

## The clinical features and outcomes of Turkish patients with IgG4-related disease: a single-center experience

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**Background/aim:** Since the majority of the IgG4-related disease (IgG4-RD) patients in the literature are from the Far East and the United States, there is a lack of large series from other parts of the world. We aimed to identify the clinical characteristics and outcome of Turkish IgG4-RD patients from a tertiary center.

**Materials and methods:** Fifty-two patients classified as having definite IgG4-RD according to comprehensive diagnostic criteria were included in the study. Patients not fulfilling the definite criteria due to lack of pathologic specimen and/or serum IgG4 levels were excluded (n = 47). Clinical, laboratory, and histopathological features and treatment approaches were analyzed.

**Results:** Median age at diagnosis was 51.1 years and sex predominance was not observed (male/female: 26/26). Median follow-up duration was 18 (IQR 25–75: 8–35) months. Retroperitoneal fibrosis was the most frequent presentation. Twenty-four (46.1%) patients had localized involvement. Corticosteroids were the mainstay of treatment (92.5%). Rituximab had been used for cases resistant to previous treatment or with relapses in 19 (47.5%) patients. A complete response was achieved in 52.5% and partial response (<50% regression) in 40%.

**Conclusion:** This large and first cohort of IgG4-RD patients from Turkey showed similar clinical features to European cohorts, except for the male predominance in previous cohorts. Corticosteroids and rituximab are effective in IgG4-RD but there is still uncertainty about the usage of corticosteroid-sparing agents.

**Key words:** IgG4-related disease, retroperitoneal fibrosis, coronary periarteritis, corticosteroids, immunosuppressive agents, rituximab

### 1. Introduction

IgG4-related disease (IgG4-RD) is an emerging immune-mediated disease with the capability of involving essentially any organ (1). It was firstly described in the first years of the 21st century and the name of IgG4-RD was proposed in 2012 by an international multidisciplinary study group (2). Clarification of the pathophysiology and diagnostic criteria is ongoing. Despite the majority of patients reported in the literature to date being from the Far East and the United States, the condition has been described all across the world (2–4). There are a few publications describing the European and Middle Eastern experience of IgG4-RD (5–8). In recent years some observational studies were published from Spain, France, and Italy (9–11). There is still a lack of large series from other parts of the world.

The frequencies of clinical features in IgG4-RD have been different among pancreatobiliary series, glandular series, and systemic series (2). In a newly published review of six cohorts, the main organs involved were diverse due to the different inclusion and diagnostic criteria used for the different cohorts (12). The prevalence of specific organ involvement varied widely between studies and is principally influenced by the nature of patient collection (unselected or selected by organ).

Serum IgG4 concentrations are often considered useful, albeit with some limitations. Approximately 30% of IgG4-RD patients have normal serum IgG4 concentrations despite classic histopathological and immunohistochemical findings (1). Moreover, false positive results could be seen in chronic sinusitis, tuberculosis, and malignancy (7).

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Multiple approaches to the management of IgG4-RD have been reported, including surgical resection of affected tissues and treatment with systemic glucocorticoids, “steroid-sparing” immunosuppressive drugs, or biologic agents (13). However, no formal treatment guidelines exist (14). Although corticosteroids are the mainstay of treatment, up to 40% of patients relapse within the first year. More data are required to elucidate the dosing of corticosteroids and possible coadministration of immunosuppressives/biologic agents.

This study aimed to identify the clinical characteristics, treatments, and outcomes of Turkish patients from a tertiary center with IgG4-RD.

