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SARS-CoV-2-specific T-cell responses after COVID-19 recovery in patients with rheumatic diseases on immunosuppressive therapy

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ABSTRACT

Background: In patients with immune-mediated rheumatic diseases (RMD), the development of T-cell responses against SARS-CoV-2 may be impaired by either the immune disturbances associated with the disease, or by the effects of immunosuppressive therapies. We aimed at determining the magnitude of SARS-CoV-2-specific interferon (IFN)-γ-producing T-cell response after COVID-19 recovery in a cohort of patients with RMD on different immunosuppressive therapies.

Patients and methods: 53 adult patients with inflammatory or autoimmune RMD and 61 sex and age-matched non-RMD patients with confirmed COVID-19 were included. Peripheral blood mononuclear cells were obtained and T-cell-IFN-γ antigen-specific responses against the S1 domain of the spike glycoprotein, the nucleoprotein (N) and the membrane (M) protein from SARS-CoV-2 were assessed by FluoroSpot assay.

Results: Patients with RMD and COVID-19 showed positive T-cells-IFN-γ responses to SARS-COV-2 antigens, in a similar proportion and magnitude as non-RMD patients at a median of 298 [151–316] and 165 [162–167] days after COVID-19 respectively. Among RMD patients 83%, 87% and 90%, and among non-RMD patients, 95%, 87% and 93% responded to S1, N and M protein respectively. Similar responses were observed in the different diagnostic and therapeutic groups, including conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), TNF-α inhibitors, IL-17 inhibitors, rituximab, JAK inhibitors or other immunosuppressants.

Conclusion: T-cell responses to the main SARS-CoV-2 antigens are present after COVID-19 recovery in most patients with RMD and are not impaired by immunosuppressive therapies.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and its associated illness coronavirus disease 2019 (COVID-19) may have a greater impact in patients with rheumatic disease (RMD), particularly in patients with systemic autoimmune diseases and those under immunosuppressive therapy. Age, comorbidities, RMD activity and some therapies represent a potential risk factor for severe illness in these patients (1–3).

Humoral IgG responses are detected in the general population within the first weeks from COVID-19 symptom onset, and persist at least 6–8 months after infection, displaying a decreasing trend over time (4). SARS-CoV-2-specific CD4 and CD8 memory T-cells with robust interferon (IFN)-γ responses are positive in most patients up to nearly one year after infection, and seem to play an essential role in long lasting immunity (5). Similarly, upon SARS-CoV-2 vaccination, T-cell responses are achieved after the first dose and may complement the protective effects of neutralizing antibodies (6). In patients with autoimmune diseases, the development of protective adaptive immune responses against SARS-CoV-2 may be impaired by either the immune disturbances associated with autoimmune disease, or by the effects of immunosuppressive therapies as observed in other groups such as solid organ transplanted (SOT) patients (7).

In response to SARS-CoV-2 vaccines, defective humoral responses have been identified in RMD patients on methotrexate (MTX), mycophenolate, rituximab (RTX) or abatacept, whereas JAK inhibitors and biologic therapies such as TNF-α, IL6 or IL-17 inhibitors do not seem

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to hamper seroconversion (8). However, information on T-cell responsiveness in these patients after COVID-19 is lacking. Recent data show that T-cell specific responses to SARS-CoV-2 vaccines are preserved in most RMD patients on different immunosuppressive, although their magnitude is reduced in some groups (9-12).

Since increasing evidence supports a relevant role of T-cell responses in protection after infection or vaccination, understanding the potential interference of immunosuppressive therapies or RMD on the development of these responses after COVID-19 recovery may help to predict potential risks in these patients. We aimed at determining the magnitude of SARS–CoV–2–specific IFN-γ-producing T-cells after COVID-19 recovery in a cohort of RMD patients.

Materials and methods

Study population

Adult patients with inflammatory or autoimmune RMD with laboratory-confirmed COVID-19 by either reverse transcription polymerase chain reaction (RT-PCR) or IgG serologic testing (Supplementary Methods) between March 2020 and January 2021 at the University Hospital "12 de Octubre" (Madrid, Spain) were eligible for inclusion. A similar group of age- and sex-matched patients without RMD, other immune-mediated disease, or immunosuppressive therapy, was also identified and used as control group. None of the included individuals had been vaccinated against SARS-CoV-2.

