Update on classification, diagnosis, and management of immunoglobulin G4-related disease

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Abstract

Immunoglobulin G4-related disease (IgG4-RD) is a newly recognized chronic fibro-inflammatory autoimmune disease, and its recognition has been constantly increasing worldwide over the last few years. A correct and timely recognition, as well as appropriate intervention, is crucial for the treatment of IgG4-RD. For certain subtypes of IgG4-RD, organ-specific criteria are formulated to make the diagnosis more accurate. New biomarkers have emerged in the recent years to aid the disease diagnosis, its prognosis prediction, as well as therapy response monitoring. Although recurrence is very common in IgG4-RD, glucocorticoid is still the first-line treatment for the majority of patients. The factors that affect the likelihood of disease relapse are multifaceted. The selection strategy of various steroid-sparing agents is still being explored. Besides, when patients have special sites involvement leading to severe clinical conditions, surgical operation or interventional therapy should also be considered. An update on classification, diagnosis, and management of IgG4-RD is provided in the current study to fully elucidate the recommended clinical practice of this mysterious disease.

Keywords: IgG4-related disease; Review; Update; Management

Introduction

Immunoglobulin G4-related diseases (IgG4-RD) were established as a distinct entity only in the past decade. Significantly elevated serum IgG4 concentration and tumefactive lesions are the most common clinical manifestations of this disease.[1-4] IgG4-positive lymphoplasmacytic cell infiltrations accompanied by storiform fibrosis, obliterative phlebitis, and eosinophil infiltration are typical histopathological features of IgG4-RD.[2] IgG4-RD can be misdiagnosed as malignant tumors due to the mass formation, and several patients may receive surgery due to this reason, leading to huge physical and mental pain, as well as waste of medical resources. Therefore, a precise and timely diagnosis and following appropriate treatment are crucial for the management of IgG4-RD. The first international consensus guidance statement on the management and treatment of IgG4-RD was published in 2015 and provided a standard for disease diagnosis and treatment, based on previous studies published before February 2014.[5] In the subsequent 5 years, in-depth knowledge of IgG4-RD by experts in various fields has rapidly increased, as demonstrated by the explosive growth in the number of relevant studies. Therefore, in this review, we aim to provide an update on classification, diagnosis, and management of IgG4-RD [Figure 1].

Disease Subtypes and Clinical Manifestations

Generally, tumefactive mass formation and symptoms resulting from its adjacent organ compression are the most typical clinical manifestations of IgG4-RD: for example, involvement of the pancreato-biliary system can lead to jaundice, while retroperitoneal fibrosis may lead to edema of lower limbs. Fever is rare in the disease, while the presence of allergic diseases such as bronchial asthma or allergic bronchitis is common, especially in patients with superficial glands involved.[6] Due to the unclear pathogenesis of and boundary between IgG4-RD and other mimic clinical conditions with elevated serum IgG4-levels or increased infiltration of IgG4+ cells, it is a significant challenge for clinicians to diagnose IgG4-RD, both for further treatment and clinical investigations.[7,8] In 2019, the American College of Rheumatology and European

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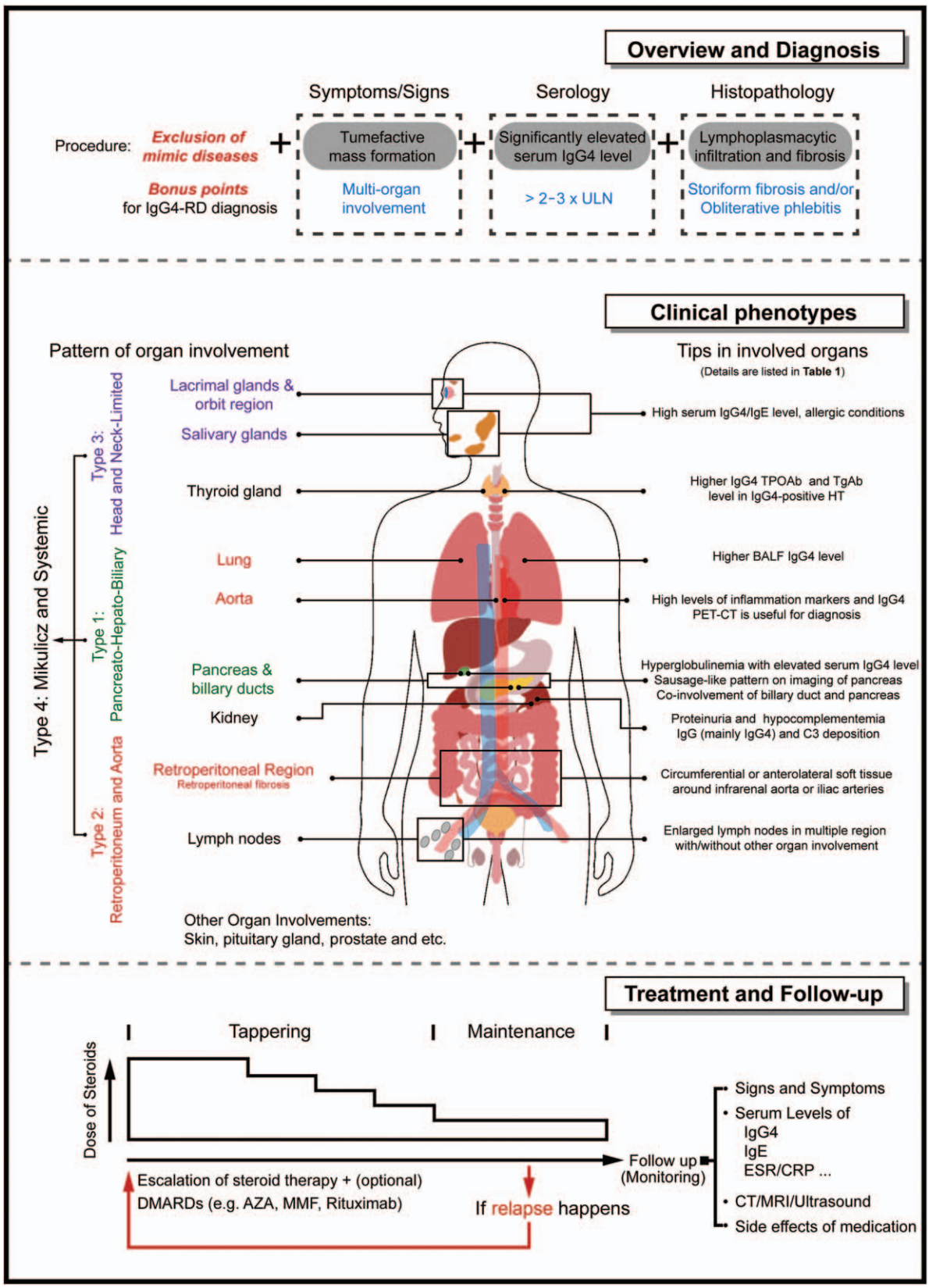

