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Therapeutic approach to IgG4-related disease

A systematic review

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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 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. 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

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1. Introduction

IgG4-related disease (IgG4-RD) is an immune-mediated systemic disease first described in Japan at the beginning of this century.^[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.^[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.^[2] Diagnosis relies on the coexistence of various clinical, laboratory, radiological, and histopathological findings, although none is pathognomonic in itself.^[3]

The optimum therapeutic management of IgG4-RD has not yet been established.^[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.^[11] 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 selected 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^[2] 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).

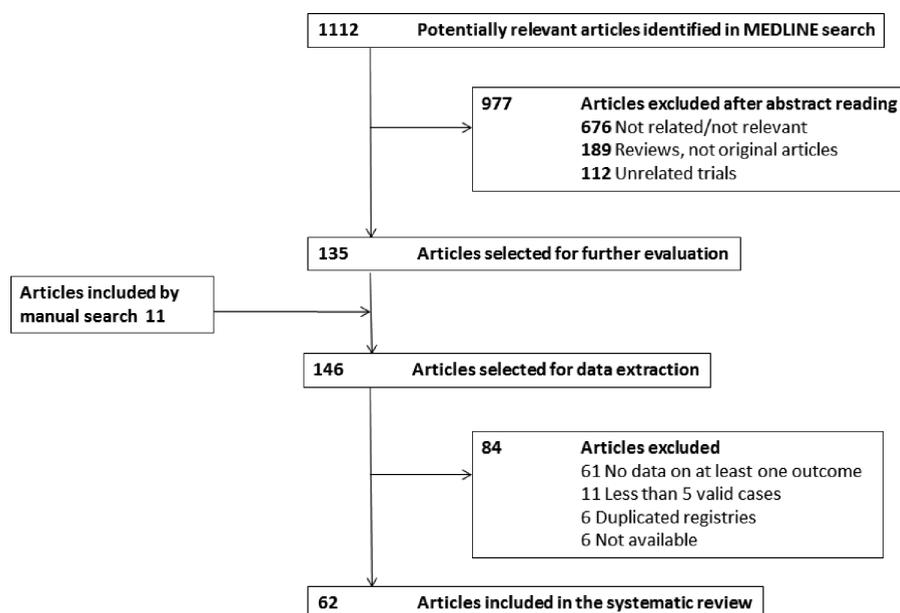


Figure 1. Results of the systematic search strategy.

Table 1
Results of the systematic search strategy: 62 studies including 3034 patients.

Total patients	N = 3034 patients
Mean age	52.96 (12–91)
Gender (males)	2067/2963 (69.76%)
Geographical distribution	Patients (studies)
Asian countries	1517 (43)
European countries	235 (6)
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* kook (1), antitubercular agents (1), and surgery + chemotherapy (3).

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 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	1246/1293 (96.4%)
Glucocorticoids alone	1186/1220 (97.2%)
Glucocorticoids + surgery	20/22 (91%)
Immunosuppressive/biological agents*	17/22 (77%)
Surgery alone	14/17 (82%)
Radiotherapy	9/12 (75%)
No therapy	68/159 (43%)
Secondary outcomes	
Relapses	464/1395 (33%)
Stop glucocorticoids	51/191 (27%)
Spontaneous remission in untreated patients	68/159 (43%)
Death	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 immunosuppressive 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),^[19,54,73] 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

Table 3
Differences in main baseline variables between Asian, American, and European studies.

