



Review article: autoimmune pancreatitis - management of an emerging disease

Evangelos Kalaitzakis, George Jm Webster

► To cite this version:

Evangelos Kalaitzakis, George Jm Webster. Review article: autoimmune pancreatitis - management of an emerging disease. *Alimentary Pharmacology and Therapeutics*, 2010, 33 (3), pp.291. 10.1111/j.1365-2036.2010.04526.x . hal-00599509

HAL Id: hal-00599509

<https://hal.science/hal-00599509>

Submitted on 10 Jun 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**Review article: autoimmune pancreatitis - management of
an emerging disease**

Journal:	<i>Alimentary Pharmacology & Therapeutics</i>
Manuscript ID:	APT-0785-2010.R1
Wiley - Manuscript type:	Review Article
Date Submitted by the Author:	13-Nov-2010
Complete List of Authors:	Kalaitzakis, Evangelos; University College Hospital London, Department of Gastroenterology Webster, George; University College Hospital London, Department of Gastroenterology
Keywords:	Pancreas < Organ-based, Pancreatitis < Disease-based, Y keyword = no topic, Z keyword = no topic

Management of AIP
Kalaitzakis E and Webster G

Review article: autoimmune pancreatitis - management of an emerging disease

Evangelos Kalaitzakis MD, PhD, George JM Webster BSc, MD, FRCP

Department of Gastroenterology, University College Hospital, London, United Kingdom

Short title: Management of autoimmune pancreatitis

Abbreviations: AIP, autoimmune pancreatitis; IgG4, immunoglobulin G4; IAC, IgG4-associated cholangitis; PSC, primary sclerosing cholangitis; OR, odds ratio; ERCP, endoscopic retrograde cholangiopancreatography;

Keywords: autoimmune pancreatitis; IgG4-associated systemic disease; immunosuppression; steroids; azathioprine

Conflicts of interest: None

Correspondence:

Dr George Webster BSc, MD, FRCP
Pancreaticobiliary medicine
Department of Gastroenterology
University College London Hospital
235 Euston Road
London
NW1 2BU
United Kingdom
tel: +442073809011
fax: +442073809239
email: george.webster@uclh.nhs.uk

SUMMARY

Background Autoimmune pancreatitis (AIP) is a steroid-responsive inflammatory pancreatic disease considered to be part of an immunoglobulin G4 (IgG4)-associated systemic disease.

Aim To review the management of AIP.

Methods We conducted a PubMed search using the following key words: autoimmune pancreatitis, IgG4-associated systemic disease, IgG4-associated cholangitis, diagnosis, natural history, treatment.

Results Although there are reports of spontaneous resolution of AIP, steroids have been shown to be effective in inducing remission, reducing the frequency of relapse, and that of long-term unfavourable events compared to historical controls. There are no randomized data on AIP treatment. Oral steroids are used for induction of remission. Reported response results are excellent with variable proportions of patients achieving remission in different studies. After a period of 2-4 weeks, steroids are tapered and usually withdrawn within several months, although long-term maintenance therapy for all AIP patients has also been proposed. Disease relapse occurs in more than 40% of patients and can be effectively treated with additional immunosuppression, including azathioprine.

Conclusion Steroids are effective in inducing remission and treating relapse in patients with AIP. Randomized trials on AIP therapy are lacking. To date, questions concerning the timing, choice, and duration of long-term immunosuppression remain unanswered.

INTRODUCTION

Autoimmune pancreatitis (AIP) is a steroid-responsive, fibroinflammatory pancreatic disease, which may be seen as part of a systemic disease involving a range of organs (immunoglobulin G4 (IgG4)-associated systemic disease) ¹⁻⁵. Although AIP was initially described more than 40 years ago ⁶, with the disease better defined by Japanese groups since 1995⁷, it is only in the last 5 years that case series from USA and Europe have led to an acceptance that it is a global disease ⁸⁻¹⁰. Typical histopathological findings include a periductal lymphoplasmacytic infiltrate with storiform fibrosis, and obliterative phlebitis ³. The lymphoplasmacytic infiltrate in AIP has abundant IgG4-positive plasma cells on immunostaining (**figure 1**) ^{3, 11} and serum IgG4 levels are usually raised ^{5, 12}. Although a response to steroid therapy is a consistently reported feature of AIP, management remains incompletely defined. In this article we report the evidence base for treatment, including indications, therapeutic regimens, and the future direction of therapy.

METHODS

An extensive PUBMED literature search was conducted using the terms "autoimmune pancreatitis", "IgG4-associated systemic disease", "IgG4-associated cholangitis", "natural history", "diagnosis", and "treatment". The results were combined with literature drawn from the reference lists of review articles yielded by this search as well as with data drawn from the author's published experience of AIP.

Clinical features

Patients with AIP are commonly male and over the age of 50 years^{8, 9, 13-16} but both sexes and all ages may be affected. Obstructive jaundice is present in 30-100% of cases^{8, 9, 15-18}, often in association with weight loss and abdominal pain. In view of imaging characteristically showing a low bile duct stricture in association with diffuse pancreatic enlargement ("sausage pancreas") or a focal mass¹⁹, AIP has historically often been misdiagnosed as pancreatic cancer^{20, 21}. Patients may also present with features of pancreatic exocrine insufficiency⁸. Although up to 65% of patients may present with new-onset mild abdominal pain¹⁴⁻¹⁸, AIP differs from other forms of chronic pancreatitis in that severe intractable pain is unusual. Imaging may show a diffusely thin and abnormal pancreatic duct (**figure 2**). Presentation with acute pancreatitis is rare, but can occur²².

Extrapancreatic disease is now recognized to occur in 40-90% of patients with AIP^{8, 9, 23, 24}. A similar lymphoplasmacytic infiltrate, containing IgG4 positive plasma cells, is seen within both pancreatic and extrapancreatic lesions^{8, 11}. Extrapancreatic sites and lesions include upper abdominal and/or mediastinal lymphadenopathy in up to 80%²³, interstitial nephritis or other renal lesions in up to 45% of cases (often with rounded or wedge-shaped cortical lesions with decreased enhancement)^{9, 25, 26}, retroperitoneal fibrosis in about 10% of patients^{23, 25}, and sialolacrimal disease and secondary Sjögren's syndrome in 5-39% of cases^{8, 23, 25}. Lung, liver, pituitary, and prostatic lesions have also been reported²⁷⁻³¹.

Biliary disease is one of the most common extrapancreatic manifestations of AIP.

Although the main cause of jaundice in AIP is obstruction at the level of the

intrapancreatic portion of the common bile duct, associated with an inflammatory pancreatic head mass, stricturing in the rest of the biliary tree is increasingly recognized. This condition has been termed IgG4-associated cholangitis (IAC) ^{32, 33} and has been reported to occur in 20-88% of cases of AIP ^{2, 8, 9, 23, 25, 34}. Although differences in cholangiographic features have been reported between IAC and primary sclerosing cholangitis (PSC), with segmental strictures, long strictures with prestenotic dilatation and strictures of the common bile duct being more common in IAC ³⁵, these distinctions can be subtle. A possible overlap between IAC and PSC is also suggested by the finding that 9-36% of patients with PSC have increased serum IgG4 levels compared with up to 1% in other liver diseases. ^{36, 37} Of note, PSC patients with raised serum IgG4 levels have a more rapid progression to liver transplantation compared with those with normal levels ³⁷.

Two types of AIP have been described; lymphoplasmacytic sclerosing pancreatitis (type 1 AIP), in which the pancreas is involved as one part of a systemic IgG4-positive disease, and duct-centric (type 2 AIP), which is characterised by granulocyte epithelial lesions in the pancreas without IgG4 positive cells and without systemic involvement ³⁸. It remains unclear whether these two types differ in terms of prognosis and should be managed in different ways, although clinical relapse after treatment appears to be less common with type 2 AIP. Patients with types 2 AIP are usually younger, have a lower prevalence of raised IgG4 levels, and more frequently have inflammatory bowel disease but less commonly other extrapancreatic manifestations compared to those with type 1 AIP ³⁸. AIP type 2 cases are mainly described in series from Europe or the United States but are absent from Asian series.

Diagnostic Criteria

There are no uniformly accepted diagnostic criteria for AIP, but several sets of criteria have been published, including the Asian diagnostic criteria for AIP proposed jointly by researchers in Japan and Korea ³⁹, and the diagnostic criteria developed at the Mayo clinic ⁸. Both systems utilize imaging, serological, and histopathological data as well as a response to steroids to diagnose AIP with the inclusion of extrapancreatic disease as a particular criterion in the latter system ^{8, 39}. The HISORt criteria of the Mayo clinic, in which five cardinal features of AIP, histology, imaging, serology, other organ involvement, and response to steroid therapy (HISORt) are taken into consideration, are outlined in table 1, and the Asian diagnostic criteria for AIP are presented in table 2. In our practice we use the Mayo clinic HISORt criteria to diagnose AIP. However, in a recent retrospective review of 26 consecutive patients treated for AIP in a single US centre, diagnostic criteria for AIP were fulfilled in only 22/26 cases (85%), whichever criteria were used ¹⁴. Although this may indicate reduced sensitivity of the Asian and HISORt criteria for the diagnosis of type 2 AIP (e.g. patients without other organ involvement or IgG4 increase), it also suggests that our understanding of the manifestations and complete spectrum of this disease is still evolving ¹⁴.

