IgG4-related hepatobiliary disease: an overview

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Abstract | IgG4-related hepatobiliary diseases are part of a multiorgan fibroinflammatory condition termed IgG4-related disease, and include IgG4-related sclerosing cholangitis (IgG4-SC) and IgG4-related hepatopathy. These diseases can present with biliary strictures and/or mass lesions, making them difficult to differentiate from primary sclerosing cholangitis (PSC) or other hepatobiliary malignancies. Diagnosis is based on a combination of clinical, biochemical, radiological and histological findings. However, a gold standard diagnostic test is lacking, warranting the identification of more specific disease markers. Novel assays — such as the serum IgG4:IgG1 ratio and IgG4:IgG RNA ratio (which distinguish IgG4-SC from PSC with high serum IgG4 levels), and plasmablast expansion to recognize IgG4-SC with normal serum IgG4 levels — require further validation. Steroids and other immunosuppressive therapies can lead to clinical and radiological improvement when given in the inflammatory phase of the disease, but evidence for the efficacy of treatment regimens is limited. Progressive fibrosclerotic disease, liver cirrhosis and an increased risk of malignancy are now recognized outcomes. Insights into the genetic and immunological features of the disease have increased over the past decade, with an emphasis on HLAs, T cells, circulating memory B cells and plasmablasts, chemokine-mediated trafficking, as well as the role of the innate immune system.

Over the past decade, substantial clinical and scientific attention has surrounded the concept and definition of IgG4-related disease (IgG4-RD), a multisystem fibroinflammatory condition with characteristic histopathological findings in the organs involved[1]. This Review focuses on the manifestations of IgG4-related hepatobiliary disease (IgG4-HBD), which includes IgG4-related sclerosing cholangitis (IgG4-SC) and IgG4-related hepatopathy, and covers the natural history and aetiopathogenesis of IgG4-HBD with an emphasis on IgG4-SC.

The natural history of IgG4-HBD

Historical perspective

Cases of sclerosing cholangitis associated with retroperitoneal fibrosis and Riedel's thyroiditis were reported as early as 1963 (REF. 2). Autoimmune pancreatitis (AIP) was associated with serum hypergammaglobulinaemia and a response to corticosteroids[3], and later evidence showed an elevated serum IgG4 level in these patients[4]. These findings were followed by the discovery that the pancreas and bile ducts were involved in a multiorgan IgG4-RD[5]. Further evidence of a distinct histological phenotype (namely, lymphoplasmacytic infiltration with abundant IgG4-positive cells, storiform fibrosis and obliterative phlebitis) supported the idea that IgG4-SC was the biliary manifestation of this systemic disease[6], and that liver biopsy samples could be supportive in diagnosis[7,8].

Terminology

Several descriptive terms for IgG4-HBD are used throughout the literature, and are detailed in BOX 1. For the purpose of this Review, IgG4-related hepatopathy includes IgG4-related autoimmune hepatitis and inflammatory pseudotumours of the liver and biliary tract. However, not all cases of inflammatory pseudotumour represent IgG4-RD, as they might be caused by other inflammatory processes and neoplastic entities, such as inflammatory myofibroblastic tumour.

Epidemiology

The epidemiology of IgG4-HBD is incompletely defined, stemming from delayed and obscured presentation of the disease, the absence of a single diagnostic test and the lack of consensus criteria to make a definitive diagnosis. The largest IgG4-SC cohorts to date are summarized in TABLE 1. IgG4-SC is the most common extrapancreatic manifestation in patients with AIP[9]. A nationwide population survey in Japan estimated the annual incidence of AIP as 1.4 per 100,000 and prevalence as 4.6 per 100,000

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Key points

- IgG4-related hepatobiliary diseases (IgG4-HBD) are part of a systemic fibroinflammatory condition, termed IgG4-related disease. IgG4-HBD includes IgG4-related sclerosing cholangitis (IgG4-SC) and IgG4-related hepatopathy
- IgG4-HBD can present with abnormal liver biochemistry, biliary strictures and/or masses, impeding the differentiation from other benign and malignant hepatobiliary disorders
- Diagnosis is based on a combination of clinical, biochemical, radiological and histological findings. A gold standard diagnostic test is lacking, although novel markers might help to differentiate IgG4-HBD from other conditions
- Treatment regimens have been reached by international consensus but are not supported by randomized controlled trials. First-line therapy is corticosteroids, often in combination with biliary stenting for patients with IgG4-SC
- The long-term outcome in IgG4-HBD is not well established. Disease-related inflammatory and fibrotic complications and an increased risk of all-cause malignancy have been reported in prospective studies
- Insights into the genetic and immunological aspects of disease pathogenesis have increased over the past decade. Defining the initiating and driving factors for fibrotic disease remains an important challenge

of the population in 2011 (REF. 10), an increase from previous estimates in 2007 (incidence 0.9 and prevalence 2.2 per 100,000)[11]. Of the 918 patients with AIP in this survey, 95 (10.3%) had IgG4-SC at the porta hepatis and 216 (23.5%) had intrahepatic disease[10]. Furthermore, a 2012 Japanese national survey of primary sclerosing cholangitis (PSC) and IgG4-SC identified 43 patients with IgG4-SC who did not have pancreatic involvement[12] which, given the estimated 8,000 IgG4-RD and 2,790 AIP cases in Japan in 2009, accounts for 1.5% of presentations[13]. However, in US and UK cohorts, isolated IgG4-SC without AIP contributes to 8% of cases[14,15]. The prevalence of IgG4-related hepatopathy is unknown, as only small series have been reported[7,16].

Risk factors and associations

Risk factors for disease development have been postulated in patients with IgG4-SC. A history of occupational exposure, especially of 'blue-collar work', has been described in 61–88% of patients with IgG4-SC or AIP in independent Dutch and UK cohorts, compared with 14% of patients with PSC and 22% of patients with PSC and elevated serum IgG4 levels[17]. These findings suggest that chronic exposure to chemicals and toxins might be critical in the development of the disease. A clinical history of allergy and/or atopy has also been described in 40–60% of patients with IgG4-SC or AIP, often in association with peripheral eosinophilia and elevated IgE levels[18,19], which might represent a separate disease phenotype[20]. A coexistent history of other autoimmune diseases (such as thyroid disorders, coeliac disease and IBD) is also found in up to 10% of patients with IgG4-SC or AIP[21].

Diagnosis

Clinical presentation

IgG4-HBD has a male preponderance, with patients usually presenting in their 6th decade of life[14]. The clinical presentation depends upon disease activity and the distribution of organs involved. Patients with IgG4-SC often present with obstructive jaundice (70–80%), weight loss and abdominal pain[21]. Those with concomitant AIP can present with symptomatic pancreatic exocrine and endocrine insufficiency[14]. However, no specific symptoms enable reliable differentiation of IgG4-SC from other causes of biliary obstruction. This fact is fundamentally important given the serious consequences of misdiagnosis, which include surgical resection for presumed malignancy and inappropriate medical therapy[14,22].

