Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Narrative review

The potential clinical utility of measuring severe acute respiratory syndrome coronavirus 2-specific T-cell responses

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ABSTRACT

Background: Both humoral and cell-mediated responses are associated with immunity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although our understanding of the potential role of T-cell responses in the context of coronavirus disease 2019 (COVID-19) is rapidly increasing, more information is still needed.

Objectives: To provide an overview of the role of T-cell immunity in COVID-19, in the context of natural infection and post-vaccination, and discuss the potential utility of measuring SARS-CoV-2-specific T-cell responses, drawing on experience of the use of interferon-γ release assays (IGRAs) in tuberculosis (TB).

Sources: PubMed articles up to 16 April 2021.

Content: T-cell responses can be detected very early in the course of COVID-19, earlier than the detection of antibody responses, and are correlated with COVID-19 outcome. Lower $CD4^+$ and $CD8^+$ T-cell counts are markers of more severe disease, longer duration of viral RNA positivity and increased mortality. In line with natural infection, SARS-CoV-2 vaccination stimulates robust T-cell responses, which probably play an important role in protection; data on long-term T-cell responses are currently limited. The utility of measuring T-cell responses is already well established in both aiding the diagnosis of TB infection using IGRAs, and evaluation of T-cell responses to TB vaccine candidates. A variety of assays have already been developed to measure SARS-CoV-2-specific T-cell responses, including IGRAs, intracellular cytokine staining and activation-induced markers. IGRAs based on SARS-CoV-2 antigens can distinguish between convalescent and uninfected healthy blood donors.

Implications: Simple assays for measuring the quantity and function of T-cell responses may have utility in the prognostication of COVID-19, and for monitoring immune responses to SARS-CoV-2 vaccination and population-based immunity to SARS-CoV-2 variants of interest. **Delia Goletti, Clin Microbiol Infect 2021;27:1784**

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Introduction

A large proportion of what is now known about the role of T-cell responses to respiratory infection has come from studies of $CD8^+$ T-cell responses against acute viral infection [1]. Such studies, as reviewed by Schmidt and Varga [2], have shown that $CD8^+$ T cells are critical for mediating viral clearance [3–5], and memory $CD8^+$ T cells can provide protection against secondary infections [6,7]. Based on findings such as these, it is reasonable to hypothesize that induction of both humoral and T-cell responses (including $CD4^+$ and $CD8^+$ T cells) are required for an optimal immune response to natural respiratory infection, and post-vaccination.

In the case of influenza A virus, strain-specific protection generally afforded by the humoral immune response is complemented by virus-specific $CD8^+$ and $CD4^+$ T cells that provide cross-reactive responses recognizing different virus subtypes [8]. The same principle of a combined humoral and cell-mediated response for optimal immunity may apply to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, with virus-specific $CD4^+$ T cells, among their other functions, probably serving critical roles in establishing protective antibody responses [9].

T-cell responses are also required for optimal immunity to bacterial respiratory pathogens. For example, as initially demonstrated in murine models [10], humoral immunity alone is not sufficient to protect against *Bordetella pertussis* infection. This and other seminal work performed by Mills and colleagues highlighted the importance of T cells in both naturally acquired [10] and vaccine-induced immunity [11]. Furthermore, the broad relevance of T-cell responses and cytokine secretion in *Mycobacterium tuberculosis* infection is widely recognized, and interferon-γ (IFN-γ) release assays (IGRAs) are used in the diagnosis of tuberculosis (TB) infection.

In this article, we review T-cell responses to SARS-CoV-2 following natural infection and post-vaccination. Furthermore, we discuss the potential clinical utility of measuring T-cell responses to SARS-CoV-2, drawing on experience of the use of IGRAs in TB.

Search strategy

We searched PubMed up to 16 April 2021 for articles that refer to 'T-cell response' and 'SARS-CoV-2 infection'. We also searched for randomized controlled trials of authorized/approved vaccines, as listed in 'RAPS COVID-19 vaccine tracker' [12], as of 15 March 2021 ($n = 12$).

