on Studies of Health Policies, Ministry of Health, Labour, and Welfare, Japan, and was revised using newly available information. The departments of internal medicine, gastroenterology, digestive surgery, and surgery in the respective hospitals were listed, and a method of stratified random sampling was used to select the departments to be surveyed. The sampling rates were 5%, 10%, 20%, 40%, 80%, 100%, and 100% for the stratum of general hospitals with fewer than 100 beds, 100 to 199 beds, 200 to 299 beds, 300 to 399 beds, 400 to 499 beds, 500 or more beds, and the affiliated university hospitals, respectively. To increase the study efficiency, we also selected some departments that were expected to treat many patients with pancreatic diseases. These departments were separately classified into a "special strata" category, and all departments in this category were surveyed.

A simple questionnaire was made to ask about the number of patients with AIP who visited the departments in 2007. This questionnaire was directly mailed in November 2008 to the heads of 3015 departments randomly chosen as described above.

Estimation of Prevalence

The number of patients with AIP in 2007 was estimated based on the assumption that the response from departments was independent of the frequency of patients.[12] The formulae to compute the number of patients and the 95% confidence interval (CI) are as follows.[12–14]

The number of patients in stratum k was estimated as

$$\hat{\alpha_k} = \frac{1}{\mathrm{SRT}_k\ \mathrm{RRT}_k}\sum_i i\,N_{ki} = \frac{1}{\frac{NS_k}{n_k}\frac{N_k}{NS_k}}\sum_i i\,N_{ki} = \frac{n_k}{N_k}\sum_i i\,N_{ki}$$

where SRT_k, RRT_k, NS_k, n_k, N_k and N_{ki} denote the sampling rate, response rate, the number of sampling departments, the total number of departments, the number of responding departments, and the number of departments with i patients in stratum k, respectively. The 95% CI of $\hat{\alpha_k}$ was

$$(\hat{\alpha_k} - 1.96s_k,\quad \hat{\alpha_k} + 1.96s_k)$$

$$s_k = \sqrt{\frac{\frac{1}{N_k}\sum_i i^2 N_{ki} - \left(\frac{1}{N_k}\sum_i iN_{ki}\right)^2}{n_k - 1}\,{n_k}^3\left(\frac{1}{N_k} - \frac{1}{n_k}\right)}$$

where S_k is the estimated standard error of $\hat{\alpha_k}$.

The total number of patients, α, was computed as follows:

$$\hat{\alpha} = \sum_k \hat{\alpha_k}$$

and the 95% CI was

$$(\hat{\alpha} - 1.96s,\quad \hat{\alpha} + 1.96s),\quad s = \sqrt{\sum_k {s_k}^2}$$

where s is the estimated standard error of $\hat{\alpha}$.

Second-Stage Survey

Requests for all individual patients' detailed clinicoepidemiological information were sent to those departments responding that they had seen patients with AIP in 2007 in the first-stage survey. The responses to the second questionnaire were collected between December 2009 and March 2010 (until 2 months after the due date). To increase the response rate, we mailed reminders before and after the due date for each survey. Because some items of the questionnaire were left blank, the numbers of patients subjected for analysis were different depending on the items.

RESULTS

First-Stage Survey

Table 1 shows a summary of the first-stage survey. Of 3015 departments, 1114 departments responded to the questionnaire in the first-stage survey (response rate: 36.9%) and 1069 patients with AIP were identified (Table 1). Among them, 391 cases (36.6%) were newly diagnosed patients as having AIP in 2007. From these data, we estimated that the total number of patients diagnosed as having AIP in 2007 in Japan was 2790 (95% CI, 2540–3040), which means an estimated overall prevalence rate of 2.2 per 100,000 populations. The number of patients who were newly diagnosed as AIP in 2007 was estimated to be 1120 (95% CI, 1000–1240), from which the annual incidence rate was calculated to be 0.9 per 100,000 populations.

Second-Stage Survey

In response to the questionnaire in the second-stage survey, we collected detailed clinicoepidemiological information on 546 patients (51.0%; 418 males, 114 females, and 14 patients of unknown sex) who were identified by the first questionnaire. One hundred seventy-two patients were newly diagnosed in 2007, and 374 patients had been already diagnosed as AIP before 2007. All patients were Japanese.

TABLE 1. Summary of the First Survey

Strata	Total No. Departments in Japan	Sampling Rate, %	No. Surveyed Departments	No. Responded Departments	Response Rate, %	Total	No. Reported Patients
Special departments	80	100	80	58	72.5	376	121
University hospital	294	100	294	184	62.6	336	107
≥500 beds	679	100	679	241	35.5	191	94
400-499 beds	633	80	506	166	32.8	100	35
300-399 beds	1156	40	462	142	30.7	43	21
200-299 beds	1689	20	338	100	29.6	14	6
100-199 beds	3903	10	390	128	32.8	5	5
≤99 beds	5324	5	266	95	35.7	4	2
Total	13,758	—	3015	1114	36.9	1069	391

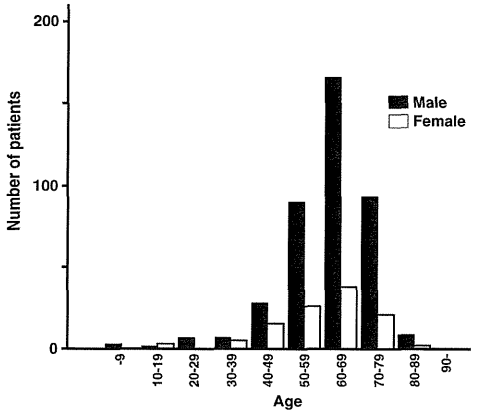

FIGURE 1. Age distribution of patients with AIP.

The male-to-female ratio of the AIP patients was 3.7. The mean (SD) age was 63.0 (11.4) years (male/female = 63.6[10.8]/60.3 [12.4]), and patients aged 60 to 69 years formed a peak in the age distribution curve (Fig. 1).

Diagnosis

Clinical profiles of the reported patients are summarized in Table 2. Approximately 90% of the cases had enlargement of the pancreas. Among them, nearly 30% cases showed localized enlargement, which was not included in the 2002 diagnostic criteria.[10] Main pancreatic duct narrowing was seen in more than 90% cases, but narrowing was within one third of the entire length in approximately one third of the cases. These cases again did not meet the 2002 criteria.

