Therapeutic approach to IgG4-related disease
A systematic review

Pilar Brito-Zerón (MD, PhD)\textsuperscript{a,b,c}, Belchin Kostov (MSc, PhD)\textsuperscript{d,e}, Xavier Bosch (MD, PhD)\textsuperscript{f}, Nihan Acar-Denizli (MSc)\textsuperscript{g}, Manuel Ramos-Casals (MD, PhD)\textsuperscript{b,c,h,*}, John H. Stone (MD, MPH)\textsuperscript{i}

Abstract
To review the reported evidence on the therapeutic management of IgG4-related disease (IgG4-RD) in clinical practice.

A systematic search of the literature was conducted. The primary outcome measured was the rate of efficacy of first-line therapeutic approaches. Secondary outcomes included the rate of disease relapse, the outcome of untreated patients, the rate of patients without drug therapy at the end of follow-up, the rate of side effects, and mortality. The MOOSE, AHRQ, STROBE, and GRACE recommendations/statements were followed.

The results of the systematic search strategy yielded 62 studies that included a total of 3034 patients. Complete information about first-line therapeutic regimens was detailed in 1952 patients, including glucocorticoid-based regimens in 1437 (74%), drug-free regimens in 213 (11%), and other therapies in 38 (2%). No therapy (wait and see management) was reported in 264 (13%) patients.

The efficacy of monotherapy with glucocorticoids was specified in 1220 patients, of whom 97% had a therapeutic response. Relapses, however, were reported in 464/1395 (33%) patients despite typically short follow-up periods. Therapeutic efficacy was reported in 219/231 (95%) of relapses treated with glucocorticoids, 56/69 (81%) of those treated with azathioprine, 16/22 (72%) of those treated with other immunosuppressive agents, and in the 9 cases treated with rituximab (100%). In 14 studies, the authors detailed the outcome of 159/246 patients with wait-and-see management; spontaneous improvement or resolution was reported in 68 (43%) cases. Wide heterogeneity was observed with respect to the first-line therapeutic approaches used for the different organ-specific disease subsets, including significant differences in the mean dose of glucocorticoids used.

Nearly 70% of reported IgG4-RD patients are treated with oral glucocorticoids in monotherapy. However, the therapeutic management is heavily influenced by geographical, epidemiological, and clinical factors, especially with respect to the predominant organ affected. The frequency of glucocorticoid failure to induce sustained remissions both during and after treatment and the assessment of glucocorticoid toxicity in IgG4-RD require further study.

Abbreviations: AIP = autoimmune pancreatitis, DM = diabetes mellitus, IgG4-RD = IgG4-related disease.

Keywords: autoimmune pancreatitis, glucocorticoids, IgG4, IgG4-related disease, rituximab

1. Introduction
IgG4-related disease (IgG4-RD) is an immune-mediated systemic disease first described in Japan at the beginning of this century.\textsuperscript{[1]} The most common clinical presentation is the development of a mass lesion or unexplained enlargement of one or more organs. Although IgG4-RD usually presents with a subacute onset, the disease leads to progressive organ failure and even death in some patients. Multiorgan disease is easier to identify at diagnosis but may evolve metachronously, with 1 organ at a time being added over months to years.\textsuperscript{[1]} The organs most frequently involved are the pancreas and biliary tract, the salivary and lachrymal glands, the kidneys, the thyroid gland, the lungs, and the aorta.\textsuperscript{[2]} Diagnosis relies on the coexistence of various clinical, laboratory, radiological, and histopathological findings, although none is pathognomonic in itself.\textsuperscript{[3]}

The optimum therapeutic management of IgG4-RD has not yet been established.\textsuperscript{[4]} In spite of an explosion in observational studies in the last decade, no randomized controlled studies on the treatment of IgG4-RD are yet available. Therefore, in the absence of high-quality scientific evidence, a systematic approach using meta-analyses of observational studies is one of the few ways to assess the degree of efficacy of the therapeutic options currently used in clinical practice. This information may be useful for the design of future prospective/controlled therapeutic trials in IgG4-RD patients.

The objective of this review was to summarize reported evidence on the therapeutic management of IgG4-RD in clinical
practice with the aim of providing physicians with the best available therapeutic evidence, tailored when possible to the possible clinical scenarios with which IgG4-RD present.

