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Humoral and cellular responses to spike of δ SARS-CoV-2 variant in vaccinated patients with immune-mediated inflammatory diseases

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ABSTRACT

Objectives: We assessed vaccination-induced antibody and cellular responses against spike from the ancestral strain and from the delta (δ) SARS-CoV-2 variant in patients with immune-mediated inflammatory diseases (IMIDs) on immunosuppressive therapy in comparison with immunocompetent subjects.
Methods: We enrolled patients with IMID and immunocompetent subjects who completed the vaccination schedule within 4–6 months from the first dose. The interferon (IFN)-γ-response to spike peptides that were derived from the ancestral and the δ SARS-CoV-2 were measured by ELISA. Anti-Receptor Binding Domain IgG antibodies were also evaluated.
Results: We enrolled 43 patients with IMID and nine immunocompetent subjects. No significant differences were found after comparing the specific immune response (IFN-γ) between patients with IMID and immunocompetent subjects to the ancestral ($p = 0.36$) or δ peptide pool ($p = 0.51$). Nevertheless, IFN-γ-specific responses to the ancestral or to the δ pools were reduced in subjects taking CTLA4-IgG or TNF-α inhibitors compared with subjects treated with IL-6 inhibitors or Disease Modifying Anti-Rheumatic Drugs. Regarding the antibody response, no significant differences were observed between patients with IMID and immunocompetent individuals.
Conclusions: Cellular responses to δ SARS-CoV-2 variant remain largely intact in patients with IMID. However, the magnitude of these responses is dependent on the specific IMID immunosuppressive regimen. Serological response was also similar between the IMID and control groups.

Introduction

The World Health Organization (WHO) identified all the viral variants as variants of concern (VOC), with increased potential to spread or capacity to evade the natural or the vaccine-induced protection. The SARS-CoV-2 VOC are the α, β, γ, and δ variants (WHO, 2021); moreover, the omicron VOC has been recognized very recently (Viana et al., 2022). At the time of writing

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this report, the δ, with 41.4% of sequences identified (WHO, 2022), was still a high-spread VOC worldwide, and was associated with an exponential increase of infections and deaths (Cherian et al., 2021; Depres et al., 2021) owing to its capacity to infect individuals with a viral load up to 1000-fold compared with the original strain (Campbell et al., 2021). Indeed, several studies evaluated the ability of these VOC to bypass the protection induced by the natural infection or by vaccines (Pullian et al., 2022; Edara et al., 2021), which are based on the ancestral SARS-CoV-2 strain. In particular, the rate of prevention against the δ variant was reduced (Lopez Bernal et al., 2021a), although the protection against severe disease and death was still maintained after a complete vaccination (Lopez Bernal et al., 2021b), indicating the importance of carrying out the vaccination schedule in the context of high circulation of the δ variant.

T cell-specific immunity is important for controlling infection. In particular, a coordinated immune response is crucial in COVID-19 (Sette and Crotty, 2021) and is pivotal for clearance of the virus and for the subsequent induction of B cell response (Sette and Crotty, 2021; Aiello et al., 2021; Cantini et al., 2020; Goletti et al., 2021).

Immune-mediated inflammatory diseases (IMIDs) are associated with increased risk of hospitalization and death from COVID-19 (Belleudi et al., 2021). Therefore, individuals with these diseases are considered as a priority target group for the COVID-19 vaccine campaign (Picchianti-Diamanti et al., 2021). Recently, we and others demonstrated that mRNA vaccines induce an immune response, both humoral and T cell response, in patients with rheumatoid arthritis (RA) (Picchianti-Diamanti et al., 2021; Connolly et al., 2021; Deepak et al., 2021; Jyssum et al., 2021). However, the magnitude of the response depends on the immunosuppressive therapy. In particular, the lowest T cell viral-specific response was observed in patients with IMID under therapy with cytotoxic T-lymphocyte antigen (CTLA) 4-IgG, tumor necrosis factor (TNF)-α, or interleukin (IL)-6 inhibitors (Picchianti-Diamanti et al., 2021).

