Evaluation of antibody response to BNT162b2 mRNA COVID-19 vaccine in patients affected by immune-mediated inflammatory diseases up to 5 months after vaccination

Davide Firinu (davide.firinu@unica.it)
University of Cagliari https://orcid.org/0000-0002-5768-391X

Andrea Perra
University of Cagliari: Universita degli Studi Di Cagliari

Marcello Campagna
University of Cagliari: Universita degli Studi Di Cagliari

Roberto Littera
Azienda per la Tutela della Salute Sardegna

Giuseppe Fenu
Azienda Ospedaliera Brotzu

Federico Meloni
University of Cagliari: Universita degli Studi Di Cagliari

Selene Cipri
ATS Sardegna: Azienda per la Tutela della Salute Sardegna

Francesca Sedda
University of Cagliari: Universita degli Studi Di Cagliari

Maria Conti
University of Cagliari: Universita degli Studi Di Cagliari

Michela Miglianti
University of Cagliari: Universita degli Studi Di Cagliari

Giulia Costanzo
University of Cagliari: Universita degli Studi Di Cagliari

Marta Secci
University of Cagliari: Universita degli Studi Di Cagliari

Gianmario Usai
University of Cagliari: Universita degli Studi Di Cagliari

Mauro Giovanni Carta
University of Cagliari: Universita degli Studi Di Cagliari

Riccardo Cappai
Azienda ospedaliero universitaria di Cagliari

Germano Orrù
University of Cagliari: Universita degli Studi Di Cagliari
Stefano Del Giacco
University of Cagliari: Universita degli Studi Di Cagliari
Ferdinando Coghe
Azienda ospedaliero universitaria di Cagliari
Luchino Chessa
University of Cagliari: Universita degli Studi Di Cagliari

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Abstract

SARS-CoV-2 vaccination with mRNA product BNT162b2 elicited high immunogenicity in healthy subjects in trials. This study aims to better understand the factors that influence the humoral immune response to vaccination against SARS-CoV-2 in patients with immune-mediated inflammatory diseases (IMIDs). We enrolled patients and healthy healthcare workers control group (HCW) that underwent mRNA BNT162b2 vaccination and measured the serum IgG anti-S-RBD response at booster dose (T1), one month after booster dose (T2) and up to 5 months (T3). Demographic, disease-specific and vaccination data were recorded. Vaccination response of 551 participants naïve to SARS-CoV-2 infection were included in HCW and 102 in the IMID group, analyzing separately those on anti-CD20. At T2 all naïve HCW developed anti-S-RBD-IgG, while 94% of IMID responded ($p < 0.001$). IMID patients had a significantly different level of IgG than HCW at both T1 ($p = 0.031$), T2 ($p < 0.001$), while there was no significant difference at T3. There were no statistically significant differences according to the IMID type or to ongoing treatment with immunosuppressants, corticosteroids or biological drugs other than anti-CD20. The proportion and magnitude of response was significantly lower in IMID treated with anti-CD20 drugs. There was a correlation with age at T1 and at T2 but not at T3, stronger in patients than in HCW. Immune response close after BNT162b2 vaccination is reduced in patients with IMID, but there is no difference at 5 months. The measured reduction is related to age and the disease itself rather than treatments, with the exception of anti-CD20 drugs

Introduction

The extent of the profound immunological and non-immunological responses linked to SARS-CoV-2 infection is currently being investigating worldwide, due to the huge death-toll of SARS-CoV-2 pandemic and the short-term consequences of COVID-19. The first SARS-CoV-2 vaccines are among the most remarkable science and medicine accomplishments in modern history and offer realistic hope for an end to the COVID-19 pandemic.

Epidemiological models to explore estimates for the magnitude and timing of future COVID-19 cases, given different assumptions regarding the protective efficacy and duration of the adaptive immune response to SARS-CoV-2, range widely from sustained epidemics to near elimination [1]. Even in the best-case scenario of an apparent elimination, a resurgence in contagion could be possible as late as 2024 [2]. Thus, to alleviate the direct consequences of the ongoing pandemic detailed and reliable data on the epidemiology, natural history and treatment possibilities of SARS-CoV-2 infection, as well as about vaccine response are needed. Vaccination represents the only reliable means to quickly mitigate the spread and impact of COVID-19 in the forthcoming period. Assessment and post-vaccine monitoring of anti-SARS-CoV-2 antibody specifically targeting and thereby inactivating the spike protein and/or its receptor binding domain (RBD) may inform about the humoral response and its duration [3].