## 2. Materials and methods

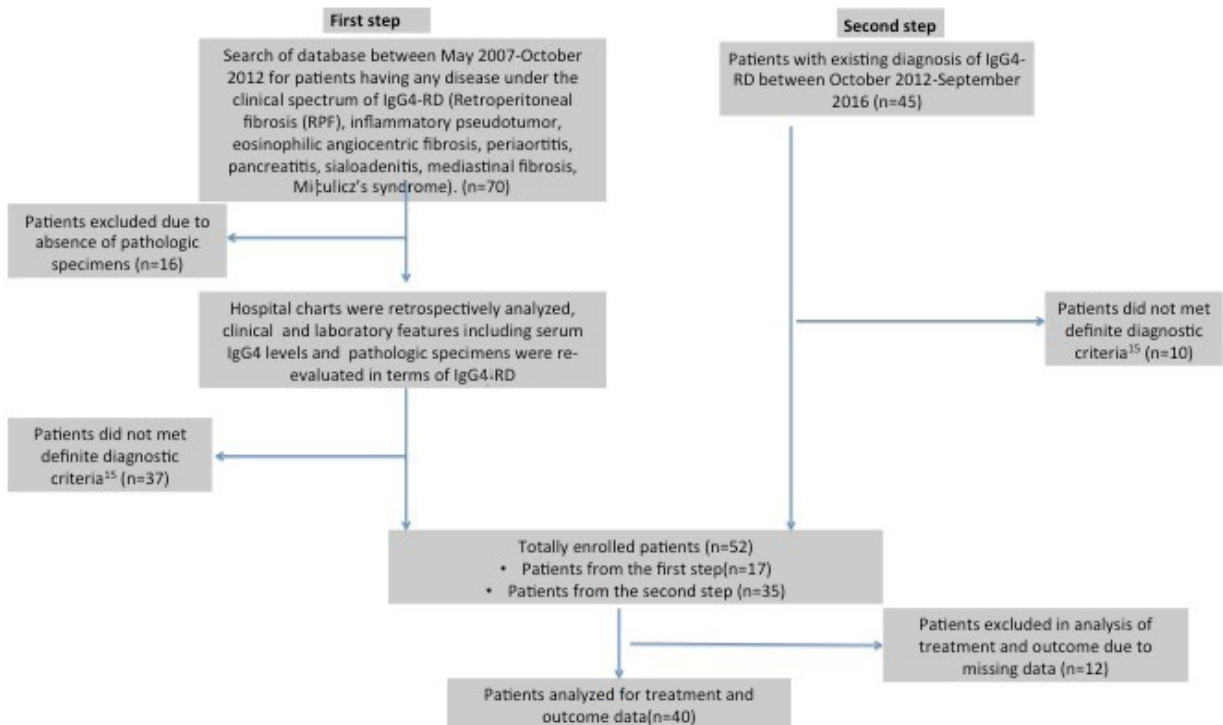
The institutional ethics committee of Hacettepe University approved the study. Patients were diagnosed with IgG4-RD according to comprehensive diagnostic criteria (15): (a) clinical/radiological examination showing characteristic diffuse or localized swelling or masses in single or multiple organs; (b) hematological examination showing elevated serum IgG4 concentrations ( $>135$  mg/dL); (c) histopathological examination showing (i) marked lymphocyte and plasmacyte infiltration, (ii) storiform fibrosis, and (iii) infiltration of IgG4+ plasma cells with a ratio of IgG4+/IgG+ plasma cells of  $\geq 40\%$  and a total of  $\geq 10$  IgG4+ plasma cells per high-power field. The

diagnosis of IgG4-RD was definitive in patients with a+b+c. Correspondingly, patients were diagnosed with IgG4-RD if they had organ-specific criteria for IgG4-related autoimmune pancreatitis, IgG4-related Mikulicz’s disease, and IgG4-related kidney disease.

Patients’ data were acquired via 2 sources (Figure 1): first, the database of our rheumatology center between May 2007 and October 2012 was screened for patients having any disease under the clinical spectrum of IgG4-RD (retroperitoneal fibrosis (RPF), inflammatory pseudotumor, eosinophilic angiocentric fibrosis, periaortitis, pancreatitis, sialoadenitis, mediastinal fibrosis, Mikulicz’s syndrome). Hospital charts of 70 patients were retrospectively analyzed and clinical, histopathology, and laboratory features including serum IgG4 levels were reviewed. Sixteen patients were excluded due to the absence of histopathologic specimens. Pathologic specimens of 54 patients were reevaluated in terms of IgG4-RD. Moreover, 37 patients did not meet the definite diagnostic criteria. At the end of the first step, 17 patients were included in the study.

In the second step, patients with an existing diagnosis of IgG4-RD between October 2012 and September 2016 were evaluated (Figure 1). Ten patients were excluded due to not fulfilling definite diagnostic criteria. Thirty-five patients were enrolled in the study from the second step.

A standardized dataset including demographic data,



**Figure 1.** Flowchart of the patients’ enrollment and data analysis of the study.

clinical characteristics, and imaging and laboratory findings of IgG4-RD was set up and completed for each patient.

