Ophthalmic manifestations in IgG4-related disease
Clinical presentation and response to treatment in a French case-series

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Abstract
IgG4-related disease (IgG4-RD) is characterized by variable tissue or organ involvements sharing common pathological findings. Orbital or orbital adnexa involvement of the disease has been reported in a few case series. The aim of our study was to characterize and analyze ophthalmic manifestations from a nationwide French case-series.

Patients with IgG4-RD and orbital or orbital adnexa involvement included in the French multicentric IgG4-RD case-registry were identified. Only patients fulfilling “modified” comprehensive diagnostic criteria with pathological documentation were retained for the study. Clinical, biological, pathological, radiological findings and data regarding the response to treatment were retrospectively analyzed.

According to our data registry, the frequency of IgG4-related ophthalmic disease (IgG4-ROD) was 17%. Mean age at diagnosis was 55.1 ± 7.1 years with a male/female ratio of 2.2. The 19 cases of IgG4-ROD consisted of lacrimal gland (68.4%), soft tissue (57.9%), extraocular muscles (36.8%), palpebral (21.1%), orbital nerve (10.5%), orbital bone (10.5%), and mononeuritis (V1 and/or V2, 10.5%) involvements. IgG4-ROD was bilateral in 57.9% of cases. Extra-ophthalmic manifestations were reported in 78.9% of cases. All patients responded to prednisone but two-thirds of patients relapsed within a mean (SD) of 9.8 (3.5) months and 72.2% required long-term glucocorticoids and/or immunosuppressive agents. Eight patients were treated by rituximab with a favorable response in 87.5% of cases.

Lacrimal involvement is the most frequent ophthalmic manifestation of IgG4-RD and is frequently associated with extra-orbital manifestations. Despite initial favorable response to steroids, the long-term management of relapsing patients needs to be improved.

Abbreviations: 18F-FDG PET/CT = 18F-fluorodeoxyglucose positron emission tomography/computed tomography, AIP = autoimmune pancreatitis, ANA = antinuclear antibodies, AZA = azathioprine, CDC = Comprehensive Diagnostic Criteria, CRP = C-reactive protein, DMARDs = disease-modifying antirheumatic drugs, dSDNA = double-stranded DNA, EOM = extra-orbital muscle, HPF = high-power field, IgG4-ROD = IgG4-related disease, IgG4-ROD = IgG4-related ophthalmic disease, IOD = idiopathic orbital inflammation, LG = lacrimal gland, LN = lymph nodes, MMF = mycophenolate mofetil, MTX = methotrexate, pIgG4+ = IgG4+ plasma cells, RTX = rituximab, SD = standard deviation, sIgG4 = serum IgG4.

Keywords: IgG4-related dacryoadenitis, IgG4-related disease, IgG4-related ophthalmic disease, orbital inflammatory pseudotumor, rituximab

1. Introduction
IgG4-related disease (IgG4-RD) is characterized by typical mass forming lesions with pathological analysis showing dense lymphoplasmacytic infiltrates, fibrosis, and numerous IgG4-plasmocytes.[1] The most frequent manifestations are type 1 autoimmune pancreatitis (AIP), salivary gland and lacrimal gland (LG) involvements, sclerosing cholangitis, tubulo-interstitial nephritis, lymph nodes (LN) enlargement, and retroperitoneal fibrosis.[2–4] Several other tissues or organs can be affected by the disease. These manifestations can be localized to a single organ or affect several organs either at the same time or metachronously.[5] Specific orbital and orbital adnexa involvement have previously been reported from case-series of IgG4-RD patients or from the retrospective analysis of pathological material obtained from orbital pseudo-inflammatory tumor or idiopathic orbital inflammation (IOI) biopsies. These studies have shown that IgG4-related ophthalmic disease (IgG4-ROD) includes several inflammatory conditions of the orbit and the ocular adnexa.[6] Dacryoadenitis, sometimes in the setting of the Mikulicz syndrome, is frequent but IgG4-ROD may also involve orbital...
soft tissues, extra-ocular muscles, eyelids, optical and trigeminal nerves, orbital bones, and the sclera. Hence, differential diagnoses are numerous and include primary Sjogren syndrome, lymphoma, sarcoidosis, granulomatosis with polyangiitis, xanthogranuloma, Erdheim-Chester and Rosai-Dorfman diseases. Because serum IgG (sIgG) elevation and IgG4+ plasma cells tissue infiltration are not specific of IgG4-RD, such diagnosis should only be retained after that an extensive diagnostic workup (including a complete clinical, biological, radiological, and pathological confrontation) has ruled out alternate diagnoses.

