Clinical Kidney Journal

ckj

OXFORD

era edta
LEADING EUROPEAN NEPHROLOGY

Clinical Kidney Journal, 2019, vol. 12, no. 6, 829–835

doi: 10.1093/ckj/sfz031
Advance Access Publication Date: 16 April 2019
Original Article

ORIGINAL ARTICLE

Clinical features and outcomes in a cohort of patients with immunoglobulin G4-related disease at a university hospital in Spain

Maria Quero [1,2], Juliana Draibe[1], Xavier Solanich[3], Inés Rama[1], Montserrat Gomà[4], Laura Martínez-Valenzuela[1], Xavier Fulladosa[1], Josep M. Cruzado[1,2] and Joan Torras[1,2]

[1]Nephrology Department, Hospital Universitari de Bellvitge, Barcelona, Spain, [2]Clinical Sciences Department, Campus Bellvitge, University of Barcelona, Barcelona, Spain, [3]Internal Medicine Department, Hospital Universitari de Bellvitge, Barcelona, Spain and [4]Pathology Department, Hospital Universitari de Bellvitge, Barcelona, Spain

Correspondence and offprint requests to: Joan Torras; E-mail: jtorras@bellvitgehospital.cat; Twitter handles: @m_quero_r; @julianadraibe; @xfulladosa; @nesirama; @Lau_Mtnz_Val; @crz_garrit

ABSTRACT

Background. Immunoglobulin G4-related disease (IgG4-RD) is a fibro-inflammatory, immune-mediated disorder, which characteristically affects the glandular tissue but has the potential to affect any organ.

Methods. We retrospectively reviewed clinical, laboratory, histological characteristics and treatment response during 12 months of follow-up of a cohort of patients with IgG4-RD diagnosed at a tertiary public hospital. Disease activity was assessed by means of the IgG4-RD responder index (IgG4-RD RI).

Results. In all, 15 patients have been diagnosed at our Institution and herein studied (80% men), with a median age of 60.7 years and a mean affectation of 2.8 organs per patient. We identified six patients with definitive diagnosis and nine with possible IgG4-RD, according to the Japanese diagnostic algorithm. IgG4-RD RI decreased from a median of 11.3 at baseline to 4.0 after 6 months and 6.2 after 12 months. Relapse occurred in five patients and was associated with lower cumulative steroid doses. Five patients (33.3%) required additional immunosuppressive (IS) drugs. Five adverse events were seen during follow-up: three infections, one deep vein thrombosis and one gastrointestinal bleeding. One patient died of pneumonia.

Conclusions. IgG4-RD is an inflammatory disease that can affect any organ. Glucocorticoids were an effective first line of treatment; however, this treatment is associated with important adverse events and relapses occurred in patients with low cumulative doses. As an alternative, IS treatment with rituximab could be an interesting option in those patients.

Keywords: fibro-inflammatory disease, glucocorticoids, IgG4-related disease, IgG4-related disease responder index, rituximab

Received: 1.8.2018; Editorial decision: 21.2.2019

INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a fibro-inflammatory disorder usually characterized by affectation of glandular tissue, but with the potential to affect any other organ. The disease was recognized as a systemic condition after 2003 when extra-pancreatic manifestations were identified in patients with autoimmune pancreatitis type 1 [1]. It was seen that patients affected with autoimmune pancreatitis had fibro-inflammatory lesions rich in IgG4 with similar findings in organs other than pancreas, thus constellating the concept of IgG4-related disease [2].

There are few population-based studies of this disease; however, some demographic data have been reported, such as male predominance (62–83%) and its highest incidence during middle age or elderly patients [3]. Clinically, this is an entity with variable presenting symptoms and the potential to affect any organ system, which makes it extremely difficult to diagnose. In general, it may present as tumefacient lesions, manifested as pseudotumoural injuries and atopic symptoms [3, 4]. Carruthers *et al.* described a responder index of the disease (IgG4-RD RI), modelled on the Birmingham Vasculitis Activity Score for Wegener's granulomatosis [5, 6]. Recently, Fernandez-Codina *et al.* [7] have described that IgG4-RD RI could be a promising measure of the activity of the disease and could be used to assess treatment response.

Most serological findings are also non-specific. Many patients with IgG4-RD have increased total serum IgG, IgG4 and IgG1 concentrations, eosinophilia, hyperproteinaemia and complement consumption, but none of these alterations was considered crucial for the diagnosis. Although IgG4 level are used in diagnosis, it is of limited use for monitoring the disease during follow-up [8].

