COVID-19 vaccine immunogenicity in 16 patients with autoimmune systemic diseases. Lack of both humoral and cellular response to booster dose and ongoing disease modifying therapies

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ABSTRACT

Background: Patients with autoimmune systemic diseases (ASDs) represent a frail population during the ongoing COVID-19 pandemic. The vaccination is the major preventive measure; however, a significant number of ASD patients show an impaired production of anti-COVID-19 neutralizing antibodies (NAb), possibly counterbalanced by adequate T-cell response. The present study aimed at evaluating both humoral and cellular response to COVID-19 vaccine booster dose in this particular setting.

Patients and methods: Serum NAb titer and T-cell response (measuring interferon gamma –IFN–γ- release) were evaluated 3 weeks after the COVID-19 vaccine booster dose, in 17 patients (12 F, mean age 68.8 $\pm$ 15.3 SD yrs) with different ASDs, compared to 17 healthy controls (HCs).

Results: The analysis excluded one patient reporting symptoms of COVID-19 only after the immunogenicity tests had been performed.

The NAb levels were significantly lower in ASD compared to HCs (p < 0.0001); moreover, patients showed a higher percentage of negative/sub-optimal humoral response (31% vs 0% of HCs; p = 0.0184).

The study of cellular response showed lower levels of IFN-γ for both Ag1 (p = 0.0032) and Ag2 (p = 0.0136) in ASD patients compared to HCs, as well lower rate of adequate T-cell response compared to HCs (50% vs 94%; p = 0.0066).

Disease modifying therapies (DMT) were administered in all patients with deficient NAb production (5/5, 100%), but in only 3/11 (27%) of responders (p = 0.025).

Worthy to note, 3/16 (19%) ASD patients developed neither humoral nor cellular responses, all treated with DMT.

Conclusions: The impaired immunogenicity to COVID-19 vaccine booster and even more the concomitant lack of both humoral and cellular response might represent a high risk for severe COVID-19, particularly in ASD patients undergoing DMT.

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These frail subjects should be tightly monitored for their immune protection and prioritized for the fourth dose of COVID-19 vaccine. Moreover, in the occurrence of SARS-CoV2 infection, treatments with specific monoclonal antibodies and/or antivirals may be highly recommendable.

1. Introduction

After more than two years from the identification of the first cases in China [1], the COronaVIrus Disease 19 (COVID-19), caused by SARS-CoV-2 infection, continues to claim victims worldwide. Although the introduction of mass vaccination programs in many countries contributed to greatly *reduce spreading, disease severity, and* deaths, segments of frail population are still vulnerable and at high risk. Patients with autoimmune systemic diseases (ASDs) are considered frail subjects, thus studies regarding vaccination immunogenicity in this setting may suggest possible key tools and strategies against the worse COVID-19 consequences. In this context, different analyses have been performed to ascertain either the COVID-19 overall impact on ASDs [2–4] and the vaccination immunogenicity and safety [5–10]. The reported prevalence of COVID-19 in ASD patients compared to the general population is variable, often increased [3,11]. Conversely, the vaccine-induced humoral response, after a complete vaccination cycle, is significantly attenuated in ASDs compared to healthy controls [5,12]. Even if the booster dose increases the percentage of ASD patients developing a humoral response, a subgroup of them still does not show a protective antibody titer [5,13,14].

To achieve the desired long-lasting immunity, a vaccine should not only evoke a robust humoral response but also drive a strong $CD4^+$ and $CD8^+$ T cell response.

Assessing the ability of ASD patients to build a specific T cell response to COVID-19 vaccination has a great interest to understand if subjects with an impaired humoral response have a partial immune protection.

Nevertheless, there is still controversy regarding the T cell response in the ASD setting due to the variability of the diagnoses and to the different effect of ongoing disease modifying therapies (DMT) on the cellular immunity [15–24].

The majority of the available studies assessed the T cell response among ASD patients after the first 1–2 doses of COVID-19 vaccination [15–17,19,22–24] but results concerning both humoral and cellular post booster immunogenicity are still very limited [14,18,25,26].