In view of its presentation with obstructive jaundice and pancreatic enlargement, AIP frequently needs to be distinguished from pancreatic cancer. Two structured strategies have been described for this purpose, one from Japan ⁴⁰ and another from the United States ⁴¹. Both strategies rely mainly on imaging findings to stratify patients to receive treatment for AIP or pancreatic cancer, or to proceed to further diagnostic work-up. The Japanese strategy includes both CT and endoscopic retrograde pancreatogram (ERP) features, whereas the American strategy employs CT features alone to select patients for

further cancer work-up, mainly by means of attempts to obtain a tissue diagnosis. As ERP features have been reported to have limited sensitivity to diagnose AIP in Western centres ⁴², in our practice, we use the American strategy (**figure 3**). Further cancer work-up by means of brush cytology at ERCP and endoscopic ultrasound guided fine-needle aspiration is required in patients with indeterminate imaging, i.e. with focally enlarged gland without features highly suggestive of cancer: low-density mass, pancreatic ductal dilatation, pancreatic duct cut-off, upstream pancreatic atrophy, or liver lesions suggestive of metastases ⁴¹. Even in the event of negative cancer work-up, a pancreatic core biopsy, steroid trial, or surgery (**figure 3**) is required for diagnosis in approximately 30% of patients with AIP ⁴¹.

TREATMENT OF AIP

Medical therapy

Is treatment necessary?

An important observation related to AIP is that whilst a response to steroids is a criterion for diagnosing the disease, there is no prospective randomized placebo controlled data related to steroid use. So are steroids of benefit, and do they ameliorate the disease?

The inflammatory process of IgG4-associated systemic disease typically responds to steroid treatment and this is also the case with AIP (**figure 4**). Yet spontaneous resolution of symptoms, and of abnormal imaging (including the inflammatory pancreatic mass) is well described ^{13, 43}, and occurred in 30% of cases in one AIP series

43. Kubota et al performed a retrospective study on 20 patients with AIP, 12 of who improved on steroid treatment whereas the remaining 8 patients improved spontaneously ⁴⁴. Spontaneous remission was shown to be associated with normal IgG4 levels at diagnosis, the absence of obstructive jaundice, diabetes, or oedema of the major papilla, negative immunostaining of papillary biopsies for IgG4-positive plasma cells, and focal pancreatic swelling ($p < 0.05$ for all). In multivariate analysis, negative immunostaining of the duodenal papilla for IgG4-positive plasma cells was the only independent predictor of spontaneous remission of AIP (odds ratio (OR) 1.4, $p = 0.03$) ⁴⁴. This finding would need to be confirmed in larger prospective studies.

The effect of steroids on the natural history of AIP is largely unknown due to the lack of longitudinal placebo-controlled trials. However, a recent large retrospective study of 563 AIP patients in 17 Japanese centres showed that the remission rate was significantly higher ($p < 0.0001$) in the group of patients receiving steroids (451/459, 98%) compared to those who received only supportive care (77/104, 74%) ⁴⁵. Similarly, significantly fewer patients ($p = 0.003$) experienced a relapse among those who received steroids (110/451, 24%) compared to those who received only supportive care (32/77, 42%) ⁴⁵. Furthermore, Hirano et al reported the results of a retrospective review of 42 AIP patients (of whom 19 were treated with steroids), aiming to determine the effect of steroids on the long-term outcome of AIP by comparing unfavourable events in patients treated with steroids with those in untreated historical controls ⁴⁶. Unfavourable events were defined as the development of obstructive jaundice due to a distal biliary stricture, sclerosing cholangitis (i.e. IAC) with elevated liver enzymes, pancreatic pseudocyst or other extrapancreatic manifestations requiring treatment. At follow-up unfavourable events were significantly less frequent ($p < 0.05$) in the steroid treated group (6/19, 32%,

mean follow-up 23 months) compared to controls (16/23, 70%, mean follow-up 25 months)⁴⁶. In multivariate analysis, steroid therapy (OR 0.33, p=0.029) and obstructive jaundice at presentation (OR 3.09, p=0.026) were significant predictors of unfavourable events. The authors concluded that steroid therapy could reduce subsequent disease relapse and recommended early introduction of steroids particularly in patients presenting with obstructive jaundice ⁴⁶.

Steroid use as a diagnostic trial

As a response to steroids is a diagnostic criterion for AIP, should a trial of steroids be used to resolve diagnostic uncertainty (specifically between AIP and pancreatic cancer, the most important differential diagnosis)? This question was recently addressed in a study of 22 consecutive patients with atypical imaging for AIP, but without classical imaging criteria for pancreatic cancer ⁴⁷. After a 2-week steroid trial, response to steroids was assessed on the basis of a marked improvement in pancreatic duct narrowing, and a reduction in size of the pancreatic mass. All patients who responded to steroids (15/22) were diagnosed as AIP after a median follow-up of 27 months, whereas all patients who did not respond to steroids (7/22) were diagnosed with pancreatic cancer, with a complete resection being possible in 6/6 patients who accepted surgery ⁴⁷. Thus, a trial of steroids may be useful in supporting the diagnosis of AIP (without compromising the results of surgical therapy in the event of the diagnosis of pancreatic cancer being made), which reflects both the Asian and HISORt diagnostic criteria ^{8, 39}. However, a steroid trial should not be given as a substitute for a thorough search for a definitive diagnosis, including relevant tissue sampling **e.g. by means of endoscopic ultrasound-guided fine needle aspiration**. It should be performed only by pancreatology specialists and only in the context of a structured strategy to distinguish pancreatic

cancer from AIP (**figure 3**)^{40, 41} in which a multidisciplinary team of physicians, surgeons, radiologists, and pathologists familiar with the two diseases is involved⁴⁸. It should be borne in mind that resolution of a pancreatic mass may occur coincidental to steroid therapy (e.g. focal acute pancreatitis), and that a steroid response may be seen in lymphoma of the pancreas, and even in pancreatic adenocarcinoma^{47, 49, 50}.

Indications for treatment

There is no clear consensus as to which patients with a diagnosis of AIP should receive steroids. In series reported to date, the indications for steroid treatment have been obstructive jaundice (due to a distal common bile duct stricture and/or concomitant IAC) in 29-100% of cases^{8, 9, 45, 51, 52}, abdominal pain or other symptoms in 5-11%^{45, 52}, and active extrapancreatic disease in 6-11%^{8, 45}. Although in some series, patients have received treatment solely on the basis of radiological, biochemical, and/or serological findings^{8, 45, 52} it is unclear whether asymptomatic disease without active extrapancreatic involvement should be treated. Whilst a significantly raised serum IgG4 predicts extrapancreatic disease, and by association a subsequently more complicated course, with greater risk of post-steroid relapse, there is insufficient data to commence steroid therapy based upon the serum IgG4 *per se*^{45, 52}. **In our practice, we treat patients with AIP and symptomatic disease, e.g. obstructive jaundice, abdominal pain, and/or the presence of symptomatic extrapancreatic disease, which is also in accordance with the Japanese guidelines for AIP¹⁵. On the other hand we do not commence treatment based solely on radiological findings (i.e. in patients without obstructive jaundice or any other symptoms^{15, 46}), or**, for example, as an attempt to improve pancreatic exocrine function or glycaemic control in a patient with a 'burnt out' atrophic chronic pancreatitis due to AIP. Nevertheless, whilst the introduction of steroids during an early (predominantly

inflammatory) phase of disease would be expected to be more successful than in patients with a longer duration of disease (likely to be more fibrosclerotic), favourable responses may sometimes be seen in longstanding disease, in particular with respect to extrapancreatic involvement. The indications for, and timing of, steroid treatment in AIP may change as our understanding of the effect of steroids on its natural history evolves.

Initial steroid treatment

As there are no randomized studies on the efficacy or dosing of steroids in AIP, steroid treatment of these patients is based mainly on case series and expert opinion. Although the use of parenteral steroids has been described in a case report ⁵³, oral steroids have been used for induction of remission in all large AIP patient series ^{8, 9, 13, 14, 16, 45, 51, 52, 54-57}. Different starting prednisolone doses have been used ranging from 5 mg to 60 mg once daily ^{13, 16, 45, 52} but most clinicians in Japan, Korea, USA and UK use 30 - 40mg daily ^{8, 9, 13, 14, 16, 45, 51, 52, 54, 56}. Retrospective studies from Japan have shown that there is no correlation between the degree of morphological improvement on imaging and the initial prednisolone dose (30mg/day vs. 40mg/day) ⁵² and that there is no difference in the period of time required to induce remission between an initial prednisolone dose of 30mg/day and that of 40mg/day (mean time 6.8 months vs. 6.3 months, $p>0.05$) ⁴⁵. Thus, according to the data published to date, 30mg of prednisolone once daily seems to be adequate as a starting dose for induction of remission in AIP, which is also in line with our clinical experience and practice ^{9, 56}.

