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Review

Clinical Updates in IgG4-Related Pancreatic and Hepatobiliary Disease

Hoyun Lee[1,2], Rodrigo Vieira Motta[3,4], Emma L Culver[3,4,*]

[1]Department of Medicine, Royal Prince Alfred Hospital, Camperdown, Sydney, NSW 2050, Australia
[2]Faculty of Medicine & Health, Central Clinical School, The University of Sydney, Sydney, NSW 2050, Australia
[3]Translational Gastroenterology Unit and Oxford NIHR Biomedical Research Centre, John Radcliffe Hospital, OX3 9DU Oxford, UK
[4]Nuffield Department of Medicine, University of Oxford, OX3 7BN Oxford, UK
*Correspondence: emma.culver@nhs.net (Emma L Culver)

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Abstract

Immunoglobulin G4-related disease (IgG4-RD) is a systemic fibro-inflammatory immune-mediated condition. The Pancreato-Hepato-Biliary subtype is the most frequent phenotype. The subtype encompasses immunoglobulin G4 (IgG4)-related pancreatitis (autoimmune pancreatitis type 1), IgG4-related cholangitis, IgG4-related hepatopathy and IgG4-related cholecystitis. The condition is characterised by multi-organ involvement and unpredictable recurrent disease flares, which lead to organ damage and failure in the absence of early recognition and adequate treatment. It is associated with a 2-fold increase in mortality and higher incidences of malignancies, such as solid-organ tumours and lymphoma. Diagnostic delays result from the lack of awareness and the absence of a single diagnostic test, leading to multiple generalist and specialist visits prior to the initiation of therapy. There have been major advances in the management of IgG4-RD to include a move to more targeted therapies. This includes the novel cluster of differentiation 19 (CD19)-depletion therapy inebilizumab, which has been approved in the United States, Europe and Japan for the treatment of IgG4-RD. This review highlights crucial diagnostic clues and emerging therapeutic advances in the evolving field of the Pancreato-Hepato-Biliary subtype of IgG4-RD.

Keywords: IgG4; IgG4-related disease; hepatobiliary; autoimmune pancreatitis; cholangitis; cholecystitis; hepatopathy; inflammation

1. Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a chronic, systemic, fibro-inflammatory immune-mediated condition. IgG4-RD is characterised by tumefactive swellings, thickening in affected organ systems, elevated serum immunoglobulin G4 (IgG4) levels, and characteristic histopathological findings. Characteristic histological findings include a lymphoplasmacytic infiltrate, abundant IgG4+ plasma cells, a storiform pattern of fibrosis, and obliterative phlebitis [1]. IgG4-RD has been described in many organ systems, with multi-organ involvement being reported in up to 75% of patients [2,3]. There are four disease subtypes defined by the pattern of organ involvement: the Pancreato-Hepato-Biliary, Retroperitoneal fibrosis and Aortitis, Head and neck-limited disease and Mikulicz with systemic disease [3]. These subtypes vary in clinical presentation, serological levels, response to therapy and risk of relapse and organ damage.

The Pancreato-Hepato-Biliary subtype is the most frequently observed subtype [3]. It incorporates IgG4-related pancreatitis (autoimmune pancreatitis (AIP) type 1), IgG4-related cholangitis (IRC), IgG4-related hepatopathy and IgG4-related cholecystitis. All use of AIP in this review refers to autoimmune pancreatitis type 1 unless otherwise specified. AIP and IRC are common manifestations of IgG4-RD and have been reported in 50% and 25% of IgG4-RD cases, respectively. AIP and IRC can be concomitant in up to 90% of cases [4].

Diagnosis of the Pancreato-Hepato-Biliary subtype of IgG4-RD remains challenging. There is no definitive diagnostic test. A combination of clinical, serological, radiological and histopathological features is often needed in accordance with diagnostic criteria [5]. IRC and AIP can mimic other conditions, including malignancies (cholangiocarcinoma (CCA), pancreatic cancer, lymphoma), autoimmune conditions (primary sclerosing cholangitis (PSC), AIP type 2), inflammatory conditions (secondary sclerosing cholangitis, chronic pancreatitis, sarcoidosis) and infective disorders (tuberculosis, viral infections) [6]. Diagnostic delays are common, with a median time to diagnosis of 3.2 years and a median of 4 specialist referrals being required prior to receiving a correct diagnosis [7]. These delays can lead to health-related anxiety and frustration for patients and can increase the risk of fibrotic progression and organ damage from unchecked inflammation [8,9].

Current treatment paradigms are centred on the control of inflammation to improve symptoms and minimise damage. Corticosteroids are first line for inducing remission but are associated with significant short and longer-term side effects. Disease relapse occurs often, and maintenance immunosuppressives and biological agents are utilised off-label to reduce relapse events [10]. In the MITIGATE phase-3 randomised controlled trial (RCT), inebilizumab, a novel anti-cluster of differentiation 19 (CD19) therapeutic agent that targets B cells, plasmablasts and plasma cells, demonstrated its efficacy and safety in reducing relapse

[11]. Inebilizumab has received recent approval in the United States, Europe and Japan for the treatment of active IgG4-RD.

The purpose of this review is to delineate important clinical, radiological, serological and histopathological findings that should prompt a higher index of suspicion for the diagnosis of IgG4-RD with an emphasis on the Pancreato-Hepato-Biliary subtype; to summarise emerging diagnostic biomarkers in the field; and to highlight novel and expanding therapeutic options. A detailed literature search strategy is provided in the **Supplementary Material**.

1.1 Epidemiology of AIP and IRC

There is limited epidemiological data for the Pancreato-Hepato-Biliary subtype of IgG4-RD. National epidemiological surveys for AIP (type 1 and 2) have been conducted since 2002 in Japan. The estimated incidence and prevalence of AIP and IRC in Japan have risen over the last few decades [12]. In 2016, an incidence of 3.1 and a prevalence of 10.1 per 100,000 of the population were reported for AIP [13]. In 2019, a point prevalence of 2.18 per 100,000 persons for IRC was reported [14]. Using an algorithmic analysis of insurance claims data to identify cases in North America, an incidence of 1.39 and prevalence of 5.3 per 100,000 persons were reported for IgG4-RD in 2019 [15]. The earlier identification of AIP and IRC as disease entities, and data capture methods used for national epidemiological surveys may account for the higher prevalence and incidence reported in the East [16].

1.2 Demographics, Risk Factors and Disease Associations in AIP and IRC

A complex interplay of genetic and environmental factors may account for the development of AIP and IRC (Fig. 1) [17]. Important genetic factors in those with AIP include Human Leukocyte Antigen (*HLA*)-class II DR Beta 1 (*DRB1*) and non-*HLA* genes such as those for Cytotoxic T-lymphocyte associated protein 4 (*CTLA-4*), Fc gamma receptor IIb (*FCGR2B*) and Fc Receptor Like 3 (*FCRL3*). Rare germline variants in genes such as Ikaros family zinc finger 1 (*IKZF1*) and Ubiquitin Protein Ligase E3 Component N-Recognin 4 (*UBR4*) have been identified in familial studies and may play a role in pathogenesis [18]. Epigenetic changes, including DNA methylation of the *HLA* focus and epigenetic age acceleration have been described in AIP and IRC [19]. Familial risk of other autoimmune diseases has been described in up to 15% of IgG4-RD patients, as is described in other autoimmune diseases [20].