Few evidences are available on the impact of VOCs on the vaccine-induced T cell response in vulnerable populations. The comparison of the interferon (IFN)-γ-secreting T cells that are specific for the ancestral spike and VOC, induced by a SARS-CoV-2 inactivated vaccine or by mRNA vaccine showed no differences among healthy subjects (Melo-González et al., 2021; Cassaniti et al., 2021). Recently, a study evaluated the T cell response against the ancestral viral strain and against the α, β, γ viral variants in subjects on immunosuppressive therapy, including patients with chronic inflammatory diseases (Collier et al., 2021), demonstrating a reduction of the cellular response against viral variants, particularly in individuals on triple immunosuppressive therapy. However, the impact of the most spread δ variant has never been evaluated in patients with IMID.

Therefore, in this study, we assessed the cellular response against δ SARS-CoV-2 variant after COVID-19 vaccination in patients with IMID on immunosuppressive therapy in comparison with the results from immunocompetent subjects. The vaccine-induced antibody response was also evaluated.

Materials and Methods

Study Population

Patients with IMID were enrolled at Sant'Andrea University Hospital in Rome (Approval number 318/2021), at San Camillo Hospital in Rome (Approval number 1532/2021), and at the National Institute for Infectious Diseases (INMI) Lazzaro Spallanzani-IRCCS (Approval number 59/2020). Immunocompetent subjects were included in the study as controls and were enrolled at INMI (Approval numbers 59/2020, 72/2015 and 297/2021). The diagnosis of IMID was based on objective criteria (ie, RA diagnosis on the basis of the 2010 criteria of the European League Against Rheumatism/American College of Rheumatology [Aletaha et al., 2010] and disease activity on the basis of clinical examination through the Disease Activity Score based on C-reactive protein [DAS28-CRP]). The inclusion criterion for all the subjects was a vaccination schedule that was completed within four and six months from the first dose, whereas the exclusion criterion was a recent or remote SARS-CoV-2 infection. Some of the patients with IMID are part of the cohort previously described within a month of completed vaccination (Picchianti-Diamanti et al., 2021). Immunocompetent subjects have been described also in a recent study (Petrone et al., 2022). Written informed consent was required to consecutively enroll immunocompetent subjects and patients with IMID; clinical and demographic information were recorded at enrollment.

Stimuli

Two different spike SARS-CoV-2 peptide pools were used: the "ancestral" peptide pool, which was designed and carried out on the Wuhan-Hu-1 strain (GenBank ID:MN908947) and the "δ" peptide pool, which was designed and carried out on the GISAID ID: EPI_ISL_2020950. Ancestral and δ peptide pools consisted of overlapping 15-mers by 10, spanning the entire spike proteins (n = 253). Peptides were synthesized as crude material (TC Peptide lab, San Diego, CA, USA) and resuspended in dimethyl-sulphoxide. Peptide pools were generated on the basis of spike composition (ancestral or delta [δ]), followed by sequential lyophilization steps (Carrasco et al., 2015). Peptide pools were used at 0.1 µg/mL.

Staphylococcal enterotoxin B (SEB) antigen (Sigma Aldrich) was used at 200 ng/mL.

IFN-γ Whole Blood Assay

The spike-specific cellular response was evaluated by the detection of IFN-γ production after the stimulation of whole blood with SARS-CoV-2 pools of peptides, as previously reported (Petrone et al., 2021a–c). SEB was used as the positive control, whereas unstimulated whole blood served as the negative control. Briefly, 600 μL of whole blood was stimulated overnight *in vitro* at 37°C (5% CO_2) with spike peptide pools or SEB in a 48-well flat-bottom plate. Then, plasma was harvested and stored at –80°C until use. IFN-γ level was measured by an automatic ELISA (ELLA, ProteinSimple) with a detection limit of 0.17 pg/mL. IFN-γ values were subtracted from the negative control value.

Anti-SARS-CoV-2 Specific IgG Evaluation

The antinucleoprotein IgG (anti-N IgG) and the anti-Receptor Binding Domain (RBD) IgG (Architect® i2000sr Abbott Diagnostics, Chicago, IL, USA) were evaluated as previously reported (Agrati et al., 2021). Anti-N IgG are expressed as index, whereas anti-RBD IgG are expressed as binding antibody units (BAU)/mL. Anti-N IgG values $\geq$1.4 or anti-RBD IgG $\geq$7.1 were considered positive.