Systemic disease was defined by the presence of 2 or more affected organs. Those with less than 2 organs affected were considered as localized cases.

### 2.1. Hematological and serological assessments

All patients' laboratory data were noted, including complete blood counts, liver and renal function assessment, and serological testing including acute phase reactants (APRs), C-reactive protein, erythrocyte sedimentation rate, and complement levels. Antinuclear antibodies (ANAs), extractable nuclear antigens (ENAs), antineutrophil cytoplasmic antibodies (ANCA), and serum IgG4 levels were measured at the time of first presentation by nephelometric methods at Düzen Laboratory Group, Ankara, Turkey, or the Hacettepe University Hospital laboratories and a level of >135 mg/dL was considered as elevated, while >405 mg/dL was very high (13). Increased APR level was accepted as an erythrocyte sedimentation rate of >30 mm/h or C-reactive protein level of >10 mg/L.

### 2.2. Follow-up, therapeutic strategies, and outcomes

The use of corticosteroids, immunosuppressive agents, and biologic therapies as well as previous radical or palliative surgery was noted. Adjuvant therapies such as radiotherapy were also recorded.

Treatment response was evaluated after 3–6 months and was assessed according to 3 outcome groups: complete (complete regression of the fibrotic mass/masses and systemic symptoms), partial (<50% of regression of the mass/masses and cessation of the systemic symptoms), and none.

During follow-up, the number and causes of death were recorded.

### 2.3. Statistical analysis

Statistical analysis was performed with SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics included mean (standard deviation, SD) and median (25th–75th quartiles). Comparisons between categorical variables were performed using chi-square tests. Correlation analysis was done with Pearson or Spearman correlation tests according to the distribution of the variables.

## 3. Results

### 3.1. Patients' characteristics and organ involvement

In total, 52 patients (26 males) were recruited into the study. All patients met the criteria for a "definite" diagnosis of IgG4-RD. Mean ( $\pm$ SD) age at diagnosis was  $51.1 \pm 12.7$  years. A history of atopy/allergy was present in 9 (17.3%) patients.

The presence of previous autoimmune disease was seen in 10 (19.2%) patients: 3 had Hashimoto's thyroiditis,

two had Graves' disease, and a previous history of systemic sclerosis, rheumatoid arthritis, vitiligo, psoriatic arthritis, or psoriasis was respectively noted in 5 other patients.

The clinical spectrum of the patients was broad, with the involvement of different anatomical sites for protean manifestations. RPF was the most frequent feature. Pancreatitis, periorbital lesions, salivary gland involvement, cardiovascular involvement, and constitutional symptoms were present in approximately one-fourth of patients. Lymphadenopathy was found in 20 (39.2%) patients and was observed alongside other common presentations as well as being the initial manifestation of the disease. Lymphadenopathy in the cervical, supraclavicular, mediastinal, hilar, and intraabdominal regions was observed. The distribution of different organs involved and the frequencies are shown in the Table. In contrast to other rheumatic diseases, no patients had arthritis/enthesopathy or deep vein thrombosis and arthralgia was seen in 11 (27.5%) of patients.

Twenty-four (46.1%) patients had localized involvement. Distribution according to organ involvement included RPF (n = 13), pancreatitis (n = 3), mediastinal fibrosis (n = 2), nasopharyngeal pseudotumor (n = 1), eosinophilic angiocentric fibrosclerosis (n = 1), dacryoadenitis (n = 1), kidney involvement (n = 1), pachymeningitis (n = 1), and orbital pseudotumor (n = 1).

No difference was found between male and female patients regarding clinical features, except for RPF (73.0% vs. 27.0%,  $P = 0.001$ ).

Median serum IgG4 level was 280 (IQR 25–75 : 98.5–642) mg/dL. Distribution of serum IgG4 levels were normal in 32.7%, elevated in 46.1%, and very high in 21.2% of cases. None of the localized cases had very high IgG4 levels (>405 mg/dL). Increased APR at first diagnosis was found in 32 (61.5%) of patients. No correlation was found between acute phase reactants and serum IgG4 levels ( $P > 0.05$ ). Moreover, the number of organ systems involved was not related to an increase in acute phase reactants ( $P > 0.05$ ).

