SARS-CoV-2 monoclonal antibody combination therapy in patients with COVID-19 and primary antibody deficiency

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Summary Anti-SARS-CoV-2 monoclonal antibodies are emerging as a potential therapeutic option for high-risk patients. Here we showed that early administration of monoclonal antibodies in patients with Primary Antibody Defects and COVID-19 reduced the time of viral replication and avoid disease evolution.

Abstract

Previous reports highlighted the efficacy of SARS-CoV-2 specific monoclonal antibodies (mAbs) against COVID-19. Here we conducted a prospective study on clinical outcome and antiviral effect of mAbs added to standard of care therapy in SARS-CoV-2 infected patients with Primary Antibody Defects. Median time of SARS-CoV-2 qPCR positivity was shorter in eight patients treated with mAbs (22 days) than in ten patients treated with standard of care therapy only (37 days, p=0.026). Median time of SARS-CoV-2 qPCR positivity from mAbs administration was 10 days. SARS-CoV-2 mAbs treatment was effective and well-tolerated in patients with Primary Antibody Defects.

Key words: COVID-19; SARS-CoV-2; Monoclonal antibodies; Common Variable Immunodeficiency; Good' Syndrome; Primary Antibody Deficiencies

Background

Due to the severely impaired immune response to immunization, Primary Antibody Deficiency (PAD) patients represent a potential at-risk group in the COVID-19 pandemic. Early reports on cohorts of PAD patients described a low number of patients infected by SARS-CoV-2 and with a variability of clinical manifestations ranging from asymptomatic to death with the fatality rate accounting for 10% (1-4). Patients with Common Variable Immunodeficiencies (CVID) are the predominant group, showing younger age at death (3) and different risk factors predisposing to severe course in comparison to the general population (4). CVID is the most frequent symptomatic PAD in adults and children, with a wide spectrum of clinical complications including recurrent infection, and autoimmune or inflammatory manifestations. Surveys reported a severe clinical course in some CVID patients having more severe defects in antibody responses, dysfunctional B cells, and immune dysregulation. In these patients, the defective B and T cell cellular immune responses might account for an increased risk for prolonged infections, leading to the possible emergence of dangerous vaccine-evasion mutants (5,6).

At present, COVID-19 directed treatments are limited, including the antiviral agent remdesivir as the first approved therapeutic option for the treatment of COVID-19. More recently, monoclonal antibodies (mAbs) have been developed with the aim to neutralize the SARS-CoV-2 spike protein, thus preventing viral binding to host cells (7). Given the poor specific antibody responses, PAD patients may be ideal candidates for SARS-CoV-2-based MoAbs treatment.

In Italy, this new therapeutic approach has become available since March 2021 when the Italian Agency for Drugs (AIFA) approved the first SARS-CoV-2 mAb for treatment in patients >12 years old at high-risk for severe COVID-19. Treatment was approved for mild to moderate COVID-19 within 10 days of symptom onset, with the exception for those with immunodeficiency, for which mAbs administration was allowed over 10 days

(https://www.aifa.gov.it/uso-degli-anticorpi-monoclonali). Data regarding mAbs-based therapy in the PAD population are lacking. The purpose of this study was to describe the clinical response and safety profile in SARS-CoV-2 positive PAD treated with mAbs and to compare data to SARS-CoV-2 PAD patients treated with COVID-19 standard of therapies not-including mAbs.

Methods

Patients. Adult (≥18 years old) PAD patients with SARS-CoV-2 infection routinely followed by Care Centers of Rome and Treviso were enrolled in this prospective study. Diagnosis of PAD was done according to the ESID criteria (www.ESID.com). Symptomatic patients were considered as positive for SARS-CoV-2 by qPCR on nasopharyngeal swabs obtained within one day after onset of symptoms. Asymptomatic patients were identified by the screening of patients attending the hospital or in case of family contact. The duration of viral positivity was calculated as the interval between the first positive and the first negative nasopharyngeal swab for SARS-CoV-2. Participants were grouped on the basis of the treatment with mAbs in two groups: standard of care treatment (Group 1) and standard of care treatment plus mAbs (Group 2). During the study time, patients were allowed to continue their therapies, including immunoglobulins replacement for the underlying antibody deficiency, and were monitored for their clinical status. During SARS-CoV-2 infection, patients were followed by qRT PCR every 7-10 days until a confirmed negative swab.