T-cell responses to SARS-CoV-2 natural infection

The role of T cells in SARS-CoV-2 infection has been demonstrated in murine models, where protection from disease was dependent on respiratory tract memory $CD4^+$ T cells alongside early induction of virus-specific $CD8^+$ T-cell responses [13]. Knowledge of T-cell responses to SARS-CoV-2 infection, particularly in the acute phase of illness, is rapidly expanding. T-cell responses can be detected very early in the course of disease [14–16], earlier than the detection of antibody responses [16]. For a detailed review on the kinetics and quantitative aspects of SARS-CoV-2 T-cell immunity, please refer to Bertoletti et al. [17].

T-cell count and IFN-γ production are inversely associated with disease severity. In a systematic review of 61 articles, symptomatic adult coronavirus disease 2019 (COVID-19) cases consistently showed peripheral T-cell lymphopenia positively correlating with increased disease severity, duration of viral-RNA positivity, and non-survival [18]. Earlier induction of IFN-γ-secreting T cells may also be a marker of better prognosis [14,15,19]. These observations help to explain why T-cell count and clonal expansion of SARS-CoV-2-specific T cells are markers of COVID-19 convalescence [20], and why delayed or insufficient activation of T-cell responses may allow for uncontrolled viral infection, resulting in severe lung damage, systemic inflammation and high mortality rates [21]. However, it is important to consider study limitations when correlating T-cell counts with disease severity, such as the possibility of much higher frequencies of SARS-CoV-2-specific T cells in the respiratory tract than can be detected through peripheral blood assays [17].

Further evidence of the importance of T-cell responses for COVID-19 recovery can be observed in patients with B-cell deficiencies, who exhibit prolonged and severe COVID-19 [22]. Soresina et al. described two patients with X-linked agammaglobulinaemia who, although they presented with pneumonia after contracting COVID-19, did not require oxygen supplementation [23], indicating that cellular responses can limit disease severity. Similarly, a study of patients with impaired humoral immunity as a result of haematological cancer found that $CD8^+$ T-cell count was associated with increased survival and lower viral load [24].

The quality of T-cell responses may also play an important role. Le Bert et al. noted increased IFN-γ and interleukin-2 (IL-2) production in asymptomatic patients compared with symptomatic patients, despite similar overall frequencies of T-cells in both groups [19]. Mild cases of SARS-CoV-2 infection are associated with early, highly specific T-cell responses, whereas severe COVID-19 cases are associated with late, disproportionate secretion of pro-inflammatory cytokines (tumour necrosis factor-α, IL-6, IL-1β) [19], a phenomenon which has also been observed in non-survivors [25,26] and is suggestive of a cytokine storm [27,28]. Notably, many patients with severe disease exhibit markers of T-cell exhaustion including increased expression of Programmed Cell Death Protein 1 (PD-1), T-cell immunoglobulin and mucin domain 3 (Tim-3) [29], and NKG2A [21].

The longevity of T-cell immunity appears in line with antibody responses, suggesting a durable immune response to natural SARS-CoV-2 infection [30]. In one study, 93% and 70% had detectable $CD4^+$ and $CD8^+$ T-cell memory, respectively, 1 month after infection [31]. $CD4^+$ T-cell memory was still detectable in 92% of participants at $\geq$6 months after infection, whereas $CD8^+$ T-cell memory had declined to 50% [31]. Supporting this observation, intracellular cytokine analysis has shown that $CD4^+$ virus-specific T-cell responses at 6 months are twice as frequent as $CD8^+$ responses [32].

Extensive research has been conducted into identifying epitopes to effectively measure T-cell responses, including a large study of overlapping peptides spanning the entire SARS-CoV-2 proteome [33]. Spike protein epitope pools are the most immunogenic stimuli [16,34]. In a study of individuals convalescing after COVID-19, 280 SARS-CoV-2 $CD4^+$ T-cell epitopes and 523 SARS-CoV-2 $CD8^+$ T-cell epitopes were identified [35]. These experimentally-defined epitopes were used to generate second-generation pools, associated with increased activity and lower complexity for measuring T-cell responses [35]. The sequences of most SARS-CoV-2 T-cell epitopes do not appear to be affected by the different SARS-CoV-2 variants currently in circulation [36].