The study was carried out in accordance with Helsinki Declaration ethical standards and the study protocol was approved by the local institutional Research Ethics Committee (ref. 20/314). All participants provided written informed consent.

SARS-CoV-2 T-cell responses assessment by IFN-γ fluorospot assay

Peripheral blood mononuclear cells (PBMCs) were freshly isolated within 8 h from sampling by density-gradient centrifugation using Ficoll-Paque and seeded at 300,000 cells/well in IFN-γ FluoroSpot^{TM} plates (MabTech, Nacka Strand, Sweden) with cell culture medium containing RPMI, 1% L-glutamine, 1% penicillin/streptomycin, 10% fetal bovine serum and anti-CD28 mAb (1 μg/mL). Test wells were performed in duplicate and supplemented with 15-mer overlapping peptides covering the S1 domain of the S glycoprotein (166 peptides) (SARS-CoV-2 S1 scanning pool, MabTech), the nucleoprotein (N protein) (102 peptides) (Epitope Mapping Peptide Set [EMPS] SARS-CoV-2 NCAP-1, JPT), and the membrane (M) protein (53 peptides) (EMPS SARS-CoV-2 VME1, JPT) at a final concentration of 1 μg/mL. Sample-specific negative and positive control wells for each patient were included. Negative control wells lacked peptides, and positive control wells included anti-CD3 mAb (MabTech). Assays were incubated for 16–18 h at 37 °C. Spots were counted using an automated IRIS^{TM} FluoroSpot Reader System (MabTech). To quantify antigen-specific responses, spots of the negative control wells were subtracted from the mean spots of test wells, and the results were expressed as IFN-γ–producing spot forming units (SFUs) per 10^6 PBMCs. Results were excluded if negative control wells had >80 SFUs/10^6PBMCs or positive control wells had <400 SFUs/10^6 PBMCs. Reponses were considered positive if the results were at least three times higher than the mean of the negative control wells and above of the following antigen-specific cut-off values (which had been established by using a control group of 30 healthcare workers with no microbiological or clinical evidence of SARS-CoV-2 infection): >25 SFUs/10^6 PBMCs for the S glycoprotein, >14 SFUs/10^6 PBMCs for the N protein, and >21 SFUs/10^6 PBMCs for the M protein. PBMCs were used in this assay, however, results regarding the specific cellular immune response are expressed as T cell response. T cells constitute the largest fraction of isolated PBMCs and are the main producers of IFN-γ.

Statistical analysis

Quantitative data were shown as the mean ± SD or the median with interquartile range (IQR). Categorical variables were compared using the $\chi 2$ or Fisher exact test. Mann-Whitney *U* test was applied to compare the magnitude of SARS-CoV-2-specific IFN-γ-producing T-cell responses between both groups. Bonferroni adjustment for multiple testing was used. Statistical analyses were performed with STATA/IC version 14.0 (Stata Corp) and GraphPad Prism 5 (GraphPad, Inc).

Results

Study population

We recruited 53 patients with RMD and 61 age- and sex-matched patients without rheumatic diseases and a confirmed COVID-19 diagnosis. Age, sex, and the presence of relevant comorbidities were similar in both groups (Table 1). The median duration of the rheumatic disease was 7 years (IQR 3–11). The RMD diagnostics, therapy, and clinical characteristics of COVID-19 are shown in Table 1.

Among those patients who received specific COVID-19 treatment (40%), the most common treatment regimens included antiviral therapy with lopinavir/ritonavir in 6 (11%) and remdesivir in 1 (2%), and/or immunosuppressive treatment with glucocorticoids in 9 (17%) and IL-6 inhibitors in 3 (6%). Conversely, none of the patients in the non-RMD group received remdesivir and 26 (43%) were given IL-6 or IL-1 inhibitors, or glucocorticoids. Severity of COVID-19 infection was greater in non-RMD patients, those were in all cases hospitalized, whereas RMD cohort also included non-hospitalized patients under follow-up at our rheumatology unit (Table 1). The interval between symptomatic COVID-19 and T-cell response testing was significantly longer in the group of RMD patients (Table 1).

