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SPECIAL ARTICLE

International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease

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Introduction

IgG4-related disease (IgG4-RD) is an immune-mediated fibroinflammatory condition that can affect multiple organs and lead to tumefactive, tissue-destructive lesions and organ failure (1). Over the last decade, the disease has become recognized as a unified systemic disorder that links many individual organ conditions once considered to be unrelated (2,3). Involvement of nearly every anatomic site has been reported, but the most commonly affected organs or anatomic sites are the pancreas, biliary tract, major salivary glands (submandibular, parotid), lacrimal glands,

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Table 1. Characteristics of the members of the expert panel*

Total	42
Specialty	
Gastroenterology	18
Rheumatology	13
Ophthalmology	3
Pulmonary–critical care	2
Hematology/oncology	2
Internal medicine	2
Nephrology	1
Endocrinology	1
Country	
Japan	24
US	9
Italy	2
Canada	1
UK	1
Germany	1
France	1
Sweden	1
South Korea	1
China	1
Years of experience with IgG4-RD patients	
<2	1
2–5	9
>5–10	11
>10	21
No. of IgG4-RD patients cared for	
5–10	5
>10–50	13
>50–100	9
>100	15

* Values are the number of individuals. IgG4-RD = IgG4-related disease.

retroperitoneum, and lymph nodes (4,5). The epidemiology of the disease remains poorly described, because of both the relative novelty of this diagnosis and continued underrecognition, but the medical literature pertaining to the diagnosis has shown a major expansion over the past 5 years, from 63 publications in 2008 to 729 in 2013. The disease is often mistaken for cancer, an infection, or another immune-mediated condition, e.g., Sjögren's syndrome, granulomatosis with polyangiitis (Wegener's), giant cell arteritis, and others.

Multiple approaches to the management of IgG4-RD have been reported, including surgical resection of affected tissues and treatment with systemic glucocorticoids, "steroid-sparing" immunosuppressive drugs, or biologic agents, but no randomized clinical trials have been conducted and there are no formal treatment guidelines. In preparation for the Second International Symposium on IgG4-RD and Associated Conditions (February 16–19, 2014), we assembled an international panel of experts to develop recommendations for the management of IgG4-RD. This consensus process involved a series of web-based questionnaires, face-to-face discussions, and a literature review.

Methods

Expert panel. Forty-two IgG4-RD experts were invited to participate by the Symposium Organizing Committee. The experts were selected because of their history of publication on IgG4-RD and their recognized clinical expertise pertaining to the condition. The goals in assembling the panel were to ensure that all organ systems and body regions frequently affected by IgG4-RD were represented by experts in those areas, and that the panel had representation by physician-investigators from all countries in Asia, North America, and Europe who have contributed to the medical literature on IgG4-RD. The panel was composed of 18 gastroenterologists, 13 rheumatologists, and 11 other specialists and subspecialists, representing a total of 8 medical specialties. Experts from Asia, North America, and Europe participated. More detailed information on the experts' specialties, nationalities, and experience in caring for patients with IgG4-RD is shown in Table 1.

Procedures. Panel members completed 2 internet-based surveys about their approaches to the diagnosis and management of IgG4-RD. The survey statements were composed by the Core Writing Committee (AK, ZSW, JLC, TC, JHS); each survey included >40 questions addressing all stages in the disease process from the diagnosis of IgG4-RD to the induction and maintenance of remission to the treatment of patients following disease flare. (The complete survey instruments are available as supplementary material on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39132/abstract.) In recognition of the fact that some experts focus primarily on single-organ systems and seldom treat multiorgan disease, the panel members were permitted to complete either a general survey about disease management, an organ-specific survey, or both.

Following completion of the survey exercises by all panel members, the Core Writing Committee organized the results into 7 topics, each associated with 1 statement relevant to a particular phase of IgG4-RD (e.g., Remission Induction, Remission Maintenance, Treatment of Disease Flares). These 7 individual statements were then redistributed to the panel members to assess their level of agreement. Participants indicated the strength of their agreement or disagreement with each statement on a scale of 1–5 (1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, 5 = strongly agree). Panel members were also permitted to provide open-response answers elaborating on their reason for agreement or disagreement with the statement or providing other input that they considered meaningful.

