Advances in the diagnosis and management of IgG4 related disease

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ABSTRACT

IgG4 related disease was recognized as a unified disease entity only 15 years ago. Awareness of IgG4 related disease has increased worldwide since then, and specialists are now familiar with most of its clinical manifestations. Involvement of the pancreato-biliary tract, retroperitoneum/aorta, head and neck, and salivary glands are the most frequently observed disease phenotypes, differing in epidemiological features, serological findings, and prognostic outcomes. In view of this multifaceted presentation, IgG4 related disease represents a great mimicker of many neoplastic, inflammatory, and infectious conditions. Histopathology remains key to diagnosis because reliable biomarkers are lacking. Recently released classification criteria will be invaluable in improving early recognition of the disease. IgG4 related disease is highly treatable and responds promptly to glucocorticoids, but it can lead to end stage organ failure and even death if unrecognized. Prolonged courses of corticosteroids are often needed to maintain remission because the disease relapses in most patients. Rapid advancement in our understanding of the pathophysiology of IgG4 related disease is leading to the identification of novel therapeutic targets and possible personalized approaches to treatment.

Introduction

IgG4 related disease (IgG4-RD) is an immune mediated condition presenting with mass forming lesions that lead to permanent organ injury and death if left untreated.[1-5] Abundant IgG4 positive plasma cells in affected tissues and fibrosis represent hallmark pathological features of this disorder.[6]

IgG4-RD was first described in 2003, when conditions regarded as unrelated entities for decades—such as type I autoimmune pancreatitis (AIP), sclerosing cholangitis, retroperitoneal fibrosis, hypertrophic pachymeningitis, Mikulicz's disease, and Riedel's thyroiditis—were shown to occur simultaneously in a proportion of patients and to share common histological findings.[7-12] Since then, IgG4-RD has been recognized with increasing frequency by both generalists and specialists worldwide. However, awareness of the diagnostic and therapeutic tools for the management of patients with IgG4-RD remains confined to tertiary care centers, and the disease is still misdiagnosed as neoplastic, inflammatory, and infectious conditions.[13-20]

In the past decade, international collaborations have produced consensus documents for the pathological diagnosis and treatment of IgG4-RD, providing clinicians with useful guidelines for improving the management of these patients.[6 21] The 2019 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria for IgG4-RD have recently been released, and disease phenotypes have been identified, paving the way for a new era of personalized therapeutic approaches.[22-24]

In this review, we outline the latest advances in diagnosis and management of IgG4-RD, touching on diagnostic and therapeutic guidelines for IgG4-RD, established and novel potential disease biomarkers, and emerging treatment options based on the most recent acquisitions in disease pathophysiology.

Epidemiology

The global incidence and prevalence of IgG4-RD remain largely underestimated. According to Japanese studies, the incidence of AIP increased from 0.8 to 3.1 cases per 100 000 people between 2007 and 2016, suggesting a rapid growth in awareness of IgG4-RD in less than a decade.[25 26] AIP, however, represents only one of more than a dozen organs potentially affected by this condition. Among 8000 patients with IgG4-RD referred to Japanese hospitals in 2009, 5190 did not show pancreatic involvement, underscoring our poor appraisal of disease epidemiology in its multiple manifestations.[27]

IgG4-RD typically affects middle aged and older people with a male to female ratio that ranges from 1.6:1 for head and neck manifestations to 4:1 for other sites of organ involvement.[1 2] No environmental and genetic risk factors are clearly associated with IgG4-RD. However, a recent genome-wide association

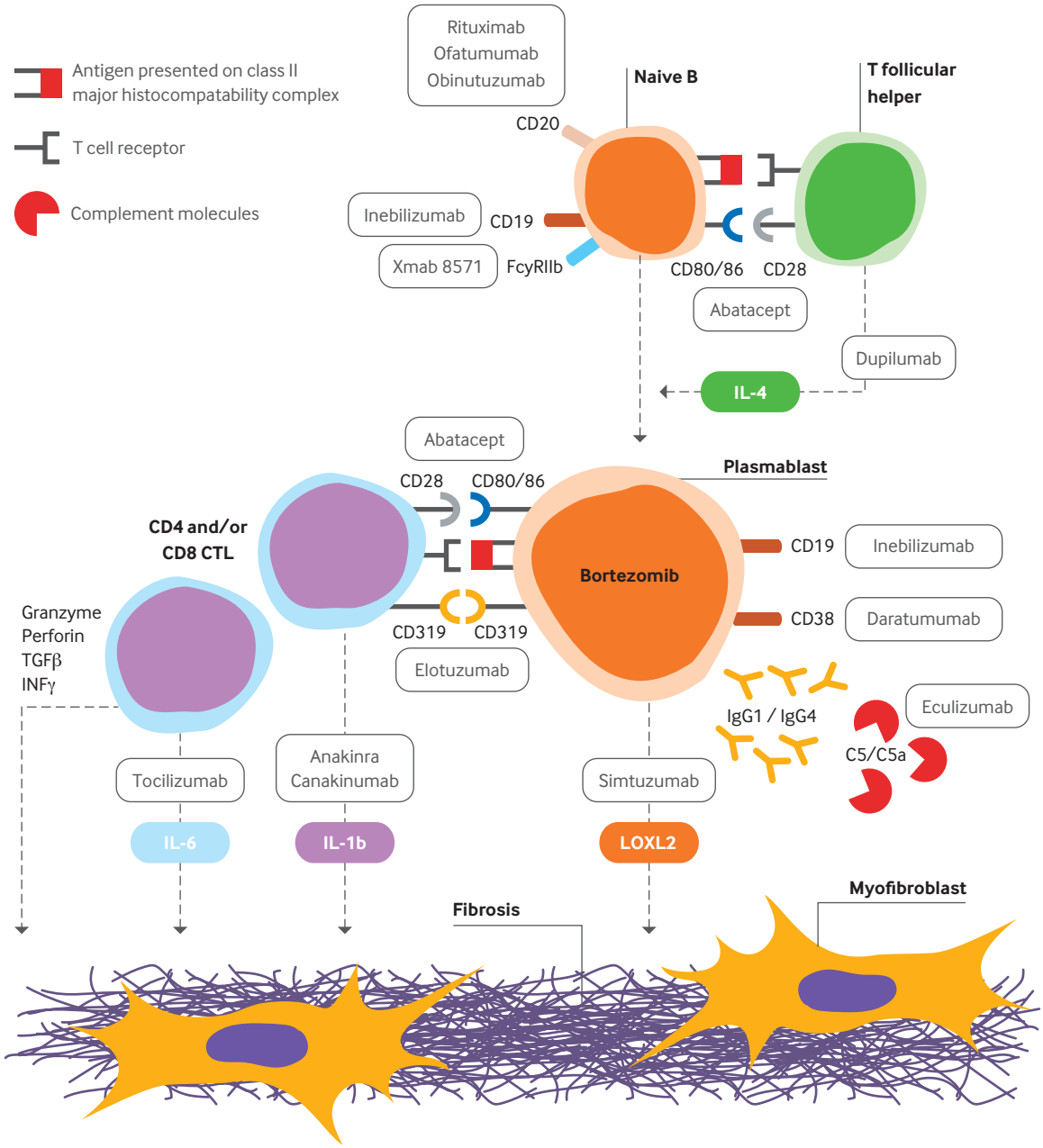


Fig 1 | Pathophysiology of IgG4 related disease (IgG4-RD) and novel potential therapeutic targets. B-T cell collaboration seems to be central to the pathophysiology of IgG4-RD at different levels. Follicular T helper cells are considered responsible for maturation of naive B cells into IgG4 secreting plasmablasts through secretion of interleukin 4. Plasmablasts migrate into inflamed tissues, where they sustain activation of CD4 and CD8 cytotoxic T lymphocytes (CTLs) through antigen presentation, SLAMF-7 mediated homodimer interactions, and CD80/86 engagement of CD28. CD4 and CD8 CTLs are considered the major drivers of tissue damage through the production of cytolytic and pro-fibrotic molecules such as granzyme, perforin, transforming growth factor β (TGFβ), interferon γ (IFN γ), interleukin 1b (IL-1b), and interleukin 6 (IL-6). Plasmablasts have also been found to orchestrate fibroblast activation and extracellular matrix deposition through the production of lysyl oxidase homologue 2. IgG4, and possibly IgG1, antibodies secreted by plasmablasts/plasma cells might form immune complexes and further perpetuate tissue damage via complement activation. Several targeted therapies are available for interfering with these pathogenic mechanisms at different levels, including depletion of B cells, inhibition of B-T cell co-stimulation, complement activation, cytokine blockade, and impairment of extracellular matrix organization

study in 850 Japanese patients identified HLA-DRB1 and FC-γ receptor IIb regions as susceptibility loci for the development of IgG4-RD, suggesting a possible genetic predisposition.[28]

Sources and selection criteria

We based our review on PubMed and Medline online databases and searched for papers published in the English literature before 1 March 2020, using the following MeSH keywords and keywords combinations: "IgG4-related disease", "IgG4-sclerosing disease", "diagnosis", "pathology", and "treatment". The search identified 3960 reports. We prioritized multicenter, randomized trials and high quality epidemiological studies when available. We also considered systematic reviews and meta-

analyses. Given the breadth of this review, the recent appraisal of IgG4-RD as a unique entity, and the dearth of comprehensive studies on diagnostic and therapeutic aspects, we decided to include observational, basic science, and translational studies, as well as case series, driving future investigation in the area, in addition to high quality abstracts from the EULAR and ACR annual meetings between 2016 and 2019.

