

**Clinical features and outcomes of COVID-19 in patients with IgG4-related disease:
a European multi-center study.**

AUTHORS. Giuseppe A. Ramirez^{1,2*}, Marco Lanzillotta^{1,2*}, Mikael Ebbo³, Andreu Fernandez-Codina^{4,5}, Gaia Mancuso^{1,2}, Olimpia Orozco-Galvez^{6,7}, Lorenzo Dagna^{1,2}, Nicolas Schleinitz³, Fernando Martínez-Valle^{6,7}, Emma L. Culver^{8,9}, Emanuel Della-Torre^{1,2}.

*GAR and ML contributed equally

AFFILIATIONS. ¹Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy; ²Università Vita-Salute San Raffaele, Milan, Italy; ³Internal Medicine Department, Hôpital de la Timone, Assistance Publique Hôpitaux de Marseille, Aix Marseille Université, Marseille, France; ⁴Windsor Regional Hospital, General Internal Medicine Division, Windsor, Canada; ⁵Western University, Rheumatology Division, London, Canada; ⁶Universitat Autònoma de Barcelona, Autoimmune Diseases Research Lab. , Barcelona, Spain; ⁷Vall d'Hebrón Hospital, Systemic Diseases Unit, Internal Medicine Service, Barcelona, Spain; ⁸Translational Gastroenterology Unit, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom; ⁹University of Oxford, Oxford, United Kingdom

Corresponding author: Emanuel Della-Torre, Università Vita-Salute San Raffaele and Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele. Via Olgettina 60, 20134 Milan, Italy. Email: dellatorre.emanuel@hsr.it

RUNNING TITLE: COVID-19 in patients with IgG4-related disease

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Key message: Concomitant treatment with rituximab and corticosteroids is associated with an increased risk of COVID-19.

Dear Editor,

Patients affected by inflammatory rheumatic disorders are at increased risk of Coronavirus Disease-19 (COVID-19) related adverse outcomes due to concomitant immunosuppressive medication and comorbidities [1,2]. IgG4-related disease (IgG4-RD) is an increasingly recognized systemic fibro-inflammatory condition that predominantly affects elderly males whose standard of care is based on glucocorticoids and rituximab regimens, all established risk factors for poorer COVID-19 outcomes [3-7]. In addition, elevation of serum IgG4 has been recently identified as a predictor of mortality in hospitalized COVID-19 patients, raising the possibility that an immunological background prone to preferential IgG4 production may favour life-threatening SARS-CoV-2 infection [8]. In the present observational retrospective study, we collected epidemiological and clinical features of patients with biopsy proven IgG4-RD and followed at tertiary care centres in France, Italy, Spain, and the United Kingdom. Patients were interrogated by phone call between December 2020 and February 2021 and asked to answer to an ad hoc questionnaire built up by consensus among IgG4-RD experts from each centre to capture COVID-19 related events occurred between February and December 2020 (**Supplementary Data S1**, available at *Rheumatology* online). COVID-19 was deemed “confirmed” (cCOVID) in case of a positive reverse transcriptase-polymerase chain reaction test for SARS-CoV-2 and “presumed” (pCOVID) in the presence of highly suggestive clinical and/or

radiological features. Informed consent was obtained from each participant in the framework of local observational studies approved by local ethics committees (**Supplementary Data S1**). A total of 305 patients (87 women) with a median age of 64 (54-74) years were enrolled. At the time of the interview, 156 (51%), 89 (29%), and 89 (29%) patients, respectively, were on corticosteroids, and/or disease-modifying anti-rheumatic drugs (DMARDs), or were infused with rituximab during the period of observation (**Supplementary Table S1**, available at *Rheumatology* online).