Seven patients had an ANA titer of  $\geq 1/160$ , but none of them had ENA positivity. MPO-ANCA was found in one patient. Hypocomplementemia was not seen in any of patients.

### 3.2. Follow-up, therapeutic strategies, and outcomes

Twelve patients had missing data regarding follow-up and treatment. Subsequently, analysis was performed with 40 patients.

Surgical resection was performed in 10 (25%) patients as a diagnostic/therapeutic process and all were done before IgG4-RD was diagnosed. Eight had RPF-related surgery (including ureteral stent insertion) and two required surgery for periorbital lesions. Only 3 (7.5%) patients underwent surgery alone and were not treated;

**Table.** Distribution of clinical findings and organ involvement (n = 52).

Constitutional symptoms	
· Fatigue	· 31 (59.6%)
· Tiredness	· 16 (30.7%)
· Night sweats	· 15 (28.8%)
· Weight loss	· 14 (26.9%)
· Fever	· 13 (25%)
Retroperitoneal fibrosis	23 (44.2%)
Lymphadenopathy	20 (39.2%)
Any cardiovascular involvement	15 (28.8%)
· Periaortitis	· 12 (23.1%)
· Pericardium	· 5 (9.6%)
· Coronary periarteritis	· 4 (7.7%)
· Abdominal aorta aneurysm	· 1 (1.9%)
Orbital pseudotumor	12 (23.1%)
· Orbital mass/proptosis	· 6 (11.5%)
· Extraocular muscles	· 6 (11.5%)
Pancreas	12 (23.1%)
Major salivary glands	11 (21.2%)
Lacrimal glands	9 (17.3%)
Mediastinal fibrosis	6 (11.5%)
Ear, nose, sinuses	5 (9.6%)
Lung fibrosis	5 (9.6%)
Skin	4 (7.7%)
Pleura	4 (7.7%)
Gall bladder and biliary ducts	4 (7.7%)
Thyroid	3 (5.8%)
Liver	3 (5.8%)
Kidneys (mass)	3 (5.8%)
Pachymeningitis	2 (3.8%)
Breast involvement	1 (1.9%)
Tubulointerstitial nephritis	1 (1.9%)

one of them was a totally resected kidney-involved patient, while one with cervical lymphadenopathy and one with RPF was surgically treated. Later two patients progressed and medical therapy was started (Figure 2).

The initial therapeutic approach in all treated patients (n = 37) was the administration of glucocorticoids (GCs). Pulse methylprednisolone was used for 1–3 days according to severity in patients with pachymeningitis (n = 2), orbital pseudotumor (n = 3), periaortitis (n = 3), mediastinal fibrosis (n = 3), and coronary periarteritis (n = 4). Oral prednisolone was started at a daily dose of 0.5–0.6 mg/

kg in patients with localized involvement and 1 mg/kg in patients with multiorgan involvement. GCs were gradually tapered over a period of 6 months. Six (42.8%) patients responded to treatment, but 3 of them relapsed during dose reduction. Rituximab was used in 9 of these patients because of resistance and/or adverse effects (Figure 2).

The combination of GCs with immunosuppressive agents (methotrexate (MTX) 10–20 mg/ week or azathioprine (AZA) 2–3 mg/kg per day or pulse cyclophosphamide (CYC) 500 mg 2–4 weeks apart, total dose less than 6 g) was used as first-line induction therapy in 23 (57.5%) patients. Eight patients responded well to the GC+MTX/AZA combination (Figure 2). Even though patients on GC+CYC responded well, relapse was seen frequently in this group. Four patients were switched to rituximab.

Rituximab (1 g twice 2 weeks apart) was used as a second-line treatment for patients resistant to previous treatments or relapsed patients. Nineteen (47.5%) patients had used rituximab (Figure 2). In 10 of these patients, rituximab was given once more (2 g). In two of these patients, two additional courses of rituximab (1 g) were used because of lack of response. No relapse was observed after rituximab treatment.

No difference was found regarding treatment between patients with systemic and localized disease (P = 0.456).

