Managing IgG4-related disease – the Portuguese rheumatology cohort

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Dear Editor,

IgG4-related disease (IgG4-RD) is an uncommon fibro-inflammatory pseudotumoral entity characterized by slowly progressive systemic manifestations. It affects mainly middle-aged and older men[1], involving various organs like the pancreas, salivary and lacrimal glands, retroperitoneal region, and vessels. Diagnosing IgG4-RD is challenging since it mimics malignancies, vasculitis and granulomatous disorders. The available diagnostic criteria[2] still lack validation, and the 2019 ACR/EULAR criteria[3] purpose classification only. Corticosteroid (CCT) treatment has shown positive outcomes[4], although relapses are common[5]. Therefore, maintenance treatment with immunomodulatory drugs is often necessary.

To characterize the Portuguese population of IgG4-RD patients under Rheumatology care, we conducted a national multicenter observational study focused on patients with a clinical IgG4-RD diagnosis (62.5% met the 2019 ACR/EULAR classification criteria) followed-up in Rheumatology departments. Data collection occurred from 30/03/2022-20/12/2022.

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We included twenty-four patients with a mean current age of 59.95 years (standard deviation [SD]=13.35). The mean age at diagnosis was 56.09 years (SD=14.13), and the mean age at the onset of symptoms was 53.96 years (SD=14.19). Twelve (50%) patients were male. Table 1 depicts this cohort's characteristics. The most common overall manifestations involved salivary glands (37.5%), followed by orbits, lacrimal glands and aorta (25% each), and pancreas (20.8%). We documented single organ disease in six (25%) patients. An intra-ductal pancreato-biliary papillary mucinous neoplasm was documented. None of the patients had a tomographic "sausage pancreas", three (12.5%) patients had lung nodules, one (4.2%) had a bronchovascular pattern, one (4.2%) had a non-specific interstitial pneumonia pattern, and four (16.7%) had groundglass opacities. Histology regarding the most suspect, accessible, and replicable lesion revealed storiform fibrosis in four (16.7%) patients, lymphoplasmacytic infiltrates in twenty (83.3%) patients, and an IgG4/IgG ratio >40% in five (20.8%) patients. Five (20.8%) patients were biopsied after treatment initiation due to a high index of suspicion, and the others prior to this measure. All patients underwent PET scans at disease's peak activity revealing inflammation in ten (41.7%) cases. Blood analysis, during the span of disease, revealed peripheral eosinophilia in five (20.8%) patients; twelve (50%) had elevated erythrocyte sedimentation rate, sixteen (66.7%) had elevated C-reactive protein, sixteen (66.7%) had high levels of IgG4, two (8.3%) had high levels of IgG1 and one (4.2) had high levels of IgE. One death of unknown cause occurred

in a patient of 65 years old. The initial therapy included oral CCT in seventeen (70.8%) cases, with a mean dosage of 21.17mg/day (SD=22.55) (maximum=80mg/day). Six (25%) patients received either CCT pulses, cyclophosphamide, or rituximab; the other were managed with mycophenolate mofetil (MMF) and methotrexate (MTX). Currently, one (4.2%) patient is undergoing CCT pulses due to lung and aortic disease; oral CCT has been slowly tapered, with only one patient fully stopping it; the remainder treatment lies on table 1. Seventeen (70.8%) patients responded well to the initial CCT, thirteen (54.2%) showed decreased IgG4 serum levels, eight (33.3%) normalized their IgG4 levels, and eight (33.3%) relapsed, requiring a medication switch/addition.

The Portuguese cohort showed diverse characteristics without a gender bias. We should, however, be aware that IgG4-RD patients might be scattered throughout a vast number of medical specialties, so these numbers and features might be just a fraction of the sum. Middle-aged and older individuals were predominantly affected, with orbital, vascular and glandular involvement being common, consistent with literature data[6]. The frequency of elevated IgG4 levels and eosinophilia were also concordant with previous studies[7]. Corticosteroid therapy effectively reduced IgG4 levels (with equivalent doses than those described in literature[8]) but had limitations (the recurrence rate is set at 46%[9]), demanding the use of alternative immunomodulators. Treatment choices varied based on the affected organs, with MTX initially having limited effectiveness and MMF demonstrating a favorable response. RTX was moderately utilized as an alternative treatment option, similarly to other studies[10].