Statistical analysis

Data were analyzed using GraphPad software (GraphPad Prism 8 XML ProjecT). Median and interquartile range (IQR) were reported. The following nonparametric tests were applied: Kruskal-Wallis test for comparisons among groups and Mann-Whitney *U* test or Wilcoxon test (for unpaired or paired data, respectively) for pairwise comparisons with Bonferroni correction. Categorical variables were analyzed by the chi-square test. Spearman rank test

Table 1
Demographical and clinical characteristics of the 52 enrolled subjects

Characteristics		IMID	immunocompetent	P value
N (%)		43	9	
Age median (IQR)		60 (55–66)	28 (25–53)	0.0006*
Female N (%)		37 (82.2)	5 (55.6)	0.08**
Origin N (%)	**West Europe**	39 (90.7)	9 (100.0)	0.91 **
	East Europe	2 (4.7)	0 (0)	
	Africa	1 (2.3)	0 (0)	
	Sud America	1 (2.3)	0 (0)	
Positive anti-RBD IgG		39 (90.7)	9 (100)	0.34**
Rheumatologic Treatment N (%)				
	TNF-α-inhibitors +/- DMARD/corticosteroids	6 (14.0)	-	
	IL-6-inhibitors+/- DMARD/corticosteroids	8 (18.6)	-	
	CTLA4-IgG +/-DMARD/ corticosteroids	8 (18.6)	-	
	JAK-inhibitors+/-DMARD/ corticosteroids	3 (6.9)	-	
	DMARD +/- corticosteroids	17 (39.5)	-	
	corticosteroids	1 (2.3)	-	
Disease activity median (IQR)	**DAS28-CRP**	3.1 (2.2–3.8)§	-	

Footnotes: DMARDs, Disease-Modifying Antirheumatic Drugs; DAS28, Disease Activity Score 28; N, Number; IQR, Interquartile range; *Mann-Whitney test; ** Chi-square test. § data available in 42/43 patients.

was used to evaluate correlations: r >0.7 indicated a high correlation, 0.7 < r > 0.5 indicated a moderate correlation, and r <0.5 a low correlation. Differences were considered significant if p-values were <0.05 or <0.008 after Bonferroni correction.

Results

Characteristics of the enrolled subjects

We enrolled 43 patients with IMID and nine immunocompetent subjects. The 97.7% (42/43 subjects) of patients with IMID had RA and one patient had pemphigus. All patients with IMID were under treatment for their disease. The treatments included methotrexate or other disease-modifying antirheumatic drugs (DMARDs), low dosage of corticosteroids (prednisone <7.5 mg/day or equivalent), biologic drugs, and/or combinations of these therapies. Patients with IMID were stratified according to the therapy regimen. In particular, the following groups were considered: CTLA4-IgG with or without DMARDs or corticosteroids (n = 8 patients); IL-6-inhibitors with or without DMARDs or corticosteroids (n = 8 patients); TNF-α-inhibitors with or without DMARDs or corticosteroids (n = 6 patients); DMARDs with or without corticosteroids (n = 17 patients); Janus Kinases (JAK)-inhibitors with or without DMARDs or corticosteroids (n = 3 patients), and corticosteroids only (n = 1 patient). The majority of patients with RA had a moderate disease activity with a median DAS28-CRP of 3.1 (IQR: 2.2–3.8). The majority of the subjects with IMID (40/43) interrupted methotrexate and/or JAK-inhibitors intake for one week after each vaccine dose; patients assuming CTLA4-IgG stopped the drug one week before and after the first dose only (Picchianti-Diamanti et al., 2021).

The group of immunocompetent subjects included five healthy donors, three subjects with tuberculosis infection, and one subject with pneumonia (not COVID-19 related).

The IMID group showed a significantly higher median age than the immunocompetent subjects (p = 0.0006). However, within the IMID group, the median age of patients taking different therapies was similar (p = 0.165) (Table 2).

The demographic and clinical information of the enrolled subjects are described in Table 1.