Table 2. International consensus guidance statements on the treatment of IgG4-related disease (IgG4-RD), voting agreement, level of evidence, and citations

Statement	% agreement	Evidence level/grade of recommendation	References
1. The most accurate assessment of IgG4-RD are based on a full clinical history, physical examination, selected laboratory investigations, and appropriate radiology studies.	96	4/C	37, 51, 53, 54, 66, 67
2. Diagnostic confirmation by biopsy is strongly recommended for the exclusion of malignancies and other IgG4-RD mimics.	94	5/D	26, 57, 68
3. All patients with symptomatic, active IgG4-RD require treatment, some urgently. A subset of patients with asymptomatic IgG4-RD require treatment.	87	4/C	39, 47, 48, 51, 55, 67, 69–74
4. Glucocorticoids are the first-line agent for remission induction in all patients with active, untreated IgG4-RD unless contraindications to such treatment are present.	94	2b/B	38, 39, 47, 50, 51, 53, 54, 57, 66, 67, 69, 70, 72–77
5. Some but not all patients require the combination of glucocorticoids and a steroid-sparing immunosuppressive agent from the start of treatment. This is because glucocorticoid monotherapy will ultimately fail to control the disease and long-term glucocorticoid toxicities pose a high risk to patients.	46	4/C	38, 55, 56, 66, 78
6. Following a successful course of induction therapy, certain patients benefit from maintenance therapy.	94	2b/B	38, 47, 48, 50, 51, 54, 55, 67, 73
7. Re-treatment with glucocorticoids is indicated in patients who relapse off of treatment following successful remission induction. Following relapse, the introduction of a steroid-sparing agent for continuation in the remission maintenance period should be considered.	81	4/C	45, 56, 57, 59, 60, 77, 78

We performed an initial analysis of the consensus statement responses, modifying the wording to ensure clarity of meaning as appropriate based on the panel members' open-ended responses. Controversial topics were discussed by the experts at the symposium, during a 2-hour panel discussion devoted to disease management. Following the symposium, revised statements were distributed, and the experts completed 2 rounds of scoring these revised statements in the interest of maximizing consensus.

Literature review. A systematic search of PubMed for original and review articles in English published from March 2001 to February 2014 was performed using key words and text words related to IgG4-RD, including "IgG4-related disease," "autoimmune pancreatitis," "inflammatory pseudotumor," "sclerosing cholangitis," "glucocorticoids," "azathioprine," "mycophenolate mofetil," "6-mercaptopurine," "cyclophosphamide," "rituximab," "diagnosis," and "treatment," and specific to the 7 statements developed by the panel. Case reports and articles focusing only on pathology issues were excluded. Data relevant to each statement regarding the management or treatment of IgG4-RD were extracted, and the articles' methodologic quality was graded according to the levels of evidence described by the Oxford Centre for Evidence-Based Medicine (www.cebm.net, March 2009).

Results

Thirty-eight of the invited experts participated in all parts of the consensus exercise. Twenty-two (58%) completed the general survey, 18 (47%) completed the organ-specific survey, and 9 (24%) completed both. Table 2 shows a summary of each statement, the corresponding level of evidence, and the degree of consensus among the experts. The statements are discussed in detail below.

Patient evaluation (statement 1): The most accurate assessment of IgG4-RD is based on a full clinical history, physical examination, selected laboratory investigations, and appropriate radiology studies. (96% agreement). A thorough clinical history guides the initial evaluation of a patient with possible IgG-RD and subsequent

decisions regarding laboratory testing, imaging, and biopsies. A detailed review of past medical problems often reveals unrecognized manifestations of IgG4-RD (6). A complete physical examination may reveal involvement of an organ that is accessible for biopsy (e.g., major salivary gland swelling). Reexamination of archived biopsy samples with immunostaining for IgG4+ plasma cells may provide additional supportive diagnostic evidence.

Neither clinical nor pathologic findings alone are sufficient to diagnose IgG4-RD in most cases. The rigorous exclusion of diseases that mimic IgG4-RD both clinically and pathologically, through clinicopathologic correlation, is essential. A variety of diseases can be mistaken for IgG4-RD, and the list of disorders to consider varies by organ involvement. The clinicopathologic correlation required to make the correct diagnosis is determined most effectively with both clinicians and pathologists reviewing and discussing the patient's clinical features and pathologic findings. Table 3 summarizes conditions that can present with tumefactive lesions and increased IgG4+ plasma cells on tissue biopsy.