Figure 1: Overview of clinical phenotypes, diagnosis, and treatment in IgG4-RD. Upper panel: the clinical characteristics and diagnostic procedures of IgG4-RD; middle panel: clinical phenotypes (left side) and tips in involved organs (right side) in IgG4-RD; lower panel: strategy of treatment and follow-up in IgG4-RD. AZA: Azathioprine; BALF: Bronchoalveolar lavage fluid; DMARDs: Disease modifying anti-rheumatic drugs; ESR: Erythrocyte sedimentation rate; HT: Hashimoto's thyroiditis; IgG4-RD: Immunoglobulin G4-related diseases; MMF: Mycophenolate mofetil; PET-CT: Positron emission tomography-computed tomography; TgAb: Anti-thyroglobulin antibody; TPOAb: Anti-thyroid peroxidase antibodies; ULN: Upper limit of normal.

League Against Rheumatism (ACR/EULAR) convened an international multispecialty group involving 86 physicians from rheumatology and other specialties and proposed new criteria for IgG4-RD, which emphasized the importance of identifying distinct organ involvement for clinical judgment, and can help accurately classify the related patients.[9] In addition, based on the cohorts used in the classification criteria, four clinical phenotypes of IgG4-RD were roughly identified: type 1, pancreato-hepato-biliary disease; type 2, retroperitoneal fibrosis and/or aortitis; type 3, head and neck-limited disease; and type 4, classic Mikulicz syndrome with systemic involvement.[9] Considering that IgG4-RD can involve almost all the regions in the body, in the present study, we reviewed the characteristics and research advances of IgG4-RD based on the potential involving organs.

IgG4-related ophthalmic disease (IgG4-ROD)

A range of orbital and orbital adnexal structures involving the lacrimal glands, extraocular muscles, and infraorbital and other orbital nerves can be affected in IgG4-ROD unilaterally or bilaterally.[10] The involvement of scleral and intraocular tissues, such as conjunctiva, sclera, uvula, and retina only presented in case reports.[10] Gender predisposition in IgG4-ROD is not observed. The mean age of onset of IgG4-ROD is lower than that of the whole IgG4-RD entity.[11] A limited number of patients were diagnosed with IgG4-ROD even in their childhood.[10] Patients with IgG4-ROD usually presented with high levels of serum IgG4, as well as elevated serum immunoglobulin E (IgE) levels, increased number of peripheral eosinophilia and type II helper T cells (Th2 cells) cells, as well as increased expression of Th2-associated cytokines, such as interleukin (IL)-4, IL-5, and IL-10.[12,13] The enlargement of the infraorbital nerve and canal is rare, while a strong diagnostic sign of IgG4-ROD was evident, notably in the presence of ipsilateral extraocular muscle enlargement, sinus disease, or focal orbital disease.[14] At the level of histopathology, besides the significant lymphoplasmacytic infiltration in IgG4-ROD, the fibrosis is also commonly observed, despites that the presence of storiform pattern is infrequent. Obliterative phlebitis is rarely seen.[15]

