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Letter to the Editor (Other)

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

Rheumatology key message

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

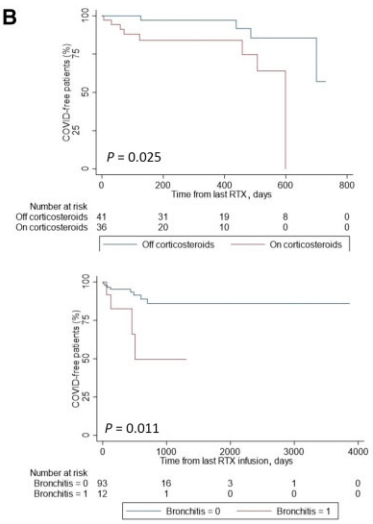
Dear Editor, Patients affected by inflammatory rheumatic disorders are at increased risk of Coronavirus Disease-19 (COVID-19)-related adverse outcomes due to concomitant immunosuppressive medication and comorbidities [1, 2]. IgG4-related disease (IgG4-RD) is an increasingly recognized systemic fibro-inflammatory 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 UK. Patients were interrogated by phone call between December 2020 and February 2021 and asked to answer an *ad hoc* questionnaire built up by consensus among IgG4-RD experts from each centre to capture COVID-19-related events that 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 transcription 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, available at *Rheumatology* online). 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 DMARDs, or

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

A

	Patient 1	Patient 2	Patient 3	Patient 4
Sex	M	M	M	M
Age	84	92	88	50
Disease duration	>3 years	>3 years	>3 years	>3 years
ACR/EULAR score	50	50	27	29
Comorbidities	Type II DM, COPD	COPD, CAD, AH	CAD, AH	CAD, AH
IgG4-RD phenotype [13]	Phenoype I	Phenoype II	Phenoype II	Phenoype I
Ongoing treatments				
Prednisone (mg)	5	5	0	0
DMARDs	–	–	–	–
DMARDs history	Rituximab 17 months before	–	–	–
COVID-19 symptoms				
Fever	–	–	+	+
Dry cough	–	–	+	+
Wet cough	–	+	–	–
Dyspnoea	+	+	+	+
Myalgia	+	–	–	–
Nausea	–	+	+	–
Rhinorrhoea	–	–	–	–
Sore throat	–	–	–	–
Hypo/anosmia	–	–	–	–
Hypo/ageusia	–	–	–	–
Conjunctivitis	–	–	–	–
Diarrhoea	–	–	–	–
Other	–	Thirst	–	–
Causes of death	MOF secondary to COVID-19	MOF secondary to COVID-19	MOF secondary to COVID-19	MOF secondary to COVID-19 and septic endocarditis

B



(**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 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 2 years were considered. AH: arterial hypertension; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; MOF: multiorgan failure.

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were infused with rituximab during the period of observation (Supplementary Table S1, available at *Rheumatology* online).

Thirty-two out of 305 patients (10%) (23 cCOVID and nine pCOVID) had COVID-19 between February and December 2020; 29/32 patients with COVID-19 (91%) had symptomatic disease, with fever (69%), dry cough (63%) and dyspnoea (51%) being the most frequently reported manifestations. Eleven out of 32 patients with COVID-19 (34%) were hospitalized; two (6%) required admission to an intensive care unit and four (13%) died. All deceased patients were men with a history of IgG4-RD >3 years and multiple comorbidities (Fig. 1A). Patients treated with glucocorticoids and rituximab within the previous 24 months had an increased risk of COVID-19 compared with those treated with rituximab alone (hazard ratio [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; $P = 0.011$; $n = 105$) (Fig. 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.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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