**Name of Journal:** ***World Journal of Nephrology***

**Manuscript NO: 37042**

**Manuscript type: Review**

**Immunoglobulin G4-related kidney diseases: An updated review**

Salvadori M *et al.* IgG4-related kidney diseases

**Maurizio Salvadori, Aris Tsalouchos**

**Maurizio Salvadori,** Renal Unit, Department of Transplantation,Careggi University Hospital, Florence 50139, Italy

**Aris Tsalouchos,** Division of Nephrology,Nephrology and Dialysis Unit, Saints Cosmas and Damian Hospital, Pescia 2-51017, Italy

**ORCID number:** Maurizio Salvadori (0000-0003-1503-2681); Aris Tsalouchos (0000-0002-8565-4059).

**Author contributions**: Salvadori M and Tsalouchos A contributed equally to the manuscript; Salvadori M designed the study, perfored the last revision and provided answer to the reviewers; Tsalouchos A collected the data from literature; Salvadori M and Tsalouchos A analyzed the collected data and wrote the manuscript.

**Conflict-of-interest statement:** The authros do not have any conflict of interest in relation to the manuscript, as in the attached form.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Correspondance to: Maurizio Salvadori, MD,** Renal Unit, Department of Transplantation,Careggi University Hospital, viale Pieraccini 18, Florence 50139, Italy. maurizio.salvadori1@gmail.com

**Telephone:** +39-55-597151

**Fax:** +39-55-597151

**Received:** November 6, 2017

**Peer-review started:** November 9, 2017

**First decision:** December 1, 2017

**Revised:** December 15, 2017

**Accepted:** December 28, 2017

**Article in press:**

**Published online:**

**Abstract**

This review will encompass definition, pathogenesis, renal clinical manifestations and treatment of immunoglobulin G4-related diseases (IgG4-RDs). IgG4-RD is a recently recognized clinical entity that often involves multiple organs and is characterized by high levels of serum immunoglobulinsG4, dense infiltration of IgG4+ cells and storiform fibrosis. Cellular immunity, particularly T-cell mediated immunity, has been implicated in the pathogenesis of IgG4-RDs. The most frequent renal manifestations of IgG4-RD are IgG4-related tubulointerstitial nephritis (TIN), membranous glomerulopathy (MGN) and obstructive nephropathy secondary to urinary tract obstruction due to IgG4-related retroperitoneal fibrosis. IgG4-RD diagnosis should be based on specific histopathological findings, confirmed by tissue immunostaining, typical radiological findings and an appropriate clinical context. The first line treatment is the steroids with two warnings: steroid resistance and relapse after discontinuation. In the case of steroid resistance, B cell depleting agents as rituximab represent the second-line treatment. In the case of relapse after discontinuation, steroid treatment may be associated with steroid sparing agents. Since the disease has been only recently identified, more prospective, long-term studies are needed to an improved understanding and a more correct and safe treatment.

**Key words:** Immunoglobulin G4-related disease; Lymphoplasmacytic infiltration; Storiform fibrosis; Tubulointerstitial nephritis; Steroid treatment; B cell depleting agents

**© The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** [Immunoglobulin](http://www.sciencedirect.com/topics/medicine-and-dentistry/immunoglobulin) G4-related disease (IgG4-RD) is a recently recognized clinical entity that often involves multiple organs; it is characterized by high levels of serum immunoglobulin G4 dense infiltration of IgG4+ cells, and storiform [fibrosis](http://www.sciencedirect.com/topics/medicine-and-dentistry/fibrosis). [Cellular immunity](http://www.sciencedirect.com/topics/medicine-and-dentistry/cellular-immunity), particularly T [cell-mediated immunity](http://www.sciencedirect.com/topics/medicine-and-dentistry/cell-mediated-immunity), has been implicated in the [pathogenesis](http://www.sciencedirect.com/topics/medicine-and-dentistry/pathogenesis) of IgG4-RD. The most frequent renal manifestations of IgG4-RD are IgG4-related [tubulointerstitial nephritis](http://www.sciencedirect.com/topics/medicine-and-dentistry/interstitial-nephritis), membranous glomerulonephropathy and obstructive [nephropathy](http://www.sciencedirect.com/topics/medicine-and-dentistry/nephropathy) secondary to [urinary tract obstruction](http://www.sciencedirect.com/topics/medicine-and-dentistry/urinary-retention) due to IgG4-related [retroperitoneal fibrosis](http://www.sciencedirect.com/topics/medicine-and-dentistry/retroperitoneal-fibrosis). In IgG4-membranous glomerulopathy, [proteinuria](http://www.sciencedirect.com/topics/medicine-and-dentistry/proteinuria) can be in the nephrotic range. Steroid treatment is the first-line therapy. For [relapsing](http://www.sciencedirect.com/topics/medicine-and-dentistry/relapse) or refractory cases, [immunosuppressants](http://www.sciencedirect.com/topics/medicine-and-dentistry/immunosuppressant) could be combined with [steroids](http://www.sciencedirect.com/topics/medicine-and-dentistry/steroid).

Salvadori M and Tsalouchos A. Immunoglobulin G4-related kidney diseases: An updated review. *World J Nephrol* 2017; In press

**INTRODUCTION**

Immunoglobulin G4-related disease (IgG4-RD) is a recently identified systemic fibroinflammatory condition recently that mimics several autoimmune, malignant and rheumatologic diseases. IgG4-RDs may affect several organs as recognized since the 1st international symposium held in Boston in 2011[1] (Table 1). To date the diagnosis of IgG4-RDs unifies several pathologic conditions previously considered well-defined and distinct disorders and now recognized as organ manifestations of IgG4-RD[2-4] (Table 2). Other diseases merely mimic IgG4-RD and hence should be considered and classified separately because they represent diseases with distinct features (Table 3).

Consequently, the classification is rather confusing; hence the American College of Rheumatology recently recommended a revised nomenclature of IgG4-RD and its individual organ system manifestations[5].

Basing on clinical presentation per site of involvement IgG4-RD may be classified as in Table 4.

In this review, following the description of the hallmarks characteristic of IgG4-RD, its epidemiology and its pathophysiology, we principally highlight the so-called IgG4-related kidney disease (IgG4-RKD), its clinical and histological manifestations, the diagnostic criteria and treatment.

**RESEARCH METHODOLOGY**

We have analyzed the available papers on IgG4-RD pathogenesis, IgG4-RKD clinical and diagnosis and IgG4-RD therapy by a review of the currently available papers. A literature search was performed using PubMed (NCBI/NIH) with the search words “IgG4-RD pathogenesis”, “IgG4-RKD clinical and diagnosis”, “IgG4-RD treatment”, “IgG4-RD classification”. As first line research the papers published in the last three years were examined. Paper selection has been made according the relevance of the journal, the authors, and the dimension of the study and the novelty of the findings. So doing 40 papers recently published have been selected, then we proceeded in a backward way and studies previously published have also been included.

**HISTOLOGICAL ASPECTS OF IgG4-RD**

The major histopathological features associated with IgG4-RD are represented in Table 5.

Pathological features of IgG4-RD may vary according to the organ involved. Obliterative arteritis and neutrophilic infiltration rarely occurs. When present they are characteristic of lung lesions and occur in the alveolar spaces[6]. Absence of storiform fibrosis and lack of obliterative phlebitis may be observed in diseases involving the salivary glands, lymph nodes and kidney[7].

Hallmarks of the diseases are a lymphoplasmacytic infiltrate enriched with IgG4 plasma cells, a storiform pattern of fibrosis and obliterative phlebitis[3,8]. The pattern is often similar to a cartwheel with the bands of fibrosis emanating from the center representing the spokes of the wheel. Immunoperoxidase staining revealed that nearly all plasma cells are strongly positive for IgG4, whereas the small lymphocytes are negative. A total obliteration of venous channels (obliterative phlebitis) may be present. Eosinophils and fibroblasts are present as well[9,10].

Several caveats must be considered in the interpretations of tissue lesions and particularly IgG4 positive plasma cells: (1) IgG4 positive plasma cells are generally present in the lesions, but focal aggregations of IgG4-positive cells are atypical; (2) The absolute number of IgG4 positive plasma cells should be interpreted according to the specific tissue[8]; (3) The ratio of IgG4 to IgG positive plasma cells must be at least 40%; and (4) IgG4-RD cannot be diagnosed on the basis of infiltration by IgG4-positive plasma cells alone because these cells may also be present in other inflammatory or neoplastic disorders[11].

**EPIDEMIOLOGY**

IgG4-RD was first recognized as a systemic entity in the early 2000s, when autoimmune pancreatitis (AIP) type I patients demonstrated similar conglomerations of fibroinflammatory tissue in other organs or lesions, such as retroperitoneal and mediastinal fibrosis, inflammatory pseudo tumor of lung and liver as well as interstitial nephritis[12-14] . Due to the relatively recent discovery, minimal epidemiological data exist. The majority of the patients reported in the literature are from Japan[15]; however, to date it is not clear whether this higher prevalence is due to genetic or environmental causes or simply because the disease was specifically investigated within this population. The average age of disease onset is between 61 and 70 years and there is a clear male predilection with the exception of the forms involving the head and neck[16,17].

