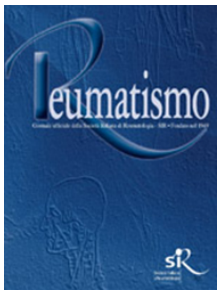

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Adherence to vaccination against SARS-CoV-2 and vaccine safety in patients with immunoglobulin G4-related disease

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Key words: IgG4 related disease, SARS-CoV-2, COVID-19, vaccination.

Contributions: LM, prepared the database, performed statistics and wrote the article; FG, helped write the article, followed IgG4-RD patients and gathered data; AG, SC, BL, followed IgG4-RD patients and gathered data; ES, helped with the database; FRS, ST, gathered the data regarding controls, RP, organized the whole project; FC, revised the manuscript.

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Summary

Objective. To assess the adherence to the vaccination campaign against SARS-CoV-2 in patients with immunoglobulin-G4-related disease (IgG4-RD) and to evaluate the development of local and systemic adverse events (AEs) following vaccination. Additionally, to investigate the rate and outcome of SARS-CoV-2 infection in IgG4-RD patients.

Methods. Patients with IgG4-RD in follow-up before the onset of the SARS-CoV-2 pandemic were contacted by telephone and asked to answer an *ad hoc* questionnaire regarding their vaccination status against SARS-CoV-2 and related AEs following vaccination. The occurrence and the outcome of SARS-CoV-2 infection were also recorded. The same questionnaire was proposed to healthy controls (HC).

Results. 20 patients and 40 HC were enrolled. In the patient's cohort, 90% were vaccinated with at least one dose; among them, 9 reported AEs: 44.4% systemic and 22.2% local. Within the HC group, 100% were vaccinated with at least one dose. 13 out of 40 HC had systemic AEs (50%), and 27 (67.5%) reported local AEs. Neither in IgG4-RD nor in HC, serious adverse reactions were observed. Among the patient's cohort, 60% contracted SARS-CoV-2 infection, and 41.67% were on immunosuppressants at the time of the infection. One patient presented with severe COVID-19. No disease flares following vaccination or infection were reported.

Conclusions. Results from our study indicate a good adherence to the vaccination campaign against SARS-CoV-2 in patients with IgG4-RD and support a relatively good safety profile of this vaccine. Compared to controls, patients with IgG4-RD reported slightly more systemic AEs and fewer local AEs. A similar rate of COVID-19 development was observed between IgG4-RD patients and HC.

Introduction

Immunoglobulin-G4-related disease (IgG4-RD) is a rare, immune-mediated, fibro-inflammatory disorder possibly affecting any organ or tissue mostly including the pancreas, the hepatobiliary system, the salivary and lacrimal glands, the kidneys, and the retroperitoneum. Treatment generally includes glucocorticoids, conventional steroid-sparing immunosuppressive agents, or B cell-targeted therapies, such as rituximab (1).

Similarly to other rare rheumatic and musculoskeletal diseases (RMDs) (2), patients with IgG4-RD may be at higher risk of developing SARS-CoV-2 infection with a poor outcome due to the underlying disease, the associated comorbidities, and the use of immunosuppressive treatments. The COVID-19 pandemic caused by SARS-CoV-2 has had an unprecedented impact on global health services. Different vaccines have been developed to limit the spread of the virus and prevent its most serious complications. Information on the rate and outcome of SARS-Cov-2 infection in patients with IgG4-RD is limited (3-5), and even more scarce are the data regarding the adherence and safety of SARS-CoV-2 vaccines.

In this study, we aimed to assess retrospectively the adherence to the vaccination campaign against SARS-CoV-2 in patients with IgG4-RD from a single-center cohort and to evaluate the development of local and systemic adverse events (AEs) following vaccination. The incidence and severity of SARS-CoV-2 infection in this population were also estimated.