A diagnosis of IgG4-HBD might also be reached during the investigation of nonspecific symptoms in the setting of abnormal liver function test results[23]. IgG4-HBD can be asymptomatic and can be found incidentally on cross-sectional imaging performed for other reasons. Other cases are identified in patients presenting with symptoms related to other organs affected by IgG4-RD.

Laboratory evaluation

Liver function test results are often abnormal in IgG4-HBD. A pattern of raised serum levels of bilirubin, alkaline phosphatase and gamma-glutamyltransferase is most commonly observed in IgG4-SC, whereas raised transaminase levels are more frequent in IgG4-related hepatopathy[7,14]. Elevated inflammatory markers are nonspecific for disease subtype and serum protein electrophoresis reveals a polyclonal hypergammaglobulinaemia[24]. Antinuclear antibody titres are positive in almost 50% of patients, and rheumatoid factor levels are raised in 20%, but no specific autoantibody has been identified to date[25].

Total serum IgG levels are increased in >50% of patients with AIP or IgG4-SC, but can be normal despite an elevated serum IgG4 subclass level[26]. Serum IgG4 levels are raised (>1.4 g/l) in 65–80% of patients at diagnosis[14,15]. However, increased serum IgG4 levels are also observed in 5–25% of inflammatory, autoimmune and malignant pathologies, and in 5% of healthy individuals[27–29]. Several studies have explored methods to optimise the diagnostic value of serum IgG4 levels. Levels >2.5 g/l gave a sensitivity of 67–89% and specificity of 95% to differentiate IgG4-SC from PSC in Dutch and UK cohorts[26]. Within the subgroup of patients with PSC and an elevated serum IgG4 level of 1.4–2.8 g/l (15% of patients), the use of an IgG1:IgG4 ratio >0.24 gave a sensitivity of 86% and specificity of 95% to distinguish PSC with high serum IgG4 levels from IgG4-SC[26]. A serum IgG4 level >5.6 g/l increases the specificity and positive predictive value to 100% for differentiating IgG4-SC from PSC and cholangiocarcinoma[26,29]. A further study suggested that serum IgG4 levels >1.8 g/l and >2.1 g/l gave a specificity of 97% and 100% to distinguish type 3 (distal and hilar strictures) and type 4 (hilar stricture) IgG4-SC from cholangiocarcinoma, respectively[30]. TABLE 2 shows the classification of IgG4-SC based on the site of biliary involvement[31,32].

Patients with IgG4-SC and normal serum IgG4 levels (20–25%) are a challenge to differentiate from disease mimics, such as PSC and hilar cholangiocarcinoma[14]. This subgroup seems to have a distinct clinical phenotype, with a reduced risk of relapse and fewer organs involved[33]. A novel quantitative PCR test analysing the blood IgG4:IgG RNA ratio has shown promise in differentiating IgG4-SC with normal or high IgG4 serum levels from PSC and cholangiocarcinoma with normal

Box 1 | **Terminology used to describe IgG4-related hepatobiliary disease**

IgG4-associated cholangitis
First proposed in 2007 and adopted by the European Association for the Study of the Liver (EASL) guidelines for cholestatic liver disease in 2009. Biliary disease considered as steroid-reversible, non-sclerosing and associated with IgG4[14,132].

IgG4-related sclerosing cholangitis (IgG4-SC)
Proposed at the 1st international symposium of IgG4-RD in Boston 2011, and included in the nomenclature of IgG4-related disease in 2012. The term 'sclerosing' is used, given the fibrotic and potentially irreversible nature of more advanced disease[1].

IgG4-related hepatopathy
Originally used to describe the presence of IgG4-positive plasma cells in the liver of patients with autoimmune pancreatitis. Might also include small-duct intrahepatic IgG4-SC. The term has been used to describe all liver involvement in IgG4-related disease since 2012[7,56].

IgG4-related autoimmune hepatitis
Describes the presence of IgG4-positive plasma cells in the liver of patients with autoimmune hepatitis. This term does not infer that these patients have IgG4-related disease in the absence of other morphological or radiological features[8,66,133].

Inflammatory pseudotumours of the liver and biliary tract
Describes a classical lymphoplasmacytic infiltrate, storiform fibrosis and obliterative phlebitis in a hepatic and/or hilar mass lesion. The term 'IgG4-related hepatopathy' has been used to include these pseudotumours[16].

or high IgG4 serum levels, and has been validated in independent cohorts[34]. Furthermore, peripheral blood plasmablasts (derived from the B cell lineage; an intermediate between an activated B cell and a plasma cell), which are rare in healthy individuals, are expanded in active and relapsing disease and are independent of the serum IgG4 level[35,36]. Circulating plasmablasts have similarly been described in rheumatoid arthritis and systemic lupus erythematosus, and might have clinical utility for IgG4-RD in the future[37,38].

Serum IgE levels are raised in 35–60% of patients with AIP or IgG4-SC, and peripheral eosinophilia is evident in 25–38% of these patients[18]. Serum IgE levels >408 kU/l (equivalent to 979.2 ng/ml) at diagnosis have a sensitivity of 88%, a specificity of 86% and a likelihood ratio of 5.6 to differentiate IgG4-RD from non-IgG4-RD conditions with an elevated serum IgG4 level[39]. Patients with a history of allergy and/or atopy seem more likely to have a raised IgE level and/or eosinophilia than patients without atopy[18,19].

Table 1 | **Reported worldwide frequencies of IgG4-SC and AIP**

Cohort	Country	Number of patients	Number of patients with IgG4-SC (%)	Number of patients with AIP (%)
AIP[10]	Japan	918	311 (34)	918 (100)
IgG4-SC and AIP[21]	UK	115	69 (60)	106 (92)
IgG4-SC and AIP[14]	USA	53	53 (100)	49 (92)
IgG4-RD[134]	China	118	21 (18)	45 (38)
IgG4-RD[135]	Japan	235	30 (13)	142 (60)
IgG4-RD[136]	Spain	55	30 (4)	142 (60)
IgG4-RD[137]	Italy	41	4 (10)	17 (41)

AIP, autoimmune pancreatitis; IgG4-RD, IgG4-related disease; IgG4-SC, IgG4-related sclerosing cholangitis.

Radiological features

Imaging features can raise initial clinical suspicion of IgG4-HBD (TABLE 2). Abdominal ultrasonography might demonstrate biliary dilatation, extrahepatic biliary stenosis or a mass lesion including pancreatic enlargement (suggestive of coexistent AIP), and could exclude other causes of biliary obstruction[40]. However, cross-sectional imaging is vital. CT scans might demonstrate biliary stricturing with thickened bile duct walls, an associated liver or hilar mass and/or evidence of other organ involvement[41]. Magnetic resonance cholangiography might show symmetrical biliary wall thickening, smooth inner and outer margins and/or a homogenous echo appearance of the internal bile duct wall[42]. Certain MRI features have also been suggested to support a diagnosis of IgG4-SC over PSC, including continuous bile duct involvement (rather than skip disease), common bile duct wall thickness >2.5 mm, and the presence of gallbladder, pancreatic and renal involvement[43].