The Pfizer-BioNTech COVID-19 (BNT162b2) vaccine consisting of a lipid nanoparticle-formulated mRNA vaccine encoding the prefusion spike glycoprotein of SARS-CoV-2 received the conditional marketing

authorisation from the European Medicine Agency (EMA) on December 21th 2020 and was approved by the Food and Drug Administration (FDA) on January 14th 2021. The overall immune response to BNT162b2 has been reported [4], inducing SARS-CoV-2 neutralizing antibody response and RBD-specific CD8 + and CD4 + T-cells generation. Although the overall immune effects of the BNT162b2 vaccine has been reported, the profile of humoral immune profile remain to be further investigated in selected subgroups such as immune-mediated inflammatory diseases (IMID) [5].

Since infections are a relevant cause of morbidity and mortality in patients with IMID [6, 7], [6, 7], it is relevant to address this question because the worldwide spread of the SARS-CoV-2 infection forces a rapid vaccination of patients suffering from these diseases.

Moreover, in these patients the infection risk may be even higher for both the altered regulation of the immune system itself and for the immunosuppressive effects of medications [8].

Indeed, vaccinations in this population are complicated by disease-modifying immunosuppressive agents or antirheumatic drugs (either conventional, targeted synthetic or biologicals), which modulate or suppress key targets of the immune system and potentially decrease the immunogenicity and efficacy of the vaccines [9].

However, there is scant available data on real-world cohorts of vaccinated subjects and very limited data about response to COVID-19 mRNA vaccines in patients affected by IMID. In a prospective observational study focused on COVID-19 infection and vaccination (CORIMUN study), we tested the antibody response to SARS-CoV-2 spike protein over 5 months after vaccination. This study aimed to describe the characteristics of humoral response induced by mRNA based vaccine BNT162b2 [10] in subjects affected by IMID and analyze the impact of treatments.

Methods

Patient selection

We enrolled consecutive subjects aged >18 years, having received COVID-19 vaccine Pfizer/BioNTech BNT162b2 (two doses 21-days apart of 30 µg mRNA vaccine Comirnaty by Pfizer Inc, NY, USA) and deliberately given their Informed Consent to participate in the study. Pregnancy, transplantation, known immunodeficiency or lymphoproliferative disorders were exclusion criteria. Among enrolled subjects, we defined two groups:

a) vaccinated subjects at our hospital with concurrent IMID, grouped as: 1) ankylosing spondylitis (AS), psoriasis, psoriatic arthritis (PsA); 2) rheumatoid arthritis (RA) 3) systemic lupus erythematosus; 4) miscellaneous systemic disorders 5) inflammatory bowel disease 6) multiple sclerosis;

b) a control group of well-characterized subjects enrolled among healthy healthcare workers (HCW) enrolled at our hospital, with any of the immune-mediated diseases listed above, no evidence of immunodeficiency or taking relevant medications.

Each group included both naïve and previously infected subjects. Naïve subjects had not previously been infected by SARS-CoV-2 (testing since April 2020 gave repeatedly negative rt-PCR test for SARS-CoV-2 and repeatedly undetectable IgG or IgM antibodies by serum assays capturing also the response to Nucleocapsid).

Sample Collection and Storing

10 mL of peripheral blood was obtained by venopuncture immediately before each vaccine dose and defined as T0, before first dose; T1, at second vaccine shot (+21 days from T0); T2 at day 51 (T1+28 days); T3 at day 151 after the first vaccine dose. The serum was separated by centrifugation (2,000 x g for 15 minutes) within 3 hours of collection and aliquots were stored at -80°C until use.