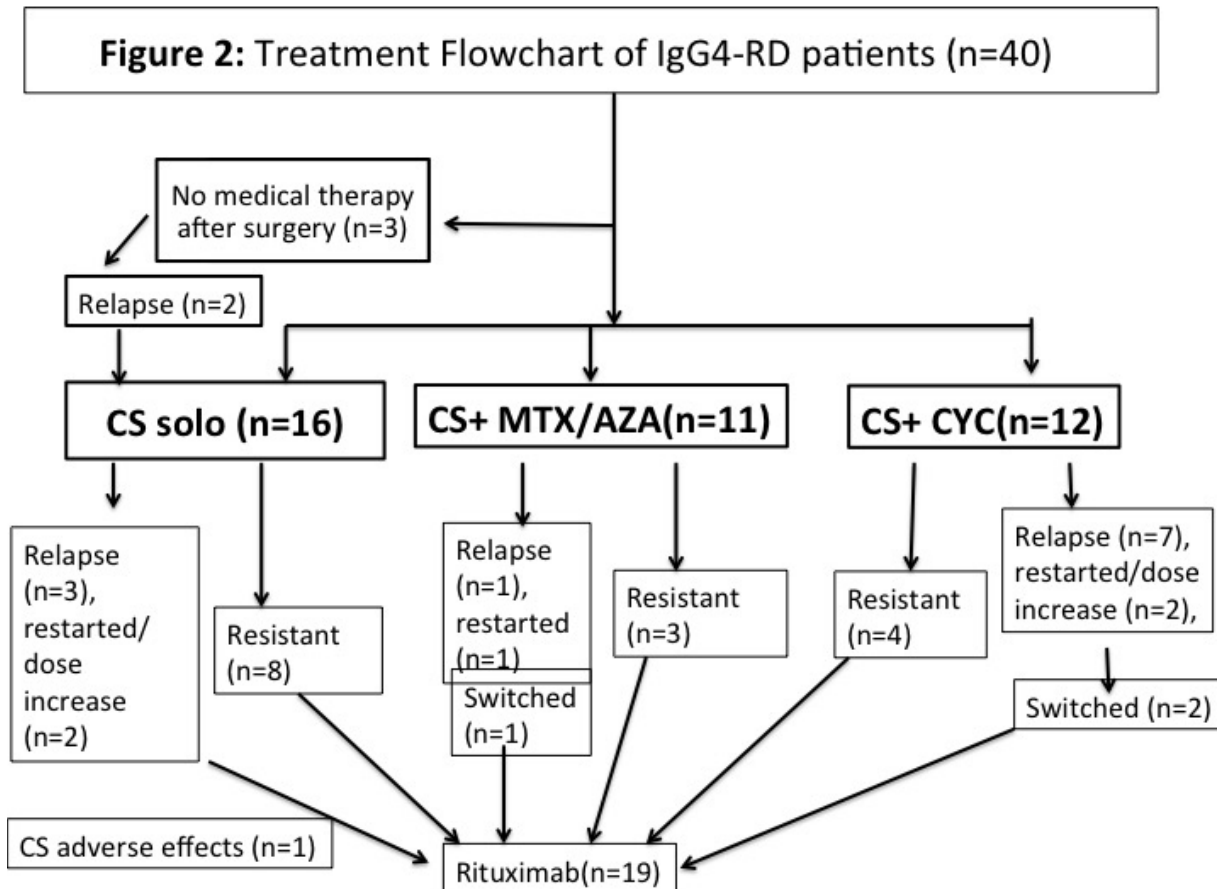
Local radiotherapy was used as adjunctive therapy in a patient with eosinophilic angiocentric fibrosis. However, it was unsuccessful and this patient was switched to rituximab.

Thirteen subjects (32.5%) presented relapses. No statistical difference was found regarding tendency to flare between systemic and localized IgG4-RD forms (P = 0.901).

Twenty-one (52.5%) patients achieved a complete response and 16 (40%) presented a partial response (<50% of regression) after a median of 18 (IQR 25–75: 8–35) months of follow-up. One patient with RPF and coronary periarteritis failed to respond to all treatments including prednisolone, cyclophosphamide, and rituximab. Eventually, coronary artery by-pass graft was performed due to persistent angina pectoris. No difference was found between systemic and localized patients regarding complete/partial response rates (P = 0.513).

Within the 14 subjects who started prednisone only, 4 had complete resolution and 1 had partial resolution with only prednisolone. Among the patients who used GC in combination with any other immunosuppressive agent as first-line treatment, five had complete response and six had a partial response.