There is a strong male preponderance for AIP and IRC with patients most often in their sixth decade of life at diagnosis [21,22]. However, the age of presentation in IgG4-RD is broad and can occur in paediatric and older adult populations [22]. Blue-collar work and chronic exposure to occupational and environmental contaminants such as mineral dust, pesticides, fumes and solvents are seen more frequently in European cohorts of patients with AIP and IRC than PSC [23]. A clinical history of atopy and/or allergy, raised serum immunoglobulin E (IgE) and eosinophilia is more frequently seen in proliferative subtypes of IgG4-RD including AIP [24]. Cigarette smoking and asbestos exposure have been linked to IgG4-related retroperitoneal fibrosis and lung disease, but their role in the Pancreato-Hepato-Biliary subtype remains unclear [25].

2. Diagnostic Tools

There is no single diagnostic test for IgG4-RD. Several organ-specific and consensus diagnostic criteria have been developed and validated to help support diagnosis. Classification criteria have helped to identify a homogeneous population with high specificity for IgG4-RD and the criteria exclude disease mimics, which is important in the development of diagnostic biomarkers and clinical trials for novel therapies [26].

2.1 Organ-Specific Criteria

The HISORt criteria for AIP, named to reflect the incorporation of histology, imaging, serology, other organ involvement and response to therapy findings, are perhaps the most well-recognised and simple-to-use diagnostic tool [27]. The International Consensus Diagnostic Criteria (ICDC) segregate AIP into type 1 (IgG4-related) and type 2, with a more detailed description of imaging characteristics of the pancreas than the HISORt criteria [28–33]. AIP type 2 is characterised by granulocytic epithelial lesions and is frequently associated with inflammatory bowel disease. AIP type 3 is an immune-related adverse event associated with checkpoint inhibitor agents and is often non-responsive to steroid therapy [34]. It is important to distinguish between these three AIP subtypes as they have different therapeutic management and disease trajectories (Table 1).

The HISORt criteria for IRC, like the AIP HISORt criteria, incorporate biliary imaging features, elevated serum IgG4 levels, characteristic histopathological findings, other organ involvement and response to steroid therapy. There is a focus on strictures of the intra-hepatic and proximal extra-hepatic segments of the biliary tract [35]. The Japanese IRC criteria highlight the symmetrical thickening of the biliary wall as an important additional characteristic [36]. Cholangiographic criteria are helpful in classifying IRC according to the distribution of strictures in the biliary tree (Table 2) [37]. Distal common bile duct involvement of IRC, a type 1 disease according to the Japanese IRC criteria, may be the most common variant [38]. Important disease mimics for this variant of IRC include chronic pancreatitis, pancreatic malignancies and cholangiocarcinoma [39]. Type 4 IRC with isolated hilar involvement is often mistaken for CCA on imaging and most frequently leads to unnecessary Whipple's surgery.

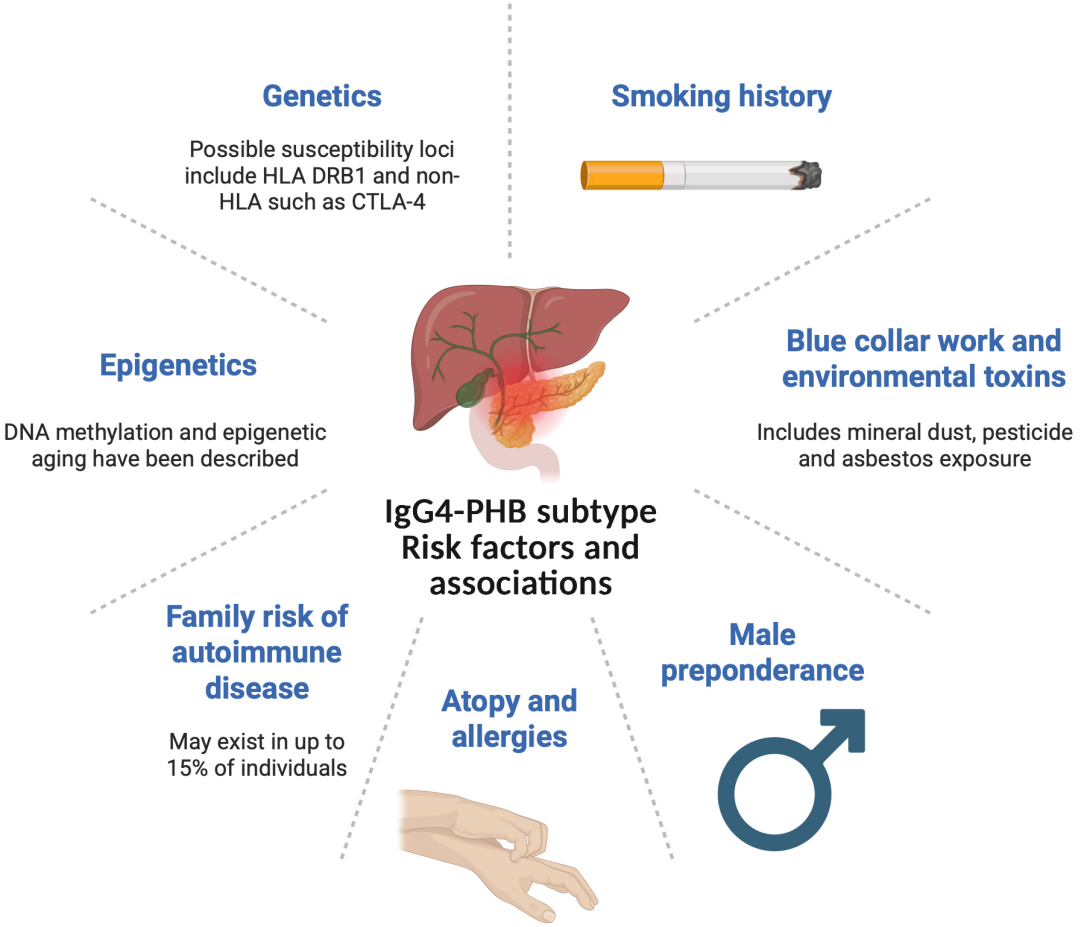

Fig. 1. Risk factors and associations in the Pancreato-Hepato-Biliary subtype of IgG4-RD. IgG4-RD, immunoglobulin G4-related disease. IgG4-PHB, immunoglobulin G4-related pancreato-hepato-biliary disease; CTLA-4, Cytotoxic T-lymphocyte associated protein 4; HLA DRB1, Human Leukocyte Antigen-class II DR Beta 1; HLA, Human Leukocyte Antigen. The Figure was created using BioRender (https://www.biorender.com/).

