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OPINION
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Common Variable Immunodeficiency Disorders as a Model for Assessing COVID-19 Vaccine Responses in Immunocompromised Patients

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INTRODUCTION

COVID-19 has had a disastrous impact on the world with over 5 million deaths, hundreds of millions infected and many more plunged into poverty. COVID-19 has affected almost all countries. The origin of the virus is the subject of ongoing study (1–3).

SARS-CoV-2 initially infects the nasal mucosa. The Spike (S) glycoprotein engages cell-surface ACE2. Host proteases including TMPRSS-2 cleave the S glycoprotein, allowing the S2 subunit to fuse with the cell membrane (4). The viral genome is then able to hijack cellular organelles leading to production of daughter virus particles.

In the initial asymptomatic nasal phase, the innate immune system is silenced resulting in an exponential increase in viral progeny. SARS-CoV-2 deploys several mechanisms to evade cytoplasmic viral sensors. Following the nasal phase, the virus infects the lungs, probably by microaspiration from the nasopharynx and stomach (5, 6). Patients suffering pneumonitis experience increasing dyspnoea and have elevated inflammatory markers.

The smaller percentage entering the systemic phase suffer acute respiratory distress syndrome (ARDS) and multiple organ dysfunction. Increased d-dimers indicate a risk of arterial and venous thromboembolic disease. In spite of invasive ventilation and extracorporeal membrane oxygenation, mortality remains very high in such patients.

PATIENTS AT INCREASED RISK

There is a high case fatality rate in the elderly (7). In addition, patients with comorbidities including obesity, diabetes, hypertension, coronary artery disease, malignancy, renal and pulmonary disease are at increased risk of adverse outcomes (7–9). Patients of Black, Hispanic and South Asian origin also have a higher case fatality rate. Inequitable access to healthcare is at least partly responsible for these ethnic differences (10, 11).

Current data also suggests individuals with some immunodeficiency disorders are at increased risk of severe outcomes (12, 13). Patients with innate immune defects and T cell disorders are at greater risk than healthy individuals (14–16). In contrast, most studies indicate patients with X-linked agammaglobulinemia (XLA) without comorbidities appear to be at lower risk, inferring antibodies can in some circumstances be detrimental (17–20). Some authors are however less certain about the protective effect of XLA in COVID-19 outcomes (21, 22).

Immunocompromised patients are at risk of Chronic COVID-19, a dangerous stalemate between SARS-CoV-2 and impaired cellular immunity (23). Patients with Chronic COVID-19 can shed virus for months before either succumbing to or recovering from the infection. Such patients are vulnerable to intra-host viral evolution which could result in variants of high consequence (24). This is a public health emergency and prevention of Chronic COVID-19 is of the utmost priority.

RESPONSE TO COVID-19 VACCINES

Vaccines have proved effective in mitigating COVID-19. Vaccines do not prevent breakthrough infections, but markedly reduce the risk of a destructive immune response (**Figure 1**) (25). Hospitalisations and deaths from COVID-19 have dramatically decreased following vaccination. Most vaccinated patients dying from breakthrough infections are elderly or those with comorbidities. Vaccinated patients have variable levels of antibodies to the S glycoprotein at the time of breakthrough infections (26). There is no specific antibody level, which reliably prevents breakthrough infection (27, 28). The S glycoprotein is post-translationally modified with carbohydrates and antibody responses are less durable. In many studies antibody levels decrease six months after vaccination (29).

