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 DMARDs + corticosteroids. A total of 18 patients (6%) were on immunosuppressive therapy at the time of onset of COVID-19. 30 patients were treated with rituximab (RTX) within 2 years of diagnosis. The majority of patients had anti-CCP antibodies (42%), IgG4 above 100 mg/l (40%) or biopsy proven IgG4-RD (94%). 14 patients (4.6%) died due to COVID-19 and 27 (8.9%) due to other causes. COVID-19 was associated with increased mortality in patients treated with RTX (p = 0.025) (A). The 1-year survival rate was significantly lower in patients with chronic bronchitis (p = 0.011) (B). The Kaplan–Meier curve was calculated using the log-rank test. COVID-19 was diagnosed in 150 patients (49%), 111 patients (37%) were not tested, and 54 (18%) were awaiting test results. The median time from the onset of RTX to COVID-19 diagnosis was 20 weeks (range 0–163). A total of 214 patients were hospitalized, of whom 165 (77%) developed pneumonia, 110 (52%) had multiorgan failure, 90 (42%) suffered from diabetes mellitus, 120 (56%) had coronary artery disease and 80 (38%) had chronic obstructive pulmonary disease. COVID-19 was more frequent in patients receiving RTX within 2 years of diagnosis (41%) compared to those treated more than 2 years (24%). The presence of a positive RTX reaction was associated with increased risk of COVID-19 (p = 0.035). Concomitant treatment with rituximab and corticosteroids is associated with an increased risk of COVID-19.

**Rheumatology key message**

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

**Fig. 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 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.
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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