In large series, lacrimal gland (dacryoadenitis) involvement varies from 22% to 50%

and orbital involvement from 4% to 22%.

Retrospective analysis of pathological specimen from benign lymphoproliferative disorders and orbital inflammation have reported specific characteristics of IgG4-RD in up to 40% of cases.

Such discrepancies between studies in the rates of IgG4-RD can, at least partly, be explained by the differences in the disease criteria retained for tissue IgG4+ plasma cells infiltrate (i.e., either > 10/high power field (HPF), or > 30/HPF

or > 50–100/HPF

with an IgG4+/IgG ratio > 40%). One hundred seventy-two pooled cases of IgG4-ROD from case-series or case reports have been recently analyzed in a review. The great majority of patients were from Asia or North America.

Larger series are needed to better characterize this rare condition and to improve patient care. Here, we report on the clinical, biological, and pathological characteristics and the response to treatment from 19 patients with IgG4-ROD from a nationwide French case-registry.

2. Patients and methods

The French multicentric database for IgG4-RD (n = 147) was used to select patients presenting with ophthalmic manifestations. Patients were included between 2009 and 2016 and their data were recorded retrospectively from each center. All patients fulfilled the IgG4-RD “modified” comprehensive diagnostic criteria, defined by in all patients: clinical or radiological diffuse/localized swelling or masses in characteristic single or multiple organs; in possible and definite cases: elevated serum IgG4 levels (> 1.35g/L); in probable and definite cases: lymphoplasmacytic polyclonal infiltrate, fibrosis, obliterator phlebitis, and/or increased numbers of eosinophils, with either a ratio of IgG4+/IgG+ (or IgG4+/CD138+) cells > 40% or > 10 IgG4+ plasma cells/HPF (supplemental Table 1, http://links.lww.com/MD/B594). Immunostaining criterion n°3 was modified from the original pathological statement since in our retrospective and multicentric study some tissue biopsies were performed before the latter publication was released and these 2 criteria were not systematically reported in the pathological reports. Patients who did not meet concomitantly both criteria had missing data (IgG-immunostaining or even staining). In all cases a stringent clinicopathologic confrontation was performed in order to rule out all potential alternate diagnoses (especially those in which positive IgG4+ plasma cell infiltrates have been described).

For all cases, the diagnosis of IgG4-RD was retained by the treating physician based on clinical, biological, radiological, and pathological findings. Patients were defined as having IgG4-RD when they had ≥1 ophthalmic manifestation(s) and above-mentioned histological criteria for IgG4-RD in either orbital, periorbital or extra- orbital tissues (supplemental Table 1, http://links.lww.com/MD/B594). Ophthalmic manifestations were defined as lacrimal gland (LG), soft tissue, extra- orbital muscle (EOM), eyelid, cranial nerve, and/or contiguous bone involv- ments. The detection of LN by either clinical, radiological or 18F-FDG PET/CT was considered an IgG4-RD involvement in the absence of another obvious cause.

When evaluable, response to treatment was retrospectively analyzed based on the clinical, biological, and radiological evaluations performed during follow-up. Complete response was defined by a total improvement, partial response by an incomplete improvement and nonresponse by the absence of any improvement or by worsening. Biological response was based on normalization of sIgG4 titers. Values are given as mean±SD.