Materials and Methods

Patients affected by IgG4-RD, classified according to the revised comprehensive diagnostic criteria by Umehara *et al*. (6), in follow-up for at least one year before the SARS-CoV-2 pandemic at the Rheumatology Unit of the University Hospital Policlinico Umberto I of Rome, were retrospectively enrolled. Patients were contacted by telephone to capture anti-SARS-CoV-2 vaccination-related events and COVID-19 occurrences between March 2020 and January 2023. A dedicated *ad hoc* questionnaire (*Supplementary Material*) was used to assess the patient's vaccination status, including the type of vaccine, the number of received doses, and the AEs. The same questionnaire was proposed to healthy controls (HC) by telephone or email. AEs were divided into three categories: no reactions, local reactions (pain, swelling, or skin reaction around the injection site), and systemic reactions such as arthromyalgia, headache, fever, asthenia, lymphadenopathy, malaise, or others. Disease flare, defined as the new onset of signs and symptoms related to IgG4-RD occurring within 2 months after the last dose of vaccine and requiring treatment modifications, was also investigated. The occurrence of SARS-CoV-2 infection, before or after vaccination, was evaluated along with the infection's duration and severity, the type of related symptoms (such as fever, asthenia, ageusia and anosmia, headache, cough, dyspnea, bronchitis, pneumonitis, and respiratory failure), the outcome, and the ongoing therapy. Only confirmed SARS-CoV-2 infections with a positive reverse transcription polymerase chain reaction or rapid antigen-based assay were considered. The main demographic, clinical, and therapeutic features were collected on a dedicated electronic database. The study (approved by Policlinico Umberto I Ethical Committee - protocol 0501/2021) complied with the Declaration of Helsinki. Statistical analysis was performed by RStudio (v. 2023.03.2-454.pro2) using Fisher's exact test.

Results

A total of 24 patients were contacted by phone; 4 did not respond or declined to participate. 20 IgG4-RD patients (12 F, 8 M), with a median age of 53.7 (±11.5) years, were enrolled, 9 of them (45%) had a definite diagnosis of IgG4-RD while 11 (55%) had a probable/possible diagnosis. The patients' features are detailed in Table 1. At the time of the interview, 18 patients (90%) reported vaccination against SARS-CoV-2, and only 2 patients had refused vaccination. 15 out of 18 patients (83.3%) were vaccinated with the Comirnaty vaccine, while the remaining patients were vaccinated with Spikevax, Janssen, and Vaxzervia; 14/18 (77.8%) received at least one booster dose. 11 out of 18 (61,1%) patients presented with AEs following vaccination. Most patients [55.6% of cases (10/18)]

experienced systemic AEs (arthromyalgia, fever, headache, asthenia, lymphadenopathy, malaise) with an average duration of 3.6 days (±1.99). Local AEs were reported in 22.2% of cases (4/18), with an average duration of 2.3 days (±0.5). Three patients presented with both systemic and local AEs. Table 1 shows the current therapy at the time of vaccination. Vaccination was administered only in a remission phase of the disease and, after at least 5 months from the last rituximab infusion. Table 2 summarizes the AEs according to the type and dose of vaccination. No systemic anaphylaxis and no severe AEs were reported. There were no cases of disease flares following vaccination or infection.
40 sex and age-matched HC (28 F, 12 M) were enrolled, all of them were vaccinated with at least one dose, and 32/40 (80%) with at least a booster dose. In 70% (28/40) of HC, the Comirnaty vaccine was administered, while Vaxzervia, Spikevax, and Janssen vaccines were administered in the 15% (6/40), 7.5% (3/40) and 5% (2/40) respectively. In the HC group, twenty out of 40 (50%) patients presented with systemic AEs following vaccination [average duration of 2.9 days (±2.03)], while 27 (67.5%) reported local AEs in the site of injection [average duration of 1.7 days (±1.5)]. 14 HC presented with both systemic and local AEs. In the HC group, no serious reactions were reported.
Local AEs were more prevalent in the HC group compared to IgG4-RD ($p=0.0008$). Between patients and HC, no significant differences in systemic AE occurrence were detected ($p=1.0$) except for lymphadenopathies more frequently reported in IgG4-RD patients ($p=0.048$) as shown in Figure 1.
Among the IgG4 cohort, 12/20 patients (60%) reported a confirmed diagnosis of COVID-19 between January 2020 and February 2023; before diagnosis, 9/12 (75%) received at least one dose of vaccine against SARS-CoV-2. At the time of infection, 5/12 (41.67%) patients were receiving immunosuppressive treatments including glucocorticoids (3/5) and rituximab (2/5). One patient developed COVID-19 soon after rituximab administration, while the other contracted the infection 3 months later. The remaining cases were off treatment due to a long-lasting state of remission. 10/12 patients (83.3%) reported fever, 8/12 (66.67%) had respiratory symptoms (cough and/or pharyngitis), and 2/12 (16.6%) had pneumonia. One of them, vaccinated with two doses of the mRNA vaccine and previously treated with rituximab, developed a serious form of COVID-19 requiring hospitalization. The same patient presented with a recurrence of COVID-19 after the third dose of vaccine, this time with a very mild course.
Monoclonal antibodies were administered in 3/12 (25%) patients, while oxygen therapy was necessary for a further patient with pneumonia treated at home. Excluding the hospitalized patient, the COVID-19 mean duration, defined as the time between disease onset and SARS-CoV-2 negative test detection, was 9.93 days (±5.31).
30 HC reported a confirmed diagnosis of COVID-19; among them, 23/40 (57.5%) had fever, 17/40 (42.5%) had respiratory symptoms (cough and/or pharyngitis), and none had pneumonia.
No significant difference in the infection rate between patients and controls was observed ($p>0.5$).