Serum IgG4 level was increased (≥135 mg/dL) in 87.6% of the patients. The level of IgG was increased in 56.9%, but the positive rates for γ-globulin, anti–nuclear antibody, rheumatoid factor, and eosinophil were less than half.

Tissue specimens, including both accurate and inaccurate diagnosis, were obtained from various organs including the pancreas in 233 (49.1%) of 475 cases, whereas histological examination was not performed in 242 cases (Table 3). Endoscopic ultrasonography–guided fine needle aspiration was most frequently performed for obtaining pancreatic tissue samples. Pancreatic resection was performed in 51 cases on the suspicion of pancreatic cancer.

Sclerosing cholangitis was the leading extrapancreatic lesion and found in more than half of the patients (Table 4). Other relatively common extrapancreatic lesions included sialadenitis, lymphadenopathy, and retroperitoneal fibrosis.

Steroid was used for a diagnostic purpose in 36 (6.8%) of 530 patients. The reasons (52 in total) for steroid trial were as follows: the absence of characteristic imaging findings for AIP in 17 cases, negative serological findings in 19 cases, and lack of typical histological findings in 11 cases.

TABLE 2. Clinical Profiles of the Reported AIP Patients

Pancreatic imaging	
Enlargement	478/530 (90.2%)
Diffuse enlargement	322/478 (67.4%)
Localized enlargement	141/478 (29.5%)
N/A	15/478 (3.1%)
MPD narrowing	468/508 (92.1%)
≥1/3	307/468 (65.6%)
<1/3	151/468 (32.3%)
N/A	10/468 (2.1%)
Serology	
γ-Globulin (≥2.0 g/dL)	153/381 (40.2%)
IgG (≥1.8 g/dL)	292/513 (56.9%)
IgG4 (≥135 mg/dL)	388/443 (87.6%)
ANA (≥80-folds)	154/458 (33.6%)
RF (≥20 IU/mL)	86/315 (27.3%)
Eosinophil (≥8%)	71/388 (18.3%)

ANA indicates anti–nuclear antibody; IgG, immunoglobulin G; N/A, not available; RF, rheumatoid factor.

TABLE 3. Histological Examination Performed in the Reported AIP Patients

Organs	Procedures	No. Patients*
Pancreas	Resection	51/233 (21.9%)
	EUS-FNA	92/233 (39.5%)
	EUS-TCB	4/233 (1.7%)
	Percutaneous biopsy	43/233 (18.5%)
Salivary gland	Biopsy	18/233 (7.7%)
Bile duct	Biopsy	35/233 (15.0%)
Duodenal papilla	Biopsy	6/233 (2.6%)

*Including overlapping cases.

EUS-FNA indicates endoscopic ultrasonography–guided fine needle aspiration; EUS-TCB, endoscopic ultrasonography–guided trucut biopsy.

Treatment

Four hundred fifty-three (83.0%) of the 546 patients were treated by steroid, whereas the remaining 17% patients received no particular medication. No patients received immunosuppressants in this study. Biliary drainage was performed in 41.4% patients owing to obstructive jaundice by associating sclerosing cholangitis.

Relapse

Among the 458 patients who had received the steroid treatment, 134 patients (29.6%) relapsed on imaging studies. Relapse occurred in the pancreas in 49 patients (36.6%), in the extrapancreatic organs in 57 patients (42.5%), and in both the pancreas and extrapancreatic organs in 24 patients (17.9%).

DISCUSSION

There are numerous reports on cases of AIP not only from Japan but also from various Asian and Western countries.[15–19]

TABLE 4. Extrapancreatic Lesions

Sclerosing cholangitis	289/541 (53.4%)
Sialadenitis	76/540 (14.1%)
Mediastinal/abdominal lymph nodes swelling	69/539 (12.8%)
Retroperitoneal fibrosis	44/543 (8.1%)
Dacryoadenitis	36/525 (6.9%)
Interstitial pneumonia	20/542 (3.7%)
Thyroiditis	14/543 (2.6%)
Interstitial nephritis	14/543 (2.6%)

But most of them were based on the experience of single institutes or a combination of at most several affiliated hospitals or high-volume centers. The present study is a large-scale epidemiological study of AIP in a whole country, using established statistical methods. Because the results of this survey did not contain data from races other than Japanese, they may represent the clinicopathological features of AIP that was originally reported and defined in Japan in 1995.[15] The results are summarized as follows: (i) the overall prevalence rate of AIP in Japan is estimated to be 2.2 per 100,000 populations, with an annual incidence rate of 0.9 per 100,000 populations; (ii) most patients with AIP in Japan presented with positive serological findings such as increased level of serum IgG4; (iii) two thirds of AIP patients show typical diffuse enlargement of the pancreas and diffuse narrowing of the MPD as well, whereas one third show localized imaging findings in the pancreas; and (iv) histological diagnosis is actively performed in Japan by biopsy of the pancreas, whereas diagnostic steroid therapy is in limited use.

The estimated number of AIP patients in this study, 2790, was 3.1 times higher than the estimated number of 900 in the earlier nationwide survey in 2002[9] and was 1.64 times higher than the 1700 (Nishimori I, et al; unpublished observation that included the number of suspected AIP patients who were not diagnosed as AIP according to the 2002 diagnostic criteria).[10] The rapid increase in the number of AIP may be explained by (i) different diagnostic criteria used in the 2 surveys and (ii) the increasing recognition of AIP as a disease entity in recent years. In this survey, we used the Japanese clinical diagnostic criteria of AIP 2006).[11] in order not to overlook the patients with localized type AIP. The earlier nationwide survey in Japan[9] used the original 2002 Japanese criteria,[10] which were designed to detect typical diffuse type AIP and to avoid misdiagnosis of pancreatic cancer as AIP. Therefore, it is highly possible that considerable numbers of patients presenting localized type AIP were missing in the earlier survey. Future nationwide surveys using fixed diagnostic criteria would address whether the number of AIP patients will continuously increase.