2.2 Consensus Diagnostic Criteria

The Japanese consensus diagnostic criteria for IgG4-RD are valuable for those with multi-organ involvement, especially when AIP and IRC are not the predominant phenotype [2]. These criteria rely on a high index of clinical suspicion and fail to adequately exclude disease mimics.

2.3 Classification Criteria

The American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) Classification Criteria for IgG4-RD provide a 3-step framework with high specificity and sensitivity for classifying IgG4-RD, distinguishing the condition from disease mimics (Fig. 2) [26]. The entry criteria include clinical, radiological or histopathological involvement of at least one of 11 typical organs. There are 32 features in the exclusion criteria and meeting one or more criteria rules out diagnosis. This is a unique feature in the classification criteria, and important for a variable condition with multiple disease mimics. The eight inclusion criteria are weighted as not all features share the same diagnostic weight or specificity for IgG4-RD diagnosis. Weights were assigned by a computer, completed with 160 calculation iterations. Classification requires a minimum of 20 points. These criteria have been well validated in experimental and real-world cohorts. However, they may under-estimate those with a Pancreato-Hepato-Biliary subtype. The criteria may not fully account for patients with focal pancreatic enlargement, isolated biliary disease, and fibrotic non-mass forming presentations [40].

3. Clinical Presentation

For the Pancreato-Hepato-Biliary subtype, symptomatic assessment for abdominal pain, bloating, obstructive jaundice, cholestatic itch, weight loss, steatorrhoea, hyperglycaemia and fatigue is important. Signs of icteric sclera, scratch marks, abdominal fullness and tenderness should be elicited. All patients with IgG4-RD, irrespective of primary organ involvement, should have an assessment at baseline for the presence of other organ involvement.

Table 1. Comparisons of AIP type 1, 2, 3.

	AIP type 1	AIP type 2	AIP type 3
Histopathology	Lymphoplasmacytic inflammation, storiform fibrosis and obliterative venulitis, high IgG4+ plasma cells (>10 cells/high power field)	Granulocytic epithelial lesions; Lobular neutrophilic infiltration	Neutrophil and lymphocyte predominant infiltrate
Common clinical presentation	Insidious course becoming chronic pancreatitis. Painless jaundice is common	Acute pancreatitis is common	Acute pancreatitis or Asymptomatic elevation of pancreatic enzymes
Serum IgG4	Elevated	Not elevated	Not elevated. Amylase/Lipase elevation common
Other organ involvement	Common	Rare	None
Treatment and response	Highly steroid responsive; relapses frequent	Highly steroid responsive; Relapses are infrequent	Aggressive intravenous fluids and cease immune checkpoint inhibitors. Steroids are 2nd line
Common imaging findings	Diffuse pancreas enlargement; capsule-like rim common	Focal pancreas enlargement; Capsule-like rim rare	Diffuse and focal enlargement common
Associated conditions	Atopy, allergies, diabetes	Inflammatory Bowel Disease (Ulcerative Colitis)	Unknown

IgG4, immunoglobulin G4; AIP, autoimmune pancreatitis.

Table 2. Classification of IgG4-related cholangitis.

IRC type classification	Anatomical location of lesion
Type 1	Strictures of the common bile duct
Type 2a	Extended narrowing of intrahepatic bile duct
Type 2b	Extended narrowing of intrahepatic bile ducts without pre-stenonic dilatation and reduced number of bile duct branches
Type 3	Stenosis in both hilar and lower part of common bile duct
Type 4	Stenosis exclusive to the hilar region

IRC, IgG4-related cholangitis.

Clinical examination of the head and neck is recommended to detect any glandular enlargement and lymphadenopathy, and skin assessment for cutaneous rashes. Evaluation for peripheral oedema is useful to document.

3.1 Autoimmune Pancreatitis Type I

Patients with AIP often present with obstructive jaundice, weight loss and abdominal symptoms [41–44]. Clinical features of pancreatic exocrine insufficiency such as steatorrhea, abdominal bloating and flatus and endocrine insufficiency such as hyperglycaemia or diabetes mellitus may present as early disease complications [45]. Fat soluble vitamin deficiencies are often described. Pancreatic stones may develop over time. Due to the indolent presentation of disease, the development of organ damage with pancreatic insufficiency may be found in up to 60% of first-presentation AIP cases (Fig. 3) [10,46].

3.2 IgG4-Related Cholangitis

Patients with IRC present with obstructive jaundice, cholestatic pruritus, abdominal pain and fatigue [47,48]. The rate of asymptomatic and incidental IRC cases was 37% in one retrospective study of 1045 IRC patients [14]. Cholangitis is infrequent but may occur in the context of a tight biliary stricture, requiring endoscopic intervention alongside medical therapy [49]. Marked cachexia and severe abdominal pain requiring narcotic analgesics are atypical [50]. A persistent fever not precipitated by a stricture is an exclusion criterion [26].

3.3 IgG4-Related Hepatopathy

Patients with IgG4-related hepatopathy present with pseudotumours of the liver, which may be asymptomatic and detected incidentally on cross-sectional imaging for abnormal liver tests. Cases present similarly to IRC with hepatitis, jaundice and abdominal pain. Constitutional symptoms such as fatigue have been described, but swinging fevers would make an alternative diagnosis more likely.

3.4 IgG4-Related Cholecystitis

IgG4-related cholecystitis can be asymptomatic and detected radiologically with an inflamed gallbladder. When