2. Methods

2.1. Data sources and searches

A systematic search of the literature was conducted on MEDLINE and EMBASE and using the OVID interface to search for evidence-based medicine reviews in the Cochrane Databases of systematic reviews and controlled trials. We also searched for unpublished trials using ClinicalTrials.gov (last day of access to the databases, October 31, 2014). Due to the lack of specific Medical Subject Headings for IgG4-RD, a text-word search was conducted using the free text “IgG4-related disease” as the currently most-accepted term.[1] No restrictions were placed on language or type of publication. We manually searched reference lists of selected articles for relevant citations that our searches missed. We followed the AMSTAR recommendations on data sources and searches.[5]

2.2. Study selection

Study selection was made by independent review. Two independent reviewers (MRC and XB) examined abstracts retrieved by the literature search for potentially eligible articles. Studies marked for possible inclusion by either reviewer underwent dual, independent full-text review. Differences between reviewers were resolved by consensus. Criteria for inclusion were the following: inclusion of at least 5 patients, enrollment of adults (aged ≥18 years), diagnosis of IgG4-RD according to current classification criteria sets,[6] and availability of data on at least one of the following outcomes: therapeutic efficacy; disease outcomes (relapses, maintenance drug therapy, and/or death); and/or adverse drug effects.

2.3. Data extraction and quality assessment

A data extraction form was developed by PBZ prior to manuscript review to gather relevant data from each article. All data extractions were reviewed for completeness and accuracy by PBZ, XB, and MRC. Study design was classified according to the STROBE recommendations for observational studies (case-control, cross-sectional, and cohort studies).[7] Variables collected for each study included the mean age of the cohort, gender frequencies, country, inclusion criteria, first-line therapeutic approaches, drug therapies (types, dose, length, and adverse effects), therapeutic efficacy, relapses and therapeutic management, side effects, mean time of follow-up, therapies at the last visit, and death. The primary outcome measured was the rate of efficacy of first-line therapeutic approaches. Secondary outcomes measured included the rate of disease relapse, the outcome of untreated patients, the rate of patients without drug therapy at the end of follow-up, the rate of side effects, and mortality. Relapses were defined as a disease exacerbation following a period of improvement – whether or not the treatment response was complete.

For quality assessment, a prespecified study protocol was developed by BK and XB prior to the literature review, according to the MOOSE,[8] AHRQ,[9] STROBE,[7] and GRACE[10] recommendations/statements. Supplementary Table 1, http://links.lww.com/MD/B85 summarizes the quality domains evaluated for each study. Possible overlapping data were managed by contrasting the following variables between studies: name of authors, participating centers, number of patients, epidemiological features, type of organ involvement, period of patient recruitment, and name of the database/multicenter group. When there was more than 1 report from the same group, we included only the publication having the most detailed therapeutic information for the entire cohort.

The ethical approval was not necessary because the study uses existing data (literature review).

2.4. Statistical analysis

Descriptive data were presented as means and standard deviation (SD) for continuous variables and numbers and percentages for categorical variables. Subset statistical analyses searching for potential sources of heterogeneity in the therapeutic approaches suggested by a previous study[5] were carried out according to the geographical origin and the organ predominantly involved. The Chi-square test for contingency tables was used to compare gender, geographical origin, first-line regimens, therapeutic efficacy, relapses, side effects, mortality, and therapeutic management. Continuous outcomes such as mean age of the cohort, mean time of follow-up, and mean starting doses were compared using the nonparametric Kruskal–Wallis test. Forest plots with the odds ratios (ORs) and their 95% confidence intervals (CIs) were constructed to represent the association between study characteristics and outcomes. All significance tests were 2-tailed, and values of P < 0.05 were considered significant. All analyses were conducted by BK and NAD using the R V.3.2.3 for Windows statistical software package.

3. Results

The results of the systematic search strategy are summarized in Fig. 1: 62 studies[11–72] including 3034 patients were analyzed (Supplementary Table 2, http://links.lww.com/MD/B85). Table 1 summarizes the main patient characteristics.

3.1. Outcomes

3.1.1. Efficacy of first-line therapeutic approaches

Complete information about first-line therapeutic regimens was detailed in 1952 patients included in 48 studies (Table 1). First-line therapies included glucocorticoid-based regimens in 1437 (74%) patients, drug-free regimens (surgery or radiotherapy) in 213 (11%) patients, and other therapies in 38 (2%). No therapy, that is, wait-and-see management, was reported in 264 (13%) patients. Glucocorticoids were administered orally in all patients except for 10, who were treated with topical glucocorticoid preparations. The mean starting dose was ≤0.6 mg/kg/d (equivalent to 40 mg/d) in 24 (73%) of the 33 studies in which this information was provided. The efficacy of first-line therapies was detailed in 1293 patients, of whom 1246 (96%) were reported as having a therapeutic response. The efficacy of monotherapy with glucocorticoids was specified in 1220 patients, of whom 1186 (97%) were reported as having a therapeutic response. However, the glucocorticoids response was classified as complete in only 84/130 (65%) of the patients, partial/incomplete in 31/130 (24%), and absent (no response) in 15/130 (11%). The efficacy of other therapies was 14/17 (82%) for surgery, 20/22 (91%) for combined glucocorticoids/surgery, 17/22 (77%) for immunosuppressive/biological agents, and 9/12 (75%) for radiotherapy (Table 2).
Therapeutic failure with first-line therapies was reported in 47 patients (4%). The response to rescue therapies was detailed in only 18 cases and included glucocorticoids in 2 (response in both), surgery in 1 (no response), rituximab in 6 (response in 4), and immunosuppressants in 9 (response in 6) (Supplementary Table 3, http://links.lww.com/MD/B85).

