Recent Advances in Autoimmune Pancreatitis

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Autoimmune pancreatitis (AIP) is a form of chronic pancreatitis that is characterized clinically by frequent presentation with obstructive jaundice, histologically by a dense lymphoplasmacytic infiltrate with fibrosis, and therapeutically by a dramatic response to corticosteroid therapy. Two distinct diseases, type 1 and type 2 AIP, share these features. However, these 2 diseases have unique pancreatic histopathologic patterns and differ significantly in their demographic profiles, clinical presentation, and natural history. Recognizing the popular and long-standing association of the term “AIP” with what is now called “type 1 AIP,” we suggest using “AIP” solely for type 1 AIP and to acknowledge its own distinct disease status by using “idiopathic duct-centric chronic pancreatitis” (IDCP) for type 2 AIP. AIP is the pancreatic manifestation of immunoglobulin G4–related disease (IgG4-RD). The etiopathogenesis of AIP and IgG4-RD is largely unknown. However, the remarkable effectiveness of B-cell depletion therapy with rituximab in patients with AIP and IgG4-RD highlights the crucial role of B cells in its pathogenesis. IDCP is less commonly recognized, and little is known about its pathogenesis. IDCP has no biomarker but is associated with inflammatory bowel disease in ~25% of patients. Recently, the international consensus diagnostic criteria for AIP identified combinations of features that are diagnostic of both diseases. Both AIP and IDCP are corticosteroid responsive; however, relapses are common in AIP and rare in IDCP. Therefore, maintenance therapy with either an immunomodulator (eg, azathioprine, 6-mercaptopurine, or mycophenolate mofetil) or rituximab is often necessary for patients with AIP. Long-term survival is excellent for both patients with AIP and patients with IDCP.

Subtypes of AIP: History and Nomenclature

The term “AIP” was used by Yoshida et al to describe a corticosteroid-responsive disease associated with features of autoimmunity. The association of AIP and elevated serum immunoglobulin (Ig) G4 levels was recognized by Hamano et al. The observation by Kamisawa et al that not only the pancreas but also the extrapancreatic organs involved in AIP had abundant infiltration with IgG4 plasma cells led to the notion that AIP was part of a multiorgan disease, recently named IgG4-related disease (IgG4-RD).

Studies from Europe and the United States have highlighted 2 histopathologic patterns, both called AIP, in patients with chronic pancreatitis who underwent pancreatic resection for presumed pancreatic cancer. Lymphoplasmacytic sclerosing pancreatitis (LPSP) matched Japanese descriptions of histology in AIP, and idiopathic duct-centric pancreatitis (IDCP) or granulocytic epithelial lesion (GEL) plus pancreatitis resembled “duct destructive pancreatitis” as reported earlier in Europe. Patients with LPSP and IDCP also had distinct clinical profiles. Thus, in 2009, 2 subtypes of AIP (defined by their histopathology), called type 1 (LPSP) and type 2 (IDCP), were formally recognized. It was decided to call both “AIP” because of the many similarities between the 2 entities (discussed later in this review).

However, despite the distinction of subtypes, the term “AIP” continues to be equated with type 1 AIP and elevated serum IgG4 levels, a feature typically absent in IDCP. Therefore, IDCP remains underrecognized and is often inappropriately treated on the mistaken belief that the treatments for the 2 diseases must be the same. Providing distinct disease names will help minimize confusion between the 2 diseases. Recognizing the popular and long-standing association of the term “AIP” and elevation of serum IgG4 levels with what is now called type 1 AIP, we...
suggest using “AIP” solely for type 1 AIP and “IDCP” for type 2 AIP.

Before the use of the term “type 2 AIP,” the entity had been called “nonalcoholic duct destructive pancreatitis.”10 “GEL-positive pancreatitis,”17 and “IDCP.”6 All 3 terms highlight the “duct-centric” nature of the disease. Because the etiology is still unknown, IDCP appears to be a reasonable choice. Rather than suggesting a new title to replace IDCP, we chose to retain this. It is fitting to retain this title because the histology is its defining feature. In the future, biomarkers will hopefully make it possible to more accurately distinguish AIP and IDCP without the need for histopathology.

AIP (IgG4-Related Pancreatitis)

Definition. AIP is the pancreatic manifestation of IgG4-RD; using currently proposed nomenclature, it is also called IgG4-related pancreatitis.11 IgG4-RD is a multiorgan syndrome characterized by typical histology (see the description of LPSP) in affected organs, frequent elevations of serum IgG4 levels, abundant IgG4+ plasma cells in affected organs, and dramatic response to corticosteroid therapy.12 An individual patient with IgG4-RD may not exhibit all features and patients without IgG4-RD may have some features; however, a cohort of subjects with a particular clinical phenotype of IgG4-RD (eg, AIP) would meet all criteria.