Overview of disease pathophysiology

IgG4-RD follows a biphasic progression characterized by an "inflammatory" phase that eventually culminates in a "fibrotic" outcome (fig 1).[3 29-31] Clonal expansion of presumably pathogenic B cell and T cell subpopulations in patients' blood and tissues indicates that IgG4-RD is likely sustained by an antigen driven immune response, but the nature of the antigen(s) and the reason for disease targeting of particular organs remain unclear.[32-36] A variety of self-antigens have been identified, including galectin-3, annexin-A11, laminin-511, and prohibitin, suggesting that a breach of immunological tolerance might initiate the disease.[37-40]

The first inflammatory phase of IgG4-RD is characterized by the appearance of antigen experienced B and T lymphocytes that accumulate at disease sites, engage in mutual activating antigen driven interactions, and secrete pro-fibrotic molecules such as interleukin 1β, interleukin 6, interferon γ, transforming growth factor β, platelet derived growth factor B, and lysyl oxidase homologue 2.[41-43] These populations of activated lymphocytes include circulating plasmablasts, T effector memory (T_{EM}) cytotoxic T lymphocytes (CTLs), and CD45RA+TEM (T_{EMRA}) CTLs.[32-36] Both plasmablasts and effector memory T cells express the signaling lymphocytic activation molecule F7 (SLAMF7), a surface protein that has been implicated in cell-cell interaction and chronic lymphocyte activation.[32-36] Although involvement of T_{EM} and T_{EMRA} CTLs in tissue fibrosis has not been clearly demonstrated, plasmablasts/plasma cells from patients with IgG4-RD have been shown to prompt fibroblast activation and collagen production in vitro, thus partially explaining the improvement of fibrotic lesions with B cell depletion.[34 41-43]

Other T cell subsets presumably involved in the inflammatory phase of IgG4-RD are CD4 follicular T helper (Tfh) cells, T regulatory cells, and Th2 cells.[1] Circulating Tfh1 and Tfh2 cells expressing programmed cell death protein 1 (PD1) are expanded in patients with IgG4-RD and correlate with disease activity, plasmablast numbers, and serum concentrations of IgG4 and interleukin 4.[44-46] PD1 positive Tfh2 cells drive IgG4 class switch in vitro, enhance proliferation of IgG4 committed B cells, and facilitate differentiation of naive B cells into plasmablasts/plasma cells, resulting in increased IgG4 secretion.[46-48] Activated Tfh cells expressing interleukin 4 and interleukin 21 are also found in tertiary lymphoid structures of IgG4-RD affected tissues and likely contribute to germinal center formation.[1 49-51] On the other hand, the contribution of T regulatory cells and Th2 cells to disease pathogenesis is controversial. Indirect evidence based on interleukin 5, interleukin 10, and interleukin 13 expression in disease lesions suggests activation of Th2 and regulatory immune reactions, but other studies failed to show significant expansion of Th2 and T regulatory cells in IgG4-RD.[1 52-55]

The role of innate immunity in the pathogenesis of IgG4-RD is much less studied, although innate immune cells seem to be implicated in the transition from the inflammatory to the fibrotic phase of the disease. In particular, M2 macrophages have been shown to infiltrate IgG4-RD lesions and to express pro-fibrotic cytokines such as interleukin 10, interleukin 13, interleukin 33, and CCL18.[56 57]

During the fibrotic phase of IgG4-RD, lymphocytes and innate immune cells are replaced by a dense stromal reaction that progressively leads to tissue distortion and organ damage.[31] The mechanisms implicated in this second phase of the disease are less characterized but likely involve extracellular matrix deposition by activated fibroblasts and a still poorly understood contribution of IgG4 antibodies. Compared with other immunoglobulin subclasses, IgG4 antibodies are known to participate in the resolution of tissue inflammation because of intrinsic anti-inflammatory properties.[58 59] However, monoclonal IgG4 antibodies targeting pancreatic cells that express ovalbumin have been shown to induce pancreatic inflammation in mice only when injected with ovalbumin specific CTLs and not when injected alone, suggesting a possible synergistic effect of IgG4 antibodies and CTLs in causing tissue damage.[60] Research areas on IgG4-RD pathogenesis are listed in the "Questions for future research" box.

Diagnosis of IgG4 related disease

General considerations

Definitive diagnosis of IgG4-RD requires rigorous clinical-pathological correlation because clinical assessments, laboratory evaluations, and imaging studies are often insufficient to distinguish neoplastic, inflammatory, and infectious mimickers.

Serological findings in patients with IgG4-RD are largely non-specific. Erythrocyte sedimentation rate (ESR) can be elevated to a moderate degree. C reactive protein (CRP) is usually normal except in some clinical manifestations such as retroperitoneal and aortic involvement, in which a slight increase can be observed.[61-67] Marked elevation of acute phase reactants should raise concern about infectious or inflammatory conditions that closely mimic IgG4-RD, such as ANCA (anti-neutrophil cytoplasmic antibody) associated vasculitis and multicentric Castleman disease.[68-74] Peripheral blood eosinophilia and increased serum IgE concentrations occur in almost 30% of patients.[54 62-65] Some have low titer antinuclear antibodies, positive rheumatoid factor, or both.[62-65]

Serum IgG4 elevation occurs in 55-97% of cases, especially in Asian patients, and correlates with the

number of organs involved.[13 14 62-65 75-79] In a meta-analysis of nine case-control studies including 1235 patients with IgG4-RD and 5696 controls, a cut-off value of serum IgG4 ranging from 1.35 g/L to 1.44 g/L yielded a pooled sensitivity of 87.2% (95% confidence interval 85.2% to 89.0%) and a specificity of 82.6% (81.6% to 83.6%). When twice the upper limit of normal was used as the cut-off (range 2.70-2.80 g/L), the pooled sensitivity and specificity were 63% (60.0% to 66.0%) and 94.8% (94.1% to 95.4%), respectively.[80] Although useful for initial screening, however, elevation of serum IgG4 has poor diagnostic utility because it can occur in a broad spectrum of neoplastic, infectious, and autoimmune diseases.[1 13 14 75] In addition, measurement of serum IgG4 is not free from analytical errors. Most laboratories worldwide quantify IgG4 concentration by either turbidimetry or nephelometry, with the former method giving spuriously normal IgG4 values in case of antigen excess ("prozone phenomenon").[81 82]

Other IgG subclasses—namely, IgG1, IgG2, and IgG3—are often elevated, although generally not to the same extent as IgG4, and may be responsible for the complement consumption observed in nearly a quarter of patients with active IgG4-RD.[62-65 83] In these patients, baseline urinalysis with evaluation of the urinary sediment is warranted because decreased serum C3 and C4 concentrations might indicate subclinical or overt renal involvement.[84 85] Disease specific autoantibodies such as ANCA, SSA/Ro or SSB/La, double stranded DNA, RNP, and Sm, are not observed in IgG4-RD and should orient diagnosis towards mimicking autoimmune conditions.[68-74]

Radiological findings are also largely non-specific in most affected organs.[86 87] IgG4 related AIP with diffuse involvement is the sole exception, because computed tomography and magnetic resonance imaging classically show a diffusely enlarged "sausage shaped" pancreas with a surrounding halo of edematous tissue (fig 2).[88 89]

Because of the shortcomings of serological and radiological findings, histological examination remains the mainstay for definitive diagnosis and should be done whenever possible. Guidelines for pathological diagnosis of IgG4-RD are reported in the Guidelines section below.[6] However, obtaining optimal biopsy samples might be challenging in many scenarios, such as in case of retroperitoneal, large vessels, or dural involvement, and invasive procedures might be needed. A full picture of disease involvement should therefore be obtained at the time of diagnosis with a whole body computed tomography scan or an ^{18}fluoro-deoxyglucose positron emission tomography (^{18}FDG-PET) scan both for staging purposes and for identifying sites that can be sampled more easily (fig 2).[90 91] In certain circumstances, such as in case of salivary gland involvement, the intensity of ^{18}FDG uptake may be also used for diagnostic purposes.[92] Finally, the 2019 ACR/EULAR classification criteria for IgG4-RD have recently been released, providing a useful framework for disease recognition.[22 23] The classification criteria will be discussed in detail in the Guidelines section of this review.

Novel diagnostic biomarkers

Along with a better understanding of the immunological perturbations that occur in IgG4-RD, several novel serological and cellular biomarkers have been proposed and are awaiting validation in large prospective multicenter studies.

Increased ratios of serum IgG4 to total IgG (>10%) or IgG1 (>24%), for instance, have been shown to improve diagnostic specificity, especially when IgG4 concentrations are only slightly raised.[93] Quantitative polymerase chain reaction of the IgG4:IgG RNA ratio on peripheral blood seemed to accurately distinguish IgG4 related cholangitis from hepatobiliary malignancies and inflammatory processes with a sensitivity of 94% and a specificity of 99%.[94] An increase in serum IgG2 concentration above 5.3 g/L provided a sensitivity of 80% and a specificity of 91.7% for orbital IgG4-RD.[95]

Multicolor flow cytometry, next generation sequencing, and gene expression analyses led to the identification of disease specific B cell and T cell subpopulations expanded in the peripheral blood of patients with IgG4-RD and in affected tissues. $CD19^{low}CD20^{neg}CD27+CD38^{hi}$ plasmablasts, for instance, are increased in patients with both elevated and normal concentrations of serum IgG4, showing higher sensitivity and specificity for diagnosis of IgG4-RD than serum IgG4 concentrations.[96-98] Next generation sequencing of circulating plasmablasts also showed that class switched IgG4 positive clones are preferentially expanded in patients with IgG4 related cholangitis compared with other disorders of the biliary tract, representing a promising diagnostic biomarker of pancreato-biliary IgG4-RD.[94 99]

Finally, several autoantigens have been described in IgG4-RD, including prohibitin, annexin A11, laminin 511, and galectin-3, but autoantibodies against these proteins are found at low frequency in patients' serum and can also be measured in some healthy donors and mimicker conditions, bearing low specificity and sensitivity for diagnostic purposes.[37-40 100] Table 1 gives an overview of traditional and novel biomarkers used for diagnosing IgG4-RD.