According to the current French Legislation (Loi Huriet-Serusclat 88-1138, December 20, 1988, and its subsequent amendments, text available at http://www.chu-toulouse.fr/IMG/pdf/loihurstier.pdf), an observational study that does not change routine management of patients does not need to be declared or submitted to the opinion of a research ethics board.

3. Results

3.1. General characteristics

Twenty-five patients from the French case registry for IgG4-RD presented with ophthalmic manifestations. Hence, the overall estimated prevalence of IgG4-ROD in patients with IgG4-RD was 17%. Six patients were excluded due to insufficient data or the absence of sufficient pathological documentation and 19 patients (13 males and 6 females) with a mean age at diagnosis of 55.1 ± 7.1 years (range: 22–86 years) were retained in the final analysis (Table 1). Females with IgG4-RD (mean age: 48.5 years) were younger than males (56.7 years).

All patients fulfilled the definition of either definite or probable IgG4-RD according to the “modified” comprehensive diagnostic criteria (supplemental Table 1, http://links.lww.com/MD/B594). Among 18 patients with available serum IgG4 values, 11 patients (61.1%) presented a definite diagnosis, 7 patients (38.9%) a probable diagnosis.

3.2. Clinical characteristics

IgG4-RD consisted of LG (68.4%), soft tissue (57.9%), extra-ocular muscles (EOM, 36.8%), palpebral (21.1%), orbital nerve (10.5%), and mononeuritis (V1 and/or V2, 10.5%) involvements (Table 1). In addition, disease-specific keratitis was reported in a single patient. Overall, IgG4-RD’s extra-ophthalmic manifestations were reported in 78.9% of cases and consisted of pancreatic (n = 7), salivary gland (n = 11), retroperitoneal (n = 2), biliary tract (n = 1), LN (n = 13), sinuses (n = 3), renal (n = 3), pulmonary (n = 2), prostatic (n = 1), testicular (n = 1), hypophysial (n = 1), thyroid (n = 1), and paravertebral (n = 1) involvements. In 6 of 15 IgG4-RD patients, extra-ophthalmic manifestations were restricted to the head and neck area: salivary gland±LN (n = 4), sinuses (n = 1), Riedel thyroiditis (n = 1), lacrimal gland involvement was associated with other features of IgG4-RD including 61.5% (8/13) of cases with soft tissue (n = 5), palpebral (n = 4), EOM (n = 3), orbital nerve (n = 1), and V2 (n = 1) involvements. All 13 patients with LG involvement presented with extra-ophthalmic features of IgG4-RD.
IgG4-ROD was bilateral in 11 cases (57.9%) among which 10 patients (90.9%) presented with dacryoadenitis (LG) and the remaining patient presented with bilateral soft tissue involvement. Of note, all patients with bilateral IgG4-ROD presented with extra-orbital manifestations, with disease symptoms restricted to the head and neck area in 27.7%. Unilateral involvement was reported in 8 cases (42.1%) and was not restricted to a specific localization of IgG4-ROD. The rates of unilateral involvement according to each subtype of IgG4-ROD manifestations were: 23.1% in LG, 54.5% in soft tissue, 57.1% in EOM, 50% in optical nerve, 50% in trigeminal V1/V2 nerve, and 100% (2/2) in orbital bone involvements.

IgG4-ROD was associated with visual acuity impairment or loss of vision in 4 patients. All of the latter patients presented with soft tissue involvement and 2 had bilateral IgG4-ROD. In 1 patient (patient 12), orbital soft tissue involvement was isolated with no other IgG4-ROD or extra-orbital IgG4-RD manifestations. In the 3 other patients, soft tissue involvement was associated with neural (optical nerve in 2, V2 in 1) and EOM involvements (2/3).