Variables	Geographical origin of studies			P
	Asian	American	European	
Number of studies (S)	43	10	6	–
Patients (P)	1517	293	235	–
Mean age, y	62 ± 5.5	56.9 ± 5.5	57.9 ± 7.8	0.034
Males	945/1451 (65.1)	199/288 (69.1)	165 (70.2)	0.173
Months	24.2 ± 14.2	24.8 ± 12.3	56.7 ± 5.2	0.098
Mean glucocorticoids, mg/dL	33.9 ± 6.4	32.5 ± 10.6	37 ± 2.6	0.548
First-line regimens	S: 33–P: 692	S: 8–P: 200	S: 4–P: 148	<0.001
Glucocorticoid-based	497 (71.8)	123 (61.5)	122 (82.4)	
Free drug-based	45 (6.5)	32 (16)	9 (6.1)	
Other therapies	5 (0.7)	10 (5)	0 (0)	
No therapies	145 (21)	35 (17.5)	17 (11.5)	
Response evaluation*	S: 27–P: 341	S: 7–P: 84	S: 3–P: 118	0.004
Response	319 (93.5)	72 (85.7)	115 (97.5)	
No response	22 (6.5)	12 (14.3)	3 (2.5)	
Relapsed patients	S: 16–P: 275	S: 6–P: 151	S: 2–P: 124	<0.001
Relapses	61 (22.2)	47 (31.1)	59 (47.6)	
No relapses	214 (77.8)	104 (68.9)	65 (52.4)	
Remission†	S: 12–P: 84	S: 3–P: 11	S: 0–P: 0	0.534‡
Remission	26 (31)	5 (45.5)	0	
No remission	58 (69)	6 (54.5)	0	

Statistically significant P-values in bold. Number of studies (S), patients (P).

* The efficacy of first-line glucocorticoid-based regimens.

† In untreated patients.

‡ Without European patient population category.

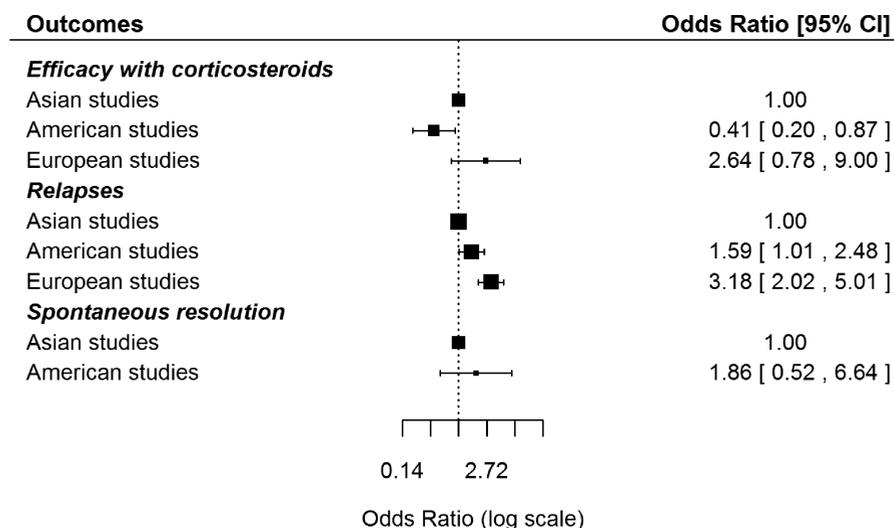


Figure 2. Differences in the main outcomes (efficacy of glucocorticoids, relapses, and spontaneous resolution) between Asian, American and European studies.

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 1.59, 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

Table 4
Comparison of the main variables according to the predominant involved organ selected for each study: AIP/SC, lymphadenopathy or skin involvement, ocular involvement, other involvements, renal involvement, salivary involvement, and systemic/multiorgan involvement.