Even if the data of AIP patients reported in Japan are compared, there have been some differences depending on the institute in the percentages of diffuse type, elevation of serum IgG4 level, appearance of autoantibodies, and presence of extrapancreatic lesions.[6] Therefore, it can be said that the data of this nationwide survey represent the clinicopathological features of AIP in Japan and can be summarized as higher occurrence in elderly males, diffuse type-dominant, elevated serum IgG4 level in nearly 90% patients, and association with various extrapancreatic lesions, among which sclerosing cholangitis is most frequently seen in more than 50% patients. These features are in line with those of AIP originally described by Yoshida et al[15] in 1995 and with the features of AIP subsequently clarified such as a specific elevation of serum IgG4[20] and the appearance of IgG4-producing plasma cells not only in the pancreas but also in involved extrapancreatic organs.[21,22] Kamisawa and Okamoto[23] proposed a concept of "IgG4-related systemic sclerosing disease" in which AIP is considered to be the manifestation of a systemic disease characterized by the overproduction of IgG4.

In addition to the original concept of AIP, recent reports from Western countries suggest the existence of another type of AIP, named idiopathic duct–centric chronic pancreatitis[24] or granulocytic epithelial lesion,[25] which is defined solely by histopathological findings. According to the recently reported clinical features of this type of AIP,[26,27] it develops more frequently in younger patients and occurs equally in both sexes, shows negative serum biomarkers, and lacks associating extrapancreatic lesions other than ulcerative colitis or Crohn disease. Sugumar and Chari[27] named the former IgG4-related AIP as type 1 and the latter one characterized by idiopathic duct–centric chronic pancreatitis/granulocytic epithelial lesion as type 2 AIP, and the nomenclature became widely used. Accordingly, AIP observed in Japanese patients can be classified mostly into type 1 AIP judging from the high frequency of serum IgG4 elevation and the spectrum of associating extrapancreatic lesions. This is in agreement with the previous study showing that most patients with AIP in Japan and Korea are considered to be IgG4-related type 1 AIP.[28]

In this survey, approximately 10% of patients were negative for serum IgG4. Since the 2006 diagnostic criteria used not only IgG4 but also IgG, γ-globulin, and autoantibodies for the serological factors, it is possible that these IgG4-negative AIP patients can be classified into at least 2 groups, one with totally negative results of serological factors and the other with IgG4 negative but positive for IgG, γ-globulin, or autoantibodies. They may include not only type 1 AIP patients with low disease activity and low IgG4 production, but also patients with type 2 AIP or other types of pancreatitis with an autoimmune nature. To clarify the exact nature, histological investigation in combination with IgG4 immunostaining is required. In addition, extrapancreatic lesions, if any, are helpful in classifying AIP into type 1 and type 2 because they have distinct spectra in the respective types: type 1 AIP has a unique spectrum of lesions such as sclerosing cholangitis, sclerosing sialoadenitis, and retroperitoneal fibrosis, whereas type 2 is occasionally associated with inflammatory bowel disease.[26,27] Of note, the 2006 Japanese diagnostic criteria do not include extrapancreatic organ involvement in the diagnostic items, and the histological definition is incomplete for discrimination between type 1 and 2 AIP. Recently, new criteria that enabled the diagnosis of type 1 and 2 AIP were compiled based on a consensus of an international panel.[29] To make the nature of IgG4-negative AIP patients clear, the international consensus criteria could be helpful for reclassification of this category.

Japanese pancreatologists are cautious about the facile use of diagnostic steroid administration because it may delay surgical operation if the correct diagnosis is pancreatic cancer. Accordingly, both the 2002[10] and 2006[11] Japanese diagnostic criteria for AIP did not include steroid trial as a diagnostic item, in contrast to other diagnostic criteria proposed by Korea[30] and Mayo Clinic.[31] Reflecting this background, this nationwide survey revealed that diagnostic steroid treatment was applied to only 6.8% of patients. On the other hand, histological examination was performed in 49.1% of the patients, suggesting efforts by Japanese experts to histologically confirm the diagnosis of AIP. This tendency may be favorable for the future clarification of the histopathological nature of AIP. However, because the success rates of endoscopic ultrasonography-guided fine needle aspiration and endoscopic ultrasonography-guided trucut biopsy are not always satisfactory,[32,33] it is important to establish more reliable methods to obtain pancreatic specimens for histopathological evaluation.

In conclusion, we reported the results of the nationwide survey for AIP in Japan in 2007. The results demonstrated the statistically verified prevalence of this disease and clarified the clinicopathological characteristics of AIP in Japan. Although most AIP patients in Japan are considered to have type 1 AIP, 10% of the patients may have AIP of a heterogeneous nature. To compare the exact distribution and types of AIP worldwide, large-scale surveys using international consensus based common criteria are required.

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Recent advances in autoimmune pancreatitis: type 1 and type 2

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ABSTRACT

Autoimmune pancreatitis (AIP) is a form of chronic pancreatitis characterised clinically by frequent presentation with obstructive jaundice, histologically by a lymphoplasmacytic infiltrate with fibrosis, and therapeutically by a dramatic response to steroids. When so defined, AIP can be sub-classified into two subtypes, 1 and 2. Recent international consensus diagnostic criteria for AIP have been developed for diagnosis of both forms of AIP. Type 1 AIP is the pancreatic manifestation of a multiorgan disease, recently named IgG4-related disease. Little is known about the pathogenesis of either form of AIP. Despite frequent association of type 1 AIP with elevated serum IgG4 levels and infiltration with IgG4-positive plasma cells, it is unlikely that IgG4 plays a pathogenic role in AIP. Type 1 AIP responds to steroids, but there needs to be consensus on treatment regimens for induction and therapeutic end points. Relapses are common, but can be reduced by long-term use of low-dose steroids. Recent reports suggest that immunomodulators (azathioprine, 6-mercaptopurine and mycophenolate mofetil), as well biological agents (the antibody to CD20, rituximab) may have a role in maintaining remission in relapsing type 1 AIP. Future studies should clarify the best management options for treatment of relapses and maintenance of remission. Type 2 AIP is a pancreas-specific disorder not associated with IgG4. It presents in younger individuals equally with obstructive jaundice and pancreatitis. The inflammatory process responds to steroid therapy; relapses are uncommon. The clinical spectrum and long-term outcomes of medically treated type 2 AIP are still being evaluated.