### 3.3. Pathological findings

Pathological analysis of IgG4-ROD involvement was available in 10 cases: soft tissue in 8/11 and LG in the remaining 2 patients (Table 2). A dense lymphoplasmacytic infiltrate was the main feature reported in all cases, while fibrosis was found in 8 of 10 biopsies and eosinophilic infiltrates in 3 of 10. Obliterative phlebitis was never reported and a storiform pattern was not mentioned in the only available lacrimal specimen with fibrosis. Immunohistochemistry for IgG4-positive plasma cells was performed in 9 of 10 cases showing either an IgG4+/IgG+ plasma cells ratio >40% (n=5) or a IgG4+ plasma cells count/HPF >10 (n=7) (Table 2). In the patient without available data regarding IgG4 immunostaining on orbital tissue (patient 17), the pathological assessment of IgG4-ROD was performed on a pancreas biopsy showing a IgG4+/IgG+ cells ratio of 50% with 45 IgG4+ plasma cells (plgG4+)/HPF. In patients without pathological documentation of IgG4-ROD, pathological examination and IgG4 immunostainings were assessed in pancreas biopsy for patients 1 (>10 plgG4+/HPF) and 5 (>50 plgG4+/HPF); in salivary gland biopsies for patients 3 (ratio >40% and

Table 1
Clinical characteristics of 19 patients with IgG4-ROD.

| Case | Age/ gender | Orbital manifestations | Extra-orbital manifestations | Bilateral | VAI | Serum IgG4 (g/L) |
|------|-------------|------------------------|------------------------------|-----------|-----|-----------------|
| 1    | 58/F        | Lacrimal gland, eyelid | RPF, AIP, salivary gland, sclerosing cholangitis, LN | Yes | No | 0.3 |
| 2    | 68/M        | EOM, soft tissue, optical nerve, orbital bone | None | No | Yes | 1.031 |
| 3    | 86/M        | Lacrimal gland, soft tissue | Salivary gland, LN | No | No | 0.153 |
| 4    | 32/F        | Lacrimal gland, soft tissue, palpebral, EOM | LN | Yes | No | 4.01 |
| 5    | 63/M        | Lacrimal gland | AIP, Salivary gland, LN | Yes | No | 2.9 |
| 6    | 61/M        | Soft tissue | Salivary gland | Yes | No | 0.32 |
| 7    | 53/M        | Lacrimal gland | AIP, salivary gland, TIN, LN | No | No | 0.133 |
| 8    | 61/F        | Soft tissue, EOM, V1 and V2 | none | No | No | 7.3 |
| 9    | 35/M        | Lacrimal gland | TIN, prostate, testis, lung, AIP, LN | Yes | No | 18.5 |
| 10   | 42/M        | Lacrimal gland, EOM, eyelid | Sinus, AIP, salivary gland, TIN, LN, lung | Yes | No | 3 |
| 11   | 38/F        | Soft tissue, EOM | None | No | No | 1.04 |
| 12   | 42/M        | Soft tissue | None | No | Yes | ND |
| 13   | 65/M        | Soft tissue, EOM, orbital bone | Sinus | No | No | ND |
| 14   | 62/M        | Lacrimal gland, soft tissue | AIP, salivary gland, LN, sinus | No | No | 12.3 |
| 15   | 67/M        | Lacrimal gland, soft tissue | Riedel thyroiditis, LN | Yes | No | 5.2 |
| 16   | 70/F        | Lacrimal gland, eyelid | Salivary gland, LN, prevertebral infiltration, RPF | Yes | No | >5 |
| 17   | 61/F        | Lacrimal gland, soft tissue, optic nerve | AIP, salivary gland, hypophysitis, LN | Yes | Yes | 28.7 |
| 18   | 54/M        | Lacrimal gland, soft tissue, EOM, V2 | Salivary gland, LN | Yes | Yes | 12.25 |
| 19   | 48/M        | Lacrimal gland | Salivary gland, LN | Yes | No | 8.78 |

*AP = autoimmune pancreatitis, EOM = extra-orbital muscle, F = female, LN = lymph node, M = male, RPF = retro-peritoneal fibrosis, TIN = tubulo-interstitial nephritis, VAI = visual acuity impairment.