T-cell responses to SARS-CoV-2 vaccination

Given the high mortality risk and potential for long-term disability associated with COVID-19, development of effective vaccines is a global public health priority, with multiple candidates already approved or authorized for use [12]. At the time of writing, randomized controlled trials of approved vaccines have reported significant protection from severe disease [37–40]. However,

efficacy could be affected by variants of concern [41] meaning that updates to vaccines may be required.

Considering the important role of T cells in the response to natural SARS-CoV-2 infection, a combination of strong humoral and cellular response to vaccination is likely to be a key factor in their clinical success. $CD4^+$ T-cell responses observed across clinical trials demonstrate that cellular immunity is achieved through vaccination, with levels peaking at ~14 days post-vaccination (in line with natural infection), and remaining detectable at the end of the analysis period in studies reporting T-cell responses [42–44]. Studies indicate that SARS-CoV-2-specific T cells are detectable as early as 7–14 days post-vaccination, whereas neutralizing antibodies are only present at low titres in this early phase [45,46]. As the protective effect of vaccination has been observed from day 12 post-administration [39], it is likely that T cells play an important early role in vaccine-mediated immunity [43,46]. Considering the functional role of T cells in containing the spread of infection by eliminating infected cells, early induction of T cells through vaccination is crucial. Currently, little is known about long-term SARS-CoV-2 T-cell responses to vaccination, because of their recent introduction; one study reported a robust cellular response at day 84 following vaccination with ChAdOx1 [42]. Long-term data on the correlates of protection from vaccine-induced T-cell responses are needed.

Clinical utility of measuring T-cell responses

Experience in TB

Quantifying T-cell responses is a well-established diagnostic tool for TB infection. Whole blood or peripheral blood mononuclear cell-based tests are currently used in clinical practice for measuring T-cell responses to *M. tuberculosis* antigens, such as IGRAs, based on ELISA or ELISpot platforms [47]. IGRAs are shown to have high sensitivity in detecting *M. tuberculosis* infections [48,49]; however, IGRAs by themselves are not recommended as a rule-out or rule-in test for active TB in clinical practice [50]. Instead, IGRAs, along with tuberculin skin tests, are useful to identify TB infection among those at high risk of infection, and to propose preventive treatment as a measure to stop the spread of infection [51]. IGRAs have performance and practical advantages over tuberculin skin tests, including improved predictive performance [52,53]. Interestingly, in a small study using IGRAs in patients with active TB and SARS-CoV-2 co-infection, patients had impaired T-cell responses to SARS-CoV-2, as evidenced by the inability to mount a spike-specific response [54], indicating that co-infection may limit the ability to respond to the virus.

Similar to SARS-CoV-2 vaccination trials, most trials of candidate TB vaccines also measure T-cell responses to epitopes in the vaccine over time as a marker of long-term immunity [55–57]. A study of the M72/AS01 vaccine showed that $CD4^+$ T-cell responses persist for at least 3 years post-vaccination, with no evidence of diminishing in this time [56]. Furthermore, there is growing interest in using IGRA conversion rates as a correlate of protection in TB vaccine candidate trials. This has potential cost-saving and time-saving benefits over long-term assessments of traditional vaccination end points, although data are currently limited.

Potential in COVID-19

A variety of assays have been used to measure SARS-CoV-2-specific T-cell responses, including intracellular cytokine staining [15], activation-induced markers [33] and IGRAs [45,58]. Each platform has distinctive advantages and disadvantages related to ease of implementation and execution and granularity of information collected; however, a detailed discussion of these platforms is beyond the scope of this review. Simple, robust assays requiring a