INTRODUCTION

Autoimmune pancreatitis (AIP) is a benign fibroinflammatory disease of the pancreas that has recently attracted worldwide attention.[1 2] The term AIP was first proposed in 1995[3] for a steroid-responsive pancreatic inflammatory disease; since then it has become recognised as a distinct clinicopathological entity. Patients with AIP often present with painless obstructive jaundice mimicking pancreatic cancer, which is far more common and has a dismal prognosis. As AIP dramatically responds to steroids, a correct and timely diagnosis of AIP saves unnecessary surgery. However, AIP sometimes relapses[4 5] and its long-term prognosis is unknown. Review of worldwide data indicates that AIP comprises two subtypes, presently termed types 1 and 2.[6–9] Here we review the pathology, pathogenesis, clinical features, diagnosis, treatment and natural history of types 1 and 2 AIP.

EVOLUTION OF THE CONCEPT OF AIP AND ITS SUBTYPES

As with many diseases, hints at recognition of a distinct entity were made several decades before the formal recognition of AIP and it took even longer for their worldwide acceptance. Even though both type 1 and type 2 are called 'autoimmune' pancreatitis, historically they followed different paths to that designation (tables 1 and 2).[3 8–26] The concept of the entity that was later called type 1 AIP was proposed and developed predominantly in Japan with the diagnostic emphasis being on the clinical phenotype.[3 11–14] Importantly, however, the histopathological features of this entity had previously been reported from Japan even before the concept of AIP was known.

On the other hand, the concept of what was later termed type 2 was first mooted in Europe on the basis of its unique histopathological features.[25] The American contribution to the field of AIP nomenclature was to recognise that the entity of 'AIP' consisted of two distinct histopathological and clinical forms of pancreatitis; the one reported from Japan was termed type 1 and the one reported from Europe was termed type 2.[8 9] The latest development in the field is the recognition of type 1 AIP as the pancreatic manifestation of a multiorgan disorder named IgG4-related disease (IgG4-RD).[27 28]

Diagnostic criteria for these entities, including multiple iterations of them from the same groups, had been proposed from Japan,[13 29] Korea,[18] USA,[17 22] Germany[30] and Italy.[31] The original Japanese criteria relied heavily on imaging and mandated a typical appearance on cross-sectional imaging and an endoscopic pancreatogram for diagnosis.[13] With understanding of the full spectrum of clinical presentations of AIP, the American[17 22] and Korean[18] criteria incorporated additional diagnostic features, including varied appearance on CT, other organ involvement (OOI) and response to steroids. International consensus diagnostic criteria (ICDC) were developed to incorporate the diagnostic strategies used in the different criteria, keeping in mind differences in clinical practice throughout the world.[23]

As far as treatment is concerned, there has been a natural experiment as different therapeutic strategies have been adopted by different groups for initial management of disease and prevention of disease relapse.[4 5] Although head-to-head comparisons of these strategies in a randomised controlled trial have not been performed, one can obtain a fair idea of the efficacy of the different strategies from the published literature.

Table 1 Type 1 AIP: timeline of most important clinical observations in the field

Year	Reference	Reported findings
1961	Sarles *et al*[10]	Reported a form of idiopathic chronic pancreatitis associated with hypergammaglobulinaemia; suspected an autoimmune mechanism
1991	Kawaguchi *et al*[11]	Described the histopathological pattern of what was later called type 1 AIP ('lymphoplasmacytic sclerosing pancreatitis (LPSP)')
1995	Yoshida *et al*[3]	Coined the term 'autoimmune pancreatitis'. Described all the major clinical features of what was later called type 1 AIP
2001	Hamano *et al*[12]	Reported that elevated serum IgG4 levels were highly specific and sensitive for the diagnosis of AIP
2002	Japan Pancreas Society (JPS)[13]	First JPS diagnostic criteria for AIP
2003	Kamisawa *et al*[14]	Proposed that AIP was a systemic disease based on the findings that the pancreas and other involved organs have abundant infiltration with IgG4+ve plasma cells
2003	Notohara *et al*[15]	Reported two histological patterns in patients with 'idiopathic chronic pancreatitis with lymphoplasmacytic infiltration sometimes called autoimmune pancreatitis' (a) LPSP and (b) idiopathic duct centric pancreatitis (IDCP)
2004	Kamisawa *et al*[16]	Japanese experience of steroid therapy in AIP
2006	Chari *et al*[17]	HISORt criteria for AIP published
2006	Kim *et al*[18]	Korean criteria for AIP published
2008	Ghazale *et al*[19]	First report of use of azathioprine in AIP
2008	Topazian *et al*[20]	First report of use of rituximab in AIP
2008	Moon *et al*[21]	Steroid trial to distinguish AIP from pancreatic cancer
2009	Chari *et al*[22]	Revised HISORt criteria
2010	Chari *et al*[9]	International consensus on classification of AIP into type 1 and type 2
2011	Shimosegawa *et al*[23]	International consensus diagnostic criteria
2012	Hart *et al*[24]	Proposed an algorithm for managing AIP using steroids, immunomodulators and rituximab

AIP, autoimmune pancreatitis.

PATHOGENESIS

Although there is now a consensus that two entities, namely type 1 and type 2, are to be distinguished within the disease designator AIP[7–9] and that both subtypes undergo remission when treated with corticosteroids,[5 32 33] there is little agreement about their pathogenesis. The categorisation of AIP as an autoimmune disorder is based on the observations that the disease is associated with infiltration of immune cells into pancreatic tissue and that the disease dramatically responds to steroid therapy; type 1 AIP is also associated with hypergammaglobulinaemia and autoantibodies, albeit non-specific.

