Review

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IgG4-related cholangitis – a mimicker of fibrosing and malignant cholangiopathies

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Summary

IgG4-related cholangitis (IRC) is the major hepatobiliary manifestation of IgG4-related disease (IgG4-RD), a systemic fibroinflammatory disorder. The pathogenesis of IgG4-RD and IRC is currently viewed as multifactorial, as there is evidence of a genetic predisposition while environmental factors, such as blue-collar work, are major risk factors. Various autoantigens have been described in IgG4-RD, including annexin A11 and laminin 511-E8, proteins which may exert a partially protective function in cholangiocytes by enhancing secretion and barrier function, respectively. For the other recently described autoantigens, galectin-3 and prohibitin 1, a distinct role in cholangiocytes appears less apparent. In relation to these autoantigens, oligoclonal expansions of IgG4$^+$ plasmablasts are present in patients with IRC and disappear upon successful treatment. More recently, specific T-cell subtypes including regulatory T cells, follicular T helper 2 cells, peripheral T helper cells and cytotoxic CD8$^+$ and CD4$^+$ SLAMF7$^+$ T cells have been implicated in the pathogenesis of IgG4-RD. The clinical presentation of IRC often mimics other biliary diseases such as primary sclerosing cholangitis or cholangiocarcinoma, which may lead to inappropriate medical and potentially invalidating surgical interventions. As specific biomarkers are lacking, diagnosis is made according to the HISORt criteria comprising histopathology, imaging, serology, other organ manifestations and response to therapy. Treatment of IRC aims to prevent or alleviate organ damage and to improve symptoms and consists of (i) remission induction, (ii) remission maintenance and (iii) long-term management. Glucocorticosteroids are highly effective for remission induction, after which immunomodulators can be introduced for maintenance of remission as glucocorticosteroid-sparing alternatives. Increased insight into the pathogenesis of IRC will lead to improved diagnosis and novel therapeutic strategies in the future.

Introduction

IgG4-related disease (IgG4-RD) is a rare systemic fibroinflammatory disorder of unknown pathogenesis which can affect almost every secretory organ in the human body.[1,2] Since its first description as a multiorgan fibroinflammatory autoimmune disease in 2003,[3] numerous manifestations of the head and neck, thorax, abdomen, and pelvic organs have been reported (Table 1).[1] Already in the 19th century, various organ manifestations of IgG4-RD such as Mikulicz's disease, Küttner's tumour or Riedel's struma were described for the first time. IgG4-related cholangitis (IRC), although only described in 2004 as IgG4-related sclerosing cholangitis with or without hepatic inflammatory pseudotumour[4] and defined in 2007 as IgG4-associated cholangitis,[5] was most probably first reported 140 years earlier. In 1867, a 60-year-old previously healthy factory employee from Basel (Switzerland) developed severe, and after a few months fatal, hepatobiliary injury with jaundice and weight loss.[6] Autopsy revealed an enlarged, dark brown-green discoloured liver with a smooth surface, marked fibrotic longitudinal thickening (up to 3 mm) of the common hepatic duct wall and the right and left hepatic ducts (without any microscopic evidence of malignancy), cystic dilatation of the intrahepatic ducts (without intrahepatic stenoses or pruning), a small gallbladder, an indurated and enlarged pancreas, but a barely enlarged spleen and no evidence of colitis. These findings are compatible with IRC and IgG4-RD of the digestive tract rather than a first description of primary sclerosing cholangitis (PSC) as assumed over decades. Case reports from 60 years ago documented the combined appearance of sclerosing cholangitis with Riedel's struma and retroperitoneal fibrosis, a typical organ pattern of IgG4-RD manifestations.[7] In the late nineties, the first five men with a 'sclerosing pancreato-cholangitis' were described as responding well to glucocorticosteroids, today fulfilling the diagnostic criteria of IRC and type 1 autoimmune pancreatitis (AIP).[8,9]

Keywords: Autoimmune pancreatitis; biliary bicarbonate umbrella; cholangiocarcinoma; CCA; IgG4-RD; IgG4-related disease; primary sclerosing cholangitis; PSC.
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Keypoints

- Genetic predisposition and blue-collar work are risk factors for development of IRC.
- Oligoclonal expansions of $IgG4^+$ plasmablasts in IRC disappear upon treatment.
- IRC autoantigens annexin A11 and laminin 511-E8 strengthen cholangiocyte defence.
- Multiple T cell lineages have a pathogenic role in IgG4-RD.
- The HISORt criteria are the standard for the diagnosis of IRC.
- Glucocorticosteroids and immunomodulators are cornerstones of IRC treatment.

IRC with or without inflammatory pseudotumour is the major hepatobiliary manifestation of IgG4-RD.[1,2] The clinical presentation of IRC may mimic other hepatobiliary diseases such as PSC or cholangiocarcinoma (CCA). IRC is an under-recognised and often misdiagnosed disease as no single accurate diagnostic test is available to distinguish IRC from PSC or CCA. Misdiagnosis of IRC carries the risk of inappropriate medical and potentially invalidating surgical interventions.[10] IRC is mainly diagnosed in elderly men and is closely associated with type 1 AIP, the most frequent manifestation of IgG4-RD of the digestive tract, in >90% of affected individuals in well-characterized cohorts.[2,11]

In recent years, IRC has drawn remarkable clinical and scientific attention and notable advances have been made in the field. Herein, we review the actual state of knowledge on the pathophysiology, clinical presentation, diagnosis (and differential diagnosis) and treatment of IRC, one of the major manifestations of systemic IgG4-related disease.

The pathogenesis of IgG4-related cholangitis (and IgG4-RD)

The potential role of genetic, microbial and environmental factors

The pathogenesis of IgG4-RD is largely unknown, but it is conceivable that both host and environmental factors influence susceptibility and disease progression (Fig. 1). Similar to other autoimmune diseases, certain HLA variants are associated with

Table 1. Organ manifestations of IgG4-RD associated with IRC.

Organ	Nomenclature[160]	Involvement in IRC*,[11,96,97,148,150,161–164]
Pancreas	Type I AIP (IgG4-related pancreatitis)	92%
Salivary glands	IgG4-related sialadenitis	5%, 13%, 17%, 18%, 26%
Parotid glands	IgG4-related parotitis	
Submandibular glands	IgG4-related submandibular gland disease	
Kidney	IgG4-related kidney disease (subtypes)	1%, 5%, 9%, 11%, 26%
Tubuli	Tubulointerstitial nephritis	
Glomeruli	Membranous glomerulonephritis	
Pyelum	Renal pyelitis	
Retroperitoneum	IgG4-related retroperitoneal fibrosis	3%, 5%, 7%, 9%, 10%, 17%
Lymph nodes	IgG4-related lymphadenopathy	2%, 4%, 8%, 9%, 15%, 43%
Lacrimal glands	IgG4-related dacryoadenitis	8%
Lung	IgG4-related lung disease	1%, 6%, 7%
Eyes	IgG4-related ophthalmic disease	2%, 15%
Aorta	IgG4-related aortitis/periaortitis	1%, 6%
Arteries	IgG4-related periarteritis	6%
Gallbladder	IgG4-related cholecystitis	2%, 7%
Pleura	IgG4-related pleuritis	5%
Hypophysis	IgG4-related hypophysitis	2%
Stomach**	IgG4-related gastric disease	2%
Prostate	IgG4-related prostatitis	2%
Joints**	IgG4-related synovitis	1%
Liver***	IgG4-related hepatopathy	1%
Testis**	IgG4-related testicular disease	?
Pachymeninges	IgG4-related pachymeningitis	?
Thyroid gland	IgG4-related thyroiditis	?
Mediastinum	IgG4-related mediastinitis	?
Pericardium	IgG4-related pericarditis	?
Breast	IgG4-related mastitis	?
Mesentery	IgG4-related mesenteritis	?
Intestine**	IgG4-related intestinal disease	?
Ileal pouch**	IgG4-related pouchitis	?
Skin	IgG4-related skin disease	?

The different organs that can be affected by IgG4-RD (left column), their official nomenclature (middle column), and the percentage of people with IRC affected by IgG4-RD in the respective organs.

*Reported percentages likely differ due to cohort varieties in case-ascertainment (biopsy proven yes/no, imaging modality used, extent of search of other organ involvement), size of the cohort and ethnicities.