Lesions can also occur in regions where no identifiable biliary stricture exists on cholangiography[44]. PET–CT has been used to demonstrate clinically silent organ involvement in extrapancreatobiliary sites, both at diagnosis and after disease relapse, although its role in IgG4-HBD remains undefined[45].

Endoscopic features

Endoscopic retrograde cholangiopancreatography has an integral role in the investigation and management of patients with suspected IgG4-SC. Cholangiogram features that are characteristic of IgG4-SC include long (over one-third the length of strictures in the bile duct) and multifocal strictures, mild upstream dilatation and proximal biliary disease in conjunction with diffuse pancreatic swelling, with a thin, diffusely-narrowed pancreatic duct[22,31,46]. However, when experts were required to differentiate IgG4-SC, PSC and cholangiocarcinoma on the basis of endoscopic retrograde cholangiopancreatography features alone, this modality provided 88% specificity but only 45% sensitivity[47]. Endoscopic biliary brushings for cytology, fluoroscopy-directed intrabiliary or ampullary biopsies for histology, and bile fluid sampling can also all be obtained to aid diagnosis[42,48].

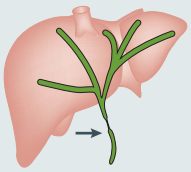
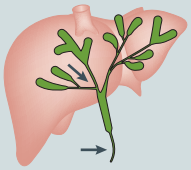
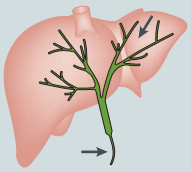
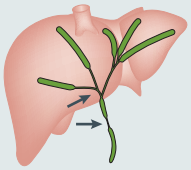
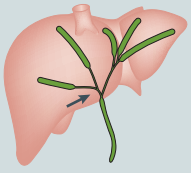
Cholangioscopy enables direct visualisation of the intrabiliary mucosa and stricture assessment, which can show characteristic features and permit targeted biopsies[49]. Biliary stenting of dominant strictures is performed to decompress the biliary tree for symptomatic benefit and in the setting of biliary sepsis[14]. Endoscopic and intraductal ultrasonography can demonstrate pancreatic or biliary mass lesions, diffuse biliary wall thickening in stenotic segments in IgG4-SC, pancreatic ductal abnormalities in AIP and can also permit fine-needle aspiration[50].

Histological features

Tissue acquisition to enable accurate pathological diagnosis is a priority in IgG4-HBD. Cytological samples from brushings of biliary strictures or endoscopic ultrasonography fine-needle aspiration can be used to identify malignancies — albeit with a sensitivity of 20–50% — but do not show diagnostic features of IgG4-SC[51]. Intrabiliary

biopsies often yield small samples but might show characteristic features of IgG4-SC[52]. Ampullary biopsies from the major papilla are also technically feasible and safe[53], although care must be taken to avoid the pancreatic duct orifice and biopsy-related acute pancreatitis. These techniques can support a diagnosis of IgG4-SC in the setting of an IgG4-positive lymphoplasmacytic infiltrate (53–80% of patients with AIP), but IgG4-positive cells alone are nonspecific and other diagnostic features are rarely present[53,54]. The involvement of small intrahepatic bile ducts in IgG4-SC can be observed from liver biopsy samples (26% of cases), which might be especially useful for patients with intrahepatic biliary strictures on cholangiography[44]. Analysis of biliary fluid has shown elevated IgG4 levels compared with other biliary disorders, including PSC and cholangiocarcinoma, but this analysis is not clinically useful as it is nonspecific[55].

Table 2 | **Cholangiogram-based classification of IgG4-SC**

Subtype	Involvement	Differential diagnosis	Comments
Type 1 	Distal common bile duct stricture	Pancreatic carcinoma, distal cholangiocarcinoma, chronic pancreatitis	Most frequent pattern, often with AIP
Type 2		PSC, SSC, pancreatic carcinoma, distal cholangiocarcinoma	Can exhibit additional extrahepatic strictures
Type 2a 	• Diffuse intrahepatic cholangiopathy and a lower common bile duct stricture • Prestenotic dilatation		
Type 2b 	• Diffuse intrahepatic cholangiopathy and a lower common bile duct stricture • Without prestenotic dilatation		
Type 3 	Hilar and distal common bile duct stricture	Hilar cholangiocarcinoma, pancreatic carcinoma, distal cholangiocarcinoma, gall bladder carcinoma	
Type 4 	Hilar stricture	Hilar cholangiocarcinoma	Most challenging to diagnose

AIP, autoimmune pancreatitis; IgG4-SC, IgG4-related sclerosing cholangitis; PSC, primary sclerosing cholangitis; SSC, secondary sclerosing cholangitis.

IgG4-SC usually affects the extrahepatic, hilar and perihilar bile ducts but it can also involve the small intrahepatic ducts and gallbladder[56]. Macroscopic and microscopic features are shown in BOX 2 and FIG. 1 (REFS 7,44,57). Limitations to interpretation include patchy disease, insufficient tissue sampling and the fact that not all features might be seen in a single specimen[58]. In one IgG4-SC series, in which transpapillary biopsy specimens were collected using intraductal ultrasonography, obliterative phlebitis was absent and IgG4-positive cell counts were inadequate in the majority of patients[59]. Reduced numbers of IgG4-positive plasma cells are seen in patients with long-standing fibrotic disease[60]. In this instance the IgG4:IgG ratio becomes invaluable; with a plasma cell ratio >40% highly suggestive of IgG4-SC[60]. Similarly, an abundance of IgG4-positive cells is not sufficient for diagnosis, and can also be seen in a variety of inflammatory and malignant diseases such as diverticulitis, rheumatoid arthritis and adenocarcinoma[61–64].

Hepatic tumefactive nodules or inflammatory pseudotumours are possible manifestations of intrahepatic IgG4-SC[65]. Histologically, two forms have been described, fibrohistocytic and lymphoplasmacytic, but only the latter has characteristic features of the disease. IgG4-related hepatopathy has five histological patterns: evident portal inflammation (with or without interface hepatitis); large bile duct obstructive features; portal sclerosis; lobular hepatitis; and canalicular cholestasis in perivenular areas[7]. Whether some of these changes are secondary to extrahepatic biliary obstruction of IgG4-SC is uncertain. IgG4-related autoimmune hepatitis might either be a hepatic manifestation of IgG4-RD or, more likely, a subtype of classic autoimmune hepatitis, and is characterised by IgG4-positive plasma cell infiltration in the liver, often without other classic features of AIH[66]. Specimens from other involved organs, such as the gallbladder, can also support the diagnosis of IgG4-RD in the absence of sufficient biliary or liver histology[58].

