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Common Variable Immunodeficiency Disorders, T-Cell Responses to SARS-CoV-2 Vaccines, and the Risk of Chronic COVID-19

COVID-19 has had a calamitous effect on the global community. Despite intense study, the immunologic response to the infection is only partially understood. In addition to older age and ethnicity, patients with comorbidities including obesity, diabetes, hypertension, coronary artery disease, malignancy, renal, and pulmonary disease may experience severe outcomes. Some patients with primary immunodeficiency (PID) and secondary immunodeficiency also appear to be at increased risk from COVID-19. In addition to vulnerability to SARS-CoV-2, patients with PIDs often have chronic pulmonary disease and may not respond to vaccines, which exacerbates their long-term risk. Patients with common variable immunodeficiency disorders, the most frequent symptomatic PID in adults and children, have a spectrum of B- and T-cell defects. It may be possible to stratify their risk for severe COVID-19 based on age, ethnicity, the severity of the T-cell defect, and the presence of other comorbidities. Patients with common variable immunodeficiency disorders and other immunodeficiencies are at risk for Chronic COVID-19, a dangerous stalemate between a suboptimal immune response and SARS-CoV-2. Intra-host viral evolution could result in the rapid emergence of vaccine-resistant mutants and variants of high consequence; it is a public health emergency. Vaccination and prevention of Chronic COVID-19 in immunodeficient patients is therefore of the utmost priority. Having a reliable diagnostic assay for T-cell immunity to SARS-CoV-2 is critical for evaluating responses to vaccines in these patients. New treatments for SARS-CoV-2 such as NZACE2-Patari are likely to be particularly beneficial for immunodeficient patients, especially those who fail to mount a robust T-cell response to COVID-19 vaccines. © 2021 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;9:3575-83)

Key words: SARS-CoV-2; COVID-19; T-cell assays; Antibody tests; Vaccination; CVID; CVID-like disorders

INTRODUCTION

COVID-19 has had a disastrous impact on the international community. SARS-CoV-2, the agent responsible for the disease, originated in Wuhan City, China in late 2019. The origin of the infection is the subject of intense study. It has since rapidly spread globally, leading to calamitous medical, economic, and societal consequences. The current death toll, in excess of 4 million, is likely to continue rising until there is universal deployment of effective vaccines and therapeutics.

Of grave concern is the rapid emergence and dominance of several new variants of the virus, which are more infectious than the original founder (Wuhan) strain. In addition to the early D614G mutant, variants of concern include the UK/alpha (B.1.1.7), South Africa/beta (B.1.351), Brazil/gamma (B.1.1.288), India/ delta (B.1.617) strains. Clades-bearing mutations such as E484K appear to have rendered ineffective several monoclonal antibodies to the virus.5,6

On the more hopeful side have been successful trials and rollout of multiple vaccines. The ultimate global death toll will be determined by a race between the deployment of vaccines and emergence of newer escape mutants. Escape mutants will arise rapidly in areas where the virus is not contained and allowed to circulate.

The Three Overlapping Clinical Phases of SARS-CoV-2

COVID-19 appears to progress in three overlapping clinical stages. In the first asymptomatic phase, the nasal mucosa is infected. During early infection, the spike (S) glycoprotein engages cell surface ACE2 to facilitate viral entry. Host proteases
including TMPRSS-2 cleave the S glycoprotein, allowing the S2 subunit to fuse with the cellular membrane. Fusion of the virus with the cell allows the viral genome to enter and hijack intracellular organelles, leading to the production of daughter virus. After this initial stage, which lasts approximately 5 days, some patients enter a second pulmonary phase, probably from microaspiration of the virus. This is characterized by dyspnea, fatigue, and fever. Computerized tomography scans of the thorax often show ground-glass appearances in this stage of the infection.

Patients who progress to the third systemic viremic phase are at high risk for multiple-organ failure, leading to intensive care admission. Despite invasive ventilation and extracorporeal membrane oxygenation, mortality remains high in those experiencing viral sepsis.