Histology has been considered the gold standard for the diagnosis, with lymphoplasmacytic infiltrates composed of polyclonal CD20+ lymphocytes, T-cells and IgG4+ plasma cells in immunohistochemistry (defined as ≥10 IgG4-bearing plasma cells per high-power field or an IgG4/IgG plasma cell ratio ≥40%). Characteristically, the infiltrate is organized with a storiform pattern, obliterative phlebitis and tissue eosinophilia. The inflammatory lesion is the structural basis of the tumefacien mass that may destroy the involved organ. Granulomas and neutrophils are rarely detected [3].

Regarding treatment, glucocorticoids (GCs) are considered the first line of therapy. They are effective in most cases but relapse rates at the time of dose reduction or after withdrawal of treatment are high [9, 10]. Other immunosuppressive (IS) treatments, such as mycophenolate mofetil (MMF), calcineurin inhibitors (CNI) or rituximab (RTX), have been used to help prolong the period of remission or maintenance after remission with GC therapy, but they are not useful to induce remission on their own [4].

In the present article, we retrospectively reviewed all the patients diagnosed with IgG4-RD at a tertiary university hospital in Catalonia from 2008 to 2015.

MATERIALS AND METHODS

Study population

We retrospectively reviewed clinical, laboratory, histological features and treatment response during 12 months of follow-up of all patients diagnosed with IgG4-RD at our Institution, the Hospital Universitari of Bellvitge (Barcelona, Catalonia, Spain) from 2008 to 2015. The outcomes were evaluated at baseline, and at 6 and 12 months.

We used the comprehensive diagnostic criteria for IgG4-RD described by a Japanese group [11] stratifying patients into definitive, probable and possible diagnostic of IgG4-RD (Table 1) [12].

Clinical assessment

IgG4-RD RI score [6] was used to evaluate disease activity at the moment of diagnosis, and 6 and 12 months later.

IgG4-RD RI score ≥3 was used to identify active disease, and disease response was defined as a decrease of at least 2 points over baseline, for six consecutive months [6]. Remission was defined as IgG4-RD RI of 0, and relapses as recurrent symptoms, an increased ≥2 in the IgG4-RD RI or the necessity for the restart of treatment.

Complementary studies

A complete blood test was performed in all patients including renal function, liver enzymes, haemogram, total immunological study [immunoglobulins (Ig), IgG subtypes] and complement fractions C3 and C4. Normal values in our laboratory are: IgG from 6900 to 14 000 mg/L, IgG4 80–1400 mg/L, C3 750–1400 mg/L and C4 100–340 mg/L.

Concerning histological analysis, we considered diagnostic biopsy of IgG4-RD when previously described histological findings were present (lymphoplasmocytic infiltrate composed of polyclonal CD20+ lymphocytes, storiform pattern fibrosis, obliterative phlebitis and tissue eosinophilia). Regarding immunohistochemical studies we considered compatible findings when there were ≥10 IgG4-bearing plasma cells per high-power field or an IgG4/IgG plasma cell ratio ≥40% [2].

In addition, a PET-SCAN or simple scan was performed in all patients at diagnosis and, in some cases, during follow-up, with the objective of monitoring metabolic changes in affected organs.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 6. We used Kolmogorov–Smirnov test to check normal distribution, and normally distributed variables were compared using the Student's *t*-test. A P-value <0.05 was considered statistically significant.

RESULTS

Patients and clinical assessment

We included 15 patients in our study, 4 patients with definitive diagnosis and 11 with possible IgG4-RD, according to comprehensive diagnostic criteria for IgG4-RD [12] (Table 2). Median age at the time of diagnosis was 60.7 ± 14.8 years (ranging from 30 to 80 years); males were more frequently affected (80%); and mean organ involved was 2.8 ± 1.2 organs per patient. There were two cases with only one organ affected, four patients with two organs, three organs were involved in six cases and the remaining three patients had four (two patients) and seven (one patient) affected organs, respectively. Mainly affected organs were adenopathies (60% patients), kidneys (40%), salivary glands (33.3%), pancreas (20%), vascular disease (20%) and lungs (20%).