Discussion and Conclusions

Since December 2020, different vaccines against the SARS-CoV-2 virus became available in the European Union and this tool has proved to be the most powerful weapon to fight the COVID-19 pandemic. However, the possibility of reaching herd immunity and curtailing the virus could be highly compromised by vaccine hesitancy. The European Alliance of Associations for Rheumatology has encouraged patients with RMDs to be vaccinated against COVID-19 (7); however, in Italy, the acceptance to receive vaccination against SARS-CoV-2 infection in patients with RMDs turned out to be lower than HC (55% *versus* 82.3%) (8). In our study, we report a good willingness to vaccination among Italian patients with IgG4-RD, with only 10% refusal.
The efficacy of SARS-CoV-2 vaccines has been thoroughly demonstrated both in the general population and in patients with RMD with parallel evidence of a good safety profile even in most fragile patients with rare rheumatic disorders (9-13). To our knowledge, no prior studies have specifically assessed the safety of anti-SARS-CoV-2 vaccines in patients with IgG4-RD. In our study, we demonstrate a prevalence of systemic AEs in the IgG4-RD cohort comparable to HC with a similar safety profile to other chronic immune-mediated disorders (9). For the local AEs, patients with IgG4-

RD seem to have fewer events compared to HC. However, since patients with RMDs were the first to be vaccinated, this finding could be biased by the different types of vaccine (RMD patients mainly received Comirnaty or Spikevax vaccine). Furthermore, no serious, life-threatening AEs were observed, being both systemic and local AEs generally mild and short-lasting.

Although IgG4-RD reactivation following vaccination against SARS-CoV-2 has been described (14), in line with previous larger studies, we failed to report any flares following vaccination (4, 5). Therefore, considering the risks and benefits, vaccination is highly recommended also in the IgG4-RD population as well as in patients with other RMDs (7).

Despite good adherence to vaccination practice, Italian patients with IgG4-RD presented with a rate of SARS-CoV-2 infection similar to the HC group. This observation is apparently in contrast with previous findings demonstrating lower rates of infection in both Europe and China, 10% and 2.2%, respectively (3-5). However, these studies date back to the first phase of the pandemic when the chance of detecting the infection was lower. Considering the same pre-vaccination period of the COVID-19 pandemic in 2020, a similar rate of COVID-19 infection (1.6%), with no mortality, was reported in a multicentric study involving patients with pancreatobiliary IgG4-RD. However, the infection rate rose to 20% after the Omicron outbreak despite vaccine availability (4). In terms of mortality, our results are consistent with previous studies, suggesting that IgG4-RD itself is not a negative prognostic factor for COVID-19 severity.

The SARS-CoV-2 infection rate and disease outcomes have changed over time in different geographic areas, because of variable social distance rules, or the availability of new, more effective therapeutic approaches. Moreover, over time, new COVID-19 variants with variable virulence and infectivity have arisen. In the present study, SARS-CoV-2 infection was assessed throughout the entire pandemic period up until 2023.

At the onset of the pandemic, clinicians were concerned about immunosuppressive therapy in patients with RMDs. In our cohort, one rituximab-treated patient required hospitalization, and another one needed home oxygen treatment. This evidence is in line with the previous observations suggesting how the use of B cell depletion agents is predictive of a more severe COVID-19 and its related deaths (15, 16).