Variables	The predominant type of organ involvement							P
	AIP/SC	Lymph/skin	Ocular	Other	Renal	Salivary	Systemic	
Number of studies (S)	12	4	8	14	5	5	14	–
Patients (P)	1651	67	101	207	140	173	695	–
Asian countries	358/673 (53.2)	67 (100)	66 (65.3)	175 (84.5)	96 (68.6)	173 (100)	582 (83.7)	<0.001
Mean age	60.8±6.5	62.4±4.3	54.4±5.5	62±4.5	62±2.9	62.1±4.5	61.9±7.1	0.104
Males	1190 (72.1)	52 (77.6)	53 (52.5)	170/202 (84.2)	106 (75.7)	87 (50.3)	409/629 (65)	<0.001
Months	20±11.1	34.9	33.4±13.9	30.5±16	21.8±14.9	NA	25.2±24.4	0.676
Mean glucocorticoids	34.7±3	20	39±14.3	35.2±5.7	42.7±10.3	27.6±3.7	35.5±6.2	0.309
First-line regimens	S: 8–P: 1238	S: 3–P: 26	S: 8–P: 100	S: 14–P: 172	S: 5–P: 128	S: 3–P: 82	S: 7–P: 206	<0.001
Glucocorticoid-based	931 (75.2)	16 (61.5)	52 (52)	123 (71.5)	114 (89.1)	52 (63.4)	149 (72.3)	
Free drug-based	167 (13.5)	0 (0)	21 (21)	24 (14)	1 (0.8)	0 (0)	0 (0)	
Other therapies	23 (1.9)	0 (0)	12 (12)	1 (0.6)	1 (0.8)	0 (0)	1 (0.5)	
No therapies	117 (9.5)	10 (38.5)	15 (15)	24 (14)	12 (9.4)	30 (36.6)	56 (27.2)	
Response evaluation*	S: 8–P: 912	S: 3–P: 14	S: 7–P: 37	S: 11–P: 92	S: 5–P: 107	S: 3–P: 52	S: 2–P: 18	<0.001
Response	899 (98.6)	11 (78.6)	32 (86.5)	78 (84.8)	102 (95.3)	52 (100)	18 (100)	
No response	13 (1.4)	3 (21.4)	5 (13.5)	14 (15.2)	5 (4.7)	0 (0)	0 (0)	
Relapsed patients	S: 6–P: 1111	S: 3–P: 18	S: 7–P: 77	S: 6–P: 77	S: 3–P: 68	S: 1–P: 38	S: 1–P: 6	<0.001
Relapses	394 (35.5)	7 (38.9)	26 (33.8)	10 (13)	11 (16.2)	15 (39.5)	1 (16.7)	
No relapses	717 (64.5)	11 (61.1)	51 (66.2)	67 (87)	57 (83.8)	23 (60.5)	5 (83.3)	
Remission†	S: 3–P: 73	S: 2–P: 7	S: 2–P: 12	S: 5–P: 14	S: 3–P: 9	S: 0–P: 0	S: 1–P: 47	<0.001‡
Remission	42 (57.5)	2 (28.6)	1 (8.3)	2 (14.3)	1 (11.1)	0	20 (42.6)	
No remission	31 (42.5)	5 (71.4)	11 (91.7)	12 (85.7)	8 (88.9)	0	27 (57.4)	

Statistically significant P-values in bold. Number of studies (S), patients (P). AIP/SC=autoimmune pancreatitis/sclerosing cholangitis, NA=not available.

* The efficacy of first-line glucocorticoid-based regimens.

† In untreated patients.

‡ Without salivary selection category.