IgG4-related sialoadenitis

IgG4-related sialoadenitis patients further demonstrated lower age at disease onset and diagnosis, whereas the time from onset to diagnosis was longer than that of IgG4-RD patients without salivary gland involvement.[16] The female incidence rate was higher.[17] In addition, IgG4-related sialoadenitis patients exhibited higher serum IgG4 levels, higher IgG4/IgG ratio, and higher peripheral eosinophil counts and serum IgE levels.[6,16] Allergic conditions and multi-organ involvement were more commonly seen in IgG4-RD patients with salivary gland involvement.[6,17]

IgG4-related hypophysitis

IgG4-related hypophysitis usually conceals onset and has a relatively long disease duration. Panhypopituitarism is the most common clinical symptom, followed by anterior hypopituitarism and central diabetes insipidus, and the trend of which is consistent with magnetic resonance imaging (MRI) findings: pituitary-stalk enlargement, stalk enlargement, and pituitary enlargement, respectively.[18] Although histopathological findings can provide the most important information for the final diagnosis of IgG4-related hypophysitis, a pituitary biopsy is a highly invasive procedure and very difficult to put into effect.[18] In 2011, Leporati *et al*[19] put forward a new diagnostic criterion for the disease without the need of pituitary biopsy, which is very helpful for physicians to identify the disease at an earlier step in clinical practice.

IgG4-related respiratory disease (IgG4-RRD)

All lesions in the thorax (lung parenchyma, bronchus, mediastinum, and pleura) in IgG4-RD have been comprehensively classified as IgG4-RRD.[20] The characteristics of chest computed tomography (CT) include hilar and mediastinal lymphadenopathy, thickening of the perilymphatic interstitium, with or without subpleural and/or peribronchovascular consolidation, nodules, and pleural thickening and/or masses.[21,22] Pleural lesions can occur alone or in the presence of lung parenchymal lesions. Mediastinal fibrosis can exist alone or in the presence of retroperitoneal fibrosis, and may cause pulmonary hypertension as a serious but treatable complication.[22,23] Occasionally, the dense irregular infiltrates in IgG4-RRD can mimic lung cancer and can present as mass-like lesions with high-grade uptake of 18-fluorodeoxyglucose.[24] The bronchoalveolar lavage fluid levels of IgG4 were found higher in IgG4-RRD compared with pulmonary sarcoidosis, which may be a promising tool to aid disease diagnosis.[21]

IgG4-related autoimmune pancreatitis (type 1 autoimmune pancreatitis [type I AIP])

Type 1 AIP mainly occurs in elder men. The obstructive jaundice is the initial and most common symptom presented in type I AIP, while type 2 AIP is more likely to present with abdominal pain.[25] The typical radiologic features of CT and/or MRI include diffuse (so-called "sausage-like pattern"), focal, or multifocal swelling of the pancreas, with delayed enhancement in the venous phase.[26,27] Capsule-like rim is seen as a bandlike low-intensity area on T2-weighed images. Narrowing or invisibleness of the main pancreatic duct is seen on magnetic resonance cholangiopancreatography, with multiple or focal irregular strictures, and with or without bile duct stricture.[28] Negative findings of malignancy by endoscopic ultrasound-guided fine-needle aspiration combined with comprehensive evaluation of serological findings and other organ involvement are also necessary in the diagnostic procedure.[28] In clinical practice, it is difficult to distinguish type I AIP from type 2 AIP or pancreatic cancer solely based on imaging data. Type 1 AIP usually presents with hyperglobulinemia and with elevated serum IgG4 levels. Serum IgG4 levels can also be elevated in a small number of patients with pancreatitis or cholangiocarcinoma, and therefore, differential diagnosis is needed despite its elevation. Lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis

can be seed in both type 1 and type 2 AIP. However, only type 1 AIP exhibits abundant IgG4-positive plasma cell infiltration (>10 positive cells/high power field), whereas type 2 AIP presents always with neutrophilic infiltration and disruption of the pancreatic ducts (termed granulocytic epithelial lesion).[29,30] In addition, the extrapancreatic involvement (such as proximal biliary stricture, lacrimal and/or salivary gland swelling, and retroperitoneal fibrosis) would be of help in diagnosis.[27]

IgG4-related sclerosing cholangitis (IgG4-SC)

The majority of IgG4-SC is combined with pancreatic involvement. Since elevated serum IgG4 levels are not a specific indicator for the diagnosis, Doorenspleet *et al*[31] indicated that the serum IgG4/IgG RNA ratio may provide additional and more accurate discrimination of IgG4-SC from primary sclerosing cholangitis (PSC) and biliary/pancreatic malignancies. It is worth mentioning that certain IgG4-SC patients exhibited slightly higher levels of serum CA199 that were usually decreased to the normal range after steroid therapy. Cholangiography includes endoscopic retrograde cholangiography and magnetic resonance cholangiography, which are critical for the diagnosis of IgG4-SC. In IgG4-SC, the wall of bile duct becomes thicker, along with diffuse or segmental strictures of intra- and/or extra-hepatic bile ducts.[32] According to the stricture parts of bile ducts, IgG4-SC can be classified into four types[32] as follows: type 1 IgG4-SC: stenosis only in the lower part of the common bile duct and is the most common type; type 2: strictures throughout intrahepatic bile ducts: segmental strictures with prestenotic dilation (type 2a) and diffuse strictures without prestenotic dilation (type 2b); type 3: stenosis in the hilar hepatic lesions and the lower part of the common bile duct; and type 4: strictures only in the hilar hepatic lesions. The proximal bile duct involvement is a strong predictor of disease relapse.[33] Although it is considerably difficult in clinical practice, bile duct biopsy via endoscopy can provide important information for the diagnosis of IgG4-SC.[30]