Table 1. Comprehensive clinical diagnostic criteria

Comprehensive clinical diagnostic criteria
(1) Clinical study shows characteristic diffuse/localized swelling or masses in single or multiple organs
(2) Haematological study shows elevated levels of serum IgG4 (≥135 mg/dL)
(3) Histopathological study shows the following two findings
(i) Histological findings: marked lymphocyte and plasmacytic infiltration and fibrosis
(ii) IgG4-positive plasma cell infiltration: ratio of IgG4/IgG positive cell >40%, and IgG4-positive plasma cells/HPF >10 of the above
When (1), (2) and (3) are fulfilled, it is definite
When (1) and (3) are fulfilled, it is probable
When (1) and (2) are fulfilled, it is possible
However, it is important to differentiate from malignant tumours of each organ (cancer, lymphoma, etc.) and similar diseases (Sjogren's syndrome, primary sclerosing cholangitis, Castleman's disease, secondary retroperitoneal fibrosis, Wegener's granulomatosis, sarcoidosis, Churg–Strauss syndrome, etc.) with additional histopathological examination as much as possible
Even in the case that patients cannot be diagnosed with CCD criteria for IgG4-RD, they may be diagnosed using organ-specific diagnostic criteria for IgG4-RD

HPF, high-power field.

Laboratory outcome

The mean value of IgG4 was 6823.3 mg/L (SD ±7730.14) at baseline, and 1676.8 mg/L (SD ±968.8) and 3804.9 mg/L (SD ±4520.3) at 6 and 12 months follow-up, respectively (Figure 1). All 15 patients had increased levels of IgG4 at baseline and in 13 of them (86.7%) IgG4 decreased after 6 months of treatment. In the two remaining cases (13.3%), IgG4 levels increased. When we analysed these cases, in one patient, GCs were withdrawn after 3 months and the other had an erratic medication intake. Total serum IgG was also increased in nine patients with a mean value of 20 660.7 (SD ±13 776.9), decreasing in seven patients with a mean value of 11 214.6 (SD ±4244.2) at 6 months of treatment.

Regarding complement fractions (serum C3 and C4), we obtained data from eight patients. Two of them had only one reading during the follow-up. Six cases had complement fractions at the time of diagnosis, and were clearly reduced in two of them (33.3%), and in both cases the values corrected after 6 and 12 months of follow-up.

Four patients (26.7%) had hypereosinophilia, described as >390 eosinophils/μL according to laboratory data of our hospital. Only one of the four patients persisted with high level of eosinophils after 6 months, and also presented a relapse and needed to add CNI to his treatment.

Considering renal function, six patients (40%) presented renal failure (mean creatinine 274.15 μmol/L) and 33.3% presented proteinuria [mean value 226.9 g/mol (SD ±317.3)]. Table 3 shows renal function IgG4-RD RI and treatment progression, diagnostic criteria, other affected organs and histological findings in this cohort of patients.

Imaging studies

PET-SCAN was performed at the time of diagnosis in 11 patients; 6 of them (54.5%) evidenced hypermetabolism at adenopathies, 4 (26.6%) at salivary glands, 4 (26.6%) at the gastrointestinal tract and 3 presented kidney hypermetabolism (36.3%). Three patients presented pulmonary affectation, two of them had vascular hypermetabolism and one patient had prostatic affectation (6.7%). No patients had pancreatic hypermetabolism. This could be explained by physicians not performing the exploration at the time of diagnosis in those patients.

Table 2. Patients grouped according to the diagnostic criteria and histological findings they meet

Number of patients	Clinical diagnostic criteria	Biopsy
Four	1+2+3	Histological findings and IGG4-positive plasma cell infiltration
Four	1+2	Biopsy was not perform by physician's decission
One	1+2	Biopsy was not perform by patient's decission
Five	1+2	Histologically compatible but with <40% of IGG4/IgG ratio and <10 IgG4-positive plasma cells/HPF
One	1+2	Fibrosis and sclerosis

During follow-up, four patients underwent a new PET-SCAN, two at 6 months and the other two at 12 months; in all cases there was a decrease in hypermetabolism, and in one patient, it disappeared.

In Figure 2, we include a PET-SCAN study showing a focal hypermetabolic lesion in the posterior wall of the bladder, and an increased size left kidney with doubtful cortical uptake in relation to acute renal failure versus underlying inflammatory process. Doubtful morphometabolic asymmetry in left palatal amygdala has been described, and increases in gastric level uptake in a diffuse manner, probably physiological in the absence of clinical symptoms (although not adequate gastric preparation).

Histology

In our cohort, 10 patients had a diagnostic biopsy. In the other five, histological confirmation was not done mainly because their physicians made the diagnosis through reliable clinical and imaging features, and an adequate and positive empirical response to the treatment. More than that, the main affected organs in those cases were the pancreas (50%) and an aortitis diagnosed through PET-SCAN (50%), which made access to biopsy difficult.

The most frequent findings were: lymphoplasmocytic infiltration (80%) at different tissues, tissue eosinophilia (20%) and in one sample (10%), storiform fibrosis. Immunohistochemical studies of IgG4+ plasma cells were performed in eight biopsies and were compatible with IgG4-RD diagnosis in 50% of cases. In Figure 3 kidney biopsy is shown with lymphoplasmocytic infiltration with predominance of plasma cells in Figure 3A and an immunohistochemical compatible study in Figure 3B.

