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Severity of adverse reactions is associated with T-cell response in mRNA-1273 vaccinated health care workers

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Knowledge about mRNA-1273 elicited T-cell response is limited. We investigated adverse reactions and interferon gamma release by specific T-cells among mRNA-1273 vaccinated health care workers. Seven to 13 weeks after complete vaccination low levels of specific T-cells were detected not correlating with antibody response. Severity of symptoms after first and number of symptoms after second immunization were associated with T-cell response. Assessment of T-cell response in addition to antibody response is crucial because even few specific T-cells could add to protection against infection. Investigation of mRNA-1273 induced inflammatory processes might help improve reactogenicity and immunogenicity.

Keywords: Adverse reactions, Antibody response, SARS-CoV-2, T-cell response, Vaccine mRNA-1273

Global effort has been made to rapidly develop vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to stop the ongoing pandemic of coronavirus disease 2019 (COVID-19) [1]. The messenger RNA based vaccine mRNA-1273 (Moderna Vaccine; Moderna, Cambridge, MA, USA) has shown to induces an antibody and type 1 helper T- (Th1-) cell mediated immune response against the viral spike (S) protein in humans [2]. Human CD8 T-cell response to mRNA-1273 has been reported to be low [2]. Lacking a definite correlate of protection for SARS-CoV-2 in humans, investigation not only of humoral but also cellular immune response is of paramount importance [1]. T-cells are expected to persist longer than antibodies and promise to contribute to protection against severe COVID-19 by supporting clearance of infected cells and coordinating humoral immune response [3]. However, reliable knowledge about the durability of T-cell response after mRNA-1273 vaccination and the connection with humoral immune response and adverse reactions remains limited. So far, trials on the durability of mRNA-1273 induced immunity have focused on antibody mediated immunity [4]. Furthermore, studies on the correlation of humoral and cellular immune response have reported differing results for other mRNA vaccines against SARS-CoV-2 [5-7] and are widely lacking for mRNA-1273. While previous findings suggest that adverse reactions are associated with humoral immune response to mRNA vaccines against SARS-CoV-2 [8], an association with T-cell response has not been described. To extend the knowledge about T-cell response after vaccination against SARS-CoV-2 and the correlation with humoral immune response and adverse reactions we

conducted a study on mRNA-1273 vaccinated health care workers.

Twenty health care workers who were vaccinated twice with 100 μg of mRNA-1273 consented to participate in the study. No screening for past or current SARS-CoV-2 infection was performed prior to vaccination. Each participant completed a questionnaire regarding local (local pain, swelling, and redness) and systemic (fatigue, headache, fever, chills, myalgia, arthralgia, diarrhea, vomiting, rash, pruritus, edema, being bedridden) adverse reactions. Symptoms were graded as mild, moderate, or severe and the approximate beginning and duration of each symptom were recorded. Between 7 and 13 weeks after the second vaccination heparinized blood from each participant was collected to measure interferon gamma (IFN-γ) release by CD4 and CD8 T-cells specific to the S protein of SARS-CoV-2 using the QuantiFERON SARS-CoV-2 test (Qiagen, Venlo, Netherlands) [7]. Binding and neutralizing antibodies were measured from serum samples collected between 2 and 3 weeks after the second immunization using the Liaison SARS-CoV-2 S1/S2 IgG assay (DiaSorin, Saluggia, Italy) [9] and a SARS-CoV-2 Surrogate Virus Neutralization Test (Genscript Biotech, Piscataway, NJ, USA) [10]. Statistical analysis was performed using IBM SPSS Statistics ver. 27.0 for Windows (IBM Corp., Armonk, NY, USA). Categorical variables are expressed as number of participants or frequencies and are compared using Fisher's exact test. Metric variables are given as arithmetic mean±standard deviation and are compared using two-sided Mann-Whitney U test. Correlation between metric variables is assessed by Spearman correlation analysis. All p-values below 0.05 are considered significant.

The participants were aged from 25 to 65 years with a mean of 48.4±14.00 years and 60% of the participants were female. Total specific T-cell response including CD4 and CD8 T-cell response ranged from 0.022 to 2.478 IU/mL with a mean of 0.467±0.7435 IU/mL. And 45% of the participants had a total T-cell response above a cut-off of 0.15 IU/mL [11]. All participants had binding and neutralizing antibodies above the test specific cut-offs with a mean of 159.08±98.026 AU/mL and 76.11%±18.141%, respectively. Humoral immune response was not significantly correlated with T-cell response ($p_{\text{binding antibodies}}=0.057$, $p_{\text{neutralizing antibodies}}=0.484$). Comparison of participants with and without T-cell response revealed no age or sex specific differences ($p_{\text{age}}=0.926$, $p_{\text{sex}}=0.197$). The frequency, beginning and duration of symptoms, and the frequency of temporary inability to work after first and second dose of immunization were comparable between the two groups. However, participants with a detectable T-cell response reported a significantly higher intensity of symptoms in general and local pain in particular ($p_{\text{symptoms}}<0.05$, $p_{\text{local pain}}<0.05$) after the first immunization as well as a significantly higher number of symptoms (7±3 versus 4±3) and systemic symptoms (5±3 versus 2±3) after the second vaccination ($p_{\text{symptoms}}<0.05$, $p_{\text{systemic symptoms}}<0.05$) than participants without a T-cell response (Table 1). The intensity of all other symptoms and the number of symptoms after the first vaccination were similar in both groups.