**PATHOPHYSIOLOGY**

Several immune-mediated mechanisms are involved in the pathophysiology of IgG4-RD. They are divided into: (1) initiating mechanisms; and (2) specific disease pathways.

***Potential initiating mechanisms***

**Genetic background:** In Japanese populations, the frequencies of human leukocyte antigen (HLA) serotypes DRB1\*0404 and DRB1\*0401 are significantly higher in patients with AIP, a common manifestation of IgG4-RD[18] .

Non-HLA genes with single nucleotide polymorphisms (SNPs) are also involved in the expression of disease encoding proteins, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), tumor necrosis factor alpha (TNFα) and Fc receptor like 3, expressed on B cells (FCRL3)[19-21] .

**Bacterial infection and molecular mimicry:** Homologies existing between human carbonic anhydrase II and the alpha carbonic anhydrase of *Helicobacter pylori* (*H. pylori*), as well as between the plasminogen binding protein of *H. pylori* and the ubiquitin-protein ligase E3 component n-recognin 2 expressed on pancreatic cells have raised the question of a possible pathogenetic role of molecular mimicry involving *H. pylori*[22,23]. The contribution of the innate immune response to IgG4-RD is highlighted by the fact that various species of bacteria may induce the stimulation of toll-like receptor ligand in the production of IgG4 and interleukin-10 (IL-10) from peripheral blood mononuclear cells (PBMCs)[24].

**Autoimmunity:** The involvement of autoimmunity in activating Th cells in IgG4-RD is suspected because of the presence of auto antibodies against carbonic anydrases, lactoferrin, pancreatic secretory trypsin inhibitors and trypsinogens[25-27]. In addition, electron-dense deposits have been observed in the renal tubular membrane and pancreatic ducts of patients affected by IgG4-RD[28].

***Specific disease pathways***

**Th cells and regulatory immune reaction**

T cells may ultimately be implicated in the pathogenesis of IgG4-RD. Potential triggers, such as foreign pathogen-associated molecular patterns (PAMPs) and damage- associated molecular patterns (DAMPs) may be recognized by Toll-like receptors (TLR), which may induce the productionof IgG4 by CD19+[29]. More importantly these triggers by activating the innate immune system, may determine the state of polarization of T helper cells in IgG4-RD. Treg cells are also activated, as indicated by the high expression levels of forkhead box P3 (FOXP3) mRNA in the tissue[30].

Activated T helper cells and Treg cells may produce inflammatory cytokines, including interferon gamma (IFNγ), IL-4, IL-10, IL-5 and IL-13. IL-4 and IL-10, possibly produced by T follicular helper cells, and may cause class switching of auto reactive B cells to IgG4 and IgE and induce differentiation and expansion of IgG4 plasma cells[31,32] . IL-5, IL-13 and tumor growth factor beta (TGFβ) may lead to the recruitment of eosinophils and the activation of fibroblasts[4,33] . IFNγ may also contribute to the activation of macrophages that induce fibrosis[4] and induce a dense storiform fibrosis. On the other hand, B cells that recognize self antigens are capable of efficient antigen presentation to auto reactive T cells, thereby mediating a vicious cycle between T and B lymphocytes[34].

**Role of IgG4 antibodies：**It is likely that IgG4 per se have a poor role in generating IgG4-RD.　The IgG4 antibodies bind weakly to complement C1q and Fcy receptors. As a consequence, they are not involved in antibody-dependent cell-mediated cytotoxicity[35]. Additionally, IgG4 form half antibodies through the process of Fab arm exchange[35]. The consequence is a reduced ability to bind to the antigen and to generate immune complexes. Moreover, IgG4 antibodies seem to be stronger suppressors than inducers of inflammation[33].

All the aforementioned mechanisms and pathways are summarized in fig. 1, which unifies all the different mechanisms. Auto-antibodies may drive the Th2-cell response. Molecular mimicry as well as microbial components may also act as triggers for IgG4-RD, wherein they may stimulate innate immune mechanisms by activating nucleotide-activating factors belonging to the tumor necrosis factor (TNF) family (NODR) and the toll-like receptor 2 (TLR2) to produce B cell activating factor (BAFF) and a proliferative-inducing ligand (APRIL), which leads to B cell modifications in a T cell-independent manner. An expansion in Treg cells may contribute to both B-cell Ig class switching and fibrosis. A treatment sensitive expansion in circulatory plasma blasts is present in the active disease.

**IgG4-KIDNEY RELATED DISEASES**

The kidney may be affected by different histopathologic lesions in the course of IgG4-KRD.　This fact represents a peculiarity with respect to other organs that may be affected by IgG4-RD.

The kidney may be affected directly by histopathologic lesions affecting the parenchyma or indirectly as in the case of retroperitoneal fibrosis, which causes renal function impairment because of the obstruction of the urinary tract.

IgG4-related tubule interstitial nephritis (TIN) represents the parenchymal lesions more often affecting the kidney. The other more frequent lesion is represented by membranous glomerulopathy, in which lymphoplasmacytic infiltrate and storiform fibrosis, typical of IgG4-RD are not present. Other types of glomerular lesions, such as Schonlein Henoch purpura nephritis, may be infrequently observed during the course of IgG4-RD. When present, it is often associated with TIN[36,37]. IgA nephropathy, membrano-proliferative glomerulonephritis and minimal change disease have also been described[38]. Recently, a case of AA Amyloidosis affecting the kidney in the course of IgG4-RD has been reported[39]. Altogether, renal involvement in the course of IgG4-RD occurs in approximately 15% of patients.

***IgG4 related TIN***

As mentioned above, IgG4-TIN is the most common renal manifestation of IgG4-RD, and the majority of data concerning this lesion come from two series of biopsies: a Japanese cohort[40] and an American cohort[41].

IgG4-related TIN is often diagnosed in the setting of already known extra renal disease. The most common associated manifestations are sialoadenitis, lymphadenopathy, type I AIP and dacryadenitis. When IgG4-KRD with TIN is the only manifestation, the diagnosis is made by a renal biopsy performed because of acute or progressive renal failure.

The Japanese Society of Nephrology proposed a useful algorithm for the diagnosis of IgG4-related TIN[42]. According to the algorithm, in the case of abnormal renal function, principally when associated with high serum IgG or serum IgE, after exclusion of secondary diseases, such as lupus, vasculitis, *etc.,* and with serum IgG4 higher than 135 mg/dl, characteristic radiologic findings, such as multiple low density lesions, diffuse kidney enlargement and/or solitary hypovascular mass should be looked for and renal histology should be performed.

***Laboratory findings***

In addition to signs of renal dysfunction, nearly all patients with IgG4-related TINhave elevated serum concentrations of IgG and IgG4. Sixty percent of the patients have hypocomplementemia. Peripheral eosinophilia is observed in approximately 40% of the patients and positive anti-nuclear auto antibodies (ANA) are observed in 32%[43,44].

***Radiologic features***

Multiple hypodense lesions are the most common observation[40,41]. Such lesions were present in 69.6% of the Japanese cohort and in 78.3% of the Mayo Clinic cohort. Using diffusion-weighted magnetic resonance imaging (MRI), a recent study reported 100% sensitivity with respect to computed tomography (CT)[45]. However, a caveat is that when a solid mass is observed, it may be misdiagnosed as a malignant neoplasm and lead to an unnecessary nephrectomy[46,47].

***Histopathological features***

Plasma cell-rich TIN with fibrosis and often infiltrating eosinophils represent the typical histopathologic appearance[8,48]. This aspect represents the gold standard for diagnosis and allows for filtering out malignancies and other mimicking diseases[49] (Figure 1). Fibrosis often has a storiform pattern. In IgG4-TIN, fibrosis is generally more severe than the fibrosis observed in other forms of TIN[1]. Obliterative phlebitis, a critical pathological feature of IgG4-RD is rarely observed in IgG4-TIN, probably because of the lack of veins in the biopsy specimen[8,41] . Other histopathological features are represented by the fact that affected and unaffected areas are clearly demarcated[50]. Additionally, sometimes the lesions infiltrate the renal capsule and beyond[51].

Overall there is a spectrum of microscopic appearances, which includes TIN with minimal fibrosis, interstitial fibrosis with marked inflammatory infiltrate and an extensive tubular destruction and atrophy[41,52]. More recently, according to the Mayo Clinic series, 3 histological patterns of IgG4-TIN were described: (1) acute TIN with minimal interstitial fibrosis; (2) chronic TIN with expansive interstitial fibrosis; and (3) advanced sclerosing pattern[43].

Immunohistochemical staining for IgG4 reveals IgG4+ plasma cells, even if the increased number of interstitial IgG4+ plasma cells is not specific for IgG4-TIN and 80% of patients have granular IgG and C3 deposits along the tubular basement membrane (TBM)[41]. Deposits of immune complexes have been observed as electron dense deposits in the TBM[41,53]. Because IgG4 cannot activate the complement system, other subclasses, such as IgG1, may play a role in activating complement and forming immune complexes.