Table 3. Conditions that can mimic IgG4-related disease clinically and histopathologically

Antineutrophil cytoplasmic antibody–associated vasculitides
Granulomatosis with polyangiitis (Wegener's)
Microscopic polyangiitis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
Adenocarcinoma and squamous cell carcinoma, peritumoral infiltrate
Castleman's disease (multicentric or localized)
Cutaneous plasmacytosis
Erdheim-Chester disease
Inflammatory myofibroblastic tumor
Inflammatory bowel disease
Lymphoproliferative diseases
Extranodal marginal zone lymphomas
Lymphoplasmacytic lymphomas
Follicular lymphomas
Perforating collagenosis
Primary sclerosing cholangitis
Rhinosinusitis
Rosai-Dorfman disease
Sarcoidosis
Sjögren's syndrome
Splenic sclerosing angiomatoid nodular transformation
Xanthogranuloma

Serologic testing. In 2001, an association of type 1 autoimmune pancreatitis (AIP) with elevated serum IgG4 concentrations was reported (7). Subsequent diagnostic criteria for both IgG4-RD and type 1 (IgG4-related) AIP have typically included an elevated serum IgG4 concentration (8–10). Other studies have demonstrated variability in the sensitivity of serum IgG4 elevation for the diagnosis of IgG4-RD. Between 3% and 30% of IgG4-RD patients have normal serum IgG4 concentrations (8–12). The sensitivity and other test characteristics of the serum IgG4 concentration depend on a variety of factors, including the means of case identification, the diagnosis of "definitive" IgG4-RD, the type of assay used to measure serum IgG4 levels, the number of organs involved, and possibly the geographic origin of the patient.

Measurements of the serum IgG4 concentration remain important in the evaluation and longitudinal assessment of patients with possible IgG4-RD, but elevated levels are neither necessary nor sufficient for the diagnosis of IgG4-RD (9). Elevated serum IgG4 concentrations have been observed in patients with a variety of other disorders, making it a poor stand-alone diagnostic test for this condition (13,14). However, the degree of serum IgG4 elevation correlates with the number of organs involved: the greater the extent of disease, the higher the likelihood of an elevated serum IgG4 level (15–18).

Other laboratory markers. Recent studies indicate that IgG4-RD patients have substantial elevations of circulating plasmablasts and that plasmablast levels correlate with disease activity (18,19). Additional studies of circulating plasmablasts and IgG4+ plasmablasts as biomarkers are needed before their broad use can be endorsed.

Complement levels are a helpful indicator of disease activity in some IgG4-RD patients, particularly those with renal disease. Most patients with IgG4-related tubulointerstitial nephritis have hypocomplementemia at the time of disease relapse (19).

Radiology. Radiologic studies are often obtained early in the evaluation of a patient with possible IgG4-RD. Indeed, the diagnosis is often suggested by incidental findings on radiologic studies performed for reasons related or unrelated to IgG4-RD. Computed tomography (CT), CT performed with positron emission tomography (PET), magnetic resonance (MR) imaging, MR cholangiopancreatography, and endoscopic ultrasound are modalities that are commonly used to evaluate IgG4-RD. Selection of the imaging modality appropriate to the assessment of IgG4-RD is based on the organ under evaluation, local radiology expertise, and availability, as well as considerations such as radiation exposure and cost. Studies of fluorodeoxyglucose (FDG)–PET/CT imaging in IgG4-RD have emphasized its potential role at the time of initial evaluation (20,21). However, the utility of serial FDG-PET studies in gauging disease activity and guiding treatment decisions has not been demonstrated. Therefore, decisions regarding the use of PET must be made according to the individual patient's clinical features.

Many of the considerations relevant to diagnosis apply equally to longitudinal disease assessment. No single means of assessing disease response is currently adequate for all patients with IgG4-RD. An IgG4-RD Responder Index (IgG4-RD RI) has been developed as a quantitative means of assessing overall response to treatment (22). The instrument has been used successfully in clinical studies of IgG4-RD (15,16).