Diagnostic criteria

The diagnosis of IgG4-HBD depends on the combination of clinical, radiological, pathological and laboratory parameters, and no test in isolation is definitive. Several guidelines for IgG4-SC have been developed[14,42,67]. The HISORt (histology, imaging, serology, other organ involvement and response to therapy) criteria, originally developed for AIP and adapted for IgG4-SC, are the most widely used[14,68]. The Japanese clinical diagnostic criteria for IgG4-SC classify the diagnosis as being definite, probable or possible[42]. Both guidelines include typical imaging features of a thickened bile duct wall with segmental or diffuse biliary strictures, raised serum IgG4 levels, evidence of other organ involvement and classic histological features. A radiological and biochemical response to corticosteroid therapy is supportive for diagnosis, with the caveat that steroids can improve the infiltrate around other malignant and inflammatory conditions[14]. Although these criteria provide guidance in clinical practice, malignancy must be excluded, which in practice often requires tissue sampling. A helpful diagnostic aid with red flags for IgG4-HBD is shown in BOX 3.

Box 2 | **Histological features of IgG4-SC**

Macroscopic[7,44,57,65,138]
- Bile duct tissue
  - Bile ducts are diffusely thickened with a stenotic lumen
  - A mass lesion is present in some cases
  - Biliary epithelium is well preserved but inflammation can extend into local veins, glands and nerves
- Liver tissue
  - Portal-based micro-inflammatory nodules of lymphocytes, plasma cells, eosinophils and a myxoid stroma

Microscopic[60]
- IgG4-hepatobiliary disease shares the same pathological lesion seen in almost all tissues affected by IgG4-related disease. Classic features include:
  - lymphoplasmacytic infiltration
  - storiform pattern of fibrosis
  - obliterative phlebitis with a variable presence of eosinophils
- Tissue IgG4 and IgG immunostaining on all specimens
  - A mean count of $IgG4^+$ plasma cells in three high-power fields (HPF) and a ratio of $IgG4^+$:IgG^+ plasma cells are calculated
- Boston histological consensus criteria for bile duct and liver*
  - >10 $IgG4^+$ plasma cells per HPF in a biopsy specimen
  - >50 $IgG4^+$ plasma cells per HPF in a resection specimen
  - Plus an $IgG4^+$:IgG^+ plasma cell ratio of >40% in the context of two of three classic features

IgG4-SC, IgG4-related sclerosing cholangitis. *Features considered in the appropriate clinical context.

Differential diagnosis

Differentiating IgG4-HBD from other benign and malignant conditions is of fundamental importance and is detailed in TABLE 3. Important differentials from IgG4-SC include PSC, secondary sclerosing cholangitis, cholangiocarcinoma and pancreatic carcinoma. Differentials from IgG4-related hepatopathy include autoimmune hepatitis and both benign and malignant hepatic tumours.

Treatment

The aims of treatment in IgG4-HBD are to alleviate symptoms and to prevent disease-related complications and irreversible fibrosis. An international consensus of experts on disease management concluded that urgent treatment is appropriate in biliary disease, even when asymptomatic, to prevent infectious cholangitis and permanent fibrosis that might complicate untreated disease[69]. Substantial spontaneous improvement of type 1 IgG4-SC is sometimes seen, with stricture improvement probably correlating with reduced pancreatic inflammation around the distal common bile duct. However, in IgG4-SC types 2–4, an improvement without treatment is unusual.

Despite an absence of randomized placebo-controlled trials, the mainstay of treatment is systemic corticosteroids, extrapolated from findings in AIP. Steroid use was shown to induce remission quicker, more consistently and with a lower relapse rate than a conservative approach in this disease[70]. International consensus regarding initiation therapy with oral steroids has been reached for IgG4-RD[69], and a starting dose of prednisolone 30–40 mg daily for 4 weeks, before reducing by 5 mg every 2 weeks — depending on response — is recommended. However, one retrospective analysis suggested that a reduced starting dose of 10–20 mg of prednisolone might be enough to induce remission in a cohort of patients with AIP (60% of whom had IgG4-SC)[71], although this finding has not been validated in prospective controlled trials. This approach might be particularly beneficial in patients with coexistent diabetes mellitus, osteoporosis or psychological disturbance, who might not tolerate high-dose steroids without adverse effects.

In patients with a high clinical suspicion of IgG4-SC but who do not fulfil the diagnostic criteria of definite disease, some clinicians advocate a steroid trial to confirm diagnosis (after thorough evaluation and exclusion of malignancy)[72]. This approach should only be performed under close observation in centres with experience in managing the disease.

During treatment, patients should be reviewed for evidence of steroid-induced adverse effects, biliary obstruction and cholangitis or sepsis. Clinical, biochemical and cholangiographic improvement should be seen within 4–6 weeks of starting treatment, and should be confirmed by repeat imaging[14]. Serum IgG4 levels decrease with corticosteroid therapy (although they only normalize in the minority of patients) and this

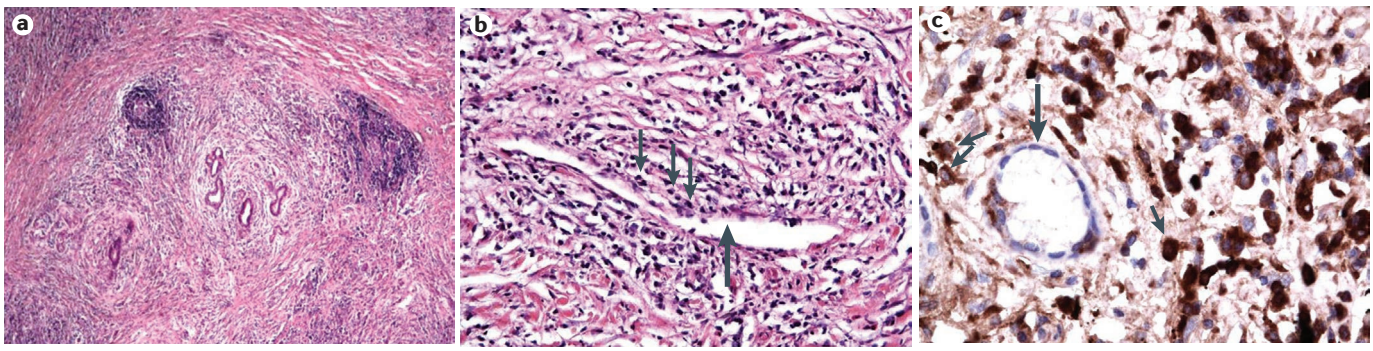


Figure 1 | **Histological sections of IgG4-related sclerosing cholangitis. a** | Bile duct resection demonstrating a lymphoplasmacytic cell infiltrate with periductal distribution (×10 magnification). **b** | Bile duct resection demonstrating obliterative phlebitis: a thin-walled vessel (large arrow) surrounded by numerous plasma cells and lymphocytes (small arrows), which seem to partially compress the luminal diameter (×20 magnification). **c** | Immunohistochemical staining of the bile duct (large arrow) surrounded by abundant IgG4-positive plasma cells (small arrows; dark brown cells), >50 per high power field (×40 magnification).