3.1.2. Relapses. Relapses were reported in 464/1395 (33%) patients. The ongoing use of glucocorticoids at relapse was specified in 381 patients. Among these 381, the disease relapse occurred in 245 (64%) after the cessation of glucocorticoids. In more than one third of the patients, however (136; 36%), disease relapses occurred while patients were still receiving glucocorticoids.

Information on the therapeutic management of relapses was detailed in 378 cases and included mainly glucocorticoid use.

Table 1

| Geographical distribution | Patients (studies) |
|---------------------------|--------------------|
| Asian countries           | 1517 (43)          |
| European countries        | 235 (8)            |
| American countries        | 293 (10)           |
| Australia                 | 11 (2)             |
| International registries  | 978 (1)            |

| Organ-specific selection of patients | Patients (studies) |
|-------------------------------------|--------------------|
| Autoimmune pancreatitis/sclerosing cholangitis | 1651 (12) |
| Ocular involvement                  | 101 (8)           |
| Salivary gland involvement          | 173 (5)           |
| Renal involvement                   | 140 (5)           |
| Lymph nodes/skin involvement        | 67 (4)            |
| Other organ-specific involvements    | 207 (14)          |
| Unselected patients (systemic)      | 695 (14)          |

| First-line therapeutic regimens | N = 1952 patients |
|--------------------------------|-------------------|
| Glucocorticoid-based regimens   | 1437 (74%)        |
| Alone                           | 1362              |
| In combination with other therapies | 75              |
| No drugs-based regimens         | 213 (11%)         |
| Surgical approaches             | 200               |
| Radiotherapy                    | 13                |
| Other therapies*                | 38 (2%)           |
| No therapy                      | 264 (13%)         |

| Follow-up of studies | N=22 studies |
|----------------------|--------------|
| Mean (months)        | 23.25 (1–224) |
| <1 y                 | 2 studies (9%) |
| 1–4 y                | 17 studies (77%) |
| >4 y                 | 3 studies (14%) |

* Other therapies: palliative (23), rituximab (6), methotrexate (3), angiotensin-converting enzyme inhibitors (1), extract of Tripterygium wilfordii hook (1), antitubercular agents (1), and surgery + chemotherapy (3).

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Table 2

| Efficacy of first-line therapeutic regimens and secondary outcomes. Variables were not detailed in all studies, and the prevalence of a specific feature has been stated as number of cases with that feature/number of cases in which the feature was detailed. |
|------------------------------------------------------------------------------------------------------------------|
| Efficacy of first-line therapies                                                                                   |
| Global efficacy                                                                                                     |
| Glucocorticoids alone                                                                                                |
| Glucocorticoids + surgery                                                                                           |
| Immunosuppressive/biological agents*                                                                               |
| Surgery alone                                                                                                       |
| Radiotherapy                                                                                                        |
| No therapy                                                                                                          |
| Secondary outcomes                                                                                                  |
| Relapses                                                                                                            |
| Stop glucocorticoids                                                                                                |
| Spontaneous remission in untreated patients                                                                        |
| Death                                                                                                               |
| 464/1395 (33%)                                                                                                      |
| 51/191 (27%)                                                                                                        |
| 68/159 (43%)                                                                                                        |
| 26/294 (8.8%)                                                                                                       |

* Fourteen out of the 22 patients also received glucocorticoids.
(either as a new course or as an increase/slow tapering of the ongoing dose) in 250 (66%) cases. The use of immunosuppressive agents was reported in 149 (39%) cases, principally in association with glucocorticoids (azathioprine was used in 126/149 cases). Rituximab use was reported in 9 (2%) cases. Therapeutic efficacy was reported in 219/231 (95%) of relapses treated with glucocorticoids, 56/69 (81%) of those treated with azathioprine, 16/22 (72%) of those treated with other immuno-suppressive agents, and in all 9 cases treated with rituximab (100%).