***Diagnosis and differential diagnosis***

In order to diagnose IgG4-TIN, two sets of diagnostic criteria have been proposed as shown in Table 6. The criteria proposed by Raissian[41] require a TIN with > 10 IgG4+ plasma cells per high-power field (HPF) in addition to either elevated serum IgG4 or evidence of extra renal IgG4-RD. Moreover, Kawano[54] classified patients with features of IgG4-TIN into three categories: definite, probable and possible.

Contrasted enhanced computed tomography (CT) is widely used to identify radiographic abnormalities in IgG4-TIN[55], even though MRI has a higher sensitivity [45] The most common finding in CT are bilateral, hypodense lesions often multiple that involve the renal cortex and may have the aspect of small peripheral cortical nodules, well or poorly defined round lesions and diffuse patchy lesions[55].

Differential diagnosis of IgG4-TIN includes distinction from allergic TIN, chronic pyelonephritis, granulomatosis with polyangiitis, Castleman disease and other autoimmune TINs. Allergic TIN does not have storiform fibrosis and does not have as many plasma cells in the infiltrate.

Chronic pyelonephritis has several neutrophils in the infiltrate and a typical radiographic pattern. Granulomatosis with polyangiitis has necrotizing vasculitis or granuloma. Moreover, ANCA antibodies in the serum are not present in IgG4-TIN.

Differential diagnosis with Castleman disease may be difficult, and recently, two cases of Castleman disease with kidney involvement closely mimicking IgG4-TIN have been reported[56]. Finally, TIN due to other autoimmune diseases demonstrates clinical and laboratoristic signs of the autoimmune disease, such as lupus or Sjogren syndrome[41].

**GLOMERULAR NEPHROPATHIES RELATED TO IGG4-RD**

The most important and frequent glomerular lesion is membranous glomerular nephropathy (MGN), which represents 7% of all IgG4-RKD cases according to the two largest biopsy series[40,41] . Other rare glomerular lesions are classified into two subgroups according to the prevalence of a Th2 response. Henoch Schonlein purpura nephritis and minimal change syndrome are associated with a prevailing Th2 response[38,57], whereas IgA nephropathy and membrano proliferative glomerulonephritis are associated with a poor Th2 response[58,59].

***Clinical and laboratory features***

IgG4-related MGN occurs principally in males. Other extra renal manifestations of IgG4-RD are often present[60]. Heavy proteinuria with nephritic syndrome is the principal clinical feature. Half of the patients have concomitant TIN. In these patients, TIN is probably the cause of renal dysfunction[61].

***Renal histopathology***

All patients exhibit sub-epithelial deposits in a membranous pattern. Immunofluorescence demonstrated IgG4 to be the prevailing immunoglobulin. No anti phospholipase A2 receptor (PLA2r) antibody has been observed in IgG4-MGN. Some patients affected by IgG4-MGN also had mesangial and sub-epithelial deposits[41]. Whether the target antigen in IgG4-MGN is located in the podocytes, as in idiopathic MGN, is not known.

***Renal amyloidosis related to IgG4-RD***

To date only one case of renal AA amyloidosis associated with extra-renal IgG4-RD has been described[39].

***Clinical features***

The patient suffered from a mesenteric IgG4-RD with involvement of the lymph nodes. AA amyloidosis developed after 16 years; however, whether or not the treatment of IgG4-RD caused a delay in the development of AA amyloidosis, is not known.

**RETROPERITONEAL FIBROSIS**

Compared to the described renal diseases, wherein renal dysfunction is caused by parenchymal lesions, retroperitoneal fibrosis causes renal dysfunction by obstruction of the urinary tract.

***Pathogenesis***

Development of retroperitoneal fibrosis in the periaortic and periiliac retroperitoneum results in hydronephrosis and inflammatory abdominal aortic aneurysm[62,63].

Hydronephrosis is caused by the diffusion of the periaortic inflammation to the ureter, resulting in its obstruction. Involvement of both kidneys may result in end-stage renal failure.

**TREATMENT**

The optimal treatment for IgG4-RD is unknown. Indeed, to date, there have been no randomized clinical trials that have evaluated and compared the effectiveness of different treatment regimens[33]. Although some patients affected by IgG4-RD may have spontaneous remission and do not require treatment[64], a prompt treatment is generally recommended to avoid deleterious complications and consequences of the evolving disease.

Glucocorticoids are currently the first line treatment for IgG4-RD[65,66] and IgG4-RKD[33,42]. An alternative are the B depleting agents as rituximab (RTX), which is still under investigation in clinical trials[67,68]. An international panel of experts developed recommendations for the management of IgG4-RD and recommended steroids as first line agents for remission induction, while there was low agreement on the use of RTX[49].

IgG4-RD may affect several organs. Recently, Della Torre *et al*[69] categorized six principal clinical phenotypes.

In all the phenotypes the authors confirmed the efficacy of a 4-to 6-month course of glucocorticosteroids. In the case of steroid toxic effects or steroid resistance, steroid sparing agents or RTX may be considered. According to the aforementioned international consensus[49] IgG4-RD treatment should comprise the following three steps[70]: (1) Induction treatment (prednisolone 40 mg/d). Consider B cells depletion therapy if patient is resistant or intolerant to glucocorticosteroids; (2) Tapering treatment with a duration of 3-6 mo; and (3) Maintenance treatment (low dose prednisolone associated or not with azathioprine or other agents, such as cyclophosphamide, mycophenolate mofetil or calcineurin inhibitors). Maintenance is necessary only in multiorgan disease, elevated serum IgG4, and relapse).

A prompt response to corticosteroid therapy is characteristic of IgG4-RD and renal involvement is not an exception[41]. In patients with renal dysfunction, a recovery of renal function after glucocorticoid therapy has been documented[71]. Data on the use of steroids in IgG4-TIN are principally reported by the Japanese and the Mayo Clinic series[41]. Data on long-term outcomes of IgG4-TIN treated with steroids are available from a retrospective analysis of 40 patients[72]. These data confirm the beneficial effects of corticosteroids in a majority of the patients. However, 60% of the patients who underwent CT imaging during follow up exhibited evidence of a notable renal atrophy. For these disappointing results, a multicenter phase II prospective clinical trial of glucocorticoid for patients with untreated IgG4-RD is to date ongoing[73].

Data on IgG4-MGN are limited to a retrospective analysis of seven patients[60]. Steroid treatment seems to be effective in these patients; however, the retrospective study has several limitations: some patients had a concomitant IgG4-TIN and other patients received other immunosuppressants in addition to steroids.

A renal amyloidosis merits few comments. Only one patient has been reported[39], and because of the long-standing IgG4-RD, the authors argue that the treatment of IgG4-RD with steroids not only ameliorated the symptoms but also modulated inflammatory effects and delayed secondary amyloidosis.

Retroperitoneal fibrosis is also treated successfully with steroids, but with a relevant warning. Hydronephrosis is often associated with aortic aneurysm. The latter represents a critical contraindication to steroid treatment because it may cause aneurysm rupture.

Altogether, steroid treatment of IgG4-RD has the limitation that needs a long-term course and has unavoidable side effects. Additionally, a number of patients are steroid-resistant or steroid-relapsing.

For such patients other immunosuppressants, such as azathioprine, mycophenolate mofetil (MMF) should be considered; however, their effectiveness and safety remains to be established[65].

International consensus is to take a pragmatic approach: Start to taper the drug after two to four weeks of induction dosing and aim to stop treatment within three to six months[74]. In the case of relapse, depletion of B cells by RTX should be attempted. In the early phase, two trials have been demonstrated to be highly effective[49,68] . RTX may dramatically decrease the circulating plasma blasts that represent an index if IgG4-responders[75].

In the case of IgG4-RKD, particularly TIN, renal atrophy developed in a number of patients treated with steroids, principally in cases where treatment was started late. Relapse of renal dysfunction following steroid tapering or withdrawal is also frequently observed among patients with IgG4-TIN.

In patients with IgG4-TIN, B cell depletion with RTX may provide a durable response; however, this hypothesis requires confirmation in controlled trials[72].

The first suggestions on the efficacy of RTX in patients affected by IgG4-RD have been reported in patients affected by IgG4-associated cholangitis, AIP, and ocular involvement resistant to steroids[76].

The first, randomized, clinical trial on the efficacy of RTX on IgG-RD was performed at the Massachusetts General Hospital and the Mayo Clinic (Clinical Trials.gov identifier NCT01584388)[68]. Disease response occurred in 97% of the patients and overall, RTX appeared to be an effective treatment for IgG4-RD. Unfortunately, only 4 patients were affected by IgG4-TIN. Recently, McMahon *et al*[77] reported successful treatment with RTX in one patient affected by IgG4-TIN who was steroid resistant.

Beneficial effects of B cell depletion were observed by other investigators confirming its significant role in this condition[78]. In clinical practice RTX is usually considered the first steroid sparing agent after relapse in patients treated with steroids.

Other biologic agents, such as Bortezomib, Abatacept and Infliximab have been used in IgG4-RD refractory to steroids and with a particular disease severity[79-81]. To date their use in IgG4-TIN is not recommended, based on clinical experience.