Our study has some limitations, inherent to its transversal layout, but chiefly regarding the lack of information on: a) affected organ's activity/function (for instance, glomerular filtration rate or thyroid function); b) follow-up PET scans; c) current versus past organ involvement, with an unique description of the sum of the organic lesions; d) disease progression from single to multiple organ involvement. Nonetheless, it portrays a first picture of IgG4-RD patients receiving supervision from rheumatologists. Further research is necessary to enrich this outline.

Tables and Figures

Table I – Demographics and disease description of the participants.

Demographic data	
Male sex, n/N (%)	12/24 (50.0)
Age at the beginning of symptoms, mean (SD)	53.96 (14.19)
Age at diagnosis, mean (SD)	56.09 (14.13)
Present age, mean (SD)	59.96 (13.05)
Deaths, n/N (%)	1/24 (4.2)
Lifestyle	
Smoking	
Previously, n/N (%)	8/24 (33.3)
Presently, n/N (%)	2/24 (8.3)
Clinical data	
Pancreatic involvement, n/N (%)	5/24 (20.8)
Autoimmune pancreatitis, n/N (%)	1/24 (4.2)
Type 2 diabetes mellitus, n/N (%)	4/24 (16.7)
Lung involvement, n/N (%)	3/24 (12.5)
Retroperitoneal involvement, n/N (%)	4/24 (16.7)
Renal obstruction, n/N (%)	1/24 (4.2)
Venous thrombosis, n/N (%)	1/24 (4.2)
Retroperitoneal fibrosis, n/N (%)	2/24 (8.3)
Renal involvement, n/N (%)	3/24 (12.5)
Tubulointerstitial nephritis, n/N (%)	2/24 (8.3)
Renal tubular acidosis, n/N (%)	1/24 (4.2)
Orbital involvement, n/N (%)	6/24 (25.0)
Dacryoadenitis, n/N (%)	3/24 (12.5)
Dacryocystitis, n/N (%)	1/24 (4.2)
Orbital pseudotumor, n/N (%)	2/24 (8.3)
Biliary ducts involvement, n/N (%)	4/24 (16.7)
Ductal thickening and fibrosis, n/N (%)	3/24 (12.5)
Sclerosing cholangitis, n/N (%)	1/24 (4.2)
Lacrimal glands involvement, n/N (%)	6/24 (25.0)
Bilateral, n/N (%)	4/24 (16.7)
Meninges involvement, n/N (%)	1/24 (4.2)
Aortic involvement, n/N (%)	6/24 (25.0)
Infrarenal, n/N (%)	3/24 (12.5)
Ascending aortitis, n/N (%)	1/24 (4.2)
Iliac arteries, n/N (%)	2/24 (8.3)
Other vascular involvement, n/N (%)	2/24 (8.3)
Brain aneurysm, n/N (%)	1/24 (4.2)
Pulmonary artery encapsulation by pseudotumor, n/N (%)	1/24 (4.2)
Salivary glands involvement, n/N (%)	9/24 (37.5)
Bilateral, n/N (%)	8/24 (33.3)
Thyroid involvement, n/N (%)	2/24 (8.3)
Autoimmune hepatitis, n/N (%)	0/24 (0)
Cosntrictive pericarditis, n/N (%)	0/24 (0)
Sclerosing mastitis, n/N (%)	0/24 (0)