Pathogenesis. The pathogenetic mechanisms of AIP are incompletely understood. Studies have identified genetic predisposing factors and unique immunologic features of AIP, raising the possibility that the process is multifactorial. As with most immune-mediated conditions, a likely pathogenetic mechanism is that the disease develops in genetically susceptible people after exposure to environmental factors. This section covers potential contributions to the development of AIP from (1) genetic predisposition, (2) possible immunologic triggers, and (3) subsequent immune reactions. Although experimental AIP is beyond the scope of this review, new insights recently obtained from animal models of AIP are briefly described. Assuming that IgG4-RD at various anatomic sites shares pathogenetic mechanisms, several studies on the extrapancreatic manifestations are also mentioned.

Genetic predisposition. A potential genetic predisposition was first recognized in 2002, when HLA serotypes DRB1*0405 and DQB1*0401 were found to increase the susceptibility to AIP in Japanese populations.13 Efforts to validate these findings in a Korean population were unsuccessful, but instead identified the absence of aspartic acid at position 57 of DQB1 as a genetic factor significantly associated with disease relapse.14 Four non-HLA genes, single nucleotide polymorphisms, that have been associated with AIP encode cytotoxic T lymphocyte–associated antigen 4, tumor necrosis factor α, Fc receptor-like 3, and cationic trypsinogen (PRSS1).15–18 Although growing evidence has highlighted underlying genetic risks of AIP, more comprehensive analyses such as genome-wide association studies will be needed to fully understand the genetic aspects of this condition. Unfortunately, the large sample size needed to attain adequate statistical analysis for this type of study would be impossible, aside from a large-scale, multinational collaborative effort.

Immunologic trigger. Autoimmunity. The fact that approximately 40% of patients with AIP have antinuclear antibodies prompts us to suspect that autoimmunity may be an initial immunologic stimulus in this condition.19–20 Patients with AIP often have autoantibodies against carbonic anhydrase II (55% of patients), lactoferrin (75% of patients), and/or pancreatic secretory trypsin inhibitor (33% of patients).19 A German study identified that patients with AIP have high titers of autotantibodies against trypsinogens PRSS1 and PRSS2 but not against PRSS3.21 An interesting aspect is that all autoantibodies identified in patients with AIP are against enzymes. This may explain why pancreatic acini are more deeply involved in the inflammatory process than pancreatic ducts. Some of these enzymes are also expressed in other exocrine organs (eg, salivary amylase), which may potentially explain the association with other organ involvement. However, whether the production of these antibodies directed against pancreatic enzymes occurs primarily or secondarily to the inflammation remains to be clarified. Another caveat is that these antibodies are not entirely specific for AIP and are sometimes detected in other autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus.22

Bacterial infection/molecular mimicry. Because substantial homology between human carbonic anhydrase II and α-carbonic anhydrase of Helicobacter pylori was identified, the possible involvement of H pylori in the pathogenesis of AIP has been investigated.23 More recently, additional homology was recognized between the plasminogen-binding protein of H pylori and the ubiquitin-protein ligase E3 component n-recongniz 2, an enzyme expressed in acinar cells of the pancreas.24 The investigators speculated that H pylori infection initiates an immune reaction and the production of antibodies against the plasminogen-binding protein of H pylori and may lead to autoimmune response against the pancreatic acinar cells via molecular mimicry. However, the homologous amino acid sequence is not entirely specific for these 2 proteins, and similar peptide sequences exist in other human proteins (eg, transforming growth factor β regulator 1) as well as proteins derived from other microbes.25 Thus, the possibility of molecular mimicry in AIP has drawn interest but remains to be validated.

Environmental factors. Serum IgG4 concentrations increase in subjects with repeated exposure to antigens.26 For example, beekeepers develop elevated serum IgG4 levels in the absence of elevation of IgE levels.26 Given that occupational exposure to other antigens leads to the same phenotype, a European group investigated a possible role of occupational exposures in a group of patients with AIP and/or IgG4-related sclerosing cholangitis (previously referred to as IgG4-associated cholangitis).27 Of 25 patients in The Netherlands, 88% of these patients were blue-collar workers compared with only 14% of those with primary sclerosing cholangitis. This observation was validated by a
Th1 and Th2 cells. Nevertheless, both Th1 and Th2 cytokines are abundantly expressed in tissue. The expression level of interferon gamma in AIP is comparable to that in autoimmune liver diseases, whereas the expression of Th2 cytokines (i.e., IL-4, IL-5, and IL-13) is significantly up-regulated in AIP and IgG4-related sclerosing cholangitis. Concordant with the tissue studies, bile samples from patients with IgG4-related sclerosing cholangitis also show significantly increased levels of IL-4 and IL-5, suggesting a Th2-predominant response. A reasonable interpretation of the seemingly conflicting results is that both Th1 and Th2 immune responses occur in AIP, but the intense Th2 response represents immunologic aspects that better characterize AIP because the Th2 response is usually weak in classic autoimmune diseases. Another possibility is that the Th1/Th2 balance may shift dynamically between early and advanced AIP. Th2 cytokines (i.e., IL-4, IL-5, and IL-13) likely contribute to tissue and/or serum eosinophilia and elevated serum IgE levels, all of which are often observed in patients with AIP. IL-21, another Th2 cytokine, is also up-regulated in IgG4-related dacryoadenitis and sialadenitis. IL-21 expressed by Th2 and T follicular helper cells is known to be involved in germinal center formation, which is more prominent in IgG4-related salivary gland involvement than AIP. Lastly, IL-21 can also lead to IgG4 class switching and IgG4 production in conjunction with IL-4, indicating its potentially important role in the pathogenesis of AIP.