**CONCLUSION**

IgG4-RDs have only been recently recognized, and several features, principally concerning nomenclature, pathophysiology and treatment still remain to be completely defined.

*Nomenclature*

To better recognize which diseases should be included under the umbrella of IgG4-RDs, a consensus statement was held in Boston in 2011, which provided a set of guidelines for the diagnosis of IgG4-RDs[82]. As the spectrum of this group of diseases is continuously expanding, the committee advocated the use of strict criteria for accepting newly proposed entities as components of the group.

As a consequence, in 2015[1] (Table 1), new organs affected by the disease were recognized in addition to the organs identified in the Boston consensus conference. Additionally, pathologic conditions previously considered as well-defined disorders are now recognized as organ manifestations of IgG4-RD[3] (Table 2).

On the other hand, several conditions have been identified, which only mimic IgG4-RDs but should be classified separately because they represent diseases with distinct and different features[83] (Table 3). This point is principally relevant for IgG4-related TIN because a number of TINs have been observed, which are not related to IgG4-RDs[84]. The American College of Rheumatology recently[5] edited the recommendations for an improved nomenclature of IgG4-RDs.

***Pathogenesis***

Pathogenesis of IgG4-RD is poorly understood and controversial. IgG4 antibodies do not seem to be pathogenetic in this disease; rather they mediate a down-regulatory response to other processes[4]. In addition, IgG4s are only half-antibodies and are unable to bind the complement proteins. Several findings concerning IgG4-RD pathogenesis are consistent with both an autoimmune disorder[85,86] and an allergic disease[87].

Autoimmunity is principally evident in patients with type 1 AIP[85]. Auto antibodies have been described in IgG4-RDs but an evidence for an autoimmune disease is lacking. Cytokines and increased IgE have been described in affected tissues[87]; however, recent studies[88,89] have documented that circulating Th2 in IgG4-RDs are restricted to a subset of patients affected by atopy.

An improvement in the understanding of the physiopathology of IgG4-RD is represented by the identification of a cytotoxic CD4 T cell. These cells may produce granzyme B and perforin as well as IL-1 and TGF-β, which are important mediators of fibrosis. Moreover, these T cells are continuously stimulated by the antigen presentation by B cells and plasma blasts[88], and this fact highlights the importance of a cross-talk between innate and acquired immunity in the pathogenesis of IgG4-RD[90].

***Treatment***

The optimal treatment for IgG4-RD has not yet been established. Indeed, to date, there have been no randomized clinical trials that have evaluated and compared the effectiveness of different treatment regimens[33]. An international consensus among experts[49] recommended steroids as first line treatment. Due to some disappointing results with the long-term use of corticosteroids, a multicenter phase II prospective clinical trial with steroids is currently ongoing[73].

Steroid treatment has several drawbacks: (1) Steroid resistance or relapse at discontinuation; and (2) Long-term undesirable steroid side effects. In the case of steroid resistant patients or frequently relapsing patients, B cell depleting agents may represent an effective treatment. RTX is the most used agent and a clinical trial on the use of RTX has been conducted in the United States[68].

To avoid long-term steroid related side effects, other steroid sparing agents, such as azathioprine, MMF and cyclophosphamide, are reasonable choices for second-line agents; however, once again, their effects have not yet been adequately evaluated in IgG4-RD.