Table 1. Intensity of symptoms after first vaccination

Symptoms	QuantiFERON SARS-CoV-2 test	
	Negative (n=11)	Positive (n=9)
Any symptom		
Mild	50.0 (4/8)	0
Moderate	50.0 (4/8)	66.7 (6/9)
Severe	0	33.3 (3/9)
Any intensity	100.0 (8/8)	100.0 (9/9)
Local pain		
Mild	57.1 (4/7)	0
Moderate	42.9 (3/7)	87.5 (7/8)
Severe	0	12.5 (1/8)
Any intensity	100.0 (7/7)	100.0 (8/8)

Values are presented as participants with symptom % (number).
Frequencies have been calculated based on the number of participants in each group reporting symptoms or local pain, respectively. Participants without the respective symptom are not included in the table.

The present study aimed at evaluating the total T-cell response elicited by mRNA-1273 in health care workers and the association with humoral immune response and adverse reactions. Surprisingly, more than half of the participants did not have a T-cell response above the defined cut-off while all participants had a detectable humoral immune response. Phase 1 trials on mRNA-1273 have reported a strong Th1-cell response with expression of IFN-γ as well as a minimal type 2 helper T- (Th2-) cell and a low CD8 T-cell response [2]. Since the QuantiFERON SARS-CoV-2 test measures total specific T-cells producing IFN-γ including CD4 as well as CD8 T-cells a stronger immune response had been expected. However, phase 1 trials reported antigen specific IFN-γ expression by Th1-cells and CD8 cells to be lower than total antigen specific Th1-cell and CD8 T-cell response [2]. Therefore, measuring IFN-γ release does not represent complete T-cell response to mRNA-1273. Nevertheless, using the QuantiFERON SARS-CoV-2 test two recent studies on BNT162b2 vaccinated health

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care workers found higher T-cell responses and less non-responders after the first immunization [11] and higher T-cell responses shortly after the second immunization [7]. Using a different IFN-γ release assay 7 weeks after the second vaccination, another study reported a detectable T-cell response in 84.5% of BNT162b2 vaccinated health care workers [12]. Since we evaluated cellular immune response up to 13 weeks after the second vaccination a fast decline of SARS-CoV-2 specific T-cells after mRNA-1273 vaccination could explain our results and has been demonstrated for a different mRNA vaccine against SARS-CoV-2 in a rhesus macaque model [13]. However, specific T-cells might be measured low in blood samples because of migration to tissues [14] which was not assessed in our study. Correlation of antibody and T-cell response has not been studied extensively in a cohort consisting of exclusively mRNA-1273 vaccinated individuals, yet some studies have reported heterogenous results among individuals vaccinated with similar mRNA vaccines against SARS-CoV-2 [5-7]. Our results indicate that antibody and total T-cell response to mRNA-1273 vaccination are independent. In accordance to previous studies and the concept of CD4 T-cell help for antibody production [3,5,15] especially CD8 T-cell response might be independent of humoral immune response. Studies on rhesus macaques have demonstrated the contribution of CD8 T-cells to protection against COVID-19 [16] and the boosting of mRNA vaccine induced SARS-CoV-2 specific T-cells at low levels upon infection challenge [13]. Therefore, even low vaccine induced T-cells promise to protect against COVID-19 at least partially irrespective of eventually declining antibody levels. However, a correlate of protection for SARS-CoV-2 in humans has not been established yet. Furthermore, the QuantiFERON SARS-CoV-2 test measures total T-cell response and does not allow discrimination between CD4 and CD8 T-cells. Thus, further longitudinal evaluation of CD4 and CD8 T-cell response separately will need to prove the hypothesis that especially CD8 T-cell mediated immunity is independent of antibody mediated immunity. Previous studies on COVID-19 patients found disease severity to be associated with T-cell response [1]. Our results show that severity of adverse reactions after the first vaccination and quantity of symptoms after the second vaccination are also associated with total T-cell response in mRNA-1273 vaccinated individuals. T-cell response and intensity of symptoms are presumably linked by inflammation. Inflammation could be initiated by mRNA induced type I interferon release by local and innate immune cells and might be the driving force of reactogenicity and T-cell response [3,15]. Type I interferon expression by local and innate immune cells promotes a Th1-biased adaptive immune response [15] and upregulates major histocompatibility complex I expression and therefore supports antigen presentation to cytotoxic T-cells [3]. However, the role of type I interferons in the innate immune response to mRNA vaccines is still discussed [3] and studies on BNT162b2 vaccinated individuals have not detected a type I interferon response [17,18]. Therefore, evaluation of cytokine expression after mRNA-1273 vaccination is needed to fully understand the underlying connection between severity of adverse reactions and T-cell response. In contrast, cytokine expression by SARS-CoV-2 specific adaptive immune cells upon stimulation has been evaluated as part of the clinical trials on mRNA-1273. Th1-cells and CD8 T-cells produced tumor necrosis factor-α, interleukin 2, and IFN-γ upon *in-vitro* stimulation with S specific peptides [2]. Consequently, the QuantiFERON SARS-CoV-2 test measures IFN-γ release after *in-vitro* stimulation as an indicator of SARS-CoV-2 specific T-cells. All in all, due to the small sample size and the focus on health care workers our results will need to be confirmed in larger studies. Moreover, a definite threshold for discrimination between positive and negative T-cell response in the QuantiFERON SARS-COV-2 test has not been defined yet [7,11].

Taken together, our results indicate that 7 to 13 weeks after mRNA-1273 vaccination SARS-CoV-2 specific T-cells can be detected only at low levels. However even few specific T-cells could add to the protection against COVID-19. Furthermore, our findings indicate that T-cell response is independent of antibody response and therefore should be assessed additionally when evaluating immune response and immunity. Finally, we have demonstrated an association between intensity and number of symptoms and T-cell response that are presumably connected by inflammation.

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