Tregs. Unlike classic autoimmune diseases, in which Tregs are impaired in number and function, this subset of immune-suppressive T cells is likely activated in AIP. Pancreatic tissue with AIP contains a significantly increased number of FOXP3$^+$ CD4$^+$ CD25$^+$ Tregs. The expression of 2 regulatory cytokines, IL-10 and transforming growth factor $\beta$, is also up-regulated. These findings in tissue correlate with Treg counts in peripheral blood. Patients with AIP have a significantly larger number of CD4$^+$CD25$^{high}$ Tregs in the blood than those with other pancreatic diseases. Numbers of ICOS$^+$ or IL-10$^+$ Tregs are particularly increased and naive Tregs are decreased in the periphery.

IL-10 is a key cytokine contributing to IgG4 class switching. IL-4 induces production of both IgE and IgG4 from B cells and plasma cells, whereas additional IL-10 on top of IL-4 suppresses production of IgE and enhances production of IgG4. Thus, the combination of IL-4 and IL-10 can lead to selective induction of IgG4. Because both IL-4 and IL-10 are highly expressed in tissue from patients with AIP, Th2 and regulatory cytokines may play a central role in IgG4 class switch in this condition. Additionally, transforming growth factor $\beta$ and M2 macrophages may contribute to the later development of fibrosis.

Other T-cell subsets. Small studies have examined the potential role of Th17 and cytotoxic T cells, which appears to be less important than the mediators previously discussed. In a study of IgG4-related dacryoadenitis and sialadenitis, tissue expression of Th17-associated factors (IL-17 and RORC2) was weak. A second study showed that numbers of cytotoxic T cells are similar between IgG4-related salivary disease and Sjögren syndrome.
B cells. The observation that B-cell depletion therapy with anti-CD20 antibodies is effective for AIP highlights the crucial involvement of B cells in pathogenesis.50,51 Two subsets of B cells that have been investigated in IgG4-RD are regulatory B cells (Bregs) and plasmablasts. In patients with AIP, the number of CD19+CD24hiCD38hi Bregs significantly increases and the number of CD19+CD24loCD27+ Bregs decreases in the peripheral blood.52 Thus, a subset of Bregs may be activated in this condition (as with Tregs), but their roles in the pathogenesis and relationship to IgG4+ plasma cells remains unclear. Recent studies using a next-generation sequencing protocol have identified oligoclonal expansion of IgG4-switched B cells and CD19−CD27−CD20−CD38hi plasma blasts (or CD19lowCD27+CD20CD38+ plasmablasts) in IgG4-RD, including AIP.53–55 The circulating plasmablasts are largely IgG4 positive and have undergone extensive somatic hypermutation. Dominant clones of plasmablasts are variable among patients based on the Ig heavy chain variable region gene repertoire. Clonally expanded plasmablasts rapidly decline with treatment, but distinct plasmablast clones reappear at the time of relapse.64 Plasmablasts share some surface markers with Bregs and presumably have immune-regulatory functions, but plasmablasts in patients with AIP are only weakly correlated in number with CD19+CD27−CD20−CD38+ plasmablasts.54,56 The immune-regulatory property of plasmablasts up-regulated in patients with IgG4-RD has not been examined so far.

IgG4+ plasma cells. Massive infiltration by IgG4+ plasma cells is a histological hallmark of AIP.57 However, it remains unclear whether IgG4-type antibodies in AIP behave like tissue-destructive antibodies (ie, autoantibodies) or are overexpressed in response to an unknown inflammatory stimulus. IgG4 is considered a noninflammatory antibody because of its relative inability to fix complement and its poor capacity to bind Fc receptors.58,59 This minor IgG subclass also has a unique ability to exchange a pair of heavy and light chains (“Fab-arm exchange”).60 This immunologic process causes IgG4 molecules to lose antigen cross-linking ability, behave as monovalent antibodies, and become incapable of forming large immune complexes. Given these anti-inflammatory aspects of IgG4, it may be secondarily induced to dampen the extensive immune reaction in AIP. However, a recent study revealed that recombinant monoclonal immunoglobulins derived from the most expanded clone of IgG4+ plasmablasts in a patient with IgG4-RD appeared to be self-reactive.54 Many immune complex deposits consisting of mainly IgG4 and C3 are found in pancreatic tissue with AIP.61,62 These findings may suggest a primary tissue-destructive property of IgG4 in AIP as in pemphigus vulgaris and idiopathic membranous nephropathy, in which autoantibodies are of the IgG4 subtype.63