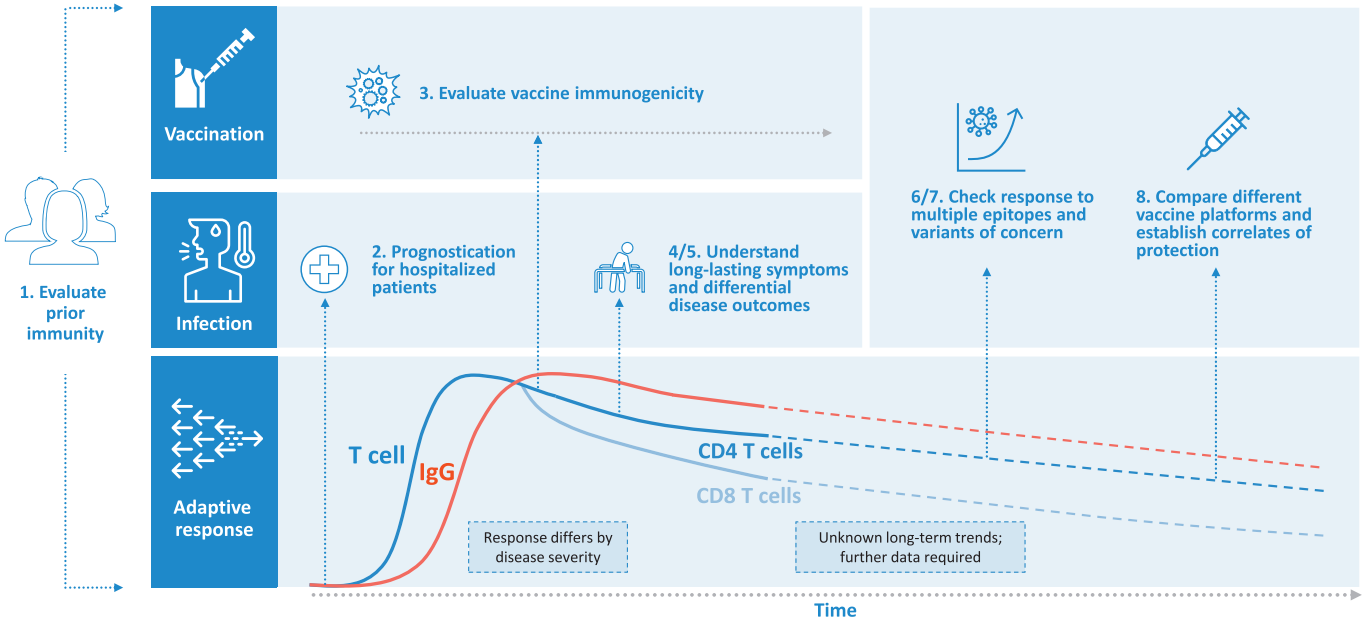

Fig. 1. Potential utility for measuring the quantity and function of SARS-CoV-2-specific T-cells. A robust and widely accessible platform to measure T-cell responses could hypothetically: (1) Provide information of response in vaccine naive and/or previously infected populations ahead of vaccination, and aid in establishing boosting schedules. (2) Aid prognosis among hospitalized patients with COVID-19 if measured early in the disease course. (3) Provide insight into long-term immunogenicity after administering vaccines. (4) Aid understanding of multisystem inflammatory syndrome in children and long COVID. (5) Uncover why different ages and subpopulations are associated with differential disease outcomes. (6) Aid understanding of responses to multiple SARS-CoV-2 epitopes among individuals with low levels of detectable antibodies. (7) Measure responses to SARS-CoV-2 variants of concern and in populations vaccinated with non-spike based vaccines. (8) Allow comparisons between different vaccine platforms and the establishment of correlates of protection. Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

low technological barrier for implementation are required to enable T-cell measurements on a global scale.

Much like the use of IGRAs in TB, a simple T-cell response assay could facilitate the detection of an immune response to SARS-CoV-2 infection or vaccination and, moreover, may aid in monitoring the immune response over time or during therapy (Fig. 1) [54,58,59]. Proof-of-concept has been demonstrated in COVID-19, where an ELISA-based whole-blood IGRA stimulated with epitope pools covering the entire viral proteome was able to accurately distinguish between convalescent and uninfected healthy blood donors [60]. Furthermore, an ELISpot-based IGRA using isolated peripheral blood mononuclear cells stimulated with peptides covering nucleoprotein, membrane and immunogenic regions of the SARS-CoV-2 spike protein was able to differentiate SARS-CoV-2-infected individuals with symptomatic or asymptomatic infection [19], and measure T-cell responses in vaccinated individuals [45]. Notably, among patients with SARS-CoV-2 infection, T-cell responses were detectable independently of disease severity, symptom onset and lymphocyte count [19,58]. Clinical study data are required to confirm correlates of T-cell responses and COVID-19 disease protection; however, early data [25,26] of high pro-inflammatory-cytokine secretion in non-survivors suggest that details of T-cell response (both quantity and function) early in the disease course of hospitalized patients with COVID-19 could provide indications of patient prognosis. It will also be important to consider confounding factors when measuring T-cell response, such as impairment of T-cell monitoring due to co-morbidities or immunosuppression that may limit the specific response [54]; a consideration that may have increased importance in the convalescent phase.