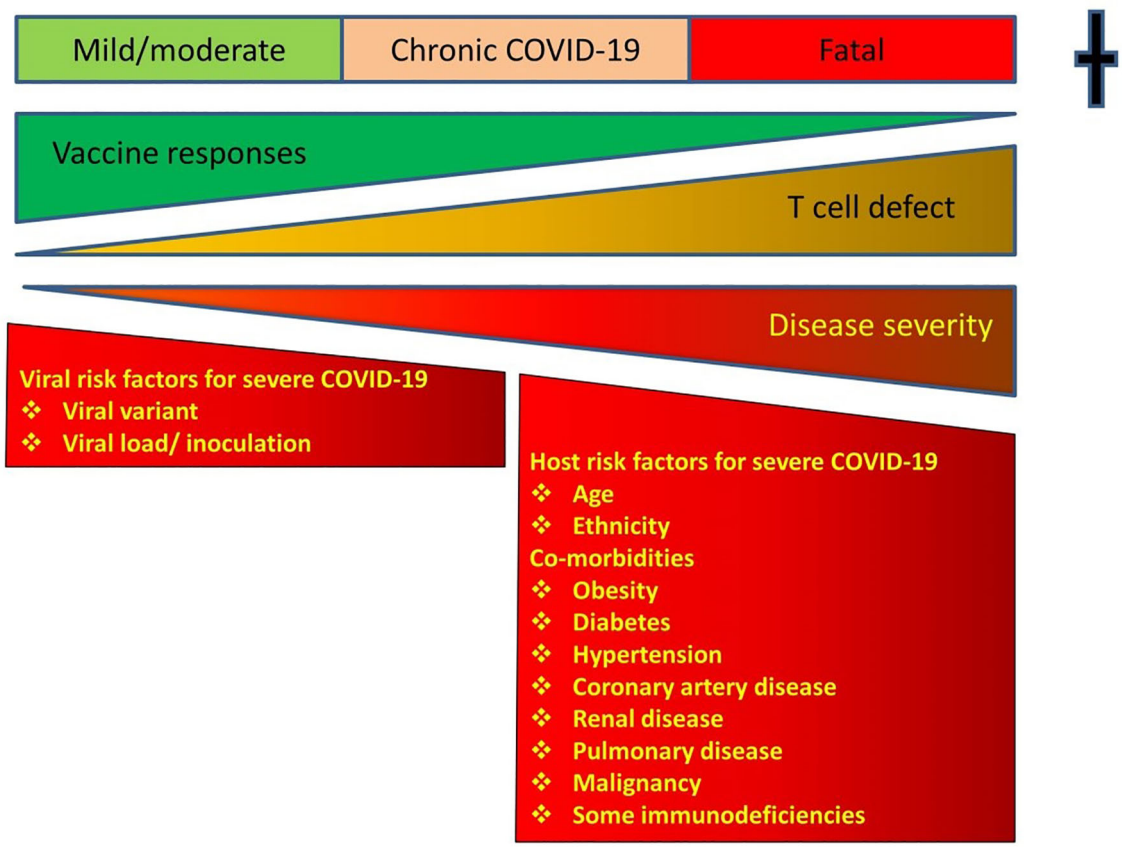

FIGURE 1 | Showing the relationship between T cell defects, responses to vaccines and outcomes. Vaccines shift the disease severity to the milder end of the spectrum. Instead of fatal disease, vaccinated patients with T cell defects will have a milder version of the infection. There is a risk of Chronic COVID-19 in immunodeficient patients and a vigorous T cell response to vaccines shifts the disease severity to the milder end of the spectrum. COVID-19 disease severity according to WHO criteria.

In contrast, memory T cell responses to vaccines correlate with protection (25, 30). Diagnostic T cell assays can be measured on different platforms, depending on the expertise of the laboratory (31). Current COVID-19 vaccines are regarded as T cell dependent and cellular responses are more durable, indicating that waning antibody levels underestimate the duration of protection (32). The S glycoprotein has strong adjuvant properties for cellular immunity, increasing its immunogenicity (and reactogenicity). Current COVID-19 vaccines do not require an additional adjuvant.

COMMON VARIABLE IMMUNODEFICIENCY DISORDERS AS A MODEL OF IMMUNOCOMPROMISED INDIVIDUALS

Common Variable Immunodeficiency Disorders (CVID) are the most frequent symptomatic primary immune defect in adults and children (33, 34). By definition, the cause of CVID is not known (35–37). In some patients an underlying genetic defect is causative (38). If a causative defect is identified, these patients are considered to have a CVID-like disorder and are removed from the broad umbrella diagnosis of CVID. In non-consanguineous populations approximately 25% have an underlying genetic defect, mostly autosomal dominant disorders (39, 40). In consanguineous societies a much higher number have autosomal recessive disorders (41).

Currently there are three sets of diagnostic criteria for CVID in common use (35–37). The original European Society of Immunodeficiencies/Pan-American Group for Immunodeficiency (ESID/PAGID) 1999 Criteria required significant hypogammaglobulinemia (IgG 2 sd. below the mean) with either impaired vaccine responses or absent isohemagglutinins (42). These were deemed difficult to use (43). In 2013 new diagnostic criteria were proposed with a lower IgG threshold (5 g/L) and vaccine responses beyond protection, to those of normal persons (35). These criteria also contained many of the more recent discoveries including reduction in switched memory B cells and genes predisposing to CVID. In contrast to the previous criteria, impaired vaccine responses were not mandatory for the diagnosis. The revised ESID registry criteria were published in 2014 (36). These were very similar to the Ameratunga et al., criteria (35), but maintained the higher IgG threshold (2 sd. below the mean) and protective vaccine responses of the original ESID/PAGID 1999 Criteria. In 2016 the International Consensus (ICON) document was published (37). Like the original ESID/PAGID 1999 criteria, poor responses to vaccine were mandatory in the ICON 2016 Criteria.

CVID and CVID-like disorders have a spectrum of B and T cell defects. The ESID 2014 and ICON 2016 criteria exclude patients with severe T cell defects, who were deemed to have late onset combined immunodeficiency (LOCID) based on reduced naïve $CD4^+$ T cell proportions (<10% $CD4^+$ T cells) (36, 37). It has however been suggested patients with LOCID should remain within the broad spectrum of CVID and CVID-like disorders (44). Individuals within the same family, carrying the identical *NFKB1* mutation, had widely differing immune defects. One brother was in excellent health, while his sister suffered multiple autoimmune complications and malignancy. She met the criteria for LOCID because of reduced T cell subsets and died prematurely from hepatic failure (45, 46).