Patients at Increased Risk

There is a steep age-related mortality gradient, with rates approaching 30% in those aged greater than 80 years. Patients with comorbidities including obesity, hypertension, coronary artery disease, malignancy, immunodeficiency, renal, and pulmonary impairment are at increased risk for adverse outcomes. Precisely how these conditions predispose to severe disease is incompletely understood.

Black and South Asian patients are at increased risk for adverse outcomes. These ethnic predispositions may be partly confounded by sociodemographic disparities including higher prevalence of comorbidities and poor access to health care.

The Immunologic Conundrum Posed by SARS-CoV-2

The immunologic response to SARS-CoV-2 is incompletely understood. In contrast to other viruses, SARS-CoV-2 is able to evade the innate immune system effectively during the first, asymptomatic phase of the infection. Cytoplasmic viral sensors such as protein kinase R, MDA5, RIG, and Toll-like receptors are rendered ineffective. Virus-encoded proteins cloak viral RNA and RIG-like receptors are ubiquitinated, leading to early degradation.

Anti-interferon antibodies contribute to disease severity. The complement cascade appears to aggravate COVID-19 and natural killer cell responses are impeded. Evasion of the innate immune system allows the virus to multiply exponentially, unchallenged, during the first nasal phase of the infection.

The virus also subverts the adaptive immune system. Persistent lymphopenia is an ominous marker of severe disease. Antibodies appear to vary in quality, and in some patients, the antibody response does not appear to be protective. Many patients dying of COVID-19 had both high viral loads and antibody titers, which indicates that the antibodies were unable to neutralize the virus. There is also concern that antibody disease enhancement (ADE) could occur in some patients. The basis of ADE is only partly understood.

The role of T cells in early disease remains to be conclusively established. Uncoordinated over- or underactivation of T cells may lead to worse outcomes. Low-avidity T-cell responses were associated with severe disease. Recent studies suggest that an effective early T-cell response is correlated with milder disease.

In contrast, long-term protection is linked to the generation of a robust memory T-cell response. In many patients with mild COVID-19, antibody responses were muted, but these individuals generated an effective cellular response. This would allow a rapid anamnestic reaction to reinfection. High titers of neutralizing antibodies to SARS-CoV-2 are likely to be a surrogate marker of a robust protective T-cell response.

The Immunologic Conundrum of Common Variable Immunodeficiency Disorders

Like COVID-19, common variable immunodeficiency disorders (CVIDs) are an immunologic conundrum. By definition, patients with CVID do not have a known cause for late-onset antibody failure leading to immune system failure. It is the most frequent symptomatic primary immunodeficiency in adults and children. Although regarded as a late-onset immunodeficiency, many patients develop symptoms of CVID in early childhood. Most CVID patients have recurrent and severe infections, whereas a substantial minority present with autoimmune and inflammatory sequelae.

In nonconsanguineous populations, approximately 25% of CVID patients have a causative genetic defect. In consanguineous societies, the rates are much higher, mostly due to highly penetrant autosomal recessive mutations. Patients with causative mutations are deemed to have CVID-like disorders, because all current definitions of CVID exclude those with an underlying explanation for hypogammaglobulinemia.

The immunologic defects are likely to vary in severity in this group of disorders, which can evolve in individual patients (Figure 1). The NZ hypogammaglobulinemia study (NZHS)
showed that many patients with mild asymptomatic hypogammaglobulinemia of uncertain significance remained in excellent health for over a decade. At the other extreme of the immunologic spectrum, some patients have late-onset combined immunodeficiency (LOCID). Patients with LOCID are at grave risk for premature death from infective, autoimmune, or malignant sequelae. Two current definitions of CVID exclude LOCID, although it has been suggested that this should remain within the broad overlapping sub-phenotypes of CVID.