IgG4-related retroperitoneal fibrosis (IgG4-RPF) and IgG4-related periaortitis/periarteritis

The diagnosis of RPF and IgG4-related periaortitis mainly relies on imaging examination. The former manifests as irregular retroperitoneal soft tissues were systemically or asymmetrically distributed around the abdominal aorta, iliac artery, inferior vena cava, kidneys, ureters, and/or lumbar muscles, resulting in relevant organ compression and resulting damage.[34] CT and MRI, as well as 18-F-fluoro-2-deoxyglucose (FDG) positron emission tomography/computed tomography (18-FDG-PET), could provide precise assessment of the extent of fibrosis, the status of adjacent organs, and the degree of inflammatory activity. However, these methods can not readily distinguish the benign from malignant forms of RPF. Histopathology from surgical biopsies remains the gold standard to diagnosis.[35] In IgG4-related periaortitis/periarteritis, aorta and medium-sized arteries, such as the carotid, celiac, iliac, mesenteric, pulmonary and coronary arteries, are the potential involved vessels.[36] Thickened aortic/arterial wall is the characteristic CT findings, which are homogeneously enhanced at the delayed phase of enhanced CT. Inflammatory aortic aneurysm accompanied by aneurysmal luminal dilatation occurs sometimes, while aortic stenosis or ischemia is rarely seen.[37] Elevated inflammatory markers C-reactive protein (CRP) are common in the disease, which is distinct from other types of IgG4-RD.[38] It is important to note that distinguishing between IgG4-RPF and IgG4-related periaortitis is sometimes difficult, and the risk of aortic rupture should be highly alerted in clinical practice.[37]

IgG4-related kidney disease (IgG4-RKD)

IgG4-RKD mainly contains IgG4-related tubulointerstitial nephritis (IgG4-TIN) and IgG4-related glomerulonephritis exhibits two forms.[35] These are usually diagnosed after the diagnosis of already known extra-renal organs involvement in IgG4-RD. When kidneys are the only involved organ, a renal biopsy is necessary for the diagnosis, notably under the condition of acute or progressive renal failure.[39] IgG4-TIN is the most common form of IgG4-RKD, manifested as decreased renal function with or without mild proteinuria or hematuria.[40,41] In addition, elevated serum IgG4 levels are commonly observed in IgG4-TIN, and >50% of patients with active disease present with hypocomplementemia.[42] Contrast-enhanced CT is an important tool to evaluate the lesions, which exhibit a variety of imaging features of the bilateral kidneys, such as diffuse patchy involvement, multiple low-density lesions, extrarenal lesions located on the renal capsule (so-called rim-like lesion), or renal pelvis thickening with smooth intraluminal surface.[42,43] A solitary mass lesion is rare and very difficult to be distinguished from a malignant tumor.[43] The histopathology of IgG4-TIN presents clearly demarcated margins between affected and unaffected areas, which corresponded to the imaging characteristics of multiple low-density lesions, and lymphoplasmacytic cells infiltrate into and beyond the renal capsule, which is a specific distribution of renal parenchymal lesions, and lesions located outside the renal capsule was thought to correspond to the rim-like lesion in imagings.[35] In addition, immunoglobulin and complement deposition in the tubular basement membrane (TBM) is another important feature of IgG4-TIN. More than 80% of IgG4-TIN patients exhibited IgG and C3 deposition in the TBM, while the major component of IgG was IgG1, with limited levels of IgG2 and IgG3.[41,44] Electron dense deposits were found in the TBM as determined by electron microscopy, which was in accordance with the immunofluorescence findings.[44]

Membranous glomerulonephritis (MGN) is the major pattern of IgG4-related glomerulonephritis. MGN patients exert mass proteinuria and hypocomplementemia, and the majority of them also present with IgG4-TIN.[45] IgG (mainly IgG4) and C3 deposition can be observed by immunofluorescence staining, while the marker of common MGN, presence of the anti-phospholipase A2 receptor, is not present in IgG4-MGN.[45,46] Other patterns of glomerular lesions, such as IgA nephropathy, membranoproliferative glomerulonephritis, and endocapillary proliferative glomerulonephritis, have also been reported in certain cases.[35]

IgG4-related hypertrophic pachymeningitis (IgG4-RHP)

IgG4-RHP is a rare subtype of IgG4-RD that is very difficult to diagnose.[47] Serum IgG4 levels are usually normal in the peripheral blood and high in cerebrospinal fluid (CSF). This phenomenon is notably common if the meninges are the only involved site in the disease.[47] Patients with elevated serum IgG4 levels are always complicated with multi-organ involvement. In addition, IgG4-RHP patients with active disease have been shown to produce IgG4 oligoclonal bands in the CSF of the intrathecal regions, which disappear after treatment, indicating that these highly restricted somatic hypermutated oligoclonal IgG4$^+$ B cells may be triggered through an unknown specific fibro-inflammatory immune reaction.[48] CT/MRI appears as a linear dural thickening or as a bulging mass spread located at the supratentorial hemispheres, skull base, or spinal cord.[19,47] Biopsy from the meninges remains the gold standard for the diagnosis of IgG4-RHP, notably when meninges are the only involved sites.