Clinical phenotypes of IgG4 related disease

The predilection of IgG4-RD for certain organs has been known since the early description of the disease. However, constant patterns of clinical manifestations were not comprehensively appraised until recently, when latent class analysis was applied to the international cohort of patients with IgG4-RD used for developing the ACR/EULAR classification criteria.[24] By analyzing the distribution of organ involvement in nearly 800 patients, latent class analysis identified four homogeneous phenotypes of IgG4-RD, providing physicians with a set of clinical frameworks for improving the recognition

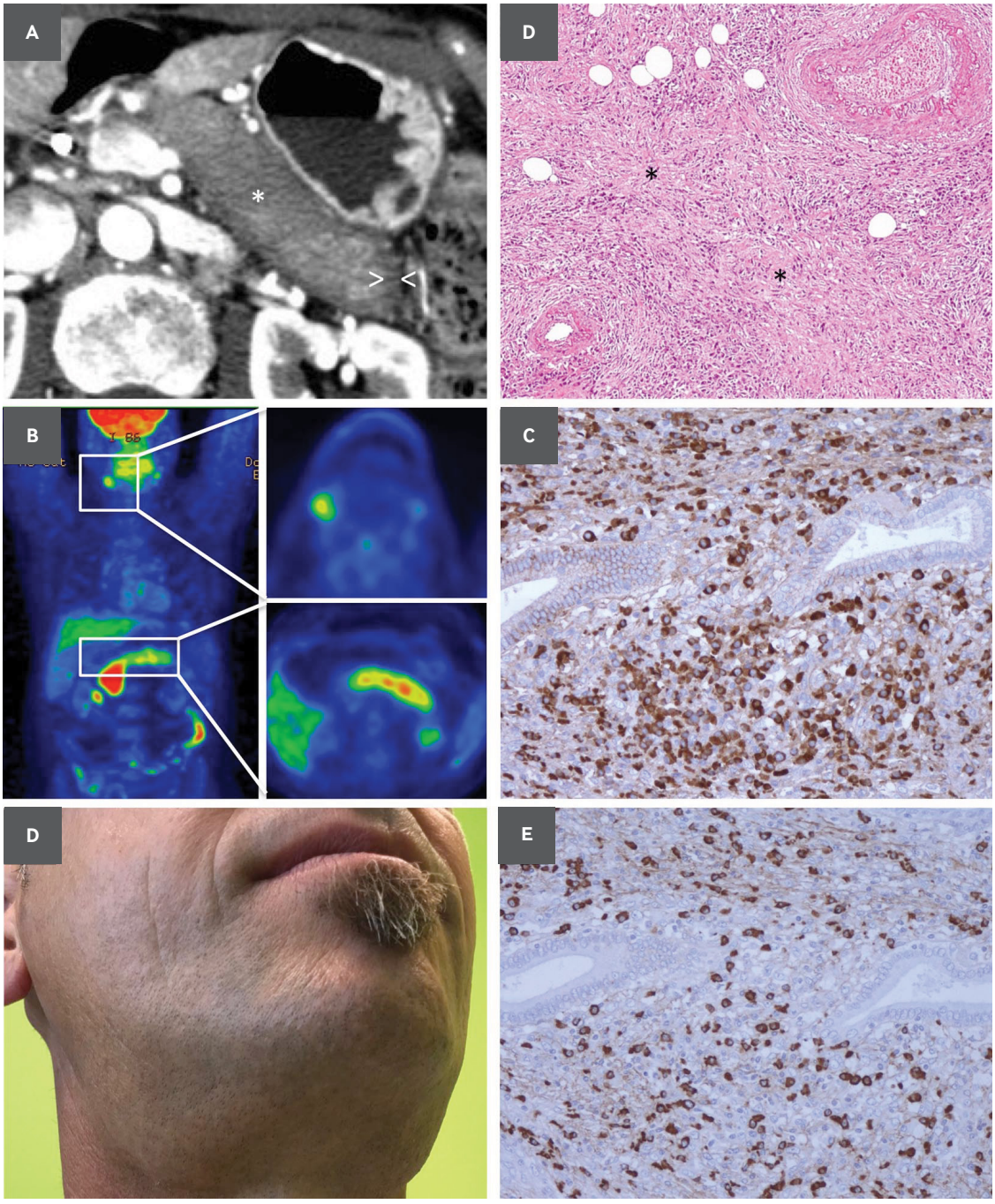


Fig 2 | Highly suggestive clinical, radiological, and pathological features of IgG4 related disease (IgG4-RD). A: abdominal computed tomography scan showing a "sausage-like" pancreas (*) with a surrounding rim of hypodense tissue (arrowheads), classic radiological features of autoimmune pancreatitis. B: positron emission tomography scan showing ^{18}fluoro-deoxyglucose uptake in the pancreas and submandibular glands. The two findings together are highly suggestive of IgG4-RD. C: bilateral swelling of the submandibular and parotid glands is a manifestation highly consistent with IgG4-RD. D-F: classic histopathological and immunohistochemical features of IgG4-RD in a pancreatic biopsy: areas of storiform fibrosis (*; hematoxylin and eosin) (D); immunohistochemistry for IgG (E), and IgG4 (F) on sequential sections shows an IgG4/IgG ratio >40%

of IgG4-RD.[24] These phenotypes were pancreato-hepatobiliary disease (31%), retroperitoneal fibrosis with or without aortitis (24%), head and neck limited disease (24%), and classic Mikulicz's syndrome with systemic involvement (22%).[24]

Interestingly, patients clustered to each phenotype shared distinctive clinical, epidemiological, and serological features. Patients with head and neck limited disease (group 3) were far more likely to be female and Asian than were patients in the other groups (fig 3).[24 101] They were also significantly younger and needed histological confirmation to achieve a final diagnosis more often than did other groups.[102] Referral to the emergency department

Table 1 | Traditional and novel potential biomarkers of IgG4 related disease (IgG4-RD)

Type and subclass of biomarker	Examples	Comments
Traditional		
Diagnosis	Serum IgG4	Elevated in 55-97% of patients. Correlates with disease burden
	Serum IgG4:IgG ratio	When >10% it increases diagnostic specificity in case of normal serum IgG4
	Serum IgE and eosinophils	Elevated in 30% of patients regardless of atopic background
	CSF IgG4 indices	Elevated in IgG4 related hypertrophic pachymeningitis
	Plasmablasts and plasma cells	Expanded in peripheral blood regardless of serum IgG4 concentration
	Serum C3, C4	Consumption may suggest subclinical or overt renal involvement and should prompt urinalysis
	^{18}FDG-PET	Useful for staging purposes and for identification of alternative sites for biopsy sampling. Caution is needed when interpreting lymph node uptake because IgG4-RD lymphadenopathy is indistinguishable from reactive and neoplastic lymph nodes
Disease activity	Serum IgG4, IgE, and eosinophils	Decrease with disease response to treatment. May not normalize at disease remission in patients presenting with marked elevation at diagnosis. Mild oscillation should not prompt additional investigations. Marked (>twofold) increase after remission should raise possibility of disease flare
	Serum IgG4:IgG ratio	Decreases with disease response to treatment
	CSF IgG4 indices	Decrease with disease response to treatment
	Plasmablasts and plasma cells	Decrease with disease response to treatment and increase at flare
	Serum ESR/CRP	More often correlate with disease activity in case of retroperitoneal and aortic involvement
	Serum C3, C4	May normalize in case of remission and decrease during flares, especially in case of renal involvement
	^{18}FDG-PET	Reduced ^{18}FDG uptake in response to treatment. Caution is needed when interpreting lymph node uptake because IgG4-RD lymphadenopathy is indistinguishable from reactive lymph nodes
Predictors of relapse	Serum IgG4, IgE, and eosinophils	The higher the baseline values, the greater the risk of relapse and the shorter the time to relapse
Fibrosis	-	-
Novel*		
Diagnosis	Anti-galectin-3; laminin 511; annexin A11; prohibitin antibodies	Present in <30% of patients with IgG4-RD
	Serum IgG2	Elevated in cohort of patients with orbital IgG4-RD. Assessed only for orbital involvement
	Serum IgG4:IgG RNA ratio	Better performance than serum IgG4 for diagnosis of hepatobiliary IgG4-RD. Assessed only for biliary involvement
	CD4 and/or CD8 SLAMF7+ CTLs	Expanded in peripheral blood during active disease
Disease activity	Serum soluble interleukin 2 receptor	Normalizes at remission, even in patients with persistent elevation of serum IgG4
	Serum IgG4:IgG RNA ratio	Decreases with disease response to treatment. Assessed only for biliary involvement
	CD4 and/or CD8 SLAMF7+ CTLs	Decrease with disease response to treatment and increase with flare
	Serum C5, C5a	Elevated during active disease. Decrease with disease response to treatment
	Activated Tfh2 cells	Decrease with disease response to treatment
Predictors of relapse	Memory B cells	Decreased in peripheral blood at disease onset. Increase after glucocorticoid induced remission in patients who will relapse within 2 years
Fibrosis	Serum ELF score; CCL-18	Indirect biomarker of disease activity. Reflect collagen deposition at tissue sites

CRP=C-reactive protein; CSF=cerebrospinal fluid; CTL=cytotoxic T lymphocyte; ELF=enhanced liver fibrosis; ESR=erythrocyte sedimentation rate; FDG=fluoro-deoxyglucose; PET=positron emission tomography; Tfh2= type 2 follicular T helper.
*Novel potential biomarkers have been tested in single center cohorts and have not yet been externally validated.

because of symptoms attributed to onset of IgG4-RD occurred more often in patients with pancreato-hepatobiliary disease (group 1).[103] Inflammatory markers were significantly higher in group 2 and lower in group 4.[104] Finally, patients with Mikulicz's syndrome and systemic involvement (group 4) had the highest median serum IgG4 concentrations (fig 3).[102] This classification will soon offer the opportunity to discover meaningful biological differences between IgG4-RD phenotypes, to assess the performance of disease biomarkers in uniform cohorts of patients and disease subtypes, and to establish personalized follow-up and therapeutic strategies.