Table 2
Pathological characteristics of orbital biopsies in patients with IgG4-ROD.

| Case | Biopsy site | Fibrosis | LP | Eo | Obliterative phlebitis | IgG4+/IgG+ ratio | IgG4+/HPF | "Modified" CDC category |
|------|-------------|----------|----|----|------------------------|-----------------|-----------|-------------------------|
| 2    | Soft tissue | +        | +  | –  | –                      | >50%            | >50       | Probable                |
| 4    | LG          | +        | +  | –  | –                      | ND              | >100      | Definite                |
| 8    | Soft tissue | +        | +  | –  | –                      | 90%             | NA        | Definite                |
| 11   | Soft tissue | +        | +  | –  | –                      | ND              | >10       | Probable                |
| 12   | Soft tissue | +        | +  | –  | –                      | ND              | >40       | Probable                |
| 13   | Soft tissue | -        | +  | –  | –                      | >50%            | >50       | NE                      |
| 14   | LG          | +        | +  | –  | –                      | 50%             | NA        | Definite                |
| 15   | Soft tissue | –        | +  | –  | –                      | ND              | >30       | Definite                |
| 17   | Soft tissue | +        | +  | –  | –                      | ND              | ND        | Definite*               |
| 18   | Soft tissue | +        | +  | –  | –                      | 50%             | 25        | Definite                |

*CDC = comprehensive diagnostic criteria, Eo = eosinophils, HPF = high power field, LG = lacrimal gland, LP = dense lymphoplasmocytic infiltrate, NE = non-evaluable (nonavailable serum IgG4).

*For patient 17, pathological assessment of IgG4-ROD was performed in a pancreas biopsy with a 50% IgG4+/IgG+ cells ratio and 45 IgG4+ plasma cells/HPF.

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50pIgG4+/HPF), 7 (100pIgG4+/HPF), and 16 (ratio 50% and 30pIgG4+/HPF); in kidney biopsies for patients 7 (ratio > 40% and 115pIgG4+/HPF) and 9 (ratio > 50% and 30pIgG4+/HPF); in LN biopsies for patients 10 (ratio > 90%) and 19 (ratio 40% and 10pIgG4+/HPF, the parotid biopsy otherwise showing only fibrosis without cell infiltrates). The latter 2 patients with only LN pathological analysis presented with other typical manifestations of IgG4-RD and high levels of sIgG4.

3.4. Biological findings

Serum IgG4 (sIgG4) levels were elevated (>1.35g/L) in 11 of 18 (61.1%) patients with available sIgG4 titers. Mean sIgG4 was 6.52g/L ± 6.00 (range: 0.1 – 28.7g/L). CRP levels were variable but usually moderately elevated, with a mean value of 16.7mg/L ± 0.7 (range: 1 – 119mg/L). Antinuclear autoantibodies were found in 7 of 17 patients, between 1/80 and 1/320 but no patient had either dsDNA or extractable nuclear antigen (especially SSA or SSB) positive autoantibodies (Supplemental Table 2, http://links.lww.com/MD/B594).

3.5. Response to treatment

All patients received first-line therapy with prednisone. Twelve patients received prednisone for orbital manifestations and in the remaining cases, the treatment was initiated for other IgG4-RD localizations (Table 3). Overall 13 of 19 patients (68.4%) relapsed after a first course of glucocorticoids. Relapses were treated by azathioprine (AZA, n=6), methotrexate (MTX, n=1), mycophenolate mofetil (MMF, n=2), and rituximab (RTX, n=8) (Table 3). At last follow-up, 72.2% of patients remained under treatment with either prednisone alone (n=11), MMF (n=1), or both (n=1). Mean follow-up was 40.2 ± 79.2 months (range: 3 – 115 months). Treatment with rituximab was associated with complete clinical and complete or partial radiological responses in all patients but one (otherwise considered a nonresponder due to clinical and radiological findings).