Serological studies

Prior to vaccination, subjects underwent to detection of both IgM and IgG antibodies against SARS-Cov-2 Spike protein and N-protein on Maglumi platform (Snibe, Shenzhen, China) (IgM cut-off is 1.0 AU/mL, while the IgG cut-off is 1.1 AU/mL) a chemiluminescent analytical system (CLIA) that detects nucleocapsid (N) IgG antibodies with high sensitivity and specificity. In order to ascertain prior infection with SARS-CoV-2, HCW were asked if they had a positive PCR test in the past and the names were cross-matched with the database of positive rt-PCR tests at the laboratory and hospital records.

The antibody response induced by vaccine to spike protein (primary endpoint) was detected with the anti-SARS-CoV-2 S-RBD IgG (Snibe Diagnostics, New Industries Biomedical Engineering Co., Ltd, Shenzhen, China) on a MAGLUMI analyser, to titrate levels of specific IgG at specific timepoints. Analytical and clinical features of the assay, including the correlation with neutralization by using plaque reduction neutralization test (PRNT) 50 titer has been previously investigated [11].

Statistical analysis

Patient characteristics were summarized using means, medians, standard deviations, ranges, and percentages as appropriate. Chi squared tests of independence and Fischer's exact tests were used for categorical data. Mann Whitney U and Kruskal Wallis tests were used for unpaired continuous data. All reported p-values represent 2-tailed tests, with $p \leq 0.05$ considered statistically significant. All variables were analysed using SPSS.

Ethical Aspects

Patients were recruited and enrolled in the study protocol at the University Hospital of Cagliari. Written informed consent was obtained from all patients and controls in accordance with the ethical standards (institutional and national) of the local human research committee. The study protocol, including informed consent procedures, conforms to the ethical guidelines of the Declaration of Helsinki and was approved by the responsible ethics committee (Ethics Committee of the Cagliari University Hospital

approval May 27th, 2020; protocol number GT/2020/10894 and extension approved Jan 27th, 2021). Records of written informed consent are kept on file and are included in the clinical record of each patient.

Results

Among subjects vaccinated and naïve to SARS-CoV-2 Infection, 551 participants were included in the control group (HCW), and 102 were in the IMID group. Vaccinated HCW with previous SARS-CoV-2 infection were 111, and 9 in the IMID group. Baseline characteristics of both groups are shown in Table 1. Both cohorts included only Caucasian participants, and patients continued their treatment before or after the two vaccine doses, without stopping or tapering their drug(s), only avoiding the administration of injective drugs on ± 3 days of the vaccine date.

Due to the well-known impairment of immunogenicity linked to anti-CD20 agents [12], patients taking this medication were analyzed separately.

There was no difference in age, gender, BMI and cigarette smoking comparing these groups (Kruskall-Wallis $\chi 2$, $p>0.05$).

Immunogenicity of BNT162b2 in SARS-CoV-2 naïve patients with IMID and controls

All subjects in the naive HCW group developed a positive antibody response (defined as >1 AU/ml or higher) at T1 (364/364) and T2 (551/551) as compared with 90% (3/30) at T1 and 94% (63/67) at T2 in the IMID group. A statistically significant different difference was found at T1 ($p=0.002$) and T2 ($p<0.001$; Fisher's exact test).

At T1, the median IgG anti-S-RBD levels in the IMID group were 14.08 AU/mL (IQR, 5.08-27.8), increasing to 146.39 AU/mL (IQR, 53.93-295) at T2 and then decreasing to 60.65 AU/mL (IQR, 21.1-96,55) at T3.

In HCW controls, at T1 the median IgG anti-S-RBD levels were 23.66 AU/mL (IQR, 9.76-47.9), increasing to 217 AU/mL (IQR, 134.8-389.9) at T2 and then decreasing to 46.76 AU/mL (IQR, 26.26-81.57) at T3.

The median IgG anti-S-RBD levels in the IMID group were significantly lower than control group test at T1 ($p=0.031$) and T2 ($p= 0,000233$), while there was no significant difference at T3 ($p=0.172$) (Figure 1).

IMID subgroups and antibody levels

There were no statistically significant differences between subgroups of IMID enrolled in the study for age, BMI and proportion of patients currently treated with immunosuppressive treatment (Kruskal-Wallis test).