Box 3 | **Red flags in the diagnosis of IgG4-HBD**

Clinical
Male in 6th decade of life
Obstructive jaundice*
History of unexplained swelling in one or more organ system

Disease associations
Occupational exposures
History of allergy or atopy
History of autoimmune diseases
Absence of IBD

Laboratory measurements
Elevated serum levels of IgG, IgG4 and/or IgE
Peripheral eosinophilia
Polyclonal hypergammaglobulinaemia

Response to steroids
Resolution of biochemical (liver function tests) and radiological (strictures or masses) findings

Imaging
Long continuous strictures in the bile duct*
Involvement of distal common bile duct with diffusely enlarged or solitary mass in pancreas*
Hilar and/or intrahepatic cholangiopathy*
Unexplained mass in the liver or biliary tract‡
Spontaneous improvement or resolution of strictures or mass*‡
Enlargement or fibrotic thickening of other organs

Histology
Lymphoplasmacytic infiltration
Storiform fibrosis
Obliterative phlebitis
Eosinophils

Immunohistochemistry
>10 $IgG4^+$ plasma cells per high-power field in a biopsy specimen
>50 $IgG4^+$ plasma cells per high-power field in a resection specimen
$IgG4^+$:IgG^+ plasma cell ratio of >40%

IgG4-HBD, IgG4-related hepatobiliary disease. *Indicative of IgG4-related sclerosing cholangitis. ‡Indicative of IgG4-related hepatopathy (inflammatory pseudotumour)

finding is not disease-specific[25]. Remission in response to steroid therapy, defined as complete resolution of strictures and/or normalization of liver test results, was reported in approximately two-thirds of patients with IgG4-SC[14] and in almost 99% of patients with AIP[73]. Nonresponse might be representative of a less inflammatory, burnt-out disease, a more fibrotic phenotype or, importantly, an alternative diagnosis.

In the setting of biliary obstruction and hilar, or dominant, extrahepatic strictures, biliary stenting at endoscopic retrograde cholangiopancreatogram is usually indicated even if a response to steroids is expected[14,21]. Stents can be removed once steroid therapy is effective[14].

Disease relapse

Patients with IgG4-SC are at high risk of relapse, the majority of which occurs within 6 months of discontinuing or tapering steroid treatment[15]. Relapse rates have been reported between 50–57% after corticosteroid therapy, similar to that reported after surgery[21,73,74]. Factors predictive of a relapse include the presence of proximal strictures (IgG4-SC type 2–4) and high serum IgG4 levels (>2.8 g/l) at diagnosis[14,33,74].

Patients whose disease improves but is slow to resolve, or relapses on taper, can be treated with a further course of corticosteroids, with or without the initiation of second-line immunosuppressive therapy[75]. In IgG4-SC, most experience has been with the use of azathioprine, although other immunomodulators have been used in the context of extrapancreatic disease and/or intolerance[21,74,75] (TABLE 4). However, the benefits of the addition of immunomodulators over low-dose steroids alone in reducing time to further relapses are uncertain[75]. Predictors of resistance to immunomodulator therapy include evidence of other organ involvement (except IgG4-SC) and retroperitoneal fibrosis[75]. Biliary stenting is an adjunct in those with a suboptimal clinical response to treatment, particularly in late-stage fibrotic disease[14].

Rituximab, a CD20-depletion agent, has been used in patients with IgG4-SC with incomplete remission, steroid dependency, or steroid or immunomodulator intolerance[75,76]. A case series and a prospective open-label study included patients with IgG4-SC[75,77]. In the latter study, 97% of patients achieved disease response and 77% had reduced disease activity, discontinued steroid therapy and did not exhibit disease relapse by 6 months. Remission, defined as inactive disease in the absence of steroids, was achieved in 47% and 46% of patients at 6 and 12 months, respectively[77]. As experience grows, a more top-down approach might be considered in patients with multiorgan disease and high risk of relapse, to reduce adverse effects and potentially modify the disease.

Clinical course and outcome

Long-term outcome data in patients with IgG4-HBD are lacking. If diagnosed and treated early, steroid-responsive IgG4-SC seems to have a favourable prognosis, with immunosuppression and adverse effects or intolerance of corticosteroids causing the most problems. Delayed therapy can lead to inflammatory and fibrotic complications, biliary cirrhosis (in 5% of patients) and increased mortality[14,21], which is also the case for patients with extrabiliary organ involvement[78]. The risk of any malignancy is increased (more than twofold) in patients with IgG4-SC or AIP compared with population controls, possibly because of the increased rate of cell proliferation inherent to long-term immune activation[15,79].

Pathogenesis of disease

Although the pathogenic mechanisms underlying IgG4-SC are poorly understood, insights into the genetic and immunological aspects of the disease have increased over the past decade.

IgG4 biology

IgG4 is the least prevalent of the four IgG subclasses in health, representing 3–6% of total IgG, but accounts for up to 80% of total IgG after chronic antigen exposure[80].

Human IgG4 has >90% amino acid sequence homology with the other IgG subclasses; however, it has unique structural and functional properties[81] (see Supplementary information S1 (box)).

Genetic studies

Studies have identified HLA molecules and other immune-regulatory genes as determinants of disease susceptibility to AIP, disease relapse after steroid therapy and extrapancreatic disease[82–84]. HLA association studies reported higher frequencies of the *HLA-DRB1*0405-HLA-DQB1*0401* haplotype in Japanese patients with AIP than healthy individuals and those with chronic calcifying pancreatitis[82]. A non-aspartic amino acid at *HLA-DQB1*57* was associated with relapse in Korean patients with AIP[83], but was not confirmed in a Japanese cohort[84]. A UK study found that *HLA-DRB1*0301-HLA-DQB1*0201* frequencies were