Therefore, we aimed at evaluating the humoral and cellular response to the booster dose of COVID-19 vaccine in a group of ASD patients compared to healthy controls (HCs), to ascertain the presence of patients particularly vulnerable to serious COVID-19 even after the third immunization shot.

2. Patients and methods

Immunogenicity of COVID-19 vaccine was evaluated 3 weeks after the booster dose of COVID-19 vaccine, in 17 ASD subjects (12 (71%) females, mean age 68.8 ± 15.3 years) and in 17 age and sex matched HCs without a past exposure to immunosuppressive therapies.

One patient, a 60 years old female affected by SLE (no. 17, Table 1) reported to have had symptoms of COVID-19 prior to the booster dose only after the immunogenicity tests had been performed; since the COVID-19 could have altered the vaccine-induced immune response, the patient was excluded from the following analysis.

In fact, she had a very high NAb titer (11,360 vs 1909 ± 690.2, the mean value of analyzed ASD subjects) together with a powerful T cell response (Ag1 value = 8.5048 IU/mL and Ag2 value = 205.8531 IU/mL vs Ag1 mean value = 0.4845 ± 0.2655 and Ag2 mean value = 1.333 ± 0.6617 for other ASD patients).

The study was performed in accordance with the principles of the Declaration of Helsinki, and it was approved by the Ethic Committee "Area Vasta Centro", Florence, Italy (study code #17886_bio); all patients gave their informed consent before participation.

Regarding the ASD diagnosis, 7/17 (41%) patients had Cryoglobulinemic Vasculitis (CV), 6/17 (35%) Systemic Sclerosis (SSc), 3/17 (18%) Rheumatoid Arthritis (RA), and 1/17 (6%) Systemic Lupus Erythematosus (SLE). We classified the corticosteroid dose as low when ≤ 10 mg/day and high when ≥ 25 mg/day. The main demographic, clinical and therapeutic features of the 17 ASD subjects are detailed in

Table 1

Humoral and cellular response to COVID-19 vaccine booster in autoimmune systemic diseases.

Patient	Sex	Age	Diagnosis	DMT (≤ 6 months)	Response to COVID-19 vaccine		
					Humoral	Cellular	
						Ag1	Ag2
1	F	83	CV	none	POS	**NEG**	**NEG**
2	M	55	CV	RTX + Bendamustine	**NEG**	**NEG**	**NEG**
3	F	83	CV	none	POS	POS	POS
4	F	70	CV	none	POS	POS	POS
5	F	87	CV	none	POS	POS	POS
6	M	79	CV	none	POS	**NEG**	**NEG**
7	M	75	CV	High-CSs (RTX^)	**SUB**	**NEG**	**NEG**
8	F	57	SSc	Low-CSs + MMF	POS	**NEG**	**NEG**
9	M	36	SSc	Low-CSs + MMF	**SUB**	POS	POS
10	F	86	SSc	Low-CSs	POS	**NEG**	**NEG**
11	F	70	SSc	HCQ	POS	POS	POS
12	F	62	SSc	AZA	POS	POS	POS
13	F	64	SSc	Low-CSs + MMF	**SUB**	**NEG**	**NEG**
14	F	54	RA	Low-CSs + LFM + JAKi	**NEG**	POS	POS
15	F	52	RA	HCQ	POS	**NEG**	**NEG**
16	M	88	RA	Low-CSs + AZA	POS	POS	POS
17	F	60	SLE + COVID19*	Low-CSs + AZA	POS	POS	POS