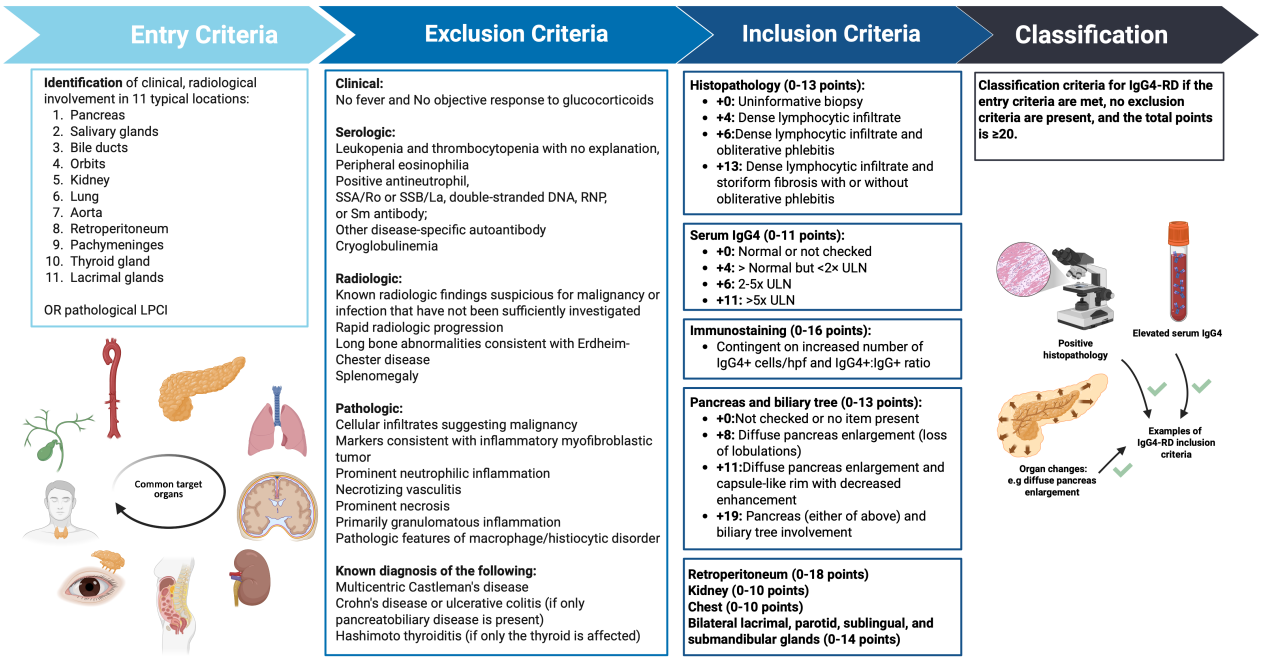

Fig. 2. 2019 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) Classification Criteria for IgG4-RD. The three-stage process and classification require a minimum of 20 points. ULN, upper limit of normal; LPCI, lymphoplasmacytic cell infiltration. The Figure was created using BioRender (https://www.biorender.com/).

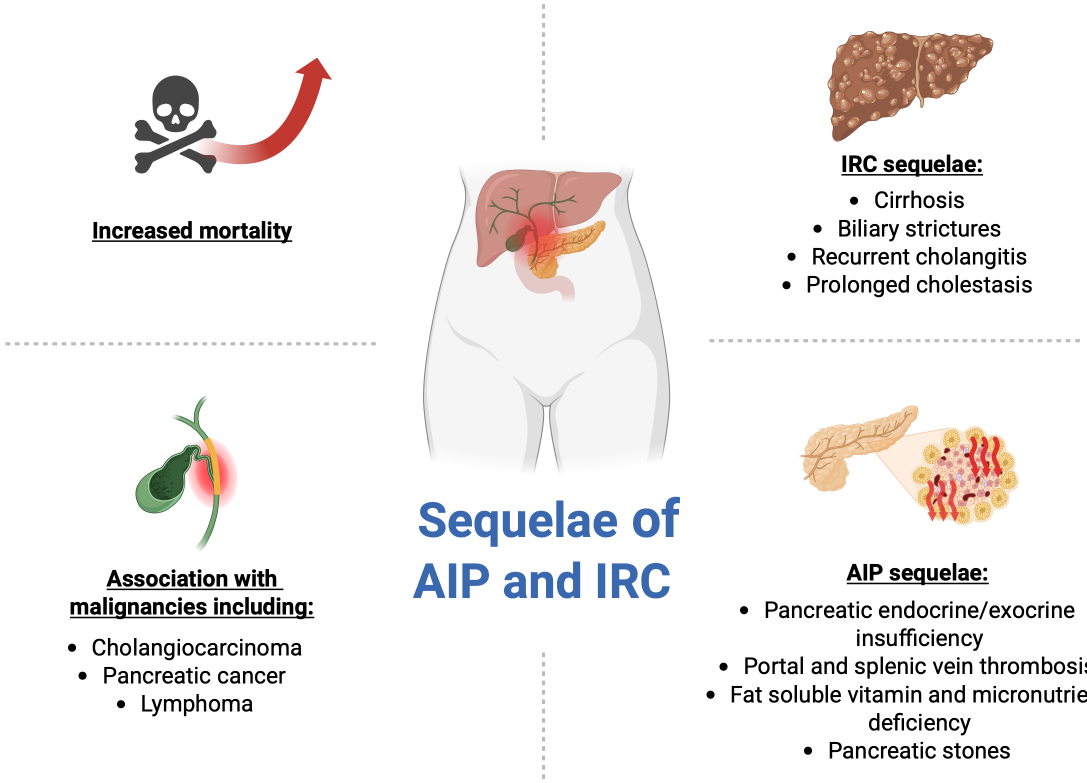

Fig. 3. Disease outcomes for Pancreato-Hepato-Biliary phenotype of IgG4-RD. Examples of end-organ damage in AIP and IRC include biliary strictures for IRC and pancreatic endocrine and/or exocrine insufficiency for AIP. In the long term, proximal IRC may increase the risk of cirrhosis. There is an increased global risk factor for malignancies, such as lymphoma and pancreatobiliary cancer. The Figure was created using BioRender (https://www.biorender.com/).

symptomatic, IgG4-related cholecystitis can cause right upper quadrant biliary-type pain and abdominal tenderness [51].

4. Radiological Features

All patients with IgG4-RD, irrespective of primary organ involvement, should be assessed at baseline to determine the systemic distribution of disease and activity of organ involvement. A computed tomography (CT) scan for the thorax, abdomen, and pelvis with contrast is recommended at baseline, alongside organ-specific ultrasound and/or magnetic resonance imaging (MRI).

4.1 Autoimmune Pancreatitis Type I

A combination of two-phase contrast CT and MRI of the pancreas is important for AIP diagnosis. Diffuse pancreatic swelling, accompanied by delayed enhancements and a hypodense capsule-like rim is seen in up to 40% of AIP cases [10,52]. Focal/segmental enlargement of the head, body and/or tail may be seen, and can be challenging to distinguish from pancreatic cancer [32]. Long strictures of the main pancreatic duct (>1/3) and multiple strictures without upstream dilatation are typical in AIP [28,53]. Findings of a low-density pancreatic mass, pancreatic duct dilatation, peri-pancreatic stranding, fluid collections and pseudocysts are atypical and suggest an alternative malignant or inflammatory aetiology [54]. In T1-weighted MRI images, high signals are lost, and in T2-weighted images, fibrotic tissue appears as a low-signal hypodense rim [55]. Magnetic resonance cholangiopancreatography (MRCP) findings can assist in the differentiation of malignant and benign causes of pancreatic lesions. The "duct-penetrating sign", a finding which shows enhancement of an intact pancreatic duct within pancreatic mass-like lesions and the "icicle sign", a tapered narrowing of the dilated main pancreatic duct, are signs that favour the diagnosis of AIP [56].

Positron emission tomography-computed tomography (PET-CT) provides functional and structural information of the pancreas and other organs. Pancreatic and other organ uptake of F-18 fluorodeoxyglucose (F-18 FDG) in AIP is common [57]. Findings of a diffuse pattern of FDG activity and other organ involvement may be discriminators for AIP from pancreatic cancer, and may assist in the biopsy of focal masses [58]. Elevation of PET-CT metabolic parameters may be associated with disease relapse [59] and elevation of standard uptake value (SUV) may assist in distinguishing pseudotumours [60].