Vaccinated patients with IMID show an IFN-γ-specific response to spike from δ SARS-CoV-2 variant, similar to immunocompetent subjects

We evaluated the IFN-γ-specific response to spike from the ancestral strain and from the δ SARS-CoV-2 variant in patients with IMID and in immunocompetent subjects. IFN-γ response to the ancestral peptide pool was slightly lower than that observed in response to the δ peptide pool in both patients with IMID (ancestral: median 2.03 pg/mL, IQR: 0.11–18.8 pg/mL; δ: median 2.27 pg/mL; IQR: 0.04–12.4) and immunocompetent subjects (ancestral: median 3.89 pg/mL, IQR: 1–79 pg/mL; δ: median 4.56 pg/mL; IQR: 0.16–95.2) (Figure 1A; Supplementary Figure 1A), reaching statistical significance in the IMID group (p = 0.0127). More importantly, no significant differences were found in the IFN-γ levels between patients with IMID and immunocompetent subjects in response to the ancestral (p = 0.36) or to δ peptide pool (p=0.51) (Supplementary Figure 1A).

IFN-γ-specific response to spike from the δ SARS-CoV-2 variant in patients with IMID is associated with the drug regimen

We stratified patients with IMID into four groups according to the drug regimen. We identified six different groups as previously reported; however, the JAK inhibitors and the corticosteroids groups were excluded from this analysis owing to the low number of the subjects included in these groups.

Although not significant, the IFN-γ-specific responses to the ancestral or to the δ pools were reduced in subjects under CTLA4-IgG or TNF-α-inhibitors compared with subjects who were treated with IL-6-inhibitors or DMARDs (Figure 1B and Supplementary Figure 1B). In particular, the IFN-γ response to the δ pool in patients under IL-6-inhibitors or DMARDs was higher than that observed in subjects taking CTLA4-IgG, although the differences were not significant after applying statistical corrections (p = 0.0468 and p = 0.022, respectively) (Supplementary Figure 1B).

Humoral response correlates with IFN-γ-specific response to spike from ancestral and δ SARS-CoV-2

We evaluated the vaccine-induced humoral response by measuring the anti-N and anti-RBD IgG levels. All the enrolled subjects

Table 2
Age and time range from the first vaccine dose of patients with IMID taking different therapies

	TNF-α-inhibitors +/- DMARDs/corticosteroids	IL-6-inhibitors +/- DMARDs/corticosteroids	CTLA-4-inhibitors +/- DMARDs/corticosteroids	JAK-inhibitors +/-DMARDs/ corticosteroids	DMARDs +/- corticosteroids	corticosteroids	P value
Age years Median (IQR)	58 (50–73)	59 (43–65)	57 (53–61)	59 (53–72)	63 (59–67)	–	0.165*
Days from 1 dose Median (IQR)	178 (170–195)	180 (170–185)	180 (176–184)	189 (178–205)	181 (174–186)	–	0.635*

Footnotes: DMARDs, Disease-Modifying Antirheumatic Drugs; IQR, Interquartile range; *Kruskall-Wallis test.