Differing patterns of steroid tapering have been proposed. In Japan, prednisolone reduction is reported to begin after 2 weeks in 75% of cases, and after 3-4 weeks in 25%, and the dose is then reduced by 5 mg every 1-2 weeks ⁴⁵. After reaching

prednisolone 15mg, the dose is reduced more slowly, by 2.5 mg to 5 mg every 2-8 weeks, until a maintenance dose of 2.5 mg to 5 mg/day is reached ^{45, 52}. Tapering by 5 mg/week after an initial treatment period of 2-4 weeks has been generally reported from the UK and USA ^{8, 9, 14, 56} with an attempt to withdraw steroids usually being made in all patients without an extended tapering period or maintenance therapy. All groups suggest close clinical follow-up, especially in the first months of treatment, with radiological, serological, and biochemical evaluation as well as assessment of symptomatic relief ^{8, 9, 14, 45, 52, 56}.

Defining treatment response

Currently there are no generally accepted definitions of disease response and remission in terms of specific radiological, biochemical, or serological variables that can be measured in an accurate and reproducible way and that are known to be reliable surrogates of long-term outcome. This is in part due to our limited knowledge of the natural history of AIP. Therefore, there is no consensus about the duration and the need of maintenance steroid therapy in AIP. Differences in definitions of remission and in steroid treatment regimens may account, at least in part, for the differences in reported frequency of disease remission on steroids among different series, ranging from 22% to 100% (table 3). In one Japanese study, 22% of patients with AIP treated with steroids showed serological and morphological resolution after an average of 19.5 months of treatment and could be weaned off steroids, whereas 78% did not and required maintenance steroids ⁵². Similarly, in two other studies, 30% of patients were thought to have reached remission, as defined by near normalization of cholangiopancreatography ^{13, 54} and could be weaned off steroids after 21-37 months ¹³. The rest of the patients required maintenance treatment due to remaining biliary and/or pancreatic duct

abnormalities ^{13, 54} and/or for symptomatic control ¹³. In a recent retrospective Japanese study, complete remission was defined as the disappearance of clinical symptoms and resolution of the pancreatic and/or extrapancreatic manifestations on imaging ⁴⁵. Remission was achieved in 98% of patients treated with steroids but 82% remained on maintenance therapy ⁴⁵. The recently published Japanese guidelines on AIP acknowledge the lack of consensus on the length of steroid therapy, but suggest that maintenance therapy (prednisolone 2.5 - 5mg daily) should be administered to all patients, with the aim of stopping treatment within 3 years, based on individual response ¹⁵. Most publications from Europe and USA report a shorter overall course of initial steroid treatment, ranging from 1.5 -17 months^{8, 9, 14, 56}. This may reflect a number of factors, including the rapid improvement in symptoms, biochemical indices (**figure 5**) and imaging (**figure 6**) that occurs within a few weeks in the majority of patients; the less common use of maintenance therapy from the outset of treatment; and the lack of requirement for complete normalization of imaging in order to define remission. In our experience, marked improvement of biliary and pancreatic duct stricturing, but less frequently complete resolution, occurs following steroids, despite a complete symptomatic response. In a recent study from our group, disease response was defined as symptomatic, biochemical and radiological improvement following commencement of treatment, and disease remission as the maintenance of symptomatic, biochemical and radiological disease control after cessation of steroids and the removal of previously sited biliary stents ⁵⁶. Of 28 patients with AIP treated with steroids, all had a disease response and 23 (82%) achieved remission and could stop steroids after a median of 5 months of treatment ⁵⁶.

Whilst failure to normalize serum IgG4 may predict disease relapse ^{45, 51} (see below), there is insufficient evidence to date to justify tailoring steroid therapy according to the level of serum IgG4, independent of other clinical parameters of disease activity. This may be particularly important in non-Asian patients with type 2 AIP whose serum IgG4 levels are less commonly elevated compared to type 1 AIP patients.

Additional initial management

Most patients with AIP present with obstructive jaundice, and should be considered for biliary drainage prior to commencing steroid therapy, particularly where there is diagnostic uncertainty. Endoscopic retrograde cholangiopancreatography (ERCP) may demonstrate the biliary features of IAC, or characteristic pancreatic duct changes ⁵⁸. It also allows biliary cytology to be taken (to help to exclude malignancy), and ampullary biopsies to identify an IgG4 positive lymphoplasmacytic infiltrate that may be present (figure 1) ⁵⁹. In the event of diagnostic uncertainty, sampling by means of endoscopic ultrasound guided fine-needle aspiration should also be undertaken in the context of a structured strategy to exclude pancreatic malignancy (figure 3). In published series, 14-64% of AIP patients underwent transhepatic or endoscopic biliary drainage prior to steroid therapy ^{9, 14, 51, 52, 54, 55}. Where there is no diagnostic doubt about AIP, ERCP may not be necessary prior to steroids in all cases. The risks of post-ERCP pancreatitis and biliary colonization may be avoided, but this needs to be balanced against the potential septic risks of introducing steroids in the setting of unrelieved biliary obstruction.

Diabetes mellitus is common in AIP, and requires management. In a recent large retrospective study, diabetes mellitus was present in 143 of 459 (31%) AIP patients prior to steroid treatment, and blood glucose levels were controlled with insulin in 73%

and with oral hypoglycaemic agents in 27% of cases ⁴⁵. Although improvement in diabetic control following the introduction of steroids for AIP has been reported ^{13, 51, 52, 55, 60, 61}, we have seen this infrequently in our practice. Nevertheless, glycaemic levels need to be monitored during steroid therapy and treatment instituted or adjusted as appropriate. Exocrine pancreatic dysfunction is also frequent in AIP, occurring in up to 88% of patients in some series ^{51, 55, 60}. Thus, we routinely measure pancreatic faecal elastase levels in these patients and prescribe pancreatic enzyme supplements as necessary. Pancreatic exocrine function may improve after steroid therapy in up to 2/3 of patients ^{51, 55, 60} although worsening has also been reported post-steroids ⁵⁵. In our patient group, pre-steroid pancreatic insufficiency persisted in most patients despite steroids and despite overall clinical improvement ⁶².

Disease relapse

Early reports emphasized the predictable and gratifying response to steroid therapy in patients with AIP ⁶³⁻⁶⁵. Over recent years disease relapse following steroids has become increasingly recognized, with series reporting its frequency ranging from 0% to 68% (table 3). This variability may reflect differences between clinical groups with respect to the definition of relapse, the length of clinical follow-up, and perhaps the use or not of very slow tapering regimens or maintenance therapy. In a large patient series, relapse of AIP was defined as reappearance of symptoms with the development or reappearance of pancreatic and/or extrapancreatic abnormalities and/or marked elevation of serum IgG or IgG4 levels ⁴⁵. In this study relapse occurred in 24% of patients treated with steroids ⁴⁵. We have recently defined relapse as recurrence of disease activity after achievement of remission and cessation of steroids, and discriminated it from failed weaning of steroids the latter being defined by a flare of disease activity whilst tapering initial

steroid course, or an inability to wean steroids completely due to biochemical and/or radiological deterioration ⁵⁶. According to our experience failure to wean steroids occurs in 18% of patients treated with prednisolone and disease relapse in 35% of patients achieving remission ⁵⁶. In non-Asian patients, in whom IgG4 levels may not be elevated (type 2 AIP) ³⁸, serum IgG4 may be less important in defining relapse and, thus, we do not define relapse in terms of serum IgG4 in isolation. Instead we rely mainly on imaging findings (e.g. pancreatic enlargement and/or reappearance of extrapancreatic lesions on follow-up imaging) and/or biochemistry ⁵⁶.

Disease relapse may involve the pancreas in up to 52% of cases ⁴⁵. Although the absence of pancreatic stones was initially reported to be a characteristic of AIP ⁷, it has recently been shown that pancreatic stones may be formed in the course of the disease and that they occur more commonly in patients experiencing disease relapse ^{52, 57, 66, 67}. The fact that pancreatic stones may occur in AIP and that 7%-12% of patients with chronic pancreatitis have raised levels of IgG4 ^{68, 69} suggest that AIP may be a cause of 'idiopathic chronic pancreatitis' ⁵⁷. Disease relapse appears to be particularly common in extrapancreatic sites, especially the biliary tree, and has been reported in 48%-100% of cases (table 3). The reason for this is unclear but it may suggest that pancreatic fibrosis is established early in the course of AIP, which is in line with the frequent observation of pancreatic atrophy (and exocrine insufficiency) following steroid therapy, despite its introduction soon after clinical presentation ^{8, 9, 51, 52, 54}. The fact that disease relapse commonly occurs outside the pancreas further supports the concept of IgG4-associated systemic disease with the pancreas being one of the organs involved ¹⁻⁵. It also suggests that immunosuppression for AIP should focus not only on the pancreas, but also on extrapancreatic disease. Disease activity may vary significantly in different organs at any

single time point, and control of disease in one organ in response to treatment may not be reflected in another ⁵⁶.