Others

Other sites of regions, such as the lymph nodes, thyroid, gastrointestinal tract, gallbladder, liver, skin, bone, testes, and prostate, can also be involved in IgG4-RD.[49-53] Enlarged lymph nodes, usually detected as asymptomatic and may occasionally be the only manifestation of IgG4-RD, need to be differentiated from malignancy or multicentric Castleman's disease.[51,52] The thyroid lesions presented with higher levels of circulating thyroid autoantibodies, subclinical hypothyroidism, larger thyroid size, and diffuse low sonographic echogenicity.[53] The gastrointestinal tract involvement often appears as inflammatory pseudotumor; wall thickening happens when the gallbladder is involved, whereas a pseudotumor can be noted in the liver, which can also develop into chronic hepatitis; involvement in ear-nose-throat regions presented with soft tissues occupied in the middle-ear/mastoid cavity or sinus or laryngopharynx; the skin involvement presents as subcutaneous nodules and/or skin plaques; the bone involvement can present with an inflammatory pseudotumor and bone erosion; the testes can develop IgG4-related epididymo-orchitis; the prostate involvement is easily misdiagnosed as chronic prostatic hyperplasia.[53-63] Although IgG4-RD in pediatrics is uncommon, it has been described in certain case reports. The commonly affected sites and diagnostic criteria in children were approximately the same as those in adults, and therefore, awareness is required for the pediatricians, when symptoms or signs similar to IgG4-RD presenting in a child.[64]

Diagnosis

Early diagnosis of IgG4-RD significantly impacts disease treatment and prognosis. At present, the original 2011 comprehensive diagnostic criteria for IgG4-RD (or its revised 2020 version)[4,65] and the consensus statement on IgG4-RD pathology[2] for diagnosis are widely used in clinical practice. Several cases, which are difficult to make a diagnosis based on the aforementioned criteria, can be finally diagnosed as IgG4-RD with organ-specific criteria [Supplementary Table 1, http://links.lww.com/CM9/A855].[4,19,20,42,66-69] The 2019 ACR/EULAR IgG4-RD classification criteria do not necessarily require either a biopsy or an elevated serum IgG4 level but focus on the comprehensive picture of clinical, serologic, radiologic, and pathologic evidences in the diagnostic process, which is suitable for clinical research and epidemiologic studies.[9] To recruit more relatively homogeneous groups, these criteria excluded patients with only infrequent organ or site involvement such as lymph nodes, pituitary, breast, gastrointestinal tract, skin, or prostate.

Utility of IgG4 in diagnosis

Certain specialists have suggested that elevated serum IgG4 levels are not a unique biological indicator of IgG4-RD and should not be regarded as a sufficient or necessary condition for disease diagnosis.[70] However, the combination of IgG4 detection with clinical manifestations and the results of imaging and pathological examinations render this biomarker a highly sensitive index for the diagnosis of IgG4-RD. This is particularly important when IgG4-RD levels are two to three times higher than the normal upper limit. In addition, the detection of IgG4 serum levels is simple, fast, and minimally invasive and can serve as an important screening indicator for IgG4-RD. Notably, serum IgG4 levels may be in the normal range at the initial stage of onset and may gradually increase in certain patients with IgG4-RD. Therefore, patients suspected of IgG4-RD should be repeatedly screened for serum IgG4 levels for the final diagnosis. In addition, elevated serum IgG4 levels often decrease following effective treatment but do not always completely fall back to the normal range, whereas the continuous increase of serum IgG4 levels is a danger signal for disease recurrence in follow-up patients.[71]

Newly emerging biomarkers

The identification of novel biomarkers for the diagnosis of disease status, the monitoring of the therapeutic response, and the prediction of disease prognosis are imperative.[72] With regard to serum biomarkers, the levels of serum IgG2, soluble IL-2 receptor, and chemokine C-C motif ligand 18 can be used to indicate inflammation and fibrosis and are considered as potential indices for diagnosis and prediction of treatment response.[73-77] Eotaxin-3 is a newly identified biomarker for IgG4-RD detected by proteomics analysis using a large number of patient serum samples.[78] Hypocomplementemia is particularly evident in IgG4-associated TIN, which may be a rewarding biomarker reflecting the activity of renal lesions.[79] Several autoantibodies against autoantigens including Laminin-511-E8, Galectin-3, Annexin-A11, and antiproliferative protein (Prohibitin) were identified, which may contribute to the pathogenic processes, and these antibodies are expected to be potential biomarkers for diagnosis.[80-83] A recent study indicated that patients with antibodies against more than two of these autoantigens presented with higher levels of IgG subclasses, and these subjects were more likely to develop hypocomplementemia with visceral organ involvement.[84] Fluctuation of cellular populations can also provide useful information. The number of circulating plasmablast/plasma cells (defined as CD20$^-$CD19^{low}CD38$^+$CD27$^+$ by Stone