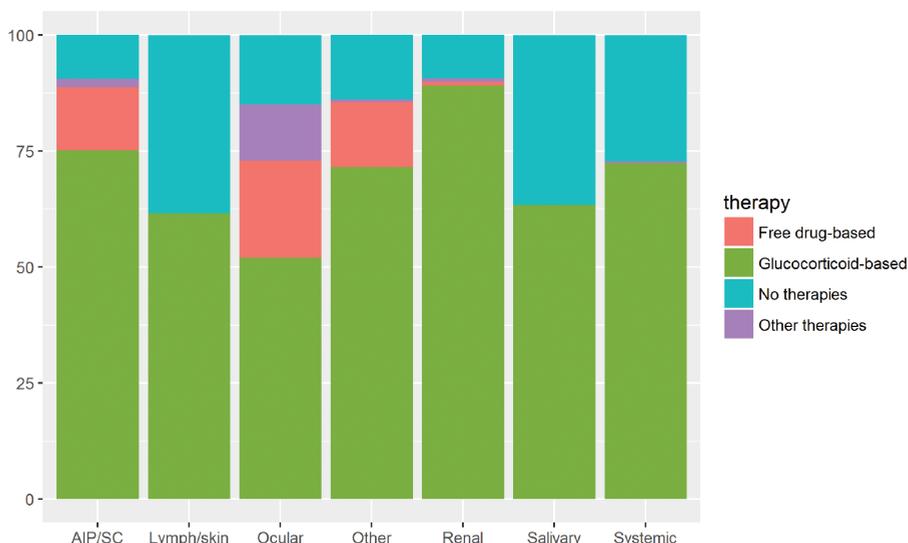


Figure 3. First-line therapeutic approaches used in the studies grouped according to the predominant organ involvement selected in each study (AIP= autoimmune pancreatitis, SC=sclerosing cholangitis).

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

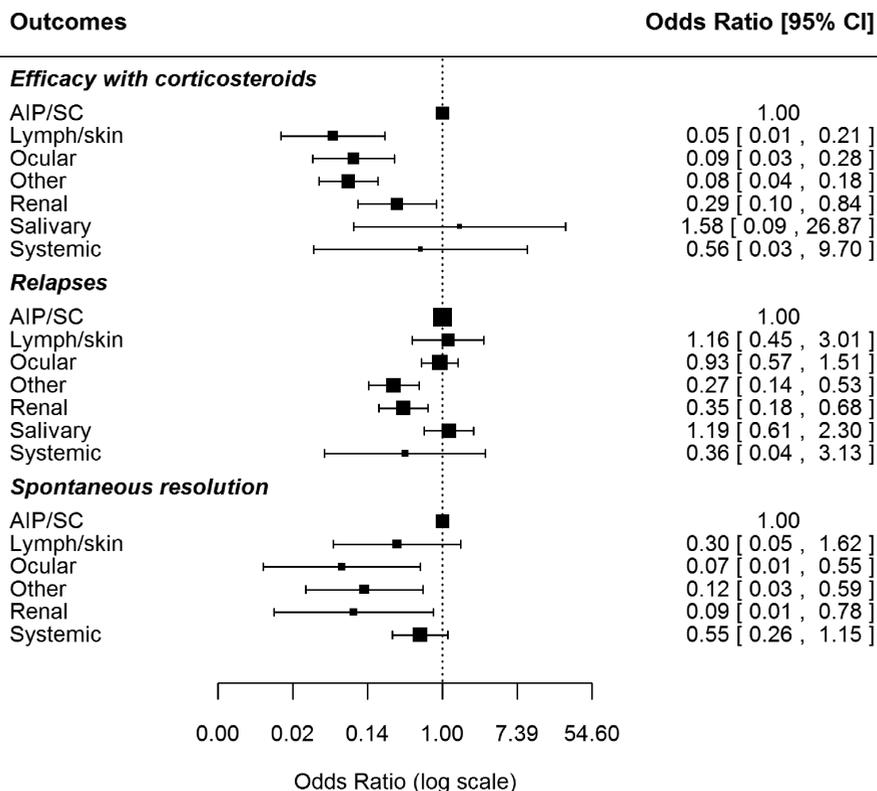


Figure 4. Differences in the main outcomes (efficacy of glucocorticoids, relapses, and spontaneous resolution) according to the predominant organ involvement selected in each study (AIP=autoimmune pancreatitis, SC=sclerosing cholangitis).