Among the 12 patients treated for IgG4-ROD, the clinical response to prednisone was reported in all patients and a biological response (normalization of sIgG4 levels) was found in 5 of 6 evaluable patients (1 nonresponder and 6 patients with...

| Treatment indication | TT | Response to TT | Relapse | TT at last visit | FwuP (m) |
|----------------------|----|----------------|---------|-----------------|----------|
| 1                    | AIP, RPF | PON | Clin: R; Bio: R; IM: R | Yes | PON 5 mg/d | 115 |
| 2                    | lgG4-ROD | PON | Clin: R; Bio: R; IM: CR | Yes | PON 4 mg/d | 29 |
| 3                    | lgG4-ROD | RTX | Clin: R; Bio: NE; IM: PR | No | PON 7 mg/d | 7 |
| 4                    | lgG4-ROD | PON | Clin: R; Bio: R; IM: NA | Yes | PON 10 mg/d | 17 |
| 5                    | AP      | PON | Clin: R; Bio: R; IM: R | No | PON 10 mg/d | 7 |
| 6                    | lgG4-ROD | PON | Clin: R; Bio NA; IM: NA | Yes | PON 10 mg/d | 23 |
| 7                    | AIP, TIN | PON | Clin: R; Bio: R; IM: R | Yes | PON 7.5 mg/d | 47 |
| 8                    | lgG4-ROD | RTX | Clin: R; Bio: R; IM: NA | Yes | PON 5 mg/d | 112 |
| 9                    | AIP, TIN | RTX | Clin: R; Bio: NE; IM: R | Yes | 0 | 40 |
| 10                   | AIP, TIN | MTX | Clin: R; Bio: R; IM: R | Yes | PON 5 mg/d | 52 |
| 11                   | lgG4-ROD | PON | Clin: R; Bio: NE; IM: PR | No | 0 | 19 |
| 12                   | lgG4-ROD | RTX | Clin: NE; Bio: NE; IM:NE | Yes | PON 10 mg/d | 51 |
| 13                   | lgG4-ROD | AZA | Clin: R; Bio: R; IM: R | Yes | MMF | 32 |
| 14                   | AIP      | PON | Clin: R; Bio: R; IM: NA | Yes | PON 5 mg/d | 14 |
| 15                   | lgG4-ROD | PON | Clin: R; Bio: NE; IM: NE | No | 0 | 11 |
| 16                   | RPF      | AZA | Clin: R; Bio: R; IM: R | Yes | PON 10 mg/d + MMF | 60 |
| 17                   | AIP and lgG4-ROD | AZA | Clin: R; Bio: PR; IM: PR | No | NE | 75 |
| 18                   | lgG4-ROD | AZA | Clin: R; Bio: R; IM: PR | No | NE | 75 |
| 19                   | lgG4-ROD | AZA | Clin: R; Bio: R; IM: PR | No | 0 | 3 |

For each line of treatment (column 3) responses to treatment for clinical (Clin), biological (Bio), and imagery (IM) are detailed in column 4. When the treatment was stopped for side effects “toxicity” is noted in column 4.

*AP = autoimmune pancreatitis, AZA = azathioprine, Bio = biological, Clin = clinical, FuP = follow-up, IgG4-ROD = IgG4-related ophthalmic disease, IM = imagery, MMF = mycophenolate mofetil, NE = not evaluable, NR = nonresponder, PDN = prednisone, PR = partial response, R = response, RPF = retroperitoneal fibrosis, RTX = rituximab, TN = tubulointerstitial nephritis, TT = treatment.

∗ Patient deceased at 75 months follow-up by an unrelated cause.
when managing patients with IgG4-ROD. A radiological response was reported in all 6 evaluable patients (complete response, n = 2; partial response, n = 4). Five patients initially treated for IgG4-ROD required no other treatment. Seven patients (38.3%) relapsed with a mean time to first relapse of 9.8 ± 3.5 months (range: 6–15), and received as second-line therapy AZA in 3 and RTX in 7.