In total, 3 patients died during this period. Two of the deaths were attributed to IgG4-RD: cardiac failure due to constrictive pericarditis (n = 1) and pulmonary failure due to mediastinal fibrosis (n = 1). A patient with pancreatitis



**Figure 2.** Treatment flowchart of IgG4-RD patients (n = 40).

died due to myocardial infarction 5 years after the first diagnosis and this was not thought to be related to IgG4-RD.

One patient had previous acute lymphoblastic leukemia (ALL) 20 years before the diagnosis of IgG4-RD. No malignancy was observed during follow-up.

#### 4. Discussion

In this single-center observational study, we aimed to describe the clinical features of 52 Turkish patients with IgG4-RD together with the treatments and outcomes. Middle-aged individuals were the most affected, in line with previous studies. No sex predominance was observed. The clinical features observed were similar to those previously described from European cohorts. Nearly half of the patients had localized disease. Even though additional immunosuppressive agents were used in more than half of the patients, treatments had to be switched to rituximab in a subgroup. Most patients had an acceptable response. Two deaths were directly related to the disease and we observed no malignancy during follow-up.

IgG4-RD is characterized by the involvement of multiple organ systems. The pancreas is frequently involved. Autoimmune pancreatitis has been reported in approximately 50% of cases (2). Other studies reported the predominance of involvement of salivary glands and lymphadenopathy in American and Chinese cohorts, whereas a Spanish cohort was characterized by the predominance of RPF and orbital pseudotumor. According to an Italian cohort, the predominance of pancreatic involvement and RPF was seen (2,12). In our cohort, RPF was the most frequent presentation; other common features were, in descending order, lymphadenopathy, orbital pseudotumor, pancreatitis, and salivary gland involvement. Few cases of tubulointerstitial nephritis or biliary involvement were observed. The incidence of localized IgG4-RD (46.1%) in our series is similar to that reported by previous studies (ranging between 22% and 59%).

Cardiovascular involvement may be manifested as cardiac pseudotumors, inflammatory periaortitis, coronary arteritis, and/or pericarditis (16). IgG4-related cardiovascular disorders can severely affect prognosis.

Panarteritis in a coronary artery of a patient with RPF was initially described in 1966 (17). There are few cases of IgG4-related coronary periarteritis (17–20). Delayed diagnosis can result in development of giant aneurisms, as in a patient of our cohort. Inflammatory pericarditis leading to constrictive pericarditis can be fatal, as described in one patient in our cohort (18). Physicians should be aware of the importance and mortality potential of coronary periarteritis/inflammatory pericarditis in IgG4-RD.

We did not find any malignancy related to IgG4-RD, except for one case of ALL, which had been diagnosed 20 years previously. No malignancy was reported during follow-up. We did not observe a link between IgG4-RD and neoplasms. Concomitant lymphadenopathy is often found in patients with IgG4-RD. More than one-third of our patients had lymphadenopathy, which is line with previous studies. Lymph nodes in cervical, supraclavicular, mediastinal, hilar, and intraabdominal areas have been involved. Lymphadenopathy sometimes represents the initial manifestation of the disease, but it is usually discovered by imaging of patients with known IgG4-RD (21). When the lymphadenopathy is generalized, the differential diagnosis includes lymphoma, Castleman's disease, and disseminated malignancy. Even though previous reports mentioned no fever or weight loss in IgG4-RD, one-third of our patients had constitutional symptoms and weight loss was reported in 14 patients. Constitutional symptoms in addition to generalized lymphadenopathy can be seen in malignancy and IgG4-RD. Exclusion of an underlying malignancy is therefore paramount.

Our patients had a similar age at diagnosis and no sex predominance was noted in comparison to previous studies (2,12). In a few previous reports, patients with IgG4-RD had increased allergic features such as atopy and asthma (1). However, atopy/asthma was not found in the majority of subjects and the prevalence was similar to that expected in the general adult Turkish population (22). Sex predominance in IgG4-RD studies is mainly influenced by the major organ involvements seen in a given study (2,12). There was a male predominance in a pancreatobiliary series but in a glandular series no sex difference was reported in the pooled analysis of Brito-Zeron et al. (2). Inoue et al. reported that males presented with more periaortitis/RPF (23). In our cohort RPF was three times more frequent in males, but even for that there were no sex differences observed regarding all IgG4-RD patients. There could be slight differences related to organ involvement between males and females (12,23). Sex predominance would be better projected in further pooled international analysis with different clinical presentations.