3.1.3. Side effects. Only 7 studies detailed the prevalence and/or types of side effects associated with therapies.\[^{12,18,24,49,50,66,70}\] Ebbo et al\[^{18}\] reported side effects related to glucocorticoids in 14/21 (67%) patients. Diabetes mellitus (DM) was the most frequently reported side effect in all studies. Other reported side effects included infections (n = 3), osteonecrosis (n = 2), psychosis (n = 1), vertebral fracture (n = 1), weight gain (n = 1), and hypertension (n = 1). Side effects related to azathioprine, reported in 17/49 (35%) patients, pertained primarily to gastrointestinal intolerance.\[^{70}\] There was also 1 case of azathioprine-induced pancreatitis.\[^{70}\]

3.1.4. Glucocorticoid cessation. Eleven studies detailed information on how many patients treated with glucocorticoids as first-line therapy were successful in discontinuing glucocorticoids completely at the time of the last visit. Only 51 (27%) of the 191 patients in whom this outcome was reported had been able to discontinue glucocorticoids entirely by the last visit. Three studies reported somewhat higher frequencies of glucocorticoid discontinuation (>50% of patients),\[^{19,24,71}\] but the relapse rates were higher in these studies compared to those in which patients remained on glucocorticoids. In summary, successful discontinuation of glucocorticoids for prolonged periods of time appears to be the exception rather than the rule for most patients with IgG4-RD.

3.1.5. Outcome of untreated patients. In 14 studies, the authors detailed the outcome in 159 out of the 246 patients who did not receive treatment. Spontaneous improvement or resolution was reported in 68 (43%) cases, but long-term follow-up of the patients were seldom reported.

3.1.6. Mortality. Information on survival was detailed in only 7 studies,\[^{16,18,19,24,50–52}\] which included a total of 294 patients. After a mean follow-up of 29.2 months (range 1–224 months), mortality was reported in 26 (8.8%) patients. The main causes of death included IgG4-RD progression (n = 7, including pulmonary disease in 4, aneurysm in 1, cholangitis in 1, and renal failure in 1) and cancer (n = 7). Other causes of death included cardiovascular disease (n = 4), infection (n = 3), and other/unknown (n = 5).

3.2. Association between study characteristics and outcomes

3.2.1. Classification criteria bias. Four studies\[^{19,22,24,49}\] used classification criteria that include a positive response to glucocorticoids as one of the inclusion criteria (ICDC and HiSort criteria for autoimmune pancreatitis [AIP]); the efficacy of first-line glucocorticoid-based regimens was reported in 817/830 (98%) patients (no significant difference with respect to the remaining studies).

3.2.2. Geographical bias. Table 3 summarizes the differences in the main baseline variables between Asian, American, and European studies. Epidemiologically, Asian studies included...
patients with a higher mean age (62 years vs 56.9 in American studies and 57.9 in European studies; \( P = 0.034 \)). With respect to first-line therapeutic regimens, European studies more-frequently used glucocorticoids, American studies more-frequently used drug-free regimens, and Asian studies had the highest frequency of untreated patients (\( P < 0.001 \)). With respect to outcomes (Fig. 2), American studies reported a lower efficacy (OR 0.41, 95% CI 0.20–0.87). Both American and European studies a higher frequency of relapses (OR 1.39, 95% CI 1.01–2.48 and OR 3.18, 95% CI 2.02–5.01, respectively) compared with Asian studies.

### 3.2.3. Organ-by-organ selection bias.

Table 4 compares the main variables according to the predominant organ involvement.
selected for each study. With regard to epidemiological features, we found significant differences with respect to the geographical ($P < 0.001$) and gender distribution ($P < 0.001$). In addition, wide heterogeneity was observed with respect to the first-line therapeutic approaches used for the different organ-specific subsets of patients (Fig. 3) and the outcomes reported (Fig. 4), including differences in the mean dose of glucocorticoids used for the different types of organ involvement (Fig. 5).

4. Discussion
IgG4-RD, first described some 15 years ago, remains an emerging disease. The rapid increase in number of studies has mainly been due to descriptive characterizations of the disease. Few studies have been designed specifically to evaluate the therapeutic response, and information on treatment has, to date, been presented almost exclusively in descriptive studies rather than formal clinical trials. As a result, the evidence base on which to
developing steroid-related side effects,

or patients aged higher doses in patients with severe complications (pancreatic, years.

Although the optimal starting glucocorticoids dose therapy, and the balance between efficacy and side effects. Some studies used higher doses in patients with severe complications (pancreatic, pulmonary, renal, and retroperitoneal involvement), while others used lower doses in patients with diabetes, those at high risk of developing steroid-related side effects, or patients aged >80 years. Although the optimal starting glucocorticoids dose remains undefined, it appears that doses equivalent to <10 mg/d of prednisone are associated with a lack of response.