Endoscopic ultrasound (EUS) of the pancreas may show a homogenous, hypoechoic diffuse mass with hyperechoic inclusions (Table 3) [61–65]. Fine needle aspiration (FNA) can be used to identify atypical cells, and a fine needle biopsy (FNB) can be acquired from a focal mass lesion to assess the histological features of AIP. The use of contrast-enhanced and detective flow imaging EUS may improve diagnostic capabilities [66]. A systematic review and meta-analysis evaluating the performance of machine learning systems for EUS image analysis reported a pooled accuracy of 93% when identifying pancreatic masses, including AIP [67]. Marya and colleagues reported a sensitivity of 90% and specificity of 93% when using a convolutional neural network model to differentiate AIP from pancreatic malignancies [68].

Radiomics is an emerging imaging analysis technique, producing quantifiable and reproducible data from MRI, PET-CT and CT modalities. Early radiomics studies for CT imaging demonstrated an area under the curve (AUC) value of 0.83 when discriminating focal AIP against Pancreatic Ductal Adenocarcinoma (PDAC) using a radiomics nomogram model [69] and PET-CT images reported an accuracy of 89.91% when discriminating AIP lesions from pancreatic malignancies [70].

4.2 IgG4-Related Cholangitis (IRC)

Magnetic resonance cholangiopancreatography (MRCP) can determine the presence of strictures. Narrowing of the intra- and extra-hepatic bile duct and/or thickening of the bile duct walls (>1 mm) are features of IRC [37]. Strictures are frequently elongated and continuous in nature [71]. Differentiating isolated-IRC from disease mimics (CCA, PSC) can be challenging radiologically [72]. Common cross-sectional imaging (CT/MRI) features of IRC include symmetrical wall changes, skip lesions, preservation of the bile duct wall lumen and delayed-phase homogenous enhancements (Table 4) [73–76]. In a retrospective study of 25 IRC and 500 CCA patients, a smooth and gradual common bile duct narrowing was significantly associated with IRC cohorts [77]. Whilst PET-CT may identify areas of metabolic activity, other organ activity and biopsy access points, it is less useful in the context of IRC, where strictures are better visualised on MRI [73].

Bile duct wall changes may be further explored with EUS and intraductal ultrasonography (IDUS). Changes typical for EUS and IDUS include thickening (>1 mm) of bile ducts, symmetrical wall thickening, preservation of wall architecture, smooth outer and inner walls and homogenous hypo-echogenicity [78–81]. A proposed EUS scoring system to discriminate IRC from CCA demonstrated a high specificity (86%) and sensitivity (95%) when using a cut off score of 3 or more IRC-associated imaging features [79].

Endoscopic retrograde cholangiopancreatography (ERCP) is infrequently employed for the diagnosis of IRC but has an important role in the discrimination of biliary strictures, tissue sampling via brush cytology and therapeutic management by stricture dilatation and/or stenting. Direct visualisation of the bile duct is possible via peroral cholangioscopy, with improved image resolution and sampling. Common cholangioscopic findings of IRC includes a smooth mucosal surface lumen, dilated

luminal vessels, luminal vessel tortuosity and a lack of easy vessel bleeding. These features may be more common in IRC when compared to extrahepatic CCA [82]. A multicenter RCT of 61 patients reported a significantly higher sensitivity of peroral cholangioscopy versus ERCP (95.5% vs. 66.7%) when discriminating CCA from benign biliary strictures (unclear how many of these were IRC) [83]. A systematic review reported a pooled sensitivity and specificity of 94.7% and 92.1% respectively of peroral cholangioscopy machine learning models when discriminating CCA against benign biliary lesions [84].

Novel quantitative imaging techniques using MRCP-plus with Liver Multiscan for AIP/IRC (Perspectum Diagnostics) have shown promise in highlighting features in the pancreas and biliary system suggestive of disease activity pre and post therapy.

4.3 IgG4-Related Cholecystitis and IgG4-Related Hepatopathy

Typical CT and MRI changes in IgG4-related cholecystitis include diffuse gallbladder thickening, cystic duct thickening, and a speckled appearance of the gallbladder [51]. IgG4-related cholecystitis or suspected cases due to gallbladder thickening are frequently associated with AIP with or without IRC and can be a disease mimic of gallbladder carcinomas [51,74,85]. Pseudotumours of the liver may occur as seen in other organs, and can mimic intra-hepatic CCA, other inflammatory masses and less frequently hepatic abscesses. There are no specific imaging features that can confirm a liver mass as being IgG4-related hepatopathy and diagnosis relies on histopathology.

5. Pathological Findings

Biopsy and resection specimens in the pancreas, bile duct, liver and gallbladder demonstrate important morphological characteristics in the histopathological specimens of IgG4-RD.

In AIP, EUS-FNA cytological samples of the pancreas are limited to the exclusion of dysplasia as the technique does not typically preserve tissue architecture [86]. EUS-guided trucut FNB is recommended by the ICDC guidelines to diagnose AIP [28]. Two systematic reviews report higher yield and improved diagnostic accuracy of FNB in comparison with FNA in AIP patients [87,88]. Use of larger needle sizes such as 19 and 20G, is viable and may improve the diagnostic yield of endoscopic biopsies without a significant increase in complications [87].

In IRC, ERCP-guided brush cytology is used for superficial biliary tissues to identify cellular atypia and dysplasia [37,89]. Peroral cholangioscopy forceps samples may have increased sensitivity when compared to conventional ERCP scrapings [83]. The performance of peroral cholangioscopy was non-superior in comparison to conventional methods in other studies [90]. Tissue samples of the Ampulla of Vater/duodenal papilla with more than 10 IgG4+ lymphocytes per high power field (HPF) and/or a gross swollen appearance can occur in a minority of IRC cases [81].

In IgG4-related disease, gallbladder biopsy specimens are rarely acquired, and diagnosis is made after cholecystectomy with typical morphological characteristics and immunostaining [91].

In IgG4-related hepatopathy, pseudotumours of the liver have classical histopathological findings on biopsy and/or resection. An IgG4-related variant of autoimmune hepatitis has been described, with serum and tissue IgG4 elevation and steroid responsiveness. However, given the absence of mass lesions or strictures in described cases, it is unlikely that it is a bona fide IgG4-related hepatopathy [92].

5.1 Serology

Elevated serum IgG4 forms a part of the diagnostic criteria and when elevated is a biomarker for disease monitoring [93,94]. Very high levels of IgG4 elevation (5$\times$ $\geq$the upper limit of normal (ULN)) can confer a high positive predictive value for IgG4-RD diagnosis when compared to moderate elevation (2$\times$ $\geq$ULN) [95]. However, IgG4-RD disease mimics including malignancies, autoimmune conditions and infectious diseases can also present with very high IgG4 concentrations and IgG4 alone is not a specific or sensitive diagnostic test [95,96]. AIP and IRC can exhibit no serum IgG4 elevation [24,97] and AIP cohorts with no serum IgG4 elevation may have a preponderance for focal pancreatic enlargement and higher rates of surgical interventions [98]. Additional diagnostic adjuncts and biomarkers include increased serum IgE levels, increased peripheral eosinophil counts, and C3/4 hypocomplementaemia [24,99]. Complement levels are independent of renal involvement [100]. Circulating plasmablasts are insensitive for diagnosis but may be used as a biomarker for active and relapsing disease [101].