Management of IgG4 related disease

General considerations

Because of its recent recognition as a systemic disorder, comprehensive management of IgG4-RD in its various manifestations remains at an early stage of definition, based primarily on expert opinion and on retrospective studies in gastroenterological settings.[105] Only recently have data begun to emerge from prospective studies, but these remain small and not randomized.

In general, once the diagnosis of IgG4-RD has been made with reasonable certainty, clinicians must consider both the pattern and the severity of organ involvement to define the most appropriate course of treatment and follow-up strategy. Clinical-pathological correlation should also be considered to establish the likelihood of response to immunosuppressive therapies. IgG4-RD lesions are more likely to shrink early in the presence of a prominent lymphoplasmacytic infiltrate (inflammatory phase) than at later stages when both inflammatory cells and myofibroblasts are rare (fibrotic phase), indicating that a "window of therapeutic opportunity" for preventing irreversible organ damage exists and possibly varies from organ to organ.[30 42 106-108] Finally, clinicians should consider the relapsing-remitting nature of this condition and the potential side effects of glucocorticoids. Corticosteroids are highly effective in IgG4-RD, but they will ultimately fail to control inflammation when tapered to a low dose.[21] In addition, their long term use can become problematic in a disease that often affects middle aged and older people.[109]

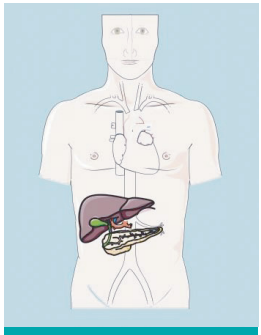
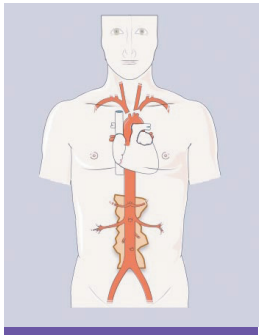
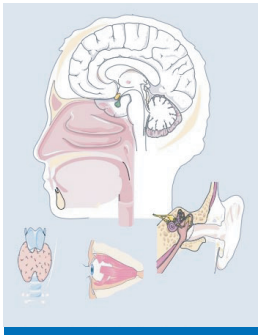
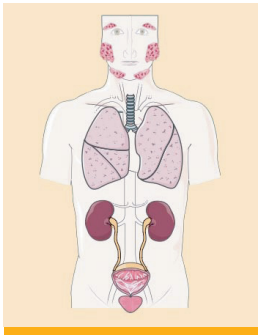
	PANCREATO-BILIARY	RETROPERITONEAL/AORTITIS	HEAD AND NECK LIMITED	MIKULICZ/SYSTEMIC*
IgG4-RD phenotypes				
Diagnosis	MALE White Older – IgG4 ↑↑ IgE ↑ –	MALE White Older – IgG4 ↑ / = – ESR / CRP ↑	FEMALE Asian Younger History of atopy IgG4 ↑↑ – –	MALE – Older – IgG4 ↑↑↑ IgE ↑ –
Management	– – Treatment responsive –	– Fibrotic disease Treatment refractory Higher cumulative GCs	– Fibrotic disease Treatment refractory Higher cumulative GCs	IgG4-RD RI ↑ – Treatment responsive –
Outcomes and morbidities	**Pancreas**: diabetes melititus and malabsorption due to exocrine insufficiency **Billiary tract and liver**: Billiary stenting, infectious cholangitis, hepatic failure	**Pericardium**: constrictive percarditis **Heart**: coronary artery disease **Aorta**: inflammatory thoracic or abdominal aortic aneurisms **Retroperitoneum**: renal atrophy or injury due to hydronephrosis, chronic abdominal pain syndrome **Mediastinum**: compression of local structures	**Orbits:** proptosis, vision loss, diplopia Meninges: cranial nerve palsies Ear: hearing loss, bone destruction Skull bones and sinuses: chronic sinusitis, midline destructive lesions, anosmia Thyroid and pituitary gland: hypothyroidsim, hypopituitarism	**Lacrimal glands:** sicca **Salivary glands:** sicca **Pancreas:** diabetes mellitus and malabsorption due to exocrine insufficiency **Lungs:** pulmonary fibrosis and interstitial lung disease **Pleura:** effusion and thickening **Kidneys:** renal failure due to interstitial/glomerulo nephritis
Treatment	**Remission induction** (disease onset/relapse): **1** Oral PREDNISONE (0.6-1 mg/kg) for 3 weeks and then taper over 3-6 months; **2** RITUXIMAB (two 1 g iv infusions 15 days apart) **Remission maintenance**: **1** Low dose glucocorticoids; **2** DMARDs: AZA – MTX – CTX – MMF – LFN – CSA; **3** RITUXIMAB (two 1 g iv infusions 15 days apart/single 1 g infusion) every 6 months			

Fig 3 | Differences and similarities among IgG4 related disease (IgG4-RD) phenotypes in clinical and serological features, outcomes, and therapeutic approaches. IgG4-RD has a strong male predominance. Compared with white patients, Asian patients are at higher risk of developing IgG4-RD in the head and neck region. Patients with head and neck involvement also seem to more often have atopic manifestations. Patients with Mikulicz's/systemic disease have more organs involved, higher values of IgG4-RD responder index (RI), and serum IgE concentrations. Patients with retroperitoneal and head and neck involvement seem more prone to have a fibrotic outcome than do those with other IgG4-RD phenotypes, and are thus more challenging to treat. Organ specific long term complications are reported for each disease phenotype. Available treatments for inducing and maintaining remission are the same for all IgG4-RD phenotypes. Glucocorticoids (GCs) should be used as first line therapy to induce remission. In case of relapse, rituximab represents the most promising second line agent to re-induce remission. Maintenance of remission can be pursued with long term low dose glucocorticoids (oral prednisone 5-7.5 mg daily), disease modifying anti-rheumatic drugs (DMARDs; for specific dosages, refer to table 3), or rituximab infused every six months. *Mikulicz/systemic disease might also include organs involved more typically in other disease phenotypes. AZA=azathioprine; CRP=C reactive protein; CsA=(ciclosporin); CTX=cyclophosphamide; ESR=erythrocyte sedimentation rate; iv=intravenous; LFN=leflunomide; MMF=mycophenolate mofetil; MTX=methotrexate

By analyzing a large single center cohort of IgG4-RD patients, our group recently found interesting differences in the long term outcomes of IgG4-RD phenotypes that might be useful to consider in order to foster personalized therapeutic strategies.[102] Head and neck manifestations of IgG4-RD, for instance, seem to be more challenging to treat and more prone to relapse in a shorter period of time, leading to higher exposure to glucocorticoids over time. On the other hand, patients with pancreato-biliary manifestations and Mikulicz's/systemic disease seem to be at significantly increased risk of developing diabetes mellitus owing to long term administration of glucocorticoids.[102] Therapies for induction of remission should therefore be followed by strategies for maintaining remission in patients at risk of relapse, and management of IgG4-RD patients should take into account the aforementioned variables to avoid organ damage and to reduce cumulative exposure to corticosteroids.

In this section, we will explore different therapeutic approaches to IgG4-RD and discuss the latest strategies to induce and maintain remission. Most of the information is derived from the International Consensus Guidance Statement on the Management and Treatment of IgG4-RD, discussed in the Guidelines section of this review.[21]

Induction of remission

Glucocorticoids

Glucocorticoids represent the first line agent for inducing remission in all patients with active IgG4-RD.[21] Induction of remission should aim to resolve symptoms and biochemical and radiological abnormalities, and improvement should typically be observed within days to several weeks, depending on the organs involved. The starting dose of corticosteroids typically consists of 30-40 mg/day (0.6-1 mg/kg) of prednisone or steroid equivalent.[105 110] One retrospective study and one randomized controlled trial reported no differences in terms of remission rate between patients with IgG4-RD treated with high dose (0.8-1 mg/kg) and medium dose (0.5-0.6 mg/kg) corticosteroids, although a higher frequency of relapse was observed in the latter group.[111 112] High dose glucocorticoids can be also administered intravenously (for example, 1 g methylprednisolone for three consecutive days) when urgent treatment is warranted to avoid organ damage such as cranial or spinal nerve involvement.[113 114] Delayed or unsatisfactory response to steroid treatment should prompt additional evaluations—including repeated biopsy procedures to confirm the diagnosis—because patients typically respond well to this intervention.[21]