Tissue confirmation prior to treatment (statement 2): Diagnostic confirmation by biopsy is strongly recommended for the exclusion of malignancies and other IgG4-RD mimics. (94% agreement). Although comprehensive diagnostic criteria for IgG4-RD, AIP, and IgG4-related kidney disease have been proposed (6,23–25), the results of clinical assessment, laboratory evaluation, and imaging studies are often insufficient to distinguish the tumefactive lesions of IgG4-RD from cancer, and biopsy is typically necessary to exclude malignancy. International consensus guidelines outline the histopathologic and immunohistochemistry features that support the diagnosis of IgG4-RD and, in the proper clinical setting, can be viewed as diagnostic (26,27). Needle biopsy is usually inadequate for the histopathologic diagnosis of IgG4-RD, but generally yields quantities of tissue large enough to exclude malignancy with some confidence. In some settings, e.g., isolated submandibular gland enlargement, a small open biopsy as opposed to complete glandular excision may suffice (28). Archived tissue samples from previous biopsies may be diagnostic if reviewed along with immunostaining for IgG4+ plasma cells; immunostaining can be performed on paraffin-embedded specimens.

The presence of significant IgG4+ plasma cell infiltrates in biopsy specimens is not specific to IgG4-RD. Extensive IgG4+ plasma cell infiltration has been described in other conditions that commonly mimic IgG4-RD, including malignancy, granulomatosis with polyangiitis (Wegener's), eosinophilic granulomatosis with polyangiitis (Churg-Strauss), and multicentric Castleman's disease (29–35) (Table 3). Findings of storiform fibrosis and obliterative phlebitis heighten diagnostic specificity, but clinicopathologic correlation is always essential (26).

In cases of type 1 (IgG4-related) AIP, characteristic radiologic findings along with an elevated serum IgG4 concentration are typically sufficient to establish a diagnosis. However, fine-needle aspiration to exclude malignancy is often needed (27,36,37). Definitive diagnosis in patients with biliary disease is frequently challenging because diagnostic tissue is difficult to obtain in the absence of surgical resection. This is particularly true in the setting of IgG4-related sclerosing cholangitis involving intrahepatic and the proximal extrahepatic common bile duct. Biliary brushings and fine-needle biopsies are usually sufficient to exclude cholangiocarcinoma but are generally inadequate to distinguish IgG4-RD from primary sclerosing cholangitis (10,38–40). Endobiliary biopsy sometimes yields diagnostic tissue (41,42). Percutaneous liver biopsy may provide a diagnosis if biliary tract abnormalities are evident radiologically.

Indications for therapy (statement 3): All patients with symptomatic, active IgG4-RD require treatment, some urgently. A subset of patients with asymptomatic IgG4-RD require treatment. (87% agreement). *Treatment of asymptomatic disease.* Subclinical disease can lead to severe, irreversible sequelae in the biliary tree, kidney, aorta, mediastinum, retroperitoneum, mesentery, and other organs (43). However, not all manifestations of IgG4-RD require immediate treatment. "Watchful waiting" may be appropriate, for example, in patients with asymptomatic lymphadenopathy or mild submandibular gland enlargement.

Involvement of certain organs may be relatively asymptomatic until the late stages of disease, by which time chronic inflammation and fibrosis may have caused irreversible damage. Patients with AIP who are not treated with induction immunosuppression are less likely to achieve remission and more likely to experience disease complications (38,39). The importance of early intervention to prevent complications related to progressive fibrosis in the salivary glands has also been demonstrated (40).

Urgent treatment. A proportion of patients require treatment urgently because uncontrolled disease in certain organs can lead to irreversible damage (Table 4). Urgent treatment may include a combination of glucocorticoids at moderate-to-high doses, as well as other mechanical interventions in specific organs (e.g., stents for the biliary tract or ureter) (41). Rituximab (RTX), when available, may also be appropriate in some cases, if glucocorticoid treatment is contraindicated.

Other triggers for therapy. Spontaneous remissions of IgG-RD, or at least temporary remissions, without treatment have been reported (42,44), but the duration of followup in such cases has generally been short, and a relapsing-remitting pattern with progressive organ injury has been well described (45). Further, the metachronous nature of IgG4-RD suggests that although the disease may appear to improve at least temporarily in one organ, it may re-emerge months or years later at a different site (46).