The pancreas of patients with AIP is often infiltrated by various types of immune cells, including CD4-positive T-cells, IgG4-producing plasma cells (in type 1 AIP), and granulocytes (in type 2 AIP), among others. Moreover, a variety of circulating autoantibodies including those directed against lactoferrin, carbonic anhydrase, ubiquitin ligase, trypsin and pancreatic secretory trypsin inhibitor (PSTI), nuclear antigen and helicobacter pylori antigens, most of which are IgG1-class antibodies, have been reported from different populations of patients with AIP.[34 35] It remains unclear whether the formation of these antibodies constitutes a pathogenetic event or whether they merely represent an epiphenomenon of AIP.[36–38] What seems clear is that treatment directed against B-cells (eg, with the CD20 antibody, rituximab), a mature form of which, so called plasma cells, are responsible for antibody production, is effective in patients with AIP who have disease recurrence after corticosteroid treatment.[24]

None of the serum antibody markers described so far has a high enough specificity to be of much use for diagnostic discrimination between AIP and other pancreatic disorders, with the notable exception of increased IgG4 levels in type 1 AIP. Could this observation be a clue to the pathogenesis of the disease? It accounts for less than 5% of the total IgG circulating in a healthy person[36–38] and its levels vary widely between individuals. The way it is composed via a complex 'Fab-arm exchange' make it, at least in theory, unable to crosslink antigens or to form immune complexes. It also does not activate the classical complement cascade. Therefore, it would be an unusual immunoglobulin to be playing a pathogenic role in AIP. Not surprisingly, no IgG4 antibodies against specific antigens (rather than antibodies from other IgG subclasses) have been detected in patients with AIP or other varieties of IgG4-RDs. Physiological IgG4 responses are induced by prolonged antigen exposure and controlled by type 2 helper T-cells.[38] Most likely, the increased IgG4 levels are therefore an epiphenomenon

Table 2 Type 2 AIP: timeline of most important observations in the field

Year	Reference	Reported findings
1997	Ectors *et al*[25]	Provided first description of the histological pattern of what was later termed type 2 AIP ('nonalcoholic duct destructive pancreatitis')
2003	Notohara *et al*[15]	Reported two histological patterns in patients with 'idiopathic chronic pancreatitis with lymphoplasmacytic infiltration, sometimes called autoimmune pancreatitis' (a) lymphoplasmacytic sclerosing pancreatitis (LPSP) and (b) idiopathic duct centric pancreatitis (IDCP)
2004	Zamboni *et al*[26]	Described the 'granulocytic epithelial lesion (GEL)', the pathognomonic lesion of type 2 AIP
2010	Sah *et al*[8]	Described a series of type 2 and compared with type 1

AIP, autoimmune pancreatitis.

rather than the cause of AIP, but the mechanism that induces them—related to T-cells—may play a role in pathogenesis.

In addition to the T-cell infiltrates in the pancreas of patients with AIP, some genetic studies also point to an involvement of T-cells. Polymorphisms in the gene for the cytotoxic T-lymphocyte antigen-4 (CTLA-4, CD152) have been reported to be a susceptibility factor in Chinese[39] and Japanese[40] patients. Animal experiments confirm that the inhibition of CTLA-4, which reduces regulatory T-cells, increases the severity of experimental AIP.[41]

Polymorphisms that are known to impair innate immunity, such as those in Toll-like receptor 4, could be linked with neither autoimmune[42] nor other varieties of pancreatitis.[43] For HLA class II subtypes, the evidence is more equivocal and inconclusive. While in Japanese patients the HLA class II haplotype DRB1*0405-DQB1*0401 conferred susceptibility to AIP,[44] this was not confirmed in a Korean cohort where DQβ1 was found to be a predictor of relapse.[45]

While these studies have not solved the ultimate question of pathogenesis of AIP, they point to an involvement of T-cells. Further evidence comes from genetically modified animals that were generated to mimic AIP. The most recent example is the lymphotoxin α/β model in which a cytokine from the tumour necrosis factor (TNF) superfamily was first found to be overexpressed in the pancreatic tissue of patients with AIP and then, when overexpressed in the acinar cells of the mouse pancreas, resulted in a disease phenotype that closely mimics AIP.[46] The disease severity further depended on the presence of lymphocytes, and steroid treatment could reduce pancreatitis but not the associated production of antibodies. This study was therefore one of the first to experimentally discriminate between bona fide T-cell and B-cell effects in AIP. Lymphotoxins are interesting cytokines because they are physiologically secreted by activated immune cells but can, under pathological conditions, be expressed by epithelial cells as well. Other members of the TNF superfamily, such as TNFα, have recently been found to have a role in pancreatitis that goes far beyond the induction of apoptosis and implicates immune cells in the premature and intrapancreatic activation of digestive proteases,[47] a process that has previously been implicated in other varieties of pancreatitis,[48 49] specifically in hereditary pancreatitis,[50] but not necessarily in AIP. In the pancreas of patients with AIP, the critical protease, trypsin (which includes cationionic as well as anionic trpysin), is greatly downregulated, whereas, in parallel, the patients carry high serum antibody titres against trypsin (PRSS1) as well as PSTI.[35] Whether this finding indicates that pancreatic proteases represent a disease-specific target in AIP, as could be the case for ubiquitin ligases of the N-end rule pathway with their known role in pancreatic inflammation,[34 51] or are merely indicative of pancreatic damage and subsequent antibody formation against circulating pancreatic proteins, remains at present unknown.

Experimental models of AIP have provided further evidence for the assumption that the disease is most likely T-cell-mediated. Agents that increase the number or activity of regulatory T-cells, such as the mammalian target of rapamycin (mTOR) inhibitor, sirolimus, or which decrease the number or activity of effector T-cells, such as the calcineurin inhibitor ciclosporin A, have highly beneficial effects on the course of experimental AIP.[41] Successful treatment in this model was not paralleled by a reduction in either the level of serum autoantibodies or in the concentrations of mouse IgG1, IgG2 or IgG3.

Future perspectives

As noted above, the pathogenesis and pathophysiology of human AIP remain largely unknown. Research studies have so far mainly addressed immunological aspects of IgG4-related type 1 AIP, and have delivered inconclusive results, which have recently been summarised by Okazaki and coworkers[36] and elsewhere in this review. This lack of knowledge on pathogenesis and pathophysiology contributes to the relatively slow progress in the development of novel treatment approaches—for example, a maintenance therapy for relapsing AIP.