Although no universal consensus exists about duration of treatment and tapering regimens, experts suggest that the initial steroid dose should be upheld for at least two to four weeks and then gradually reduced by 5 mg every two weeks over a period of three to six months.[21] In a multicenter, phase II, prospective clinical trial on the use of glucocorticoids in IgG4-RD, an initial dose of 0.6 mg/kg/day was reduced by 10% every two weeks and clinical response was observed in 93% of patients.[115] Faster tapering and early discontinuation of treatment are associated with a higher risk of flare.[116] Relapses occur in 46-90% of patients within three years from diagnosis in the same affected organ or at a different anatomical site, both during tapering (26-40% of patients) and after withdrawal of glucocorticoid therapy (46-54% of patients).[65 117-119] Flares typically respond well to the same dose of glucocorticoids used for induction of remission. Addition of immunosuppressive agents or rituximab and slower tapering of the corticosteroid therapy are also indicated in case of relapse, but attitudes vary depending on organ involvement and expertise.[21 105]

Immunosuppressive drugs

When predictors of relapse—such as multi-organ involvement, elevation of serum IgG4 and IgE at baseline, and peripheral blood eosinophilia—are present, disease modifying anti-rheumatic drugs (DMARDs) can be added to first line steroid therapy to improve the likelihood of obtaining disease remission. Azathioprine, mycophenolate mofetil, methotrexate, leflunomide, tacrolimus, ciclosporin A, iguratimod, and cyclophosphamide have been all used in combination with glucocorticoids, but little evidence exists for the additional efficacy of these drugs and most data derive from retrospective studies.[120-130] In the only four prospective studies that we are aware of (all uncontrolled and only one randomized), DMARDs combined with steroid therapy led to a higher remission rate (93%) compared with glucocorticoids alone (79%) at six months.[131] Mycophenolate mofetil (1-1.5 g/day), cyclophosphamide, and iguratimod seemed to be particularly effective in this regard, although the latter has been used only in localized sialadenitis without internal organ involvement.[122 123 129] A meta-analysis of 15 observational, uncontrolled, non-randomized clinical trials involving 1169 patients confirmed these findings and reported that patients treated with combination therapy had a higher remission rate than those given only glucocorticoid (odds ratio 3.36, 95% confidence interval 1.44 to 7.83) or DMARD (55.31, 13.73 to 222.73) monotherapy.[120]

The addition of immunosuppressive agents should be also aimed at reducing the cumulative toxicity of prolonged treatment with glucocorticoids, especially in patients prone to relapse who might need repeated courses of corticosteroids. Patients with IgG4-RD are typically older people with comorbidities that represent major contraindications to corticosteroids, such as diabetes, osteoporosis, glaucoma, and hypertension.[110] Definitive data showing the steroid sparing effect of DMARDs in the long term are lacking, however, and optimal management of these patients would ideally require avoidance of glucocorticoids. We are aware of a single case series showing induction of sustained remission without concomitant use of corticosteroids. In this

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study, three patients with IgG4-RD AIP and poorly controlled diabetes were treated with methotrexate (20 mg/week) alone, with disease remission, serum IgG4 reduction, and plasmablasts depletion seen in all patients.[132] Further studies within the context of clinical trials are, however, needed to confirm the efficacy of DMARDs alone as therapy for induction of remission and to identify the best clinical scenarios in which they might be used instead of glucocorticoids. This is important because access to biological agents and advanced therapies varies depending on geographical, economic, and social factors.

Biological agents

Rituximab was the first targeted therapeutic agent administered to patients with IgG4-RD and is the most widely used biological agent in this condition.[133] Data from uncontrolled non-randomized prospective and retrospective studies indicate that rituximab leads to disease remission in 67-83% of cases, allowing early tapering of glucocorticoid therapy.[134-137] Rituximab decreases circulating expanded plasmablasts and CD4 CTLs, indicating that it likely interferes with chronic activation of CD4 CTLs by disrupting B-T cell interactions and antigen presentation.[43] B cell depletion also improves tissue fibrosis in IgG4-RD by directly targeting a subset of B lymphocytes with pro-fibrotic properties involved in fibroblast activation and recruitment of inflammatory cells.[41 42] Rituximab was effective when administered either as two 1 g infusions 15 days apart (rheumatological protocol) or in four weekly 375 mg/m^2 infusions (hematological protocol), as well as at lower doses (single 1 g infusion) in a few reports.[138 139] However, although rituximab has been administered in more than 200 patients with IgG4-RD worldwide, the best dosage and timing of administration remain to be defined, and some drawbacks are emerging that are similar to those observed in hematological settings and other autoimmune disorders. In a French nationwide study, for instance, IgG4-RD relapsed in 42% of patients treated with rituximab, and serious infections or hypogammaglobulinemia were observed in one third of patients.[135] In addition, allergic reactions or reduced response to rituximab are increasingly reported, underscoring the need for alternative approaches to treatment.[139-141]

Because of our partial knowledge of the pathophysiological mechanisms sustaining IgG4-RD, however, the use of other targeted therapies remains limited to single anecdotal case reports. Abatacept, an anti-CTLA4 antibody interfering with T cell co-stimulation, induced and maintained remission in a Japanese patient with rituximab resistant Mikulicz's disease and AIP.[141] Similarly, infliximab, a chimeric anti-tumor necrosis factor α antibody, was successfully used in a patient with orbital pseudotumor refractory to multiple immunosuppressive agents.[142] More recently, dupilumab, a monoclonal antibody that blocks interleukin 4 receptor-α, markedly improved retroperitoneal fibrosis in a patient with IgG4-RD and severe atopic manifestations.[143-145] Interestingly, despite targeting different molecular mechanisms, abatacept, infliximab, and dupilumab all reduced serum IgG4 concentrations and induced marked clinical responses, supporting the notion of a complex interplay between inflammatory pathways and cellular and humoral immunity at the basis of IgG4-RD pathophysiology.

Maintenance of remission

The selection of patients who need maintenance therapy and the modalities of treatment administration remain unclear and based on expert opinion. In general, patients presenting with multi-organ disease, elevation of serum IgG4 and IgE, and peripheral eosinophilia show the highest risk of relapse and might benefit from therapy for maintenance of remission.[146 147] Patients with organ threatening manifestations should also be considered for maintenance treatment in an effort to minimize disease morbidity related to a potential relapse.[148] Maintenance may consist of either low dose glucocorticoids or any of the steroid sparing agents discussed above.[21]

Glucocorticoids

A Japanese retrospective study of 563 patients with AIP showed a lower relapse rate (23%) in patients kept on low dose glucocorticoid treatment than in those who stopped treatment after remission was achieved (34%).[149] Similar results were obtained in a multicenter randomized controlled trial in 49 patients with AIP—namely, a significantly higher relapse rate (58%) in those who stopped low dose (5-7.5 mg daily) steroid therapy after 26 weeks compared with those who continued maintenance therapy for up to three years (23%).[150] Of note, among patients kept on the maintenance regimen, the higher risk of flare was observed in those receiving lower doses of prednisone (<5 mg/day).[116 122]

Immunosuppressive drugs

A retrospective cohort study in 116 patients compared the addition of different DMARDs to glucocorticoid monotherapy and found no differences in terms of relapse-free survival at two years.[127] Conversely, two prospective Chinese clinical trials showed a reduced relapse rate at one year when either mycophenolate mofetil (1-1.5 g/day) or oral cyclophosphamide (50-100 mg/day) was added to low dose corticosteroids, compared with steroid treatment alone (21% *v* 40% and 12% *v* 39%, respectively).[122 123] These findings were further confirmed by a meta-analysis of 15 studies involving 1169 patients, whereby combination therapy with glucocorticoid and immunosuppressive drugs was associated with a lower relapse rate compared with glucocorticoids alone (odds ratio 0.39, 0.20 to 0.80).[120] Other scant reports, mostly focused on AIP, described positive experiences with tacrolimus, azathioprine, methotrexate, or leflunomide in preventing relapse of IgG4-RD, but these studies remain small, retrospective, and uncontrolled.[120 124 125 151]

Biological agents

According to available retrospective studies and to a single meta-analysis, rituximab performs better than DMARD therapies in reducing the rate of relapses (odds ratio 0.10, 0.01 to 1.63), but the interval between rituximab doses and the protocols of administration largely differ from patient to patient.[120 148] Maintenance treatment with rituximab was performed either with two 1 g infusions 15 days apart or with four weekly 375 mg/m^2 infusions, typically when evidence of disease flare existed rather than at predetermined time intervals. In this regard, our group and a retrospective French multicentric study cohort showed that periodical administration of rituximab at fixed intervals (every six months) prevents relapse of IgG4-RD with a favorable safety profile.[135 152] Our study also provided preliminary evidence that a single infusion of 1 g rituximab every six months is as effective in maintaining disease remission as two 1 g doses of rituximab administered 15 days apart.[152]

Regardless of the strategy chosen, insufficient data are available to define the optimal duration of maintenance treatment for each patient, and several patient specific factors probably need to be considered. A commonly accepted strategy suggests discontinuing maintenance therapy within three years in the case of persistent serological and radiological improvement,[110] but biochemical and radiological follow-up remains warranted even after discontinuation of treatment. Table 2 provides a summary of available therapeutic regimens used for inducing and maintaining disease remission. Table 3 gives an overview of established, emerging, and novel potential biological therapies for IgG4-RD.

Novel biomarkers of disease activity and relapse

In general, none of the available disease biomarkers alone can be considered a reliable mirror of disease activity because they can be normal at disease onset, thus being unhelpful in ascertaining response to treatments and predicting relapse. However, as experience in managing patients with IgG4-RD grows, we now recognize specific clinical scenarios in which these biomarkers might still be useful.