**No official nomenclature established.

***Debated whether a distinct IgG4-RD manifestation or a consequence of IRC.

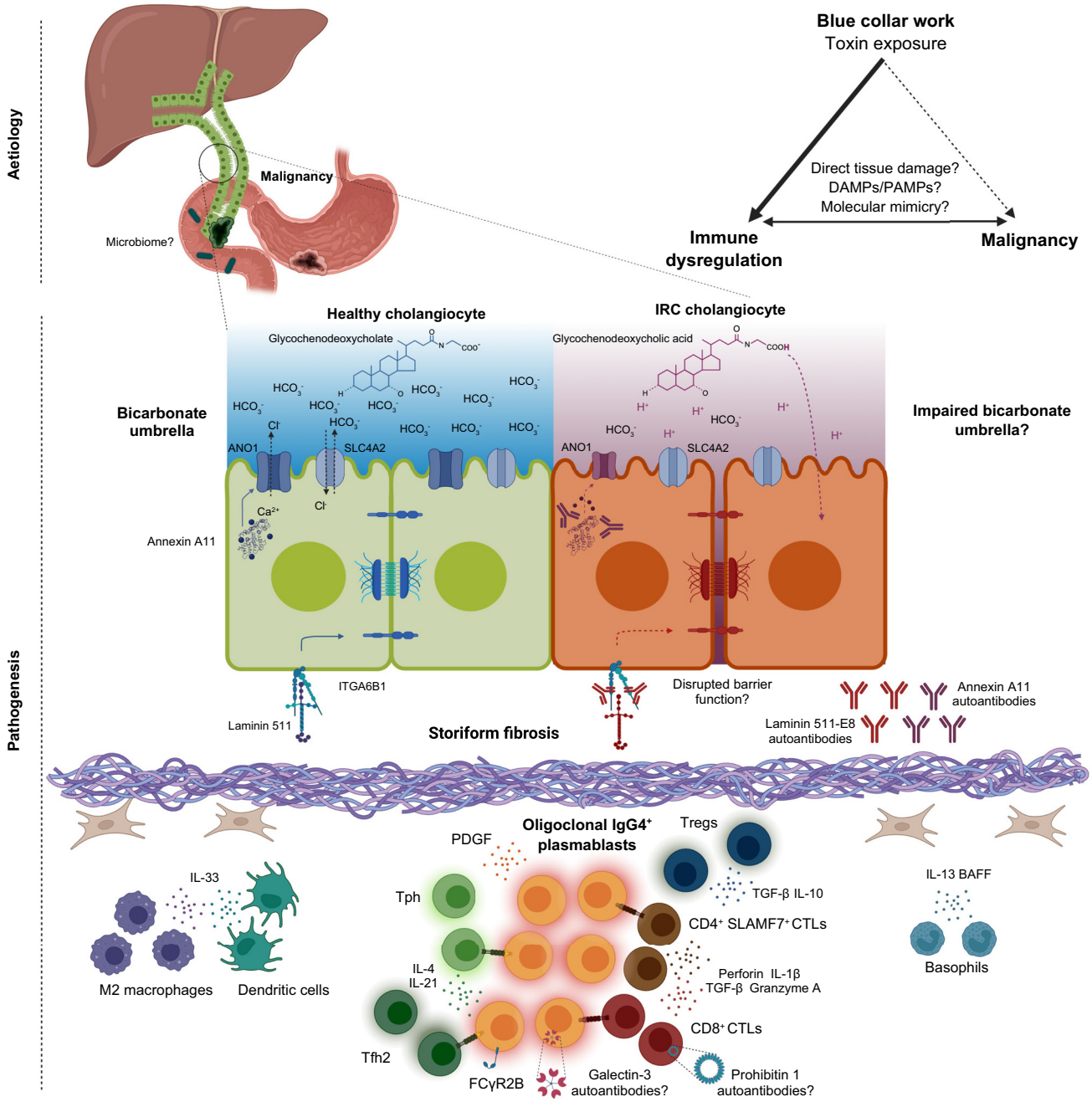

Fig. 1. Pathogenic concept of IgG4-related cholangitis. (Upper) Hypothesised aetiological factors that lead to the characteristic immunological dysregulation of IRC. Exposure to (occupational) toxins during blue-collar work, autoantigens and/or DAMPs/PAMPs which are possibly released by malignancies and the microbiome are hypothesised to function as aetiological agents, possibly through mechanisms of molecular mimicry. (Lower) The immune dysregulation and its potential effect on cholangiocellular function. After activation of the innate immune system by aetiological agents, an extensive dysregulation of the adaptive immune system occurs in IRC. Oligoclonal IgG1$^+$ and IgG4$^+$ plasmablasts could produce autoantibodies against annexin A11, laminin 511-E8, galectin-3 and prohibitin 1. Autoantibodies against annexin A11 may disrupt the protective bicarbonate umbrella by inhibiting the trafficking of the Cl^- channel ANO1 to the apical cholangiocyte membrane. Autoantibodies against laminin 511-E8 may block its binding to membrane receptors (ITGA6B1), thereby impairing cholangiocellular barrier function. The role of galectin-3 and prohibitin 1 autoantibodies is unclear at present but could potentially be in the immunological context of B and T cells. Additionally, oligoclonal IgG4$^+$ plasmablasts could perpetuate the immune dysregulation due to stimulation and reactivation of oligoclonal CD4$^+$ SLAMF7$^+$ cytotoxic T cells and could contribute to the formation of storiform fibrosis by secreting PDGF. ANO1, anoctamin 1; BAFF, B-cell activation factor; Ca^{2+}, calcium; CD4, cluster of differentiation; Cl^-, chloride; CTLs, cytotoxic T lymphocytes; DAMPs, damage-associated molecular patterns; FCγR2B, Fc γ receptor 2 B; HCO_3^-, bicarbonate; IL, interleukin; IRC, IgG4-related cholangitis; ITGA6B1, integrin α6β1; PAMPs, pathogen-associated molecular patterns; SLAMF7, signalling lymphocytic activation molecule family member 7; SLC4A2, solute carrier family 4 member 2; Tfh, follicular T helper 2 cells; TGF-β, Transforming growth factor-β; Tph, peripheral T helper cells; Tregs, regulatory T cells. Image created with BioRender.

IgG4-RD, suggesting that antigen presentation and recognition play an important role.[12] A recent genome-wide association study among 835 Japanese citizens with various manifestations of IgG4-RD identified *HLA-DRB1*, but also the non-HLA gene *FCGR2B* as susceptibility loci for IgG4-RD.[13] Notably, FCγR2B is the only FCγ receptor family member expressed in B cells. It has inhibitory functions in contrast to other FCγ receptors and is thought to play a role in the elimination of autoreactive B cells.[14] Thus, *FCGR2B* gene variants may weaken suppressive effects on the immune response and increase susceptibility to autoimmunity.[14] Another recent genome-wide association study found that *IL1R1* genetic polymorphisms contributed to IgG4-related periaortitis/periarteritis, suggesting the possibility that certain genetic factors might affect the risk of specific IgG4-RD manifestations.[15] Additionally, in a small cohort of individuals with type I AIP, polymorphisms in *CTLA4* (a gene coding for an inhibitory receptor expressed on activated memory T cells) were identified.[16] For IRC, comparable findings are not yet reported, and are therefore of particular interest when designing future genetic analyses.

The potential pathogenic role of the human microbiota in the development of IRC has recently been addressed. Faecal analysis from people with IRC, PSC and healthy controls revealed reduced alpha diversity and a shift in microbial communities in IRC and PSC.[17] Notably, next to common variations in microbial composition and metabolic activity in IRC and PSC, integrative analyses also identified distinct host-microbe associations. A dysregulated response to the intestinal microbiome has previously been hypothesized to play a role in the pathogenesis of IRC via activation of Toll-like receptors,[18] and intestinal dysbiosis plays an essential role in the development of type I AIP in experimental mouse models.[19]

We identified 'blue-collar work' and long-term, often lifelong exposure to occupational toxins as independent risk factors for the development of IRC and type I AIP.[20,21] An occupational history of 'blue-collar work' was reported by 68% of patients with IgG4-RD, compared to only 39% of age- and sex-matched controls (odds ratio [OR] 3.66; CI 2.18–6.13; n = 404; p <0.0001). Industrial contaminants appeared to potentially drive the elevated risk, including asbestos and VDGF (vapours, dusts, industrial gases and fumes).[20] Typical work environments included exposure to oil products, metal industry, truck driving, automobile repair, woodworking or painting. Notably, these work profiles are strongly male dominated. We speculate that male-dominated 'blue-collar work' may contribute to the remarkable overrepresentation of men (80-85%) among people with IRC and type 1 AIP. In line with our findings, cigarette smoking was recently identified to be more common among a large group of patients from a rheumatology unit with different organ manifestations of IgG4-RD compared to matched controls, but this relation was primarily seen in people with IgG4-related retroperitoneal fibrosis.[22] Nevertheless, these data suggest that smoking, like VDGF, may be a potential modifiable risk factor.

How exposure to (occupational) toxins plays a role in the pathogenesis of IgG4-RD can only be speculated upon at this time: (i) Chemical agents might directly damage tissues, exposing the immune system to autoantigens and damage-associated molecular patterns which fuel an autoimmune response. (ii) Alternatively, toxic substances could trigger autoreactive B and T cells through molecular mimicry. (iii) Toxins could cause genetic and epigenetic changes, skewing the immune response towards autoimmunity. (iv) Toxin exposure could lead to the development of malignancies,[23] which have been proposed to play a role in the pathogenesis of IgG4-RD. Nonetheless, toxin exposure would lead to a break in self-tolerance with both B and T cells at play.

The potential role of malignancies

Malignancy prior to the onset of IgG4-RD is a possible predisposing factor in a subset of patients with multi-organ IgG4-RD.[24] A history of malignancy was three times more prevalent in people with manifestations of IgG4-RD (mainly outside the digestive tract – 19% type I AIP) compared to matched controls.[24] In a recent Japanese study, 32% of people with IRC had a history of malignancy before the development of IgG4-RD.[25] One might speculate about the potential pathophysiological mechanisms linking malignant disease to the subsequent development of IgG4-RD: (i) Cancer-induced autoimmunity has been discussed for several rheumatic diseases and appears plausible as a stimulus for an abnormal immune response against tumour autoantigens in antigen-expressing organs. (ii) Cancer and IgG4-RD might share the same risk factors (such as toxin exposure) or have pathological pathways in common. (iii) Medical therapies administered to treat malignancies might induce tumour destruction and tumour destruction-related autoimmune responses against tumour peptides, leading to IgG4-RD of non-affected organs.

The potential role of autoantigens

Our finding of dominant oligoclonal $IgG4^+$ B cell populations in sera and affected tissues of patients with IRC raised the suspicion that the immune response in IgG4-RD could be targeting specific autoantigens.[26] This has led to the discovery of numerous autoantigens and autoantibodies (Table 2). Most of these autoantibodies are not disease specific. In IRC, the presence of autoantibodies against annexin A11, laminin 511-E8, galectin-3 and prohibitin 1 has been confirmed, in line with the expression of these autoantigens in cholangiocytes (Figs 1 and 2).

The potential pathogenicity of these autoantibodies has been strongly supported by the observation that mice injected with IgG isolated from sera of patients with IgG4-RD develop typical organ lesions.[27] Furthermore, patients who were positive for multiple autoantibodies were shown to have more severe disease,[28] and autoantibody levels decreased upon successful treatment.[29,30] With regard to the pathogenicity of IgG subtypes, some data suggest a more detrimental role for IgG1 and a possible protective role of IgG4 autoantibodies.[27,31]

Autoantibodies could potentially contribute to the pathogenesis of IRC by directly affecting the function of the targeted autoantigen, or by eliciting an excessive immune response after binding of the autoantibody.

The first identified IgG4/IgG1 target autoantigen in IRC is annexin A11.[31] Annexin A11 has been implicated in Ca^{2+}-

Table 2. Identified autoantigens in IgG4-RD.

Autoantigen	Organ manifestation	Positivity in IgG4-RD	Positivity in other diseases	Detection method	Autoantibody subtype
Carbonic anhydrase I[165]	Type I AIP	21%	Sjögren's syndrome[165] Aplastic anaemia like syndrome[166] Behçet's disease[167]	ELISA	IgG
Carbonic anhydrase II[165]	Type I AIP	25%-73%	Primary sclerosing cholangitis Sjögren's syndrome[165] Diabetes type II[168]	ELISA	IgG
Carbonic anhydrase IV[169]	Type I AIP	27%	Sjögren's syndrome[169] Pancreatic cancer[169] Systemic lupus erythematosus[170]	ELISA	IgG
Lactoferrin[171–172]	Type I AIP	54%-76%	Sjögren's syndrome[171] Primary sclerosing cholangitis[173]	ELISA	IgG
Pancreatic secretory trypsin inhibitor[172]	Type I AIP	42% (ELISA) 31% (WB)	-	ELISA WB	IgG IgG1
Amylase alpha-2A[174]	Type I AIP	100%	Diabetes type I and II[174]	ELISA	IgG
Heat shock protein 10[175]	Type I AIP	92%	Diabetes type I[175] Chronic alcohol-related pancreatitis[175] Pancreatic cancer[175]	ELISA	IgG
Trypsinogen[176]	Type I AIP	79%	Chronic (alcohol-related) pancreatitis[176]	ELISA	IgG
Plasminogen binding protein[177]	Type I AIP	95%	Pancreatic cancer[177]	DELFIA	IgG
Type IV collagen[178]	Type I AIP	55%	Crohn's disease[178] Pancreatic cancer[178]	WB/ELISA	IgG
IL-1RA[179]	Type I AIP, aorta, kidney, lacrimal-, salivary glands, liver, retroperitoneum	16%	Systemic lupus erythematosus Rheumatoid arthritis	ELISA	IgG1, IgG2, IgG3, IgG4
Prohibitin 1[56]	Type I AIP Mikulicz's disease Retroperitoneum Other probable IgG4-RD IRC	74% 53% 55% 90% 62%*	Primary sclerosing cholangitis* Sjögren's syndrome[56] Behçet disease[180] Idiopathic pulmonary fibrosis[28]	ELISA	IgG
Laminin 511-E8[29]	Type I AIP IRC	51% 13%*	Idiopathic pulmonary fibrosis[28]	ELISA	IgG (IgG1, IgG4) IgG
Integrin alpha6 beta1[29]	Type I AIP	16%	-	ELISA	IgG
Galectin-3[30]	Type I AIP, IRC, lacrimal and salivary glands Lungs, retroperitoneum, kidney Retroperitoneum, kidney, IRC	28% (IgG4) 10% (IgE) 13%* (IgG)	Idiopathic pulmonary fibrosis[30] Systemic lupus erythematosus[181] Crohn's disease[182]	ELISA	IgG4, IgE
Annexin A11[31]	Type I AIP, IRC	18%	Idiopathic pulmonary fibrosis[28] Systemic lupus erythematosus[183] Antiphospholipid syndrome[183]	WB	IgG1, IgG4