Table 1 legend: F: Female; M: Male; Ag1: Antigen 1; Ag2: Antigen 2; CV: cryoglobulinemic vasculitis; DMT: disease modifying therapies; SSc: systemic sclerosis; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; RTX: Rituximab; CSs: Corticosteroids; MMF: Mycophenolate mofetil; HCQ: Hydroxychloroquine; AZA: Azathioprine; LFM: Leflunomide; JAKi: JAK-inhibitors. Low-CSs dose: ≤ 10 mg/; High-CSs dose: ≥ 25 mg/day. *The patient had symptoms of COVID-19 prior to the booster dose, and she reported it only after the immunogenicity tests had been performed; ^ RTX was administered 12 months before the booster shot.
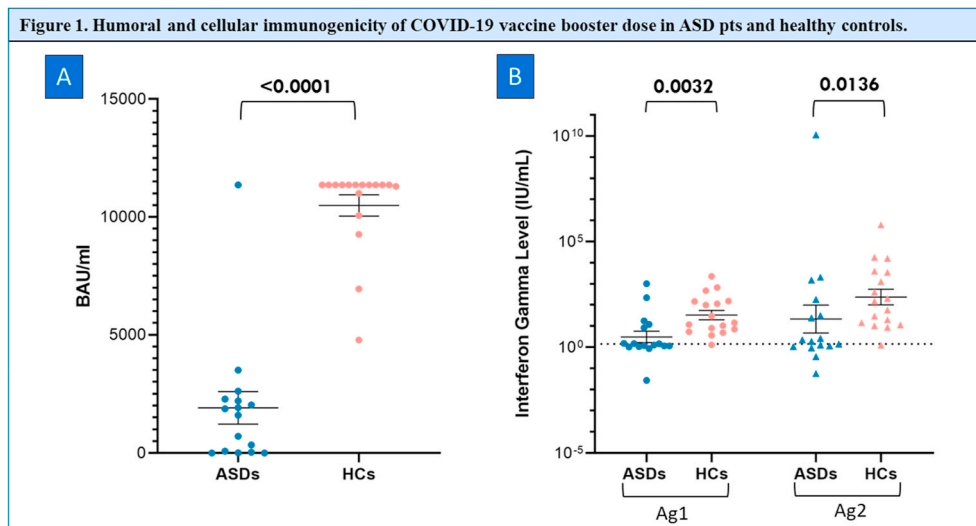
Fig. 1. Humoral and cellular immunogenicity of COVID-19 vaccine booster dose in ASD pts and healthy controls.

Table 1.

COVID-19 vaccine was administered to both patients and controls by intramuscular injection in the deltoid muscle according to the manufacturer indications and the Italian national guidelines; all the subjects received BNT162b2 vaccine.

Peripheral blood was collected 3 weeks after the booster dose and was used to assess both humoral and cellular immune response.

The humoral response to COVID-19 vaccines was evaluated by measuring the titer of NAb against SARS-CoV-2 trimeric spike S1/S2 glycoproteins on serum samples, using SARS-CoV-2 IgG II Quant antibody test kit (Abbott Laboratories, Chicago, IL). As recommended by the World Health Organization (WHO), antibody titers are expressed as Binding Antibody Units (BAU)/ml, with a cut-off for positive testing of 7 BAU/ml. A NAb serum titer >7 BAU/ml and ≤10x upper limit of normal (70 BAU/ml) was classified as suboptimal response.

T cell response was assessed by measuring interferon-gamma (IFN-γ) production by peripheral blood lymphocytes upon SARS-CoV-2 glycoprotein stimulation using the QuantiFERON® SARSCoV-2 Starter Set (Qiagen), an interferon gamma release assay (IGRA). Specimens were processed as per the manufacturer's guidelines.

Briefly, the assay consists of two Antigen (Ag) tubes, SARS-CoV-2 Ag1 and SARS-CoV-2 Ag2, that use a combination of antigens specific to SARS-CoV-2 to stimulate T cells in heparinized whole blood. QuantiFERON Nil and Mitogen blood collection tubes were used as negative and positive controls, respectively.

Plasma collected after the stimulation was used for IFN-γ detection through a specific QuantiFERON ELISA (Qiagen).

Elevated response was defined as a value of at least 0.15 IU/mL greater than the background IU/mL value from the QuantiFERON SARS-CoV-2 Nil tube [27].

No patients had moderate-severe lymphopenia and/or an alteration of inflammation indexes that are known to affect the sensitivity of QuantiFERON.

2.1. Statistical analysis

Data are expressed as mean ± standard error of mean (SEM), or number (percentage) as appropriate. The Student's T test (Mann-Whitney for paired samples or Wilcoxon test for unpaired samples) was used for comparing means of continuous variables between two groups. Fisher's exact test was used to compare categorical variables between two groups. All tests were two tailed and a p value < 0.05 was considered significant. Analyses were performed using the GraphPad Software v 9.