Role of the complement system. Complement C3 and C4 are reduced in 40% of patients, particularly those with high levels of circulating immune complexes, suggesting immune-mediated complement activation.64 Hypocomplementemia is particularly common in patients with AIP who have renal involvement.65 Among 3 complement activation systems, the classic pathway seems to be predominantly involved, whereas the alternative and mannose-binding lectin pathways are less activated.66 Given that IgG4 cannot activate the classic pathway, complement fixation in AIP may be induced by other IgG subclasses that fix complements more efficiently.

Chemotactic factors. Although the chemotactic process of massive cellular infiltrate is poorly understood, CCL1−CCR8 interaction seems to be important in the recruitment of lymphocytes, particularly Th2 cells and Tregs, because 50% of Th2 lymphocytes and 60% of FOXP3+ Tregs express CCR8.66 Interestingly, CCL1 is expressed in the duct and glandular epithelium and endothelial cells, including those involved in obliterator phlebitis, in AIP and IgG4-related sclerosing cholangitis.67 The CCL1+ sites are infiltrated by CCR8+ lymphocytes. Thus, the CCL1−CCR8 interaction may create a microenvironment in which Th2 cells and Tregs are abundant, leading to an IgG4 class switch through IL-4 and IL-10. This immunologic reaction is assumed to underlie the histological changes of periductal and periglandular inflammation and obliterator phlebitis in AIP.

Although pancreatic ducts expressing CCL1 are surrounded by CCR8+ lymphocytes, intraepithelial lymphocytes are few. One possible explanation for this is that Th2 lymphocytes and Tregs are not strong enough to invade through the basement membrane. The duct epithelium is histologically well preserved in AIP but seems to be damaged at the molecular level. Cystic fibrosis transmembrane conductance regulator (CFTR), a channel protein expressed on the cellular membrane, is mislocalized in the cytoplasm of the duct epithelium in untreated AIP.68 Corticosteroids recover the expression of CFTR on the apical membrane. In addition, IL-4 and IL-13 distort the expression of claudins and subsequently reduce barrier function of the biliary epithelium. Biliary epithelial cells isolated from patients with IgG4-related sclerosing cholangitis have unbalanced expression of claudin-1 and claudin-2, which probably represents the direct impact of Th2 cytokines on the ductal epithelium.38

Future perspective. Most studies of the pathogenesis of AIP have been molecular-targeted investigations, including the examination of several potentially important molecules, and are summarized in Figure 1. Global approaches will help determine the immunologic features of this condition in a systematic manner. A comprehensive tissue proteomic study is now under way.

Epidemiology. AIP is rare, with an estimated prevalence of <1 per 100,000 in the general population.69 although uncommon, AIP is a globally recognized disease, with large published series from Asia, Europe, and North America. Risk factors for developing the disease remain poorly understood.

Clinical presentation. AIP is typically diagnosed late in life (the mean age at diagnosis is older than 60 years) and has a 3:1 male predominance.2 Its most common presentation is with painless jaundice (60%–75%), but other potential presentations include a pancreatic mass or focal pancreatic enlargement without jaundice, pancreatic
insufficiency in the form of new or worsened hyperglycemia and steatorrhea, and (uncommonly) acute pancreatitis.\(^2\) Despite intense inflammation, AIP is relatively painless; chronic narcotic-requiring pain should suggest an alternate diagnosis. Patients with AIP may also initially present with symptoms due to extrapancreatic involvement of IgG4-RD.

**Clinical features.** AIP is identified by abnormalities on histology, imaging, serology, other organ involvement, and response to therapy (remembered by the mnemonic "HISORt").\(^7\) Different combinations of these cardinal features are diagnostic.