Table 3 | **Differential diagnosis of IgG4-SC types 1–4**

Category	Feature	Details	Ref.
Type 2 IgG4-SC versus PSC			
Clinical	IBD	In 75% of PSC and 5% of IgG4-SC or AIP	139–141
	Age and gender	• Age of onset <40 years in PSC and >50years in IgG4-SC, but not absolute • Males predominate; ratio 1.5:1 in PSC and 7:1 in IgG4-SC	141
Lab	pANCA	In 40% of PSC and <10% IgG4-SC	142
	sIgG4 >1.4 g/l	In 9–18% of PSC and 65–80% of IgG4-SC	27,143
	sIgG4 >5.6 g/l	100% specificity for IgG4-SC versus PSC	26
	sIgG1:IgG4 ratio	95% specificity of ratio >0.24 for IgG4-SC versus PSC-high IgG4 (sIgG4 1.4–2.8 g/l)	143
	HLA haplotypes	• In PSC-high IgG4 (sIgG4 >2 g/l), *HLA-B*07* and *HLA-DRB1*15* • In PSC-normal IgG4, *HLA-B*08* • In IgG4-SC, *HLA-DRB1*0301*	144,145
Imaging	Cholangiogram	• Beaded or pruned-tree appearance and short band-like strictures in PSC • Long continuous strictures with prestenotic dilatation, involvement of the distal common bile duct and hilar or intrahepatic cholangiopathy in IgG4-SC	31
	CT scan	• Evidence of other organ involvement, especially pancreatic involvement (92%) in IgG4-SC • Other autoimmune conditions coexist with PSC but pancreatitis less frequent (<5%)	146
Histology	Morphology	• Onion-skin fibrosis and periportal sclerosis in PSC • Two of three classic features, including LPCI, SF and OP in IgG4-SC	22
	$IgG4^+$:IgG^+ plasma cell ratio	• In PSC-high IgG4, ratio <40% • In IgG4-SC, $IgG4^+$plasma cells >10/HPF (biopsy) or >50/HPF (resection), ratio >40%	60
Treatment	Steroids	• Response in IgG4-SC with biochemical and radiological improvement at 4 weeks in two-thirds of patients with IgG4-SC and almost 100% of patients with AIP • No response in PSC; however, variable response in overlap syndromes and in patients with PSC-high IgG4	14,21
Type 2 IgG4-SC versus SSC			
Clinical	Clinical history guides investigation	Infection (e.g. AIDS cholangiopathy), vascular (e.g. hepatic artery thrombosis), toxic (e.g. after chemotherapy), congenital (e.g. Caroli disease), infiltrative (e.g. histiocytosis X), trauma (e.g. after biliary trauma), immunological (e.g. eosinophilic cholangitis)	147
Type 1–4 IgG4-SC versus cholangiocarcinoma (de novo and PSC-associated)			
Clinical	None	Both present with jaundice and weight loss	
Lab	CA19-9 levels (>37 U/ml)	In 63% of IgG4-SC and 77% cholangiocarcinoma	142,148
	sIgG4 >5.6 g/l	100% specificity for IgG4-SC versus cholangiocarcinoma	29
	sIgG4 >5.6 g/l	100% specificity for IgG4-SC versus cholangiocarcinoma	29
Imaging	Cholangiogram	Biliary dilation >10 mm proximal to a confluent distal common bile duct stricture, in association with a pancreatic mass, is more suggestive of type 1 IgG4-SC; role for cholangioscopy in this setting	46
Histology	Morphology	• ERCP, EUS or US–CT-guided biopsy • Two of three classic features of LPCI, SF, OP in IgG4-SC • Dysplastic and malignant cells in cholangiocarcinoma	22,149
	$IgG4^+$:IgG^+ plasma cell ratio	• In cholangiocarcinoma, ratio <40%. • In IgG4-SC, ratio >40%	60
Treatment	Steroids	• Response in IgG4-SC with biochemical and radiological improvement at 4 weeks in two-thirds of patients with IgG4-SC and almost 100% of patients with AIP • Inflammatory area around malignant strictures can improve so is not diagnostic	46

AIP, autoimmune pancreatitis; ERCP, endoscopic retrograde cholangiopancreatogram; EUS, endoscopic ultrasonography; HPF, high-power field; IgG4-SC, IgG4-related sclerosing cholangitis; LPCI, lymphoplasmacytic infiltrate; OP, obliterative phlebitis; pANCA, perinuclear anti-neutrophil cytoplasmic antibodies; PSC, primary sclerosing cholangitis; SF, storiform fibrosis; sIgG4, serum IgG4; SSC, secondary sclerosing cholangitis; US, ultrasonography.

Table 4 | **Immunosuppresive therapies for IgG4-SC***

Agent	Regimen	Mechanism of action
Azathioprine‡	2 mg/kg per day in a single dose	Thiopurine analogue, and is the prodrug of mercaptopurine
Mycophenolate mofetil§	750–1,000 mg twice per day	Inosine-5′-monophosphate dehydrogenase inhibitor
Mercaptopurine§	2.5 mg/kg per day in two divided doses	Thiopurine analogue
Methotrexate‖	10–25 mg per week plus folic acid	Antimetabolite and antifolate agent
Tacrolimus‖	Adjusted to a target blood level range of 4–11 ng/mL	Macrolide calcineurin inhibitor
Rituximab	1,000 mg week 0 and week 2 by intravenous infusions	$CD20^+$ B cell depletion agent

IgG4-SC, IgG4-related sclerosing cholangitis. *In the context of patients experiencing adverse effects, therapy intolerance, disease relapse or extrapancreatic disease. ‡Azathioprine is the most widely used second-line immunosuppressive agent in IgG4-related sclerosing cholangitis. §Mycophenolate and mercaptopurine are recommended in treatment of extra-hepatopancreatobiliary manifestations and in those intolerant of azathioprine. ‖Methotrexate and tacrolimus used in case reports or series only in IgG4-realted sclerosing cholangitis.

higher in patients with IgG4-SC or AIP than healthy individuals[85]. Single nucleotide polymorphisms involved in AIP disease susceptibility or recurrence have been reported to be present within genes encoding proteins such as cytotoxic T-lymphocyte protein 4, TNFα and Fc receptor-like protein 3 (REFS 86–88) (TABLE 5).

Antigens

The presence of oligoclonal B cells in peripheral blood and tissues of patients with IgG4-SC supports an antigen-mediated response[35,89]. Antibodies against a range of autoantigens and nonself antigens in AIP have been proposed, including lactoferrin, carbonic anhydrase 2 and 4, pancreatic secretory trypsin inhibitor, trypsinogens, pancreatic alpha-amylase and heat shock protein[90–92] (see Supplementary information S2 (table)). However, none of these antigens have been found consistently in the disease, and those tested are of the IgG1 and not IgG4 subclass. A proteomics study identified a 13.1 kDa protein as a candidate autoantigen, but the sequence has not been clarified[93].

Gastric *Helicobacter pylori* infection has been proposed to trigger AIP (and hence IgG4-SC) in genetically predisposed individuals through a process of molecular mimicry or antibody crossreactivity[94,95]. Antibodies against *H. pylori* plasminogen-binding protein were detected in 94% of Italian patients with AIP, but were not disease-specific[96]. Other studies did not detect *H. pylori* DNA in tissue or pancreatic juice from patients with AIP[97]. Further evidence in patients with IgG4-SC or AIP from the UK suggested no increased risk of *H. pylori* infection, or evidence of immunological memory to *H. pylori* plasminogen-binding protein[98].

Table 5 | **Single nucleotide polymorphisms in patients with AIP and IgG4-SC**

Proteins	Single nucleotide polymorphisms	Association	Ref.
CTLA-4	• 49A haplotype • -318C/+49A/CT60G • +6230 3′-untranslated region • +6230G/G • +6230A • 49A/A and +6230A/A genotypes	• Higher frequencies in China • AIP susceptibility in China • AIP susceptibility in Japan • AIP susceptibility in Japan • AIP resistance in Japan • AIP relapse in Japan	86, 88
TNF-α	863A haplotype	Extrapancreatic involvement in China	88
FcR-3	-110A/A genotype	AIP susceptibility in Japan	87

AIP, autoimmune pancreatitis; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FcR-3, Fc receptor 3; IgG4-SC, IgG4-related sclerosing cholangitis

IgG4 autoantibodies

Convincing evidence that IgG4 itself is driving the pathology of IgG4-RD is lacking. IgG4-type autoantibodies have not been detected in IgG4-SC, although IgG4 in the sera of patients with AIP binds with normal pancreatic and biliary epithelial tissue[99]. Circulating IgGs from patients with IgG4-RD (especially IgG1 and IgG4) can also bind pancreatic tissue in patients with AIP and neonatal BALB/c mice, with more destructive changes induced by IgG1 than IgG4, and IgG1 activity inhibited by simultaneous IgG4 injection[100]. Furthermore, IgG4 autoantibodies have an important role in immune-mediated disorders unrelated to AIP or IgG4-SC (see Supplementary information S3 (table)).