Certain factors have been reported to predict relapse in patients with AIP. In a series of 20 AIP patients, raised serum IgG4, diffuse pancreatic enlargement, and the presence of a lower bile duct stricture were found to be significantly associated with a relapse of AIP ⁴⁴. However, after multivariate analysis only diffuse pancreatic enlargement was found to be an independent predictor of relapse (OR 26.2, p=0.03) ⁴⁴. In a study from our group, 54% of patients with AIP who also had IgG4-associated cholangitis subsequently relapsed or failed to wean steroids compared to all AIP patients without IgG4-associated cholangitis who achieved and maintained remission ⁵⁶. Serum IgG4 levels fall in response to steroids ^{12, 51, 52, 54} and persistently raised serum IgG4 may be associated with relapse ^{45, 51} and failure of disease control with steroids ⁵⁴. However, serum IgG4 levels have also been reported to fluctuate by more than 3g/L in patients under maintenance therapy ⁴⁵ and data confirming the predictive value of serum IgG4 in predicting relapse are not unanimous in the literature ⁵⁶. Several other factors have been reported to be related to disease relapse including immune complex formation ⁶⁸, consumption of the complement factors C3 and C4 ⁷⁰, raised liver function tests ⁹, and specific HLA ⁷¹ and cytotoxic T-lymphocyte antigen 4 polymorphisms ⁷². To date, it is unclear whether it is possible to reliably identify patients who may experience early relapse based on any of these parameters as their operating characteristics for relapse prediction have not been fully defined.

The proportion of patients undergoing pancreatic resection for presumed pancreatic cancer in whom AIP is subsequently diagnosed is about 3% according to a large

retrospective series⁷³. In this study, 1287 patients who had undergone pancreaticoduodenectomies mainly for presumed pancreatic malignancy were included. Eight out of 29 patients (28%) diagnosed with AIP following pancreaticoduodenectomy developed relapse after a median of 11 months postoperatively (median follow-up 38 months). Seven out of 8 patients had jaundice and were shown to have biliary strictures on cholangiography⁷³. Relapse occurred faster in the group of patients undergoing distal pancreatectomy compared to those undergoing pancreaticoduodenectomy. The authors concluded that close follow-up is mandatory for all patients diagnosed with AIP following pancreatic resection⁷³. This work emphasizes that not only can a misdiagnosis of pancreatic cancer in patients with AIP lead to high-risk, unnecessary surgery, but also that this surgery may frequently not 'cure' the disease.

Management of relapse

Published data on management of disease relapse in AIP are scarce and randomized trials are again lacking. Most Japanese groups report treatment of relapse with a further course of steroids^{45, 51, 52}, often commencing at prednisolone 30-40mg per day⁴⁵. According to the Japanese guidelines for AIP¹⁵, steroids need to be tapered more gradually after a relapse (by 1mg every two weeks)⁵¹, with 97%-100% of patients responding to this approach⁴⁵. In the USA and the UK relapse is commonly treated with further steroids and the introduction of azathioprine^{8, 9, 14, 56}. We have reported on the successful reintroduction of prednisolone 30 mg per day and azathioprine 1 mg/kg per day, increasing to a target dose of 2 mg/kg per day⁵⁶. Pancreatitis is a known side-effect of azathioprine, occurring in approximately 1.5% of cases of azathioprine use (usually mild)^{74, 75}, but there is no evidence that this risk is increased in AIP. Steroid therapy is tailored to clinical, biochemical and radiological response with the majority of patients

being able to cease their steroid course within 3-9 months in our series⁵⁶. It is uncertain how long treatment following relapse should be continued, but the lesson of managing autoimmune hepatitis ⁷⁶, that cessation of azathioprine should not be considered for 3 years, even in the setting of disease control, may be appropriate. Similarly, some patients may require the maintenance of low dose prednisolone (2.5-5 mg per day) whilst on azathioprine, as is advocated in some patients with autoimmune hepatitis ⁷⁶.

In the event of relapse or failure to wean steroids, in our practice, we routinely restart, (or increase, respectively) steroids to prednisolone 30 mg per and also commence azathioprine treatment, with a target dose of 2 mg/kg per day. We tailor steroid therapy to clinical, biochemical and radiological response. With this approach the majority of patients are able to cease their steroid course within 3-9 months.

Should prolonged maintenance therapy be commenced at the outset of treatment?

Maintenance therapy from the outset has been proposed in the Japanese guidelines for AIP ¹⁵, as it has been reported to correlate with lower relapse rates (23% compared to 34% in patients who stopped maintenance therapy, p=0.048) ⁴⁵. An analogy with the management of autoimmune hepatitis again seems relevant, as both conditions are steroid-responsive and show high relapse rates that may necessitate long-term immunosuppressive treatment. Azathioprine monotherapy is effective for long-term maintenance of remission in autoimmune hepatitis ⁷⁶. However, disease relapse occurs in virtually all patients with autoimmune hepatitis who stop immunosuppression early ⁷⁷ whereas relapse of AIP following steroid therapy is frequent (table 3), but does not seem to be universal. Thus, to date, we believe that there is insufficient data to suggest long-term maintenance therapy from the outset in all AIP patients. Nevertheless, further

studies may help to define subgroups that carry a very high risk of relapse, such that long-term immunosuppression needs to be considered from diagnosis.

Alternative immunosuppressive agents

Long-term immunosuppression with steroids is effective in maintaining remission and treating relapse and it is proposed in the recent Japanese guidelines for AIP¹⁵. However, potential side effects of steroid therapy, such as osteoporosis and worse glucose tolerance, raise the issue of whether alternative drugs could be used. Apart from azathioprine, several other agents, including methotrexate¹⁴, mycophenolate mofetil³³, cyclosporin³³, and rituximab^{78,79} have been used, most in small numbers of patients. It is currently unknown whether long-term immunosuppression may alter the natural history of AIP, or whether any of these agents has an advantage over long-term steroid monotherapy.

FURTHER QUESTIONS

Although randomized placebo controlled trial data to support the initial use of steroid therapy is absent, it is very unlikely that such a study can now be performed, due to the extensive data suggesting benefit. More feasible may be trials comparing treatment strategies (e.g. initial limited steroid course versus long-term maintenance from the outset), or specific therapies (e.g. low-dose steroids versus azathioprine for maintenance). A better understanding of the natural history of AIP would allow new endpoints for such trials to be defined, with a focus on the prevention of irreversible organ dysfunction (both pancreatic and extrapancreatic). In particular, the identification

of patients with AIP who need long-term maintenance treatment as well as the timing, choice, and duration of immunosuppression in AIP warrant further study.

REFERENCES

1. Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, et al. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003;**38**(10):982-4.

2. Hirano K, Shiratori Y, Komatsu Y, Yamamoto N, Sasahira N, Toda N, et al. Involvement of the biliary system in autoimmune pancreatitis: a follow-up study. *Clin Gastroenterol Hepatol* 2003;**1**(6):453-64.

3. Kamisawa T, Funata N, Hayashi Y. Lymphoplasmacytic sclerosing pancreatitis is a pancreatic lesion of IgG4-related systemic disease. *Am J Surg Pathol* 2004;**28**(8):1114.

4. Kamisawa T, Nakajima H, Egawa N, Funata N, Tsuruta K, Okamoto A. IgG4-related sclerosing disease incorporating sclerosing pancreatitis, cholangitis, sialadenitis and retroperitoneal fibrosis with lymphadenopathy. *Pancreatology* 2006;**6**(1-2):132-7.

5. Kamisawa T, Okamoto A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. *J Gastroenterol* 2006;**41**(7):613-25.

6. Sarles H, Sarles JC, Muratore R, Guien C. Chronic inflammatory sclerosis of the pancreas--an autonomous pancreatic disease? *Am J Dig Dis* 1961;**6**:688-98.

7. Yoshida K, Toki F, Takeuchi T, Watanabe S, Shiratori K, Hayashi N. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. *Dig Dis Sci* 1995;**40**(7):1561-8.

8. Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Zhang L, et al. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. *Clin Gastroenterol Hepatol* 2006;**4**(8):1010-6; quiz 934.
9. Church NI, Pereira SP, Deheragoda MG, Sandanayake N, Amin Z, Lees WR, et al. Autoimmune pancreatitis: clinical and radiological features and objective response to steroid therapy in a UK series. *Am J Gastroenterol* 2007;**102**(11):2417-25.
10. Frulloni L, Scattolini C, Falconi M, Zamboni G, Capelli P, Manfredi R, et al. Autoimmune pancreatitis: differences between the focal and diffuse forms in 87 patients. *Am J Gastroenterol* 2009;**104**(9):2288-94.
11. Deheragoda MG, Church NI, Rodriguez-Justo M, Munson P, Sandanayake N, Seward EW, et al. The use of immunoglobulin g4 immunostaining in diagnosing pancreatic and extrapancreatic involvement in autoimmune pancreatitis. *Clin Gastroenterol Hepatol* 2007;**5**(10):1229-34.
12. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001;**344**(10):732-8.
13. Kamisawa T, Yoshiike M, Egawa N, Nakajima H, Tsuruta K, Okamoto A. Treating patients with autoimmune pancreatitis: results from a long-term follow-up study. *Pancreatology* 2005;**5**(2-3):234-8; discussion 238-40.
14. Raina A, Yadav D, Krasinskas AM, McGrath KM, Khalid A, Sanders M, et al. Evaluation and management of autoimmune pancreatitis: experience at a large US center. *Am J Gastroenterol* 2009;**104**(9):2295-306.
15. Okazaki K, Kawa S, Kamisawa T, Ito T, Inui K, Irie H, et al. Japanese Clinical Guidelines for Autoimmune Pancreatitis. *Pancreas* 2009.

16. Kim KP, Kim MH, Song MH, Lee SS, Seo DW, Lee SK. Autoimmune chronic pancreatitis. *Am J Gastroenterol* 2004;**99**(8):1605-16.
17. Uchida K, Okazaki K, Konishi Y, Ohana M, Takakuwa H, Hajiyo K, et al. Clinical analysis of autoimmune-related pancreatitis. *Am J Gastroenterol* 2000;**95**(10):2788-94.
18. Song Y, Liu QD, Zhou NX, Zhang WZ, Wang DJ. Diagnosis and management of autoimmune pancreatitis: experience from China. *World J Gastroenterol* 2008;**14**(4):601-6.
19. Sahani DV, Kalva SP, Farrell J, Maher MM, Saini S, Mueller PR, et al. Autoimmune pancreatitis: imaging features. *Radiology* 2004;**233**(2):345-52.
20. Kamisawa T, Egawa N, Nakajima H, Tsuruta K, Okamoto A, Kamata N. Clinical difficulties in the differentiation of autoimmune pancreatitis and pancreatic carcinoma. *Am J Gastroenterol* 2003;**98**(12):2694-9.
21. Nakazawa T, Ohara H, Sano H, Ando T, Imai H, Takada H, et al. Difficulty in diagnosing autoimmune pancreatitis by imaging findings. *Gastrointest Endosc* 2007;**65**(1):99-108.
22. Sah RP, Pannala R, Chari ST, Sugumar A, Clain JE, Levy MJ, et al. Prevalence, Diagnosis, and Profile of Autoimmune Pancreatitis Presenting with Features of Acute or Chronic Pancreatitis. *Clin Gastroenterol Hepatol*; **8**(1):91-96.
23. Hamano H, Arakura N, Muraki T, Ozaki Y, Kiyosawa K, Kawa S. Prevalence and distribution of extrapancreatic lesions complicating autoimmune pancreatitis. *J Gastroenterol* 2006;**41**(12):1197-205.
24. Fujinaga Y, Kadoya M, Kawa S, Hamano H, Ueda K, Momose M, et al. Characteristic findings in images of extra-pancreatic lesions associated with autoimmune pancreatitis. *Eur J Radiol* 2009.

25. Okazaki K, Uchida K, Matsushita M, Takaoka M. How to diagnose autoimmune pancreatitis by the revised Japanese clinical criteria. *J Gastroenterol* 2007;**42 Suppl 18**:32-8.
26. Takahashi N, Kawashima A, Fletcher JG, Chari ST. Renal involvement in patients with autoimmune pancreatitis: CT and MR imaging findings. *Radiology* 2007;**242**(3):791-801.
27. Taniguchi T, Hamasaki A, Okamoto M. A case of suspected lymphocytic hypophysitis and organizing pneumonia during maintenance therapy for autoimmune pancreatitis associated with autoimmune thrombocytopenia. *Endocr J* 2006;**53**(4):563-6.
28. Ando N, Yasuda I, Saito M, Moriwaki H. Hilar lymphadenopathy associated with autoimmune pancreatitis. *Pancreas* 2006;**33**(1):101-2.
29. Umemura T, Zen Y, Hamano H, Kawa S, Nakanuma Y, Kiyosawa K. Immunoglobulin G4-hepatopathy: association of immunoglobulin G4-bearing plasma cells in liver with autoimmune pancreatitis. *Hepatology* 2007;**46**(2):463-71.
30. Wong S, Lam WY, Wong WK, Lee KC. Hypophysitis presented as inflammatory pseudotumor in immunoglobulin G4-related systemic disease. *Hum Pathol* 2007;**38**(11):1720-3.
31. Uehara T, Hamano H, Kawakami M, Koyama M, Kawa S, Sano K, et al. Autoimmune pancreatitis-associated prostatitis: distinct clinicopathological entity. *Pathol Int* 2008;**58**(2):118-25.
32. Bjornsson E, Chari ST, Smyrk TC, Lindor K. Immunoglobulin G4 associated cholangitis: description of an emerging clinical entity based on review of the literature. *Hepatology* 2007;**45**(6):1547-54.

Management of AIP

Kalaitzakis E and Webster G

33. Ghazale A, Chari ST, Zhang L, Smyrk TC, Takahashi N, Levy MJ, et al. Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. *Gastroenterology* 2008;**134**(3):706-15.
34. Nishino T, Toki F, Oyama H, Oi I, Kobayashi M, Takasaki K, et al. Biliary tract involvement in autoimmune pancreatitis. *Pancreas* 2005;**30**(1):76-82.
35. Nakazawa T, Ohara H, Sano H, Aoki S, Kobayashi S, Okamoto T, et al. Cholangiography can discriminate sclerosing cholangitis with autoimmune pancreatitis from primary sclerosing cholangitis. *Gastrointest Endosc* 2004;**60**(6):937-44.
36. Hirano K, Kawabe T, Yamamoto N, Nakai Y, Sasahira N, Tsujino T, et al. Serum IgG4 concentrations in pancreatic and biliary diseases. *Clin Chim Acta* 2006;**367**(1-2):181-4.
37. Mendes FD, Jorgensen R, Keach J, Katzmann JA, Smyrk T, Donlinger J, et al. Elevated serum IgG4 concentration in patients with primary sclerosing cholangitis. *Am J Gastroenterol* 2006;**101**(9):2070-5.
38. Park DH, Kim MH, Chari ST. Recent advances in autoimmune pancreatitis. *Gut* 2009;**58**(12):1680-9.
39. Otsuki M, Chung JB, Okazaki K, Kim MH, Kamisawa T, Kawa S, et al. Asian diagnostic criteria for autoimmune pancreatitis: consensus of the Japan-Korea Symposium on Autoimmune Pancreatitis. *J Gastroenterol* 2008;**43**(6):403-8.
40. Kamisawa T, Imai M, Yui Chen P, Tu Y, Egawa N, Tsuruta K, et al. Strategy for differentiating autoimmune pancreatitis from pancreatic cancer. *Pancreas* 2008;**37**(3):e62-7.
41. Chari ST, Takahashi N, Levy MJ, Smyrk TC, Clain JE, Pearson RK, et al. A diagnostic strategy to distinguish autoimmune pancreatitis from pancreatic cancer. *Clin Gastroenterol Hepatol* 2009;**7**(10):1097-103.

42. Sugumar A, Levy MJ, Kamisawa T, Webster JMG, Kim MH, Enders FB, et al.

Utility of endoscopic retrograde pancreatogram to diagnose autoimmune pancreatitis:

An international, double blind, randomized, multicenter study. *Gut* 2010:Accepted for

publication.

43. Okazaki K, Uchida K, Chiba T. Recent concept of autoimmune-related

pancreatitis. *J Gastroenterol* 2001;**36**(5):293-302.

44. Kubota K, Iida H, Fujisawa T, Yoneda M, Inamori M, Abe Y, et al. Clinical

factors predictive of spontaneous remission or relapse in cases of autoimmune

pancreatitis. *Gastrointest Endosc* 2007;**66**(6):1142-51.

45. Kamisawa T, Shimosegawa T, Okazaki K, Nishino T, Watanabe H, Kanno A,

et al. Standard steroid therapy for autoimmune pancreatitis. *Gut* 2009.

46. Hirano K, Tada M, Isayama H, Yagioka H, Sasaki T, Kogure H, et al. Long-

term prognosis of autoimmune pancreatitis with and without corticosteroid treatment.

Gut 2007;**56**(12):1719-24.

47. Moon SH, Kim MH, Park DH, Hwang CY, Park SJ, Lee SS, et al. Is a 2-week

steroid trial after initial negative investigation for malignancy useful in differentiating

autoimmune pancreatitis from pancreatic cancer? A prospective outcome study. *Gut*

2008;**57**(12):1704-12.