Common variable immunodeficiency disorders and CVID-like disorders are characterized by marked genetic, allelic, and phenotypic heterogeneity. The severity of the antibody and the T-cell defect varies within families carrying the identical mutation in CVID-like disorders. In one of three families in which NFκB1 mutations (c.465dupA) were first identified, one affected brother was completely asymptomatic whereas his sister died prematurely after multiple autoimmune, inflammatory complications and malignancy. She had a severe T-cell defect consistent with LOCID. Other members of this kindred had autoimmunity. These observations underscore the great heterogeneity of immune defects in patients with CVID and CVID-like disorders.

Understanding the spectrum of immunologic disease severity in CVID and CVID-like disorders may allow better predictions of who may be at increased risk for COVID-19 complications and which patients may fail to respond to vaccines. Some studies indicated that patients with CVID and CVID-like disorders are at high risk for severe outcomes, although this is inconsistent. In contrast, patients with X-linked agammaglobulinemia (XLA) without comorbidities appear to have milder disease. These observations also infer that T cells have a dominant role in mitigating disease severity in COVID-19.

Analogous to XLA, patients with CVID who have a pure antibody defect may be at lower risk than those with mostly cellular defects. The reader should consult the World Health Organization Web site for up-to-date information on the rapidly changing status of vaccines against SARS-CoV-2.

### TABLE I. Examples of vaccine candidates and their underlying technology

| Mechanism of vaccine | Advantages | Disadvantages | Companies/vaccines (examples) |
|----------------------|------------|---------------|------------------------------|
| Live attenuated vaccine | Robust immunity | Risk for reactogenicity, risk for disease in immunodeficient patients. Stringent storage and transport requirements. | Codagenix |
| Inactivated vaccine | Lower risk of vaccine-induced disease | Immunity not long-lasting. Adjuvants may increase reactogenicity | Sinopharm, Bharat |
| Subunit vaccine | Lower risk of adverse reactions | Immunity not long-lasting. Adjuvants may increase reactogenicity | Sanofi, Novavax, and others |
| mRNA | Flexibility to change expressed proteins | Cellular entry may require innovation. Cold storage and transport. Rare cases of myocarditis | Pfizer, Moderna |
| Plasmid vaccine | Flexibility to change expressed proteins | Difficulty with cellular entry. May need multiple doses. | Zydus |
| Viral vector | Robust immunity | Potential adenovirus neutralization. Rare cases of vaccine induced thrombosis and thrombocytopenia with some adenovirus vaccines | Oxford/Astra-Zeneca, Gamaleya (Sputnik V), Johnson and Johnson, CanSinoBio |
| Bacterial vector | Can be used with commensal bacterium such as Lactobacillus | Insufficient data on effectiveness | Pasteur |
| Boosting innate immunity | Well-characterized vaccines | May not improve response to SARS-CoV-2. Contraindicated in patients with T-cell defects. | BCG |

BCG, Bacillus Calmette-Guérin.

This is not a comprehensive list, but it illustrates diverse approaches to inducing protective immunity to SARS-CoV-2. The reader should consult the World Health Organization Web site for up-to-date information on the rapidly changing status of vaccines against SARS-CoV-2.
that the immune defect in CVID will be exacerbated by older age and ethnicity and by other well-known comorbidities including obesity and diabetes (Figure 1). A recent study suggested that some CVID patients have common cold coronavirus cross-reacting T cells, which could potentially protect against SARS-CoV-2.69 All of these complexities may explain the varying outcomes of CVID patients with COVID-19.

Assessing Risk for COVID-19 Severity in CVID

The outcome of COVID-19 in CVID patients might be predicted by assessing both pathogen and host risk factors. Pathogen risk factors include the viral variant, including the B.1.1.7, B.1.351, B.1.1.248, and B.1.617 strains. The dose of viral inoculation is likely to be a factor, as seen early in the pandemic in China, where young health care workers who were not wearing personal protective equipment succumbed to the infection.70 The viral load, as judged by the reverse transcriptase quantitative polymerase chain reaction cycle threshold early in the disease, may offer valuable prognostic information.71

Figure 1 shows host risk factors for severe COVID-19. Host risk factors include the nature of the immune defect, its sequelae,42 and other well-established risk factors including age, ethnicity, and comorbidities (Figure 1). This would allow rapid assessment of prognosis and escalation of supportive care preemptively. Hospital admission could be facilitated early, particularly in regions of the world experiencing a reduction in COVID-19 infections because of successful vaccination campaigns.73