Gastritis, n/N (%)	1/24 (4.2)
Malignancy, n/N (%)	1/24 (4.2)
Hidradenitis suppurativa, n/N (%)	1/24 (4.2)
Lymphadenopathy, n/N (%)	1/24 (4.2)
Polyserositis, n/N (%)	1/24 (4.2)
Mediastinic pseudotumor, n/N (%)	2/24 (8.3)
Epidural pseudotumor with spinal cord compression, n/N (%)	1/24 (4.2)
Imaging	
Tomography - *Sausage pancreas*, n/N (%)	0/24 (0)
Tomography – Lung nodules, n/N (%)	3/24 (12.5)
Tomography – Lung bronchovascular pattern, n/N (%)	1/24 (4.2)
Tomography – Lung interstitial pattern, n/N (%)	1/24 (4.2)
Tomography – Lung groundglass opacities, n/N (%)	4/24 (16.7)
PET – Inflammatory findings, n/N (%)	10/24 (41.7)
Histology	
Storiform fibrosis, n/N (%)	4/24 (16.7)
Lymphoplasmacytic infiltrate, n/N (%)	20/24 (83.3)
Phlebitis obliterans, n/N (%)	0/24 (0)
IgG4/IgG ratio >40% in high magnification field, n/N (%)	5/24 (20.8)
Blood analysis	
Positive rheumatoid factor, n/N (%)	0/24 (0)
Positive anti-nuclear antibodies, n/N (%)	4/24 (16.7)
Peripheral eosinophilia, n/N (%)	5/24 (20.8)
Elevated C-Reactive Protein, n/N (%)	16/24 (66.7)
Elevated erythrocyte sedimentation rate, n/N (%)	12/24 (50.0)
Elevated serum IgG4 levels, n/N (%)	16/24 (66.7)
Elevated serum IgG1 levels, n/N (%)	2/24 (8.3)
Elevated serum IgGE levels, n/N (%)	1/24 (4.2)
Initial treatment	
Corticosteroids - pulses, n/N (%)	2/24 (8.3)
Corticosteroids - oral, n/N (%)	17/24 (70.8)
Dose in milligrams, mean (SD)	21.17 (22.55)
Cyclophosphamide, n/N (%)	1/24 (4.2)
Mycophenolate mofetil, n/N (%)	2/24 (8.3)
Azathioprine, n/N (%)	0/24 (0)
Methotrexate, n/N (%)	2/24 (8.3)
Leflunomide, n/N (%)	0/24 (0)
Hydroxychloroquine, n/N (%)	0/24 (0)
Tacrolimus, n/N (%)	0/24 (0)
Ciclosporin, n/N (%)	0/24 (0)
Intravenous immunoglobulins, n/N (%)	0/24 (0)
Rituximab, n/N (%)	3/24 (12.5)
TNFa-inhibitor, n/N (%)	0/24 (0)
Other - antibiotic, n/N (%)	1/24 (4.2)
Present treatment	
Corticosteroids - pulses, n/N (%)	1/24 (4.2)
Corticosteroids - oral, n/N (%)	16/24 (66.7)
Dose in milligrams, mean (SD)	4.67 (8.47)
Cyclophosphamide, n/N (%)	0/24 (0)
Mycophenolate mofetil, n/N (%)	2/24 (8.3)
Azathioprine, n/N (%)	1/24 (4.2)
Methotrexate, n/N (%)	1/24 (4.2)
Leflunomide, n/N (%)	0/24 (0)
Hydroxychloroquine, n/N (%)	1/24 (4.2)
Tacrolimus, n/N (%)	0/24 (0)

Ciclosporin, n/N (%)	0/24 (0)
Intravenous immunoglobulins, n/N (%)	0/24 (0)
Rituximab, n/N (%)	7/24 (29.2)
TNFa-inhibitor, n/N (%)	2/24 (8.3)
Other - surgery, n/N (%)	1/24 (4.2)
Result	
Corticosteroid response, n/N (%)	17/24 (70.8)
Decreased serum levels of IgG4, n/N (%)	13/24 (54.2)
Normalization of serum levels of IgG4, n/N (%)	8/24 (33.3)

SD: standard deviation

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