T-cell-IFN-γ-producing responses to SARS-CoV-2 antigens

Positive SARS-CoV-2-specific T-cell-IFN-γ-producing responses to S1, N, or M proteins were detected in most patients with or without RMD. Globally, patients with RMD showed positive T-cell IFN-γ responses to each of the three tested SARS-CoV-2 antigens after COVID-19, in a statistically similar proportion as non-RMD patients (Table 2). Four patients did not respond to any of the three antigens (two RMD and two non-RMD patients). Among RMD patients 83%, 87% and 90%, and among non-RMD patients, 95%, 87% and 93% responded to S1, N and M protein respectively. A non-significant numerical difference was only observed for S1 protein responders. Responses to S1 protein were not detected in three of the non-RMD group (5%) and in nine of the RMD group (17%). Among RMD patients not responding to S1 protein, three were on csDMARDs, three on low dose glucocorticoids, one on TNF-α inhibitor, one on IL17-inhibitor, and one on azathioprine.

The proportion of responders among RMD patients was not modified by the severity of COVID-19 infection nor by the time between COVID-19 and T-cell response testing (Supplementary Table S1 and supplementary Figure S1). No differences in the magnitude of T-cell-IFN-γ response to each individual antigen in hospitalized versus non-hospitalized patients were found in the RMD group (Supplementary Table S2).

The magnitude of the IFN-γ-producing T-cell response to SARS-COV-2 antigens was also similar strenght of the RMD and non-RMD groups as shown in Fig. 1A and Supplementary Table S3. A similar level of response was also observed independently of the therapy received (Fig. 1B) or the diagnosis (Fig. 1C). No differences were found in the level of response at different intervals after COVID-19 diagnosis neither in RMD nor in non-RMD group (Supplementary Figure S1).

Table 1
Demographics and clinical characteristics of the study population.

	Rheumatic *n* = 53	**Non-Rheumatic *n* = 61**	**p-value**
Age	53 (44–61)[a]	53 (49–66)	0.365
Female sex	40 (75)	42 (69)	0.433
Comorbidities[b]	27 (51)	28 (46)	0.555
Rheumatic disease diagnosis			
Rheumatoid arthritis	20 (38)		
Psoriatic arthritis	7 (13)		
Spondyloarthritis	11(21)		
Systemic lupus erythematosus (SLE)	8 (15)		
AI/IMID non-SLE[c]	7 (13)		
Baseline rheumatic disease medications			
Glucocorticoids	17(32)		
Hydroxychloroquine	15 (28)		
Methotrexate	16 (30)		
Leflunomide	4 (8)		
Sulfasalazine	6 (11)		
Azathioprine	4 (8)		
Calcineurin inhibitors	1(2)		
Mycophenolate	4(8)		
TNF-α inhibitor	10 (19)		
IL-17 inhibitor	6 (11)		
Rituximab	4 (8)		
JAK inhibitors	4 (8)		
Active disease	10 (19)		
Covid-19 associated variables			
Follow-up from diagnosis to T-cell testing	298 (151–316)	165 (162–167)	<0.001
Hospitalization *n* = 114	17 (32)	61 (100)	<0.001
Radiographic pneumonia, *n* = 114	21 (40)	61 (100)	<0.001
Respiratory failure, *n* = 114	10 (19)	34 (56)	<0.001
Clinical severity			
Low-flow nasal cannula (Fi02[d]<40%)	9 (17)	22 (36)	0.022
High-flow nasal cannula (Fi02≥40%)	4 (8)	11 (18)	0.099
Non-invasive ventilation	0 (0)	2 (3)	0.184
Intensive care unit admission	2 (4)	4 (7)	0.684
Treatment			
Antiviral therapy[e]	7 (13)	41 (67)	<0.001
Immunosuppressive treatment[f]	9 (17)	26 (43)	<0.005

[a] Values represent n (%) or median (IQR).
[b] Comorbidities: obesity, diabetes mellitus, hypertension, cardiovascular disease, lung disease.
[c] AI/IMID non-SLE: polymyositis, cryoglobulinemia, granulomatosis with polyangiitis, Sjogren's syndrome, systemic sclerosis.
[d] FiO2: fraction of inspired oxygen.
[e] Antiviral therapy: lopinavir/ritonavir or remdesivir.
[f] Immunosuppressive treatment: IL-6 inhibitors, IL-1 inhibitors and/or glucocorticoids.

