



Letters

IgG4-related disease and allergen-specific immunotherapy

IgG4-related disease (IgG4-RD) is a fibroinflammatory disorder named after the prominent IgG4⁺ plasma cell infiltrate in affected organs.^{1–4} The cause of IgG4-RD is unknown, and the pathogenicity of IgG4 antibodies remains a matter of a live debate.^{1–5} In general, IgG4 antibodies are believed to dampen chronic inflammation because of their anti-inflammatory properties.¹ However, injection of patient-derived IgG4 in mice induces IgG4-RD-like lesions, suggesting that IgG4 antibodies can cause tissue damage.¹ Understanding the drivers of IgG4 production in patients with IgG4-RD is key to decipher the pathophysiology of this condition.

Allergen-specific immunotherapy (AIT) is an immune tolerance-inducing treatment that currently represents the only disease-modifying therapy for individuals with allergy.^{6,7} By suppressing T_H2 immunity, AIT engages interleukin 10 and transforming growth factor β cytokine pathways, induces regulatory T and B cells, and increases serum concentration of allergen-specific IgG4 up to 100-fold.^{6,7} Because these mechanisms have been largely implicated in IgG4-RD pathogenesis, we performed an epidemiologic study to assess whether AIT might represent a trigger for IgG4-RD at least in a proportion of individuals.¹

A total of 116 Italian patients with biopsy-proven IgG4-RD were included and signed written informed consent forms for the described investigations. The latest Allergic Rhinitis and Its Impact on Asthma, Global Initiative for Asthma, and European Academy of Allergy and Clinical Immunology consensus statements were used to classify patients as atopic or nonatopic, to grade the severity of allergic rhinitis and asthma, and to identify individuals who fulfilled international indications for AIT.^{5,6} A 20-question allergist-developed survey was administered to all patients at their baseline visit. Total serum IgG4 and IgE levels, circulating plasmablast counts, eosinophil counts, and the IgG4-RD responder index (RI) were measured at the time of diagnosis before immunosuppressive therapy. In particular, the IgG4-RD RI is a tool designed for clinical trials to define IgG4-RD activity based on organ involvement and on the need for urgent treatment.⁸ Results were analyzed by the *t* test, χ^2 test, or Fisher exact test, as appropriate. The data on eligibility for AIT and frequency of AIT administration in patients with IgG4-RD were compared with available data from the Italian population.^{9,10}

Clinical and serologic characteristics and allergic manifestations of the patient cohorts are summarized in Table 1. An atopic background was identified in 29 patients (25%). Atopic and nonatopic patients with IgG4-RD shared similar epidemiologic, clinical, and serologic features. Eosinophil counts, circulating plasmablast counts, and serum IgG4 and IgE levels were similar between

groups. The IgG4-RD RI was higher in atopic individuals, likely reflecting a higher, yet not significantly different, number of organs involved and of manifestations that required urgent care. To find clues about a possible association between AIT and IgG4-RD, we calculated the frequency of individuals eligible for AIT and the rate of AIT administration in our cohort of patients with IgG4-RD and compared them with data from the Italian population.^{7,8} Fifteen of 29 patients with atopic IgG4-RD (52%) reported a history of allergic symptoms or sensitization to aeroallergens. Fourteen (93%) reported a history of moderate-to-severe allergic rhinitis and/or not severe allergic asthma, thus being eligible for AIT according to European Academy of Allergy and Clinical Immunology indications.⁶ Six (43%) were treated with sublingual or subcutaneous AIT. Three patients received sublingual AIT with grass pollen extracts (2 patients) and house dust mite extracts (1 patient), and 3 patients received subcutaneous AIT with house dust mites extracts (2 patients) and grass pollen extracts (1 patient). Three patients were diagnosed as having IgG4-RD more than 10 years after AIT completion, and in 3 patients, IgG4-RD developed within the first 2 years of AIT. No difference was found in epidemiologic, clinical, and immunologic features between patients with IgG4-RD eligible for immunotherapy treated or not with AIT (data not shown). Data from multicenter Italian registries indicated that the prevalence of atopic manifestations in Italy is 37% and eligibility for AIT among atopic individuals is 56%.^{9,10} However, less than 2% of eligible individuals in the Italian population actually undergo AIT, a finding that is in line with international surveys, whereby, despite regional differences, AIT is used in less than 10% of eligible patients with allergic rhinitis and asthma.^{6,9,10}

Our work is the first to address the association between IgG4-RD and AIT. Although atopic manifestations do not seem to be increased in IgG4-RD, AIT is apparently used more frequently in patients with IgG4-RD than in the general population. These results, however, do not support a pathogenic link between AIT and IgG4-RD but likely reflect an increased eligibility for AIT possibly because of a higher prevalence of difficult-to-treat allergic manifestations. Moreover, although IgG4-RD developed in half of our patients undergoing AIT while receiving immunotherapy, the remaining received a diagnosis of IgG4-RD more than 10 years after AIT completion, which does not support a clear association between the 2 events. In addition, we were unable to observe any clinical, serologic, or immunologic differences between patients with IgG4-RD eligible for AIT who were treated with AIT and those who were not treated, reinforcing the notion that AIT does not seem to represent a trigger for IgG4-RD. On another note, we observed an increased IgG4-RD RI in atopic individuals compared with nonatopic ones, suggesting a higher disease burden in the former group of patients. This finding has never been reported before and, if confirmed in large international cohorts, would be relevant for optimizing personalized

Drs Della-Torre and Germanò contributed equally to this work.