Overview of the identified autoantigens in IgG4-RD (first column), the IgG4-RD organ manifestations in which they were detected (second column), percentage of patients tested positive in the respective organ manifestation (third column), respective autoantibody positivity in other diseases (fourth column), detection method used (fifth column) and the autoantibody subtype detected (sixth column).
AIP, autoimmune pancreatitis; DELFIA, dissociation-enhanced lanthanide fluorescence immunoassay; ELISA, enzyme-linked immunosorbent assay; IRC, IgG4-related cholangitis; WB, western blot.
*Submitted for publication.

dependent membrane trafficking in various cell types.[32,33] In cholangiocytes, this process is important for the maintenance of an apical defence mechanism against the toxic effects of glycine-conjugated bile acids, referred to as the 'biliary HCO_3^- umbrella'.[34–36] Glycine-conjugated bile acid permeation due to an impaired biliary HCO_3^- umbrella likely contributes to the progressive bile duct destruction found in immune-mediated cholangiopathies.[37–39] Annexin A11 is predominantly expressed in cholangiocytes within the human liver, the cell type that is mainly affected in IRC. Furthermore, in human cholangiocytes annexin A11 mediates the plasma membrane insertion of the Ca^{2+}-sensitive Cl^- channel anoctamin-1 (ANO1). ANO1 is crucial for the formation of a stable biliary HCO_3^- umbrella as it creates the Cl^- gradient necessary for apical HCO_3^- secretion. The membrane insertion of ANO1 by annexin A11 was markedly inhibited after human cholangiocytes were incubated with cholestatic IRC serum with high titers of anti-annexin A11 IgG1 and IgG4 autoantibodies, but not after incubation with cholestatic PSC control sera.[40] Thus, IgG1/IgG4-mediated autoreactivity against annexin A11 may contribute to the pathogenesis of IRC by weakening the biliary HCO_3^- umbrella.

Autoantibodies against laminin 511-E8 were previously detected in just over 50% of patients with type I AIP.[29] We also confirmed the presence of laminin 511-E8 autoantibodies in IRC (submitted for publication).[41] Laminins are heterotrimeric

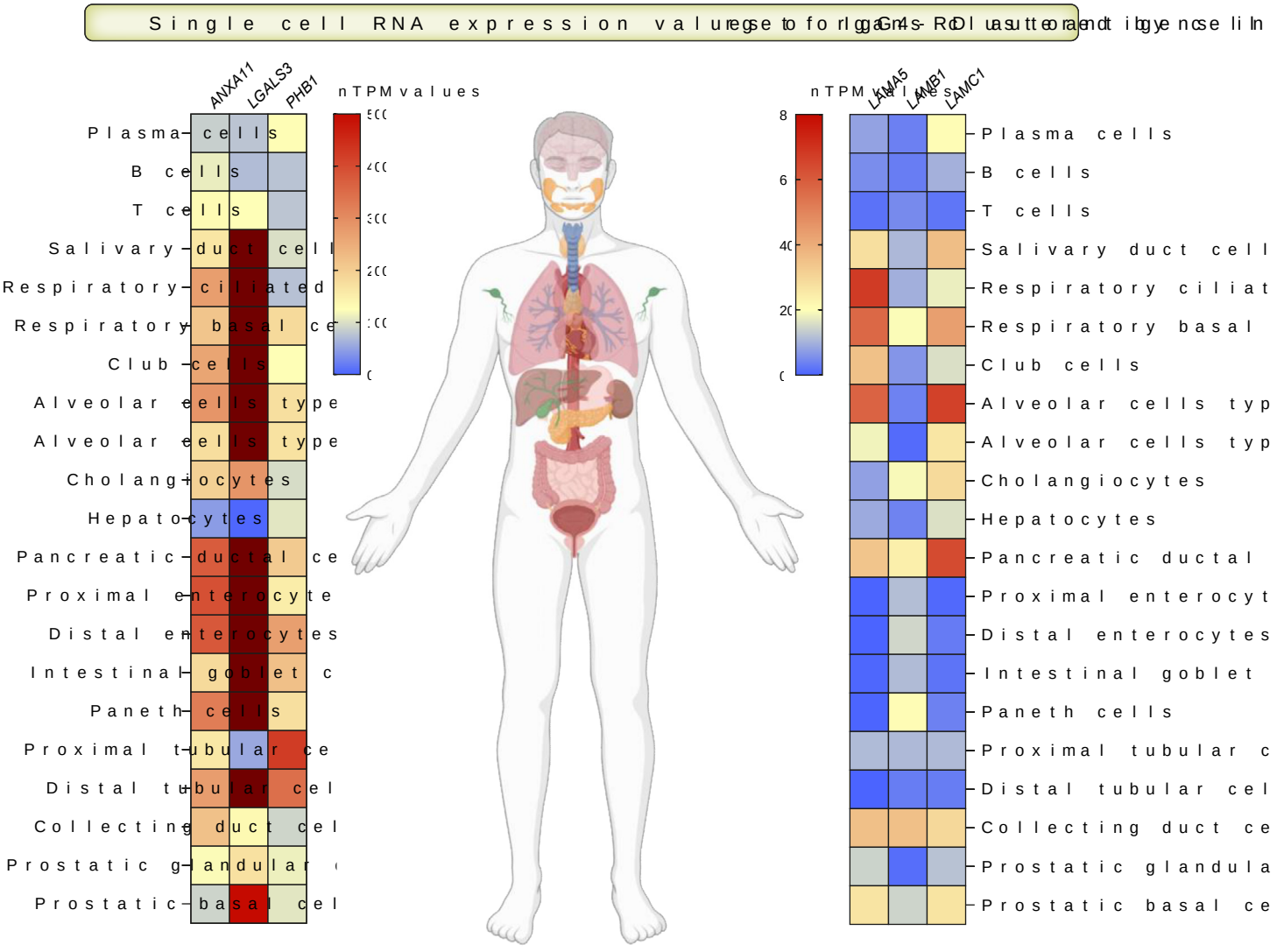

Fig. 2. Cellular gene expression of autoantigens in target organs of IgG4-RD. Single-cell RNA expression of the confirmed IRC autoantigens annexin A11 (*ANXA11*), galectin-3 (*LGALS3*), prohibitin 1 (*PHB1*) (left heatmap) and the laminin 511 gene constituents *LAMA5*, *LAMB1* and *LAMC1* (right heatmap). Note the relatively low expression of the IgG4-RD autoantigens in hepatocytes compared to cholangiocytes. Publicly available single cell RNA-sequencing data was acquired from the single cell atlas as part of the human protein atlas platform in March 2023. Inclusion criteria of the datasets, clustering of cells, defining cell types and normalisation are described in detail (https://www.proteinatlas.org/about/assays+annotation#singlecell_rna). Data are presented as nTPM. The dark red expression values of *LGALS3* exceed the scale of 500 nTPM. *ANXA11*, annexin A11; IRC, IgG4-related cholangitis; *LAMA5*, laminin alpha 5; *LAMB1*, laminin beta 1; *LAMC1*, laminin gamma 1; *LGALS3*, galectin-3; *PHB1*, prohibitin 1; nTPM, normalized transcripts per million.

extracellular matrix proteins, with laminin 511-E8 being the truncated form of laminin 511 and an important binding partner for integrin α6β1.[42,43] Notably, of the type I AIP patient sera where no anti-laminin 511-E8 antibodies were detected, four patients had autoantibodies directed against integrin α6β1.[29] Laminin 511-E8 promotes cholangiocyte differentiation of human induced pluripotent stem cells, thereby upregulating secretory components of the biliary HCO_3^- umbrella, such as the apical cAMP-sensitive Cl^-/HCO_3^- channel CFTR (cystic fibrosis transmembrane conductance regulator), the G protein-coupled bile acid receptor 1 (GPBAR1, also known as TGR5) and the basolateral secretin receptor.[44] Further supporting a role for laminin 511 in epithelial fluid secretion is the increased diameter of laminin 511-E8-treated cholangiocyte cysts.[44] Of additional interest are the findings that laminin 511 regulates barrier function and impairs leukocyte migration in endothelial cells.[45] In turn, tight junction-associated barrier function was impaired *in vitro* by IL-4 (which is enriched in IRC bile) via activation of claudin-2-mediated paracellular pore pathways.[46] Given the reported functions of laminin 511 and the apparent cholangiocyte barrier dysfunction in IRC, we recently identified autoantibodies against laminin 511-E8 in a subset of people with IRC and observed, *in vitro*, that laminin 511-E8 helped protect human cholangiocytes against T lymphocyte-induced barrier dysfunction and toxic bile acids (submitted for publication).[41]

Galectin-3 is a carbohydrate binding lectin recently identified as an autoantigen in IgG4-RD. High expression of galectin-

3 was found in both the serum and affected tissue of patients with IgG4-RD; galectin-3 was indirectly related to disease activity but remained high during glucocorticosteroid therapy.[47] Anti-galectin-3 autoantibodies were identified in an IgG4-RD cohort and were predominantly of the IgG4 and IgE isotype, but not the IgG1 isotype.[30] Galectin-3 sorts proteins into vesicles for transport to the apical plasma membrane, thereby exerting a function comparable to annexin A11.[48] Similar to laminin 511, galectin-3 interacts with integrin β1 and regulates its apical sorting.[49] Galectin-3 appears to be involved in biliary inflammation, as *Lgals3* knockout or galectin-3 inhibitor treatment led to an absence of bile duct damage with reduced mononuclear cell infiltrates, granulomas and fibrosis compared to controls in mouse models of 'autoimmune cholangitis'.[50] Using a murine model of xenobiotic-induced primary biliary cholangitis (PBC), the deletion of *Lgals3* exacerbated the PBC-like phenotype, increasing periportal inflammation (with more pro-inflammatory lymphocytes), granuloma formation and fibrosis.[51] Additionally, galectin-3 may inhibit the differentiation of B cells towards immunoglobulin-secreting plasma cells, and galectin-3 has an ascribed profibrotic role in various fibrotic diseases.[52–54] Collectively, for immune-mediated cholestatic liver diseases, a protective role for galectin-3 is not inconceivable. This role may be hampered in IRC by specific autoantibodies targeting galectin-3.