48. Sugumar A, Chari ST. Distinguishing pancreatic cancer from autoimmune

pancreatitis: a comparison of two strategies. *Clin Gastroenterol Hepatol* 2009;**7**(11

Suppl):S59-62.

49. Shimosegawa T. Are glucocorticoids really useful for the treatment of acute

pancreatitis? *J Gastroenterol* 2002;**37**(7):580-1.

50. Rutz HP. Effects of corticosteroid use on treatment of solid tumours. *Lancet*

2002;**360**(9349):1969-70.

51. Nishino T, Toki F, Oyama H, Shimizu K, Shiratori K. Long-term outcome of autoimmune pancreatitis after oral prednisolone therapy. *Intern Med* 2006;**45**(8):497-501.
52. Kamisawa T, Okamoto A, Wakabayashi T, Watanabe H, Sawabu N. Appropriate steroid therapy for autoimmune pancreatitis based on long-term outcome. *Scand J Gastroenterol* 2008;**43**(5):609-13.
53. Matsushita M, Yamashina M, Ikeura T, Shimatani M, Uchida K, Takaoka M, et al. Effective steroid pulse therapy for the biliary stenosis caused by autoimmune pancreatitis. *Am J Gastroenterol* 2007;**102**(1):220-1.
54. Kamisawa T, Egawa N, Nakajima H, Tsuruta K, Okamoto A. Morphological changes after steroid therapy in autoimmune pancreatitis. *Scand J Gastroenterol* 2004;**39**(11):1154-8.
55. Ito T, Nishimori I, Inoue N, Kawabe K, Gibo J, Arita Y, et al. Treatment for autoimmune pancreatitis: consensus on the treatment for patients with autoimmune pancreatitis in Japan. *J Gastroenterol* 2007;**42 Suppl 18**:50-8.
56. Sandanayake NS, Church NI, Chapman MH, Johnson GJ, Dhar DK, Amin Z, et al. Presentation and Management of Post-treatment Relapse in Autoimmune Pancreatitis/Immunoglobulin G4-Associated Cholangitis. *Clin Gastroenterol Hepatol* 2009;**7**(10):1089-96.
57. Kawa S, Hamano H, Ozaki Y, Ito T, Kodama R, Chou Y, et al. Long-term follow-up of autoimmune pancreatitis: characteristics of chronic disease and recurrence. *Clin Gastroenterol Hepatol* 2009;**7**(11 Suppl):S18-22.
58. Sugumar A, Levy MJ, Kamisawa T, Kim MH, Enders FB, Amin Z, et al. Utility of endoscopic retrograde pancreatogram to diagnose autoimmune pancreatitis: An

international, double blind, randomized, multicenter study. *Gastrointest Endosc* 2009;**69**(5):AB124.

59. Kamisawa T, Tu Y, Nakajima H, Egawa N, Tsuruta K, Okamoto A. Usefulness of biopsying the major duodenal papilla to diagnose autoimmune pancreatitis: a prospective study using IgG4-immunostaining. *World J Gastroenterol* 2006;**12**(13):2031-3.

60. Kamisawa T, Egawa N, Inokuma S, Tsuruta K, Okamoto A, Kamata N, et al. Pancreatic endocrine and exocrine function and salivary gland function in autoimmune pancreatitis before and after steroid therapy. *Pancreas* 2003;**27**(3):235-8.

61. Nishimori I, Tamakoshi A, Kawa S, Tanaka S, Takeuchi K, Kamisawa T, et al. Influence of steroid therapy on the course of diabetes mellitus in patients with autoimmune pancreatitis: findings from a nationwide survey in Japan. *Pancreas* 2006;**32**(3):244-8.

62. Sandanayake N, Chapman MH, Kalaitzakis E, Amin Z, Novelli M, Winstanley A, et al. Do steroids improve the long-term outcome of autoimmune pancreatitis. *Gut* 2010;**59**(4 (Suppl 1)):A1.

63. Clark A, Zeman RK, Choyke PL, White EM, Burrell MI, Grant EG, et al. Pancreatic pseudotumors associated with multifocal idiopathic fibrosclerosis. *Gastrointest Radiol* 1988;**13**(1):30-2.

64. Chutaputti A, Burrell MI, Boyer JL. Pseudotumor of the pancreas associated with retroperitoneal fibrosis: a dramatic response to corticosteroid therapy. *Am J Gastroenterol* 1995;**90**(7):1155-8.

65. Erkelens GW, Vleggaar FP, Lesterhuis W, van Buuren HR, van der Werf SD. Sclerosing pancreato-cholangitis responsive to steroid therapy. *Lancet* 1999;**354**(9172):43-4.

66. Takayama M, Hamano H, Ochi Y, Saegusa H, Komatsu K, Muraki T, et al. Recurrent attacks of autoimmune pancreatitis result in pancreatic stone formation. *Am J Gastroenterol* 2004;**99**(5):932-7.

67. Kamisawa T, Okamoto A. Prognosis of autoimmune pancreatitis. *J Gastroenterol* 2007;**42 Suppl 18**:59-62.

68. Kawa S, Hamano H. Clinical features of autoimmune pancreatitis. *J Gastroenterol* 2007;**42 Suppl 18**:9-14.

69. Choi EK, Kim MH, Lee TY, Kwon S, Oh HC, Hwang CY, et al. The sensitivity and specificity of serum immunoglobulin G and immunoglobulin G4 levels in the diagnosis of autoimmune chronic pancreatitis: Korean experience. *Pancreas* 2007;**35**(2):156-61.

70. Muraki T, Hamano H, Ochi Y, Komatsu K, Komiyama Y, Arakura N, et al. Autoimmune pancreatitis and complement activation system. *Pancreas* 2006;**32**(1):16-21.

71. Park do H, Kim MH, Oh HB, Kwon OJ, Choi YJ, Lee SS, et al. Substitution of aspartic acid at position 57 of the DQbeta1 affects relapse of autoimmune pancreatitis. *Gastroenterology* 2008;**134**(2):440-6.

72. Umemura T, Ota M, Hamano H, Katsuyama Y, Muraki T, Arakura N, et al. Association of autoimmune pancreatitis with cytotoxic T-lymphocyte antigen 4 gene polymorphisms in Japanese patients. *Am J Gastroenterol* 2008;**103**(3):588-94.

73. Weber SM, Cubukcu-Dimopulo O, Palesty JA, Suriawinata A, Klimstra D, Brennan MF, et al. Lymphoplasmacytic sclerosing pancreatitis: inflammatory mimic of pancreatic carcinoma. *J Gastrointest Surg* 2003;**7**(1):129-37; discussion 137-9.

74. Bermejo F, Lopez-Sanroman A, Taxonera C, Gisbert JP, Perez-Calle JL, Vera I, et al. Acute pancreatitis in inflammatory bowel disease, with special reference to azathioprine-induced pancreatitis. *Aliment Pharmacol Ther* 2008;**28**(5):623-8.
75. Prefontaine E, Macdonald JK, Sutherland LR. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2009(4):CD000545.
76. Johnson PJ, McFarlane IG, Williams R. Azathioprine for long-term maintenance of remission in autoimmune hepatitis. *N Engl J Med* 1995;**333**(15):958-63.
77. Hegarty JE, Nouri Aria KT, Portmann B, Eddleston AL, Williams R. Relapse following treatment withdrawal in patients with autoimmune chronic active hepatitis. *Hepatology* 1983;**3**(5):685-9.
78. Topazian M, Witzig TE, Smyrk TC, Pulido JS, Levy MJ, Kamath PS, et al. Rituximab therapy for refractory biliary strictures in immunoglobulin G4-associated cholangitis. *Clin Gastroenterol Hepatol* 2008;**6**(3):364-6.
79. Rueda JC, Duarte-Rey C, Casas N. Successful treatment of relapsing autoimmune pancreatitis in primary Sjogren's syndrome with rituximab: report of a case and review of the literature. *Rheumatol Int* 2009;**29**(12):1481-5.

Figure 1 Lymphoplasmacytic infiltrate with abundant IgG4-positive plasma cells in a pancreatic biopsy from a patient with type 1 AIP.

Figure 2 Endoscopic retrograde cholangiopancreatogram in a patient with AIP IgG4-associated cholangitis, showing diffuse pancreatic duct stricturing and intrahepatic biliary stricture.

Figure 3 Strategy for distinguishing AIP from pancreatic cancer.

Reprinted from Clinical Gastroenterology and Hepatology 7(10), authors: Chari ST, Takahashi N, Levy MJ, Smyrk TC, Clain JE, Pearson RK, Petersen BT, Topazian MA, Vege SS. A diagnostic strategy to distinguish autoimmune pancreatitis from pancreatic cancer, pp 1097-1103, Copyright (2009), with permission from Elsevier

Figure 4 Abdominal computed tomography scan of the pancreas in a patient with AIP showing a diffusely enlarged "sausage" pancreas (a), with subsequent radiological remission after 2 months of steroid therapy (b).