et al[87] or $CD19^+CD24^-CD38^{hi}$ by Zhang *et al*[85]) was significantly increased in active IgG4-RD and was decreased following treatment, suggesting that the level of these cells may be a potential indicator that can assist the diagnosis of IgG4-RD, and the monitoring of the disease activity and the treatment response.[85-87] A useful biomarker in IgG4-RD is in essence a reflection of its potential pathogenesis: Chen *et al*[88] demonstrated that the cTfh cell subsets from IgG4-RD patients were abnormally amplified and exhibited augmented function. Activated follicular T helper 2 (Tfh 2) cells could facilitate B-cell proliferation and inhibit B-cell apoptosis, whereas they could also enhance the differentiation of naive B cells into switched memory B cells and plasmablasts/plasma cells, with a resultant increase in the secretion of IgG4.[88-91] $CD4^+$ cytotoxic T lymphocytes (CTLs) is a novel T-cell subset that can secrete pro-fibrotic cytokines (including interleukin-1β, transforming growth factor-β1, and interferon-γ) and cytolytic molecules (perforin, granzymes A and B). These cells are also highly expanded in IgG4-RD and correlate with disease activity and the number of involved organs. The number of CTLs is significantly decreased after disease remission realized.[92] The level of follicular regulatory T cells (Tfr) and peripheral helper T (Tph) cells can also be potential biomarkers in IgG4-RD.[72]

Management

Who should be treated for IgG4-RD?

All IgG4-RD patients with active, symptomatic disease require treatment. The involvement of the pancreas, bile duct, lung, kidney, liver, hypophysis, retroperitoneum, endocranium, and other vital organs that may cause further irreversible damage due to severe inflammatory reactions and fibrosis are all indications for early therapeutic intervention, even if the patients are asymptomatic. In addition, treatment is recommended after detailed evaluation of the patient's status via detection of organ injury by imaging findings and/or laboratory examination.[5,93] It has been confirmed that IgG4-RD patients who receive early treatment can achieve complete remission in a shorter period of time and possess a lower rate of long-term complications and recurrence.[94,95] Emergent treatment is required in cases of rapid progression of IgG4-RD since this has the potential to cause an irreversible damage to specific organs in a short period of time: aggressive treatment including medium to high doses of glucocorticoids and rituximab (RTX) combined with some mechanical intervention (eg, patients with obstructive jaundice can obtain relief of symptoms by undergoing drainage) must be initiated as soon as possible to improve patients' prognosis.[5,96]

A minority of asymptomatic IgG4-RD patients with single organ involvement, such as lymphadenopathy or mild submandibular/lacrimal gland enlargement, could be temporarily observed without treatment.[5,97] Due to the indolent nature of the disease, follow-up can be made approximately every 3 to 6 months. Although certain case reports have suggested that untreated IgG4-RD patients exhibit spontaneous and temporary improvement, it is worth mentioning that the course of IgG4-RD exhibits a "relapse-remission" pattern, and the involved organs may be subjected to progressive damage.[96,98-100]

How should steroids be used to induce remission?

The majority of the recommendations suggest 0.6 $mg \cdot kg^{-1} \cdot day^{-1}$ as the standard dose for IgG4-RD treatment. Generally, 30 to 40 mg prednisone is administrated orally per day at the very beginning of steroid treatment.[96,101] Based on the disease activity or severity (symptoms, serum IgG4 levels, and imaging data), glucocorticoid administration with an initial dose can persist 2 to 4 weeks. Subsequently, a taper can be initiated by decreasing the daily dosage by 5 mg every 1 to 2 weeks. The majority of the patients respond to steroid therapy rapidly. Current cohort studies demonstrated that the vast majority of patients with IgG4-RD receiving an initial prednisone dose of 30 to 40 mg/day for 2 to 4 weeks followed by a gradual tapering could receive remission at the level of symptoms, laboratory, and radiologic indices.[102-104] Failure to respond to an appropriate dose of glucocorticoid therapy has been deemed as an exclusion criterion in ACR/EULAR classification criteria for IgG4-RD.[9] A 4-week steroid trial is valuable in cases where the diagnosis of IgG4-RD is uncertain. Patients who receive no unequivocal improvement of the clinical lesions, biochemical abnormalities, or radiological findings following a dose of 0.6 $mg \cdot kg^{-1} \cdot day^{-1}$ of oral prednisone administration within 4 weeks should be considered as an exclusion criterion for IgG4-RD diagnosis.[9]

Wu and Chang *et al* conducted a prospective randomized controlled trial involving 40 newly diagnosed IgG4-RD patients, in which the enrolled patients were randomly grouped into a high- and medium-dose group that received 0.8 to 1.0 $mg \cdot kg^{-1} \cdot day^{-1}$ and 0.5 to 0.6 $mg \cdot kg^{-1} \cdot day^{-1}$ prednisone, respectively.[105] The dosage was reduced by 5% to 10% every 2 weeks and then maintained at 7.5 to 10 mg/day. The results indicated no difference in the efficacy and adverse effects between these two groups at either week 12 or 24, while patients with additional organ involvement and a higher initial IgG4-RD responder index (IgG4-RD RI) score were more likely to undergo relapse. Therefore, the strategy of the lower dose steroid administration to reduce the steroid mediated side effects can be applied for IgG4-RD patients in mild to moderate status, while larger doses of glucocorticoid therapy are required if patients are in severe condition, notably with vital organ failure.