The proportion of responders and the magnitude of the T-cell responses to each of the SARS-CoV-2 proteins in RMD and non-RMD patients treated with glucocorticoids or anti-cytokine (anti-IL-6 or anti-IL-1) as therapy for COVID-19 were similar to those in the group of not treated with immunosupressive agents (data not shown).

Discussion

Whether SARS-CoV-2 infection confers immunity to reinfection and for how long is yet uncertain. At this point, more than one year after the first cases were diagnosed in Europe, reinfection rates are very low and most cases are milder than the first episode, pointing to a long-lasting protective immunity (13). Immunity relies on both IgG antibodies that can neutralize S-protein-receptor interaction, and T-cell effector responses against several structural viral antigens in infected cells (14). Whereas IgG antibodies seem to rapidly decline, memory T-cells seem responsible for long-lasting protection (5).

In patients with compromised immune responses, the development of both T-cell and humoral immunity after immunization is usually hampered (8). However, in solid organ transplant (SOT) recipients recovered from COVID-19, T-cell responses against SARS-CoV-2 antigens do not seem different in magnitude or duration compared to the general population (15-17). In these patients, the humoral and cellular responses to SARS-CoV-2 vaccines were significantly lower (7,18). Several conventional or biologic immunosuppressive therapies may also reduce the response to SARS-CoV-2 vaccines in patients with RMD, including high dose glucocorticoids, mycophenolate, or rituximab, although T-cell responses are usually better preserved than humoral responses (9-12). These patients might remain at higher risk for COVID-19 despite vaccination, but data on the incidence are lacking. In a large cohort of inflammatory bowel disease (IBD) patients on different immunosuppressive regimes, clinical effectiveness of vaccines was similar to what reported in the general population, but the therapies in these patients and RMD patients can be different (19).

In this study, we have observed that most patients with rheumatic diseases under different immunosuppressive therapies achieve a T-cell immune response after natural SARS-COV-2 infection. We did not find differences in T-cell responses in relation to the different diseases or immunosuppressive therapies. More than 80% of the patients achieve a response under csDMARDs, bDMARDs (biologic disease-modifying anti-rheumatic drugs), JAK inhibitors or other immunosuppressants such as mycophenolate or calcineurin inhibitors. Remarkably, all rituximab or JAK inhibitors treated patients, although in small numbers, showed positive responses. Whereas humoral and