Figure 5 Response of serum bilirubin to steroid therapy in 11 patients with AIP.

Reprinted by permission from Macmillan Publishers Ltd: Am J Gastroenterol 2007;102:2417-25, copyright 2007

Figure 6 Endoscopic retrograde cholangiogram in a patient with AIP and IgG4-associated cholangitis, demonstrating changes in the biliary tree before (a) and after (b) a course of steroids.

Table 1 The HISORt diagnostic criteria for autoimmune pancreatitis ⁸

1. <u>H</u> istology	<p>One or more of the following:</p> <ul style="list-style-type: none"> i. Pancreatic histology showing lymphoplasmacytic sclerosing pancreatitis ii. Lymphoplasmacytic infiltrate and storiform fibrosis with abundant (>10 cells/HPF) IgG4-positive cells in the pancreas
2. <u>I</u> maging	<p>Typical:</p> <ul style="list-style-type: none"> i. diffusely enlarged pancreas with delayed (rim) enhancement ii. diffusely irregular, attenuated main pancreatic duct <p>Others:</p> <ul style="list-style-type: none"> i. focal pancreatic mass ii. focal pancreatic duct stricture iii. pancreatitis iv. pancreatic atrophy v. pancreatic calcification
3. <u>S</u> erology	Raised serum IgG4 level
4. Other <u>o</u> rgan involvement	<p>hilar/intrahepatic biliary strictures, persistent distal biliary stricture, parotid/lacrimal gland involvement, mediastinal lymphadenopathy,</p>

	retroperitoneal fibrosis
5. <u>R</u> esponse to steroid <u>t</u> herapy	Resolution/marked improvement of pancreatic/extrapancreatic manifestation with steroid therapy
Diagnosis	Group A: diagnostic histology only Group B: typical imaging + serology Group C: unexplained pancreatic disease with serology or other organ involvement (with abundant IgG4-positive cells) and response to steroid therapy

HPF, high-power field

Table 2 The Asian criteria for the diagnosis of AIP ³⁹

1. Imaging	Both the following: i. Diffuse/segmental/focal enlargement of the pancreas, occasionally with a mass and/or hypoattenuation rim ii. Diffuse/segmental/focal pancreatic ductal narrowing, often with bile duct stricturing
2. Serology	At least one of the following: i. High levels of serum IgG or IgG4 ii. Detection of autoantibodies
3. Histopathology	Pancreatic lymphoplasmacytic infiltration with fibrosis and abundant IgG4-positive plasma cells
Response to steroids (optional criterion)	Diagnostic trials of steroid therapy should be conducted carefully by pancreatologists and only in patients fulfilling criterion 1 with negative work-up for pancreaticobiliary cancer
Diagnosis	AIP should be diagnosed when criterion 1 and at least one of criteria 2 and 3 are satisfied, or when histology shows the presence of lymphoplasmacytic sclerosing pancreatitis in the resected pancreas

Table 3 Frequency of disease response, remission, and relapse in patients with AIP treated with oral steroids

	No of patients	Response	Remission	Relapse	Average follow-up (months)
Kamisawa et al, 2004 ⁵⁴	10	100%	30%	0%	-
Kamisawa et al, 2005 ¹³	10	100%	30%	0%	47.2
Nishino et al, 2006 ⁵¹	12	100%	25%	33% ^a	41
Chari et al, 2006 ⁸	17	100%	-	-	6.5
Ito et al, 2007 ⁵⁵	14	100%	100%	28%	-
Church et al, 2007 ⁹	11	100%	-	54% ^b	18
Kamisawa, et al 2008 ⁵²	41	100%	22%	10% ^c	43.5
Raina et al, 2009 ¹⁴	19	100%	79%	68% ^d	9.7
Sandanayake et al, 2009 ⁵⁶	28	100%	82%	46% ^e	26

Kamisawa et al, 2009 ⁴⁵	459	-	98%	24% ^f	-
Kawa et al, 2009 ⁵⁷	42	-	-	41%	72

Disease response, remission and relapse were defined differently between studies (see text).

^aBiliary stricturing - 8%, salivary gland swelling - 25%

^bHilar mass - 6%, biliary stricturing - 6%, renal impairment - 6%, raised liver

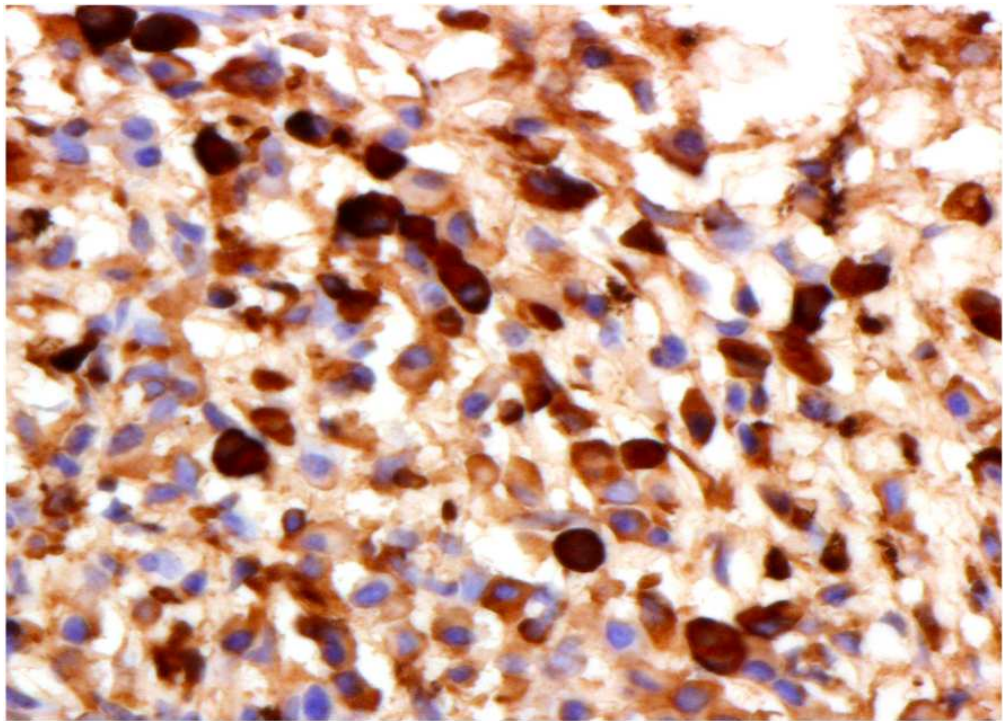
biochemistry and renal impairment- 6%, recurring biliary and pancreatic abnormalities - 6%, neurological impairment - 6%

^cBiliary stricturing - 7.5%, retroperitoneal fibrosis - 2.5%, enlargement of pancreas - 2.5%

^dBiliary stricturing post-steroids - 21%, enlargement of pancreas post-steroids - 16%, pancreatic duct stricturing post-steroids - 16%, persistent enlargement of pancreas - 10%, persistent biliary stricturing - 10%

^eBiliary stricturing post-steroids - 28.5% and failed steroid weaning due to raised liver biochemistries - 3.5%, biliary stricturing - 3.5%, renal impairment 7%, neurological impairment 3.5%

^fPancreatic abnormalities - 52%, biliary stricturing - 34%, other extrapancreatic disease - 14%



Lymphoplasmacytic infiltrate with abundant IgG4-positive plasma cells in a pancreatic biopsy from a patient with type 1 AIP.
150x108mm (150 x 150 DPI)

review



Lymphoplasmacytic infiltrate with abundant IgG4-positive plasma cells in a pancreatic biopsy from a patient with type 1 AIP.
142x140mm (150 x 150 DPI)

Patients presenting with obstructive jaundice and/or pancreatic mass

Pancreatic findings on CT/MRI: stratify patients into imaging groups 1, 2, or 3

Imaging group 1
Highly suggestive of AIP

**Serology and
other organ involvement**

One supportive or
highly suggestive feature of
AIP (S1/2 or O1/2)

Yes

No

Highly suggestive/supportive of AIP

Treat with prednisone 40mg/day x 2 weeks

Reassess serum IgG4, CA 19-9, pancreatic morphology

Response to steroids

No

Yes

Reconsider diagnosis

AIP diagnosis confirmed

Imaging group 2
Indeterminate

Cancer work-up negative

OOI
present

**Serology and
other organ involvement**

One highly
suggestive or two
supportive
features of AIP
(S1/2 or O1/2)

None or only one
supportive feature
of AIP (S2 or O2)