**REFERENCES**

1. **Kawano M**, Saeki T. IgG4-related kidney disease--an update. *Curr Opin Nephrol Hypertens* 2015; **24**: 193-201 [PMID: 25594543 DOI: 10.1097/MNH.0000000000000102]
2. **Quattrocchio G**, Roccatello D. IgG4-related nephropathy. *J Nephrol* 2016; **29**: 487-493 [PMID: 26972314 DOI: 10.1007/s40620-016-0279-4]
3. **Stone JH**, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med* 2012; **366**: 539-551 [PMID: 22316447 DOI: 10.1056/NEJMra1104650]
4. **Mahajan VS**, Mattoo H, Deshpande V, Pillai SS, Stone JH. IgG4-related disease. *Annu Rev Pathol* 2014; **9**: 315-347 [PMID: 24111912 DOI: 10.1146/annurev-pathol-012513-104708]
5. **Stone JH**, Khosroshahi A, Deshpande V, Chan JK, Heathcote JG, Aalberse R, Azumi A, Bloch DB, Brugge WR, Carruthers MN, Cheuk W, Cornell L, Castillo CF, Ferry JA, Forcione D, Klöppel G, Hamilos DL, Kamisawa T, Kasashima S, Kawa S, Kawano M, Masaki Y, Notohara K, Okazaki K, Ryu JK, Saeki T, Sahani D, Sato Y, Smyrk T, Stone JR, Takahira M, Umehara H, Webster G, Yamamoto M, Yi E, Yoshino T, Zamboni G, Zen Y, Chari S. Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. *Arthritis Rheum* 2012; **64**: 3061-3067 [PMID: 22736240 DOI: 10.1002/art.34593]
6. **Zen Y**, Inoue D, Kitao A, Onodera M, Abo H, Miyayama S, Gabata T, Matsui O, Nakanuma Y. IgG4-related lung and pleural disease: a clinicopathologic study of 21 cases. *Am J Surg Pathol* 2009; **33**: 1886-1893 [PMID: 19898222 DOI: 10.1097/PAS.0b013e3181bd535b]
7. **Zen Y**, Nakanuma Y. IgG4-related disease: a cross-sectional study of 114 cases. *Am J Surg Pathol* 2010; **34**: 1812-1819 [PMID: 21107087 DOI: 10.1097/PAS.0b013e3181f7266b]
8. **Deshpande V**, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, Klöppel G, Heathcote JG, Khosroshahi A, Ferry JA, Aalberse RC, Bloch DB, Brugge WR, Bateman AC, Carruthers MN, Chari ST, Cheuk W, Cornell LD, Fernandez-Del Castillo C, Forcione DG, Hamilos DL, Kamisawa T, Kasashima S, Kawa S, Kawano M, Lauwers GY, Masaki Y, Nakanuma Y, Notohara K, Okazaki K, Ryu JK, Saeki T, Sahani DV, Smyrk TC, Stone JR, Takahira M, Webster GJ, Yamamoto M, Zamboni G, Umehara H, Stone JH. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012; **25**: 1181-1192 [PMID: 22596100 DOI: 10.1038/modpathol.2012.72]
9. **Deshpande V**, Gupta R, Sainani N, Sahani DV, Virk R, Ferrone C, Khosroshahi A, Stone JH, Lauwers GY. Subclassification of autoimmune pancreatitis: a histologic classification with clinical significance. *Am J Surg Pathol* 2011; **35**: 26-35 [PMID: 21164284 DOI: 10.1097/PAS.0b013e3182027717]
10. **Della Torre E**, Mattoo H, Mahajan VS, Carruthers M, Pillai S, Stone JH. Prevalence of atopy, eosinophilia, and IgE elevation in IgG4-related disease. *Allergy* 2014; **69**: 269-272 [PMID: 24266692 DOI: 10.1111/all.12320]
11. **Strehl JD**, Hartmann A, Agaimy A. Numerous IgG4-positive plasma cells are ubiquitous in diverse localised non-specific chronic inflammatory conditions and need to be distinguished from IgG4-related systemic disorders. *J Clin Pathol* 2011; **64**: 237-243 [PMID: 21233087 DOI: 10.1136/jcp.2010.085613]
12. **Celis IM**, Kriekaart RL, Aliredjo RP, van Lochem EG, van der Vorst MJ, Hassing R. IgG4-related disease: a disease we probably often overlook. *Neth J Med* 2017; **75**: 27-31 [PMID: 28124667]
13. **Kamisawa T**, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, Okamoto A, Egawa N, Nakajima H. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003; **38**: 982-984 [PMID: 14614606 DOI: 10.1007/s00535-003-1175-y]
14. **Zhang L**, Smyrk TC. Autoimmune pancreatitis and IgG4-related systemic diseases. *Int J Clin Exp Pathol* 2010; **3**: 491-504 [PMID: 20606730]
15. **Uchida K**, Masamune A, Shimosegawa T, Okazaki K. Prevalence of IgG4-Related Disease in Japan Based on Nationwide Survey in 2009. *Int J Rheumatol* 2012; **2012**: 358371 [PMID: 22899936 DOI: 10.1155/2012/358371]
16. **Brito-Zerón P**, Ramos-Casals M, Bosch X, Stone JH. The clinical spectrum of IgG4-related disease. *Autoimmun Rev* 2014; **13**: 1203-1210 [PMID: 25151972 DOI: 10.1016/j.autrev.2014.08.013]
17. **Yamamoto M**, Takahashi H, Shinomura Y. Mechanisms and assessment of IgG4-related disease: lessons for the rheumatologist. *Nat Rev Rheumatol* 2014; **10**: 148-159 [PMID: 24296677 DOI: 10.1038/nrrheum.2013.183]
18. **Kawa S**, Ota M, Yoshizawa K, Horiuchi A, Hamano H, Ochi Y, Nakayama K, Tokutake Y, Katsuyama Y, Saito S, Hasebe O, Kiyosawa K. HLA DRB10405-DQB10401 haplotype is associated with autoimmune pancreatitis in the Japanese population. *Gastroenterology* 2002; **122**: 1264-1269 [PMID: 11984513 DOI: http://dx.doi.org/10.1053/gast.2002.33022]
19. **Chang MC**, Chang YT, Tien YW, Liang PC, Jan IS, Wei SC, Wong JM. T-cell regulatory gene CTLA-4 polymorphism/haplotype association with autoimmune pancreatitis. *Clin Chem* 2007; **53**: 1700-1705 [PMID: 17712006 DOI: 10.1373/clinchem.2007.085951]
20. **Umemura T**, Ota M, Hamano H, Katsuyama Y, Muraki T, Arakura N, Kawa S, Kiyosawa K. Association of autoimmune pancreatitis with cytotoxic T-lymphocyte antigen 4 gene polymorphisms in Japanese patients. *Am J Gastroenterol* 2008; **103**: 588-594 [PMID: 18341485 DOI: 10.1111/j.1572-0241.2007.01750.x]
21. **Zen Y**, Nakanuma Y. Pathogenesis of IgG4-related disease. *Curr Opin Rheumatol* 2011; **23**: 114-118 [PMID: 21045701 DOI: 10.1097/BOR.0b013e3283412f4a]
22. **Guarneri F**, Guarneri C, Benvenga S. Helicobacter pylori and autoimmune pancreatitis: role of carbonic anhydrase via molecular mimicry? *J Cell Mol Med* 2005; **9**: 741-744 [PMID: 16202223 DOI: 10.1111/j.1582-]
23. **Frulloni L**, Lunardi C, Simone R, Dolcino M, Scattolini C, Falconi M, Benini L, Vantini I, Corrocher R, Puccetti A. Identification of a novel antibody associated with autoimmune pancreatitis. *N Engl J Med* 2009; **361**: 2135-2142 [PMID: 19940298 DOI: 10.1056/NEJMoa0903068]
24. **Akitake R**, Watanabe T, Zaima C, Uza N, Ida H, Tada S, Nishida N, Chiba T. Possible involvement of T helper type 2 responses to Toll-like receptor ligands in IgG4-related sclerosing disease. *Gut* 2010; **59**: 542-545 [PMID: 20332525 DOI: 10.1136/gut.2009.200972]
25. **Aparisi L**, Farre A, Gomez-Cambronero L, Martinez J, De Las Heras G, Corts J, Navarro S, Mora J, Lopez-Hoyos M, Sabater L, Ferrandez A, Bautista D, Perez-Mateo M, Mery S, Sastre J. Antibodies to carbonic anhydrase and IgG4 levels in idiopathic chronic pancreatitis: relevance for diagnosis of autoimmune pancreatitis. *Gut* 2005; **54**: 703-709 [PMID: 15831920 DOI: 10.1136/gut.2004.047142]
26. **Asada M**, Nishio A, Uchida K, Kido M, Ueno S, Uza N, Kiriya K, Inoue S, Kitamura H, Ohashi S, Tamaki H, Fukui T, Matsuura M, Kawasaki K, Nishi T, Watanabe N, Nakase H, Chiba T, Okazaki K. Identification of a novel autoantibody against pancreatic secretory trypsin inhibitor in patients with autoimmune pancreatitis. *Pancreas* 2006; **33**: 20-26 [PMID: 16804408 DOI: 10.1097/01.mpa.0000226881.48204.fd]
27. **Löhr JM**, Faissner R, Koczan D, Bewerunge P, Bassi C, Brors B, Eils R, Frulloni L, Funk A, Halangk W, Jesenofsky R, Kaderali L, Kleeff J, Krüger B, Lerch MM, Lösel R, Magnani M, Neumaier M, Nittka S, Sahin-Tóth M, Sänger J, Serafini S, Schnölzer M, Thierse HJ, Wandschneider S, Zamboni G, Klöppel G. Autoantibodies against the exocrine pancreas in autoimmune pancreatitis: gene and protein expression profiling and immunoassays identify pancreatic enzymes as a major target of the inflammatory process. *Am J Gastroenterol* 2010; **105**: 2060-2071 [PMID: 20407433 DOI: 10.1038/ajg.2010.141]
28. **Cornell LD**, Chicano SL, Deshpande V, Collins AB, Selig MK, Lauwers GY, Barisoni L, Colvin RB. Pseudotumors due to IgG4 immune-complex tubulointerstitial nephritis associated with autoimmune pancreatocentric disease. *Am J Surg Pathol* 2007; **31**: 1586-1597 [PMID: 17895762 DOI: 10.1097/PAS.0b013e318059b87c]
29. **Watanabe T**, Yamashita K, Fujikawa S, Sakurai T, Kudo M, Shiokawa M, Kodama Y, Uchida K, Okazaki K, Chiba T. Involvement of activation of toll-like receptors and nucleotide-binding oligomerization domain-like receptors in enhanced IgG4 responses in autoimmune pancreatitis. *Arthritis Rheum* 2012; **64**: 914-924 [PMID: 21971969 DOI: 10.1002/art.33386]
30. **Miyoshi H**, Uchida K, Taniguchi T, Yazumi S, Matsushita M, Takaoka M, Okazaki K. Circulating naïve and CD4+CD25high regulatory T cells in patients with autoimmune pancreatitis. *Pancreas* 2008; **36**: 133-140 [PMID: 18376303 DOI: 10.1097/MPA.0b013e3181577553]