The rate of seropositivity at T2 was similar among the subgroups of diseases included in the study and there were no statistically significant differences between subgroups of subjects at T1, T2, and T3 ($p>0.05$, Kruskal-Wallis test).

The median IgG anti-S-RBD levels and IQR at T1 and T2 for each IMID subgroup are presented in the supplementary materials, Table S1.

Correlation of treatments and antibody levels

Comparing the response to vaccination in patients treated with GC, GC and/or immunosuppressive drug we did not find a significant difference in IgG anti-S-RBD levels at T1, T2, T3 (p>0,05). Similarly we found no differences for those under anti-TNF-alpha drugs (median of those treated at T2 139.7 AU/mL; IQR, 61-279) for the subgroups of RA and PsA/Psoriasis, or for those treated with biologicals different from TNF-alpha inhibitors (ustekinumab, secukinumab, abatacept, tocilizumab, vedolizumab) (p>0,05), csDMARDs (supplementary materials, Table S2), or for other drugs (interferon, colchicine, Jak-inhibitors, belimumab, dimethyl fumarate); (for all at T1, T2 T3; comparison drug vs no drug).

Correlation with subjects' characteristics

Among the demographic characteristics, age could influence the response to vaccination in both patients and healthy controls. In fact, the Spearman test showed a correlation between age and antibody response at T1 and at T2. This correlation is stronger in patients than in healthy controls (T1: rho:- 0.24 in HCW vs -0.41 in patients). At T3, there was no correlation between age and antibody response (supplementary materials, Tables S4 and S5).

A multivariate analysis showed no relationship between serum anti-S-RBD at T3 and gender, age, IgG anti-S-RBD at T2, intake of immunosuppressants (including GC) and being affected by IMID, $F(5, 95) = 1,272$, $p < .282$, $R^2 = .063$.

Immunogenicity in the group of patients treated with anti-CD20 drugs

At T2, 2/7 (28.6%) subjects were non responders in the IMID subjects previously treated with B-cell depleting agents (rituximab or ocrelizumab) after 2 doses of BNT162b2. They were non-responders also at T1. The median time from last drug infusion until vaccination was 5.5 months (IQR 5.5-6). The median IgG anti-S-RBD levels in this group were significantly lower than other patients with IMID naive to anti-CD20 at both T1 (p=0.018) and T2 (p= 0.011) (supplementary materials, Table S3).

Immunogenicity of BNT162B2 in previous SARS-CoV-2 infection IMID and controls

In the HCW group 100% (111/111) developed a positive antibody response (defined as >1 AU/ml or higher) and increase in IgG titer at T1 as compared with 88.8% (8/9) of responders at both T1 and T2 in the IMID group.

At T1, the median IgG anti-S-RBD levels in the IMID group were 980.2 AU/mL (IQR, 632-1000), then 714.9 AU/mL (IQR, 58.31-292.35) at T2.

In controls, at T1 the median IgG anti-S-RBD levels were 778.2 AU/mL (IQR, 416-100), 670 AU/mL (IQR, 363.15-1000) at T2 and then decreasing to 162 AU/mL (IQR, 45.44-590) at T3.

The median IgG anti-S-RBD levels in the IMID group with previous SARS-CoV-2 were not significantly different than HCW group at T1 (p=0.323) and T2 (p= 0.976).

Tolerability of BNT162b2 in patients with IMID

In general, vaccination was well tolerated in all patients and controls. No relapse or overshooting inflammatory response to vaccination was observed in patients with IMID. We detected no relevant safety issues in the enrolled subject of both groups. Side effects were generally more frequent after the booster dose. Pain at the injection site was most frequently observed in both groups. Systemic side effects (injection site reaction, headache, chills, arthralgia) were less frequent in patients than in controls.