Four patients had renal biopsy, which showed: tubulointerstitial nephritis (one patient), tubulointerstitial nephritis associated with minimal change disease (one patient), interstitial fibrosis and glomerulosclerosis (one patient) and membranous nephropathy associated with mild eosinophilic interstitial infiltrate. In the last case, immunofluorescence showed a glomerular granular parietal pattern, positive for IgG, C3 and lambda chains and IgG4-positive immunohistochemistry.

Table 3. Patients grouped according to the diagnostic criteria and histological findings they incur

Patient	Creatinine[a] (μmol/L)	Proteinuria[b] (g/day)	Clinical diagnostic criteria	IgG4-RD RI	Biopsy	Prednisone dose (mg)[c]	Another IS	Relapse
1	HD–HD–287	0.15 to undetectable	1+2 possible	12→4→10	Interstitial fibrosis and glomerulosclerosis	30 October	No	Yes (11 months)
2	94–101–104	4.91–0.43	1+2 possible	12→3→3	Changes of MN and interstitial involvement. <40% IgG4/IgG ratio and <10 IgG4-possitive plasma cells/HPF	30 May	Tacrolimus previous. He was misdiagnosed with MN	No after PDN initiation
3	150–187–244	0.63–0.86	1+2 possible	12→6→6	Biopsy was not perform by patient's decision	20–12.5	No	No
4	660–283[d]	0.63–1.08	1+2+3 definitive	12→7→2	TIN with predominance of plasmatic cells. >10 IgG4+plasma cells/HPF	60–30	MMF and later RTX	Yes (6 months)
5	91[e]–335–120	2.72–0.09	1+2+3 definitive	15→5→7	Minimal change-disease and TIN with polyclonal plasmatic cells IgG4+. IgG4/IgG is >10%	60–7.5	No	No
6	119–239–238	0.63–1.38	1+2 possible	15→5→5	Retroperitoneum biopsy: histologically compatible but with <40% of IgG4/IgG ratio and <10 IgG4+plasma cells/HPF	60–10–7.5	Myfortic (during first year)	No

HD, haemodialysis; HPF, high-power field; MN, membranous nephropathy; PDN, prednisone; TIN, tubulointerstitial nephritis.
[a]Creatinine 1 year before diagnosis, at diagnosis and 12 months after therapy.
[b]Proteinuria at diagnosis and 12 months after therapy.
[c]Prednisone dose in mg at diagnosis and 12 months after therapy.
[d]We do not have previous data.
[e]We have data for 6 years before the diagnosis.

FIGURE 1: IgG4 levels and IgG4 time.

One patient with kidney affectation presented a previous perivesical biopsy that showed lymphoplasmacytic chronic inflammatory infiltration and lymphoid follicles. That patient had already been diagnosed with IgG4-RD and was under treatment with oral corticosteroids, and for this reason did not have a renal biopsy.

Other biopsied organs were: submandibular gland (one patient), retroperitoneal tissue (two patients) with inflammatory lymphoplasmocytic infiltration not conclusive for IgG4-RD and chest wall with inflammatory lymphoplasmocytic infiltration with immunihistochemical study compatible with IgG4-RD. One patient had a lymphadenopathy biopsy suggestive of IgG4-RD.

Follow-up and treatment

All patients were followed up for 1 year. All of them received oral prednisone at the diagnosis in a dosage of 0.5–1 mg/kg depending on the severity of symptoms, and was tapered gradually during follow-up.

All patients presented a clinical and analytical response in a mean time of 5 ± 2.6 months. IgG4-RD RI decreased from a median of 11.3 ± 4.2 at baseline to 4.0 ± 1.8 after 6 months and 6.2 ± 5.5 to 12 months of therapy (Figure 4).

Five patients (33.3%) also needed IS therapy. One patient was treated with CNI from diagnosis; he was initially misdiagnosed with membranous nephropathy and initiated CNI before prednisone, resulting in a temporary improvement of the proteinuria with a subsequent relapse at 30 months. After the beginning of the corticoid therapy, he presented an improvement of the nephrotic syndrome and remained in remission for 2 years with low dosage of prednisone. Moreover, four patients (26.7%) needed the addition of a second IS treatment, due to clinical or analytical worsening in the context of low dose of prednisone. In those cases, we used tacrolimus (1/5), MMF (4/5) and RTX (1/5).