In most of the IgG4-RD studies, patients were included using the comprehensive diagnostic criteria or 2012

consensus criteria (15,24). We used the former criteria and included only "definite" IgG4-RD patients. Some of our patients were diagnosed using organ-specific criteria. The comparison of these criteria has not been evaluated in this study. The International Consensus criteria are based on pathological findings, leaving IgG4 serum elevation as a complementary finding (24). Thirty percent of our patients had serum IgG4 levels within the normal range, as in previous studies (12). On the other hand, increased IgG4 levels might raise suspicion of systemic involvement. Carruthers et al. reported a mean level of 405 mg/dL associated with systemic involvement (13). None of the localized cases had serum IgG4 levels higher than 405 mg/dL. Serum IgG4 levels could be useful not only for diagnosis but also as an important clue especially at much higher levels.

Even though increased APRs are useful in the monitoring of many rheumatic diseases, there is no consensus for the use of APR in IgG4-RD. As in our study, about 30% of patients have APRs within the normal range (1,2). Moreover, the number of organ systems involved is not related to an increase in APRs. APRs do not have informative roles in IgG4-RD, as mentioned in the recent International Consensus guidelines (14).

First-line therapy for IgG4-RD is corticosteroids. However, there is a subgroup in which corticosteroid monotherapy results in an incomplete response or high relapse rate (12). Nonresponders were more likely receiving glucocorticoid-sparing agents and/or rituximab. Steroid nonresponders were more likely receiving glucocorticoid-sparing agents in a range of 34.5%–60%. In our series, more than 90% of patients had used corticosteroids. In contrast to previous studies, more than half of our patients had been on additional agents as first-line treatment. Although our patients did not follow any previously defined treatment regime, we observed a slightly lower relapse rate (32.5%) compared to previous cohorts (24%–63%).

There is very little evidence about the clinical utility of corticosteroid-sparing medications. Wallace et al. demonstrated that all patients treated in their cohort with steroid-sparing agents discontinued them due to lack of response (4). The fibrotic components that occur in the later phase of the disease could prevent the drugs interfering with the inflammatory chain (12). Because of the small patient numbers and no homogeneous evaluation of disease activity index, further analysis could not be done. However, early use of these agents might be a rational approach to obtain better response with lower relapse rates even though they have not been studied in a controlled or prospective manner.

Rituximab has been described as a highly effective treatment in IgG4-RD when combined (or not) with

steroids (14,25). Half of our patients used rituximab due to resistance to previous drugs or relapse. Moreover, no relapse was observed. B-cell depletion achieves its effects at least in part by interfering with the repletion of short-lived plasma cells that are producing IgG4. Rituximab appears to be an important and well-tolerated alternative agent for patients who do not respond to corticosteroids and/or corticosteroid-sparing agents (14).

Most of our patients had an acceptable response. Response rates differ between previous studies due to heterogeneous evaluation methods. However, the majority of patients had complete or partial responses in all of the studies.

Limitations of our study arise from the inclusion of retrospective cases, absence of standardized treatment protocols, and lack of use of a disease activity index. However, our data give an illustration of IgG4-RD in Turkey in comparison to other cohorts. There is no outcome measurement tool validated for IgG4-RD, but a prototype activity index was proposed in 2012 (26). We used a semiquantitative response index, also used in the Spanish cohort (10). Using a disease activity index like an 'IgG4-RD responder index' might be useful in assessing

disease activity and damage and also in treatment efficacy.

In conclusion, we have described the largest series of patients with IgG4-RD from Turkey. These patients had a preponderance of disease involving the retroperitoneum, salivary glands, and periorbital region. Overall, there was a good response to treatment and corticosteroid-sparing agents might be useful, especially in the early phase of the disease. The introduction of rituximab may be the start a new treatment era. Malignancy and mortality were infrequent. Our work provides additional insights into the clinical characteristics, natural history, and response to treatment of IgG4-RD in a European population. International collaborative studies and randomized clinical trials will help in clarifying these areas of uncertainty.

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