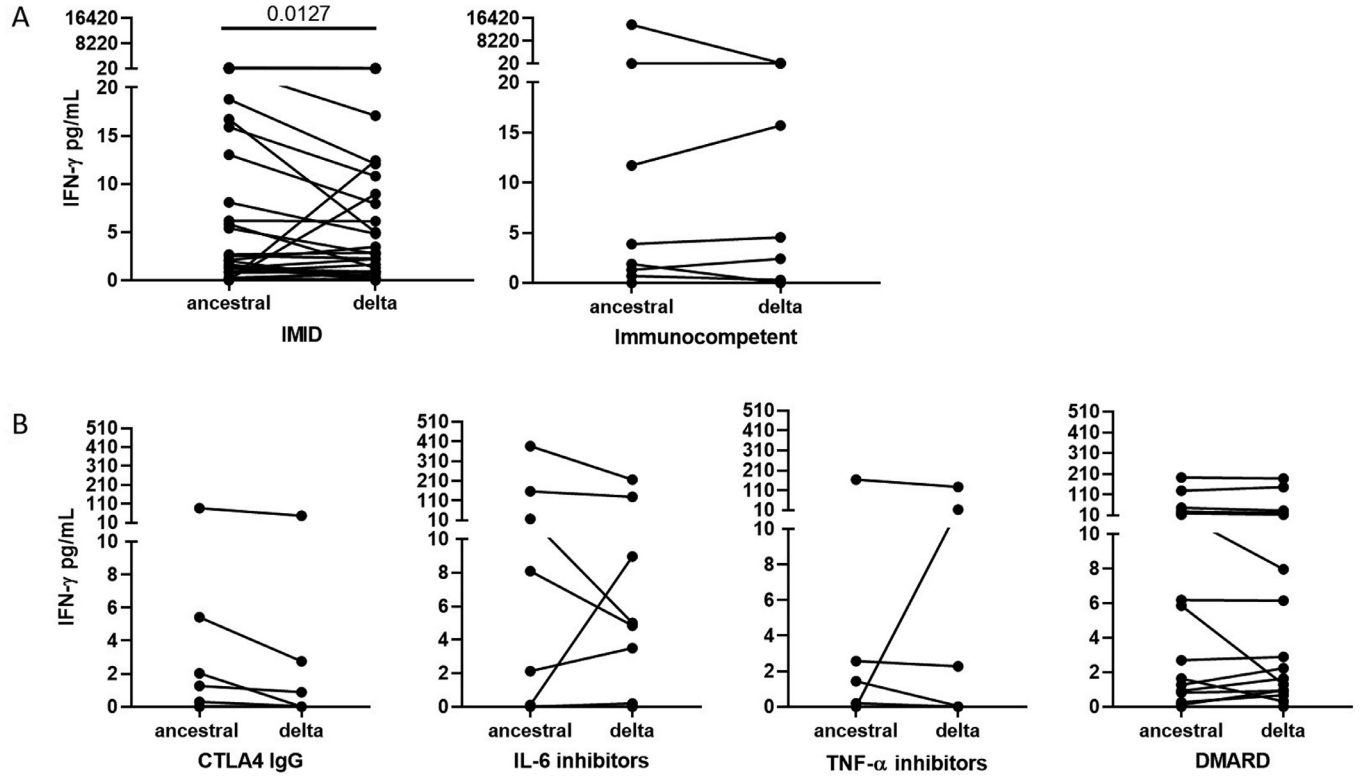

Figure 1. Vaccinated patients with IMID show a T cell-specific response to spike from δ SARS-CoV-2 variant. A. IFN-γ levels in response to spike from ancestral or δ SARS-CoV-2 in each patient with IMID (left panel) and immunocompetent subject (right panel). **B.** IFN-γ levels in response to spike from ancestral or δ SARS-CoV-2 in each patient with IMID treated with CTLA4-IgG (± DMARDs or corticosteroids), IL-6 inhibitors (± DMARDs or corticosteroids), TNF-α inhibitors (± DMARDs or corticosteroids) or DMARDs (± corticosteroids). IFN-γ levels were measured by ELLA. Wilcoxon test was used for pairwise comparisons. Differences were considered significant if $p<0.05$. Footnotes: IFN: Interferon; CTLA4: Cytotoxic T-Lymphocyte Antigen 4; TNF: Tumor Necrosis Factor; IL: Interleukin; DMARD: Disease-Modifying Anti-Rheumatic Drug; IMID: Immune-Mediated Inflammatory Diseases.

scored negative in the anti-N IgG evaluation (Supplementary Figure 2). Regarding the anti-RBD response, no significant differences were observed between IMID and immunocompetent IgG levels (Figure 2A); moreover, all the immunocompetent subjects scored positive (9/9, 100%), whereas within the IMID group, 39/43 (90.7%) subjects had detectable anti-RBD IgG and four subjects were non-responders (Table 1). Stratifying patients with IMID on the basis of therapy, no significant differences were observed among the groups analyzed (Figure 2B); however, 2/4 (50%) of nonresponder subjects fell in the CTLA4-IgG group (Figure 2B).

A low significant correlation was found between the anti-RBD IgG and the IFN-γ levels in response to both the ancestral and the δ spike (ancestral: $r_s = 0.38$, $p = 0.006$; δ: $r_s = 0.36$, $p = 0.009$) (Supplementary Figure 3).