Prohibitins 1 and 2 are scaffold proteins involved in a wide array of cellular functions, such as proliferation, survival, metabolism, mitochondrial dynamics and inflammation.[55] Prohibitin 1 autoantibodies have been detected in the presence of various organ manifestations of IgG4-RD,[56] but also other immune-mediated disorders including PSC and Sjögren's syndrome (Table 2). Notably, expression of prohibitin 1 is reduced in patients with PBC, biliary atresia and Alagille syndrome.[57] Additionally, in bile duct-ligated mice, prohibitin 1 knockout resulted in increased bile duct proliferation and liver fibrosis.[57] From an immunological viewpoint, prohibitin 1 is involved in IgG1 production by B cells and survival of T cells.[58,59]

Antigen recognition by the innate immune system

Activation of the innate immune system is a prerequisite for formation of the aforementioned autoantibodies by the adaptive immune system. Considering the tendency of IgG4-RD to affect epithelia of the digestive tract, such as the bile ducts that are frequently exposed to environmental stressors, it has been speculated that damage-/pathogen-associated molecular patterns could activate the innate immune system in IgG4-RD.[18,60,61] Chronic exposure to (occupational) toxins, bacteria and self-antigens could function as damage-/pathogen-associated molecular patterns, possibly through mechanisms of molecular mimicry. Notably, mice that are injected with an activator of the innate immune system (polyinosinic polycytidylic acid) develop lesions typical of type I AIP, IRC and IgG4-related sialadenitis, in conjunction with the formation of autoantibodies directed against lactoferrin, carbonic anhydrase II and pancreatic secretory trypsin inhibitor.[62]

The innate immune system is activated via Toll-like receptors and NLRs (nucleotide-binding oligomerization domain-like receptors) on monocytes, $CD163^+$ M2 macrophages and basophils in various organ manifestations of IgG4-RD.[60,61,63,64] Their activation leads to an increased production of IgG4 by plasmablasts via BAFF (B cell activating factor), IL-33 and IL-13.[64–66] Notably, $CD163^+$ M2 macrophages and plasmacytoid dendritic cells play a role in inflammation and fibrosis formation via secretion of IL-33.[19,67–69] The innate and adaptive immune systems are thoroughly interconnected and their crosstalk is extensive in IgG4-RD.[70] Antigen presentation by the innate immune system has been hypothesized to initiate the aberrant B and T cell responses in IgG4-RD.[71]

The potential role of T cells

Where initial research implicated T helper 2 cells in the pathogenesis of IgG4-RD, this paradigm has been questioned.[72,73] Pathogenic roles for regulatory T cells (Tregs), follicular T helper 2 (Tfh2) cells, peripheral T helper (Tph) cells, and $CD4^+$ $SLAMF7^+$ / $CD8^+$ cytotoxic T lymphocytes have recently been described.

Tregs play an important role in the regulation of self-tolerance and secrete the anti-inflammatory cytokines IL-10 and TGF-β, which promote IgG4 class switching and fibrosis.[74,75] Increased infiltration of Tregs in the bile ducts in IRC correlates with the amount of IgG4-positive cells, whilst this is not the case in PBC, PSC and autoimmune hepatitis.[76,77] With respect to gene expression, higher ratios of *IL-4/IFN-γ, IL-5/IFN-γ, IL-10/CD4* and *TGF-β/CD4* were observed in affected tissues in IRC samples compared to PSC and PBC samples, suggesting that Tregs are involved in IgG4 class switching and fibrosis.[77]

Tfh2 cells have recently drawn attention in IgG4-RD. They differ from T helper cells in that they stimulate antigen-specific B cell proliferation, somatic hypermutation, isotype class switching and germinal centre development.[78] Tfh2 cells express BCL6, CXCR5, CXCR13 and PD-1 and secrete the cytokines IL-4 and IL-21.[79] IL-21 allows for plasmablast and plasma cell differentiation, whilst IL-4 induces isotype class switching.[74,80] Evidence supporting a key role for Tfh2 cells in IgG4-RD are: (i) Tfh2 cells promote the differentiation of naïve B cells towards IgG4-secreting plasmablasts, (ii) the Tfh2 cell subset is increased in blood and positively correlates with disease activity, number of affected organs and serum IgG4 levels and (iii) Tfh2 cells decrease after glucocorticosteroid treatment.[81] In IRC, circulating and tissue-infiltrating Tfh2 cells are expanded and correlate with disease activity.[82]

Tph cells, like Tfh2 cells, are implicated in the immune response of IRC. Tph cells lack CXCR5 and therefore do not enter lymph nodes but form ectopic lymphoid structures that are often seen in IgG4-RD.[79] Tph cells are increased in active IRC, correlate with serum IgG4 levels and disease severity, and their levels decrease upon treatment.[83] As Tph cells are able to travel to the site of inflammation and form ectopic lymphoid structures that could maintain the inflammatory process, they may even play a more critical role than their Tfh2 counterparts in IRC.[83] Notably, Tph-like cells express cytotoxic mediators, such as granzyme and perforin, that can cause tissue damage.[84,85]

In addition, two types of CTLs may play a critical role in IgG4-RD. The presence of dominant oligoclonal subsets of $CD8^+$ CTLs in both the blood and affected tissues was recently demonstrated.[86] These $CD8^+$ CTLs express granzyme A and preferentially induce apoptosis in mesenchymal cells.

Independently, both blood and affected tissues are dominated by oligoclonal expansion of $CD4^+$ $SLAMF7^+$ CTLs, which are characterized by their ability to secrete granzyme A, perforin and IFN-γ to kill target cells and secrete cytokines such as IL-1β.[87,88] Notably, $CD4^+$ $SLAMF7^+$ CTLs decrease upon rituximab treatment. $CD4^+$ $SLAMF7^+$ CTLs do not express CD20[88] which implies that B cells can regulate the maintenance of effector/memory $CD4^+$ T cells in IgG4-RD.[89] The relevance of $CD4^+$ $SLAMF7^+$ CTLs and $CD8^+$ CTLs has yet to be demonstrated in IRC.

The potential role of B cells

The B cell lineage, including plasmablasts, plays a critical role in the pathogenesis of IgG4-RD, but the exact nature of its contribution is still uncertain. In IRC- and type 1 AIP-dominated IgG4-RD, we have shown that the B cell receptor repertoire of patients contains oligoclonal expansions of $IgG4^+$ plasmablasts which exhibit signs of affinity maturation, suggesting an antigen-driven response.[26] Independent studies have confirmed that these $IgG4^+$ plasmablasts disappear upon treatment of IgG4-RD.[26,90] At relapse, the $IgG4^+$ plasmablasts that reappear were distinct from the ones present during the initial peak of disease activity, indicating that new naïve B cells are recruited by $CD4^+$ T cells to undergo repeated rounds of mutation and selection driven by a self-reactive disease process.[90]

At present it is unclear whether $IgG4^+$ B cells play a pathogenic role in IRC and IgG4-RD in general. $IgG4^+$ B cells could produce potentially pathogenic IgG4 autoantibodies[31,40] or could stimulate and reactivate $CD4^+$ CTLs as suggested by the finding that rituximab treatment reduces clonally expanded $CD4^+$ $SLAMF7^+$ CTLs.[91] They could also actively affect tissue fibrosis[92] corresponding with the finding that rituximab treatment decreased ELF (enhanced liver fibrosis) scores and myofibroblast volume in people with IgG4-RD.[93] An alternative is that IgG4 produced by $IgG4^+$ B cells solely functions to dampen an excessive IgG1-mediated immune response in IRC, type 1 AIP and IgG4-RD in general.[27,31,40]

In comparison to plasmablasts, other cell types of the B cell lineage have been understudied. Increases in circulating memory B cells have been shown to precede disease relapse,[94] and $CD21^{low}$ memory B cells were reported to be increased in patients with IgG4-RD.[91]

Formation of storiform fibrosis

The aetiology and exact pathophysiological processes that lead to storiform fibrosis formation in IgG4-RD and IRC have not been clarified. However, given the roles of the above described immune cells, the following cell types and mechanisms could play important roles:[84,95] (i) $CD4^+$ $SLAMF7^+$ CTLs, $CD8^+$ CTLs and Tph cells could induce tissue damage by secreting cytotoxic mediators such as granzymes and perforins. In addition, the secretion of profibrotic cytokines such as IL-1β and TGF-β by these cells would lead to the activation of an excessive wound healing response. (ii) B cells from patients with IgG4-RD express extracellular matrix remodelling enzymes and are able to secrete PDGFB (platelet-derived growth factor subunit B), leading to collagen production by fibroblasts.[92] (iii) M2 macrophages and plasmacytoid dendritic cells secrete cytokines (IL-33, IL-1β) that activate fibroblasts and lead to fibrosis formation.[67,68] Understanding the pathogenic mechanisms of storiform fibrosis formation in IRC and its potential reversibility will be relevant in preventing disease complications and end-stage liver disease.

Clinical presentation, diagnosis and differential diagnosis of IRC

IRC typically affects males aged 50-60 years or above.[1,2] They present with obstructive jaundice, substantial weight loss and episodes of upper abdominal pain or discomfort.[1,2] Cholestatic pruritus is reported by a minority of affected individuals (*e.g.* 13% in a Japanese cohort).[96] The close association of IRC and type 1 AIP can explain an endocrine pancreatic insufficiency (type 3c pancreatogenic diabetes mellitus) and exocrine pancreatic insufficiency, which are often detected in the presence of IRC.[97] Fever or night sweats are not typical in adults (for children and adolescents see below), but may also indicate a bacterial cholangitis in IRC or an underlying malignancy.[98]

The diagnosis of IRC is challenging as the clinical presentation may mimic other hepatobiliary diseases such as PSC and CCA (Table 3). Furthermore, no single validated and adequate diagnostic test is available to accurately diagnose IRC. Diagnosing IRC therefore requires a comprehensive work-up. The importance of this work-up is underlined by the fact that up to one-third of patients with IRC, often with accompanying inflammatory pseudotumours, undergo unnecessary, extensive abdominal surgery for suspected malignancy (*e.g.* extended hemihepatectomy; pylorus-preserving pancreatoduodenectomy or Whipple's procedure) before the diagnosis of IRC is made histopathologically.[10,11,99] Vice versa, 10-15% of the resection specimens from these surgical procedures may reveal fibroinflammatory lesions without malignancy. In a considerable portion of these patients, histological and clinical evidence for IgG4-RD that explains the preoperative clinical and imaging findings can be found, obviating the need for major surgery.[10,11,99]

Hepatic inflammatory pseudotumours in the context of IRC were first described in 2004[4] and further analysis[100,101] demonstrated striking histomorphological similarity and glucocorticosteroid responsiveness comparable to the inflammatory pseudotumours found in the pancreas in association with type 1 AIP.[4,102] Thus, hepatic inflammatory pseudotumours with histomorphological features of IgG4-RD are widely regarded as one manifestation of IRC.

To ensure a comprehensive work-up, various diagnostic algorithms have been developed, of which the HISORt criteria are now regarded as the diagnostic standard. These criteria comprise histology (H), imaging (I), serology (S), other organ manifestations of IgG4-RD (O), and response to glucocorticosteroid therapy (Rt).[11,103] Fig. 3 presents an overview of the diagnostic work-up and Table 3 summarizes diagnostic features of the most relevant alternative cholangiopathies when a diagnosis of IRC is considered.

Histology

Histological evaluation of biopsies or surgical resection specimens to distinguish IRC from CCA or other benign

Table 3. Differential diagnosis of IgG4-related cholangitis and respective HISORt characteristics.