32/305 patients (10%) (23 cCOVID and nine pCOVID) had COVID-19 between February and December 2020. 29/32 patients with COVID-19 (83%) had symptomatic disease with fever (69%), dry cough (63%) and dyspnoea (51%) being the most frequently reported manifestations. 11/32 patients with COVID-19 (34%) were hospitalised, two (6%) required admission to intensive care unit, and four (13%) died. All deceased patients were men with a history of IgG4-RD > 3 years and multiple comorbidities (**Figure 1A**). Patients treated with glucocorticoids and rituximab within the previous 24 months had an increased risk of COVID-19 compared to those treated with rituximab alone (HR=4.83, 95% CI=1.22-19.09; p=0.025; n=77). Patients with chronic bronchitis ever treated with rituximab also showed an increased risk of COVID-19 (HR=4.82, 95% CI=1.43-16.33; p=0.011; n=105) (**Figure 1B**).

Our study indicates that IgG4-RD represents an immune-mediated condition at risk of poor COVID-19 outcome as 13% of infected patients ultimately died. Our results also suggest that the use of rituximab in combination with corticosteroids and/or in patients with pre-existing lung disease increases the risk of SARS-CoV-2 infection [1]. Despite intrinsic limitations due to the relatively low number of IgG4-RD patients with COVID-19, the retrospective design, and possible differences in public health policies across the four countries included in the survey, our

study provides the first systematic analysis of the impact of COVID-19 in the largest multicentre European cohort of patients with IgG4-RD. As such, in addition to social, behavioural, and vaccination strategies, tailored therapeutic choices based on disease activity and on individual comorbidities should represent the most relevant measures to prevent COVID-19 in IgG4-RD.

AUTHORS' CONTRIBUTIONS. All authors were involved in the design of the study and in clinical data collection. GAR and ML performed statistical analysis and drafted the manuscript. All authors revised the manuscript critically and approved its final version. The authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work will appropriately be investigated and resolved.

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FIGURE 1. Prevalence and long-term outcomes of COVID-19 in an international cohort of IgG4-RD patients

(A) Clinical features of patients with IgG4-RD deceased due to COVID-19 in 2020. (B) Treatments and comorbidities associated with an increased risk of COVID-19. Kaplan-Meier's survival curves showing the likelihood of developing COVID-19 in patients with IgG4-RD treated with rituximab (RTX) based on recent corticosteroid therapy (upper panel) or chronic bronchitis (lower panel). In the upper panel only patients treated with RTX within two years were considered. **Abbreviations:** diabetes mellitus (DM); chronic obstructive pulmonary disease

(COPD); arterial hypertension (AH); coronary artery disease (CAD); multiorgan failure (MOF); disease modifying anti-rheumatic drugs (DMARDs).

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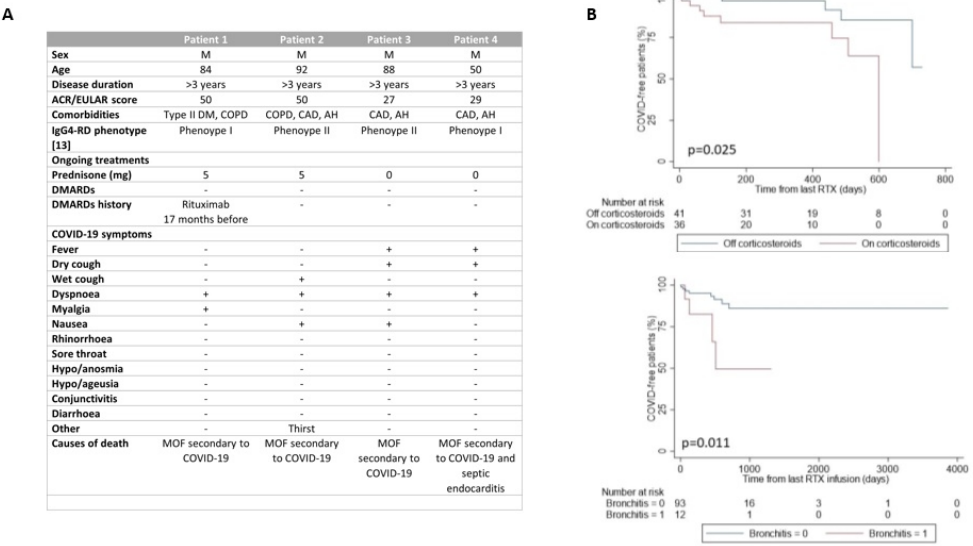


FIGURE 1.