After the first 4 weeks of induction therapy, the glucocorticoid dose can be tapered gradually. One approach, frequently employed in Japan, is to taper glucocorticoids over several months to a daily dose equivalent of somewhere between 2.5 and 10.0 mg/d of prednisone and then to maintain this dose for several years. This approach has been developed through consensus rather than through rigorous, controlled studies, however, and its long-term efficacy has not been evaluated prospectively. A retrospective, multicenter study of 459 AIP patients in Japan reported that 82% of patients still received glucocorticoids as maintenance therapy at the last visit. An alternative approach to the use of glucocorticoids, commonly employed in North America, is to taper prednisone to discontinuation after 2-3 months and to add a steroid-sparing agent if the disease relapses during or after the taper. The strategy acknowledges the facts that glucocorticoids do not cure IgG4-RD and the long-term morbidity of glucocorticoid use may be substantial in this patient population, which often has a number of comorbidities concomitantly with IgG4-RD.

Although the goal should probably be discontinuation of glucocorticoids after achieving a maintained clinical response, we found this only happened in 25% of patients in whom information on therapy at the last visit was detailed. A key finding of this review is the very limited reported information on the side effects associated with widespread glucocorticoid use. Only one small series detailed the frequency of glucocorticoid-related side effects, which were found in two thirds of patients. DM is the most frequently reported side effect. A detailed study by Ito et al evaluated the need for DM therapies after glucocorticoid treatment in 22 IgG4-RD patients without AIP and found that the percentage of untreated patients was reduced from 72% to 50% after starting glucocorticoids, while the rate of patients requiring insulin therapy increased from 4% to 27%; in addition, 83% of patients were aged >50 years and diagnosed with DM or impaired glucose tolerance.

The selection of a “steroid-sparing” agent is challenged by the paucity of data on the efficacy of conventional agents for IgG4-RD. Conventional immunomodulatory agents have been reported as first-line therapies in fewer than 10 patients. The recent therapeutic consensus reported differing clinical practice according to country, with more Japanese physicians supporting glucocorticoid monotherapy as the first-line option compared with experts from other countries (North America, Europe, Korea, and China). However, in our geographical analysis, Asian studies had the highest frequency of untreated patients while glucocorticoids were more frequently used in Europeans and drug-free treatment in US patients: surprisingly, the rate of relapses was lower in the Asian population. This might be
explained by taking into account the fact that Asian studies did not detail information on relapses (missing information would provide biased results) and because Asian studies included a lower frequency of patients affected by AIP (AIP is one of the IgG4-related involvements with the highest rate of relapses).

There is widespread consensus on the use of immunosuppressive agents as steroid-sparing agents in refractory/complicated cases. We found that immunosuppressants were used in nearly 40% of cases that relapsed but that these agents were employed overwhelmingly in combination with glucocorticoids, complicating any assessment of their efficacy alone. Azathioprine was used in 85% of cases, probably reflecting clinical practice in cases of AIP, followed by mycophenolate mofetil, methotrexate, tacrolimus, and cyclophosphamide. No study has compared the efficacy of different immunosuppressive agents. The efficacy of the azathioprine/glucocorticoid combination was estimated to be on the order of 80%. Some patients relapsed when treated with low doses of azathioprine (50 mg/d) or mycophenolate (1 g/d) and the disease was controlled by increasing the dose. This was probably in fact azathioprine coupled simultaneously with an increase in prednisone, making it difficult to be certain about how much improvement was due to azathioprine and how much to increased steroids. Interpretation of the efficacy of all conventional agents in IgG4-RD is hampered by the dearth of prospective, controlled experiences with these medications. In addition, most data describing the use of conventional immunosuppressive medications are confounded by concomitant glucocorticoid use.

The emergence of biological therapies has increased the therapeutic armamentarium available for treating the most refractory/severe cases of IgG4-RD, but their use is limited by the lack of licensing. Rituximab was the most-reported biological option in our systematic review, being used in 9 studies: it was used less frequently as induction therapy (only 8 cases with an efficacy of 75%)[10,64] and more frequently as rescue therapy in patients who failed to achieve or sustain disease remission with glucocorticoid treatment. Carruthers et al[79] have recently published the results of an open-label prospective study including 30 IgG4-RD patients treated with 2 doses of rituximab (1000 mg each), with a disease response rate of 97%. The primary outcome was achieved by 23 participants (77%); 14 (47%) were in complete remission at 6 months, and 12 (40%) remained in complete remission at 12 months. These effects were achieved largely without glucocorticoid use (26 of the 30 patients were not treated with glucocorticoids) and without readministration of rituximab for the purpose of remission maintenance. Yamamoto et al[80] have also reported the successful use of rituximab without associated glucocorticoids. Further studies are needed to better define the place of rituximab in the therapeutic approach to IgG4-RD: although currently considered a rescue therapy, it might be considered as a first-line option in some cases. The apparent success of B cell depletion strategies has raised interest in other treatment strategies targeting the B cell lineage. A trial of Xmab5871, a homodimer that binds simultaneously to CD19 and Fc-gammaRIIb – leading in theory to inhibition of the targeted cell – is now under study.