Monitoring of IgG4 concentrations, for instance, seems to be useful in assessment of disease activity only in patients with elevated serum IgG4 at the time of diagnosis. In particular, serum IgG4 concentration declines substantially with clinical improvement in most patients and typically re-increases with disease relapse.[162 163] Serial measurement of serum IgG4 concentrations, however, should not be used as the sole determinant of decisions about treatment because they do not normalize in up to 63% of cases after glucocorticoid treatment and do not rise again at disease flare in nearly 10% of cases.[62 117]

Similarly, serum IgE and eosinophils are elevated in 30% to 40% of cases, regardless of an underlying atopic background, and their increase correlates even better with disease activity in many of these patients than do IgG4 concentrations.[146 164] In addition, in some patients with concomitant asthma, a rise of serum IgE or eosinophils is often associated with worsening respiratory symptoms and might be a prelude to IgG4-RD flare.[146 165] Moreover, elevation of serum IgG4 and IgE and peripheral blood eosinophilia at disease onset represent independent risk factors for relapse of IgG4-RD with hazard ratios of 6.2 (95% confidence interval 1.2 to 32.0), 8.2 (1.4 to 50.0), and 7.9 (1.8 to 34.7), respectively.[146 163 166]

Most patients with IgG4-RD also have low to normal inflammatory markers, making ESR and CRP non-specific parameters for follow-up purposes. However, longitudinal assessment of these biomarkers is still important for monitoring disease activity in cases of retroperitoneal fibrosis and large vessel involvement because these clinical scenarios are more often associated with ESR and CRP elevation than are other disease phenotypes, and they typically show normal serum IgG4 concentrations.[62 67 102 167]

Other novel potentially useful biomarkers of disease activity are emerging as our understanding of disease pathophysiology evolves, but none has been evaluated in longitudinal studies so far. These include some tests already discussed, such as the serum IgG4:IgG ratio and the IgG4:IgG RNA ratio in peripheral blood, as well as other molecular, cellular, and imaging biomarkers.[168 169]

In particular, patients with antibodies against two or more autoantigens (prohibitin, annexin A11, laminin 511-E8, and galectin-3) have marked IgG subclass elevations, complement consumption, and visceral organ involvement, indicating that severity of IgG4-RD is associated with an increased diversity of the autoantibody profile.[100] Elevated serum concentrations of soluble interleukin 2 receptor, a surrogate marker of T cell activation, correlates with IgG4-RD activity and predicts response to glucocorticoids.[169 170] Circulating plasmablasts are expanded in active IgG4-RD, decrease after treatment in all patients, and re-emerge at disease flare, thus representing a more reliable indicator of disease activity than serum IgG4 concentration.[98 171] Memory B cells are decreased during active disease compared with healthy controls and expand after steroid induced disease remission in patients who will relapse within two years, representing a potentially useful predictor of flare.[118] Activated Tfh2 cells in the peripheral blood mirror disease activity in patients with biliary and pancreatic involvement.[46 172] ^{18}FDG uptake on PET scan correlates with plasmablast expansion in the peripheral blood and, probably, with the inflammatory infiltrate at disease sites, therefore representing a useful tool for assessing disease activity.[90] The utility of ^{18}FDG-PET scans for defining response to treatment, intercepting potential flares, and guiding intervention was confirmed by two prospective and two retrospective studies.[90 91 173 174] Close collaboration between clinicians and nuclear medicine specialists is, however, necessary to avoid overestimation or underestimation of IgG4-RD activity, especially in cases of lymph node involvement. As ^{18}FDG uptake does not discriminate

Table 2 | Available therapeutic strategies for inducing and maintaining remission of IgG4 related disease (IgG4-RD)

Drug	Initial dose	Tapering	Maintenance	Study design
Glucocorticoids[111-117 150]	po PDN 0.6 mg/kg/day (2-4 weeks)	5 mg/1-2 weeks (2-6 months)	2.5-10 mg/day (6-36 months)	Retrospective cohort studies
	po PDN 30-60 mg/day (2-4 weeks)	5 mg/1-2 weeks (2-6 months)	2.5-10 mg/day (6-36 months)	
	iv MPDN 250-500 mg/day (3-5 days) ⇢ switch po	-	-	
	po PDN 0.5 *v* 1 mg/kg/day (4 weeks)	5-10% every 2 weeks	7.5-10 mg/day (24 weeks)	RCT
	po PDN 0.6 mg/kg/day (2-4 weeks)	(12 weeks)	5-7.5 mg/day *v* 0 mg/day (36 months)	RCT
DMARDs:				
Azathioprine[125]	po 0.5-2.5 mg/kg/day*	-	0.5-2.5 mg/kg/d† (median 29-60 months)	Case series
Methotrexate[65 132 151]	po/sc 15-20 mg/week*	-	15-20 mg/week sc† (median 15-60 months)	Case series
Leflunomide[121]	po 10-20 mg/day*	-	10-20 mg/day† (mean 12 months)	Case series
Mycophenolate mofetil[63 65 122 127]	po 1-1.5 g/day* (6 months)	po 0.5-1.0 g/day† (6 months)	po 0.5-1.0 g/day† (19±6 months)	RCT
	po 1-2 g/day*	-	1-2 g/day† (15-47 months)	Retrospective cohort studies
Cyclophosphamide[123]	po 50-100 mg/day* (3 months)	-	50 mg/day or maintain starting dose† (≥9 months)	Prospective cohort study
Ciclosporin[153]	po 100 mg/day*	-	100 mg/day†	Case series
Tacrolimus[124 130]	po 1-2.5 mg/day*	-	1-2.5 mg/day†	Case series
6 Mercapto-purine[131]	po 0.7-2.6 mg/kg/day*	-	0.7-2.6 mg/kg/day†	Case report
Iguratimod[128 129]	po 50 mg/day*	-	50 mg/day*	Prospective cohort study
Rituximab[133 139 152]	iv 1 g* (2 infusions 15 days apart)	-	iv 1 g† (2 infusions 15 days apart)	Open label prospective trial
	iv 1 g* (2 infusions 15 days apart)	-	iv 1 g† (2 infusions 15 days apart or single infusion every 6 months)	Retrospective cohort study
	iv 375 mg/m^2* (4 weekly infusions)	-	iv 300 mg to 1 g† (single infusion every month to 17 months)	Retrospective cohort study

DMARD=disease modifying anti-rheumatic drug; iv=intravenous; MPDN=methylprednisolone; PDN=prednisone; po=oral; RCT=randomized controlled trial; sc=subcutaneous.
*Combined with glucocorticoids.
†With or without low dose glucocorticoids.

between reactive and affected lymph nodes, radiological interpretation out of the clinical context may complicate the overall assessment of disease burden.[90]

Finally, several serum hotspots have been used as promising biomarkers of tissue fibrosis, but they are still in the early stage of research. These include the enhanced liver fibrosis (ELF) score composed of hyaluronic acid, procollagen-III N-terminal propeptide, and tissue inhibitor of matrix metalloproteinase-1, the mL-chemokine ligand 18 (CCL-18), RANKL, BAFF, and APRIL.[175 176] In particular, the ELF score and CCL-18 are significantly higher in patients with IgG4-RD than in healthy people, and their levels correlate with the number of affected organs, likely reflecting systemic collagen deposition and disease activity.[42 177]

Experience with these novel biomarkers remains confined to single referral centers, and longitudinal studies in large numbers of patients are warranted

Table 3 | Established, emerging, and novel potential biological therapies for IgG4 related disease

Target	Mechanism of action	Biological agent	Development stage	Trial status
B cells[41 120 134-136 154-159]	B cell depletion mediated by targeting CD20+ cells	Rituximab	Open label, prospective clinical trial	Completed
		Ofatumumab	-	-
		Obinutuzumab	-	-
	B cell depletion mediated by targeting CD19+ cells	Inebilizumab	Phase IIb, prospective, randomized, blinded trial	Starting
	Plasmablast and plasma cell depletion by targeting CD38+ cells	Daratumumab; isatuximab	-	-
	Autoreactive plasma cell depletion by targeting proteasome degradation	Bortezomib	Case report	-
	B cell inhibition mediated by co-ligation of CD19 and FcγRIIb	XmAb5871	Open label, prospective clinical trial	Completed
T cells[158]	Prevention of CD28 mediated T cell activation by targeting CD80 and CD86 co-stimulatory molecules on antigen presenting cells	Abatacept	Open label, prospective clinical trial; case report	Enrolling
B and T cells[43 158]	Depletion of plasmablasts, CD4+ CTLs, and CD8+ CTLs mediated by targeting CD319/SLAMF7	Elotuzumab	-	-
Complement[83]	Inhibition of complement activation by targeting C5 and C5a/C5aR pathways	Eculizumab; avacopan	-	-
Cytokines[43 66 142-145 160 161]	Interleukin 1 blockade	Anakinra; canakinumab	-	-
	Interleukin 6 blockade	Tocilizumab	-	-
	Interleukin 4 and interleukin 13 blockade	Dupilumab	Case report	-
	Tumor necrosis factor α	Infliximab	Case report	-
Fibrosis[41]	Disrupting extracellular matrix by targeting LOXL2	Simtuzumab	-	-

CTL=cytotoxic T lymphocyte; LOXL2= lysyl oxidase homologue 2.

to validate their utility for monitoring variations in IgG4-RD activity. Table 1 provides an overview of traditional and novel biomarkers used for monitoring IgG4-RD activity.

IgG4-Related Disease Responder Index

The need for standardized measurements of IgG4-RD activity for clinical trial purposes recently prompted the development of an IgG4-RD Responder Index (IgG4-RD RI) based on the granulomatosis with polyangiitis version of the Birmingham Vasculitis Activity Score.[178] The IgG4-RD RI encompasses more than 25 items and records the following set of information for each item: (i) activity trend (through a 0-3 organ/site score); (ii) presence of symptoms due to active disease; (iii) need for urgent care; (iv) presence of damage; and (v) presence of symptoms due to damage. The final activity index is obtained by summing all organ/site scores (i) and by doubling items needing urgent care (iii).