COVID-19 Vaccines and CVID

Vaccines will have a critical role in terminating the pandemic. Currently, over 300 candidate vaccines are in various stages of production and deployment (Table I). Several vaccines have received emergency authorization for use. Their efficacy varies from 50% to over 90% in preventing disease after exposure to SARS-CoV-2. In the short term, global deployment of vaccines will face significant financial and logistical challenges. Eventual broad vaccine uptake will lead to herd immunity and reduced transmission of the virus, with a lower probability of vaccine-resistant mutants evolving.

Currently, there are many strategies for immunization against SARS-CoV-2 (Table I). The Pfizer and Moderna vaccines use mRNA, whereas the Astra-Zeneca, Gamaleya (Sputnik V), and Johnson and Johnson vaccines use an adenovirus vector to deliver protein subunits.76,80 There are many other candidate vaccines, based on different technologies including plasmids, live attenuated viruses, and so on.

Nevertheless, vaccines pose challenges for patients with CVID. Live vaccines in particular, such as bacillus Calmette-Guérin, are contraindicated in patients with LOCID. Furthermore, most patients with CVID have suboptimal responses to vaccination, as formulated in the original European Society for Immunodeficiencies/Pan-American Group for Immunodeficiency 1999 and more recent International Consensus Document 2016 diagnostic criteria for CVID.49,83 International Consensus Document 2016 criteria require impaired vaccine responses for diagnosis, unless the patient has profound hypogammaglobulinemia (IgG <1 g/L). In contrast, the Ameratunga et al 201336 and ESID 201432 criteria do not require impairment in vaccine responses to establish a diagnosis of CVID, recognizing some patients can respond to vaccines.

Two recent studies support this approach. The NZHS is a long-term prospective study of patients with hypogammaglobulinemia who did not meet criteria for CVID at the time of enrollment.49 It describes the natural history of patients with milder forms of hypogammaglobulinemia. Most asymptomatic patients with mild hypogammaglobulinemia (IgG 5-6.9 g/L) have remained well for over a decade. It was apparent most patients in the NZHS had excellent responses to Haemophilus influenzae type B ( Hib) vaccine and tetanus toxoid. In contrast, responses to diphtheria toxoid and Streptococcus pneumoniae were muted and did not differentiate patients who remained well from those who progressed to SCIG/IVIG treatment. These observations demonstrate that vaccine responses are not uniformly impaired in patients with mild hypogammaglobulinemia.

Similarly, in the recent NZ CVID study, many patients who underwent vaccine challenge responses before SCIG/IVIG treatment had excellent responses to Hib and tetanus toxoid but not to diphtheria toxoid or S pneumoniae.42,81 It is apparent that there is considerable heterogeneity in responses to vaccines within the spectrum of CVID.

These observations raise critical questions about the efficacy of COVID-19 vaccination in patients with CVID. It seems likely that patients with CVID will have variable responses to different COVID-19 vaccines, compared to persons with normal immune function. For example, there are insufficient data indicating whether mRNA-based vaccines will be more effective in immunodeficient patients than those based on an adenovirus carrier, as seen in healthy individuals.84 It is hoped that responses to SARS-CoV-2 mRNA vaccines are similar to tetanus and Hib responses seen the NZHS and NZ CVID study.49,83 Both vaccine factors and host immunologic factors shown in Figure 1 will influence the probability of protection in individual CVID patients. It is possible that patients with poor T-cell responses will require multiple doses or combinations of vaccines for optimal protection. COVID-19 vaccination will require a nuanced, individualized approach to patients with CVID and other immunodeficiency disorders.