Treatment leads to faster and more complete remission with fewer long-term complications of IgG4-RD than does waiting to treat (19,47). Treatment is therefore

Table 4. IgG4-related disease manifestations in which urgent treatment is recommended

Manifestation	Rationale for urgent treatment
Aortitis	Inflammatory aortic aneurysms can continue to enlarge and are at risk for dissection.
Retroperitoneal fibrosis	Progressive disease may lead to irreversible nerve damage/pain and/or ureteral obstruction/renal failure.
Proximal biliary strictures*	Untreated disease may lead to superimposed infectious cholangitis and eventually irreversible fibrosis and cirrhosis.
Tubulointerstitial nephritis	Untreated disease may lead to irreversible chronic kidney disease.
Pachymeningitis	Untreated disease puts the patient at risk for neurologic deficits and/or seizures.
Pancreatic enlargement	Untreated disease may lead to irreversible pancreatic exocrine and endocrine failure.
Pericarditis	Untreated disease may lead to tamponade or constrictive pericarditis

* "Proximal" denotes involvement of the intrahepatic bile ducts or extrahepatic portion of the common bile duct that is superior to the intrapancreatic portion.

justified in most cases in which laboratory or radiology findings suggest organ dysfunction (e.g., elevated serum levels of creatinine, hepatic transaminases, or bilirubin). Cosmetic concerns, particularly for periorbital or submandibular gland swelling, may also justify treatment in many cases.

Highly fibrotic lesions. In some cases, symptoms reflect fibrotic, "burnt-out" disease as opposed to active IgG4-RD. Longstanding, highly fibrotic lesions may respond poorly, if at all, to currently available pharmacologic agents. In such patients, the risk/benefit balance may not favor repeated courses of treatment. Surgical debulking is an option for IgG4-RD involvement of some organs, but the suitability of surgical interventions is governed by the anatomic regions and adjacent structures involved. Some cases of highly fibrotic orbital disease are more amenable to surgical interventions than to medical therapy. As examples, some fibrotic orbital pseudotumors and sclerosing mesenteritis respond best to surgical resection, when surgery is possible.

Remission induction with glucocorticoids (statement 4): Glucocorticoids are the first-line agent for remission induction in all patients with active, untreated IgG4-RD unless contraindications to such treatment are present. (94% agreement). Prednisone at a dosage of 30–40 mg/day is a common initial treatment for IgG4-RD (48). The dosage may be adjusted based on body weight or if the disease appears to be particularly aggressive. A lower dosage may be appropriate if the clinical IgG4-RD symptoms are mild. A review of the literature reveals a unified message that this condition responds well to initial glucocorticoid treatment. The responses to lower-dose treatment are variable, however, and glucocorticoid tapering and discontinuation are both associated with a high risk of disease relapse in many settings.

A nationwide survey by the Japanese Research Committee of Intractable Pancreatic Disease revealed no significant difference in results between prednisolone at 30 mg/day and prednisolone at 40 mg/day for the initial treatment of AIP (49). In a retrospective multicenter study of 978 patients with AIP, remission was achieved in nearly all patients (38).

In a prospective trial that included 28 patients with AIP, of whom 23 (82%) also had IgG4-related sclerosing cholangitis, patients were treated with prednisone monotherapy at an initial dosage of 30 mg/day. Remission was achieved in 82% of the patients, at a median of 5 months (50). A retrospective study by Ebbo et al showed improvement in 90% of patients treated with glucocorticoids at a mean dosage of 0.67 mg/kg/day (along with a steroid-sparing agent in 48% of the patients) (51). Improvement was regarded as the fulfillment of at least 2 of 3 criteria: improvement in overall clinical status, significant decrease in serum IgG4 concentration, and reduction of radiologic abnormalities.

Most experts agree that the initial glucocorticoid dosage should be maintained for 2–4 weeks, after which it can be tapered gradually. The tapering regimen has varied in different studies (47,52). One scenario is to taper the daily dosage by 10 mg every 2 weeks until a daily dosage of 20 mg is reached. After a short time (e.g., 2 weeks) of treatment at 20 mg/day, the tapering should resume by decreasing the daily dosage by 5 mg every 2 weeks. The goal of induction therapy at many centers is to discontinue glucocorticoid use 3–6 months after the start of treatment (53,54); many Japanese clinicians, however, recommend the use of low-dose glucocorticoid maintenance therapy for up to 3 years (48).