Relapses occurred in five patients. Prednisone dosage was tapered gradually in patients with good response, and physicians managed to withdraw it in three patients after 3, 9 and 15 months, respectively. These patients presented a relapse during the first year of treatment (Figure 5) and needed to reintroduce the treatment. There were also 2 patients (16.7%) who presented

Clinical Kidney Journal

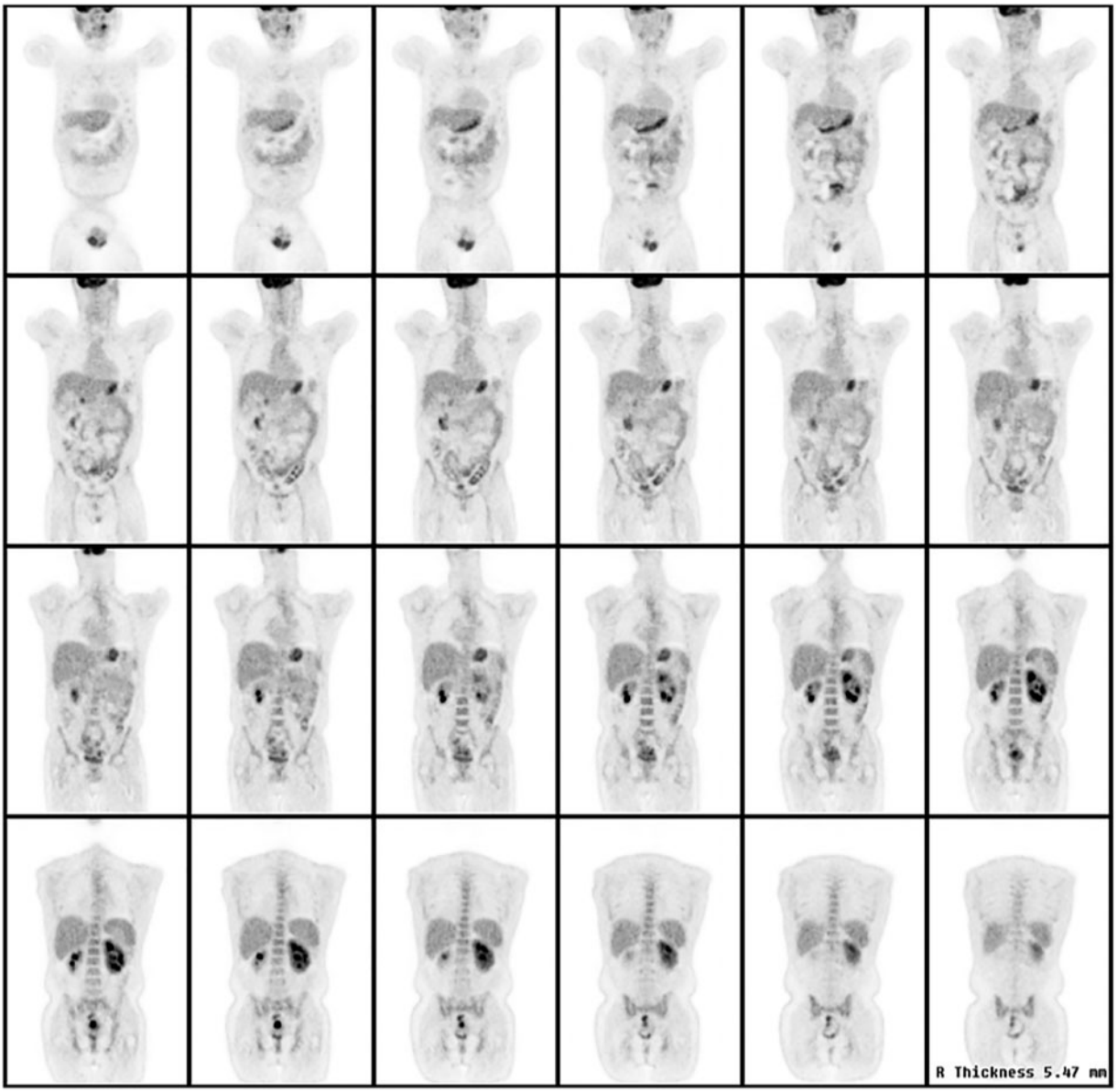

FIGURE 2: PET-SCAN. The picture shows a focal hypermetabolic lesion in the posterior wall of the bladder, and an increased left kidney size with doubtful cortical uptake in relation to acute renal failure versus underlying inflammatory process. Doubtful morphometabolic asymmetry in left palatal amygdala has been described, and increase in gastric level uptake in a diffuse manner, probably physiological in the absence of clinical symptoms (although not adequate gastric preparation).