Assessing the Immune Response to COVID-19 Vaccines

A major challenge will arise in determining protective immunity to COVID-19 in both healthy persons and patients with immunodeficiency. With greater community prevalence of COVID-19 as well as increased vaccine uptake, many plasma donors will be seropositive to SARS-CoV-2. As a result, most SCIG/IVIG preparations will soon have high titers of SARS-CoV-2 antibodies.85 Conversely, some antibody-deficient patients (eg, XLA) may have protective T-cell immunity to SARS-CoV-2 after COVID-19 infection or vaccination, but will be unable to produce antibodies to the virus. It will be impossible to determine which immunodeficient patients are susceptible and who may have protective immunity based on antibody tests.

The critical question is whether patients with CVID (and other immunodeficiency disorders) will generate robust memory T-cell responses to these vaccines. Commercial T-cell assays based on the S glycoprotein may rapidly become obsolete because of viral evolution resulting in the emergence of multiple variants. The case has been made for diagnostic laboratories urgently developing in-house T-cell assays to SARS-CoV-2.86 It will be important for diagnostic laboratories to verify the
precision of the assay in vitro and validate its accuracy clinically to ISO 9001 and 17025 standards.86

T-cell responses to antigens and lectins can be measured by a variety of techniques. Commonly used methods include IFN-gamma release assays.87,88 In the Quantiferon Gold test, T cells are cultured with peptides from Mycobacterium tuberculosis. Release of IFN-gamma is measured by enzyme-linked immunosorbent assay. The peptides confer specificity for M. tuberculosis and there is minimal cross-reactivity with Mycobacterium bovis. Other potential methods include enzyme-linked immunospot assays.89 Peripheral blood mononuclear cells are cultured in plates precoated with anticytokine antibodies. When cells are stimulated by antigen or lectins, activated T cells leave imprints of high cytokine concentration on the plate, which can then be detected by another enzyme-conjugated anticytokine antibody. Insoluble substrate precipitates on these cytokine imprints, leading to the spot.

T-cell proliferation can be detected by flow cytometry. Peripheral blood mononuclear cells are incubated with lectins and a fluorescent dye such as carboxyfluorescein succinimidyl ester. Proliferation of cells can be seen as spikes on flow cytometry. Most routine diagnostic laboratories do not have the experience to implement an antigen-specific flow cytometry test for SARS-CoV-2.

In recent years, ³H-thymidine uptake has become less popular for measuring T-cell responses to lectins and antigens because of the need to handle radioactivity. In these assays, isolated peripheral blood mononuclear cells are incubated with a series of lectins and antigens.48 On days 3 (lectins) and 7 (antigens), cultures are pulsed with ³H-thymidine. Cells are harvested the next day and ³H-thymidine incorporation into the DNA of proliferating cells is assessed in a β-scintillation counter. Uptake of ³H-thymidine is calculated against background levels. Such an assay could be rapidly established by laboratories with relevant experience with this platform.

Stimulating proteins or peptides can be varied to distinguish previous COVID-19 infection from vaccination, which uses the S glycoprotein. Vaccine-induced cross-protection against other
variants cannot be assumed from studies of healthy individuals. By altering the stimulating S glycoprotein (B.1.1.7, B.1.248, etc), valuable diagnostic and prognostic information can be obtained for individual patients. This may indicate whether each immunodeficient patient has a robust cellular response to circulating SARS-CoV-2 variants in the local community. In the future, customized testing may provide individualized prognostic information for patients with immunodeficiencies including CVID and CVID-like disorders.

The NZACE2-Patari Project and Other Potential SARS-CoV-2 Treatments for Immunodeficient Patients

*Patari* is a Māori verb for “decay that will lead to intercession.”

There is currently no widely available curative treatment for COVID-19. Repurposing existing drugs for COVID-19 has been disappointing. Given its subversion of the immune system, the absence of reliable treatments, and the scale of the pandemic, all therapeutic approaches must be urgently funded and trialed, either alone or in combination.