Feature	IRC	PSC	CCA	Fibrohistiocytic pseudotumours	Follicular cholangitis	SC-GEL
Clinical presentation	Male 50-75 years of age	Male <40 years	Identical to IRC	Sex equally affected	Sex equally affected	Mostly minors
(H) Histology	Lymphoplasmacellular infiltrate Obliterative phlebitis Storiform fibrosis	Onion skin fibrosis Mucosal ulceration Fibro-obliterative bile ducts Xanthogranulomatous inflammation	Dysplasia or malignant cells	Histiocytic infiltrate Fibrovenous occlusion Neutrophil aggregates Xanthogranulomatous inflammation	Extensive lymphoid follicles	Neutrophil infiltration epithelium
	IgG4$^+$ plasma cells: Biopsy: >10/HPF Resection: >50/HPF IgG4$^+$/IgG$^+$ ratio >0.4	No obliterative phlebitis No storiform fibrosis IgG4$^+$/IgG$^+$ typically <0.4[184]	IgG4$^+$/IgG$^+$ <0.4	IgG4$^+$/IgG$^+$ <0.4[184]	No obliterative phlebitis No storiform fibrosis IgG4$^+$/IgG$^+$ <0.4[184,185]	IgG4$^+$/IgG$^+$ <0.4[184–186]
(I) Imaging	Bile duct strictures:[111,115,187,188] - Long band-shaped strictures - Absence of short bile duct stenosis Bile duct thickness:[116] - Single wall CBD >2.5 mm in stricturing area, >0.8 mm in non-stricturing area Mass forming:[184] - Mass in biliary tree 100% - Mass in liver parenchyma 0%	Bile duct strictures:[187,188] - Circumscribed short strictures - Beaded biliary tree Bile duct thickness: - Single wall CBD <2.5 mm[111]	Bile duct strictures:[115] - Short bile duct stricture Bile duct thickness: - Caveat: intraluminal CCA	Mass forming:[184] - Mass in biliary tree 20% - Mass in liver parenchyma 80%	Bile duct strictures:[184,185] - (Peri)hilar duct stricture	Bile duct strictures:[186] - Diffuse stricturing
(S) Serology	Serum IgG4: - >ULN 80%[121] - >4x ULN pathognomonic[124] - >1 and <2x ULN: IgG4/IgG1 ratio: >0.24[125]	Serum IgG4: - >ULN 15%-25%[125,127] - >1 and <2x ULN: IgG4/IgG1 ratio <0.24[125]	Serum IgG4: - >ULN 13.5%[124]	Serum IgG4: - Unknown	Serum IgG4: - <ULN in all case reports[185,193–197]	Serum IgG4:[186,199,200] - <ULN in all case reports
	IgG2 high (PPV 91%)[126] pANCA <10%[189] CA19-9 >ULN 30%-50%[127,161]	IgG2 ≤ normal and IgG1 high (PPV 85%)[126] p-ANCA 40%[190] CA19-9 >ULN 12.5%[127]	CA19-9 >ULN 75%[191]	CA19-9 >ULN ∼ 10%-20%[100,192]	p-ANCA: unknown CA19-9 >ULN 40% (mild)[185,193,195–198]	p-ANCA 50%[186,199] CA19-9 unknown
(O) Other organs	Type I AIP >90%[2] IBD 0%-10%[96,130,201,202] (see Table 1)	IBD ∼ 80%	Metastases	Concomitant hepatobiliary disease (*e.g.* choledocholithiasis) Prior (hepatobiliary) malignancy[203]	Follicular pancreatitis[185]	Type 2 AIP? IBD >80%
(Rt) Response to therapy	Responsive to glucocorticosteroids	Caveat: variant PSC-AIH Caveat: response in PSC with high IgG4[204]	Caveat: improvement of inflammatory component	Spontaneous improvement Responsive to antibiotics, NSAIDs	Unknown	Responsive to UDCA and glucocorticosteroids

Differential diagnoses to be considered in the work-up of IRC and their characteristic HISORt features differentiating them from other biliary diseases such as PSC, CCA, fibrohistiocytic pseudotumours, follicular cholangitis and SC-GEL. These features can be weighed in the work-up of IRC to come to a working or definitive diagnosis.

AIH, autoimmune hepatitis; AIP, autoimmune pancreatitis; CA19-9, cancer antigen 19-9; CBD, common bile duct; CCA, cholangiocarcinoma; HPF, high-power field; IBD, inflammatory bowel disease; IRC, IgG4-related cholangitis; NSAIDs, non-steroidal anti-inflammatory drugs; pANCA, perinuclear anti-neutrophil cytoplasmic antibodies; PPV, positive predictive value; PSC, primary sclerosing cholangitis; SC-GEL, sclerosing cholangitis with granulocytic epithelial lesion; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

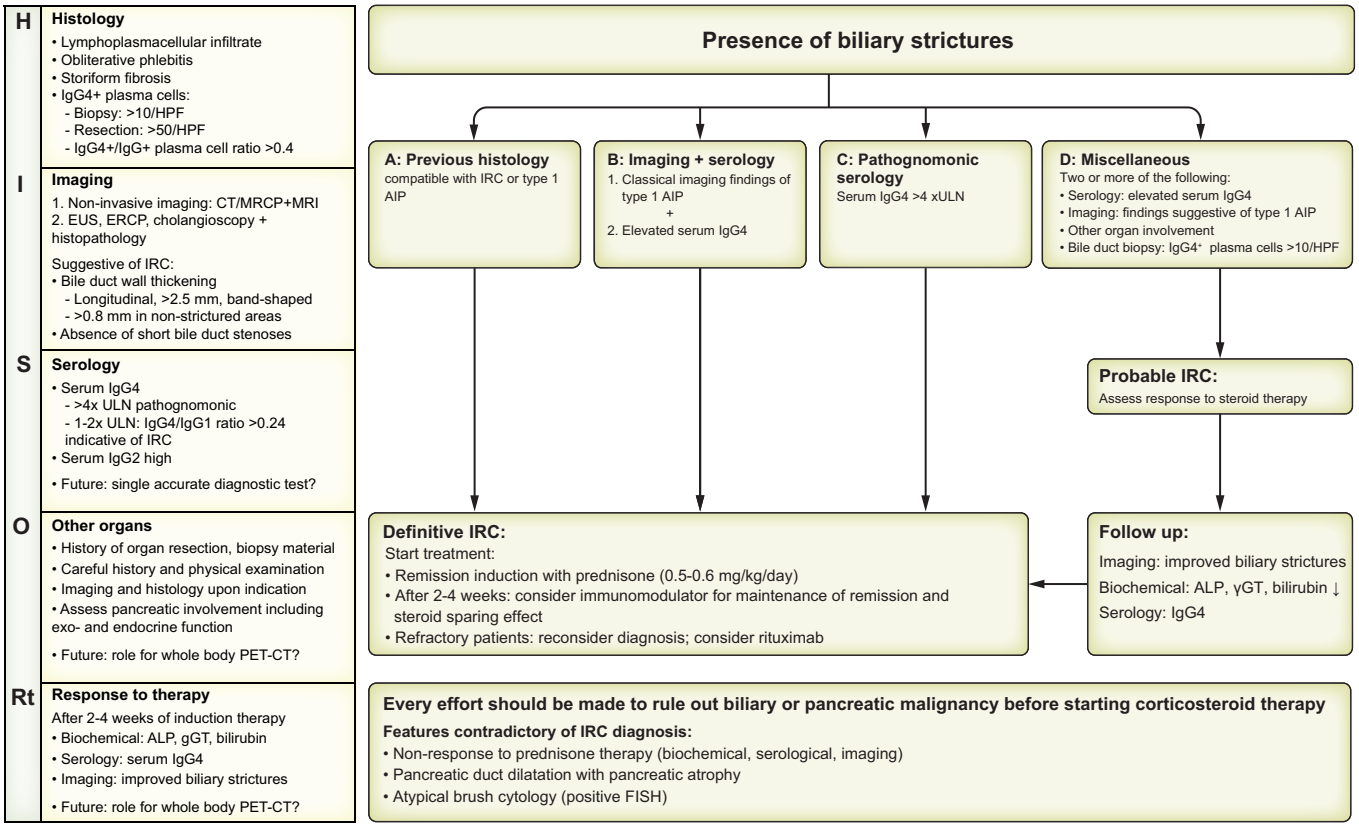

Fig. 3. Diagnosis of IgG4-related cholangitis according to the modified HISORt criteria. Patients who have biliary strictures and suspected IRC should have a work-up according to the HISORt criteria (left column). Based on the outcome of the HISORt work-up, the flow-diagram on the right is followed. Patients can be divided into four categories: patients falling into category A, B or C are assumed to have 'definitive IRC' upon which glucocorticosteroid therapy is started and an immunomodulator added when glucocorticosteroids are tapered. Patients falling into category D are defined as 'probable IRC' and should be given a trial of glucocorticosteroid therapy and have their response assessed. Of note, every effort should be made to rule out either biliary or pancreatic malignancy. AIP, autoimmune pancreatitis; ALP, alkaline phosphatase; CT, Computed tomography; ERCP, endoscopic retrograde cholangiopancreaticography; EUS, endoscopic ultrasonography; γGT, gamma-glutamyltransferase; FISH, fluorescence in situ hybridization; HISORt, histology, imaging, serology, other organs, response to therapy; HPF, high-power field; IRC, IgG4-related cholangitis; MRCP, magnetic resonance cholangiopancreaticography. PET-CT, Positron emission tomography-computed tomography; ULN, upper limit of normal.

cholangiopathies usually shows characteristic fibro-inflammatory lesions in the bile duct wall in IRC. These lesions consist of (i) a dense lymphoplasmacellular infiltration rich in $IgG4^+$ plasma cells, $CD4^+$ T lymphocytes and eosinophilic granulocytes, (ii) typical histopathological features such as obliterative phlebitis (with partial or complete venous obliteration or inflammatory para-arterial nodules), and (iii) particularly in advanced stages of the disease a cartwheel-shaped storiform fibrosis (Fig. 4).[104,105] The number of $IgG4^+$ plasma cells and the ratio of $IgG4^+/IgG^+$ plasma cells per high power field (HPF) are of secondary importance, since biopsies from patients with PSC or CCA can also contain $IgG4^+$ plasma cells.[104] The general consensus is that >10 $IgG4^+$ plasma cells per HPF in biopsy specimens and >50 $IgG4^+$ plasma cells per HPF in resection specimens are indicative of IRC.[98,104] An $IgG4^+/IgG^+$ ratio greater than 0.4 fits the diagnosis of IRC, although ratios of >0.7 are more commonly seen in IRC.[106] The HPF with the highest number of cells in the specimen is decisive as $IgG4^+$ cell distribution may be patchy. Acquiring histological material for the diagnosis of IRC comes with pitfalls. Liver needle biopsies are hampered by a lack of sensitivity but seem to be useful in patients with intrahepatic bile duct involvement as 57% of patients demonstrated >10 $IgG4^+$ per HPF *vs.* 8% of patients that only had extrahepatic bile duct involvement.[107] Bile duct biopsies can in some cases demonstrate IRC (sensitivity 52%, specificity 96%), but are too superficial to assess the criterion of obliterative phlebitis.[108] In patients with concomitant symptomatic type 1 AIP, histological assessment of duodenal papillary biopsies might provide supportive diagnostic information, but papillary biopsies are controversial due to a considerable sampling error and the risk of post-biopsy pancreatitis.[108,109] Obtaining adequate pathological specimens (endoscopic retrograde cholangiopancreaticography-brush, cholangioscopic biopsies, liver needle biopsies) of lesions that are highly suspicious for CCA is essential in the work-up of IRC.