Pancreatic core biopsy

Positive for
cancer

Inconclusive/not performed

Steroid trial

Not performed

Surgical resection

Positive for
cancer

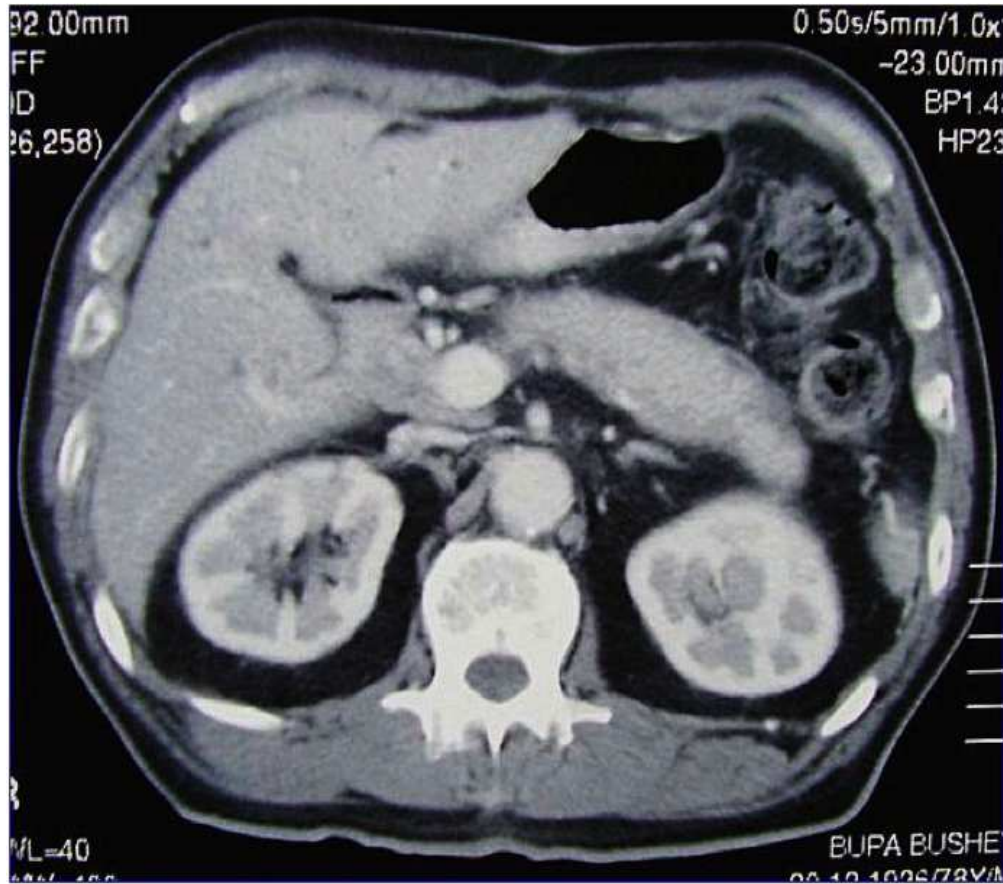
Diagnostic of AIP

Imaging group 3
Highly suggestive of PaC

Consider managing as PaC
unless OOI suggestive of
AIP (O2) on imaging

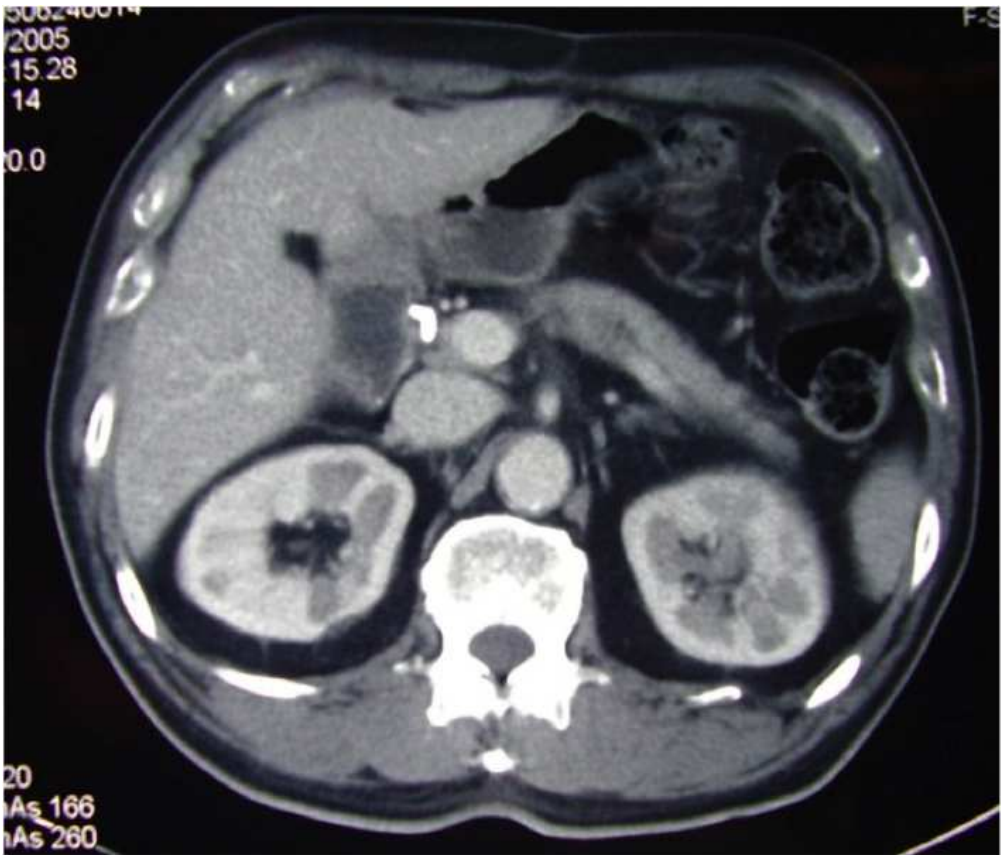
No OOI

Manage as PaC

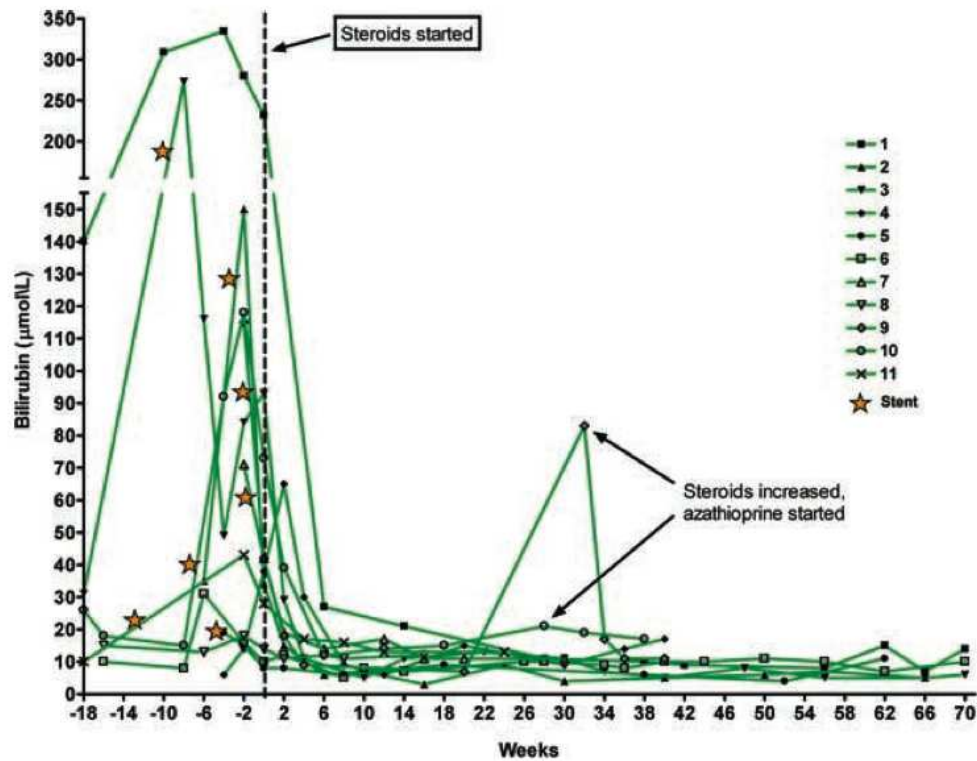


Abdominal computed tomography scan of the pancreas in a patient with AIP showing a diffusely enlarged "sausage" pancreas (a), with subsequent radiological remission after 2 months of steroid therapy (b).

117x103mm (150 x 150 DPI)



Abdominal computed tomography scan of the pancreas in a patient with AIP showing a diffusely enlarged "sausage" pancreas (a), with subsequent radiological remission after 2 months of steroid therapy (b).
119x102mm (150 x 150 DPI)



Response of serum bilirubin to steroid therapy in 11 patients with AIP.
128x100mm (150 x 150 DPI)



Endoscopic retrograde cholangiogram in a patient with AIP and IgG4-associated cholangitis, demonstrating changes in the biliary tree before (a) and after (b) a course of steroids. 110x111mm (150 x 150 DPI)



Endoscopic retrograde cholangiogram in a patient with AIP and IgG4-associated cholangitis, demonstrating changes in the biliary tree before (a) and after (b) a course of steroids.
110x111mm (150 x 150 DPI)