The IgG4-RD RI was generated through reiterated exercises on clinical vignettes and validated against a 0-100 physician global assessment scale, showing good correlation with modifications in physician global assessment over time.[178] Because of this encouraging performance, the IgG4-RD RI is now increasingly used in clinical practice to define disease status and damage.[178]

Several aspects of this new tool, however, seem to be amenable to improvements to optimize management of patients and assessment of IgG4-RD activity. In particular, the relevance of recording symptomatic disease (ii) or damage (iv) remains unclear because this information does not contribute to the final IgG4-RD RI score, even if it might be useful for clinical decision making. In addition, although viewing patients with multiple active problems as having more severe disease and higher IgG4-RD RI score is intuitive, this might not correspond to different treatments (or outcomes) compared with patients with fewer but still severe manifestations and lower IgG4-RD RI score. Hence, although the IgG4-RD RI represents the best available instrument to assess disease response to treatments in clinical trials, caution is needed when using it for assessing disease activity in clinical practice.

Guidelines

Because of its recent recognition and lack of randomized controlled trials, international guidelines for the diagnosis, management, and treatment of IgG4-RD are limited to a set of consensus statements based on expert opinion. In particular, three accepted sets of diagnostic/classification criteria exist, as well as a single guideline document on management and treatment of IgG4-RD.

Consensus statement on pathology of IgG4 related disease

This consensus statement was released after the First International Symposium on IgG4-RD held in Boston in 2011 and represents the first document aimed at providing practicing pathologists with diagnostic guidelines.[6] Five pathological hallmarks of IgG4-RD were identified: lymphoplasmacytic infiltrate, a tissue fibrosis with "storiform" pattern, obliterative phlebitis, a number of infiltrating IgG4 positive plasma cells per high power field that varies depending on the affected organ, and an IgG4 positive to IgG positive plasma cell ratio exceeding 40% on immunohistochemistry staining. Notably, the first three histopathological features are critical for diagnosis, whereas immunohistochemistry is secondary in importance because mimicker neoplastic and inflammatory disorders can also show increased tissue IgG4 counts. Neutrophils, leukocytoclastic vasculitis, granulomas, and tissue necrosis do not belong to the spectrum of pathological features of IgG4-RD and, even if accompanied by a prominent IgG4 positive plasma cell infiltrate, should prompt exclusion of other inflammatory conditions such as ANCA associated vasculitis and sarcoidosis.[16 69-75]

Comprehensive diagnostic criteria for IgG4-RD

The comprehensive criteria were proposed in 2011 by a consensus of Japanese experts to classify IgG4-RD as "definitive," "probable," or "possible" depending on a combination of clinical, serological, and pathological features.[89 179-181] In particular, a "possible" diagnosis of IgG4-RD is formulated in the absence of pathological confirmation. Although extremely practical, the criteria are not sufficiently sensitive for a "definitive" diagnosis of AIP while retaining adequate sensitivity for salivary glands and renal involvement.

ACR/EULAR classification criteria for IgG4 related disease

The classification criteria were developed in 2019 by experts from ACR and EULAR for classification purposes.[22 23] Classification criteria were generated using consensus exercises and validated on more than 1000 cases of IgG4-RD and nearly 800 cases of mimicker conditions.[22 23] Multi-criterion decision analysis was then applied to identify, weight, and test potential criteria with the highest possible specificity. A three step classification process was developed, consisting of a main entry criterion, a set of exclusion criteria, and a set of weighted inclusion criteria.

According to this process, involvement of at least one of 11 possible organs in a manner consistent with IgG4-RD (entry criterion) is required in order to enter the classification algorithm. Exclusion criteria are then applied, and the presence of any of these criteria eliminates the patient from further IgG4-RD classification. Finally, a set of inclusion criteria considering clinical, serological, radiological, and pathological findings is weighted, and a patient is classified if a cumulative score of 20 or more points is obtained.[22 23]

This classification algorithm showed excellent accuracy in distinguishing IgG4-RD from multiple mimickers, including malignant disorders,

granulomatous conditions, and small and large vessel vasculitidies,[15 16] with a specificity of 97.8% and a sensitivity of 82.0%. Moreover, high specificity and sensitivity were maintained even when exclusion and inclusion criteria related to biopsy or serum IgG4 domains were removed from the algorithm, indicating that combinations of highly suggestive clinical and/or radiological manifestations alone can accurately classify patients after entry and exclusion criteria have been passed.[22 23] In particular, the clinical and/or radiological manifestations that received the highest weight for IgG4-RD classification among the inclusion criteria were involvement of two or more sets of salivary and lacrimal glands (14 points), paravertebral band-like soft tissue in the thorax (10 points), diffuse pancreatic enlargement with capsule-like rim and biliary tree involvement (19 points), bilateral renal cortex low density areas (10 points), and circumferential/anterolateral soft tissue around the infra-renal aorta (8 points) (table 4, fig 2, and fig 4).[22 23]

Of note, in a recent retrospective single center cohort analysis, 39/40 (98%) patients with definite IgG4-RD according to the comprehensive diagnostic criteria were also classified as having IgG4-RD according to the classification criteria, further underscoring the encouraging performance of this novel algorithm.[182] It is, therefore, plausible that the 2019 ACR/EULAR classification criteria will be soon adopted worldwide, not only for classifying patients with IgG4-RD but also as a useful framework for guiding diagnosis. The criteria, however, were not meant for diagnostic purposes but rather to identify homogeneous groups of patients for clinical trials, research, and observational studies. Clinicians should, therefore, be aware of the many cases of IgG4-RD that would not fulfill the entry criterion or achieve classification owing to atypical manifestation or low to no elevation of serum IgG4 or because they are less likely to be biopsied. These clinical scenarios, especially if presenting as isolated organ involvement, might include unusual sites of infiltration such as the hypophysis, the pericardium, and the thymus, as well as more common manifestations such as focal AIP, retroperitoneal fibrosis, inflammatory aortitis, and hypertrophic pachymeningitis.

Table 4 | 2019 American College of Rheumatology and European League Against Rheumatism classification criteria for IgG4 related disease (IgG4-RD): inclusion criteria domains and items (adapted from Wallace et al)[22 23]

Inclusion criteria	Points
Step 3. Inclusion criteria: domains and items*	
Histopathology:	
Uninformative biopsy	0
Dense lymphocytic infiltrate	+4
Dense lymphocytic infiltrate and obliterative phlebitis	+6
Dense lymphocytic infiltrate and storiform fibrosis with or without obliterative phlebitis	+13
Immunostaining†	0-16‡
Serum IgG4 concentration:	
Normal or not checked	0
› Normal but ‹2 × upper limit of normal	+4
2-5 × upper limit of normal	+6
›5 × upper limit of normal	+11
Bilateral lacrimal, parotid, sublingual, and submandibular glands:	
No set of glands involved	0
One set of glands involved	+6
Two or more sets of glands involved	+14
Chest:	
Not checked or neither of items listed is present	0
Peribronchovascular and septal thickening	+4
Paravertebral band-like soft tissue in thorax	+10
Pancreas and biliary tree:	
Not checked or none of items listed is present	0
Diffuse pancreas enlargement (loss of lobulations)	+8
Diffuse pancreas enlargement and capsule-like rim with decreased enhancement	+11
Pancreas (either of above) and biliary tree involvement	+19
Kidney:	
Not checked or none of items listed is present	0
Hypocomplementemia	+6
Renal pelvis thickening/soft tissue	+8
Bilateral renal cortex low density areas	+10
Retroperitoneum:	
Not checked or neither of items listed is present	0
Diffuse thickening of abdominal aortic wall	+4
Circumferential or anterolateral soft tissue around infrarenal aorta or iliac arteries	+6
Step 4: Total inclusion points	
Case meets classification criteria for IgG4-RD if entry criteria are met, no exclusion criteria are present, and points total is ≥20	

A case can proceed to step 3 if meets entry criterion and does not meet any exclusion criteria.
*Only highest weighted item in each domain is scored.
†Biopsies from lymph nodes and mucosal surfaces of gastrointestinal tract and skin are not acceptable for use in weighting immunostaining domain.
‡0-16 score is assigned on basis of absolute number of IgG4+ cells/high power field (0-9; indeterminate; 10-50; or ≥51) and on IgG4+:IgG+ plasma cell ratio (0-40%; indeterminate; 41-70%; or ≥71%).
Head and neck gland involvement: "set" of glands refers to both lacrimal glands or both submandibular glands among others because involvement of lacrimal and salivary glands in IgG4-RD (determined by either clinical examination or radiological study) is typically bilateral.
Chest: peri-bronchovascular and septal thickening in lung must be determined by cross sectional imaging study of chest. Paravertebral band-like soft tissue in thorax is usually right sided, located between T8 and T11, and does not encase aorta.
Pancreas and biliary tree: diffuse pancreas enlargement usually encompasses more than two thirds of pancreas. Biliary tract involvement highly consistent with IgG4-RD involves thickening of intrahepatic and extrapancreatic portions of extrahepatic bile ducts.
Kidney: hypocomplementemia pertains to low serum concentrations of C3, C4, or both. Renal pelvic wall thickening can be either unilateral or bilateral. Low density areas in both renal cortices can be seen only on contrast enhanced computed tomography and are usually patchy or round shaped in appearance.
Retroperitoneum: IgG4 related retroperitoneal fibrosis is typically circumferential or on anterolateral sides of aorta.