Imaging

Imaging of the liver and biliary tree by MRI/magnetic resonance cholangiopancreaticography (MRCP), CT, endoscopic ultrasound (EUS), intraductal ultrasound, or cholangioscopy may show bile duct strictures with wall thickening of the extrahepatic, perihilar, and/or intrahepatic bile ducts, and/or lesions suspicious for malignancy like inflammatory pseudotumours.[110,111] A recent multicentre analysis from Japan and the US disclosed that – next to elevated serum IgG4 – EUS and

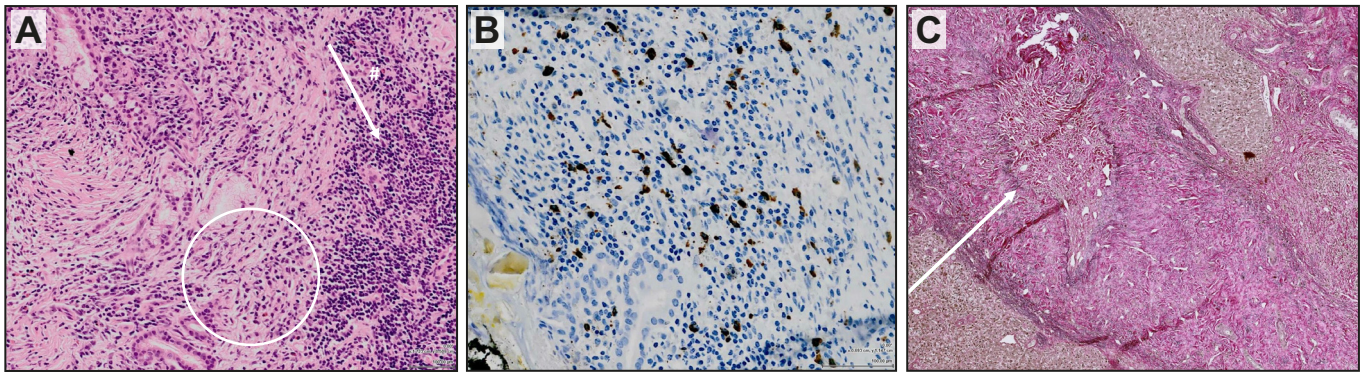

Fig. 4. Histopathologic characteristics of IgG4-related cholangitis. Characteristic findings of IRC on histopathology of a resection specimen: (A) Dense lymphoplasmacellular infiltrate (arrow), a few eosinophils within the infiltrate (#) and storiform fibrosis (circle) demonstrated by H&E staining at 40x magnification. (B) Dense infiltrate of >50 IgG4$^+$ plasma cells per HPF demonstrated by immunohistochemistry at 40x magnification (IgG4$^+$ plasma cells coloured brown after staining with an IgG4-specific monoclonal antibody). (C) Obliterative phlebitis (arrow) demonstrated by H&E staining at 40x magnification (modified from Herta, Verheij, Beuers. Der Internist. 2018; 59: 560-566). HPF, high-power field; IRC, IgG4-related cholangitis.

intraductal ultrasound are useful imaging modalities for the diagnosis of IRC.[112] The pattern of bile duct involvement has led to the differentiation of IRC into type 1 (distal stricture of the common bile duct), type 2 (intrahepatic segmental or diffuse bile duct alterations and distal stricture of the common bile duct, with prestenotic dilatation [type 2a], or without prestenotic dilatation [type 2b]), type 3 (hilar and distal stricture of the common bile duct), and type 4 (hilar stricture of the common bile duct) (Fig. 5).[113,114] A type 1 pattern is most common and found in one out of two cases.[114] Bile duct wall thickening is an important imaging criterion for the differentiation of IRC from PSC, as it results in longer and more band-shaped constrictions in IRC, in contrast to the circumscribed and short strictures found in PSC. A single-wall common bile duct thickness >2.5 mm on MRI has been proposed as a diagnostic criterion for IRC over PSC.[111] Notably, the absence of short bile duct strictures is also a helpful radiological sign suggestive of IRC over CCA.[115] On intraductal sonography, circular symmetric wall thickness with smooth inner and outer margins of the bile duct wall are suggestive of IRC, while a wall thickness of >0.8 mm in non-strictured areas is highly suggestive of IRC.[116] Positron emission tomography with computed tomography (PET-CT) is gaining considerable traction for diagnosing IgG4-RD and assessing treatment response, but its usefulness (also considering radiation exposure and costs) is still under debate.[117,118] In one study, combined PET-CT did not lead to an increased detection of bile duct involvement compared to conventional radiology, whereas another study detected 11% more IRC involvement using PET-CT.[119]

Starting with non-invasive imaging modalities such as contrast-enhanced MRI/MRCP or CT is advisable. Subsequently, invasive imaging methods such as EUS and endoscopic retrograde cholangiopancreaticography (with brush, biopsy or cholangioscopy) can be employed to obtain pathological samples from sites where there is a suspicion of malignancy.[112] Notably, inter-observer variability is moderate in most imaging studies.[115,120] Imaging findings that distinguish IRC from PSC and CCA can be found in Fig. 5.

Serology and serum biomarkers

Up to 75-80% of individuals with IRC present with elevated IgG4 serum levels.[1,2,121] However, only an elevation of more than 4x the upper limit of normal (ULN) is pathognomonic, as moderately elevated IgG4 serum levels are also observed in PSC (~15%), CCA or pancreatic adenocarcinoma (<4x ULN).[2,122–125] When serum IgG4 levels are >1.4 g/L (ULN) and <2.8 g/L (2xULN) in sclerosing cholangitis, incorporating the IgG4/IgG1 ratio with a cut-off of 0.24 improves the positive predictive value and specificity to distinguish IRC from PSC.[125] Elevated serum IgG2 may also distinguish IRC from PSC,[126] although this observation requires further confirmation. Carbohydrate antigen 19-9 (CA19-9) does not enable differentiation of IRC from CCA or pancreatic adenocarcinoma since CA19-9 serum levels may be markedly elevated in all conditions.[127] Newer biomarkers are of potential diagnostic value, although diagnostic accuracy and feasibility in routine clinical practice remain to be validated. We identified affinity maturated, class-switched IgG4$^+$ B cell receptor clones by next-generation sequencing in blood and affected tissue of people with IRC.[26] The detection of these clones probably allows for a reliable differentiation of active IRC from PSC, CCA and pancreatic adenocarcinoma.[26] A similar observation was reported for circulating plasmablast counts[90] in individuals with multi-organ involvement of IgG4-RD.[128] In contrast, we could not confirm the formerly proposed diagnostic value of serum IgG4/IgG RNA ratio in a prospective cohort study.[129] A metabolomic approach to distinguish IRC from PSC holds promise but requires validation in other cohorts, while its value for distinguishing IRC from malignancies needs to be proven.[130]

Other organ involvement

Numerous organs including various glands can be affected in IgG4-RD, as summarized in Table 1. In addition to the strong association of IRC with type 1 AIP (>90%) and vice versa (30-60%),[11,131] various other organ manifestations have been observed in people with IRC. A carefully taken medical history and meticulous physical examination may disclose former and present extrahepatic manifestations of IgG4-RD, such as IgG4-related sialadenitis or prostatitis, which may have gone undiagnosed or have disappeared over time without specific treatment. In case biopsies have been taken from potentially affected organs in the past, specific staining with monoclonal anti-IgG4 antibodies and histopathological revision for other characteristic features of IgG4-RD such as dense lymphoplasmacellular infiltrates, obliterative phlebitis and storiform

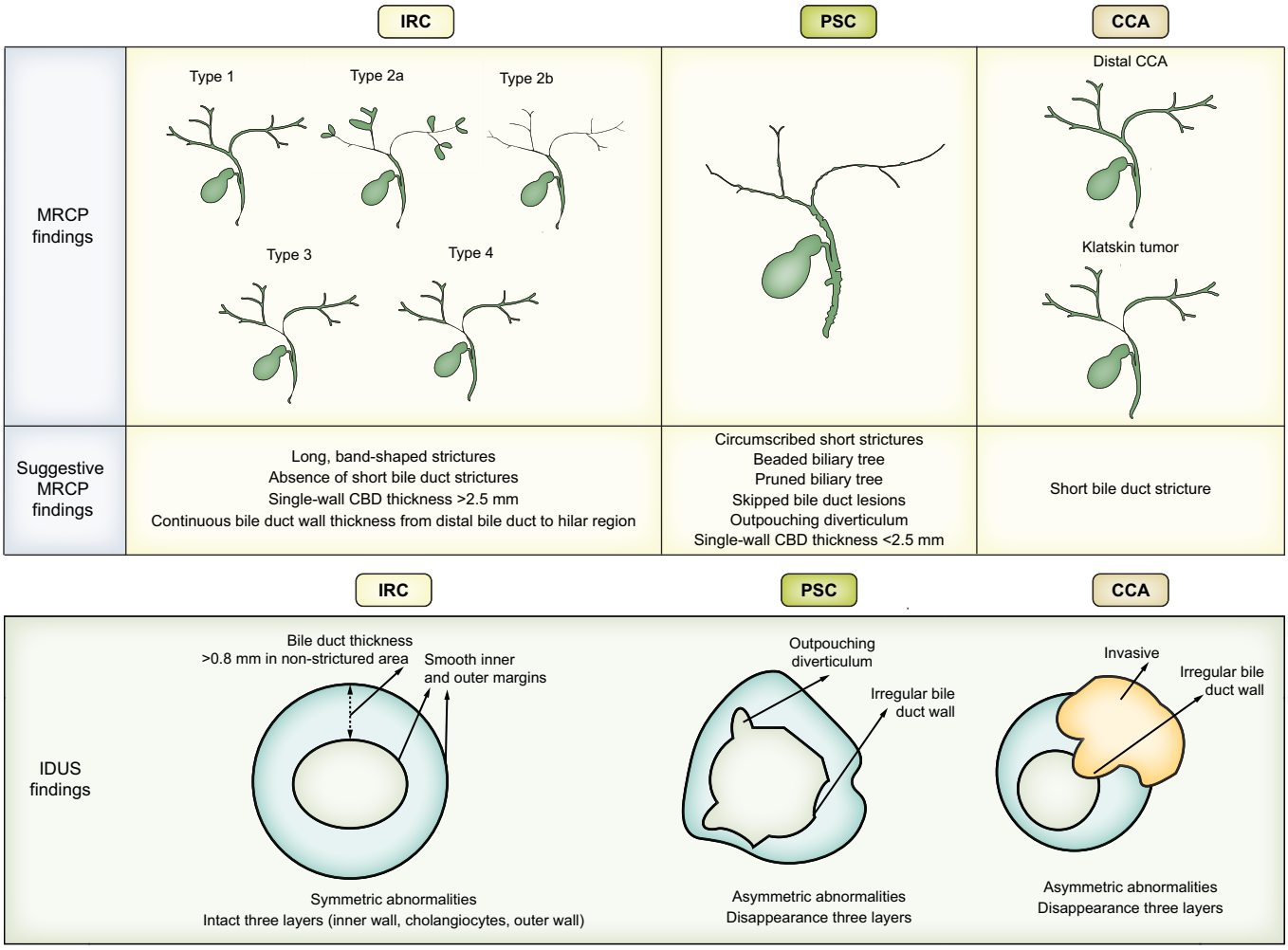

Fig. 5. Imaging findings in IgG4-related cholangitis, primary sclerosing cholangitis and cholangiocarcinoma. Cholangiographic features of IRC, PSC and CCA on MRCP imaging. IRC can be classified according to its cholangiographic subtype: type 1, distal stenosis; type 2a, distal stenosis and diffuse intraductal cholangiopathy with prestenotic dilatation; type 2b, distal stenosis and diffuse intrahepatic cholangiopathy without prestenotic dilatation; type 3, distal and hilar bile duct stricture; type 4, hilar bile duct stricture. Suggestive imaging findings for IRC, PSC and CCA are listed in the row below. Imaging by IDUS can potentially differentiate between IRC, PSC and CCA. Distinctive features are depicted in the respective figures. A step-up approach from non-invasive imaging (CT, MRI/MRCP) to endoscopic imaging (EUS, ERCP, cholangioscopy) and obtaining pathological specimens is advised in the work-up of IRC. CBD, common bile duct; CCA, cholangiocarcinoma; ERCP, endoscopic retrograde cholangiopancreaticography; EUS, endoscopic ultrasound; IDUS, intraductal ultrasonography; IRC, IgG4-related cholangitis; MRCP, magnetic resonance cholangiopancreaticography; PSC, primary sclerosing cholangitis; SSC, secondary sclerosing cholangitis; SC-GEL, sclerosing cholangitis with granulocytic epithelial lesion.

fibrosis appear mandatory. Careful examination of all lymph node stations is non-invasive and could be of help to find enlarged lymph nodes which are easily accessible for biopsy. With regards to findings on abdominal imaging, extrabiliary organ involvement, particularly of the pancreas, is a characteristic feature of IRC. The pancreas might appear enlarged and sausage-shaped, hypoechoic on ultrasound, with an oedematous swelling of the surrounding fat tissue (halo) and multifocal strictures of the pancreatic duct. Inflammatory pseudotumours that raise suspicion of pancreatic malignancy may also occur.[110] Next to pancreatic abnormalities, renal abnormalities and gallbladder wall thickening are more frequently observed in association with IRC when compared to PSC.[111] The role for whole body imaging in identifying other organ involvement is unclear at present. In small cohorts of patients with type I AIP and IRC, whole body PET-CT led to more frequent detection of other involved organs compared to conventional radiography.[117–119] PET-CT might therefore be considered in rare cases when the diagnosis of IRC is uncertain, and the involvement of other organs and easily accessible biopsy sites needs to be assessed. Still, considering exposure to radioactive material, high costs and the lack of proven diagnostic benefit in larger cohorts, PET-CT is not recommended as part of a routine diagnostic work-up in people suspected of suffering from IRC.