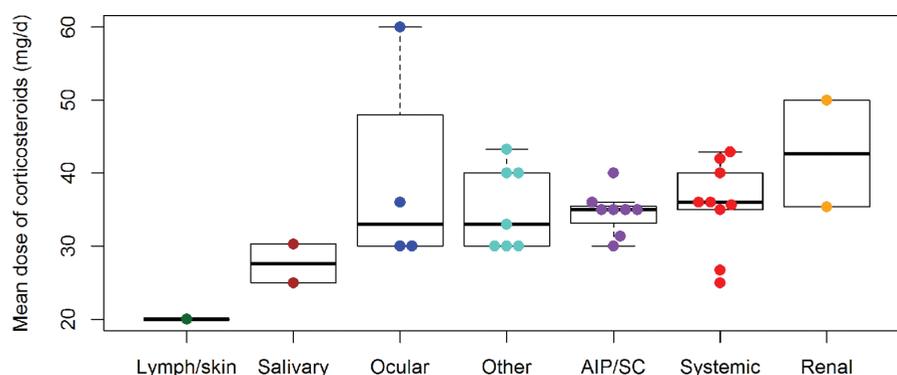


Figure 5. Differences in the mean dose of glucocorticoids used according to the predominant organ involvement selected in each study (AIP=autoimmune pancreatitis, SC=sclerosing cholangitis).

predicate therapeutic recommendations remains slim. Consequently, an evidence-based systematic review of published uncontrolled studies may provide the best available understanding of current treatment approaches. Although several reviews on IgG4-RD have recently been published,^[74,75] they did not specifically focus on the therapeutic management of the disease.

Since the first recognition of IgG4-RD as a discrete disease entity, glucocorticoid treatment has comprised the cornerstone of therapy for a majority of patients. Although such an approach is understandable given the affordability of this intervention and the substantial observational data that a majority of IgG4-RD patients respond to moderate to high doses of glucocorticoids, no controlled study has specifically evaluated their use. As a result, the optimal starting dose, the rate of glucocorticoid taper, the wisdom of discontinuing glucocorticoids altogether, patients' long-term treatment response, and multiple other questions about this treatment approach remain uncertain.

The central place of glucocorticoids in the therapeutic armamentarium for IgG4-RD was extrapolated from observational studies in patients with type 1 AIP, in whom monotherapy with glucocorticoids has been largely uncontested as the first-line therapeutic approach. Our review confirms that glucocorticoid-based regimens were the therapeutic option of choice in the majority of patients (85%) in whom a specific therapeutic intervention was reported. A recent guideline recommends glucocorticoids as the first-line therapeutic agent, with 94% of interexpert agreement.^[4] This is supported by our findings: the efficacy of glucocorticoid-based first-line regimens was 97%. However, 4 major areas of uncertainty concerning the use of glucocorticoids in IgG4-RD persist: the definition of the induction dose, how to taper glucocorticoids, the duration of therapy, and the balance between efficacy and side effects.

The recent consensus guidelines^[4] recommend the use of prednisolone (0.6 mg/kg/d) for 4 weeks as induction therapy. This mean dose was the most frequently used in our review (70% of studies), but varied widely according to geographical, epidemiological, and clinical features. Some studies^[41,68,69] 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,^[24] or patients aged >80 years.^[69] 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.^[55]

After the first 4 weeks of induction therapy, the glucocorticoid dose can be tapered gradually.^[4] 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^[76] 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.^[77] An alternative approach to the use of glucocorticoids, commonly employed in North America, is to taper prednisone to discontinuation after 2 to 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.^[51] 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^[4] 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 who 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.^[19] This was probably in fact azathioprine coupled simultaneously with an increase in prednisone dose, 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%)^[20,64] and more frequently as rescue therapy in patients who failed to achieve or sustain disease remission with glucocorticoid treatment.^[11,18,22,31,32,49,66] Rituximab use was first reported in 2010^[78] and was then used especially in patients with orbital involvement.^[64,66] 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-gammaRIIIb – 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.^[50]

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/ureterolysis,^[32] transurethral resection of the prostate/suprapubic prostatectomy,^[13] ocular surgical excision,^[53,64] 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 lymphadenopathy, 35% in IgG4-related salivary involvement, or 40% in IgG4-related skin involvement. Eight studies^[18,25,29,41,46,54,67,72] 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 of omalizumab (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 IL10 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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