31. **Bozzalla Cassione E**, Stone JH. IgG4-related disease. *Curr Opin Rheumatol* 2017; **29**: 223-227 [PMID: 28319486 DOI: 10.1097/BOR.0000000000000383]
32. **Akiyama M**, Yasuoka H, Yamaoka K, Suzuki K, Kaneko Y, Kondo H, Kassai Y, Koga K, Miyazaki T, Morita R, Yoshimura A, Takeuchi T. Enhanced IgG4 production by follicular helper 2 T cells and the involvement of follicular helper 1 T cells in the pathogenesis of IgG4-related disease. *Arthritis Res Ther* 2016; **18**: 167 [PMID: 27411315 DOI: 10.1186/s13075-016-1064-4.]
33. **Cortazar FB**, Stone JH. IgG4-related disease and the kidney. *Nat Rev Nephrol* 2015; **11**: 599-609 [PMID: 26122730 DOI: 10.1038/nrneph.2015.95]
34. **Mattoo H**, Mahajan VS, Della-Torre E, Sekigami Y, Carruthers M, Wallace ZS, Deshpande V, Stone JH, Pillai S. De novo oligoclonal expansions of circulating plasmablasts in active and relapsing IgG4-related disease. *J Allergy Clin Immunol* 2014; **134**: 679-687 [PMID: 24815737 DOI: 10.1016/j.jaci.2014.03.034]
35. **Aalberse RC**, Stapel SO, Schuurman J, Rispens T. Immunoglobulin G4: an odd antibody. *Clin Exp Allergy* 2009; **39**: 469-477 [PMID: 19222496 DOI: 10.1111/j.1365-2222.2009.03207.x]
36. **Tamai R**, Hasegawa Y, Hisano S, Miyake K, Nakashima H, Saito T. A case of IgG4-related tubulointerstitial nephritis concurrent with Henoch-Schönlein purpura nephritis. *Allergy Asthma Clin Immunol* 2011; **7**: 5 [PMID: 21450108 DOI: 10.1186/1710-1492-7-5]
37. **Ito K,** Yamada K, Mizushima I, Aizu M, Fujii H, Mizutomi K, Matsumura M, Hayashi K, Yamagishi M, Umehara H, Yamaguchi Y, Nagata M, Kawano M. Henoch-Schönlein purpura nephritis in a patient with IgG4-related disease: a possible association. Clin Nephrol. 2013;**79**:246-252. [PMID 22841022; doi: 10.5414/CN107114]
38. **Cornell LD**. IgG4-related kidney disease. *Semin Diagn Pathol* 2012; **29**: 245-250 [PMID: 23068304 DOI: 10.1053/j.semdp.2012.07.004]
39. **Karim F**, Clahsen-van Groningen M, van Laar JA. AA Amyloidosis and IgG4-Related Disease. *N Engl J Med* 2017; **376**: 599-600 [PMID: 28177871 DOI: 10.1056/NEJMc1614275]
40. **Saeki T**, Nishi S, Imai N, Ito T, Yamazaki H, Kawano M, Yamamoto M, Takahashi H, Matsui S, Nakada S, Origuchi T, Hirabayashi A, Homma N, Tsubata Y, Takata T, Wada Y, Saito A, Fukase S, Ishioka K, Miyazaki K, Masaki Y, Umehara H, Sugai S, Narita I. Clinicopathological characteristics of patients with IgG4-related tubulointerstitial nephritis. *Kidney Int* 2010; **78**: 1016-1023 [PMID: 20720530 DOI: 10.1038/ki.2010.271]
41. **Raissian Y**, Nasr SH, Larsen CP, Colvin RB, Smyrk TC, Takahashi N, Bhalodia A, Sohani AR, Zhang L, Chari S, Sethi S, Fidler ME, Cornell LD. Diagnosis of IgG4-related tubulointerstitial nephritis. *J Am Soc Nephrol* 2011; **22**: 1343-1352 [PMID: 21719792 DOI: 10.1681/ASN.2011010062]
42. **Saeki T**, Kawano M. IgG4-related kidney disease. *Kidney Int* 2014; **85**: 251-257 [PMID: 24107849 DOI: 10.1038/ki.2013.393]
43. **Zhang P**, Cornell LD. IgG4-Related Tubulointerstitial Nephritis. *Adv Chronic Kidney Dis* 2017; **24**: 94-100 [PMID: 28284385 DOI: 10.1053/j.ackd.2016.12.001]
44. **Stone JH**, Brito-Zerón P, Bosch X, Ramos-Casals M. Diagnostic Approach to the Complexity of IgG4-Related Disease. *Mayo Clin Proc* 2015; **90**: 927-939 [PMID: 26141331 DOI: 10.1016/j.mayocp.2015.03.020]
45. **Kim B**, Kim JH, Byun JH, Kim HJ, Lee SS, Kim SY, Lee MG. IgG4-related kidney disease: MRI findings with emphasis on the usefulness of diffusion-weighted imaging. *Eur J Radiol* 2014; **83**: 1057-1062 [PMID: 24768583 DOI: 10.1016/j.ejrad.2014.03.033]
46. **Shoji S**, Nakano M, Usui Y. IgG4-related inflammatory pseudotumor of the kidney. *Int J Urol* 2010; **17**: 389-390 [PMID: 20409237 DOI: 10.1111/j.1442-2042.2010.02483.x]
47. **Cai YI**, Li HZ, Zhang YS. IgG4-related inflammatory pseudotumor of the kidney mimicking renal cell carcinoma: A case report. *Oncol Lett* 2016; **11**: 3438-3440 [PMID: 27123131 DOI: 10.3892/ol.2016.4408]
48. **Yamaguchi Y**, Kanetsuna Y, Honda K, Yamanaka N, Kawano M, Nagata M; Japanese study group on IgG4-related nephropathy. Characteristic tubulointerstitial nephritis in IgG4-related disease. *Hum Pathol* 2012; **43**: 536-549 [PMID: 21889187 DOI: 10.1016/j.humpath.2011.06.002]
49. **Khosroshahi A**, Wallace ZS, Crowe JL, Akamizu T, Azumi A, Carruthers MN, Chari ST, Della-Torre E, Frulloni L, Goto H, Hart PA, Kamisawa T, Kawa S, Kawano M, Kim MH, Kodama Y, Kubota K, Lerch MM, Löhr M, Masaki Y, Matsui S, Mimori T, Nakamura S, Nakazawa T, Ohara H, Okazaki K, Ryu JH, Saeki T, Schleinitz N, Shimatsu A, Shimosegawa T, Takahashi H, Takahira M, Tanaka A, Topazian M, Umehara H, Webster GJ, Witzig TE, Yamamoto M, Zhang W, Chiba T, Stone JH; Second International Symposium on IgG4-Related Disease. International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease. *Arthritis Rheumatol* 2015; **67**: 1688-1699 [PMID: 25809420 DOI: 10.1002/art.39132]
50. **Saeki T,** Kawano M, Yoshita K, Ueno M, Nagata M, Yamaguchi Y. IgG4-related kidney disease. In: Umehara H, Okazaki K, Stone JH, Kawa S, Kawano M editors. IgG4 related disease.Springer: Tokyo; 2014: 169-179 [DOI: 10.1007/978-4-431-54228-5]
51. **Yoshita K**, Kawano M, Mizushima I, Hara S, Ito Y, Imai N, Ueno M, Nishi S, Nomura H, Narita I, Saeki T. Light-microscopic characteristics of IgG4-related tubulointerstitial nephritis: distinction from non-IgG4-related tubulointerstitial nephritis. *Nephrol Dial Transplant* 2012; **27**: 2755-2761 [PMID: 22228836 DOI: 10.1093/ndt/gfr761]
52. **Pradhan D**, Pattnaik N, Silowash R, Mohanty SK. IgG4-related kidney disease--A review. *Pathol Res Pract* 2015; **211**: 707-711 [PMID: 26341570 DOI: 10.1016/j.prp.2015.03.004]
53. **Nishi S**, Imai N, Yoshita K, Ito Y, Ueno M, Saeki T. Ultrastructural studies of IgG4-related kidney disease. *Intern Med* 2015; **54**: 147-153 [PMID: 25743005 DOI: 10.2169/internalmedicine.54.2581]
54. **Kawano M**, Saeki T, Nakashima H, Nishi S, Yamaguchi Y, Hisano S, Yamanaka N, Inoue D, Yamamoto M, Takahashi H, Nomura H, Taguchi T, Umehara H, Makino H, Saito T. Proposal for diagnostic criteria for IgG4-related kidney disease. *Clin Exp Nephrol* 2011; **15**: 615-626 [PMID: 21898030 DOI: 10.1007/s10157-011-0521-2]
55. **Takahashi N**, Kawashima A, Fletcher JG, Chari ST. Renal involvement in patients with autoimmune pancreatitis: CT and MR imaging findings. *Radiology* 2007; **242**: 791-801 [PMID: 17229877 DOI: 10.1148/radiol.2423060003]
56. **Zoshima T**, Yamada K, Hara S, Mizushima I, Yamagishi M, Harada K, Sato Y, Kawano M. Multicentric Castleman Disease With Tubulointerstitial Nephritis Mimicking IgG4-related Disease: Two Case Reports. *Am J Surg Pathol* 2016; **40**: 495-501 [PMID: 26598921 DOI: 10.1097/PAS.0000000000000575]
57. **Mattoo H**, Della-Torre E, Mahajan VS, Stone JH, Pillai S. Circulating Th2 memory cells in IgG4-related disease are restricted to a defined subset of subjects with atopy. *Allergy* 2014; **69**: 399-402 [PMID: 24382311 DOI: 10.1111/all.12342]
58. **Kawano M**, Mizushima I, Yamaguchi Y, Imai N, Nakashima H, Nishi S, Hisano S, Yamanaka N, Yamamoto M, Takahashi H, Umehara H, Saito T, Saeki T. Immunohistochemical Characteristics of IgG4-Related Tubulointerstitial Nephritis: Detailed Analysis of 20 Japanese Cases. *Int J Rheumatol* 2012; **2012**: 609795 [PMID: 22899937 DOI: 10.1155/2012/609795]
59. **Morimoto J**, Hasegawa Y, Fukushima H, Uesugi N, Hisano S, Saito T, Kaneoka H. Membranoproliferative glomerulonephritis-like glomerular disease and concurrent tubulointerstitial nephritis complicating IgG4-related autoimmune pancreatitis. *Intern Med* 2009; **48**: 157-162 [PMID: 19182426 DOI: 10.2169/internalmedicine.48.1339]
60. **Alexander MP**, Larsen CP, Gibson IW, Nasr SH, Sethi S, Fidler ME, Raissian Y, Takahashi N, Chari S, Smyrk TC, Cornell LD. Membranous glomerulonephritis is a manifestation of IgG4-related disease. *Kidney Int* 2013; **83**: 455-462 [PMID: 23254897 DOI: 10.1038/ki.2012.382]
61. **Ong AC**, Fine LG. Loss of glomerular function and tubulointerstitial fibrosis: cause or effect? *Kidney Int* 1994; **45**: 345-351 [PMID: 8164418]
62. **Khosroshahi A**, Carruthers MN, Stone JH, Shinagare S, Sainani N, Hasserjian RP, Deshpande V. Rethinking Ormond's disease: "idiopathic" retroperitoneal fibrosis in the era of IgG4-related disease. *Medicine* (Baltimore) 2013; **92**: 82-91 [PMID: 23429355 DOI: 10.1097/MD.0b013e318289610f.]