Discussion

The ongoing COVID-19 pandemic is being limited also by an unprecedented vaccine program with the innovative use of mRNA vaccines. Due to limitations in the mRNA vaccine trials and to prioritization given to IMID patients for vaccination data about response to COVID-19 mRNA vaccines are of utmost importance to provide data about immunogenicity in this population and to inform health policies. This study shows that BNT162b2, based on mRNA technology, is highly immunogenic in IMID patients as the vast majority (94%) are responders one month after the second dose; in the subgroup of patients under B-cell depleting agents, this proportion raised to about 30%. Among naïve subjects the IMID patients show a significant difference in the levels of anti-S-RBD IgG than HCW we adopted as controls (-33% at T2, after the full vaccination course), showing no difference at T3 at 5 months after vaccination.

Initial immunogenicity data available for at-risk subgroups showed a high proportion of non-responders and low antibody responses to the SARS-CoV-2 spike protein in patients who received solid-organ transplantation [13], patients treated for solid cancer [14], or in patients with ongoing hemodialysis [15]. In contrast, the available studies to date show that a full course of mRNA vaccine in patients with IMID elicit a response in 78-100% of subjects, showing reduced serum antibody IgG titers and serum neutralizing activity as compared to healthy controls [16-21]. Even with limitations due to different assays and thresholds used across the available studies, the vaccine elicited responses is largely indicative of a considerable immunogenicity. The results of the present study are in line with those findings, and highlight that IMID treatments including GC, DMARDs, biologicals different from B-cell depleting agents may not abrogate IgG anti-S-RBD response until 5 months.

Of note, a strong correlation exists between serum neutralizing activity using $PRNT_{50}$ and anti-S-RBD titer to SARS-COV-2 evaluated using the same assay used in our study [11]. The median anti-S-RBD found in this study in IMID, respectively 146.39 AU/mL and 60.65 AU/ml at T2 and T3, may correlate to a high neutralizing titer (>= 1:160 $PRNT_{50}$) for the majority of patients, and almost all those with >50 AU/ml may have neutralizing titers of 1:40 – 1:80 up to 5 months after vaccination. This is in line with predictive

models of protection from COVID-19 infection and severe disease based on different COVID-19 vaccine trials [22].

In IMID patients, with ongoing immunosuppressive regimens also based on drug combinations and no drug suspension before or during the vaccination schedule, we found no differences in rates of responders neither in anti-S-RBD titer and this may be useful to study the most appropriate vaccination strategies for this patients. Simple vaccine schedules may simplify adherence of patients. The magnitude of response impairment to mRNA COVID 19 vaccine in patients with ongoing B-cells depleting therapies suggest that precise strategies of vaccination should be implemented in the next future [12, 17, 23]. The initial finding that a third mRNA vaccine dose can rescue the immunogenicity by repeating a full vaccine course [24] or giving a third dose [25] might be explored in larger studies.

We also assessed humoral responses of nine IMID individuals receiving immunosuppression therapy who had previous confirmed natural SARS-CoV-2 infection. There was evidence of robust IgG anti-RBD response in all but one patient, and the humoral response exceeded that of our SARS-CoV-2-naive participants and was similar to that of HCW with previous infection. The non-responder subject underwent her last rituximab course and COVID-19 respectively 14 and 12 months before vaccination and peripheral B-cell depletion persisted at time of vaccination. Similar findings have been reported [19, 20].

The study limitations are the number of recruited subjects in some subgroups and the absence of formal studies with neutralization assays or cellular immunity, as well as the absence of adenoviral-vector based vaccinated subjects.

This data highlight the importance of vaccination in patients with IMID and the need of epidemiological and efficacy studies for special groups to understand whether there is a different immune response kinetics to mRNA vaccination, differentiate the risk for subgroups I order to tailor vaccination campaign and determine if further vaccine doses may be warranted.

Declarations

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Conflict of Interest: The authors have declared no conflict of interests.

Availability of data and material: Data and materials are available from corresponding authors on reasonable request.

Authors' Contributions:

Study conception and design: DF, AP, LC, MC; Cared for patients, extracted the clinical and lab data DF, SDG, MC, FM, FC, FS, MS, GU; Acquisition of data: MM, GC, RC; Analysis and interpretation of data: DF,

GF, MGC, LC; Drafting of manuscript: DF, RL, GO, AP, LC; Critical revision: SDG, RC, FC, RL, GF. All authors read and worked on the manuscript.