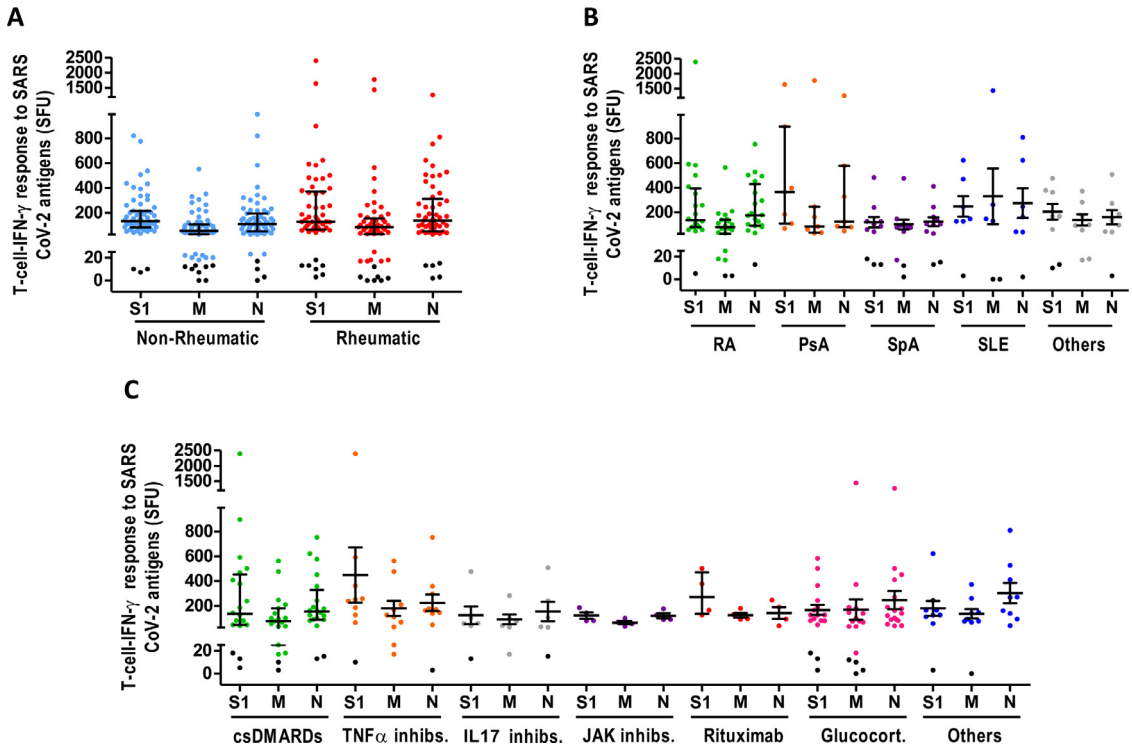

Fig. 1. Magnitude of T-cell-IFN-γ producing responses to SARS-CoV-2 antigens. A) T-cell-IFN-γ response (SFU) to S1, M and N antigens in RMD and non-RMD groups. B) T-cell-IFN-γ response across different therapies. Other IS include azathioprine, mycophenolate and calcineurin inhibitors. C) T-cell-IFN-γ response across the different RMD. Data represent median and IQR. Black dots represent patients without positive response (<25 SFU for S glycoprotein; <14 SFU for N protein and <21 SFU for the M protein). Others: non-SLE autoimmune disease.

Table 2
T-cell-IFN-γ producing responses to SARS-CoV-2 antigenic peptides.

	S1>25[a]	***N*>14[a]**	***M*>21[a]**
Non-rheumatic cohort *n* = 61	58 (95)[b]	53 (87)	57 (93)
Rheumatic cohort *n* = 53	44 (83)[c]	46 (87)	48 (90)
Rheumatic disease diagnosis			
Rheumatoid arthritis	16 (80)	16 (80)	17 (85)
Psoriatic arthritis	6 (86)	7 (100)	6 (85,7)
Spondyloarthritis	9 (81)	10 (91)	10 (91)
Systemic lupus erythematosus (SLE)	7 (88)	7 (86)	8 (100)
AI/IMID non-SLE[d]	6 (86)	6 (86)	7 (100)
Baseline rheumatic disease medications			
Glucocorticoids	14 (82)	13 (77)	17 (100)
Conventional synthetic DMARDs (csDMARDs)[e]	17 (85)	18 (90)	18 (90)
TNF-α inhibitor	9 (90)	10 (100)	9 (90)
IL-17 inhibitor	5 (83)	6 (100)	5 (83)
Rituximab	4 (100)	4 (100)	4 (100)
JAK inhibitors	4 (100)	4 (100)	4 (100)
Other immunosuppressants (IS)[f]	8 (89)	8 (89)	9 (100)

cellular response to SARS-COV-2 vaccines may be impaired in SOT recipients and RMD patients, T-cell responses in patients recovered from COVID-19 in both groups seem comparable to those in the general population (7-10, 15-18).

We acknowledge that our study has some limitations. First the population is quite heterogeneous in diagnosis and other clinical characteristics, and although comparable to the control group, it differs in two potentially important variables. First, COVID-19 severity was higher in non-RMD control group, which only included hospitalized patients on follow-up after recovery. Patients with milder disease were not followed-up, precluding their inclusion. Instead, either milder or severe patients with RMD were followed-up at our rheumatology unit. In previous studies, cellular or humoral immune responses were not found different between severe or mild disease (14, 20). In our RMD patients, differences between hospitalized or non-hospitalized patients were not found. Also, the timing from COVID-19 to T-cell response determination was significantly longer in RMD patients, but this might have led to decreased rather than increased responses in this group and therefore, it also supports the conclusion on the T-cell responsiveness of these patients.

Although this study has shown an adequate cellular immune response in rheumatic patients after SARS-COV-2 infection, further studies should be conducted to clarify the durability and preventive capacity of this response.

Declaration of Competing Interest

Ana Lledó, Miriam Retuerto, Patricia Almendro-Vázquez, Mario Fernández-Ruiz, María Galindo, Rocío Laguna-Goya, Estela Paz-Artal, Antonio Lalueza, José María Aguado and José L. Pablos do not have financial information to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2021.10.006.

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