Fifteen percent of first-line therapeutic interventions in IgG4-RD were glucocorticoid-free regimens: these were mainly surgical (11% of the total) with radiotherapy used in only 13 cases. As a cardinal feature of IgG4-RD is single or multiple organ swelling that often raises concerns about malignancy, surgery is mainly reported to treat masses located in the pancreas, kidneys, lungs, biliary tract, and prostate. In these patients, IgG4-RD is diagnosed accidentally after surgical removal of a potential tumor. Most patients were retrospectively diagnosed with IgG4-RD based on histopathologic findings. The best examples are: presumed cholangiocarcinoma,[19] pancreatic cancer,[19] pulmonary or pleural tumors,[72] prostate adenocarcinoma,[13] or renal cancer.[10]

On the other hand, an IgG4–specific surgical approach has also been used in patients with specific involvements (mainly infiltrative masses that involve tubular anatomical structures and may lead to obstructive processes). The best examples are: dilatation/stenting of the biliary tract in patients with IgG4-related sclerosing cholangitis,[49,62] ureteral stents/ureteroscopy,[32] transurethral resection of the prostate/suprapubic prostatectomy,[11] ocular surgical excision,[13,6,45] or surgical resection of submaxillary tumors.[34] In these cases, long-standing highly fibrotic lesions may respond poorly to drug-based therapies, and surgical debulking may be an appropriate and useful option.

A further key finding of our review was the lack of any therapeutic intervention in 13% of patients. In some specific organ involvements, this percentage was higher, reaching 71% in IgG4-related lymhadenopathy, 35% in IgG4-related salivary involvement, or 40% in IgG4-related skin involvement. Eight studies[18,23,29,41,46,54,67,72] detailed the reasons in 54 cases, which included mild/residual involvement or the patient refusing to be treated (n = 50), severe DM (n = 3), and active tuberculosis infection (n = 1). The outcome of these patients shows relapse or progression in nearly 60% of cases, a rate 2-fold higher than that found for patients treated with GC-therapeutic regimens. Wait and see management may be appropriate in asymptomatic patients with lymphadenopathy, cutaneous features, or mild salivary gland enlargement.

Another key finding of our review is the widespread lack of a standardized method of evaluating the therapeutic response. Of the 48 studies that evaluated the efficacy of first-line therapy, a specific definition of the type of therapeutic response was detailed in only 25. Only 2 studies[18,19] used an objective score; the remaining 23 used a subjective evaluation including clinical, laboratory, imaging, and/or organ-specific diagnostic tests (10 studies used ≥ 2 items and 13 only 1 item). Only 4 studies detailed reductions in serum IgG4 levels as a parameter of therapeutic efficacy. The development and validation of rigorous outcome measures are an important goal for the field of IgG4-RD investigation. An international effort to validate the IgG4-RD Responder Index[81] is now under way.

Recent studies have investigated novel cellular and molecular pathways involved in the pathogenesis of IgG4-RD that may be therapeutically targeted by biological therapies, including a potential role for basophil activation mediated by IgE or by Toll-like receptors.[82] Clayton et al[83] tested the use ofomalizumab (biological therapy against IgE) in patients with IgG4-related eosinophilic esophagitis, while other studies[84,85] have found a raised expression of some cytokines, such as IL-10 and Blys/BAff, opening a possible therapeutic approach by targeting these molecules.

IgG4-RD is an increasingly recognized condition in adults, with a heterogeneous clinical presentation affecting a wide range of organ systems. The principal bases of therapeutic decision-making currently remain clinical experience and expert opinion, due to the low level of evidence with respect to therapeutic data. The body of evidence relies predominantly on descriptive series including a range of 5 to 50 patients (74% of studies). Our review
found that although nearly 70% of reported IgG4-RD patients are treated with monotherapy with oral glucocorticoids, there is wide heterogeneity and therapeutic management is heavily influenced by geographical, epidemiological, and clinical factors, especially with respect to the predominant organ affected by the disease. International efforts are required to collect and characterize large multicenter and multidisciplinary cohorts of patients in order to develop consensual therapeutic approaches and endpoints.