The use of steroid-sparing agents (statement 5): Some but not all patients require the combination of glucocorticoids and a steroid-sparing immunosuppressive agent from the start of treatment. This is because glucocorticoid monotherapy will ultimately fail to control the disease and long-term glucocorticoid toxicities pose a high risk to patients. (46% agreement). Opinion among the experts was split on this statement. Practice styles vary significantly across countries with regard to the use of a second immunosuppressive agent in addition to

glucocorticoids from the start of treatment. Eighty percent of the physicians from Japan (16 of 20) disagreed with addition of an immunosuppressive agent to glucocorticoids at the beginning of treatment. Conversely, 76% (13 of 17) of the participants from other countries (Korea, China, and countries in North America and Europe) agreed that this practice is appropriate in some patients. Among the subspecialties, gastroenterologists were the least likely to add another agent to glucocorticoids for initial treatment.

The variation in practice style across countries probably relates in part to the lack of universal access to certain steroid-sparing agents, particularly B cell depletion therapies. Twenty-seven percent of the panel members, mostly gastroenterologists, reported having no experience with the use of steroid-sparing agents of any kind. RTX is not available in Japan for the treatment of IgG4-RD.

Both prospective and retrospective studies demonstrate that, although glucocorticoids are effective initially for most patients, they are often tolerated poorly, and disease recurrences during or after glucocorticoid tapering are common. In the retrospective study by Ebbo and colleagues, only 30% of the 25 patients studied were able to discontinue glucocorticoid therapy, despite the fact that nearly half of the patients also received conventional steroid-sparing agents (51). Similar findings have been observed in other retrospective series, including 2 large cohorts of 563 and nearly 1,000 patients with AIP (38,47,55).

A retrospective study of AIP patients showed relapse in 38 (40%) of 96 patients who received maintenance therapy with low-dose glucocorticoids. Relapses occurred despite a maintenance prednisolone dosage of >5 mg/day in 10 (26%) of the patients whose disease relapsed (48). In another study, relapse occurred in 14 of 26 patients (54%) after discontinuation of maintenance prednisolone treatment (54).

Most experts agree that the addition of a steroid-sparing agent is appropriate when the glucocorticoid dosage cannot be tapered due to persistently active disease. In certain circumstances, providers may consider adding steroid-sparing agents during induction therapy, with plans to continue the agent as maintenance therapy. This is especially true when the there is risk that recurrent flares during glucocorticoid tapering might precipitate irreversible organ damage.

Conventional steroid-sparing medications. Azathioprine (AZA), mycophenolate mofetil (MMF), 6-mercaptopurine (6-MP), methotrexate, tacrolimus, and cyclophosphamide have all been used as steroid-sparing agents (38,50,53,56–58). However, the efficacies of these agents have not been evaluated in prospective trials, and there are few data overall to support the notion that conventional steroid-sparing agents are effective in IgG4-RD. Hart et al retrospectively compared the results of treatment of patients at their center who had relapsing AIP with AZA, MMF, or 6-MP versus glucocorticoid monotherapy (38), and found that relapse-free survival was not significantly different between the 2 groups.

B cell depletion as a steroid-sparing approach. Data from retrospective studies suggest that B cell depletion with RTX is effective, even in many patients in whom treatment with conventional steroid-sparing agents has been unsuccessful (59–62). Patients treated with RTX often require no glucocorticoid therapy during the remission induction period beyond that received as part of the infusion regimen (typically 100 mg of methylprednisolone with each RTX infusion). Among patients who are on a glucocorticoid regimen at the time RTX is initiated, the glucocorticoid dosage can often be tapered rapidly, following RTX administration (56). Hart and colleagues reported an 83% rate of complete remission following RTX treatment (3 weekly doses of 375 mg/m^2) in a group of patients with AIP whose disease had been resistant to, or who had contraindications to, steroids or conventional steroid-sparing agents (38).

A recently completed open-label trial of RTX (2 doses of 1 gm administered intravenously) in 30 patients with IgG4-RD showed encouraging results (https://clinicaltrials.gov/NCT01584388) (63). Nearly 90% of the patients in this trial were treated with RTX alone, and disease response was observed in 97% of the patients at 6 months. At baseline the mean ± SD IgG4-RD RI and physician's global assessment scores were 11 ± 7 and 63 ± 22 mm (100-mm scale), respectively. These declined to 1 ± 2 and 11 ± 17 mm at 6 months ($P < 0.001$ for both). The primary outcome measure, defined as improvement in the IgG4-RD RI of at least 2 points and absence of disease flares without glucocorticoid treatment at 6 months, was achieved in 23 (77%) of the patients.