There are several possibilities for the use of T-cell response data in the context of vaccination (Fig. 1). In individuals with low levels of antibody response, T-cell responses may be a marker of disease [22] or vaccination-induced immunity. Furthermore, T-cell response data may provide insight into long-term immune reactivity independently of serological response, as observed in the context of natural infection [61]. T-cell responses to large numbers of SARS-CoV-2 epitopes can be measured to generate reagents with maximum sensitivity and specificity, suitable for use in diverse populations [35]. Epitope pools based on antigens other than spike [16] could be used to quantify responses that are not related to immunization with spike-based vaccines, such as those induced by SARS-CoV-2 natural infection, and to detect 'breakthrough infections' in vaccinated individuals. Additional uses could be understanding responses in vaccinated populations to SARS-CoV-2 variants of concern. Recent data among convalescent individuals after COVID-19, as well as individuals who had received mRNA-based vaccines, demonstrated that $CD4^+$ and $CD8^+$ T-cell responses were not substantially affected by mutations found in SARS-CoV-2 variants circulating at the time of study [36]. Measurement of T-cell responses will also be key for comparing different vaccine platforms to establish correlates of protection. Quantifying functional SARS-CoV-2-specific T-cell responses may also help to understand multisystem inflammatory syndrome in children and long COVID, and why different ages and subpopulations are associated with different disease outcomes.

The US Food and Drug Administration has approved the T-Detect Test (Adaptive Biotechnologies, Seattle, WA, USA) [62] as a method for indicating, through the use of a T-cell signature as a diagnostic marker, whether or not an individual is likely to have previously been infected with SARS-CoV-2. Moving forward, to accurately monitor COVID-19 immunity, it will be important to identify ways to measure both the quantity of SARS-CoV-2 specific T cells as well as their function based on the secretion of activation markers and cytokines.

Conclusions

A broad array of literature supports the potentially crucial role of T-cell responses following SARS-CoV-2 vaccination, on COVID-19 disease progression and patient outcomes. Evidence from both natural infection and vaccination studies suggests that early T-cell responses may play an important role in protection, clearing and recovering from SARS-CoV-2 infection. Studies of vaccination against SARS-CoV-2 have been highly successful and show robust T-cell responses; however, we will need to wait for further data on the longevity of T-cell responses and their correlation with protection. There is potential utility in quantifying SARS-CoV-2 T-cell responses in relation to both natural infection and vaccination. Assessing T-cell responses following natural infection may provide information on differentiating disease outcomes, but monitoring of vaccinated individuals will most likely be used to help to establish boosting schedules and measure the vaccine's ability to recognize and protect against SARS-CoV-2 variants. COVID-19 is a rapidly changing landscape and although at present the role of T-cell responses is not fully defined, measuring T-cell responses with simple and robust testing assays may hold great utility in managing future actions surrounding this disease.

Transparency declaration

DG is a consultant for QIAGEN. LP has nothing to disclose. AS is a consultant for Gritstone, Flow Pharma, CellCarta, Arcturus, Oxford-dimmunotech and Avalia. LJI has filed for patent protection for various aspects of T-cell epitope and vaccine design work. AB is a consultant for OxfordImmunotech and QIAGEN, and has filed for patent protection for aspects of detection of SARS-CoV-2 T-cells. SR and VN are employees of QIAGEN. DM is an employee of QIAGEN and owns shares in QIAGEN. NN is a former QIAGEN employee.

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Author contributions

All authors contributed to conceptualization, data interpretation, writing, and critical review and editing.

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