Future studies will have to address several related issues such as relative roles of B-cells, T-cells and other immune cells[52] in the initiation, progression or relapse of AIP. Answering this question is critical for targeting appropriate therapies during the respective phase of the disease and includes the question of whether a Th1 or a Th2 response predominates.[38] Mouse models, precisely mirroring the human disease, could help us understand the pathogenesis of AIP and thereby develop and preclinically test novel treatment approaches. The MRL/Mp mouse model mentioned above has strong resemblance to type 1 AIP,[53 54] and has recently been used for the first time to test the efficacy of various immunosuppressant treatments.[41] Although not a perfect model for human AIP, it has provided interesting clues on the mechanism of action of immunosuppressants. Interestingly, azathioprine, which has been used for maintenance therapy in relapsing AIP, was shown not to have a meaningful beneficial effect in this model. This corroborates the recent report by Hart *et al*[24] on human AIP of the equivocal benefit of this agent. The reported mouse data suggest that mTOR inhibitors may be more suitable immunosuppressants than azathioprine for long-term administration in patients.

The genetic basis of AIP is unknown at present and only a few studies report association of individual selected candidate genes or selected single-nucleotide polymorphisms with the disease.[39 40 42 55] So far no genome-wide searches for genetic risk factors—for example, by use of genome-wide association studies or the novel next-generation sequencing approaches—have been carried out for AIP, but may contribute to our understanding of the pathogenesis, or deliver novel disease-susceptibility genes and treatment targets.

Another open issue is the pathogenesis of the enigmatic type 2 AIP, whether it differs from that of type 1 AIP, whether type 2 AIP requires different treatment regimens beyond corticosteroids, and whether it is characterised by different biological or imaging[56] markers other than granulocytic epithelial lesion on histology and the absence of IgG4 elevations. This leaves much room for basic and clinical research on this fascinating disorder.

TYPE 1 AIP

Clinical features

Since type 1 AIP is the pancreatic manifestation of IgG4-RD, a multiorgan disorder, it has a variety of clinical presentations which can be divided into pancreatic and extrapancreatic manifestations (figure 1). Since AIP has been followed long term, it has become clear that its clinical and imaging profile changes over time. Therefore, pancreatic manifestation of type 1 AIP can be further divided into active and late phase presentations. The most common clinical presentation in the active phase of type 1 AIP is painless obstructive jaundice, whereas features suggestive of acute pancreatitis (abdominal pain and elevation of serum pancreatic enzymes greater than three times upper limit of normal) are more often observed in type 2 AIP.[32 57 58] It may also present as a pancreatic mass or less commonly with steatorrhoea. Patients who present late in the course of the disease after multiple relapses or those in whom the initial presentation was undiagnosed or misdiagnosed may show pancreatic parenchymal atrophy associated with stones/calcifications, similar to

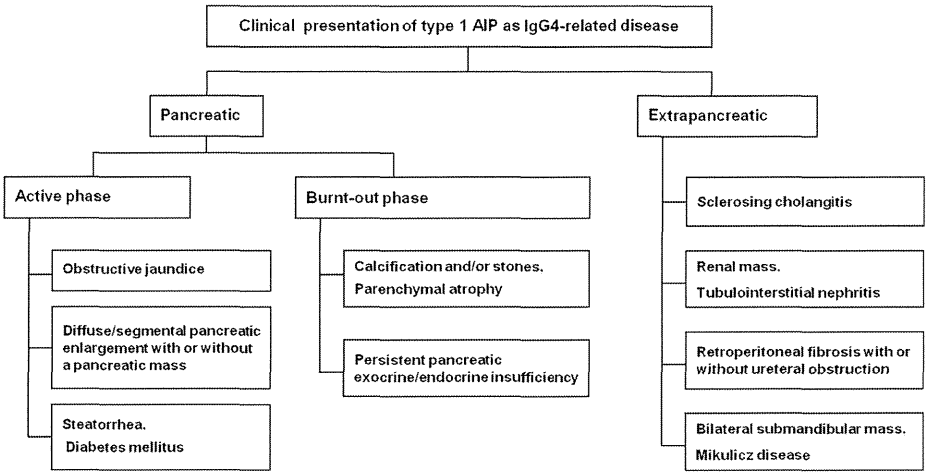

Figure 1 Clinical presentation of type 1 autoimmune pancreatitis (AIP) as IgG4-related disease.

features of advanced ordinary chronic pancreatitis.[59] Functional impairment with endocrine and exocrine failure leading to diabetes and steatorrhoea, respectively, is also common in late stages of disease.

A characteristic feature of type 1 AIP is extrapancreatic OOI, a reflection of it being the pancreatic manifestation of IgG4-RD. IgG4-RD is characterised by an IgG4-rich lymphoplasmacytic infiltrate in the affected organs including the biliary tree, salivary/lacrimal glands, retroperitoneum, kidney, lung, lymph nodes, prostate, aorta, pericardium and pituitary gland (figures 1 and 2).[28 38] OOI in type 1 AIP may precede the diagnosis of AIP, be present concurrently, or develop metachronously over months to years after diagnosis of AIP.[38]

Diagnosis and differential diagnosis: international consensus diagnostic criteria

Many diagnostic criteria for AIP have been published (table 1).[13 17 18 22 29–31] The diversity of diagnostic criteria for AIP from individual countries may reflect differences in practice patterns in the use of various tests and local expertise. Whereas Asian diagnostic criteria have focused on type 1 AIP, American and Italian diagnostic criteria may pertain to both subtypes.[8] Recently, the ICDC for AIP have been proposed because of the need to diagnose AIP regardless of practice patterns in the use of various tests and to incorporate differentiation of the two subtypes of AIP.[23]

The ICDC use the combination of five cardinal features of AIP: pancreatic imaging (parenchyma and duct), serology, OOI, histology and immunostaining, and steroid responsiveness.[23] The first four features are graded into levels 1 and 2 depending on their strength of association with type 1 AIP —for example, serology level 1, IgG4 level >2 times upper limit of normal; serology level 2, ≤2-fold elevation of serum IgG4. Different diagnostic criteria are used for the two AIP subtypes, and even in type 1 AIP the diagnostic criteria differ based on CT features (typical vs indeterminate).[23] In patients with typical CT imaging