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Table 1
Clinical and Serologic Characteristics and Allergic Manifestations of the Patient Cohorts^a

Variable	IgG4-RD cohort (N = 116)	Atopic patients (n = 29)	Nonatopic patients (n = 87)	P value
Demographics				
Male:female ratio	84:32	18:11	66:21	.16
Age at diagnosis, mean (SD), y	59.8 (13.9)	57.7 (12.7)	60.5 (14.3)	.35
Age distribution, y				
<20	2 (1.7)	0	2 (2.3)	
20–29	5 (4.3)	1 (3.4)	4 (4.6)	
30–39	3 (2.6)	2 (6.9)	1 (1.1)	
40–49	7 (6.0)	4 (13.8)	3 (3.4)	
50–59	29 (25.0)	8 (27.6)	21 (24.1)	
60–69	40 (34.5)	7 (24.1)	33 (37.9)	
70–79	25 (21.6)	7 (24.1)	18 (20.7)	
80–89	4 (3.4)	0	4 (4.6)	
Allergic history				
Inhalants	15 (12.9)	15 (51.7)		
Foods	3 (2.6)	3 (10.3)		
Drugs	18 (15.5)	18 (62.1)		
Contact allergens	3 (2.6)	3 (10.3)		
Anaphylaxis	3 (2.6)	3 (10.3)		
Allergic manifestations^b				
Mild intermittent rhinitis		2 (6.9)		
Moderate-severe and/or persistent rhinitis ^c		12 (41.4)		
Mild-moderate asthma (aeroallergens) ^c		6 (20.7)		
Mild-moderate asthma (food and drugs)		9 (31.1)		
Severe asthma		0		
Conjunctivitis		10 (34.5)		
Urticaria or angioedema		10 (34.5)		
Dermatitis		6 (20.7)		
Anaphylaxis		3 (10.3)		
Gastrointestinal symptoms		1 (3.5)		
Organ involvement				
No. of organs involved (range, 1–4)	1.9	2.1	1.9	.21
Urgent manifestations	60/116 (51.7)	18/29 (62.0)	42/87 (48.3)	.14
Head and neck (overall)	39 (33.6)	12 (41.4)	27 (31.0)	.36
Orbits, lacrimal glands	17 (14.7)	6 (20.7)	11 (12.6)	.36
Salivary glands	25 (21.6)	8 (27.6)	17 (19.5)	.43
Ear, nose, and throat	11 (9.5)	3 (10.3)	8 (9.2)	>.99
Lymph nodes	26 (22.4)	8 (27.6)	18 (20.7)	.45
Lungs	3 (2.6)	1 (3.4)	2 (2.3)	>.99
Aorta	10 (8.6)	2 (6.9)	8 (9.2)	>.99
Retroperitoneum	16 (13.8)	4 (13.8)	12 (13.8)	>.99
Pancreas	58 (50.0)	17 (58.6)	41 (47.1)	.39
Biliary tract	26 (22.4)	8 (27.6)	18 (20.7)	.45
Kidneys	6 (5.2)	1 (3.4)	5 (5.7)	>.99
IgG4-RD RI, mean (SD)	8.3 (3.2)	9.6 (3.2)	8.0 (3.0)	.01
Blood test results, mean (SD)				
IgG4, mg/dL (range, 0–140)	425 (479)	472 (461)	408 (486)	.53
Plasmablasts, cells/mL (range, 0–600)	3547 (5724)	4965 (4288)	3165 (6115)	.21
Eosinophils, 10 ⁶ cells/L (range, 0–500) ^c	464 (1074)	347 (403)	510 (1246)	.49
IgE, IU/mL (range 0–100)	490 (796)	429 (681)	515 (844)	.62

Abbreviations: IgG4-RD, IgG4-related disease; RI, responder index.

^aData are presented as number (percentage) of patients unless otherwise indicated.^bData are the number of patients with IgG4-RD affected by a specific allergic manifestation and the percentage of the total number of atopic patients with IgG4-RD (n = 29). The sum is not equal to 29 because each patient might have experienced more than 1 allergic manifestation.^cAllergic reactions due to sensitization to aeroallergens eligible for allergen immunotherapy. The sum is not equal to the number of patients eligible for allergen immunotherapy (n = 14) because some patients had both allergic rhinitis and asthma.

diagnostic, follow-up, and therapeutic strategies in atopic patients with IgG4-RD.

The present work includes major strengths and limitations. On the one hand, our study cohort is derived from one of the largest single-center cohorts of patients with IgG4-RD based in a tertiary care unit for allergic and immunologic disorders, an aspect that ensured combined allergic and immunologic evaluation, uniform inclusion criteria, and follow-up. On the other hand, we recognize that reliable data about AIT eligibility and administration are fragmented and biased by local differences, making them difficult to compare with selected patient series. However, most patients in our cohort were referred from other Italian hospitals, thus increasing the generalizability of our findings over and beyond regional differences in

AIT administration. Further studies with larger numbers of patients from international cohorts are warranted to confirm our observations and to clarify the association between atopy, AIT, and IgG4-RD worldwide.

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