3. Results

Both humoral and cellular response to COVID-19 booster dose were analyzed in 16 ASD patients and 17 HCs.

The humoral response was significantly lower in ASDs compared to HCs (1909 ± 690.2 vs 10,488 ± 454.3 BAU/mL, p < 0.0001) (Fig. 1, panel A); moreover, 5/16 (31%) ASD patients showed negative/suboptimal response while all the HCs revealed a humoral response (p = 0.0184).

The cellular response, assessed by QuantiFERON IGRA, was analyzed separately for Ag1 and Ag2 as detailed in Fig. 1, panel B.

Regarding Ag1 stimulation, mean INF-γ level was 0.4845 ± 0.2655 IU/mL in ASD subjects and 1.516 ± 0.2218 IU/mL in HCs (p = 0.0032) (Fig. 1, panel B). Similarly, the mean INF-γ level, after Ag2 stimulation, was significantly lower in ASDs compared to HCs (1.333 ± 0.6617 vs 2.371 ± 0.3677 IU/mL, p = 0.0136) (Fig. 1, panel B).

Moreover, ASD patients developed a lower rate of cellular response compared to HCs (8/16, 50% vs 16/17, 94%; p = 0.0066; Table 1).

Of note, 3/16 (19%) ASD patients develop neither humoral nor cellular responses (pts no 2, 7, and 13; Table 1).

Focusing on the therapies administered within the 6 months before the booster dose of vaccine (Table 1), 8/16 (50%) analyzed patients received DMT, while the remaining underwent low doses of corticosteroids (CSs) or hydroxychloroquine (HCQ) (3/16, 19%) or were untreated (5/16, 31%).

A negative/suboptimal humoral response was associated to DMT administration. In fact, 5/5 (100%) patients with deficient NAb production were treated with DMT, while only 3/11 (27%) were on-therapy among the responders (p = 0.025).

Regarding the cellular response, DMTs were administered in half of the patients in both groups of responders and no responders (p = n.s.) (Table 1).

Considering the two types of immune response, we found that all the 3 (100%) patients negative for both humoral and cellular response were on DMT, while 3/7 (43%) with a discordant response and 2/6 (33%) subjects with both positive responses received the therapy.

4. Discussion

The present study analyzing the boostering effect of the COVID-19 vaccine third dose in well-defined ASDs revealed a clear-cut reduction of both humoral and cellular response in a significant percentage of patients compared to HCs. The defective immunogenicity was associated with the ongoing DMT frequently employed in these frail patients'

Table 2

Humoral and cellular immunogenicity of different doses of COVID-19 vaccines in autoimmune diseases (review of the literature).