Passive immunotherapy with convalescent sera is used in some cases. Currently, it is unknown whether SARS-CoV-2 antibody containing SCIG/IVIG preparations or therapeutic CoVlg hyperimmune globulin will reduce mortality from COVID-19. There is a risk that these preparations may enhance intra-host viral evolution or cause ADE. If used in CVID patients, it is also uncertain whether such preparations will help or hinder protective T-cell responses to COVID-19 vaccines. This may be determined by the type of vaccination as well as the timing of such treatments. It is possible that if given at the time of vaccination, CoVlg hyperimmune globulin or SCIG/IVIG containing antibodies to SARS-CoV-2 may enhance T-cell responses by facilitating antigen uptake from subunit vaccines. In the case of live vaccines, such antibody preparations may neutralize the virus and impede T-cell responses. This is less relevant for CVID, because live vaccines are contraindicated in patients with T-cell defects. For mRNA vaccines, the timing of such antibody preparations may have no effect on the cellular immune response to the virus.

Monoclonal antibodies including casirivimab, bamlanavimab, imdevimab, and etesevimab have received emergency authorization for mild disease. As noted, viral evolution including the E484K mutation could render some of these drugs ineffective. TMPRSS2 inhibitors such as camostat mesilate have not proven effective in clinical trials. Other SARS-CoV-2 protease inhibitors are under development. ACE inhibitors (captopril, quinapril, etc) do not prevent infection.

The NZACE2-Patari project was recently described (Figure 2). The NZACE2-Patari project comprises modified ACE2 molecules (N90D and R273A) to intercept each wave of daughter virus in the nose to mitigate the pulmonary and systemic phases. NZACE2-Patari will be administered on several occasions over 2 days by a nasal dropper at the onset of infection. The NZACE2-Patari/SARS-CoV-2 complexes would be swallowed, leading to hydrolytic destruction of the virus in the stomach. If proven safe and effective in clinical trials, this treatment would be particularly attractive for CVID patients who have poor T-cell responses to COVID-19 vaccines.

The importance of the NZACE2-Patari project and other antiviral treatments was underscored by recent cases of vaccine-induced thrombosis and thrombocytopenia (VITT), which appears to be linked mostly to some adenovirus-based COVID-19 vaccines. mRNA based vaccines have been rarely associated with cases of myocarditis. These rare adverse events may cause reputational damage to COVID-19 vaccines in general, leading to increased vaccine hesitancy and delay in achieving herd immunity. In turn, there will be many more unvaccinated persons in the community, allowing the virus to circulate and potentially mutate. Emergence of newer virulent strains will leave immunodeficient patients even more vulnerable to COVID-19.

CVID and the Risk of Chronic COVID-19

Patients with PIDs including CVID and secondary immunodeficiency, have been described with prolonged viral shedding, termed Chronic COVID-19. Chronic COVID-19 infection may be a stalemate between SARS-CoV-2 and a suboptimal cellular immune response. Intra-host viral evolution in Chronic COVID-19 could lead to the emergence of dangerous vaccine-evasion mutants as well as variants resistant to monoclonal antibodies. Most patients developing Chronic COVID-19 appear to have had combined immune defects. Chronic COVID-19 could result in variants of high consequence and is a public health emergency; preventing this condition should be of the utmost priority. This emphasizes the importance of urgently vaccinating and evaluating T-cell responses to SARS-CoV-2 variants in immunodeficient patients to reduce the risk of Chronic COVID-19.

It is gratifying that far fewer patients with PIDs have been reported in the literature than might have been expected based on global numbers of COVID-19 infections. Although there may be underreporting, it also suggests that patients with PIDs were successfully advised to shelter in place early in the pandemic to avoid infection. The critical questions are whether these uninfected immunodeficient patients will respond to COVID-19 vaccines, and whether vaccine combinations might compensate for immune system failure. Having a validated diagnostic assay for T-cell responses to SARS-CoV-2 is an essential part of managing these patients.

Acknowledgments

The NZACE2-Patari project has not received support at this time. These drugs are undergoing in vitro testing. The SARS-CoV-2 T-cell assay is under consideration at LabPlus, Auckland Hospital. We are sharing our concepts so that colleagues with relevant resources might consider implementing these ideas. We would be pleased to share our protocols gratis to laboratories around the world who wish to set up such assays.

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