Response to therapy

Glucocorticosteroids, at a dose equivalent to 30-40 mg/day or 0.5-0.6 mg/kg/day of predniso(lo)ne, are the first-line treatment for IRC.[132,133] In the vast majority of cases, improvement of not only clinical, but also biochemical (bilirubin, alkaline phosphatase, gamma-glutamyltransferase and elevated CA19-9 levels), and imaging findings can be observed within 2 to 4 weeks of

predniso(lo)ne therapy, with treatment response supporting the diagnosis of IRC. Serum IgG4 might improve moderately in this timeframe as the biological half-life of IgG4 is around 21 days. Response to glucocorticosteroid therapy is, therefore, regarded as a diagnostic hallmark that distinguishes IRC from malignancies such as CCA. An IgG4-RD responder index has previously been proposed by rheumatologists for study and research purposes to quantify treatment response in systemic IgG4-RD.[134] It is unclear, however, whether the IgG4-RD responder index has additive value in the aforementioned analysis of therapeutic response in major manifestations of the digestive tract, IRC and type 1 AIP.

Together, the HISORt criteria form a pragmatic approach for the diagnosis of IRC (Fig. 3).[11] A 'definitive IRC' can be assumed when (A) IgG4-RD of either the bile ducts or pancreas has previously been histologically proven or, (B) imaging findings typical for AIP (sausage-like shape, focal pancreatic mass/enlargement without pancreatic duct dilatation, multiple pancreatic masses, focal pancreatic duct stricture without upstream dilatation, pancreatic atrophy) are supported by elevated serum IgG4 levels.[11] (C) Based on the high specificity of IgG4 serum levels >4x ULN,[124,125] we advocate for the addition of a third category to the HISORt flow diagram being group C with elevated serum IgG4 levels >4x ULN.[124,125] Glucocorticosteroid therapy can be started in cases falling into group A, B or C. A fourth group (D) categorized as having 'probable IRC' would need to fulfil two or more of the following criteria: elevated serum IgG4, imaging findings suggestive of type 1 AIP, other organ involvement, or a bile duct biopsy showing >10 $IgG4^+$ plasma cells per HPF. Here, a time-limited trial course of glucocorticosteroids is justified and should only be continued when treatment response within weeks is documented (Fig. 3).

Non-response to glucocorticosteroids should always question a diagnosis of IRC. However, fibrotic bile duct strictures in long-lasting IRC can lead to persistent symptoms and might not resolve upon immunosuppression. Still, exclusion of malignancy remains a major diagnostic challenge in these patients before a course of glucocorticosteroids is started. Although the HISORt criteria form a useful pragmatic approach to the diagnosis of IRC, there is an unmet need for validated diagnostic tests that can accurately diagnose IRC and distinguish it from PSC and malignancies such as CCA and pancreatic adenocarcinoma.

Therapeutic options in IRC and IgG4-RD

In IRC, prevention or alleviation of organ damage and treatment of signs and symptoms such as jaundice, weight loss, abdominal complaints, and pruritus are the primary therapeutic aims. Lack of treatment can lead to bacterial cholangitis, liver abscesses, cholecystitis, biliary fibrosis, cirrhosis and death.

Treatment of IRC is based on (i) remission induction, (ii) remission maintenance and (iii) long-term management.[2,122,132,133]

(i) Remission is induced with medium-dose predniso(lo)ne (0.5-0.6 mg/kg/day) for 4 weeks after which glucocorticosteroids are progressively tapered down by 5 mg every 2 weeks until a maintenance dose of ≤7.5 mg/day is reached.[133] The maximum dose, duration and rate of tapering down can be varied depending on the extent of disease, comorbidities, and indicators of relapse.[132,133] A recent trial demonstrated that medium-dose prednisone (0.5-0.6 mg/kg) is as effective as high-dose prednisone (0.8-1 mg/kg/day) for inducing remission.[135] Treatment responsiveness to glucocorticosteroid therapy is a nearly universal feature of IgG4-RD. Yet, disease recurrence after tapering and cessation of treatment is seen in at least 50% of affected individuals.[11] To decrease the cumulative glucocorticosteroid dose and reduce the risk of relapse, treatment regimens for remission induction of IRC and type 1 AIP have added immunomodulators to glucocorticosteroids after the initial glucocorticosteroid response has been documented as a confirmation of the diagnosis of IgG4-RD. These regimens are comparable to those widely and effectively used for the treatment of autoimmune hepatitis.[136] Observational studies are available for azathioprine, iguratimod and methotrexate.[137] Three clinical trials have assessed the additive effect of mycophenolate mofetil, leflunomide and cyclophosphamide, all of which led to higher remission rates and lower relapse rates (Table 4).[138–140] A retrospective analysis comparing cyclophosphamide and mycophenolate did not demonstrate superiority of one drug over another in terms of remission induction.[141] Alternatively, remission induction with the anti-CD20 antibody rituximab has proven to be successful in a single-arm observational study and larger cohorts of patients with IRC.[142,143] However, relapse rates after rituximab induction are still considerable and rituximab must be used with caution in IRC given the potentially increased and prolonged risk of infections in the context of typical complications of IRC such as bacterial cholangitis, cholecystitis and bile duct-derived liver abscesses. A recently performed network analysis found that glucocorticosteroids plus an immunomodulator were associated with higher remission rates in IgG4-RD compared to glucocorticosteroids only (OR 3.4), an immunomodulator only (OR 55.3) or rituximab induction treatment only (OR 7.4).[144] Currently, there is no evidence for one immunomodulator over another. Standard practice in our clinic is to induce remission with medium-dose prednisolone for 4 weeks, after which prednisolone is tapered down and an immunomodulator (azathioprine, starting dose 50 mg daily; alternatively, 6-mercaptopurine or mycophenolate mofetil) is added at mostly moderate doses. In addition to rituximab, various other new drugs, mainly monoclonal antibodies, have been developed to more specifically dampen autoimmune reactions and autoantibody effects; these new drugs are being tested in registered trials in IgG4-RD (Table 5).

(ii) Maintaining remission can currently be achieved via four strategies: (a) low-dose glucocorticosteroids plus an immunomodulator, (b) low-dose glucocorticosteroids only, (c) an immunomodulator only, or (d) rituximab maintenance therapy. Remission induction and maintenance therapy with low-dose prednisone for 3 years resulted in a markedly lower relapse rate (23.3%) compared to remission induction with only 26 weeks of prednisone treatment (57.9%) in type 1 AIP.[145] Additionally, a recently performed retrospective analysis demonstrated that low-dose prednisone maintenance (>3 years) improved survival in patients with IRC.[25] The recently performed network analysis (see above) showed that glucocorticosteroids plus an immunomodulator lowered relapse rates in IgG4-RD compared to glucocorticosteroid monotherapy (OR 0.39), whereas rituximab maintenance treatment was associated with the lowest relapse rate (OR 0.10).[144] For IRC with the inherent risk of bacterial superinfection, *i.e.*

Table 4. Overview of performed clinical studies in IgG4-RD.

Authors	Intervention	Comparator	Design	No. of patients	No. of IRC patients	Endpoints	Follow-up (months)	Outcome
Wu *et al.*[135]	High-dose prednisone (0.8-1.0 mg/kg/day)	Medium-dose prednisone (0.5-0.6 mg/kg/day)	RCT, open-label	40	14	Remission rate	6	95% *vs.* 80% (p = 0.157)
Wang *et al.*[138]	GC + leflunomide	GC	RCT, open-label	66	13	Relapse rate Time to relapse	12	18% *vs.* 42% HR 0.35, 95% CI [0.13-0.90]
Yunyun *et al.*[139]	GC + mycophenolate mofetil	GC	RCT, open-label	79	30	Remission rate Relapse rate	12	76% *vs.* 51% 21% *vs.* 40%
Yunyun *et al.*[140]	GC + cyclophosphamide	GC	RCT, open-label	104	29	Remission rate Relapse rate	12	88% *vs.* 60% 12% *vs.* 38.5%
Masamune *et al.*[145]	GC induction + maintenance	GC induction + 26 week taper	RCT, open-label	49	25	Relapse rate	36	57.9% *vs.* 23.3%
Carruthers *et al.*[143]	RTX induction	-	Single arm, open-label	30	10	Disease response Remission rate	6	77% 47%
Luo *et al.*[141]	GC + cyclophosphamide	GC + mycophenolate mofetil	Retrospective cohort	155	34	Complete response Relapse rate	12	56% *vs.* 50% 4% *vs.* 15%
Ebbo *et al.*[205]	RTX induction + maintenance	-	Retrospective cohort	33	13	Clinical response Relapse rate	25	93.5% 42%
Majumder *et al.*[142]	RTX induction + maintenance	RTX induction	Retrospective cohort	43	14	Relapse rate	36	11% *vs.* 45%
Lanzilotta *et al.*[206]	RTX induction and/or maintenance	-	Meta-analysis	101	101	Remission rate Relapse rate AE rate	19	89% 21% 25%
Omar *et al.*[144]	RTX maintenance	GC	Network analysis	1,169	392	Remission rate Relapse rate AE rate	3-60	OR = 3.53, 95% CI [0.13-94.51] OR = 0.10, 95% CI [0.01-1.63] OR = 7.69, 95% CI [0.02-∞]
Omar *et al.*[144]	RTX induction	GC	Network analysis	1,169	392	Remission rate Relapse rate AE rate	3-60	OR = 0.45, 95% CI [0.12-1.67] OR = 0.65, 95% CI [0.10-4.27] OR = 0.94, 95% CI [0.03-26.0]
Omar *et al.*[144]	GC + immunomodulator	GC	Network analysis	1,169	392	Remission rate Relapse rate AE rate	3-60	OR = 3.36, 95% CI [1.44-7.83] OR = 0.39, 95% CI [0.20-0.80] OR = 1.04, 95% CI [0.08-12.5]
Omar *et al.*[144]	Immunomodulator	GC	Network analysis	1,169	392	Remission rate Relapse rate AE rate	3-60	OR = 0.06, 95% CI [0.02-0.18] OR = 0.43, 95% CI [0.14-1.37] OR = 0.47, 95% CI [0.02-9.13]

Clinical studies in IgG4-RD that have included patients with IRC, listed by first author (first column), their intervention and comparator (second and third column), study design (fourth column), total number of included patients and number of IRC patients (fifth and sixth column), endpoints assessed (seventh column), follow-up time in months (eighth column) and the respective outcome of the intervention *vs*. comparator when applicable (ninth column).
AE, adverse event; GC, glucocorticosteroids; HR, hazard ratio; OR, odds ratio; RCT, randomised controlled trial; RTX, rituximab.