First author	Year, ref	Country	Patients no	Diagnosis	Therapies	Immunogenicity	
						Humoral response	Cellular response[#]
After the first doses of COVID-19 vaccine							
Saleem B.	2022 [20],	UK	83	RA	RTX, anti TNF, anti-IL6, MTX, ABA, Jak inhibitors	45%	53%
De Santis M.	2022 [19],	Italy	150	RA; SSc; SLE; SpA; DM	MMF	RA 100% SSc 27% SLE 100% SpA 100% DM 100%	Impaired cellular response in patients with an impaired humoral response.
Bitoun S.	2021 [15],	France	59	RA; SLE; SSc; Vasculites	RTX (24 pts) DMARDs, bDMARDs, MMF, bendamustine, CSs (35 pts)	RTX: 29.2% Other immune-suppressors: 80%	CD4 and CD8 cellular responses similar between the two groups and to HCs
Farroni C.	2022 [22],	Italy	35	RA	TNF -α inhibitors, DMARD, IL-6 inhibitors, CSs, ABA	91.4%	65.7%
Prendecki M.	2021 [16],	UK	42	SLE; AAV	nd	SLE 7/8 (87.5%) AAV 17/34 (50%)	SLE 2/2 (100%) AAV 15/19 (78.9%)
Szebeni G.J.	2022 [23],	Hungary	89	RA; SLE; SSc; AAV; SSj LVV; Spa; PsA	CSs, bDMARDs, cDMARDs, Belimumab	Vaccine-based stratification: 55% for BBIBP-CorV vaccine, 53% for Gam-COVIDVac and AZD1222 vaccine, 81% for BNT162b2 and mRNA-1273 vaccine	Vaccine-based stratification: 20% for BBIBP-CorV vaccine, 32% for Gam-COVID-Vac and AZD1222 vaccine 32% for BNT162b2 and mRNA-1273 vaccine
Oyaert M. et al.	2022 [17],	Belgium	21	RA, SSc, SLE, PsA, AAV, polymyositis, IgA granulomatosis	RTX, DMARD, CSs, MTX, belimumab, adalimumab,	11/21 (52.4%)	9/21 (42.9%)
Sieiro Santos C. et al.	2022 [24],	Spain	I cohort (ongoing immune-suppressors):100 II cohort (no immune-suppressors): 47	RA, SLE, SS, pSS	I cohort: MTX, AZA, MMF, LFM and/or bDMARDs (Belimumab, ABA, RTX) II cohort: Non-steroidal anti-inflammatory drugs and/or infliximab, tocilizumab, anakinra	I cohort Seroconversion: 55% II cohort Seroconversion: 80%	Th1 response 52% CD8 response 77% Th1 response 75% CD8 response 53%
Marty P·K.	2022 [21],	USA	17	AAV	11 B-cell depleted 8 B-cell recovered	0% 100%	90.9% 88.9%
After the booster dose of COVID-19 vaccine							
Corradini P. et al.	2022 [26],	Italy	37	AAV, SSc, mixed connective tissue disease, SLE, pSS, DM, polymyositis, and RA	MTX, MMF, AZA, cyclosporine, RTX, CSs	90%	89.2%
Firinu D. et al.	2022 [18],	Italy	31	RA, SLE, Connective Tissue Disease; MS	RTX; OCRE; ADA; ETN; MTX; MMF; csDMARDs	55% among the RTX group, 100% in IMID (immune-mediated inflammatory diseases, naïve to RTX)	21 (68%) 79% among the RTX group, 50% in IMID
Azzolini E. et al.	2022 [25],	Italy	30	PA/SpA/AS, RA, SLE, DM, pSS, SSc	MTX, MMF	96.6%	80% Ag1 83.3% Ag2
Jyssum I. et al.	2022 [14],	Norway	49	RA	All treated with RTX	16.3%	100% (evaluated in 12/49)
Present series							
Gragnani L. Visentini M. et al.		Italy	16	CV, SSc, RA	MMF, Bendamustine, RTX, CSs, AZA, HCQ, LFM + JAKi	69%	50% Ag1 50% Ag2

Table 2 legend: Abbreviations: RA: rheumatoid arthritis; SSc: systemic sclerosis; SLE: systemic lupus erythematosus; AAV, ANCA-associated vasculitis; PsA: SpA: Psoriatic arthritis; SpA: Spondyloarthritis; AS ankylosing spondylitis; DM: Dermatomyositis; pSS: Primary Sjogren's syndrome; MS: Multiple Sclerosis; IMID: immune-mediated inflammatory diseases; RTX: Rituximab; MTX: Methotrexate; DMARDs: Disease Modifying Anti-Rheumatic Drugs; bDMARDs: Biological disease modifying anti-rheumatic drugs; CSs: Corticosteriods; LFM: Leflunomide AZA: Azathioprine; MMF: Mycophenolate mofetil; ABA: Abatacept; OCRE: ocrelizumab; ADA: adalimumab; ETN: etanercept; HCs: Healthy Controls; pts: patients. [#] Cellular response was evaluated by different methods.

population. Worthy of note, almost one fifth of the patients examined showed a concomitant absence of either serum NAb and T-cell response to SARSCoV-2 antigens, all under DMT.

The available literature showed that vaccination is the major tool to control and fight the COVID-19 pandemic; this is particularly true for frail patients' populations [28] such as individuals with ASD. Several reports highlighted that ASD patients have a significantly higher prevalence of COVID-19 compared to general population [29] as well as that 3-dose vaccinated ASD subjects, compared to unvaccinated or 2-dose vaccinated patients, are more protected from severe COVID-19 consequences [30]. Nevertheless, even after the booster dose, a subgroup of ASD patients still maintains an impaired/absent humoral response,

mainly (but not exclusively), due to concomitant DMT [5,13,14].