4. Discussion

IgG4-ROD has recently been recognized as a cause of idiopathic orbital inflammation (IOI) or orbital benign lymphoproliferative disease.\(^6,14,16,17\) IgG4-ROD was first identified thanks to the reporting of patients with orbital manifestations concomitant to other IgG4-RD manifestations and to the retrospective search of IgG4-RD pathological characteristics in pathological specimen of inflammatory orbital diseases. The frequency of IgG4-ROD ranges 4% to 34% of IgG4-RD patients according to the largest case series published to date.\(^17–20\) Our findings are in line with these data since 17% of all patients included in the French case registry for IgG4-ROD presented with symptoms likely to be related to IgG4-ROD. Besides, clinical manifestations in our case series are comparable to those reported in North American or Japanese patients.\(^6\) Mean age was similar to previous reports but we found a relatively higher male/female ratio of 2.2:1.\(^6\)

Concordant with previous series, IgG4-ROD was bilateral in 58% of the patients and was associated with extra-orbital manifestations in around 80% of cases (70%–100%).\(^6,14,17\) Next, LG was the most frequent organ involved, followed by soft tissue and EOM. Because radiological findings were not systematically reviewed, we could not assess the true prevalence of trigeminal nerve enlargement otherwise considered by others as useful to differentiate IgG4-ROD with other inflammatory orbital diseases.\(^6,21,22\) Of note, we report on 2 patients with clinical involvement of the trigeminal nerve and 2 with optical nerve involvement. Bone involvement was also found in 2 additional cases. One patient presented with sclera/keratitis involvement, but none had conjunctival or lacrimal sac involvements. Contrary to previous reports suggesting that uveitis might belong to the spectrum of IgG4-ROD,\(^23\) we did not identify such case in the present study.

Visual impairment has been reported in as high as 40% of patients with IgG4-ROD presenting as IOI.\(^1,24\) In 4 (21%) patients of the present study, visual acuity impairment or loss was reported. All of these patients presented with orbital soft tissue involvement and 2 with documented optical nerve involvement. Bilateral IgG4-ROD or extra-orbital manifestations were present in only 2 of these patients and were not predictive of visual impairment. Hence, even if it has not been considered by the international consensus statement for the treatment of IgG4-ROD as an indication for urgent treatment, the risk of visual acuity impairment should be a concern when managing patients with IgG4-ROD.\(^6\)

The association with extra-orbital manifestations was the most frequent in patients with either LG (100%) or bilateral IgG4-ROD (100%). This is concordant with previously published data and further emphasizes the fact that patients with LG or bilateral IgG4-ROD should be screened for other localizations of the disease.\(^1\) Besides routine physical and biological evaluations, there is no consensus on the optimal strategy as for which radiological investigations to perform, but \(^1\)F-FDG PET/CT could be promising in this setting.\(^1,8,23\)

Biological assessment of patients showed that sIgG4 > 1.35 g/L were found in 58% of patients, which is lower than the rates reported in previous series (i.e., 63%–100%).\(^6,16,17\) As previously suggested, sIgG4 elevation was preferentially associated with bilateral forms, and was associated with extra-orbital and systemic manifestations of IgG4-RD.\(^5\) Under treatment, sIgG4 normalized in most evaluable patients (5/6 evaluable patients treated for IgG4-ROD) and correlated with clinical and radiological responses of the disease.\(^24\) CRP levels were usually normal or slightly elevated. Circulating plasmablasts were not evaluated in these patients as this is not yet performed as routine biological examination in most centers.\(^1,27\) Other causes of orbital inflammation were excluded and ANA were positive only in a small number of patients, at a low titer and without evidence of either dsDNA or extractable nuclear antigen (especially SSA or SSB) autoantibodies.