CVID AS A MODEL OF VACCINE CHALLENGE RESPONSES IN IMMUNOCOMPROMISED PERSONS

Although not mandatory in the Ameratunga et al., 2013 or ESID 2014 Criteria, vaccine challenge responses are an integral part of the diagnostic work-up of patients with suspected CVID. CVID and other antibody deficiency disorders can serve as a useful model for both susceptibility to COVID-19 as well as responses to vaccines. In contrast to CVID, vaccine challenge responses are not routinely undertaken in patients suffering from secondary immunodeficiency disorders for either diagnosis or prerequisites for therapy. These patients receive subcutaneous or intravenous immunoglobulin (SCIG/IVIG) replacement based on either profound hypogammaglobulinemia or if they have modest hypogammaglobulinemia with breakthrough infections.

Two recent studies have explored the responses to vaccines in patients with hypogammaglobulinemia as well as CVID. In the New Zealand hypogammaglobulinemia study (NZHS), asymptomatic patients with hypogammaglobulinema (aHGUS) were noted to have an excellent prognosis (47). In this long-term prospective study, only one patient experienced progressive hypogammaglobulinemia requiring SCIG/IVIG. The majority have remained well for over a decade. In contrast, those with symptoms (sHGUS) had a mixed prognosis. Many experienced progressive deterioration culminating in SCIG/IVIG treatment. Vaccine challenge responses in the two groups were indistinguishable. Importantly, both groups had excellent responses to HIB and tetanus toxoid, both T cell dependent antigens. In contrast, responses to diphtheria toxoid and Pneumovax were muted. Poor responses to diphtheria toxoid are common, particularly in the elderly. Pneumovax responses are T cell independent.

A similar outcome was noted in the New Zealand CVID Study (NZCS) (48, 49). Most patients meeting criteria for CVID had excellent responses to tetanus toxoid and HIB. As in the NZHS, the responses to diphtheria toxoid and Pneumovax were suboptimal. This indicated T cell responses were preserved for at least some antigens in CVID. Recent studies confirm many CVID patients may generate protective responses to COVID-19 vaccines (50, 51).

APPROACH TO IMMUNOCOMPROMISED PATIENTS

The most important outcome of COVID-19 vaccination is a balanced, co-ordinated cellular immune response to the virus (25, 30). This implies at least some T cell function is required for vaccine efficacy (50). Given what was noted in the NZHS and

NZCS, COVID-19 vaccines will provide at least partial protection in most immunocompromised patients. This is a strong argument for vaccinating these patients and monitoring their T cell responses to SARS-CoV-2 (50–52).

Immunocompromised patients should be individually assessed to determine the degree of cellular immune deficiency. The extent of cellular impairment can be ascertained by the types of infections as well as laboratory tests including T cell subsets and their *in vitro* function. The nature of the underlying disorder and therapy may also help identify impaired cellular immunity. Such an individualised approach can sometimes lead to unexpected findings. Patients treated with rituximab are more susceptible to COVID-19 than those with XLA (53–55). This may be because of the underlying disorder or because of the use of additional immunosuppressive agents.

The WHO, UK and other countries are now advocating a three dose primary COVID-19 immunisation program for immunocompromised persons. This may improve memory T cell responses to the vaccine (56, 57). It remains to be determined if heterologous primary immunisation, with mRNA and adenovirus-based vaccines generates a robust cellular response, as seen with humoral responses in healthy individuals (58). Again, monitoring T cell responses following vaccination will provide reassurance (50, 55).

It will be difficult to monitor antibody responses to COVID-19 vaccines if patients are on SCIG/IVIG. Most plasma donors have high titres of SARS-CoV-2 antibodies from either infection or vaccination (59). SARS-CoV-2 memory B cells could be quantified as a measure of humoral immunity in patients on IVIG/SCIG. These responses have been quantitated in PID patients receiving the influenza vaccine (60).

Antibody responses to the S glycoprotein are T cell dependent. In patients who are not on SCIG/IVIG, a good antibody response could be interpreted as a satisfactory cellular response to the vaccine. In those who have poor antibody responses, it is still possible they have protective T cell responses (50, 55). Many healthy persons failed to seroconvert but had robust T cell responses to SARS-CoV-2 (61). There have been calls for development of diagnostic T cell assays for SARS-CoV-2, which would be very useful for diagnosis or evaluating vaccine responses in immunocompromised patients (31, 61).

The best current advice is for immunocompromised patients including those with antibody deficiency to have at least three primary vaccinations and have their T cell responses measured (56, 57). If there is failure to generate cellular immunity to SARS-CoV-2, these patients should be advised to shelter in place until more effective therapeutics and vaccines are developed for COVID-19. The recent development of antiviral drugs by Merck (molnupiravir) and Pfizer (paxlovid) is encouraging. Until these drugs are widely available, patients with sub-optimal memory T cell responses remain at risk of severe outcomes or Chronic COVID-19 (**Figure 1**). If there is waning cellular immunity they should receive boosters. In the absence of a diagnostic T cell assay for SARS-CoV-2, booster COVID-19 vaccines could be routinely considered every 6 months or sooner.

AUTHOR CONTRIBUTIONS

RA wrote the first draft. All other authors contributed to editing the manuscript.

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A SARS-CoV-2 T cell assay has not been implemented in NZ.

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