248x140mm (96 x 96 DPI)

Supplementary Data S1**SUPPLEMENTARY METHODS**

Study design and variables. This is an observational retrospective study involving four European tertiary care centres for IgG4-RD from France (Hôpital de la Timone, Marseille), Italy (IRCCS Ospedale San Raffaele, Milan), Spain (Vall d'Hebrón Hospital, Barcelona) and the United Kingdom (Oxford University Hospitals NHS Foundation Trust, Oxford). IgG4-RD was diagnosed according to the “Consensus statement on the pathology of IgG4-RD” and to the “Comprehensive diagnostic criteria for IgG4-RD” when tissue sample was not available or uninformative [1]. Patients were also classified according to the 2019 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria and IgG4-RD phenotypes were clustered as previously described [2]. A diagnosis of COVID-19 was deemed “confirmed” (cCOVID) in case of a positive reverse transcriptase-polymerase chain reaction test for SARS-CoV-2 and “presumed” (pCOVID) in the absence of a positive molecular test but in the presence of highly suggestive clinical and/or radiological features. A comprehensive set of demographic and clinical variables was built up by consensus among IgG4-RD experts from each centre. Demographics included age, sex, ethnicity, country of residence, and family members affected by COVID-19. Clinical features included: duration of IgG4-RD; past and ongoing treatments for IgG4-RD with specific focus on corticosteroid at the time of COVID-19 and on rituximab use; comorbidities; and compliance with annual influenza vaccination. COVID-19 outcomes included: hospitalisation; access to intensive care unit (ICU); and death. A questionnaire based on this set of variables (**reported below in this section**) was developed and administrated to IgG4-RD patients by phone call between January 1st 2021 and January 15th 2021 to capture COVID-19 related events occurred between February 2020 and December 2020. Information was integrated with clinical notes. Informed consent was obtained from each participant in the framework of the following observational studies approved by local ethics committees: Pan-immuno (IRCCS San Raffaele Hospital, registry number 22/INT/2018); NRES Committee Oxford (10/H0604/51 UKCRN 10776); Vall d’Hebrón General Hospital, registry

number PR(AG) 19/2014; PADS21-228 health data access portal (PADS) of the Assistance Publique Hôpitaux de Marseille (AP-HM).

Statistical analysis. Categorical variables defining subgroups of IgG4-RD and/or COVID-19 were compared among groups by using the chi-squared test with Fisher's exact correction. Continuous variables were tested for normality by the Shapiro-Wilk's test and their trends compared among two or more groups by using the Mann-Whitney's test and the Kruskal-Wallis' test respectively in case of non-normal distribution. Student's t-test and ANOVA with Bonferroni's correction were used for the same purpose in case of normal distribution. Continuous variables are expressed as median (interquartile range, IQR) unless otherwise specified. Cox regression analysis was used to analyse the distribution of time-dependent outcomes among groups. IBM SPSS® and Microsoft Excel® 2019 were used to perform the analyses and generate graphs. All authors had full access to all the data in the study and accept responsibility to submit for publication.

Questionnaire for the impact of COVID-19 in patients with IgG4-RD

* indicates mandatory questions | ☐ indicates that only one option was allowed | ☐ indicates that multiple items could be selected | § indicates that the question was shown only to those who gave a positive response to question 4 | & indicates that the question was shown only to those who gave a positive response to question 11 | % indicates that the question was shown only to those who gave a positive response to question C | # indicates that the question was shown only to those who gave a positive response to question G

Question to the patient

*1. You are:

- ☐ A woman
- ☐ A man

*2. How old are you?

___ Years old

*3. How long have you been aware to have IgG4-related disease (IgG4-RD)?

- ☐ Less than 1 year
- ☐ 1 to 3 years
- ☐ More than 3 years

*4. Since the beginning (January 2020) of COVID-19 outbreak to date, have you reduced or discontinued any other medication for IgG4-RD you were taking before?