Immune-mediated pathways

An immune-mediated phenomenon in IgG4-SC is supported by the presence of serological abnormalities, infiltration of the affected tissues with lymphocytes and plasma cells and a response to corticosteroids. Immune-mediated disease pathways thought to be involved in IgG4-RD are shown in FIG. 2.

$CD4^+$ T cells

$CD4^+$ T cells are prominent in IgG4-RD disease lesions, are likely to interact with B cells when in close proximity and are necessary to support and coordinate IgG-switched B-cell responses. A T helper (T_H)2-dominant immune response is present in the peripheral blood and tissues of patients with IgG4-SC or AIP[101]. T_H2 cytokines (IL-4, IL-5 and IL-13) have been detected at the messenger RNA level in IgG4-RD disease lesions, in the blood of patients with IgG4-SC or AIP and in the bile of patients with IgG4-SC[102–105]. However, one study suggests that these circulating T_H2 cells might be restricted to patients with atopy[20]. Indeed, mast cells might be an alternative source of T_H2 cytokines in these patients with atopy[106,107].

Regulatory immune reactions are activated in AIP or IgG4-SC, rather than suppressed as in many other autoimmune disorders. Infiltration of inducible memory regulatory T cells (T_{reg}) in the blood and affected tissue of patients with IgG4-SC or AIP is associated with upregulation of IL-10 and transforming growth factor (TGF)-β, which have been suggested to have important roles in IgG4 class-switching and fibroplasia, respectively[101,108]. The numbers of T_{reg} cells in biliary tissue correlate with IgG4-positive plasma cell infiltration in IgG4-SC, whereas numbers of circulating T_{reg} cells in the blood correlate with serum IgG4 levels in AIP[109–111].

T follicular helper (T_{FH}) cells, which support B-cell differentiation into antigen-secreting cells in germinal centres, have also been implicated in IgG4-SC[112]. Next-generation sequencing of the immunoglobulin heavy-chain repertoire of circulating plasmablasts in IgG4-RD shows evidence of extensive somatic hypermutation, a process for which T_{FH} cells are integral[35]. Circulating T_{FH} cells are expanded in patients with IgG4-RD, and preferentially secrete T_H2 cytokines, which might drive B-cell differentiation to IgG4-positive plasmablasts or plasma cells[112,113]. In addition, an infiltration of C-X-C chemokine receptor type 5 (CXCR5)-positive T_{FH} cells is evident in IgG4-SC and AIP lesions[114].

Furthermore, clonal expansions of $CD4^+$ effector T cells with a cytolytic phenotype have been reported in the peripheral blood and tissue of patients with IgG4-RD[115]. These cells expressed SLAM family member 7, granzyme A, IL-1β and TGFβ1. Rituximab-mediated B-cell depletion was associated with clinical remission and a reduction in the number of these cytolytic cells.

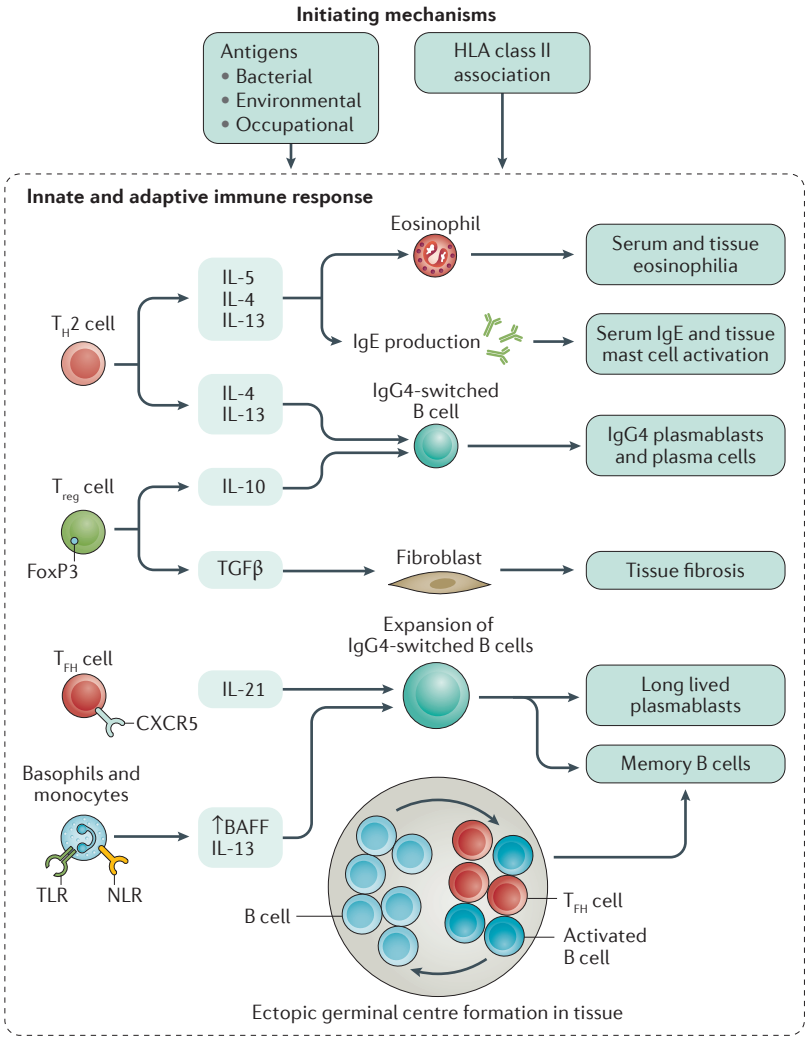


Figure 2 | **The pathogenesis of IgG4-related disease.** Chronic exposure to environmental and occupational antigens results in the rapid expansion of pre-existing IgG4-switched B cells in genetically susceptible individuals. These IgG4-positive memory B cells and plasmablasts traffic through the blood to lymphoid organs. The presence of T helper 2 (T_H2)-derived cytokines (IL-4 and IL-13) and T-regulatory cell (T_{reg})-derived cytokines (IL-10 and transforming growth factor(TGF)β), promote a switch to the IgG4 subclass and fibrogenesis. In the presence of mast cell-derived cytokines (IL-4 and IL-5), an elevated serum IgE, eosinophilia and history of allergy or atopy is seen. Ectopic germinal centres in tissues are formed, with T follicular helper (T_{FH}) cells providing cognate help for B cells and the production of IL-21, which drives proliferation of the IgG4-switched cells. Toll-like receptors (TLR) and nucelotide-binding oligomerization domain-like receptors (NLR) on monocytes and basophils enhance these IgG4 responses in the presence of B cell activating factor (BAFF) and IL-13, indicating crosstalk between the innate and acquired immune system. Distinct immunoregulatory functions of the IgG4-switched cells themselves lead to a dampening of immune surveillance, unchecked inflammation and progression to fibrosis.