63. **Kasashima S**, Zen Y, Kawashima A, Konishi K, Sasaki H, Endo M, Matsumoto Y, Kawakami K, Kasashima F, Moriya M, Kimura K, Ohtake H, Nakanuma Y. Inflammatory abdominal aortic aneurysm: close relationship to IgG4-related periaortitis. *Am J Surg Pathol* 2008; **32**: 197-204 [PMID: 18223321 DOI: 10.1097/PAS.0b013e3181342f0d]
64. **Masaki Y**, Shimizu H, Sato Nakamura T, Nakamura T, Nakajima A, Iwao Kawanami H, Miki M, Sakai T, Kawanami T, Fujita Y, Tanaka M, Fukushima T. IgG4-related disease: diagnostic methods and therapeutic strategies in Japan. *J Clin Exp Hematop* 2014; **54**: 95-101 [PMID: 25318941]
65. **Kamisawa T**, Zen Y, Pillai S, Stone JH. IgG4-related disease. *Lancet* 2015; **385**: 1460-1471 [PMID: 25481618 DOI: 10.1016/S0140-6736(14)60720-0]
66. **Khosroshahi A**, Stone JH. Treatment approaches to IgG4-related systemic disease. *Curr Opin Rheumatol* 2011; **23**: 67-71 [PMID: 21124087 DOI: 10.1097/BOR.0b013e328341a240].]
67. **Wallace ZS**, Mattoo H, Mahajan VS, Kulikova M, Lu L, Deshpande V, Choi HK, Pillai S, Stone JH. Predictors of disease relapse in IgG4-related disease following rituximab. *Rheumatology* (Oxford) 2016; **55**: 1000-1008 [PMID: 26888853 DOI: 10.1093/rheumatology/kev438.]
68. **Carruthers MN**, Topazian MD, Khosroshahi A, Witzig TE, Wallace ZS, Hart PA, Deshpande V, Smyrk TC, Chari S, Stone JH. Rituximab for IgG4-related disease: a prospective, open-label trial. *Ann Rheum Dis* 2015; **74**: 1171-1177 [PMID: 25667206 DOI: 10.1136/annrheumdis-2014-206605.]
69. **Della-Torre E**, Stone JH. "How I manage" IgG4-Related Disease. *J Clin Immunol* 2016; **36**: 754-763 [PMID: 27667138 DOI: 10.1007/s10875-016-0331-0]
70. **Haldar D**, Cockwell P, Richter AG, Roberts KJ, Hirschfield GM. An overview of the diagnosis and management of immunoglobulin G4-related disease. *CMAJ* 2016; **188**: 953-961 [PMID: 27325130 DOI: 10.1503/cmaj.151402]
71. **Saeki T**, Kawano M, Mizushima I, Yamamoto M, Wada Y, Ubara Y, Nakashima H, Ito T, Yamazaki H, Narita I, Saito T. Recovery of renal function after glucocorticoid therapy for IgG4-related kidney disease with renal dysfunction. *Clin Exp Nephrol* 2016; **20**: 87-93 [PMID: 26141243 DOI: 10.1007/s10157-015-1140-0]
72. **Saeki T**, Kawano M, Mizushima I, Yamamoto M, Wada Y, Nakashima H, Homma N, Tsubata Y, Takahashi H, Ito T, Yamazaki H, Saito T, Narita I. The clinical course of patients with IgG4-related kidney disease. *Kidney Int* 2013; **84**: 826-833 [PMID: 23698232 DOI: 10.1038/ki.2013.191.]
73. **Masaki Y**, Matsui S, Saeki T, Tsuboi H, Hirata S, Izumi Y, Miyashita T, Fujikawa K, Dobashi H, Susaki K, Morimoto H, Takagi K, Kawano M, Origuchi T, Wada Y, Takahashi N, Horikoshi M, Ogishima H, Suzuki Y, Kawanami T, Kawanami Iwao H, Sakai T, Fujita Y, Fukushima T, Saito M, Suzuki R, Morikawa Y, Yoshino T, Nakamura S, Kojima M, Kurose N, Sato Y, Tanaka Y, Sugai S, Sumida T. A multicenter phase II prospective clinical trial of glucocorticoid for patients with untreated IgG4-related disease. *Mod Rheumatol* 2017; **27**: 849-854 [PMID: 27846767 DOI: 10.1080/14397595.2016.1259602]
74. **Kamisawa T**, Okazaki K, Kawa S, Ito T, Inui K, Irie H, Nishino T, Notohara K, Nishimori I, Tanaka S, Nishiyama T, Suda K, Shiratori K, Tanaka M, Shimosegawa T; Working Committee of the Japan Pancreas Society and the Research Committee for Intractable Pancreatic Disease supported by the Ministry of Health, Labour and Welfare of Japan. Amendment of the Japanese Consensus Guidelines for Autoimmune Pancreatitis, 2013 III. Treatment and prognosis of autoimmune pancreatitis. *J Gastroenterol* 2014; **49**: 961-970 [PMID: 24639058 DOI: 10.1007/s00535-014-0945-z]
75. **Carruthers MN**, Stone JH, Deshpande V, Khosroshahi A. Development of an IgG4-RD Responder Index. *Int J Rheumatol* 2012; **2012**: 259408 [PMID: 22611406 DOI: 10.1155/2012/259408]
76. **Khosroshahi A**, Bloch DB, Deshpande V, Stone JH. Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease. *Arthritis Rheum* 2010; **62**: 1755-1762 [PMID: 20191576 DOI: 10.1002/art.27435]
77. **McMahon BA**, Novick T, Scheel PJ, Bagnasco S, Atta MG. Rituximab for the Treatment of IgG4-Related Tubulointerstitial Nephritis: Case Report and Review of the Literature. *Medicine* (Baltimore) 2015; **94**: e1366 [PMID: 26266393 DOI: 10.1097/MD.0000000000001366]
78. **Yamamoto M**, Awakawa T, Takahashi H. Is rituximab effective for IgG4-related disease in the long term? Experience of cases treated with rituximab for 4 years. *Ann Rheum Dis* 2015; **74**: e46 [PMID: 25862615 DOI: 10.1136/annrheumdis-2015-207625]
79. **Khan ML**, Colby TV, Viggiano RW, Fonseca R. Treatment with bortezomib of a patient having hyper IgG4 disease. *Clin Lymphoma Myeloma Leuk* 2010; **10**: 217-219 [PMID: 20511168 DOI: 10.3816/CLML.2010.n.034]
80. **Yamamoto M**, Takahashi H, Takano K, Shimizu Y, Sakurai N, Suzuki C, Naishiro Y, Yajima H, Awakawa T, Himi T, Nakase H. Efficacy of abatacept for IgG4-related disease over 8 mo. *Ann Rheum Dis* 2016; **75**: 1576-1578 [PMID: 27147710 DOI: 10.1136/annrheumdis-2016-209368]
81. **Balaskas K**, de Leval L, La Corte R, Zografos L, Guex-Crosier Y. Infliximab therapy for a severe case of IgG4-related ocular adnexal disorder recalcitrant to corticosteroid treatment. *Ocul Immunol Inflamm* 2012; **20**: 478-480 [PMID: 22946470 DOI: 10.3109/09273948.2012.714045]
82. **Deshpande V**, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, Klöppel G, Heathcote JG, Khosroshahi A, Ferry JA, Aalberse RC, Bloch DB, Brugge WR, Bateman AC, Carruthers MN, Chari ST, Cheuk W, Cornell LD, Fernandez-Del Castillo C, Forcione DG, Hamilos DL, Kamisawa T, Kasashima S, Kawa S, Kawano M, Lauwers GY, Masaki Y, Nakanuma Y, Notohara K, Okazaki K, Ryu JK, Saeki T, Sahani DV, Smyrk TC, Stone JR, Takahira M, Webster GJ, Yamamoto M, Zamboni G, Umehara H, Stone JH. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012; **25**: 1181-1192 [PMID: 22596100 DOI: 10.1038/modpathol.2012.72]
83. **Khosroshahi A**, Wallace ZS, Crowe JL, Akamizu T, Azumi A, Carruthers MN, Chari ST, Della-Torre E, Frulloni L, Goto H, Hart PA, Kamisawa T, Kawa S, Kawano M, Kim MH, Kodama Y, Kubota K, Lerch MM, Löhr M, Masaki Y, Matsui S, Mimori T, Nakamura S, Nakazawa T, Ohara H, Okazaki K, Ryu JH, Saeki T, Schleinitz N, Shimatsu A, Shimosegawa T, Takahashi H, Takahira M, Tanaka A, Topazian M, Umehara H, Webster GJ, Witzig TE, Yamamoto M, Zhang W, Chiba T, Stone JH; Second International Symposium on IgG4-Related Disease. International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease. *Arthritis Rheumatol* 2015; **67**: 1688-1699 [PMID: 25809420 DOI: 10.1002/art.39132]
84. **Jeong HJ**, Shin SJ, Lim BJ. Overview of IgG4-Related Tubulointerstitial Nephritis and Its Mimickers. *J Pathol Transl Med* 2016; **50**: 26-36 [PMID: 26666884 DOI: 10.4132/jptm.2015.11.09.]
85. **Ota M**, Katsuyama Y, Hamano H, Umemura T, Kimura A, Yoshizawa K, Kiyosawa K, Fukushima H, Bahram S, Inoko H, Kawa S. Two critical genes (HLA-DRB1 and ABCF1)in the HLA region are associated with the susceptibility to autoimmune pancreatitis. *Immunogenetics* 2007; **59**: 45-52 [PMID: 17119950 DOI: 10.1007/s00251-006-0178-2]
86. **Deshpande V**, Chicano S, Finkelberg D, Selig MK, Mino-Kenudson M, Brugge WR, Colvin RB, Lauwers GY. Autoimmune pancreatitis: a systemic immune complex mediated disease. *Am J Surg Pathol* 2006; **30**: 1537-1545 [PMID: 17122509 DOI: 10.1097/01.pas.0000213331.09864.2c]
87. **Zen Y**, Fujii T, Harada K, Kawano M, Yamada K, Takahira M, Nakanuma Y. Th2 and regulatory immune reactions are increased in immunoglobin G4-related sclerosing pancreatitis and cholangitis. *Hepatology* 2007; **45**: 1538-1546 [PMID: 17518371 DOI: 10.1002/hep.21697]
88. **Della Torre E**, Mattoo H, Mahajan VS, Carruthers M, Pillai S, Stone JH. Prevalence of atopy, eosinophilia, and IgE elevation in IgG4-related disease. *Allergy* 2014; **69**: 269-272 [PMID: 24266692 DOI: 10.1111/all.12320]
89. **Mattoo H**, Della-Torre E, Mahajan VS, Stone JH, Pillai S. Circulating Th2 memory cells in IgG4-related disease are restricted to a defined subset of subjects with atopy. *Allergy* 2014; **69**: 399-402 [PMID: 24382311 DOI: 10.1111/all.12342]
90. **Umehara H**, Nakajima A, Nakamura T, Kawanami T, Tanaka M, Dong L, Kawano M. IgG4-related disease and its pathogenesis-cross-talk between innate and acquired immunity. *Int Immunol* 2014; **26**: 585-595 [PMID: 25024397 DOI: 10.1093/intimm/dxu074]

