participating healthy controls.

Despite a hampered vaccination response, protective HI titers could be detected in many CVID patients after vaccination. Van Assen et al. reported HI titers of at least 1:40 in 77% (A/H1N1), 12% (A/H3N2), and 12% (influenza B) [64]. Seroprotection was achieved in 7/8 (A/H1N1), 5/8 (A/H3N2), and 5/8 (influenza B) CVID patients in the study by Hanitsch et al. [65•]. A seroprotection was also observed by Pedersen et al. in both responders after vaccination [66]. Although these patients were receiving immunoglobulins, the treatment is not likely to have influenced the measurement, since anti-influenza titers in the immunoglobulin batches were 1:5 for A/H3N2, 1:10 for A/H1N1, and 1:5 for the B strain as determined by HI assay [64]. However, patients were under immunoglobulin replacement therapy and in all three studies post-vaccination antibody titers were generally lower, when compared to healthy controls with the mean HI titer at best being slightly above 1:40 [64, 65•, 66].

All three studies used the intramuscular administration route. Only mild local or systemic side effects were observed.

There are no studies in CVID patients using intradermal or intranasal vaccination.

T Cell-mediated Response to the Seasonal Influenza Vaccine in CVID Patients

Studies on cell-mediated immunity to influenza in CVID patients are also scarce. Van Assen et al. evaluated cell-mediated immune response in 15 CVID patients and 15 matched healthy controls by determining frequencies of IFN-γ-producing PBMC, and frequencies of IFN-γ-, interleukin (IL)-2-, and tumor necrosis factor (TNF)-α-producing activated (CD69+) CD4+ and CD8+ T cells before and after influenza vaccination using IFN-γ ELISpot and flow cytometry [67]. In this study, cell-mediated immunity was found to be lower for IFN-γ than in healthy controls. No difference was reported for TNF-α [67].

In their small case collection, Pedersen et al. also reported on effects on cell-mediated immunity. Vaccination induced CD4+ Th1 cell responses in the XLA patient and the CVID patients, although the frequency of influenza-responsive cells varied among the patients [66].

Hanitsch et al. observed in their study on 8 CVID patients and 8 patients with unclassified antibody deficiency that 7/8 of the CVID patients and 6/8 of the patients with unclassified antibody deficiency had similar frequencies of vaccine-induced IFN-γ-, TNF-α-, and IL-2-producing activated CD4+CD40L+ T cells as the healthy control group [65•].

Another import aspect of cellular immunity is the generation of multifunctional T cells that are generally considered to be of crucial importance for a protective T cell response [16]. Better protection through multiple cytokine-producing Th1 cells against different other forms of infection has been shown in animals [60] and humans [68–70]. Van Assen et al. did not provide any information considering this aspect of a vaccine-induced T cell response. However, Pedersen et al. detected a similar distribution of single, double, and triple cytokine-producing T cells for IFN-γ, TNF-α, and IL-2 in both CVID patients with relatively high frequencies of influenza-responsive CD4+ T cells following vaccination [66]. Likewise, CVID patients in the study by Hanitsch et al. developed comparable frequencies of multifunctional T cells for these three cytokines with single (39.0%), double (33.2%), and triple (27.8%) producers accounting for roughly one third of IFN-γ-, TNF-α-, and IL-2-producing CD4+ T cells [65•].

Conclusions

Our knowledge of vaccine response to influenza in patients with CVID is still limited. Patients with PID are at increased risk of influenza infections. Anti-influenza antibody titers have been shown to be low in immunoglobulin products and immunoglobulin replacement treatment does therefore not transfer sufficient amounts of specific antibodies. There are no studies assessing clinical endpoints, and only a few studies investigated immunogenicity.

All studies that examined the humoral immune response in CVID showed a missing or insufficient increase of specific antibodies against influenza. Data on the cellular immune response to influenza vaccination are in part contradictory, but suggest a benefit from vaccination. Therefore, annual influenza vaccination in CVID patients and their close household contacts is recommended.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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