This study has some limitations, such as its monocentric nature and the limited number of enrolled patients. However, since IgG4-RD is a very rare condition and the literature on the topic is quite poor, even small studies are worth attention. Due to the retrospective nature of this survey, disease activity at the time of vaccination couldn’t be calculated; however, as recommended for RMD patients (17), vaccine administration has been performed only in patients with an inactive phase of the disease as assessed in our dedicated outpatient clinic where IgG4-RD patients are strictly monitored. To avoid recall bias, more than one call at different times was made proposing the same detailed questionnaire and the answers have been considered reliable only if they were identical.

In conclusion, our data demonstrate a very high adherence to the vaccination campaign against SARS-CoV-2 infection and support a relatively good safety profile of anti-SARS-CoV-2 vaccines in patients with IgG4-RD.

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Table 1. Immunoglobulin-G4-related disease (IgG4-RD) patients' characteristics. Diagnosis of IgG4-RD is reported as 'definite', 'probable' or 'possible' according to the 'Comprehensive diagnostic criteria for IgG4-RD' (6). PDN: prednisone. csDMARDs: conventional DMARDs

Characteristics	
Total, n	20
Age, y, median (±SD)	53.7 (±11.5)
Gender, male, n (%)	8 (40%)
Age at diagnosis, y, median (±SD)	53.7 (±10.9)
Disease duration, y, median (±SD)	4.3 (±3.9)
Definite diagnosis, n (%)	9 (45%)
Probable diagnosis, n (%)	4 (20%)
Possible diagnosis, n (%)	7 (35%)
Organ involvement	
Pancreas	1 (5%)
Hepatobiliary	0 (0%)
Lacrimal and salivary glands	6 (30%)
Pulmonary	2 (10%)
Retroperitoneum	2 (10%)
Orbit	2 (10%)
Aorta	3 (15%)
Nasal septum and sinuses	2 (10%)
Lymph nodes	3 (15%)
Other	5 (25%)
Treatment at time of vaccination	
PDN<7.5 mg/die, n (%)	2 (10%)
PDN>7.5 mg/die, n (%)	7 (35%)
Rituximab, n (%)	2 (10%)
csDMARDs, n (%)	1 (5%)
No treatment	9 (45%)
Treatment at time of SARS-CoV2 infection	
PDN<7.5 mg/die, n (%)	1 (5%)
PDN>7.5 mg/die, n (%)	2 (10%)
Rituximab, n (%)	2 (10%)
No treatment	15 (75%)
Previous Treatment	
PDN<7.5 mg/die, n (%)	3 (15%)
PDN>7.5 mg/die, n (%)	6 (30%)
Rituximab, n (%)	2 (10%)
csDMARDs, n (%)	3 (15%)

SD, standard deviation; PDN, prednisone; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs.

Table 2. Adverse events in the Italian immunoglobulin-G4-related disease cohort and in healthy controls.