Discussion

The impact of VOCs on the vaccine-induced immune response is of utmost importance, especially in vulnerable populations, such as patients with IMIDs. We showed that, after vaccination, patients with IMID have a similar cellular immune response to the ancestral or δ spike compared with immunocompetent subjects. However, stratifying patients on the basis of the therapy regimen, we observed a trend of decreasing T cell-specific response in patients taking CTLA4-IgG or TNF-α inhibitors. These results, if confirmed in further studies, may be helpful in guiding vaccine strategies and immunosuppressive treatment schedules during vaccination.

Regarding the T cell-specific response, the observed decrease is likely due to the well-known impact of CTLA4-IgG on the down-regulation of the antigen presentation thus preventing T cell activation (Bonelli and Scheinecker, 2018). In contrast, TNF-α is a key factor in all acute inflammatory reactions; therefore, its inhibition may have broader effects on T cell responses.

Regarding the antibody response, no significant differences were observed for the anti-RBD IgG response, both quantitatively and qualitatively, between patients with IMID and immunocompetent subjects. We only found a reduced number of responders in patients under CTLA4-IgG, although, it is known that immunosuppressive therapies may have an impact on the antibody response to anti-SARS-CoV-2 vaccines, as recently shown (Picchianti-Diamanti et al., 2021; Connolly et al., 2021; Deepak et al., 2021; Haberman et al., 2021).