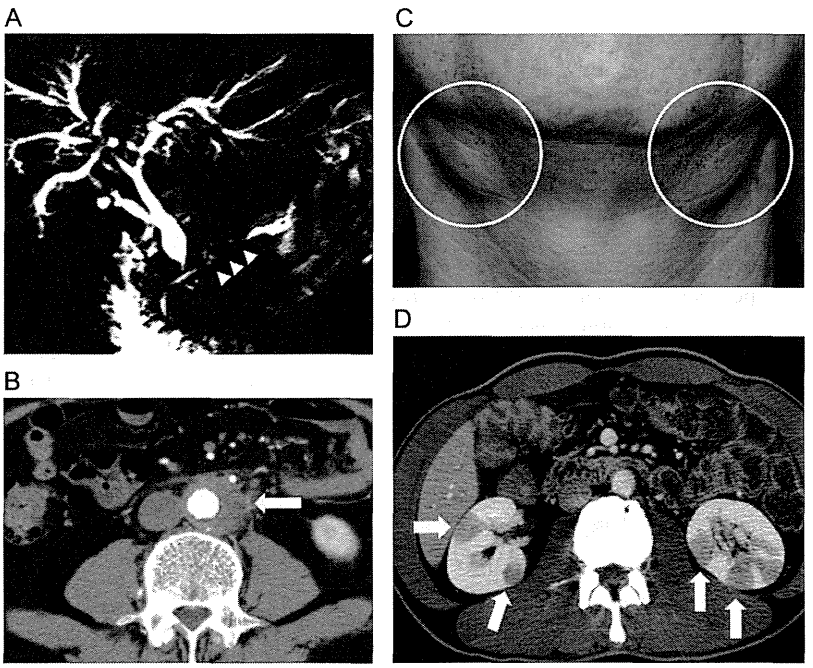

Figure 2 Spectrum of other organ involvement of type 1 autoimmune pancreatitis. (A) Magnetic resonance cholangiopancreatography shows a long-segment stricture (arrowheads) of the main pancreatic duct associated with hilar bile duct strictures. (B) Retroperitoneal fibrosis (arrow). (C) Physical examination reveals bilateral enlargement (circles) of the submandibular salivary glands. (D) Multiple round or wedge-shaped renal mass (arrows).

for AIP, if there is supporting evidence from serology (elevation of serum IgG4 level) or OOI, definitive diagnosis of type 1 AIP can be made without the need for endoscopic retrograde pancreatography (ERP).

In the ICDC, total serum IgG level or autoantibodies such as antinuclear antibody or rheumatoid factor are not included as serological criteria because of their low specificities. Because pancreatic cancer is far more common than AIP, maintaining high specificity of diagnostic criteria is more important than increasing sensitivity. In the ICDC, the performance of diagnostic ERP is not mandatory, and pancreatographic findings assume the role of collateral evidence when CT features are not typical or in seronegative patients without OOI.[23 60] It is clear that ~30% of patients with AIP cannot be diagnosed simply on the basis of CT features, serology and OOI, and will require a pancreatic core biopsy to look for unique histological and immunohistological characteristics.[22 61] In this setting, diagnostic ERP is reserved for patients who have inconclusive results on core biopsy or in whom core biopsy is not feasible. The key ERP findings highly suggestive of AIP include (i) a long stricture involving more than one-third of the duct length, (ii) lack of upstream duct dilatation from the stricture, and (iii) multifocal strictures.[62 63] In the ICDC, endoscopic retrograde cholangiopancreatography has multiple roles in the diagnosis of AIP, such as providing a direct pancreatogram and guiding bile duct/ampulla biopsy with IgG4 immunostaining, in addition to relieving biliary obstruction.

Although type 1 AIP, as a pancreatic manifestation of IgG4-RD, can involve virtually any organ in the body, the ICDC restrict the radiological/physical evidence of OOI only to proximal bile duct stricture (figure 2A), retroperitoneal fibrosis (figure 2B), symmetrically enlarged salivary glands (figure 2C) and renal involvement (figure 2D). This is because the imaging features of extrapancreatic organ involvement (eg, lymph node, lung) may be non-specific and do not permit reliable distinction between AIP and pancreatic cancer.

The use of a steroid trial to 'diagnose' AIP is included in the ICDC. A steroid trial to diagnose AIP involves use of prednisolone with reassessment of imaging after 2 weeks of steroid trial.[21] Subjects with indeterminate CT features should first be investigated for pancreatic cancer, and a steroid trial should be considered only if work-up for cancer including endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is negative.

In patients without collateral evidence, the diagnosis of AIP can be challenging, and pancreatic histology is required for definitive diagnosis. However, histopathology is often not available in the diagnostic workup of a patient with suspected AIP. Transcutaneous core biopsies should be avoided if malignancy cannot be excluded. EUS-guided biopsy is an option, but the more widely available EUS-FNA is usually not suitable for histological diagnosis. EUS-guided core biopsy would be a solution, allowing tissue specimens to be obtained for histological and immunohistochemical analysis of stromal, inflammatory and parenchymal tissue components, but it is not yet widely available, and it may not be feasible to access all areas in the pancreas requiring histological verification.[64 65] Furthermore, even if EUS-guided core biopsy samples of adequate size were available, a full histopathological evaluation may still not be possible because of the limitations in quantity and quality of biopsy samples. Criteria for diagnosing AIP in core biopsy specimens have been proposed,[66 67] but need to be validated in larger series. Establishing histopathological diagnosis on minute biopsy specimens such as micro-tissue core fragments aspirated in EUS-FNA, as previously suggested for pancreatic cancer,[68] may be a clue to optimising the diagnosis of AIP. The fact that, after a complete diagnostic workup, a few cases still require a diagnostic steroid trial and the risk of misdiagnosing or delaying the diagnosis of even a single case of the far more common pancreatic cancer underscore the necessity for novel diagnostic approaches.