Mechanistic studies performed in conjunction with RTX treatment have demonstrated that patients with IgG4-RD have increased levels of circulating plasmablasts and that serial plasmablast measurements may help estimate the risk of disease flare (15,16). In addition, B cell depletion appears to target the IgG4 subclass, which declines disproportionately to the decreases observed in the concentrations of other IgG subclasses (56). Because the CD20 marker is not present on the surface of either plasmablasts or plasma cells, this suggests that the plasmablasts and plasma cells producing IgG4 in IgG4-RD are short-lived and that the effect of RTX is due at least in part to a failure of repletion. Plasmablast

measurement is not yet widely available in general clinical care, limiting its use as a biomarker at this time.

The use of maintenance therapy following remission induction (statement 6): Following a successful course of induction therapy, certain patients benefit from maintenance therapy. (94% agreement). The concept of maintenance therapy following the achievement of remission received broad support from the panel. Anecdotal reports (55,64) and one study of 10 patients (65) suggest that patients with multiorgan disease, significantly elevated serum IgG4 concentrations, involvement of the proximal bile ducts, or a history of disease relapse are at higher risk of early recurrence following remission induction. Patients with organ-threatening IgG4-RD manifestations and those with an elevated risk of relapse will likely benefit from maintenance therapy in an effort to minimize morbidity.

Maintenance therapy may consist of low-dose glucocorticoids or any of the steroid-sparing agents discussed above. RTX has been useful as maintenance therapy but the optimal frequency and duration of treatment have not been clearly defined. When used as maintenance therapy, RTX is often administered when there is evidence of disease flare rather than at a predetermined time interval (e.g., every 6 months). This practice requires further evaluation and might vary depending on the potential risk of organ damage associated with a disease flare.

Regardless of the agent used, the optimal duration of maintenance therapy has not been evaluated rigorously and probably depends on a number of patient-specific factors. Most of these variables remain poorly understood and require further study.

The Japanese consensus guideline for AIP recommends maintenance therapy with low-dose steroids (prednisolone 2.5–5 mg/day) for patients who are at increased risk of relapse (48). The optimal duration of maintenance therapy has not been studied. In a retrospective, multicenter study of 459 AIP patients in Japan, it was found that 82% of the patients received glucocorticoids as maintenance therapy (47). A maintenance oral prednisone dosage of 5 mg/day was most common (63%), followed by 2.5 mg/day (21%). Relapse rates were significantly lower during maintenance glucocorticoid therapy (23%) than after glucocorticoid discontinuation (34%). Similar observations have been made in other studies (19,38).

Glucocorticoid monotherapy is often less effective than desired. Kamisawa et al reported that, despite the use of maintenance glucocorticoid therapy, nearly one-quarter of patients had a disease relapse (63 of 273 [23%]); however, the percentage was significantly higher among patients who stopped maintenance treatment (375 of 1,104 [34%]) (47). Similar findings have been observed in other retrospective series (55).

Continuous treatment with glucocorticoids for years, even at low doses, is associated with treatment-related morbidity, particularly in a disease such as IgG4-RD that often targets the pancreas and affects a patient population that is middle-aged to elderly (39).

Managing disease relapse (statement 7): Re-treatment with glucocorticoids is indicated in patients who relapse off of treatment following successful remission induction. Following relapse, the introduction of a steroid-sparing agent for continuation in the remission maintenance period should be considered. (81% agreement). Practices with regard to the use of remission maintenance treatments following disease flares vary among the experts. The evidence presented thus far highlights the fact that relapses of IgG4-RD are common, even with the use of glucocorticoid maintenance therapy. In a large AIP registry from Japan, 30% of patients had relapses while receiving glucocorticoid maintenance therapy, and 43% of those relapses involved organs beyond the pancreas (49). Hart and colleagues observed that in 32% of patients who had relapses, the relapse occurred while the glucocorticoid dosage was being tapered or the patient was receiving some other remission maintenance therapy (38). A history of relapse appears to be a strong predictor of future relapse.