n. vaccinated patients	**18**				
AEs	**All doses**	**I dose**	**II dose**	**other doses**	**p value (Fisher Test) IgG4-RD versus HC**
Total patients with AEs	11/18 (61.1%)	8/18 (44.4%)	5/15 (33.3%)	6/13 (46.2%)	
Local	4/18 (22.2%)	4/18 (22.2%)	4/15 (26.7%)	2/13 (15.4%)	0.0008
Systemic	10/18 (55.6%)	8/18 (44.4%)	5/15 (33.3%)	4/13 (30.8%)	1.0
Arthromyalgia	10/18 (55.6%)	6/8 (33.4%)	5/15 (33.3%)	3/13 (23.1%)	0.280
Fever	9/18 (50%)	4/8 (22.2%)	4/15 (26.7%)	3/13 (23.1%)	0.246
Headache	4/18 (22.2%)	5/8 (27.8%)	4/15 (26.7%)	3/13 (23.1%)	1.0
Lymphadenopathy	6/18 (33.3%)	7/8 (38.9%)	2/15 (13.3%)	2/13 (15.4%)	0.048
Asthenia	7/18 (38.9%)	4/8 (22.2%)	2/15 (13.3%)	1/13 (7.7%)	0.083
Malaise	5/18 (27.8%)	4/8 (22.2%)	2/15 (13.3%)	1/13 (7.7%)	0.277
n. vaccinated HC	**40**				
AEs	**All doses**	**I dose**	**II dose**	**other doses**	
Total HC with AEs	33/40 (82.5%)	29/40 (44.4%)	25/40 (33.3%)	15/32 (46.2%)	
Local	27/40 (67.5%)	26/40 (65%)	24/40 (60%)	15/32 (46.9%)	
Systemic	20/40 (50%)	13/40 (44.4%)	13/40 (32.5%)	7/32 (21.9%)	
Arthromyalgia	14/40 (25%)	10/40 (25%)	7/40 (17.5%)	2/32 (6.2%)	
Fever	12/40 (25%)	8/40 (20%)	6/40 (15%)	4/32 (12.5%)	
Headache	8/40 (25%)	6/40 (15%)	2/40 (5%)	2/32 (6.2%)	
Lymphadenopathy	4/40 (25%)	3/40 (7.5%)	1/40 (2.5%)	1/32 (3.1%)	
Asthenia	4/40 (25%)	3/40 (7.5%)	3/40 (7.5%)	1/32 (3.1%)	
Malaise	8/40 (25%)	5/40 (12.5%)	2/40 (5%)	2/32 (6.2%)	

AEs, adverse events; HC, healthy controls; IgG4-RD, immunoglobulin-G4-related disease

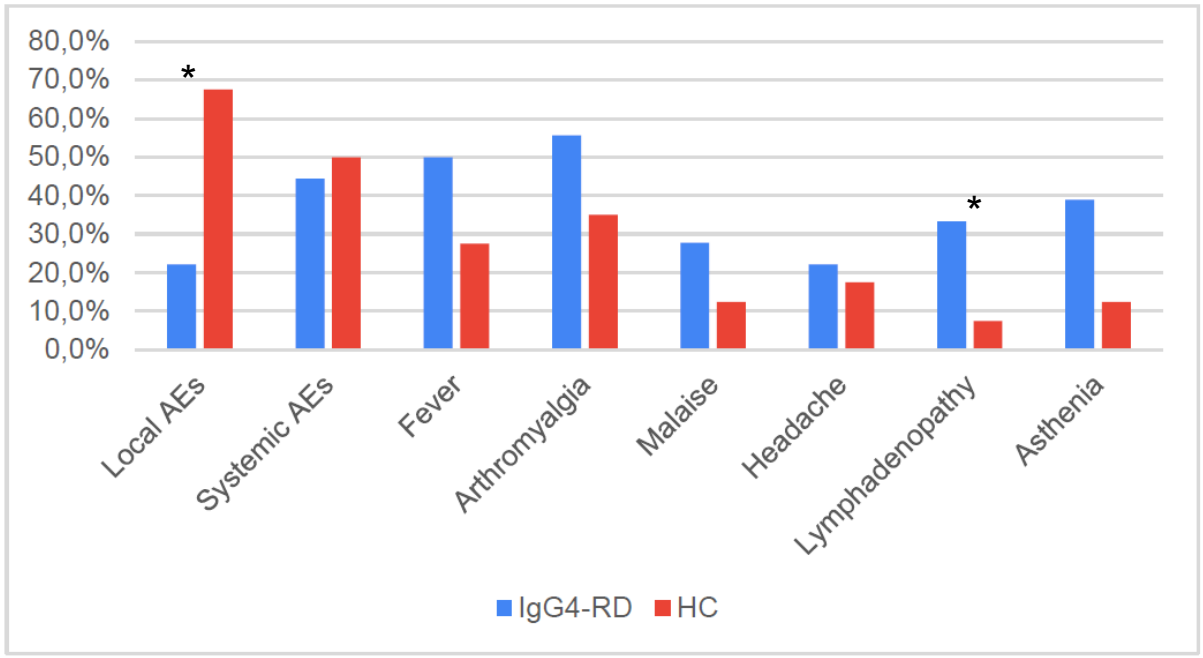

Figure 1. Adverse events in the Italian immunoglobulin-G4-related disease cohort compared to the Healthy Control group expressed in percentages. *p<0.05.

Online supplementary material:
Questionnaire for immunoglobulin-G4-related disease.