The study was approved by the Ethical Committee of the Sapienza University of Rome (Prot. 0521/2020, July 13, 2020). The study was performed in accordance with the Good Clinical Practice guidelines, the International Conference on Harmonization guidelines, and the most recent version of the Declaration of Helsinki.

ELISA for specific IgG detection. A semi-quantitative in vitro determination of human IgG antibodies against the SARS-CoV-2 (S1) was performed on serum samples by using the

Anti-SARS-CoV-2 Spike ELISA (Euroimmun), according to the manufacturer's instructions. Values were then normalized for comparison with a calibrator. Results are reported as the ratio between OD sample and OD calibrator. The ratio interpretation was as follows: <0.8 = negative, ≥0.8 to <1.1 = borderline, ≥1.1 = positive.

Statistical analysis. Patient data were analyzed with standard descriptive statistics. Baseline characteristics of patients treated with COVID-19 standard of care and patients treated with standard of care plus mAbs were compared with $\chi 2$ test for categorical variables and Mann-Whitney for continuous variables. Differences were deemed significant when $P < 0.05$. Statistical Package for Social Sciences version 15 (SPSS Inc., 233 South Wacker Drive, 11th Floor, Chicago) has been used for the analysis.

Results. From March 2020 to May 2021, a total of 18 PAD patients, 7 females and 11 males, aged 51.5 years (range 26-71) were tested positive for SARS-CoV-2 by qPCR from nasopharyngeal swabs. Four patients were asymptomatic. Fourteen patients were symptomatic: 6/14 patients required hospitalization due to progression of COVID-19 symptoms. The most common COVID-19 symptoms recorded were fever (72%), cough (61%), and dyspnea (39%). Chest CT scan showed pneumonia in 5 patients (28%).

Demographic and clinical data of SARS-CoV-2 infected patients is provided in Table 1. Ten patients received the standard of care for COVID-19 (Group 1): one patient (n. 9) received Dexamethasone; one patient (n. 10) Dexamethasone and Remdesivir, two patients (n. 1 and 5) were treated with Tocilizumab, Dexamethasone and Lopinavir/Ritonavir; six patients did not require treatment (n. 2, 3, 4, 6, 7, 8). Eight PAD patients received the standard of care for COVID-19 plus monoclonal antibodies-based therapy (Group 2): two patients (n. 11 and 12) were treated with Bamlanivimab only; 6 patients (n. 13, 15, 18) received a double therapy with Bamlanivimab/Etesevimab and patient n. 16 Bamlanivimab/Etesevimab plus Dexamethasone; patient 14 received double therapy with Calsirimab/Imdevimab plus

Dexamethasone and Remdesivir, and patient n. 17 double therapy with Calsirimab/Imdevimab plus Dexamethasone. Demographics and clinical pictures of COVID-19 were comparable between the two groups (Table 2).

Treatment with mAbs was initiated within a range of 2-15 days after the first positive nasopharyngeal swab (Table 1). Infusion of mAbs was well-tolerated in all patients. In 7 out of 8 participants symptoms disappeared within 2-5 days, and all but one (n. 14) remained asymptomatic thereafter. Nasopharyngeal swab SARS-CoV-2 qPCR was repeated every 7-10 days until negative. Treatment with mAbs significantly (p=0.026) diminished the time of qRT PCR positivity (median time from infection onset: 22 days, range 7-40; median time from mAbs administration: 10 days, range 5-30). Differently, the median time of swab positivity was longer in patients treated with standard of care therapy only (median time, from infection onset: 37.5 days, range 21-81 days) (Table 2). As expected, SARS-CoV-2 IgG antibodies - checked after a comparable median time from the first positive nasopharyngeal swab - were higher in mAbs-treated patients (median: 6.9 OD ratio, range: 6.4-11.7 OD ratio) than in patients receiving standard of care therapy only (median: 1.9 OD ratio, range 0.9-6.4 OD ratio, *p=0.001*).