Emerging diagnostic and prognostic biomarkers for AIP and IRC include serum interferon alpha (IFN-a) and interleukin-33 (IL-33), plasma-derived exosomes, leucine-rich alpha-2 glycoprotein and metabolic panelling [102–106]. The clinical role of these novel biomarkers in the diagnosis and monitoring of disease has not yet been defined [5].

5.2 Red Flags for Diagnosis

Several red flags should raise suspicion for the IgG4-RD Pancreato-Hepato-Biliary subtype, and these features are summarised in Table 5.

6. Disease Monitoring

Disease activity: An IgG4 Responder Index (IgG4-RI) has been created to measure multi-organ disease activity and record organ damage over time, on an individual basis. It relies on clinical assessment as well as radiologi-

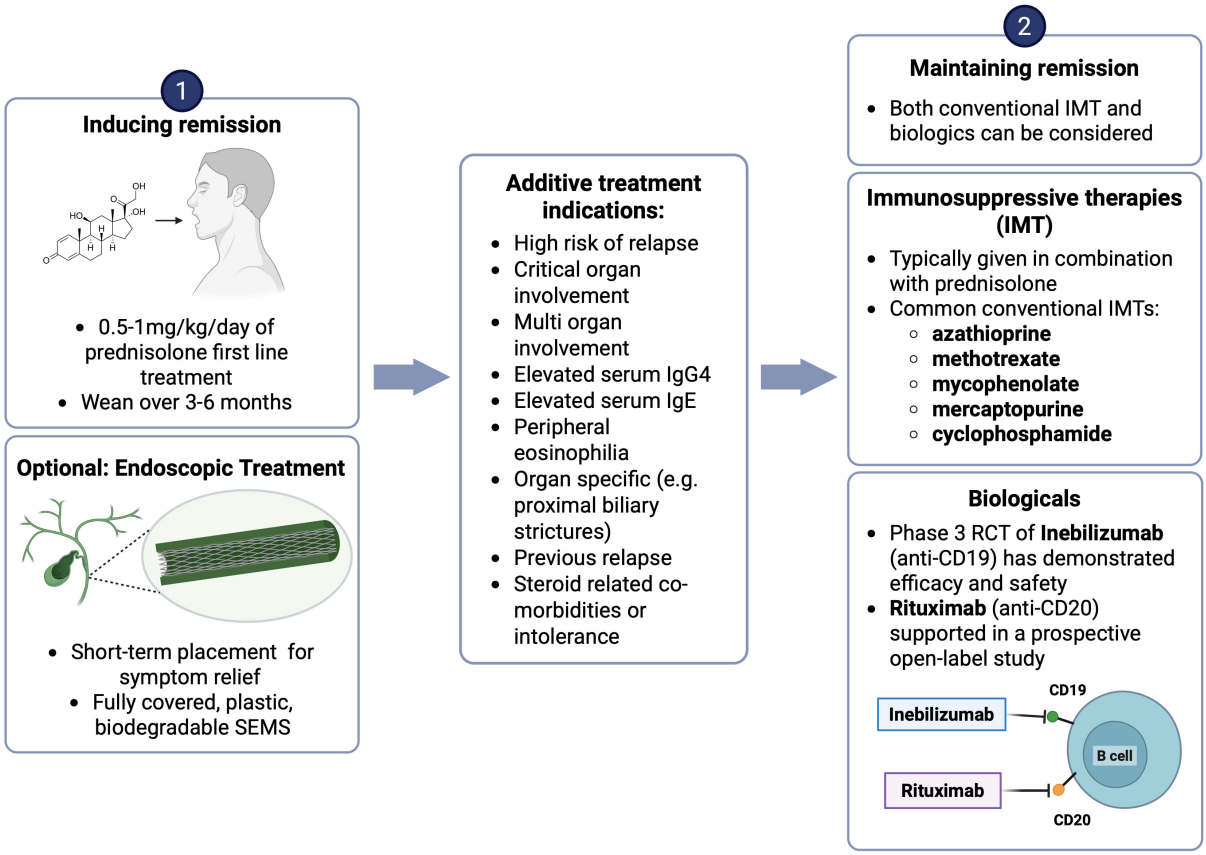

Fig. 4. Management pathway for IgG4-RD Pancreato-Hepato-Biliary subtype. Prednisolone remains an important therapy for the IgG4-RD Pancreato-Hepato-Biliary subtype. Endoscopic stents can be placed as a temporary measure for symptomatic relief. For patients at high risk of relapse or who have experienced a previous disease relapse, conventional immunosuppressive therapies (IMTs) and biologics should be administered. CD 19, cluster of differentiation 19; CD 20, cluster of differentiation 20; RCT, randomised controlled trial; SEMS, self-expandable metal stents. The Figure was created using BioRender (https://www.biorender.com/).

cal interpretation for those with AIP and IRC. Patients with higher mean IgG4-RI scores demonstrate higher disease relapse rates, and this tool is used both in clinical practice and clinical trials [107]. Whilst the IgG4-RI can numerically track disease activity and damage, measurement is binary, requires subjective clinical judgement and is organ-specific.

Disease damage: Chinese investigators have recently developed the IgG4-RD Damage Index to assess longitudinal, irreversible organ damage in IgG4 patients caused by disease, its treatments and malignancy [108]. In AIP and IRC, this includes the presence of pancreatic endocrine and exocrine insufficiency, and liver-related fibrosis and cirrhosis.

Disease-related symptoms: IgG4-RD Symptom Severity index is a tool for patient reported outcomes of disease. The index assesses self-reported quality of life and impact of disease. Patients report significant levels of anxiety and fear related to the diagnosis, the timing of a relapse and impact on quality of life [9]. This is more prevalent in those with AIP and IRC misdiagnosed with malignancy and patients experiencing chronic damage-related symptoms.

7. Management

7.1 Induction of Remission

Glucocorticoid therapy: Glucocorticoids are key treatments for the rapid induction of remission in AIP and IRC (Fig. 4) [6,54,109]. Typical dosing regimens consist of 0.5–1.0 mg/kg of prednisolone (typically 30–40 mg prednisolone) for up to 4 weeks. Initial response rates are 95–98% in AIP and over 90% for IRC [43,46]. A gradual taper in increments of 5 mg over 3–6 months is common [6]. Careful monitoring for glycaemic levels must be conducted, given that steroids may precipitate or exacerbate hyperglycaemia in AIP. Higher doses (60 mg prednisolone) or intravenous steroids may be given for organ critical presentations (e.g., a mass encroaching on the orbital nerve) [110]. Steroid responsiveness is part of the diagnostic criteria for AIP and IRC; the absence of a response suggests an alternative diagnosis or a more fibrotic, stricturing disease [28,37].