Ethics Approval: AOU IRB approval number GT/2020/10894 and its extension approved Jan 27th, 2021.

Consent to participate: Written consent to participate was obtained for enrolled subjects.

References

1. Saad-Roy CM, Wagner CE, Baker RE, et al. Immune life history, vaccination, and the dynamics of SARS-CoV-2 over the next 5 years. Science. 2020;370:811–8. doi:10.1126/science.abd7343.
2. Kissler SM, Tedijanto C, Goldstein E, Grad YH, Lipsitch M. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. Science. 2020;368:860–8. doi:10.1126/science.abb5793.
3. Bohn MK, Loh TP, Wang CB, et al. IFCC Interim Guidelines on Serological Testing of Antibodies against SARS-CoV-2. Clin Chem Lab Med. 2020;58:2001–8. doi:10.1515/cclm-2020-1413.
4. Sahin U, Muik A, Derhovanessian E, et al. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. Nature. 2020;586:594–9. doi:10.1038/s41586-020-2814-7.
5. Williams JP, Meyers JA. Immune-mediated inflammatory disorders (I.M.I.D.s): the economic and clinical costs. Am J Manag Care. 2002;8:664-81. quiz S82-5.
6. Furer V, Rondaan C, Heijstek MW, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2020;79:39–52;. doi:10.1136/annrheumdis-2019-215882.
7. Otero-Romero S, Ascherio A, Lebrun-Frenay C. Vaccinations in multiple sclerosis patients receiving disease-modifying drugs. Curr Opin Neurol. 2021. doi:10.1097/WCO.0000000000000929.
8. Gluck T, Kiefmann B, Grohmann M, Falk W, Straub RH, Scholmerich J. Immune status and risk for infection in patients receiving chronic immunosuppressive therapy. J Rheumatol. 2005;32:1473–80.
9. Curtis JR, Johnson SR, Anthony DD, et al. American College of Rheumatology Guidance for COVID-19 Vaccination in Patients With Rheumatic and Musculoskeletal Diseases: Version 2. Arthritis Rheumatol. 2021. doi:10.1002/art.41877.
10. Walsh EE, Frenck RW Jr, Falsey AR, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. N Engl J Med. 2020;383:2439–50. doi:10.1056/NEJMoa2027906.
11. Padoan A, Bonfante F, Cosma C, et al. Analytical and clinical performances of a SARS-CoV-2 S-RBD IgG assay: comparison with neutralization titers. Clin Chem Lab Med. 2021;59:1444–52. doi:10.1515/cclm-2021-0313.
12. Simon D, Tascilar K, Schmidt K, et al. Brief Report: Humoral and cellular immune responses to SARS-CoV-2 infection and vaccination in B cell depleted autoimmune patients. Arthritis Rheumatol. 2021. doi:10.1002/art.41914.