**Histology.** The grossly affected pancreas may show a localized “pseudotumor” or small discrete nodules; however, diffuse enlargement is most common. The histopathologic pattern in AIP (LPSP) is characterized by dense lymphoplasmacytic infiltrate predominantly involving lobules, obliterative phlebitis, and fibrosis arranged, at least focally, in a whorly “storiform” pattern (Figure 2).\(^5\) The unequivocal presence of all 3 features is diagnostic of AIP. IgG4 immunostaining of the infiltrate highlights diffuse infiltration of IgG\(^4\)\(^+\) plasma cells, which account for >40% of total IgG\(^+\) plasma cells.\(^74\) Infiltration with IgG4\(^+\) plasma is not pathognomonic of AIP or IgG4-RD and can be seen in benign inflammatory processes as well malignancies, such as pancreatic and bile duct cancers. The IgG4/IgG ratio of plasma cells helps distinguish AIP from histological mimics associated with IgG4\(^+\) plasma cell infiltration.\(^7\) Although histology obtained from a core tissue biopsy can produce a diagnostic specimen in AIP, the samples are often quite small and histological abnormalities can be patchy (Figure 3).\(^9,72\) As a consequence of these technical challenges, nonhistological criteria are necessary to practically diagnose AIP.

**Imaging: pancreatic parenchymal changes.** The classic appearance of AIP on cross-sectional imaging, seen in 30% to 50% of patients, is diffuse enlargement of the pancreas with loss of the normal lobulated contour (the so-called “sausage-shaped pancreas”) (Figure 4).\(^73–76\) The morphological changes are accompanied by decreased enhancement during the early phase and delayed enhancement in the late

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**Figure 1.** The proposed immunologic interactions contributing to the various clinical manifestations in AIP.

**Figure 2.** Representative histopathologic features in resected pancreatic specimens from patients with (A–C) AIP and (D) IDCP, including (A) lymphoplasmacytic inflammation, (B) storiform fibrosis (in a swirled pattern), (C) obliterative phlebitis (arrow, Elastica van Gieson stain), and (D) GEL (asterisk).
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arrow pancreatic duct, forming a small aggregate (Figure 5). Because portions of the pancreatic duct may not be visible on magnetic resonance cholangiopancreatography even in healthy people, magnetic resonance cholangiopancreatography is not a substitute for endoscopic retrograde cholangiopancreatography if ductal findings are to be used for diagnosis.

Serum IgG4 levels. Approximately two-thirds of patients with AIP have elevated serum IgG4 levels. Mild elevations of serum IgG4 levels (1–2 times the upper limit of normal) have been observed in 10% to 15% of patients with pancreatic cancer, cholangiocarcinoma, and primary sclerosing cholangitis. Even though higher elevations may improve the specificity, the extremely low disease prevalence results in a low positive predictive value (10%–15%) of elevated serum IgG4 levels for diagnosis of AIP/IgG4-RD when the pretest probability of disease is low. Thus, although elevated serum IgG4 levels are characteristic of AIP, they are helpful only to establish a diagnosis of AIP in conjunction with other diagnostic findings.

Other organ involvement. Because AIP is the pancreatic manifestation of IgG4-RD, it is not uncommon to have previous or concurrent extrapancreatic involvement, especially proximal bile duct strictures, retroperitoneal fibrosis, bilateral submandibular enlargement, and characteristic renal parenchymal lesions.

Response to therapy. The inflammatory component of AIP/IgG4-RD is very responsive to corticosteroids. The morphological abnormalities of AIP and other organ involvement seen on imaging respond within a couple of weeks of corticosteroid therapy. Thus, the lack of a convincing radiographic improvement after corticosteroid therapy should prompt additional investigation for an alternative diagnosis, namely malignancy.

Diagnosis. The primary differential diagnoses to consider in patients with suspected AIP include pancreatic cancer, idiopathic pancreatitis, primary sclerosing cholangitis, and cholangiocarcinoma. Therefore, considering the risks of an incorrect diagnosis, the initial objective for the clinician is to rule out malignancy.

Diagnostic criteria for AIP. Apart from histology, no solitary feature is pathognomonic for AIP. However, various combinations of diagnostic findings are specific for AIP, and

Figure 4. Computed tomographic imaging from 2 different patients with AIP shows the typical diffuse pancreatic enlargement as well as (A) the hypoattenuating rim seen in 30% of patients and (B) the characteristic parenchymal hypoattenuation, which is best seen during the portal phase.

Figure 5. Pancreatic duct imaging features of AIP obtained at the time of endoscopic retrograde cholangiopancreatography in 2 patients. (A) A long stricture in the head of the pancreas without upstream ductal dilation. Additionally, side branches are seen arising from the structured segment. (B) Multifocal strictures of the main pancreatic duct.
these are highlighted in the plethora of diagnostic criteria put forward by different groups around the world, with criteria often revised as knowledge of the disease improved.\textsuperscript{70,79,92–97} Recognizing the need for universal criteria, an international working group proposed the international consensus diagnostic criteria for (type 1) AIP and IDCP (type 2 AIP), considering variations in clinical practice across the world.\textsuperscript{3} The criteria provide a clinical framework to collectively evaluate diagnostic findings, which are weighted based on their specificity for AIP, and establish a diagnosis of AIP.\textsuperscript{1} The international consensus diagnostic criteria do not recommend using a corticosteroid trial to diagnose AIP in the setting of weak or absent collateral diagnostic evidence because the response can be seen in other conditions and sometimes the measurement is subjective.