Table 5. Overview of registered ongoing clinical studies in IgG4-related cholangitis.

NCT identifier	Intervention	Comparator	Target	Design	Sample size	Outcome	Follow-up (months)
NCT05662241	Obexelimab	Placebo	CD19-FCγR2B	Randomized, blinded	200	Time to flare	12
NCT05625581	Tofacitinib + glucocorticosteroid	Cyclophosphamide + glucocorticosteroid	JAK1-JAK3	Case-control, open-label	40	Remission rate	6
NCT04660565	Belimumab + prednisone	Prednisone	BAFF	Randomized, open-label	60	Risk of flare	12
NCT05728684	CM310	-	IL4RA	Single group, open-label	20	Response rate	3
NCT04540497	Inebilizumab	Placebo	CD19	Randomized, blinded	190	Time to flare	12
NCT04918147	Elotuzumab + prednisone	Prednisone	SLAMF7	Randomized, blinded	75	Response	11
NCT04520451	Rilzabrutinib	Glucocorticosteroid	BTK	Randomized, open-label, cross-over	25	Flare occurrence	4
NCT04124861	- Immunosuppressant monotherapy - No therapy	Glucocorticosteroid + immunosuppressant	-	Randomized, open-label	138	Recurrence rate	18
NCT05746689	Sirolimus + prednisone	-	mTOR	Single group, open-label	20	Relapse rate	12

List of ongoing registered clinical studies in IRC with NCT identifier, intervention, comparator, pharmacological target, study design, sample size, primary outcome measure and follow-up time.
BAFF, B cell activation factor; BTK, Bruton's tyrosine kinase; CD19, cluster of differentiation 19; FCγR2B, Fc γ receptor 2B; IL4RA, interleukin-4 receptor alpha; JAK1, janus kinase 1; JAK3, janus kinase 3; mTOR, mammalian target of rapamycin; NCT, national clinical trial; SLAMF7, signalling lymphocytic activation molecule family member.

bacterial cholangitis, we currently prefer long-term strategies (a) and (c) for the majority of our patients. Still, further studies comparing different treatment options in IRC are warranted. The optimal duration of maintenance therapy has not been established, but at least 2-3 years appears reasonable based on available data, and long-term treatment beyond 3 years may be warranted in individuals with a high risk of relapse, including those with multiorgan IgG4-RD, markedly elevated serum IgG4, involvement of hilar and intrahepatic bile ducts in IRC, multiple strictures, or thicker bile duct walls.[11] Expert consensus indicates that maintenance treatment of IgG4-RD should be patient-tailored based on predictors of relapse, comorbidities and the risk of (developing) glucocorticosteroid-induced side effects.[132,133]

A potential role for ursodeoxycholic acid (UDCA) in the maintenance treatment of IRC has not been studied so far.[2,133] Anticholestatic, hepato- and cholangioprotective effects of UDCA have been shown for a number of fibrosing cholangiopathies including PBC and PSC,[133,146] and its beneficial effect on transplant-free survival in PBC is clearly documented. Putative mechanisms of action of UDCA in fibrosing cholangiopathies have been intensely studied and discussed,[147] with the evidence suggesting that UDCA might provide bile duct protection in addition to immunosuppressive treatment and thereby exert an additional glucocorticosteroid-sparing effect in IRC.

When relevant advanced fibrotic bile duct strictures in IRC do not adequately respond (any longer) to glucocorticosteroid treatment, endoscopic intervention under antibiotic prophylaxis with balloon dilatation and – if unresponsive to balloon dilatation alone – short-term stenting may be needed to guarantee adequate bile flow into the duodenum.[132,133]

(iii) Long-term management of IRC. Depending on the clinical course, patients with IRC are seen at a 6-12-month interval in the outpatient clinic to assess the development of potential biliary and hepatic damage, other organ involvement,[122] risk of malignancy and management of their therapy-induced side effects. Currently, life-long surveillance is advised for patients with IRC.[132,133]

As IRC is associated with type I AIP in >90%, monitoring of exocrine and endocrine pancreatic function is recommended. Exocrine pancreatic insufficiency has been reported to occur in up to 53% of individuals with IRC and faecal elastase tests should be performed when indicated (*e.g.* steatorrhea, weight loss).[97,122] Endocrine pancreatic dysfunction leading to diabetes mellitus type 3c has been reported to occur in 37% of patients in one IRC cohort, but the long-term incidence may be even higher.

Development of biliary cirrhosis in IRC has been reported in 4.5%[148] to 7.5%,[11] but may be even more frequent in some cohorts with advanced disease. Of note, the risk of developing cirrhosis might be particularly relevant in people with proximal bile duct involvement (up to 9% in 5 years). No published studies have reported follow-up strategies to monitor fibrosis progression in IRC, but annual transient elastography appears as an advisable measure in line with recommendations for PSC and PBC.[133,146] Current disease-specific cut-off values for transient elastography in IRC are yet to be established. IRC-related biliary cirrhosis should be managed according to current clinical guidelines, including semi-annual screening for HCC and varices. The occurrence of splanchnic and portal vein thrombosis in up to 9% of patients with IRC is noteworthy[97] and should be treated according to the EASL clinical practice guidelines.[149]

The risk of malignancy in IRC has been reported variably in different cohorts. A large Japanese study identified malignancies in 25/527 (4.7%) patients with IRC during a follow-up of 4.1 years, which was comparable to an age/gender-matched control population.[96] Other studies have reported an increased risk, with 11%-21.5% of patients experiencing a malignancy during their disease course.[25,97,150] Notably, a prominent increase in pancreatic and biliary tract malignancies was observed.[25,150] Maintenance treatment with glucocorticosteroids has been

reported to improve survival in individuals with IRC, possibly by reducing relapse rates and inflammatory activity, and thereby the occurrence of malignancies.[25]

Renal impairment in individuals with IRC occurs in up to 12%, and is monitored by creatinine and estimated glomerular filtration rate, especially in patients who have kidney, ureter or retroperitoneal involvement of IgG4-RD.[97] Collaboration with experienced nephrologists/urologists is crucial for successful management.

Additional long-term management depends on the treatment modality chosen. Patients treated with long-term glucocorticosteroids should be assessed for osteoporosis risk (DEXA [dual x-ray absorptiometry] scan) and given calcium/vitamin D supplements. Endocrine pancreatic function should be monitored by HbA1c on a regular basis and exocrine pancreatic function by faeces elastase measurement. Additional management advice can be found in current guidelines.[133,151–153]

IRC and IgG4-RD in children

IgG4-RD has rarely been reported in paediatric patients and might, in some cases, represent systemic IgE-mediated allergic reactions with elevated serum IgG4. There are only a few case reports on IRC and hepatic fibroinflammatory masses, in patients aged 3-17 of whom 50% were girls.[154–156] A similar age range and gender distribution was reported in the only systematic review on IgG4-RD in children.[157] Intermittent abdominal pain, mild jaundice, weight loss, and – in contrast to most adult patients – fever were described as typical clinical symptoms in children with presumed IRC. Due to the absence of consensus on paediatric diagnostic criteria, the diagnosis should be based on adult criteria.[122] Elevated IgG4 serum levels were found in 16/23 (70%) children with histologically confirmed IgG4-RD,[157] but the appropriate diagnostic cut-off in children remains unknown. Transabdominal ultrasonography may demonstrate hepatomegaly, dilated bile ducts, enlarged abdominal lymph nodes, hepatic masses, or pancreatic alterations.[155] Imaging can be expanded by non-invasive, radiation-free modalities (MRI/MRCP) in unclear cases. Histology is not mandatory for the diagnosis of hepatobiliary IgG4-RD as malignancy is rare in children.[122] Only a clear distinction from other paediatric autoimmune liver diseases such as autoimmune hepatitis or juvenile sclerosing cholangitis may require a liver biopsy.[158] Still, the number of $IgG4^+$ plasma cells per HPF for the diagnosis of IgG4-RD in children is unknown. Treatment of IgG4-RD in children is based on glucocorticosteroids, immunomodulators, and UDCA.[122,158,159] Rapid response to therapy was reported in 19/23 (82%) cases, with relapse after tapering of glucocorticosteroids in 13/23 (56%).[157] In case of relapse, a new course of predniso(lo)ne, and the initiation of maintenance therapy (*e.g.*, azathioprine 1-2 mg/kg/day), is recommended.[122,158]

Outlook for future research

Insights into the pathophysiology and clinical course of IRC have led to considerable advances in its diagnosis and management during the last two decades. Still, gaps in our basic knowledge and in the clinical management of IRC remain.

Pathophysiology

Identification of potential aetiological agents and unravelling of molecular mechanisms leading to the dysregulated immune reaction that is characteristic of IRC are unmet needs. The potential pathogenic role of IgG1 and IgG4 autoantibodies needs to be further assessed. The mechanisms of storiform fibrosis formation also need to be unravelled.

Diagnosis

The development of an accurate diagnostic test that can distinguish IRC from both PSC and CCA is an unmet need and would prevent a considerable number of misdiagnoses and unjustified surgical and oncological interventions. A potential role of PET-CT in the diagnostic work-up of IgG4-RD, *i.e.* assessing other organ involvement, has to be critically investigated considering radiation load and costs.

Treatment

Prospective, randomized-controlled clinical trials comparing the most effective and safe immunomodulators in IRC would be desirable. The long-term course of IRC needs to be firmly established and patients at risk for a complicated disease course who are in need of more intensive therapy need to be identified. Adequate follow-up strategies to monitor fibrosis progression and detect malignancies early should be investigated. Therapeutic options, based on recent advances in understanding the pathophysiology of IgG4-RD, should be expanded to reduce glucocorticosteroid-induced side effects and to improve remission and relapse rates (Table 5 for current trials evaluating novel therapeutic approaches in IRC). International collaboration will be pivotal to achieve these aims.

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Abbreviations

AIP, autoimmune pancreatitis; ANO1, anoctamin 1; BTK, Bruton's tyrosine kinase; CA19-9, carbohydrate antigen 19-9; CCA, cholangiocarcinoma; CTL, cytotoxic T cell; EUS, endoscopic ultrasound; HCC, hepatocellular carcinoma; HPF, high power field; IgG4-RD, IgG4-related disease; IRC, IgG4-related cholangitis; LAMA5, laminin α5; LAMB1, laminin β1; LAMC1, laminin γ1; LGALS3, galectin-3; MRCP, magnetic resonance cholangiopancreaticography; OR, odds ratio; PBC, primary biliary cholangitis; PDGFB, platelet-derived growth factor subunit B; PET-CT, positron emission tomography with computed tomography; PPAR, peroxisome proliferator-associated receptor; PSC, primary sclerosing cholangitis; SC-GEL, sclerosing cholangitis with granulocytic epithelial lesions; SLAMF7, signalling lymphocytic activation molecule family member 7; Tfh2, follicular T helper 2 cells; Tph, peripheral T helper cells; Tregs, regulatory T cells; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

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Conflicts of interest

The authors declare no conflicts of interest regarding all work related to this article.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

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Supplementary data

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Author names in bold designate shared co-first authorship

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