On the other hands, previous observations in multiple sclerosis patients on anti-CD20 therapy [31] suggested that an impaired humoral response after the booster dose of COVID-19 vaccine could be compensated by an effective T-cell response; however, studies focusing on well-defined ASD are still very limited and partly conflicting [18,25, 26] as briefly reported in Table 2.

As we recently reported, although a percentage of non-responder ASD patients seroconverted after the booster dose, a subgroup of subjects with absent or suboptimal NAb titer persist [32]. This observation concerning the humoral response to COVID-19 vaccine is in line with the results described in the present analysis, as 31% of patients has a deficient humoral response after the booster dose. Furthermore, by analyzing the T-cell response we found that half of the ASD patients did not develop a cellular immunity while only one HC showed an INF-γ level under the positivity cut-off. Although the presence of different diagnoses and the variability of DMT make very difficult a comparison with the few previously published results [14,18,25,26], the percentage of T-cell response we found is comparable to that reported by Firinu and colleagues that stratified ASD patients based on different treatments [18]. They found 50% of no response in subjects undergoing MTX (with or without anti-TNF), MMF, and/or low doses of CSs while 21% of those on anti-CD20 had no T-cell response [18].

Azzolini and coworkers analyzed humoral and cellular immunity in different settings of immunocompromised patients, including a group affected by rheumatic diseases [25]. Their follow-up study of both responses, from the first vaccine shot to two weeks after the third dose, did not find significant improvement of cellular immunity since many patients remained below the positivity cut-off [25]. However, a comparison with our results is hard since the percentage of patients lacking in T-cell response is not reported.

Despite the clinical and therapeutic differences among the evaluated patients' series, our findings are quite consistent with the above observations (35); given the similar DMT, they seem to suggest that the booster dose of COVID-19 vaccine could be more effective on the humoral response.

In addition, while the humoral response seems to be linked to the use of DMT [6,32], 50% of ASD patients with impaired cellular response did not receive such treatments.

Interestingly, 19% of patients were negative for both humoral and cellular response and all of them were on DMT. This is an alarming finding since a non-negligible percentage of ASD patients do not develop any kind of immune protection even after the booster dose of COVID-19 vaccine.

We excluded from the analysis a woman that had a COVID-19 before receiving the third dose; the NAb titer as well as the INF-γ level were higher than the mean values recorded in the analyzed patients, despite of an DMT. This is in line with previous observations pointing out the higher immunogenic power on both humoral and cellular response of COVID-19 compared to the vaccination [33].

5. Conclusions

In conclusion, although the boostering effects of third dose of COVID-19 vaccine in ASD patients are evident on humoral response, more extensive studies are needed to clarify its effects on T-cellular immunity. The present study suggests that half of ASD patients do not develop a cellular response and that a subgroup of them did not mount an efficient humoral response; consequently, this subgroup with concomitant absence of both humoral and cellular immunoreactivity might be at high risk for SARS-CoV2 infection and severe COVID-19 manifestations.

Overall, these preliminary results stress the importance to test the immune protection status of ASD patients, even after the third shot of the COVID-19 vaccination. This may be particularly opportune for patients undergoing DMT, including high dose corticosteroids, and with

major risk factors for worse COVID-19 outcomes (older age, lung fibrosis, and/or comorbidities) [34]. These subjects might be prioritized for the fourth dose of COVID-19 vaccine, hopefully with new generation vaccines; in addition, it could be opportune to adopt adequate social distancing measures, as well preemptive treatments with monoclonal anti-SARS-CoV-2 antibody, and/or novel antiviral drugs, individually tailored considering the whole patient's clinical conditions.

Credit author statement

LG*, MV* and CF contributed to conceptualisation, writing – original draft, and writing– review & editing, supervision and methodology; SL, FLG and SAS contributed to investigation, formal analysis; FC and AT contributed to investigation, GC and PF contributed to data curation, FI, AA, MC and ALZ reviewed and edited the paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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