**Management.** AIP is a fibroinflammatory disease, which in the early phase is characterized by robust inflammation. Effective therapies target the inflammatory response to provide relief of symptoms, confirm the diagnosis (if there is remaining doubt), and perhaps decrease or delay the progression to fibrosis. Conversely, changes due to fibrosis (eg, pancreatic atrophy, intrahepatic bile duct strictures, and retroperitoneal fibrosis) may not completely resolve with treatment and can result in irreversible end-organ damage.\textsuperscript{91}

There are no randomized controlled trials of therapy in AIP; however, based on observational data, corticosteroids are the mainstay of treatment. For patients who are either intolerant of high-dose corticosteroids or have multiple relapses despite therapy, there are emerging data to support the use of other treatment options, including corticosteroid-sparing immunomodulators and B-cell depletion therapy using rituximab.

**Corticosteroid therapy.** High-dose corticosteroid therapy (equivalent prednisone dosing of approximately 30–40 mg/day) results in more rapid and consistent induction of disease remission than conservative management.\textsuperscript{90} In some patients (eg, diabetic patients and elderly patients), a lower dose may be preferred to avoid acute corticosteroid-related complications; however, there are limited data on remission rates using a low dose of corticosteroids (eg, equivalent prednisone dosing of 10–20 mg/day).\textsuperscript{73,99,100} High-dose corticosteroids are typically administered for 3 to 4 weeks, followed by an assessment of clinical response.

After remission or marked improvement in inflammation, many regimens include a slow, prolonged taper over several months to a low maintenance dose (equivalent to 2.5–10 mg/day of prednisone) continued for 1 to 3 years and, in some instances, indefinitely.\textsuperscript{101} This strategy, currently endorsed by the Japan Pancreas Society, is utilized in most Asian countries.\textsuperscript{2,81} In a retrospective analysis, Kamisawa et al showed a decreased rate of disease relapse with maintenance corticosteroid therapy compared with no maintenance therapy (23% vs 34%; \(P = .045\)).\textsuperscript{102} In another approach, favored in Europe and North America to minimize cumulative corticosteroid exposure, corticosteroid therapy is completely withdrawn after successful induction of remission.\textsuperscript{2,452,103} The most commonly used protocol consists of high-dose corticosteroids for 4 weeks followed by a taper of 5 mg each week until discontinued.\textsuperscript{102} In a hybrid approach, maintenance therapy may be contemplated at the onset of treatment in patients at high risk for relapse (as discussed in the following text).

**Disease relapse and risk factors.** Recrudescence, the development of recurrent inflammatory changes during tapering of corticosteroids, is generally managed with an increase in corticosteroid dosing followed by a prolonged taper. True disease relapses, developing after a variable period of complete remission, occur in 20% to 60% of patients with AIP.\textsuperscript{7,73,76,100,103,104} A lower frequency of relapses in some series may be due to shorter duration of follow-up, use of maintenance corticosteroids, inclusion of patients with IDCP, or previous pancreatectomy (the latter 2 factors have a very low risk of disease relapse). Relapse may occur in the organs being treated or in a previously unaffected organ system.\textsuperscript{7}

A consistently demonstrated risk factor for disease relapse is involvement of the proximal bile ducts (defined as the intrahepatic bile ducts and/or the suprapancreatic portion of the extrahepatic bile duct).\textsuperscript{7,73,76,102} Additional risk factors for disease relapse include presentation with diffuse pancreatic enlargement (in contrast to focal enlargement) and initial treatment with corticosteroids (compared with surgical resection).\textsuperscript{76} Other factors that have not been consistently associated with increased risk of disease relapse include elevated serum IgG4 levels, lack of reduction in serum IgG4 levels following corticosteroid therapy, and presence of other organ involvement.\textsuperscript{2,73,76,100}

**Treatment of relapse.** At least 3 treatment regimens have been used for relapses: (1) high-dose corticosteroids, followed by maintenance treatment with low-dose corticosteroids or a corticosteroid-sparing agent, (2) high-dose corticosteroids without maintenance treatment, or (3) rituximab induction with or without maintenance rituximab. Because corticosteroids remain highly successful for induction of remission (>95%), it is reasonable, if tolerated, to repeat a course of high-dose corticosteroids.\textsuperscript{7} Otherwise, in the absence of controlled data, the approach is based on response to previous treatments and treatment-related complications.