13. Rozen-Zvi B, Yahav D, Agur T, et al. Antibody response to SARS-CoV-2 mRNA vaccine among kidney transplant recipients: a prospective cohort study. Clin Microbiol Infect. 2021. doi:10.1016/j.cmi.2021.04.028.
14. Barriere J, Chamorey E, Adjtoutah Z, et al. Impaired immunogenicity of BNT162b2 anti-SARS-CoV-2 vaccine in patients treated for solid tumors. Ann Oncol. 2021. doi:10.1016/j.annonc.2021.04.019.
15. Grupper A, Sharon N, Finn T, et al. Humoral Response to the Pfizer BNT162b2 Vaccine in Patients Undergoing Maintenance Hemodialysis. Clin J Am Soc Nephrol. 2021. doi:10.2215/CJN.03500321.
16. Geisen UM, Berner DK, Tran F, et al. Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort. Ann Rheum Dis. 2021. doi:10.1136/annrheumdis-2021-220272.
17. Furer V, Eviatar T, Zisman D, et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. Ann Rheum Dis. 2021. doi:10.1136/annrheumdis-2021-220647.
18. Simon D, Tascilar K, Fagni F, et al. SARS-CoV-2 vaccination responses in untreated, conventionally treated and anticytokine-treated patients with immune-mediated inflammatory diseases. Ann Rheum Dis. 2021. doi:10.1136/annrheumdis-2021-220461.
19. Kennedy NA, Lin S, Goodhand JR, et al. Infliximab is associated with attenuated immunogenicity to BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines in patients with IBD. Gut. 2021. doi:10.1136/gutjnl-2021-324789.
20. Mahil SK, Bechman K, Raharja A, et al. The effect of methotrexate and targeted immunosuppression on humoral and cellular immune responses to the COVID-19 vaccine BNT162b2: a cohort study. Lancet Rheumatol. 2021. doi:10.1016/S2665-9913(21)00212-5.
21. Valor-Mendez L, Tascilar K, Simon D, et al. Correspondence on 'Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort'. Ann Rheum Dis. 2021. doi:10.1136/annrheumdis-2021-220898.
22. Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med. 2021. doi:10.1038/s41591-021-01377-8.
23. Achiron A, Mandel M, Dreyer-Alster S, et al. Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies. Ther Adv Neurol Disord. 2021;14:17562864211012835;. doi:10.1177/17562864211012835.
24. Albach FN, Burmester GR, Biesen R. Successful BNT162b2 booster vaccinations in a patient with rheumatoid arthritis and initially negative antibody response. Ann Rheum Dis. 2021. doi:10.1136/annrheumdis-2021-220834.
25. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients. N Engl J Med. 2021. doi:10.1056/NEJMc2108861.

Tables

Table 1. Characteristics of patients and controls

a Sjögren syndrome , Behçet's disease, IgA nephropathy, IgG4-related disease, Eosinophilic granulomatosis with polyangiitis, giant-cell arteritis, autoimmune hepatitis and UCTD. b csDMARDs: methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, mycophenolate, azathioprine, cyclosporin c interferon, colchicine, JAK-inhibitors, belimumab, dimethyl fumarate