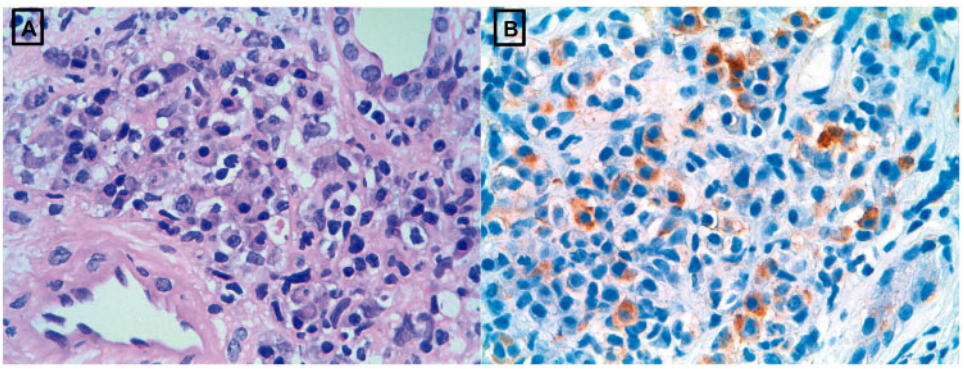

FIGURE 3: Kidney biopsy. (**A**) Optical microscopy of kidney biopsy showing lymphoplasmocytic infiltration with predominance of plasma cells. (**B**) Immunohistochemical study was performed objectifying >10 IgG4-bearing plasma cells per high-power field.

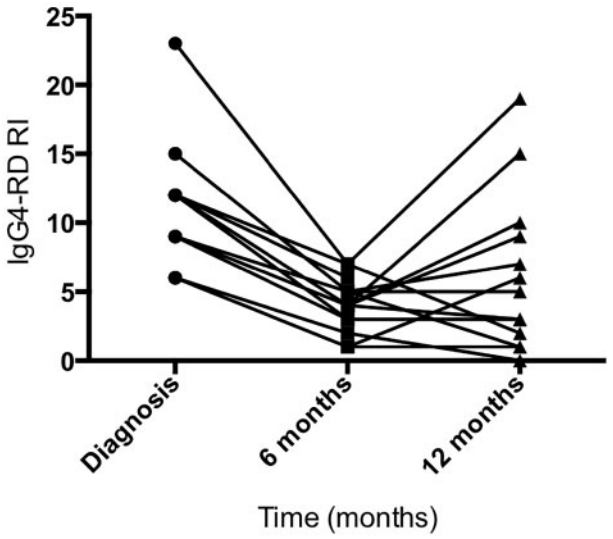

FIGURE 4: IgG4-RD RI and IgG4 time.

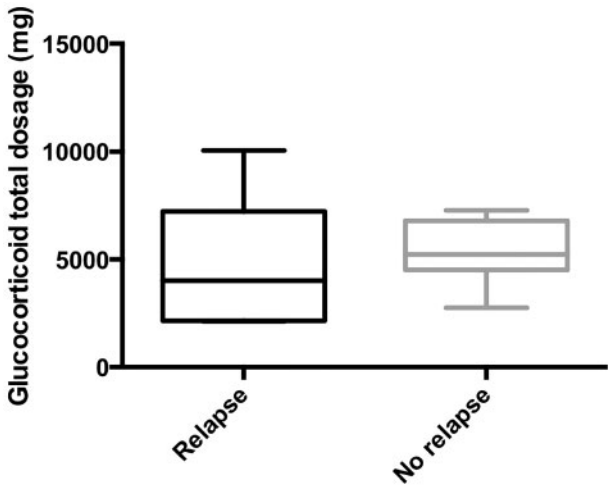

FIGURE 5: Relapse in relation to GC dose received for a year.

a relapse under prednisone therapy, and 10 patients (66.7%) showed no recurrence. Analysing patients who presented a relapse, there was a tendency to less accumulated dose of corticoids during the first year but it was not statistically significant. In our cohort, patients who had a relapse had a median of 2.6 affected organs (patients without relapse had 2.9 damaged organs) and 66.7% of patients with pancreatic manifestation presented a relapse.

Adverse events probably related to therapy occurred in five patients (33.3%). From those, three patients presented an infection (three pneumonias and one of them a surgical wound infection), one patient presented deep vein thrombosis and one a low gastrointestinal bleeding during steroids treatment. Only one patient died, because of respiratory failure due to pneumonia 8 months after starting GC therapy.