Discussion

Patients with primary antibody deficiencies are considered as a vulnerable population in the COVID-19 pandemic as they might be unprotected from vaccination, might have prolonged COVID-19 course and SARS-Cov-2 recurrences (3, 5-7). Recently, we have showed that two third of PAD patients are unable to produce specific antibodies after two doses of SARS-CoV-2 vaccine and, instead of generating classical specific memory B cells, they developed atypical memory B cells, short lived plasma blasts, and variable T cell response (7). Atypical memory B cells are mostly generated during extrafollicular reactions without the involvement of antigen selection in the germinal center reaction (8) and are considered short-lived activated memory B cells. In patients unable to mount an adequate antibody response,

additional strategies for protection are needed. So far, prevention of SARS-CoV-2 infection could not be achieved by immunoglobulin replacement treatment, due to the lack of specific antibodies in the current lots of gamma globulins (9). One still controversial option is the possibility to substitute the defective antibody production by convalescent plasma. The administration of convalescent plasma <72 hours after the onset of symptoms has been shown to reduce disease progression in immunocompetent patients with mild disease and at high risk for disease progression only (10). Moreover, the low neutralizing potency of convalescent plasma therapy is difficult to be standardized. In addition, plasma and transfusion usage in patients lacking immunoglobulins and in particular, in patients without serum IgA, should be limited in that it might cause adverse reactions (11).

Monoclonal antibody-based therapies might be a promising option for patients with antibody defects (12). During the past year, an unprecedentedly large number of mAbs have been developed to fight COVID-19 (13). Overall, this study confirmed the previous report (1-4) showing a wide range of COVID-19 spectrum of clinical conditions in PAD patients. We showed a positive clinical and antiviral response due to treatment with mAbs added to conventional therapy. Consistent with a previous report (14), the treatment was without severe side effects in all patients. Although the majority of our cohort continued to be COVID-19 symptom-free, two patients with severe underlying PAD-related comorbidities required hospitalization: a patient for a pre-existing severe pulmonary involvement and a patient for enteropathy.

The positive outcome in antibody deficient patients was restricted to an early time point of monoclonal administration during SARS-CoV-2 infection. We therefore suggest regular follow-ups of PAD patients by SARS-CoV-2 qPCR, and to consider an early administration of mAbs in order to avoid COVID-19 evolution and to shorten the time of SARS-CoV-2 positivity. The shift of mAbs administration from intravenous to different routes, such as intramuscular or subcutaneous (15), is under evaluation and will possibly contribute to an easier access to these treatments for PAD.

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Tables

Table 1. Demographic and clinical characteristics of the cohort of primary antibody deficiency SARS-CoV-2 infected patients.