Pathological analyses of lacrimal gland or orbital soft tissue biopsies were only available for half of the patients. In the remaining cases, pathological assessment of IgG4-ROD was performed on extra-orbital tissue biopsies. All patients fulfilled the “modified” CDC criteria but the pathological consensus criteria for LG were not fulfilled for all\(^6,14\) Indeed, a limitation to the present study was the frequent lack of the IgG4/1gG ratio measure due to the high background for IgG staining reported by the pathologists. In some patients, the measure of such a ratio was performed by analyzing the IgG4/1gG ratio, which theoretically can underestimate the IgG4/1gG ratio. Besides, in some cases, the pathologists did not report on the IgG4 plasma cells count/HPF despite an increased IgG4/1gG ratio >40%. Fibrosis was reported in all patients (without storiform pattern otherwise reported in lacrimal localization of IgG4-RD) except 2 cases of lacrimal gland and orbital biopsies each. Next, a dense lymphoplasmacytic infiltrate was reported in all cases. Sparse eosinophils were observed in only 3 soft tissue biopsies (that did not comprise LG) and obliterative phlebitis was never reported in the present series, as previously published in IgG4-ROD.\(^6,28\)

Yet, in all cases, a strict clinicopathologic correlation was performed to rigorously rule out diseases that mimic IgG4-RD, especially those presenting with tumefactive lesions and increased IgG4+ plasma cells on tissue biopsy. Two patients (patients 11 and 12) presented with no extra-orbital manifestations of IgG4-RD and normal serum IgG4 levels, but were included in order not to underestimate the true prevalence of IgG4-ROD or even overlook an entire pattern of patients with strictly localized orbital disease. After a follow-up period of 19 and 51 months respectively, no differential diagnosis has appeared in both patients.

All patients were treated as first-line therapy with prednisone and clinically improved with such treatment. This high rate of response to prednisone is a common feature of IgG4-RD.\(^1,29\) Yet, relapses were frequent (roughly two-thirds of the patients). This rate is close to the 67% relapse rate reported in a large international multicentric cohort of AIP.\(^24\) Moreover, 63% of patients received a second-line therapy, RTX in 9 (47%), DMARDs (AZA, MMF, or MTX) in 7 (37%), either for a disease relapse or as a steroid-sparing agent. At last visit, >70% of all patients remained under treatment with either low-dose prednisone, MMF or both, thus highlighting that glucocorticoid-sparing agents are needed in IgG4-ROD. Definite conclusions cannot be driven out of this retrospective case series but RTX seemed highly effective in the present series. Indeed, all but 1 relapsing patients who received RTX as second-line therapy responded to treatment, and 2 of 3 patients who failed to respond to a DMARDs second-line therapy were successfully challenged with RTX as third-line therapy. Overall, DMARDs were poorly
effective and were often withdrawn due to drug-related toxicity. In 7 cases, RTX was specifically indicated for IgG4-ROD presenting as: soft tissue (n = 6), EOM (n = 4), nerve (n = 2), or bone (n = 2) involvements. Of these 7 patients, 2 were off treatment and 5 remained under maintenance therapy at the last visit. These results are similar to those previously reported in other cohorts of patients with IgG4-ROD treated with RTX. While RTX indeed seems to be an effective treatment option for the management of IgG4-ROD, the optimal frequency and duration of infusions remains to be determined. Moreover, since RTX only seems to have a temporary effect and that relapses have been reported under treatment, new therapeutic approaches should be developed. Specifically targeting T-cells rather than B-cells could be another approach based on the characterization of abnormal T-cell subsets in IgG4-ROD and the efficacy reported in a recent case report with a CTLA4-agonist antibody.[12-34]

Our study has some limitations. First, the French IgG4-ROD case-registry is a declarative registry, thus possibly leading to a selection bias with the most severe cases reported and milder presentation of IgG4-ROD possibly underrepresented. Next, our study has limited sample-size and suffers from the limitations of its retrospective design, namely missing data (especially pathological findings) and lost to follow-up.

Yet, we report on a well-documented series of patients with IgG4-ROD with long-term follow-up. Interestingly, clinical and biological characteristics of IgG4-ROD in this European case-series are similar to those previously reported in North American and Asian patients. Lacrimal involvement is the most frequent manifestation of IgG4-ROD and is frequently associated with disease-specific extra-orbital manifestations. Despite initial favorable response to steroids, relapses are frequent and patients with soft tissue involvement can present with visual impairment. As second or third-line therapy, RTX was associated with high remission rates. Yet, the long-term management of relapsing patients needs to be improved.

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