DISCUSSION

In this article, we retrospectively analysed the main clinical, histological features and evolution of all patients diagnosed with IgG4-RD in our centre from 2008 to 2015. As some authors described previously [3, 8, 13], considering demographic characteristics, we found that IgG4-RD is a fibro-inflammatory condition with male predominance (80% in our population), affecting people with a mean age of 60.7 years. Concerning clinical features, in our analysis we found 86% of patients presented multiorgan involvement, defined as disease affecting at least two organs, a much higher percentage than Carruthers *et al.* [8] and Campochiaro *et al.* [13], who found in their cohorts a 46.7% and 41.5% frequency of multi-organ involvement, respectively.

Regarding involved organs, mainly affected organs in our patients were lymphadenopathies (53.3%), kidney affectation (46.7%) and salivary glands (33.3%). In most cohorts [8, 13] pancreas is one of the most frequently affected organs (60% and 38.5%, respectively), and in contrast, in our cohort only 7.1% of affected patients had a pancreatic condition.

When we compared laboratory findings we found similar values of serum IgG4 (6823.3 mg/L) as Carruthers *et al.* (6250 mg/L) [8]. In contrast, regarding complement factors, the same author reported mean values of C3 and C4 within normality in all patients (95 and 15 mg/dL, respectively) and we found only two patients with low levels at diagnosis in our cohort. Although IgG4-RD is often associated with allergic condition and hypereosinophilia [3], we only found hypereosinophilia in 26.7% of cases. Other series [13] found similar data describing hypereosinophilia in 30.8% of patients.

We performed PET-SCAN at the diagnosis in 11 patients (73.3%) and in the remaining four patients we performed a computed tomography. Along same lines, Campochiaro *et al.* [13] described that PET-SCAN was performed in 10 patients (38.5%) and the other cases had SCAN or magnetic resonance imaging, depending on organ involvement. In addition, in our population, we used PET-SCAN also for evaluating treatment response in four patients and we identified a decrease of the metabolism in all cases.

Concerning histological features, as described in other studies [13], not all biopsied patients diagnosed with IgG4-RD presented all histological criteria and in some cases the diagnosis was considered 'possible' although not 'definitive' (in our cohort six patients had definitive diagnosis fulfilling the three criteria: clinical, haematological and histopathological). Campochiaro *et al.* [13] did not find differences between those cases considered 'definitive' and the 'possible' ones, suggesting that all patients presented the same disease.

Regarding treatment, all our patients were treated with GS and we added other IS therapy in four patients. Currently, GCs are the first line of therapy in these patients, by suppression of lymphocyte activation and then reducing inflammation, including vascular disease, as Mizushima *et al.* [14] described. In relation to alternative IS treatments, Carruthers *et al.* [8] described in a prospective trial the efficacy of RTX in IgG4. RTX depletes peripheral B cells provoking a decrease in plasmablast and plasma cells that generate IgG4. They concluded that although GCs remain the first treatment, in patients with contraindications to use them for long-term use, RTX could be an alternative treatment. More recently, Quattrocchio *et al.* [15] studied the histological effect of the treatment in a study that included five patients (three with tubulointerstitial nephritis and two with retroperitoneal fibrosis) with definite IgG4-RD who were treated with RTX and GCs. They repeated renal biopsy after 12 months of therapy in patients with tubulointerstitial nephritis, observing a remarkable reduction of interstitial plasma cell infiltrates, and a normalization of IgG4/IgG positive plasma cells, and

concluding that RTX might yield a more effective and long-lasting response in IgG4-RD with kidney involvement.

In August 2017, a nationwide retrospective multicentre study was performed to analyse safety and efficacy of RTX as maintenance and induction therapy associated to other treatments in patients with IgG4-RD [16]. These investigators identified that systematic RTX maintenance treatment was a supposed protective factor, presenting a longer relapse-free survival. They did not find a different rate of relapse after comparing patients with RTX and long-term maintenance of GCs versus patients with RTX and withdrawal of GCs [16].

We found five patients presenting a relapse, three of them related to GC discontinuation. In addition, in these patients we found a tendency for a lower accumulated dose of corticoids during the first year. There are few studies related to outcomes of GCs therapy and in most of them the treatment was not discontinued, keeping low doses of them [9]. Hart *et al.* [17] described in a multicentre report that relapse rates are higher in those patients with intrahepatic biliary involvement and especially in patients with multi-organic affection, but we could not find these differences in our study. Interestingly, this group also described that relapse was most common in those patients with GC therapy discontinuation, like our patients.

Regarding the side effects of the treatment, Campochiaro *et al.* [13] did not find major adverse events related to GCs, highlighting induced diabetes in 32.3% of studied patients. In contrast, we reported five adverse events (33.3%) with one major adverse event (one patient died due to pneumonia) in our cohort. It is important to remark that this disease affects more often the elderly population who are more susceptible to severe adverse events.