- ☐ No, I have been taking them regularly
- ☐ Yes, I have reduced the dosage of one or more drugs
- ☐ Yes, I have discontinued one or more drugs
- ☐ Not applicable, I don't need any medication at the moment

*§5. If you have reduced or discontinued your medication, the reason was

- ☐ Physician's indication
- ☐ Mobility issues or drug shortages
- ☐ Personal choice

*§6. Do you think that this change in your therapy has been affected by current COVID-19 epidemic?

- Yes
- No

*7. Starting from the beginning of January 2020, have you experienced any of the following symptoms (for any reason)?

- ☐ Fever
- ☐ Dry cough, without mucus
- ☐ Wet cough with mucus
- ☐ Shortness of breath
- ☐ Muscle pain
- ☐ “a cold”, runny nose
- ☐ Sore throat
- ☐ Impaired/altered smell (feeling less or not feeling at all any smell)
- ☐ Impaired/altered taste
- ☐ Conjunctivitis, red, burning eyes
- ☐ Diarrhoea
- ☐ Nausea/lack of appetite
- ☐ None of the previous items

*8. Starting from the beginning of January 2020, has anyone among your family/cohabitants experienced any of the following symptoms (for any reason)?

- ☐ Fever
- ☐ Dry cough, without mucus
- ☐ Wet cough with mucus
- ☐ Shortness of breath
- ☐ Muscle pain
- ☐ “a cold”, runny nose
- ☐ Sore throat
- ☐ Impaired/altered smell (feeling less or not feeling at all any smell)
- ☐ Impaired/altered taste
- ☐ Conjunctivitis, red, burning eyes
- ☐ Diarrhoea

- ☐ Nausea/lack of appetite
- ☐ None of the previous items
- ☐ Not applicable

*9. Did you receive any or more than one tests (“swab”) for COVID-19?

- ☐ Yes, and at least one was positive
- ☐ Yes, they were all negative and COVID-19 was ruled out
- ☐ Yes, they were all negative, but I was still diagnosed with COVID-19 based on symptoms or other tests
- ☐ No, but I was still diagnosed with COVID-19 based on symptoms or other tests
- ☐ No and I was not diagnosed with COVID-19

*10. Did any of your family members/cohabitants receive one or more tests (“swab”) for COVID-19?

- ☐ Yes, and at least one of them had at least one positive “swab”
- ☐ Yes, and none had a positive “swab” or a diagnosis of COVID-19
- ☐ Yes, all with negative results, but at least one of my family members/cohabitants was still diagnosed with COVID-19 based on symptoms or other tests
- ☐ No, but at some of my family members/cohabitants was still diagnosed with COVID-19 based on symptoms or other tests
- ☐ No and none of them was diagnosed with COVID-19

*11. Since January 2020 have you been admitted to a Hospital?

- ☐ Yes, for coronavirus-related symptoms
- ☐ Yes, for other reasons
- ☐ No

&12. Were you diagnosed with COVID-19 during hospitalization?

- ☐ Yes
- ☐ No

*13. Have you had contacts with people who were definitely positive to the coronavirus test?

- ☐ Yes

- ☐ No

*14. Were you tested for COVID-19 antibody?

- ☐ Yes, no antibodies detected
- ☐ Yes, I have the antibodies
- ☐ No, I did not perform the test

*15. Have you received a flu shot between 2019 and 2020?

- ☐ Yes
- ☐ No

Question to the treating physician

*A. Which is the ethnicity of the patients:

- ☐ Asian
- ☐ Caucasian
- ☐ Indian
- ☐ Arab
- ☐ Hispanic
- ☐ African
- ☐ Other

*B. State the organ involved during the course of IgG4-RD:

- ☐ The pancreas
- ☐ The biliary ducts (gall bladder, choledocus)
- ☐ Salivary glands
- ☐ Lacrimal glands
- ☐ The orbit
- ☐ The aorta or retroperitoneum
- ☐ The lungs
- ☐ The meninges

- ☐ The kidneys
- ☐ The prostate
- ☐ The skin
- ☐ The hypophysis
- ☐ Nose and/or mouth
- ☐ The lymph nodes ('glands' located in the neck, axilla and/or groin)
- ☐ None of the previous items
- ☐ I don't know / I don't remember
- ☐ other _____

*C. Did the patient experience any disease relapses since January 2020?