**Immunomodulators.** Initial small case series reported high rates of maintaining corticosteroid-free remission in relapsing AIP using immunomodulators such as azathioprine, 6-mercaptopurine, and mycophenolate mofetil.\textsuperscript{103,105,106} However, a relatively large series (\(n = 41\)) with longer follow-up showed more modest results.\textsuperscript{51} The relapse-free survival was similar when relapses were treated with corticosteroids and an immunomodulator compared with corticosteroids alone without maintenance treatment.\textsuperscript{51} Additionally, approximately 25% of patients were unable to tolerate immunomodulator treatment and required drug discontinuation.\textsuperscript{51} Other agents that have been used include cyclophosphamide, methotrexate, and sirolimus; however, there are no published series to evaluate the effectiveness of these agents.

**Rituximab.** Rituximab is a monoclonal CD20 antibody that has been shown to be effective in treating AIP and other
Apart from corticosteroids, rituximab is the only agent that can induce remission in IgG4-RD. Therefore, it is extremely useful in patients who are unable to tolerate high-dose corticosteroids, require high doses of prednisone to maintain remission, or have failed to respond to immunomodulator therapy (either due to inability to tolerate treatment or relapse during treatment). It may be reasonable to consider first-line rituximab therapy in patients with previous intolerance to high-dose corticosteroids and those at high risk for relapse (e.g., patients with proximal biliary strictures or extensive multiorgan disease), because relapses can cause significant morbidity and lead to extensive testing to exclude malignancy.

Rituximab is currently approved for treating B-cell lymphoma and rheumatoid arthritis, using different treatment protocols. Both have been used to treat AIP/IgG4-RD. Using the B-cell lymphoma dosing protocol (375 mg/m² body surface area weekly for 4 weeks, followed by infusions every 2–3 months), induction of remission was convincingly achieved in 10 of 12 patients (83%), including many with difficult-to-treat disease. There were no disease relapses during maintenance treatment, which was continued for up to 2 years. Interestingly, a small number of patients were successfully treated in this study without the use of corticosteroids.

Alternatively, a 2-dose rheumatoid arthritis protocol (1000-mg doses 2 weeks apart) was used in a cohort of patients with IgG4-RD (2 of 10 patients had pancreatic and/or biliary involvement). There was improvement in disease control in 9 of 10 patients within 1 month; however, 4 of 10 patients required re-treatment with rituximab within 6 months. The same 2-dose rituximab protocol was further studied in a phase 1/2 study of 30 patients with IgG4-RD (18 of 30 had pancreatic involvement), including several who were corticosteroid naive (NCT01584388). A sustained treatment response was observed in 22 of 30 patients (73%) at 6 months, but 7 of the 30 patients (23.3%) developed a disease relapse within 12 months of follow-up. Further studies are needed to determine which patients benefit from maintenance rituximab and the optimal duration of treatment.

In conclusion, corticosteroids predictably induce remission in AIP. The optimal dosing and duration of corticosteroid therapy has not been evaluated in a clinical trial and remains unknown. Considerations for maintenance treatment are low-dose corticosteroids, immunomodulators, or close observation without maintenance treatment. Disease relapses are typically re-treated with corticosteroids and maintenance treatment (either low-dose corticosteroids or an immunomodulator) or rituximab (Figure 6). Further controlled studies are needed to help determine the optimal induction and maintenance regimens when rituximab is required. In the absence of randomized trials to dictate treatment decisions, selection of agents should take into consideration the patient’s previous disease history,

**Figure 6.** A proposed treatment algorithm for management of disease relapses for patients with firmly established AIP (i.e., malignancy has been excluded). Adapted from Hart et al with permission from the BMJ Publishing Group.
treatment failures, and the clinician’s familiarity with monitoring for treatment-related complications.

**Disease-related sequelae.** Pancreatic atrophy is observed in up to 25% of patients after corticosteroid-induced remission and is more likely to develop in those with heavy alcohol consumption (>50 g/day) and older age. Parenchymal atrophy is associated with an increased risk of having worsened glycemic control or developing new-onset diabetes mellitus. Likewise, use of tobacco has been associated with the development of diabetes mellitus in patients with AIP. Pancreatic duct stones form in approximately 10% of patients during follow-up and more frequently in those with a history of heavy alcohol consumption or relapsing disease. Some studies have observed an increased risk of cancer in patients with AIP, whereas others have failed to show a difference; however, all have been limited by short follow-up. Interestingly, one study observed a disproportionately increased risk of cancer in the first year after diagnosis of AIP, which raises the question of whether AIP may be a paraneoplastic phenomenon in a subset of patients. Death due to AIP-related complications is rare. In a study of 78 patients with AIP, 5-year survival was similar to that of age- and sex-matched population controls.

**IDCP**

IDCP is a corticosteroid-responsive form of pancreatitis that has a distinct histological and clinical profile. It is much less common than AIP, in part due to challenges in achieving a definitive diagnosis.

**Pathogenesis.** Very little is known about the pathogenesis of IDCP. The rarity of IDCP restricts our ability to investigate this condition deeply; pathogenetic studies of IDCP will require multicenter collaboration.