Biliary stents: Endoscopic placement of temporary plastic or covered metal biliary stents may be required in those with symptomatic jaundice and pruritus to minimise the risk of cholangitis, and whilst obtaining diagnostic clar-

Table 3. Summary of imaging features of AIP using different diagnostic modalities.

Imaging modality	Imaging findings	Clinical utility
Contrast enhanced-CT	Diffuse "sausage pancreas" swelling, homogenous delayed enhancement, capsule-like rim hypodensities	Common AIP presentation. May differentiate AIP from differentials including pancreatic adenocarcinoma
MRI	Diffuse swelling of the pancreas, capsule-like rim, multiple strictures of the main pancreatic duct (MPD), and homogenous delayed enhancement	Common AIP presentation. May differentiate AIP from pancreatic adenocarcinoma
MRCP	Duct-penetrating/Icicle sign	May differentiate AIP from pancreatic malignancies
PET-CT	Diffuse pattern of uptake, Other organ involvement	May differentiate AIP from pancreatic malignancies
	Elevation of metabolic parameters such as total lesion glycolysis (TLG)	May predict disease relapse
	Elevation of standard uptake value	May differentiate AIP from pseudotumours
EUS	Diffuse, homogenous and hypoechoic enlargement with hyperechoic inclusions	Common AIP presentation. Features such as homogenous enlargement may differentiate AIP from differentials including chronic pancreatitis
	Peripancreatic hypoechoic margins and duct-penetrating sign	May differentiate AIP from pancreatic cancer

CT, computed tomography; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; PET-CT, positron emission tomography-computed tomography; EUS, endoscopic ultrasound.

Table 4. Summary of imaging features of IRC using different diagnostic modalities.

Imaging modality	Imaging findings	Clinical utility
Contrast enhanced-CT/MRI	Symmetric wall thickening, long-segment strictures, preservation of wall lumen architecture and enhancement	Common IRC presentation
	Smooth and gradual common bile duct narrowing, intrapancreatic bile duct involvement and skip lesions	May differentiate IRC from CCA
MRCP/ERCP	Narrowing of the intra/extra-hepatic bile duct, thickening of bile duct walls	Common IRC presentation
EUS and IDUS	Symmetrical thickening of bile duct wall, homogenous hypo-echogenicity, lamination of bile duct wall and gall bladder thickening	Thickening of the bile duct wall is a common IRC presentation. These 4 findings may differentiate IRC from CCA according to a proposed scoring criteria
Peroral cholangioscopy	Smooth mucosal surface lumen, dilated luminal vessels, luminal vessel tortuosity and a lack of easy vessel bleeding	Common IRC presentation. May differentiate IRC from extrahepatic CCA
PET-CT	Uptake of 18F-FDG in involved bile ducts and other affected organs	Identifying other organ involvement, biopsy access points and response to treatment

IRC, IgG4-related cholangitis; CCA, cholangiocarcinoma; ERCP, endoscopic retrograde cholangiopancreatography; IDUS, intraductal ultrasonography.

ification from brushings/biopsies. Stents may be placed alongside the administration of glucocorticoid therapy, and can be removed or may fall out within weeks as the strictures resolve [111]. Longer-term biliary stents may be placed to remodel strictures [29].

Surgery: Surgery is not a preferred therapeutic option for AIP/IRC. Surgical resection via Whipple's, Biliary Bypass, and Hepatic Resection can remove a mass, stricture or the entire organ involved in AIP/IRC. However, relapse in the remnant or other organs can occur with follow up over time [112]. Approximately 20–30% of AIP cases receive surgery [41,112]. In a 2024 systematic review and meta-analysis of 8917 pancreatic resection cases, AIP (95% Type 1) cases accounted for 26% of benign and unnecessary pancreatic resections [96].

7.2 Disease Relapse

Despite the efficacy of glucocorticoid therapy for the initial management of disease, relapse rates are high and have been described in over two-thirds of patients with pancreatobiliary disease [47,113,114]. Multi-organ involvement, raised serum IgG4 levels (2× ≥ULN) at baseline, peripheral eosinophilia, raised serum IgE levels, and high IgG4-RI (≥9) have all been identified as potential relapse risk factors [24,115]. A systematic review of 3797 IgG4-RD patients identified multi-organ involvement (≥3), hypocomplementaemia and a history of allergy as significant risk factors for disease relapse [116]. A high MANNHEIM-AiP-Activity-Score (≥11) and persistently elevated serum IgG4 levels post-steroid treatment in AIP and proximal bile duct involvement in IRC may represent disease-specific risk factors for relapse [48,114,117].

7.3 Maintenance of Remission

In those with a high risk of relapse and in those who have previously relapsed, maintenance therapy is recommended.

Steroids: Low dose glucocorticoid maintenance therapy (daily 2.5–5 mg dose prednisolone) for short years is more commonly seen in Asia than in the United States or Europe [109] owing to concerns over longer-term side effects of steroids. Side effects include glucose intolerance and hyperglycaemia, mood disturbance, weight gain, a cushingoid appearance, sarcopenia, osteoporosis, osteonecrosis and increased susceptibility to infections [45]. Serious macrovascular complications such as cardiovascular and cerebrovascular events represent additional long-term risk factors associated with corticosteroid use in AIP patients [118]. Although long-term corticosteroid maintenance therapy reduces rates of relapse during treatment [109], the length of the maintenance therapy may not confer any increased protective benefits post-treatment [114].

Disease modifying antirheumatic drugs (DMARDs): Current steroid-sparing therapies include thiopurine analogues (azathioprine, mercaptopurine), anti-proliferative agents (mycophenolate mofetil (MMF)), methotrexate and cyclophosphamides [113]. Each agent is associated with side effects, specifically cytopenia, infections, and drug-induced liver/pancreatic injury but can be well tolerated in low doses [119]. Careful blood test monitoring is required to identify haematological and biochemical toxicity. When compared to glucocorticoid monotherapy, the addition of MMF or leflunomide as a combination therapy may lower relapse rates without additional safety concerns over 12 months, according to emerging single-center RCTs [120]. Furthermore, in a Chinese RCT of 146 IgG4-RD patients, continuation of either single-agent DMARDs or single-agent steroids after remission reduced relapse rates over 18 months when compared to the cessation of both agents [121]. This implies that a single-agent DMARD alone without steroids may be sufficient to reduce relapse rates. Whether this is organ, disease phenotype or disease activity specific, and which DMARD is superior, is unknown.

Biological agents: Anti-CD20 B cell targeted therapy with rituximab is considered an effective maintenance monotherapy, supported by prospective and retrospective relapse-control data, and expert consensus [122]. However, RCT data are lacking [122].

In the first multicenter randomised double-blind placebo-controlled phase 3 trial to assess safety and efficacy of inebilizumab in 135 patients with active IgG4-RD (MITIGATE), inebilizumab reduced disease flares by 87% compared to placebo [11]. Pancreatic and/or biliary involvement was reported in over 52% of the cohort. Overall, there was a reduced annualised flare rate and substantial glucocorticoid sparing using inebilizumab. Adverse events requiring withdrawal from the trial were low at 9% and 4% for the treatment and placebo groups respectively [11]. Inebilizumab became the first Food and Drug Administration (FDA) and European Medicines Agency (EMA)-approved therapy for active IgG4-RD in 2025.