Figures

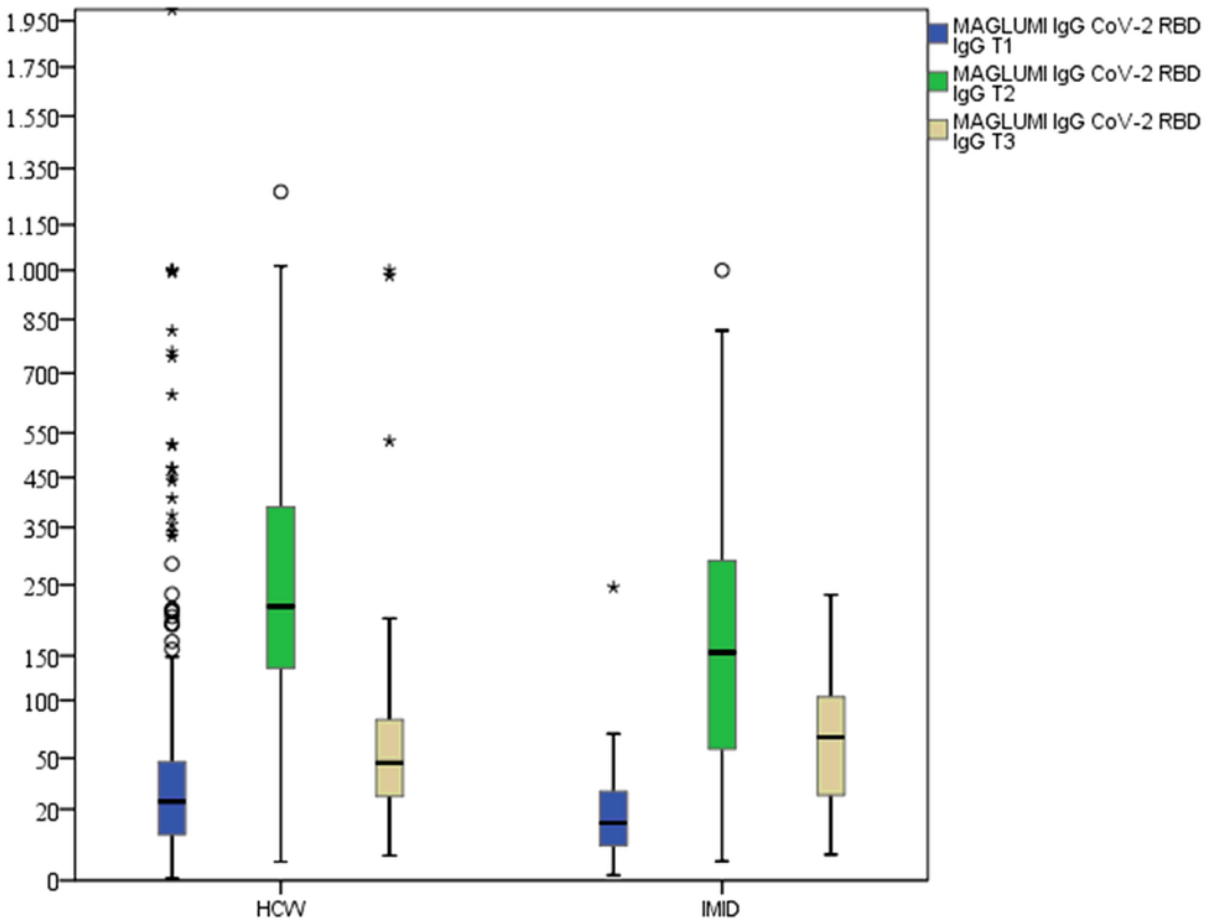

Figure 1

SARS-CoV-2 Anti-S-RBD IgG immune responses in naïve patients and control subjects. IgG titer Anti-S-RBD IgG (AU/L) elicited by BNT162b2 at T1 (booster dose), T2 (30 days after booster), and T3 (151 days

after booster) as determined by CLIA among healthy health-care workers (HCW) and IMID subjects naïve to SARS-CoV-2 infection.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial.docx

Subjects characteristics	HCW, SARS-CoV-2 naive (n = 551)	IMID, SARS-CoV-2 naive (n = 95)	IMID treated with anti-CD20 (n = 7)	HCW, previous SARS-CoV-2 (n = 111)	IMID previous SARS-CoV-2 (n =9)
Age (years), median	51 (39-58)	56 (42.5-66)	58 (50-69.25)	48 (35-55)	50 (30.5-61.5)
Males, %	31.8	27.5	14.3	38.7	33.3
BMI (IQR)	23.18 (20.79-25.95)	23.56 (21.4-26.6)	21.77 (19.9-23.7)	23.93 (21.66-26.32)	22.65 (20.47-25.53)
Current smoker, %	16.6	16.9	14.3	11.5	11
Diabetes, %	3.3	6.4	14.3	3.8	11.1
IMID type					
SLE	0	19 (23.5)	2 (28.6)	0	1 (11.1)
RA	0	19 (23.5)	1 (14.3)	0	2 (22.2)
PsA, Psoriasis, AS	0	20 (24.7%)		0	(11.1)
Miscellaneous systemic disorders [a]	0	16 (19.8)	2 (28.6)	0	(11.1)
IBD	0	4 (4.9)		0	2 (22.2)
Multiple sclerosis	0	3 (3.7)	2 (28.6)	0	2 (22.2)
Immunomodulatory treatment					
Glucocorticoids, n (%)	0	43 (53.1)	5 (71.4)	0	2 (22.2)
Prednisone eq/day, mg	0	5 (5-8.75)	5 (5-10)	0	3.75 (2.5-3.75)
Glucocorticoid and/or any immunosuppressive drug, n (%)	0 (0)	70 (74.5)	6 (87.5)	0 (0)	5 (55.6)
Anti-TNF-α n (%)	0 (0)	11 (13.6)	0 (0)	0 (0)	1 (11.1)
Non-anti-TNF biologicals (ustekinumab, secukinumab,	0 (0)	10 (12.3)	0 (0)	0 (0)	0 (0)

abatacept, tocilizumab, vedolizumab) n (%)					
csDMARDs[b] n (%)	0 (0)	41 (51.2)	3 (42.9)	0 (0)	1 (11.1)
Other drugs[c] n (%)	0 (0)	5 (6.3)	0 (0)	0 (0)	1 (11.1)