**P-Reviewer:** Kute VBB, Pedersen EB, Shrestha BM, Tanaka S, Yong D **S-Editor:** Kong JX **L-Editor: E-Editor:**

**Specialty type:** Urology and nephrology

**Country of origin:** Italy

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): B, B, B, B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0



**Figure 1 Pathogenesis of immunoglobulin G4-related disease**. The renal biopsy shows interstitial and storiform fibrosis in a patient affected by IgG4-related tubulointerstitial nephritis. CTL-4: Cytotoxic T-lymphocyte-associated antigen 4; FcR-3: Fc receptor like 3; TNFα: Tumor necrosis factor alpha; NODR: Nucleotide-activating factor belonging to the tumor necrosis factor (TNF) family; TLR2: Toll-like receptor 2; BAFF: B cell activating factor; APRIL: A proliferative-inducing ligand; TGFβ: Tumor growth factor beta.

**Table 1 Representative organ manifestations in IgG4-related disease**

|  |  |
| --- | --- |
| Organs adopted at the 1st International symposium in Boston in 2011 | |
| Pancreas | Lymphoplasmacytic sclerosing pancreatitis |
| Eye/orbit/lacrimal glands | Dacryadenitis/orbital inflammation/pseudotumour |
| Salivary glands | Sialoadenitis/Mikulicz disease/Kuttner’s tumor |
| Aorta/arteries | Aortitis/periaortitis/arteritis |
| Mediastinum/retroperitoneum | Mediastinitis/retroperitoneal fibrosis/mesenteritis |
| Kidney | Tubulointerstitial nephritis/renal pyelitis |
| Pachimeninges/hypophysis | Pachimeningitis/hypophysitis |
| Lung | Lung disease/inflammatory pseudotumor |
| Pleura/pericardium | Pleuritis/pericarditis |
| Breast | Mastitis |
| Bile ducts/gall bladder/ liver | Sclerosing cholangitis/cholecystitis/hepatopathy |
| Prostate | Prostatitis |
| Skin | Skin disease/pseudolymphoma |
| Limph node | Lymphadenopathy |
| Organs newly recognized after the Boston meeting | |
| Nerve | Infraorbital nerve swelling |
| Paranasal sinus | Chronic rhinosinusitis |
| Testis/paratestis | Paratesticular pseudotumour |
| Ureter | Ureteritis |
| Urethra | Urethritis |
| Urinary bladder | Interstitial cystitis |

**Table 2 Conditions once regarded as individual disorders now recognized to be part of IgG4-related disease**

Autoimmune pancreatitis (lymphoplasmacytic sclerosino pancreatitis)

Eosinophilic angiocentric fibrosis (affecting the orbits and upper respiratory tract)

Fibrosing mediastinitis

Hypertrophic pachymeningitis

Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits

Inflammatory pseudotumour (affecting the orbits, lungs, kidneys, and other organs)

Küttner’s tumor (affecting the submandibular glands)

Mikulicz’s disease (affecting the salivary and lacrimal glands)

Multifocal fibrosclerosis (commonly affecting the orbits, thyroid gland, retroperitoneum, mediastinum, and other tissues and organs)

Periaortitis and periarteritis

Inflammatory aortic aneurysm

Retroperitoneal fibrosis (Ormond’s disease)

Riedel’s thyroiditis

Sclerosing mesenteritis

**Table 3 Mimickers of immunoglobulin G4-related disease**

|  |  |  |
| --- | --- | --- |
| **Autoimmune** | **Malignancy** | **Other** |
| Antineutrophil cytoplasmic antibody-associated vasculitis | Adenocarcinoma and squamous cell carcinoma | Castleman’s disease |
| Granulomatosis with Polyangitis | Extranodal marginal zone lymphoma | Cutaneous plasmocytosis |
| Eosinophilic Granulomatosis with Polyangitis | Inflammatory myofibroblastic tumor | Erdheim-chester disease |
| Microscopic Polyangitis | Lymphoplasmocytic lymphoma | Inflammatory bowel disease |
| Sarcoidosis | Lymphoproliferative disease | Perforating collagenosis |
| Sjogren’s disease | Follicular lymphoma | Primary sclerosing Cholangitis |
|  |  | Rhinosinusitis |
|  |  | Rosai-dorfman disease |
|  |  | Splenic sclerosing Angiomatoid nodular transformation |
|  |  | Xanthogranuloma |

**Table 4 Clinical presentation of immunoglobulin G4-related disease** **per site of involvement**

|  |  |  |
| --- | --- | --- |
| **Organ system** | **Nomenclature** | **Clinical features** |
| Orbit | IgG4-related ophthalmic disease  IgG4-related orbital inflammatory pseudo-tumor  IgG4-related pan-orbital inflammation  IgG4-related orbital myositis | Swelling of orbital tissue and proptosis |
| Lacrimal gland | IgG4-related dacryadenitis | Bilateral swelling of the glands and impaired production of secretion |
| Salivary gland | IgG4-related sialoadenitis IgG4-related parotitis  IgG4-ralated submandibular gland disease | Bilateral swelling of the glands and impaired production of secretion |
| Thyroid | IgG4-related thyroid disease | Hypothyroidism, neck pain, dysphagia, dyspnea |
| Liver | IgG4-related hepatopathy | Jaundice, right upper quadrant mass |
| Biliary tract and gall bladder | IgG4-related sclerosing cholangitis  IgG4-related cholecystitis | Jaundice, pruritus, cholestasis |
| Blood vessels | IgG4-related aortitis/periaortitis  IgG4-related periarteritis | Chest pain, dyspnea |
| Retroperitoneal fibrosis | IgG4-related retroperitoneal fibrosis | Flank pain, obstructive symptoms, peripheral edema |
| Kidneys | IgG4-related kidney disease  Tubulo-interstitial nephritis secondary to IgG4-related disease | Hematuria, proteinuria, hypocomplementemia, chronic renal failure |
| Skin | IgG4-related skin disease | Papulonodular lesions, plaques, purpura |

**Table 5 Major histopathological features associated with immunoglobulin G4-related disease**

Dense lymphoplasmacytic infiltrate

Fibrosis, arranged at least focally in a storiform pattern

Obliterative phlebitis

Phlebitis without obliteration of the lumen

Increased number of eosinophils

**Table 6 Two proposed criteria for IgG4-TIN by the Mayo Clinic and the Japanese Society of Nephrology**

|  |  |  |
| --- | --- | --- |
| **Criterion** | **The Mayo Clinic criteria** | **JSN criteria** |
| Histology | Plasma cell-rich TIN with > 10 IgG4+ plasma cells/HPF in the most concentrated field (mandatory criterion)  TBM immune complex deposits by immunofluorescence, immunochemistry, and/or electron microscopy | Dense lymphoplasmacytic infiltrate with > 10 IgG4+ plasma cells/HPF and/or IgG4/IgG+ plasma cell ratio of > 40%;  Characteristic storiform fibrosis |
| Imaging | Small peripheral low-attenuation cortical nodules, round or wedge-shaped lesions, or diffuse patchy involvement | Multiple low-density lesions or enhanced CT, diffuse kidney enlargement, hypovascular solitary nodule, hypertrophic lesion of the renal pelvic wall |
| Serology | Elevated serum IgG4 or total IgG level | Elevated serum IgG4 or total IgG level |
| Clinical features | None | Clinical or laboratory evidence of kidney damage |
| Other organ involvement | Characteristic findings of IgG4-RD in other organs | Characteristic findings of IgG4-RD in other organs |
| Definite IgG4-TIN | The histologic feature and at least one other feature from imaging, serology or other organ involvement | The histologic feature (a and b) and at least two of other features from imaging, serology or other organ involvement |

IgG4-RD: Immunoglobulin G4-related disease; IgG4-TIN: Immunoglobulin G4-related tubulointerstitial nephritis.