A phase 2 clinical trial of 15 patients with a CD-19 and Fc gamma receptor IIb B cell inhibitor, obexelimab, demonstrated clinical improvement and rapid recovery of B-cell counts post-treatment [123]. The agent is currently in phase 3 trials. Phase 2 trials of the Bruton's Tyrosine Kinase inhibitor, rilzabrutinib, similarly showed clinical improvement in IgG4-RD, and has entered phase 3 trials. A phase 2 trial of abatacept for refractory IgG4-RD showed some response in those refractory to B cell depletion and a phase 2 trial of a Signaling Lymphocytic Activation Molecule Family member 7 (SLAM-F7) cytotoxic T cell targeting agent, elotuzumab, was discontinued early. There are case series and reports of agents targeting cytokines such as the anti-interleukin-5 (IL-5) mepolizumab [110] and Janus kinase (JAK)-inhibitors.

Table 5. Red flags for IgG4-RD Pancreato-Hepato-Biliary subtype.

	Red flags for disease
Clinical	• Obstructive jaundice • Abdominal pain • Weight loss • Cholestatic pruritus • Signs of pancreatic exocrine (steatorrhea, bloating and flatus) and endocrine (diabetes mellitus and hyperglycaemia) insufficiency • Steroid responsive • Fever without a source is uncommon
Risk factors	• Male • "Blue collar" occupational exposures • History of atopy and/or allergy
Imaging	• Diffuse swelling of pancreas with delayed enhancement (sausage pancreas) • Capsule-like rim hypodensities • Long strictures of main pancreatic duct (>1/3) • F-18 FDG PET-CT uptake • Stricture and narrowing of intra and extra-hepatic bile duct • Thickening of bile duct walls (>1 mm) • Unexplained mass in the pancreas, liver or biliary tract
Serology	• Elevated serum levels of IgG, IgG4 and/or IgE • Peripheral eosinophilia • Hypocomplementaemia (C3/4)
Pathology	• Lymphoplasmacytic infiltration • Storiform fibrosis • Obliterative phlebitis • >10 IgG4+ plasma cells per high-power field in a biopsy specimen • IgG4+: IgG+ plasma cell ratio of >40%
Other organ involvement	• Swelling and/or strictures of other organs • Symptomatic involvement of other organs

F-18 FDG, F-18 fluorodeoxyglucose; IgE, immunoglobulin E; IgG, immunoglobulin G.

7.4 Outcome

Organ damage and failure are potential complications in IgG4-RD. Up to 60% of patients have organ damage at the time of diagnosis given the current delays to diagnosis. Examples include endocrine and exocrine insufficiency in AIP with pooled prevalence rates of 37% and 45% respectively [45]. In IRC, proximal disease may confer increased risk of cirrhosis [48]. Malignancy has been reported and an increased risk of pancreatic cancer and CCA has been reported in some AIP/IRC cohorts [113]. A global risk for malignancies, especially lymphoma (60-fold), haematologic malignancies (16-fold), pancreatic cancer (14-fold), and increased mortality (2-fold) may exist for IgG4-RD [124,125]. Adequate treatment and surveillance may have a role in reducing these cases, but outcomes have not been well defined [109].

7.5 Limitations and Future Directions

Whilst we have made significant progress in the understanding of IgG4-RD, there remains much to learn. The precise aetiology of the disease, role of the IgG4 antibody, and immunological mechanisms that determine the degree of disease activity, organ involvement, disease flares and fibrotic progression remain uncertain [126]. Diagnosis remains a challenge, and requires increased education and multi-speciality input. The new 2023 International Classification of Diseases 10th revision code (ICD-10) for IgG4-RD is under-utilised in clinical coding practice. Clinical descriptions of disease phenotypes based on organ clustering are arbitrary and we search to uncover different pathogenic mechanisms that define organ system involvement. The definition of a disease flare (clinical, serological, radiological), their timing and distribution will need further focus. Furthermore, the relationship with malignancy and IgG4-RD and the reason for this is being actively explored.

Our current approach to controlling disease activity and symptoms with corticosteroids is leading to long-term toxicity and side effects for our patient cohort. A change in mind set to a more targeted precision-medicine approach should be adopted, especially for those with critical organ involvement, at the highest risk of relapse, and intolerant of steroid therapy. This could target the different subtypes (proliferative and fibrotic) as well as the organ system clusters. Current guidelines and consensus on treatment

in IgG4-RD and the Pancreato-Hepato-Biliary subtype are outdated, and do not include the recent phase 3 clinical trial data or consider therapies for refractory disease. Furthermore, implementation of such guidelines in clinical practice remains suboptimal [127]. A multi-disciplinary approach is needed to overcome many of these diagnostic and therapeutic barriers [7]. Lastly but importantly, patient awareness is growing thanks to advocacy groups such as IgG4Ward, guided by an expert panel of clinicians who can guide consensus guidelines and education on the disease and its management.

8. Conclusion

Current understanding of the Pancreato-Hepato-Biliary subtype of IgG4-RD is rapidly developing. This review has highlighted established and emerging clinical, imaging, serological and histopathological features, as well as existing and emerging biomarkers and treatments. While advancements such as machine learning, novel biomarkers and targeted therapies are promising, it first requires the patient to be presented to an IgG4-RD specialist. An understanding of patterns of organ presentation, classical radiological and histopathological findings are essential to improve diagnosis and to ensure optimal treatment for patients.

Key Points

• IgG4-related disease is a chronic systemic fibro-inflammatory condition that affects a wide range of organ systems, most frequently the pancreas and hepatobiliary system.

• Diagnosis relies on a combination of clinical, serological, imaging and histopathological features, as well as response to corticosteroid therapy; however, diagnostic delays are common due to limited awareness and the absence of a single definitive diagnostic test.

• Unpredictable disease flares lead to end-organ dysfunction and damage, most notably endocrine and exocrine insufficiency in the pancreas and progressive cholestasis and biliary strictures in the biliary system.

• Patients experience substantial symptoms from disease activity and damage, and have considerable anxiety and fear associated with the diagnostic journey and long-term sequelae.

• Corticosteroid treatment regimens are efficacious for inducing control of inflammation but have a high side-effect profile and disease relapse is common on reduction and/or discontinuation.

• Therapies that target B cells, plasmablasts and plasma cells (such as inebilizumab anti-CD19) can reduce the risk of disease relapse and have steroid-sparing potential with a favourable safety profile in the IgG4-RD population.

Availability of Data and Materials

Not applicable.

Author Contributions

HL: Conceptualisation, Literature analysis, Writing—original draft. RVM: Conceptualization, Supervision. ELC: Conceptualization, Literature analysis, Supervision. All authors contributed to revising the manuscript critically for important intellectual content. HL generated all figures for this study. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

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Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/BJHM55132.

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