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References

[1] Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med 2012;366:539–51.
[2] Brito-Zeron P, Ramos-Casals M, Bosch X, et al. The clinical spectrum of IgG4-related disease. Autoimmun Rev 2014;13:1203–10.
[3] Stone JH, Brito-Zeron P, Bosch X, et al. Diagnostic approach to the complexity of IgG4-related disease. Mayo Clin Proc 2015;90:927–39.
[4] Khosroshahi A, Wallace ZS, Crowe JL, et al. Diagnostic utility of diagnostic approach and endpoints.
[5] Khosroshahi A, Carruthers MN, Stone JH, et al. Rethinking Ormond disease and periarteritis: CT findings in 17 patients. Radiology 2011;261:625–33.
[6] Khosroshahi A, Carruthers MN, Stone JH, et al. Rethinking Ormond disease and periarteritis: CT findings in 17 patients. Radiology 2011;261:625–33.
[7] Moteki H, Yasuo M, Hamano H, et al. IgG4-related chronic rhinosinusitis: a new clinical entity of nasal disease. Acta Otolaryngol 2011;131:518–26.
[8] Matsuo T, Ichimura K, Sato Y, et al. Immunoglobulin G4 (IgG4)-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related diseases. Ann Rheum Dis 2010;69:1310–5.
[9] Matsui S, Hebisawa A, Sakai F, et al. Immunoglobulin G4-related lung disease: clinicoradiological and pathological features. Respirology 2011;16:728–34.
[10] Shamliyan T, Kane RL, Jansen S. Quality of systematic reviews of observational studies and periarteritis: CT findings in 17 patients. Radiology 2011;261:625–33.
[11] Dreyer NA, Schneeweiss S, McNeil BJ, et al. GRACE principles: part 6. Systematic reviews and meta-analyses of observational studies. Prev Chronic Dis 2010;7:A133.
[12] Bosco JJ, Suan D, Varikatt W, Lin MW. Extra-pancreatic manifestations of Idiopathic retroperitoneal fibrosis: a clinicopathological study of 12 cases, with emphasis to possible relationship to IgG4-related disease. Virchows Arch 2013;463:721–30.
[13] Lindstrom KM, Cousar JB, Lopes MBS. IgG4-related meningeal disease: clinicopathological features and proposal for diagnostic criteria. Acta Neuropathol 2010;120:763–76.
[14] Kiyama K, Kawabata H, Hosono Y, et al. Immunoglobulin G4-related disease, in whom autoimmune pancreatitis was ruled out by diagnostic imaging. Endocr J 2014;61:765–72.
[15] Yamada T, Kise K, Yamauchi Y, et al. Radiographic patterns of orbital involvement in IgG4-related disease. Ophthalm Plast Reconstr Surg 2013;29:261–6.
Brito-Zerón et al. Medicine (2016) 95:26

[47] Oh H-C, Kim M-H, Lee KT, et al. Clinical clues to suspicion of IgG4-associated sclerosing cholangitis disguised as primary sclerosing cholangitis or hilar cholangiocarcinoma. J Gastroenterol Hepatol 2010;25:1831–7.

[48] Ohta N, Kurakami K, Mizushima I, et al. The clinical course of patients with IgG4-related sclerosing sialadenitis. Laryngoscope 2012;122:572–7.

[49] Patel H, Khalili K, Kyoung KT, et al. IgG4-related disease – a retrospective descriptive study highlighting Canadian experiences in diagnosis and management. BMC Gastroenterol 2013;13:168.

[50] Russiain Y, Narsh SH, Larsen CP, et al. Diagnosis of IgG4-related tubulointerstitial nephritis. J Am Soc Nephrol 2011;22:1341–52.

[51] Saeki T, Kawano M, Mizushima I, et al. The clinical course of patients with IgG4-related kidney disease. Kidney Int 2013;84:826–33.

[52] Sakamoto A, Nagai R, Sato K, et al. Idiopathic retroperitoneal fibrosis, inflammatory aortic aneurysm, and inflammatory pericarditis-retrospective analysis of 11 case histories. J Cardiol 2012;59:139–46.

[53] Sato Y, Ohshima KI, Ichimura K, et al. Ocular adnexal IgG4-related disease: single-center experience and literature review. Medicine (Baltimore) 2012;91:57–66.

[54] Sato Y, Inoue D, Asano N, et al. Association between IgG4-related disease and progressively transformed germinal centres of lymph nodes. Mod Pathol 2012;25:956–67.

[55] Sato Y, Takeuchi M, Takata K, et al. Clinicopathologic analysis of IgG4-related skin disease. Mod Pathol 2013;26:523–32.

[56] Suzuki M, Nakamaru Y, Akawa S, et al. Nasal manifestations of immunoglobulin G4-related disease. Laryngoscope 2013;123:829–34.

[57] Tabata T, Kamisawa T, Takuma K, et al. Serial changes of elevated serum IgG4 levels in IgG4-related systemic disease. Intern Med 2011;50:69–75.

[58] Takahashi H, Yamashita H, Morooka M, et al. The utility of FDG-PET/CT and other imaging techniques in the evaluation of IgG4-related disease. J Bone Spine 2014;81:331–6.

[59] Takagi Y, Nakamura H. IgG4-related Mikulicz’s disease: ultrasonographic findings of the salivary and lacrimal glands for monitoring the efficacy of corticosteroid therapy. Clin Exp Rheumatol 2013;77:5–

[60] Takagi D, Nakamura Y, Fukuda S. Otorologic manifestations of immunoglobulin G4-related disease. Ann Otol Rhinol Laryngol 2014;123:420–4.