When should steroid sparing medications be considered?

Relapse in IgG4-RD is not rarely seen, notably in patients suffering from bile duct and pancreatic involvement.[106] When IgG4-RD cannot be controlled with steroid therapy alone (eg, poor response, relapse, etc) or severe side effects due to continuous application of glucocorticoids, disease-modifying anti-rheumatic drugs (DMARDs) can be applied as steroid-sparing agents. Synthetic disease-modifying anti-rheumatic drugs (sDMARDs) include mycophenolate mofetil (MMF), azathioprine (AZA), cyclophosphamide, leflunomide, methotrexate, and tacrolimus (FK506).[107-111] Among these drugs, MMF and

AZA are the most widely used in clinical practice. The recommended dose of 750 to 1000 mg bid po for MMF and 2 to 2.5 $mg \cdot kg^{-1} \cdot day^{-1}$ po for AZA has shown high efficacy for patients with pancreato-biliary and dural involvement.[108,112] Other DMARDs may also be considered when the response to MMF and AZA therapy is poor or when the patients are intolerant. The indication and duration of their application are primarily based on the clinician's experience. In addition, iguratimod plus corticosteroid is also considered an effective and safe therapeutic approach, which may be an optimal choice as bridge therapy for the treatment of mild IgG4-RD.[113]

RTX is the only single drug that can be used for inducing remission without the combination of corticosteroid therapy.[114,115] RTX application can be considered for predictable disease recurrence in the whole therapeutic process and when steroid resistance, sDMARD intolerance, or severe side effects resulted from steroid treatment happen.[114-116] At present, usages of 375 mg/m^2 qw intravenous injection for 4 weeks or 1000 mg × 2 times every 2 weeks are recommended.[40,114,116-118] The clinical symptoms were rapidly relieved, and the levels of serum IgG4 as well as counts of peripheral plasma cells and IgG4 + plasma cells were significantly reduced following RTX therapy.[116,119]

Previous evidence has indicated that the treatment of glucocorticoids combined with these immunosuppressive agents is associated with higher remission rates and lower relapse rates, as well as comparable safety profiles compared with glucocorticoid (GC) or immunosuppressive agents (IM) monotherapy, or RTX induction only.[120] However, large randomized controlled studies examining the validity of these approaches are required in the future. Recently, some agents targeting T/B lymphocytes or pro-inflammatory molecules/processes in IgG4-RD are emerging, including obexelimab and inebilizumab (targeting CD19), bortezomib and lenalidomide (targeting proteasome and ubiquitination), elotuzumab (targeting SLAMF7), abatacept (targeting CD80/86) and prezalumab (targeting inducible costimulatory ligand), dupilumab (targeting IL-4Rα, which mediates IL-4 and IL-13 signaling), anakinra (targeting IL-1/IL-1R) and infliximab (targeting tumor necrosis factor), belimumab (targeting B-cell-activating factor), as well as mepolizumab (targeting IL-5). Janus kinases inhibiting small-molecule drugs including tofacitinib (inhibiting Janus kinase [JAK]3, JAK1, and to a lesser degree JAK2), ruxolitinib (inhibiting JAK 1/2), and itacitinib (inhibiting JAK1) may also function in some IgG4-RD patients.[121]

How can treatment response be assessed?

During follow-up, the IgG4-RD RI created in 2012 was recommended to assess disease activity. Indices in IgG4-RD RI include disease status in each involved organ and serum IgG4 level.[122] An international, multi-specialty validation study conducted by Wallace and colleagues concluded that the IgG4-RD RI is a valid and reliable disease activity assessment tool to measure patient response to therapy.[123] However, this standard has certain flaws. Subjective factors can significantly influence the judgment of the patient's clinical conditions (eg, normal, improved, persistent, new/recurring, worsened). If a patient has visceral involvement (eg, pancreas), imaging examinations must be made to evaluate its therapeutic response to score the corresponding index in IgG4-RD RI accurately, which is always not realistic in clinical practice.[124] While serum IgG4 levels in several patients were not elevated and may not fall back to normal range even when they have a good response to treatments, index of serum IgG4 level was removed from the revised 2015 version to avoid the misjudgment based on that. Assessment of other potentially being involved organs, monitoring of percentages of peripheral eosinophil counts, measurement of total serum IgE, IgG, and IgG4 values and inflammation-related biomarkers (eg, levels of erythrocyte sedimentation rate, hypersensitive CRP, cytokines, etc), and monitoring of the changes noted in imaging results for affected organs were recommended in follow-up processes.

Is long-term maintenance therapy beneficial?