	IEI	SEX	Age	Underlying chronic lung disease	Time of SARS-CoV-2 infection	SARS-CoV-2 associated symptoms	Pneumonia	Days of SARS-CoV-2symptoms	SaO2 %	Days of hospital admission	mAbs therapy	Time point of mAbs administration (days from first SARS-CoV-2 qPCR positivity)	Additional COVID-19 specific therapy	Days of SARS-CoV-2 qPCR positivity	Days of SARS-CoV-2 qPCR positivity after mAbs therapy	Outcome
1	SIgAD	F	33	Bronchiectasis	March, 2020	fever, cough dyspnea	yes	30	85	28	no	-	Lopinavir/ Ritonavir, Tocilizumab, Dexamethasone	45	-	Recovery
2	CVID	M	55	COPD bronchiectasis	September, 2020	asymptomatic	no	0	97		no	-	no	51	-	Recovery
3	CVID	M	57	no	September, 2020	fever, cough	no	17	98		no	-	no	79	-	Recovery
4	CVID	F	61	Bronchiectasis	November, 2020	fever	no	2	97		no	-	no	30	-	Recovery
5	CVID	F	47	COPD, bronchiectasis	November, 2020	fever, cough, dyspnea	yes	95	81	90	no	-	Lopinavir/ Ritonavir, Tocilizumab, Dexamethasone	75	-	Dyspnea
6	CVID	M	55	Bronchiectasis	December, 2020	asymptomatic	no	0	98		no	-	no	81	-	Recovery
7	CVID	M	38	Bronchiectasis	January, 2021	fever, cough	no	30	94		no	-	no	23	-	Recovery
8	CVID	M	46	COPD	January, 2021	cough	no	10	95		no	-	no	30	-	Recovery
9	CVID	M	33	COPD, bronchiectasis	February, 2021	fever, cough, dyspnea	no	14	95	12	no	-	Dexamethasone	21	-	Recovery
1	CVID	M	46	no	February,	fever, cough,	yes	13	90	12	no	-	Remdesivir, Dexamethason	22	-	Recovery

0					2021	dyspnea						e				
11	CVID	M	52	COPD, bronchiectasis	March, 2021	asymptomatic	no	0	95		Bamlanivimab	12	no	23	11	Recovery
12	CVID	F	51	no	March, 2021	fever, cough, dyspnea	no	13	93		Bamlanivimab	2	Dexamethasone	7	5	Recovery
13	CVID	M	60	Bronchiectasis	March, 2021	fever, cough	no	2	98		Bamlanivimab / Etesevimab	10	No	17	7	Recovery
14	CVID	F	49	GLILD, bronchiectasis, COPD	March, 2021	fever, cough, dyspnea	yes	40	87	35	Calsirimab/ Imdevimab	14	Remdesivir, Dexamethasone	40	26	Dyspnea
15	CVID	F	68	COPD, bronchiectasis	March, 2021	asymptomatic	no	0	96		Bamlanivimab / Etesevimab	2	no	32	30	Recovery
16	CVID	F	70	GLILD, bronchiectasis	April, 2021	fever, cough, dyspnea	yes	28	88	26	Bamlanivimab / Etesevimab	15	Remdesivir, Tocilizumab, Dexamethasone	21	6	Recovery
17	CVID	M	71	no	April, 2021	fever	no	9	98		Calsirimab/ Imdevimab	2	Dexamethasone	30	28	Recovery
18	CVID	M	26	no	May, 2021	fever	no	1	99		Bamlanivimab / Etesevimab	2	no	11	9	Recovery

Abbreviation: CVID: Common Variable Immune Deficiency, COPD: Chronic Obstructive Pulmonary Disease, GLILD: Granulomatous and Lymphocytic Lung Interstitial Disease, SIgAD: Selective IgA Deficiency.

Table 2. Comparison of data between SARS-CoV-2 infected PAD patients grouped by COVID-19 treatment.

	Standard of care (n=10)	**Standard of care + mAbs (n=8)**	**p value**
Female, n (%)	3 (30)	4 (50)	0.630
Age (years), median (IQR)	64.5 (40-55)	56 (50.5-68.5)	0.156
Fever, n (%)	7 (70)	6 (75)	1.000
Cough, n (%)	7 (70)	4 (50)	0.630
Dyspnea, n (%)	4 (40)	3 (37)	1.000
Pneumonia, n (%)	3 (33)	2 (25)	1.000
Hospital admission, n (%)	4 (40)	2 (25)	0.638
Days of SARS-CoV-2 qPCR positivity, median (range)	37.5 (21-81)	22 (7-40)	0.026
Days of symptoms, median (range)	13.6 (0-95)	5.5 (0-40)	0.393
Spike specific (IgG1) IgG (OD ratio), median (range)	1.9 (0.9-6.4)	6.9 (6.4-11.7)	0.001