[61] Takuma K, Kamisawa T, Anjiki H, et al. Metachronous extrapancreatic lesions in autoimmune pancreatitis. Intern Med 2010;49:529–33.

[62] Tanaka A, Tazuma S, Okazaki K, et al. Nationwide survey for primary sclerosing cholangitis and IgG4-related sclerosing cholangitis in Japan. J Hepatobiliary Pancreat Sci 2014;21:43–50.

[63] Triantopoulou C, Malachias G, Maniatis P, et al. Renal lesions associated with autoimmune pancreatitis: CT findings. Acta Radiol 2010;51:702–7.

[64] Wallace ZS, Deshpande V, Stone JH. Ophthalmic manifestations of IgG4-related disease: single-center experience and literature review. Semin Arthritis Rheum 2014;43:806–17.

[65] Watanabe T, Maruyama M, Ito T, et al. Clinical features of a new disease concept, IgG4-related thyroiditis. Scand J Rheumatol 2013;42:325–30.

[66] Wu A, Andrew NH, Tsirbas A, et al. Rituximab for the treatment of IgG4-related orbital disease: experience from five cases. Eye (Lond) 2015;29:122–8.

[67] Yamada K, Hamaguchi Y, Saeki T, et al. Investigations of IgG4-related disease involving the skin. Mod Rheumatol 2013;23:986–93.

[68] Yamamoto M, Takahashi H, Ishigami K, et al. Relapse patterns in IgG4-related disease. Ann Rheum Dis 2012;71:1753–755.

[69] You JJ, Park JJ, Kang EH, et al. Risk factors for the recurrence of IgG4-related sclerosing disease without autoimmune pancreatitis. J Clin Rheumatol 2011;17:392–4.

[70] You M-W, Kim JH, Byun JH, et al. Relapse of IgG4-related sclerosing cholangitis after steroid therapy: image findings and risk factors. Eur Radiol 2014;24:1039–48.

[71] Zen Y, Inoue D, Kira O, et al. IgG4-related lung and pleural disease: a clinicopathologic study of 21 cases. Am J Surg Pathol 2009;33:1886–93.

[72] Khoroshavi A, Carruthers MN, Deshpande V, et al. Rituximab for the treatment of IgG4-related disease: lessons from 10 consecutive patients. Medicine (Baltimore) 2012;91:57–66.

[73] Karim AF, Verdijk RM, Guenoun J, et al. An inflammatory condition with different faces: immunoglobulin G4-related disease. Neth J Med 2016;74:110–5.

[74] Mulholland GB, Jeffery CC, Satija P, et al. Immunoglobulin G4-related diseases in the head and neck: a systematic review. J Otolaryngol Head Neck Surg 2014;43:24.

[75] Kamisawa T, Okazaki K, Kawa S, et al. Japanese consensus guidelines for management of autoimmune pancreatitis: III. Treatment and prognosis of AIP. J Gastroenterol 2010;45:471–7.

[76] Kamisawa T, Shimosegawa T, Okazaki K, et al. Standard steroid treatment for autoimmune pancreatitis. Gut 2009;58:1504–7.

[77] Khoroshavi A, Bloch DB, Deshpande V, et al. Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease. Arthritis Rheum 2010;62:1755–62.

[78] Carruthers MN, Topazian MD, Khoroshavi A, et al. Rituximab for IgG4-related disease: a prospective, open-label trial. Ann Rheum Dis 2015;74:1171–7.

[79] Yamamoto M, Awakawa T, Takahashi H. Is rituximab effective for IgG4-related disease in the long term? Experience of cases treated with rituximab for 4 years. Ann Rheum Dis 2015;74:e46.

[80] Carruthers MN, Stone JH, Deshpande V, et al. Development of an IgG4-RD responder index. Int J Rheumatol 2012;2012:259408.

[81] Sharma B, Bayry J. Autoimmunity: basophils in autoimmune and inflammatory diseases. Nat Rev Rheumatol 2015;11:129–31.

[82] Clayton F, Fang JC, Gleich GJ, et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. Gastroenterology 2015;148:602–9.

[83] Furukawa S, Moriyama M, Tanaka A, et al. Preferential M2 macrophages contribute to fibrosis in IgG4-related dacryoadenitis and sialoadenitis, so-called Mikulicz’s disease. Clin Immunol 2015;156:9–18.

[84] Lin W, Jin L, Chen H, et al. B cell subsets and dysfunction of regulatory B cells in IgG4-related diseases and primary Sjogren’s syndrome: the similarities and differences. Arthritis Res Ther 2014;16:R118.