To prevent disease relapse in patients considered at high risk of relapse, low-dose steroid maintenance therapy is recommended following a successful course of induction remission, particularly for patients with high IgG4 levels, multiple organ involvement, and a history of recurrence or upper bile duct obstruction.[96] The maintenance dose was 2.5 to 7.5 mg/day, and the maintenance period was at least 6 months. Steroid maintenance can decrease the risk of relapse: a study that enrolled 138 type 1 AIP patients who were followed up demonstrated that glucocorticoid maintenance therapy could effectively reduce the rate of disease recurrence.[93,125] In addition, RTX can also be used in maintenance therapy, which exhibits a larger reduction in the relapse rate compared with GC and sDMARD monotherapy.[120] However, no consensus about the frequency of use and duration of maintenance therapy has been reached.[115]

Can we predict who will relapse?

Disease recurrence is common in IgG4-RD. Even during the glucocorticoid maintenance stage, nearly 30% of patients relapsed.[106,126] In general, the factors that affect likelihood of disease relapse include male sex, younger onset, longer disease duration, higher serum IgG4 level onset (higher than two times), higher IgG4-RD RI scores at onset, lower steroid dose in initial and maintenance stage, faster tapering of steroids, no maintenance therapy, delayed treatment, and history of recurrence.[17,33,34,106,109,127-130] Patients with low serum IgG4 levels and substantially severe findings on imaging are also prone to recurrence.[108,109] Moreover, treated patients with increased circulating memory B cells were found to relapse within 2 years.[131] Different sites of involvement can have specific relapse predictors: for patients with IgG4-related cholangitis, the presence of proximal bile duct involvement is one of the predictors of recurrence, whereas for patients with IgG4-RKD, renal insufficiency and elevated serum IgE are predictors of renal atrophy development following glucocorticoid therapy.[132,133] There are also some indicators for predicting recurrence under different treatment therapies. Indicators of recur-

rence after glucocorticoid monotherapy include the following: elevated eosinophil count before initial treatment, high baseline IgG4-RD RI scores, involvement of more than five organs, and lacrimal gland inflammation.[109] Particularly, the incidence of relapse in patients having more than three of these risk factors was increased to 70%.[109] For RTX therapy, higher baseline levels of serum IgG4, IgE, and higher blood eosinophil count are optimal relapse predictors.[128]

How should relapsing disease be managed?

Patients who experience flares of IgG4-RD following glucocorticoid tapering can be treated with glucocorticoids again, whereas steroid-sparing agents as mentioned above are recommended for remission maintenance. The majority of the relapse patients can receive remission after resuming the initial therapeutic dose of glucocorticoids. The glucocorticoid dose can be increased or the treatment time can be prolonged to obtain better disease control if necessary.[134,135] A multicenter retrospective study in Japan suggested that the effective rate of remission for relapsing AIP patients who resumed glucocorticoid therapy was 97%.[136] An international multi-center study involving 210 relapsing AIP patients demonstrated that the effective rate for glucocorticoid resumption to control the disease reached 95%.[137]

When should surgical treatment be considered?

When patients have special sites involved, which may cause compression and lead to organ dysfunction or other emergency situations in which drug treatment cannot quickly relieve the symptoms, a rapid and effective surgical operation or interventional therapy should be adopted to avoid disease progression and create conditions for subsequent drug treatment.[103,137,135] For example, when IgG4-RPF leads to severe hydronephrosis and acute renal failure caused by ureteral obstruction, a ureteral stent placement or nephrostomy is needed to relieve the obstruction rapidly; when IgG4-associated arteritis causes aneurysmal ectasia, it is necessary to perform stent implantation, arterial intima repair, or arterial wall replacement to avoid angiorrhexis; when IgG4-SC causes severe biliary obstruction, stent implantation and drainage can quickly relieve jaundice; when IgG4-RTD causes tracheal and esophageal compression, surgical excision is required to relieve the compression; when IgG4-RD associated with mesentery involvement and causes ischemic necrosis of the bowel, surgical excision is required to remove the necrotic bowel. In addition, for long-term severe and irreversible organ fibrosis, such as periorbital fibrosis pseudotumor and sclerosing mesenteritis, surgical treatment can also be considered, especially when the effect of glucocorticoid and other drugs is not satisfactory.

Conclusions

In summary, the rapid advances in both clinical and basic research studies have facilitated the diagnosis and treatment of IgG4-RD, which further contribute to the cognition that IgG4-RD is not as rare as expected. IgG4-RD is a benign inflammatory disease. However, it may severely affect patients' life quality or can even be life-threatening when it affects some vital organs. Diagnosis, treatment, and follow-up of IgG4-RD patients should be carried out with a multidisciplinary approach under the guidance of a rheumatologist. Relapse of IgG4-RD is not rare. In treatment, the medication and timing of subsequent visits should be adjusted based on the changes of patient's conditions. Although steroid remains the mainstay of treatment, steroid-sparing drugs like sDMARDs and RTX should also be considered to induce remission in some conditions together with/without steroids. Some newly identified biomarkers may have enormous application prospects, and further validations should be made in both basic research and clinical practice.

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Conflicts of interest

None.

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