Consensus guidance statement on the management and treatment of IgG4-RD

This consensus statement was released after the Second International Symposium on IgG4-RD in 2015 and engaged international panels of experts in web based questionnaires, face to face discussions, and a literature review.[21] Although not specifically designed as a guideline, seven overarching principles for disease management and treatment were provided, but the level of evidence (range 2b/B-5) and strength of recommendations (range B-D) were generally low. Strong agreement among experts was achieved with regard to the importance of a comprehensive clinical-pathological assessment for diagnosis of IgG4-RD and the role of glucocorticoids as first line therapy (range 94-96%). Conversely, expert opinion diverged with respect to the use of DMARDs for both induction and maintenance of IgG4-RD remission (range 46-81%), likely reflecting different practice styles across countries.

Emerging treatments

Few ongoing or recently completed clinical trials have investigated novel therapeutic approaches

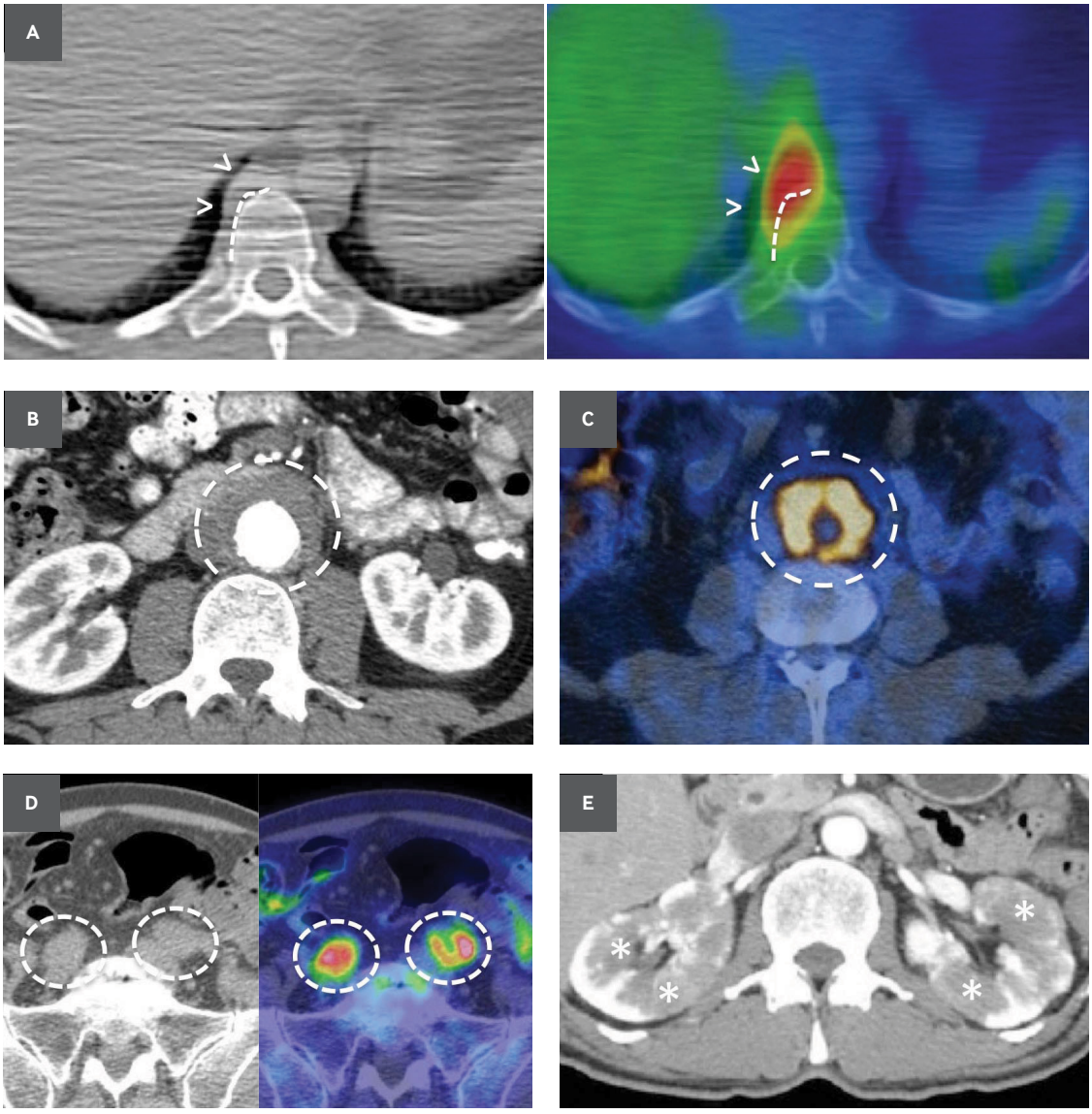

Fig 4 | Radiological findings suggestive of IgG4 related disease (IgG4-RD) included in the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria. Together with diffuse pancreatic enlargement and bilateral salivary gland swelling (shown in figure 2), the 2019 ACR/EULAR classification criteria for IgG4-RD consider the following radiological findings to be highly suggestive of IgG4-RD: paravertebral band-like soft tissue (A: axial positron emission tomography (PET)/computed tomography (CT) scan, arrowheads and broken line); circumferential tissue around the infra-renal aorta (B: axial CT scan, broken circle; C: PET/CT scan, broken circle) or iliac arteries (D: axial CT scan, broken circles); and bilateral renal cortex low density areas (E: axial CT scan, asterisks)

in IgG4-RD. A phase II open label study evaluating the effect of XmAb5871 (a humanized bi-specific monoclonal antibody directed against FcγRIIb and CD19) on IgG4-RD activity in 12 patients was recently completed (clinicialtrials.gov: NCT02725476), with preliminary results suggesting 100% achievement of the primary endpoint—namely, a 2 point reduction in the IgG4-RD RI on day 169.[159] None of the 12 patients needed corticosteroids after month 2. Eight (53%) patients achieved remission (IgG4-RD RI of 0 and no corticosteroids after two months), and the other four achieved IgG4-RD RI scores of 4 or lower at day 169. Two cases of pneumonia and one adverse reaction due to anti-drug antibodies were observed. A phase II proof of concept, open label study assessing the safety and efficacy of abatacept in IgG4-RD (clinicialtrials.gov: NCT03669861) is recruiting 10 patients and is expected to report in June 2020. A randomized open label trial evaluating the efficacy of leflunomide as a steroid sparing agent in 70 patients is now recruiting and is expected to report in December 2020 (clinicialtrials.gov: NCT03715699). Finally, a phase IIb randomized, double blind, multicenter, placebo controlled study assessing the efficacy and safety of inebilizumab (a humanized monoclonal anti-CD19 antibody) is starting, representing the first international trial on IgG4-RD.

GLOSSARY OF ABBREVIATIONS

- ^{18}FDG-PET—^{18}fluoro-deoxyglucose positron emission tomography
- ACR—American College of Rheumatology
- AIP—autoimmune pancreatitis
- ANCA—anti-neutrophil cytoplasmic antibody
- CRP—C reactive protein
- CTL—cytotoxic T lymphocyte
- DMARD—disease modifying anti-rheumatic drug
- ELF—enhanced liver fibrosis
- ESR—erythrocyte sedimentation rate
- EULAR—European League Against Rheumatism
- IgG4-RD—IgG4 related disease
- IgG4-RD RI—IgG4-RD Responder Index
- PD1—programmed cell death protein 1
- T_{EM}—T effector memory
- T_{EMRA}—CD45RA+TEM
- Tfh—follicular T helper

QUESTIONS FOR FUTURE RESEARCH

- Is a genetic background implicated in IgG4 related disease (IgG4-RD)?
- Does an infectious, environmental, or autoimmune trigger for IgG4-RD exist?
- Are different diagnostic biomarkers likely, depending on IgG4-RD involvement, or does a single diagnostic biomarker for all IgG4-RD manifestations exist?
- How does the classification of IgG4-RD into clinical phenotypes affect patient management, therapeutic strategies, and prevention of disease related morbidities?
- What parameters (clinical, serological, radiological) can guide tapering of immunosuppressive treatments and predict response to therapies?
- When should changes in serum IgG4 concentrations prompt a change in treatment?

PATIENT INVOLVEMENT

We invited four patients with IgG4 related disease (IgG4-RD) (one for each disease phenotype) to review advanced drafts of this manuscript. We asked them for their comments about what areas they thought had been missed and what may have been correctly or incorrectly emphasized, and they provided suggestions on which sections were most and least relevant to their personal history. As a result of their input, we discussed in detail clinical, serological, and prognostic differences among disease phenotypes, even if derived from the experience of our group and from still unpublished data. The patients also asked us to emphasize the limited treatment options for IgG4-RD, to provide details about emerging and novel potential therapeutic strategies, and to remind people of the importance of continuing to work to better understand the pathogenic mechanisms of IgG4-RD.

Conclusion

Recognition of IgG4-RD is increasing around the world, and clinicians from nearly every specialty are now becoming confident with most of its manifestations. The optimal management of patients with IgG4-RD has to be grounded in careful clinical-pathological correlation and should take into account all of the potential presentations of this diverse condition. Continued follow-up is crucial, as the cumulative effects of indolent disease or repeated flares can lead to severe organ damage over time.

The growing understanding of the pathophysiology of IgG4-RD is rapidly unveiling promising therapeutic targets and a new era of biological treatments—some of which are already in clinical trials—is on the horizon (fig 1; table 3**)**. However, many areas of uncertainty and unsolved questions pertaining to the management and long term outcomes of patients with IgG4-RD remain. Looking ahead, the recent definition of distinct disease phenotypes and the release of the ACR/EULAR classification criteria represent the most significant advances in the evolving field of IgG4-RD, providing a robust platform for future epidemiological studies and personalized therapeutic approaches.

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