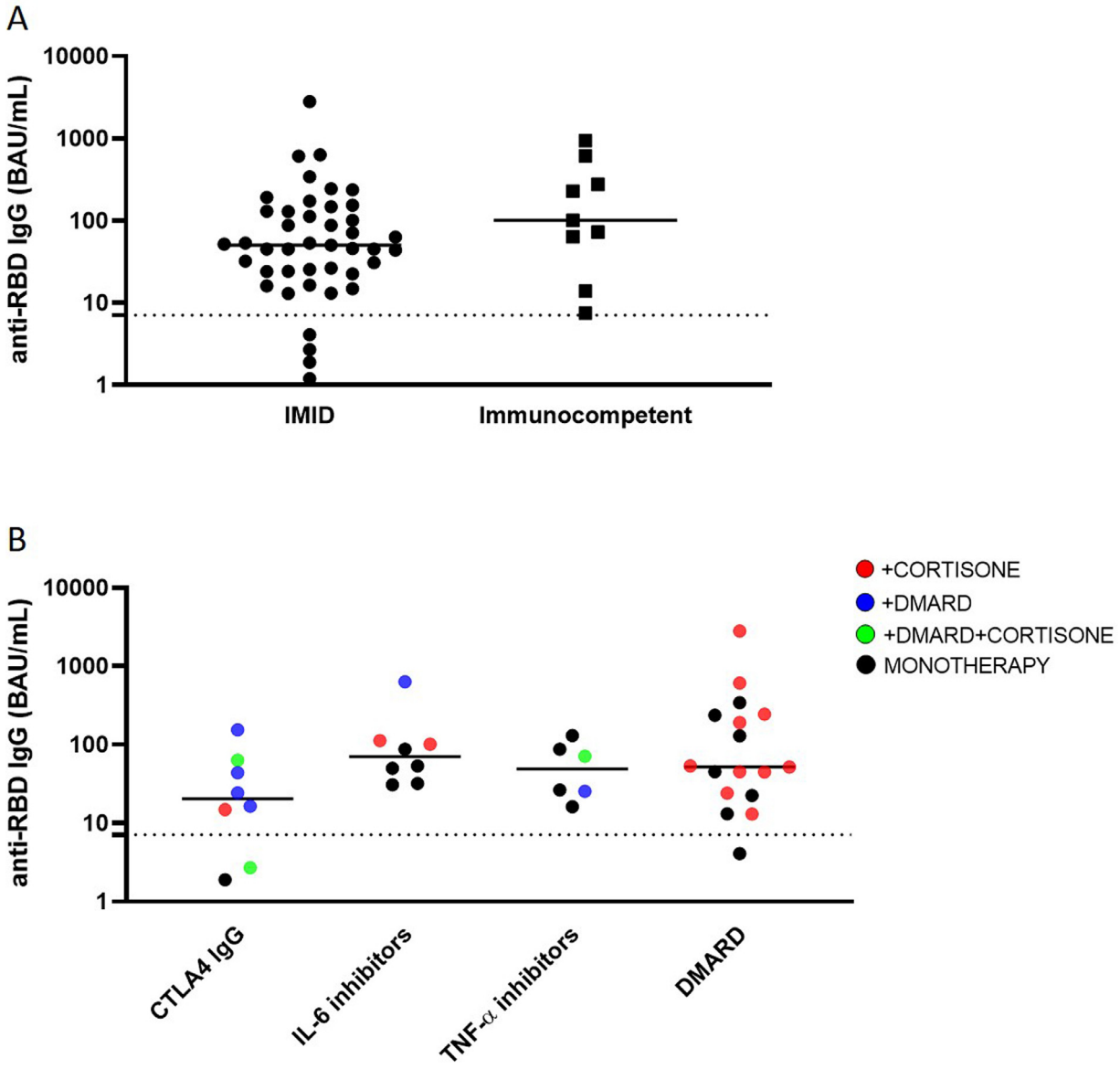

Figure 2. Vaccinated patients with IMID show a humoral response similar to immunocompetent subjects. A. IMID patients and immunocompetent subjects have similar anti-RBD IgG level. **B** Patients with IMID stratified based on the ongoing immunosuppressive therapy do not have significant different anti-RBD responses. Horizontal lines represent medians. Dotted lines represent ELISA IgG cut-off; anti-RBD IgG levels were measured by ELISA. Mann-Whitney test was used for pairwise comparisons. Differences were considered significant if $p<0.05$ (A) or $p<0.008$ (B). Footnotes: RBD: Receptor Binding Domain; BAU: Binding Antibody Units; CTLA4: Cytotoxic T-Lymphocyte Antigen 4; TNF: Tumor Necrosis Factor; IL: Interleukin; DMARD: Disease-Modifying Antirheumatic Drug; IMID: Immune-Mediated Inflammatory Diseases.

All these findings are relevant in light of new VOC identification and of co-circulation of different VOCs. In this regard, recently, the T cell response to spike of the omicron variant has been found in both mRNA-vaccinated subjects at 6 months from the second dose and in convalescent subjects with COVID-19 who were infected with the ancestral strain, demonstrating that spike-specific CD4+ and CD8+ T cell responses are not weakened by the omicron variant (Gao et al., 2022). Further studies on vaccinated patients with IMID are warranted to confirm these data.

Limitations of the study are related to the low number of subjects evaluated. However, the patients with IMID described here represent the real-world clinical scenario of the patients with RA under different immunosuppressive therapies, and they are homogeneous in terms of age and disease activity. Altogether, these parameters are the premise to generate results that can lead to reliable considerations. Moreover, the study performed is complete in terms of immune responses evaluated, as both T and B cell components were studied.

In conclusion, we demonstrated that cellular responses to δ SARS-CoV-2 variant remain largely intact in IMID. However, the magnitude of these responses may be dependent on the type of immunosuppressive regimen. These findings are important to increase our knowledge on the vaccines against COVID-19 and to make strategies to halt the COVID-19 pandemic.

Declaration of Competing Interest

AS is a consultant for Gritstone Bio, Flow Pharma, Arcturus Therapeutics, ImmunoScape, CellCarta, Avalia, Moderna, Fortress and Repertoire. LJI has filed for patent protection for various aspects of T cell epitope and vaccine design work.

None for the other authors.

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Ethical approval statement

The ethics committees of Sant'Andrea University Hospital (Approval number 318/2021), San Camillo Hospital (Approval number 1532/2021), and National Institute of Infectious Diseases (INMI) Lazzaro Spallanzani-IRCCS (Approval numbers 59/2020, 72/2015 and 297/2021) approved the study.

Author contributions

LP analyzed and interpreted data and wrote the manuscript. APD enrolled patients, collected clinical data, and participated in the interpretation of the data. VV processed blood samples and performed the IFN-γ ELISA. GDS, BL, GC, GG, MF, and EN enrolled patients and controls and collected clinical info. CC and SM performed serology. AG and AS provided peptide reagents and participated in the interpretation of data. AA and FV participated in the interpretation of data. DG designed and wrote the study, coordinated and supervised the project, contributed to the interpretation of the results, and wrote the manuscript with LP. All authors approved the final version of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.04.027.

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