In the vast majority of patients who experience flares of IgG4-RD, the flares respond well to glucocorticoid-based strategies for reinduction. If a short initial course

Table 5. Research priorities for advances in the management and treatment of IgG4-related disease

Management
1. Validation of clinical diagnostic criteria
2. Further evaluation of the relative value of various biomarkers (e.g., serum IgG4 concentration, circulating plasmablast levels) for diagnosis and monitoring disease activity
3. Large cohort studies that can identify clinically useful disease subgroups and clarify the natural history of the condition
4. Evaluation of the relative utility of various imaging modalities to identify and monitor disease activity at different anatomic sites
Treatment
1. Randomized controlled trials comparing glucocorticoids and steroid-sparing agents
2. Mechanistic studies designed to clarify aspects of disease pathophysiology and identify specific targets for therapy
3. Longitudinal cohort studies that clarify risk factors for disease flares
4. Studies clarifying the optimal timing of re-treatment to prevent disease flares

of glucocorticoid treatment yields prolonged disease remission, then a repeat glucocorticoid course without additional therapy may be the most prudent strategy in the setting of a flare.

Discussion

Recognition of IgG4-RD has expanded across medical specialties and around the world over the past decade. Early in the history of a newly recognized disease, before the availability of rigorous evidence obtained from prospective, controlled trials, guidance from clinicians who are experienced in the management of the disease is helpful in discerning the appropriate approach to the treatment of individual patients. This consensus statement, representing the collaborative efforts of 42 experts from 10 different countries and representing 8 medical subspecialties, is the first approach to summarizing treatment strategies used in different parts of the world. The goal is to provide guidance to clinicians with regard to questions that are important in the field today (Table 5).

IgG4-RD presents a challenge to physicians' full complement of skills because of its multiorgan nature and the necessity of close clinicopathologic correlation in disease management. Although IgG4-RD has pathologic characteristics that are highly suggestive of the diagnosis, most of its organ manifestations cannot be diagnosed definitively in the absence of input from the clinician about the patient's clinical phenotype. Conversely, although a growing number of typical clinical features are now recognized, clinicians who see patients with IgG4-RD are seldom comfortable making the diagnosis without histopathologic confirmation and the exclusion of potentially dangerous mimics (e.g., malignancy). Clinical experts from a variety of medical subspecialties believe that proof of the diagnosis through biopsy of an affected organ is essential in the great majority of cases. The sole exception includes some cases of AIP, assuming that the nearly diagnostic imaging features are accompanied by a compatible clinical scenario.

As clinical experience with IgG4-RD has grown in recent years, the pendulum has swung decisively away from reliance on serum IgG4 concentrations for the purposes of diagnosis and longitudinal assessment of disease activity. As treatment approaches are refined, identification of biomarkers that are more reliable than serum IgG4 levels becomes important for the assessment of longitudinal disease activity. Flow cytometry–based assays that measure plasmablasts appear to have important potential for this purpose but, as noted above, are not yet widely available.

The consensus among experts in IgG4-RD is that the threshold for initiating treatment in patients with active disease is low. Irreversible injury to some organs can occur within weeks or months if effective therapy is not initiated. The prevention of fibrosis and its potentially destructive impact on organs is a major aim of treatment. Once fibrosis is established, therapeutic options are currently limited.

Glucocorticoids remain the preference among experts as the initial therapy. It is increasingly clear, however, that in many patients, disease response is not maintained as glucocorticoids are tapered. There is no consensus approach regarding the use of remission maintenance agents, and in fact there are few data to suggest that conventional steroid-sparing agents are effective in IgG4-RD.

Approaches to both remission induction and remission maintenance vary significantly from country to country, based partly on the availability of B cell depletion therapy. Most countries' health insurance structures do not pay consistently (or at all) for RTX treatment of IgG4-RD. As a result, experience with B cell depletion in IgG4-RD differs across countries and even across subspecialties. Gastroenterologists in many countries are less experienced with the use of RTX than are rheumatologists or oncologists. This consensus exercise highlighted the tendency of Japanese experts to rely upon glucocorticoid-based treatment regimens—usually glucocorticoid monotherapy. In contrast, North American and European panel members tend to emphasize the early introduction of glucocorticoid-sparing agents, including B cell–depleting strategies.

Many questions with regard to general approaches to the treatment of IgG4-RD, as well as treatment approaches for individual organ manifestations, remain to be answered in randomized, controlled clinical trials. As knowledge of the pathophysiology of this fibroinflammatory disorder advances, treatment algorithms are also likely to evolve to include therapies that target the problematic fibrotic lesions as well as the highly cellular lymphoplasmacytic inflammation present in earlier phases of the disease.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Stone had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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