Memory B cells and plasmablasts

The presence of IgG4-positive plasma cells in disease lesions and raised serum IgG4 levels in the majority of patients are indications that B cells and antibody production are important in IgG4-HBD pathogenesis[34]. Important differences in the frequency and phenotype of IgG1 and IgG4 B cells in health and IgG4-SC or AIP have been identified. In particular, differences in their potential to react to complement and Fc-receptor activation might help explain the differential regulation of the IgG4 antibody response[116]. Expansions of IgG4 memory B cells and plasmablasts in the blood have been reported in active disease[35,116]. Given the high levels of surface major histocompatibility complex class-II on plasmablasts, these cells might serve as vital antigen-presenting cells to $CD4^+$ T cells.

These plasmablasts might be secondarily induced bystanders in the disease. This idea is supported by evidence of a generalised IgG4 response to multiple non-infectious environmental antigens in IgG4-SC or AIP, in which antigen-specific responses correlated with serum IgG4 levels and reduced with corticosteroid therapy[24]. This finding is perhaps due to the expansion of pre-existing IgG4-switched B cells rather than being driven by a specific antigen or autoantigen. Factors that induce proliferation and expansion of IgG4-switched cells, enhance IgG4 class-switch and drive the process of recombination, somatic hypermutation and affinity maturation include IL-21, IL-10, IL-4, activation-induced cytidine deaminase, B-lymphocyte induced maturation protein 1 and X-box protein 1 — all of which have been shown to be present in IgG4-RD[108].

Factors promoting lymphocyte recruitment

Factors local to the pancreatobiliary system have been implicated in IgG4-SC, with evidence of inflammation in the peribiliary glands of IgG4-SC lesions containing pancreatic acini[117]. A role for C-C motif chemokine (CCL)1–C-C chemokine receptor (CCR) type 8 interaction in lymphocytic recruitment is supported by the abundant expression of CCL1 in pancreatic duct epithelium, peribiliary glands and the vascular endothelial cells of patients with IgG4-SC or AIP, with infiltration of the CCL1-expressing sites by CCR8-positive lymphocytes, and the infiltrate consisting predominantly of T_{reg} and T_H2 cells[118]. Other chemokines and ligands overexpressed in IgG4-SC or AIP tissue include CXCL13, CCL17, CCL19 and CCL21, but their role in the disease is unclear[119]. Furthermore, gene expression analysis in the blood of

patients with IgG4-SC or AIP implicates CCL23 and CCL25, which are important in homing to the gut–liver axis and as biomarkers for other autoimmune diseases[120].

Innate immunity

Toll-like receptor and nucelotide-binding oligomerisation domain (NOD)-like receptor stimulation have been implicated in IgG4-SC or AIP lesions, as IL-10 and IgG4 are produced in response to stimulation in a B-cell-activating, factor-dependent manner[121]. Macrophages, eosinophils and basophils are also often detected in involved tissue, although their role in the disease is not understood[122,123].

Future directions

Rituximab has been used to successfully treat patients with IgG4-SC that is refractory to steroids and immunosuppressants[124–126]. Circulating oligoclonal IgG4-positive plasmablasts in active IgG4-RD have been shown to remit after rituximab treatment and re-expand during relapse[35,127]. The re-emergence of IgG4-positive plasmablasts are either derived from a subset of memory B cells that survive the rituximab therapy, or are newly generated naive B cells (unaffected by depletion therapy) that interact with an unidentified antigen or pathogenic T-cell repertoire[35,124]. Characterizing these T cells could be central to understanding the pathogenesis of this disease. The role of rituximab in reversing active fibrosis in IgG4-RD lesions has also been demonstrated using the enhanced liver fibrosis test as a surrogate marker and evidence of collagen deposition by secretory myofibroblasts[128]. Although these data are novel, targeting fibrosis and the processes driving it will surely be critical if the complications of IgG4-SC are to be prevented.

The complex interplay between IgG4-SC phenotypes with a history of allergy or atopy, elevated IgE and eosinophilia have led to an interest in the prostaglandin D_2 receptor 2 (PTGDR2) as a therapeutic target[18,129]. PTGDR2 is expressed on T_H2 and innate cells, such as eosinophils, responds to mast-cell-derived factors and is important in allergic inflammation[129]. The number of PTGDR2-$CD4^+$ T-cells is increased in patients with IgG4-related sialadenitis, and correlates with serum IgE levels and eosinophilia[130]. Upregulation of prostaglandin D_2 and PTGDR2 has similarly been reported in gene expression analysis of blood from patients with AIP or IgG4-SC[120]. Blockade of PTGDR2 can reduce allergic inflammation in rodent models of antigen-induced airway inflammation, allergic rhinitis, atopic dermatitis, and hyperresponsiveness in asthma[132], and this approach might be applied in the allergic-subtype of patients with IgG4-SC.

Conclusions

More than a decade after the first studies demonstrating that IgG4-HBD are manifestations of a multisystem condition, a reliable diagnosis remains a major challenge. The PCR-based and plasmablast frequency assays for discrimination of IgG4-HBD from pancreatobiliary malignancy and other forms of sclerosing cholangitis require careful scrutiny.

Current therapy follows expert consensus, but randomized controlled trials are lacking and international collaboration is required. The ability to reliably predict and target patients who require longer duration and early escalation of therapy, or who are likely to develop fibrotic complications, is still in its infancy. However, rituximab has provided an option in patients with refractory disease, as well as some clues to disease pathogenesis.

Studies have implicated both dysregulation of the immune system and genetic susceptibility as important mechanisms in IgG4-HBD. Further international collaboration to establish an IgG4-RD registry with biobanking of samples, in order to determine risk factors and mechanisms of fibrotic disease, and to develop novel therapeutic approaches to tackle them, is an important aim.

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Author contributions

E.L.C. wrote the article, researched data and provided a substantial contribution to discussions of the content. E.L.C. and R.W.C. contributed equally to the reviewing and/or editing of the manuscript before submission

Competing interests statement

The authors declare no competing interests.

Review criteria

We searched online literature databases including Pubmed, Medline and EMBASE from Jan 1st 1961 until Feb 1st 2016. Search terms included IgG4-related disease, IgG4 systemic disease, IgG4-related sclerosing cholangitis, IgG4-associated cholangitis, IgG4-associated liver disease, IgG4-related hepatopathy, IgG4-related autoimmune hepatitis and inflammatory pseudotumour. Publications were reviewed and high-quality, original review articles and selected abstracts were selected, predominantly from the past 10 years.

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