In line with our findings and according to Perugino *et al.* [9], we recommend initiating GCs at a dosage of 0.5–1 mg/kg depending on the severity of symptoms, and keeping low doses for at least the first year of treatment.

Our study has some limitations, the most important being the short duration of follow-up, the retrospective nature of the study and the fact that only 26.6% of cases have definitive diagnostics. It is important to remark that in 26.6% of cases patients were not biopsied by physician's decision, and the main affected organs in those cases were pancreatic involvement (50%) and aortitis diagnosed by PET-SCAN (50%).

In conclusion, in this manuscript we reported 15 patients with IgG4-RD diagnosed in our centre. GCs were an effective first line of treatment; however, they was related to substantial adverse events, highlighting serious infections, and relapse with lower cumulative doses or treatment discontinuation. In light of, an alternative IS treatment, like RTX, could be an interesting option for treating those patients.

AUTHORS' CONTRIBUTIONS

The results presented in this article have not been published previously in whole or part, except in abstract form. M.Q. and J.D. have collected information on patients and contributed to writing the manuscript. L.M. contributed by collecting data on patients. X.S., I.R., X.F. and J.T. are the doctors who treated this group of patients in the Outpatient Clinic. M.G. evaluated all biopsies and histological findings. J.M.C. made corrections. J.T. made corrections and annotations, and wrote the final manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Kamisawa T, Funata N, Hayashi Y *et al*. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003; 38: 982–984
2. Deshpande V, Zen Y, Chan JKC *et al*. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012; 25: 1181–1192
3. Stone JH, Zen Y, Deshpande V. IgG4-related disease. *The New England Journal of Medicine* 2012; 366: 539–551
4. Sah RP, Chari ST. Serologic issues in IgG4-related systemic disease and autoimmune pancreatitis. *Curr Opin Rheumatol* 2011; 23: 108–113
5. Stone JH, Hoffman GS, Merkel PA *et al*. A disease-specific activity index for Wegener's granulomatosis: Modification of the Birmingham Vasculitis Activity Score. *Arthritis and Rheum* 2001; 44: 912–920
6. Carruthers MN, Stone JH, Deshpande V *et al*. Development of an IgG4-RD responder index. *Int J Rheumatol* 2012; 2012. doi: 10.1155/2012/259408
7. Fernandez-Codina A, Pinilla B, Pinal-Fernandez I *et al*. Treatment and outcomes in patients with IgG4-related disease using the IgG4 responder index. *Joint Bone Spine* 2018; 85: 721–726
8. Carruthers MN, Topazian MD, Khosroshahi A *et al*. Rituximab for IgG4-related disease: a prospective, open-label trial. *Ann Rheum Dis* 2015; 74: 1171–1177
9. Perugino CA, Stone JH. Treatment of IgG4-related disease. *Zeitschrift für Rheumatologie* 2016; 75: 681–686
10. Kamisawa T, Shimosegawa T, Okazaki K *et al*. Standard steroid treatment for autoimmune pancreatitis. *Gut* 2009; 58: 1504–1507
11. Umehara H, Okazaki K, Nakamura T *et al*. Current approach to the diagnosis of IgG4-related disease–Combination of comprehensive diagnostic and organ-specific criteria. *Mod Rheumatol* 2017; 27: 381–391
12. Umehara H, Okazaki K, Masaki Y *et al*. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol* 2012; 22: 21–30
13. Campochiaro C, Ramirez GA, Bozzolo EP *et al*. IgG4-related disease in Italy: clinical features and outcomes of a large cohort of patients. *Scand J Rheumatol* 2016; 45: 135–145
14. Mizushima I, Inoue D, Yamamoto M *et al*. Clinical course after corticosteroid therapy in IgG4-related aortitis/periaortitis and periarteritis: a retrospective multicenter study. *Arthritis Res Ther* 2014; 16: R156
15. Quattrocchio G, Barreca A, Demarchi A *et al*. IgG4-related kidney disease: the effects of a Rituximab-based immunosuppressive therapy. *Oncotarget* 2018; 9: 21337–47
16. Ebbo M, Grados A, Samson M *et al*. Long-term efficacy and safety of rituximab in IgG4-related disease: data from a French nationwide study of thirty-three patients. *Plos One* 2017; 12: e0183844
17. Hart PA, Kamisawa T, Brugge WR *et al*. Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis. *Gut* 2013; 62: 1771–1776

Clinical Kidney Journal
ckj