**Histological features.** Both pancreatic ducts and acini are involved in IDCP, but periductal inflammation is usually dominant. The epithelium lining pancreatic ducts is extensively infiltrated by neutrophils (GEL), which is a diagnostic feature of IDCP (Figure 1). Lobular neutrophilic infiltration also supports the diagnosis of IDCP in appropriate settings but is not entirely specific for this condition. IgG4+ plasma cells are, if present at all, small in number and never exceed 40% of IgG+ plasma cells. Obliterative phlebitis and storiform fibrosis are less prominent than in LPSP (AIP).

**Clinical profile.** IDCP is typically diagnosed at a younger age than AIP (mean age at diagnosis is 40 vs 61 years, respectively; \( P < .001 \)) and without a sex bias (55% male) compared with male predominance in AIP. Clinical presentations of IDCP are limited to the pancreas. The common presentations are acute pancreatitis and jaundice (secondary to extrinsic compression of the distal common bile duct from pancreatic enlargement); less commonly, IDCP presents with abdominal pain and imaging abnormalities but without biochemical evidence for pancreatitis. Although there is no associated other organ involvement, approximately 15% of subjects have concurrent inflammatory bowel disease, which is predominantly chronic ulcerative colitis.

**Diagnosis.** The radiographic features of the pancreatic parenchyma and pancreatic duct imaging abnormalities are similar in IDCP and AIP. Conversely, elevated serum IgG4 levels are less common than in AIP. In a series of subjects with histologically proven disease, serum IgG4 levels were elevated in only 23% (11/47) of patients with IDCP. Because elevations of serum IgG4 levels and other organ involvement are typically absent in IDCP, the only means of definitively confirming a diagnosis is by demonstration of GEL on histology; however, as previously discussed, these are not easy to diagnose on a core biopsy.

**Management.** IDCP is a corticosteroid-responsive disorder, and the symptoms and inflammatory changes

### Table 1. Comparison of AIP and IDCP

<table>
<thead>
<tr>
<th></th>
<th>AIP</th>
<th>IDCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, mean</td>
<td>7th decade</td>
<td>5th decade</td>
</tr>
<tr>
<td>Male sex</td>
<td>75%</td>
<td>50%</td>
</tr>
<tr>
<td>Elevation of serum IgG4 level</td>
<td>~ 66%</td>
<td>~25%</td>
</tr>
<tr>
<td>Other organ involvement</td>
<td>50%</td>
<td>No(^\text{a})</td>
</tr>
<tr>
<td>Histological findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoplasmacytic infiltration</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Periductal inflammation</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Storiform fibrosis</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Obliterative phlebitis</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>GEL</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>IgG4 tissue staining</td>
<td>Abundant (&lt;10 cells/high-power field)</td>
<td>Scant (&lt;10 cells/high-power field)</td>
</tr>
<tr>
<td>Response to corticosteroids</td>
<td>~100%</td>
<td>~100%</td>
</tr>
<tr>
<td>Risk of relapse</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>(20%–60%)</td>
<td></td>
<td>(&lt;10%)</td>
</tr>
<tr>
<td>Associated with IgG4-RD</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

\(^{a}\)Inflammatory bowel disease is seen in approximately 10% to 20% of patients with IDCP but may also occur in patients with AIP.
respond rapidly to corticosteroid therapy. However, unlike AIP, disease relapses are uncommon (<10%) in IDCP with or without corticosteroid therapy.27,76 When relapses do occur, they remain isolated to the pancreas and respond to re-treatment to corticosteroids. Due to the low relapse rates in IDCP, maintenance therapy is unnecessary. Long-term complications, including pancreatic insufficiency, pancreatic duct stones, and malignancy, are also exceedingly uncommon in IDCP.2

**Conclusions**

AIP and IDCP are two distinct steroid-responsive pancreatitis. AIP is a unique form of chronic pancreatitis defined by characteristic histological features. Despite the frequent association with elevated levels of IgG4 in the serum and IgG4+ plasma cells in tissue, IgG4 is not believed to play a critical role in its pathogenesis. The initial triggering events and predisposing factors to AIP remain elusive and require additional exploration. A diagnosis of AIP requires a high index of clinical suspicion and is established by combining diagnostic evidence from radiographic imaging of the pancreatic parenchyma and pancreatic duct, serum IgG4 levels, other organ involvement, histology, and response to corticosteroid therapy (ie, HISORT) features. AIP is the pancreatic manifestation of a multiorgan syndrome called IgG4-RD and is a relapsing-remitting disease. Controlled studies are needed to better understand the optimal treatment approach to these patients, and ongoing follow-up is necessary to more accurately define long-term complications. AIP and IDCP are distinguished according to their histological features and have different clinical phenotypes (Table 1).

**References**


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Conflicts of interest
The authors disclose no conflicts.