- ☐ Yes
- ☐ No

%D. Was increased the dose of therapy and/or added an immunosuppressant drug?

- ☐ Si
- ☐ No

*E. How would you score patient disease activity /aggressiveness on a scale from 1 (complete wellbeing) to 10 (worst imaginable condition) at the moment?

- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6
- ☐ 7
- ☐ 8
- ☐ 9
- ☐ 10

F. Does the patient have one or more of the following diseases in his medical history?

- ☐ Arterial hypertension

- ☐ Stroke or myocardial infarction
- ☐ Diabetes
- ☐ COPD (chronic obstructive pulmonary disease/chronic bronchitis)
- ☐ Asthma

*G. Is he currently taking prednisone?

- ☐ No
- ☐ Yes

#H. At which dosage?

___ mg

*I. Which of these therapies has he been taking for IgG4-RD?

- ☐ Azathioprine, ongoing
- ☐ Azathioprine, stopped
- ☐ Methotrexate (subcutaneous injection), ongoing
- ☐ Methotrexate (subcutaneous injection), stopped
- ☐ Rituximab (intravenous injection), ongoing
- ☐ Rituximab (intravenous injection), stopped
- ☐ Mycophenolate, ongoing
- ☐ Mycophenolate, stopped
- ☐ Cyclophosphamide, ongoing
- ☐ Cyclophosphamide, stopped
- ☐ Other
- ☐ None

*J. State the ACR/EULAR Classification criteria for this patient.

Supplementary References

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Supplementary Table S1. Epidemiological, clinical, and treatment features of IgG4-RD patients during COVID-19 pandemic in 2020.

Item	Value
Females: n (%) Males n (%)	87 (29) 218 (71)
Number (%) of patients by Country of residence	
France	31 (10)
Italy	132 (43)
Spain	29 (10)
United Kingdom	113 (37)
Age: median (IQR)	64 (54-74)
Comorbidities: n(%)	
Diabetes	81 (27)
Chronic bronchitis	37 (12)
Respiratory allergy	53 (17)
Cardiovascular disorders	67 (22)
Hypertension	119 (39)
Patients having received a flu jab: n(%)	153 (51)
IgG4-RD Phenotype [13], n (%)	
Type I (pancreato-biliary)	119 (39)
Type II (retroperitoneal fibrosis/aortitis)	49 (16)
Type III (head and neck)	57 (19)
Type IV (Mikulicz's disease and systemic)	79 (26)
Organ involvement, n (%)	
Pancreas	143 (47)
Biliary	103 (34)
Aorta	46 (15)
Retroperitoneum	52 (17)
Salivary	71 (23)
Lacrimal	29 (10)
Lungs	50 (16)
Kidneys	39 (13)
Orbits	24 (8)
Meninges	12 (4)
Lymph-nodes	43 (14)
Serosal layers and mesenterium	10 (3)
Mesenterium	7 (2)
Pleura and pericardium	3 (1)
Skin	6 (2)
Thyroid	3 (1)
Prostate	6 (2)
Hypophysis	3 (1)
Upper airways and midline	8 (3)
Paravertebral	2 (1)
Jaw	2 (1)
Arterial vessels	2 (1)
Other	5 (2)
Gums	1 (<1)
Conjunctiva	1 (<1)
Liver	1 (<1)
Bladder	1 (<1)
Testis	1 (<1)
Treatments	
Prednisone or equivalents, n (%)	156 (51)
DMARDs, n (%)	89 (29)
Azathioprine: n (%)	35 (11)
Methotrexate: n (%)	28 (9)
Mycophenolate mofetil: n (%)	22 (8)
Cyclophosphamide: n (%)	4 (1)
Rituximab	89 (29)