Future perspectives

To improve conventional EUS imaging of the pancreas, several techniques of image enhancement such as contrast-enhanced EUS to evaluate vascularisation patterns and EUS plus elastography to estimate the elasticity of hypoechoic masses in the pancreas have been used.[64 69] It has been suggested that contrast-enhanced EUS shows hypervascularisation of AIP lesions, whereas pancreatic cancer lesions appear to be more hypovascular masses.[70] With elastography, masses caused by AIP in contrast with pancreatic cancer show loss of tissue elasticity not only in the mass but also in the surrounding pancreatic parenchyma.[71] Furthermore, preliminary data from small numbers of patients suggest that AIP lesions show reduced 'apparent diffusion coefficient' values in diffusion-weighted MRI[72] and reduced maximal 'standardised uptake values' (SUVmax) in [^{18}F]fluorodeoxyglucose positron emission tomography CT.[73]

In addition, novel serum markers for initial diagnosis, in particular for type 2 AIP and for monitoring of treatment response, are urgently needed. Some efforts have been made in this field and include antibodies in the serum of patients with AIP detecting a peptide with homology to the amino acid sequence shared by the *Helicobacter pylori* plasminogen-binding protein and ubiquitin protein ligase E3 component n-recognin 2 highly expressed in pancreatic acinar cells,[34] autoantibodies against the trypsinogens, PRSS1, PRSS2 and PSTI,[35] or an autoantibody against amylase α-2A.[74]

However, none of the novel imaging modalities and serum markers has so far been validated in larger independent series or been established in clinical routine.

Treatment

Induction of remission

The first goal of therapy in type 1 AIP is to induce remission. Response to steroid therapy in patients with AIP is dramatic and consistently leads to clinical improvement regardless of the subtypes.[5] As a result, steroids have become the standard therapy for inducing remission in AIP.[4 75] In the ICDC the starting dose of steroid for remission induction is defined as 0.6–1 mg/kg per day.[23]

Issues to be solved in the induction of remission

Many issues need to be agreed upon in the initial management of AIP. For example, there is still no consensus on the details of the steroid regimen to be used to induce remission, including the duration of induction therapy and tapering schedule. Also, there is as yet no consensus on the definition of 'clinical remission', how much radiological improvement should be seen before steroid tapering is initiated,[76] or what constitutes 'radiological remission'. Clearly defining remission would be a very important issue in the treatment of AIP because patients who experience relapse during the course of steroid taper or while on steroid maintenance might represent a recrudescence of residual disease which is not yet in remission.[76]

There are some patients, especially those with severe diabetes, who tolerate steroids poorly or have serious adverse effects during steroid therapy (eg, psychosis, infection or avascular necrosis of the hip). In such patients the only drug that has been

reported to induce remission is the CD20 antibody, rituximab.[24] On the basis of initial reports of efficacy of this drug in AIP and IgG4-related sclerosing cholangitis, an open label trial is underway in the USA to determine its role in the management of IgG4-RD.

Maintenance of remission

Disease relapse is common in type 1 AIP, ranging from 30% to 50%.[4 8] Relapse rates reported in different publications vary and may be caused by inconsistent definitions of disease relapse, study design (retrospective trials, short follow-up, small patient populations), inconsistent separation of subtypes and, most likely, ethnic variability. The issue of whether maintenance therapy should be used on all patients with AIP or restricted to patients who relapse at least once also remains to be resolved.

The primary purpose of maintenance therapy is prevention of relapse; however, the choice of medication (ie, steroid or immunomodulator) and the optimal duration of maintenance therapy have not yet been standardised. Currently there are three options for managing patients with a relapse of type 1 AIP (figure 3).[24] To prevent relapses in type 1 AIP, Japanese groups advocate maintenance therapy with a low dose of prednisone for an extended time period after induction of remission.[4 75] In contrast, the Mayo group suggests that not all patients receive maintenance therapy since, in their experience, nearly half of patients have not relapsed 3 years after the induction therapy with steroids.[19]

In a recent study by the Mayo group in patients with relapsing AIP, immunomodulators such as azathioprine were not shown to be better than an additional course of steroids alone.[24] In the same study, a small case series (n=12) with a high clinical response to rituximab treatment and low risk of disease relapse and treatment-related side effects was reported.[24] Unfortunately, it is at present difficult to set a standard for maintenance treatment since the different studies are usually based on small numbers of patients and use different regimens, different criteria for patient selection and different study designs.

Issues to be resolved in the maintenance of remission

Overall, what is needed most in the field of AIP are prospective studies of novel diagnostic and treatment approaches, since what is known so far is mostly based on uncontrolled and retrospective data. Thus, the degree of evidence is low for virtually all aspects of diagnosis and treatment of AIP. In view of the rareness of the disease, multicentric and multinational concerted actions are needed to create a critical mass of patients to allow performance of clinical trials with sufficient statistical power to develop internationally accepted treatment regimes. Approaches such as the recently published international survey of long-term outcomes of AIP patients[24] point in the right direction and should be the basis for designing and conducting prospective trials.

Natural history

According to a recent international multicentre study, 31% of patients with type 1 AIP experienced at least one disease relapse.[5] More than half of patients who experienced multiple relapses had pancreatic calcifications or stones. With multiple relapses, type 1 AIP may result in irreversible damage with intense fibrosis, and these patients do not show steroid responsiveness.[38 59] However, the long-term survival of patients with type 1 AIP has been reported to be similar to age- and gender-matched subjects from the general population.[8]

Several cases of pancreatic cancer have been reported in patients with AIP, where most were suspected to have type 1 AIP.[75 77] Pancreatic cancers were diagnosed synchronously with AIP or detected during the follow-up after the remission of AIP. The lessons learned from these cases are that diagnosis of AIP using pancreatic biopsy alone should be performed carefully and close follow-up examinations are mandatory for AIP even after remission.

Future perspectives

While sporadic cases of cancer complicating AIP have been reported, no systematic case–control studies have been performed to evaluate the risk of cancer in AIP. Since type 1 AIP is a disease of the elderly, the risk of cancer may be underestimated. It would require long-term follow-up of a relatively young cohort of patients to determine if AIP truly increases the risk of cancer in affected organs.

TYPE 2 AIP

The evolution of the concept of two subtypes of AIP started with the identification of two distinct histopathological patterns in subjects undergoing pancreatic resection for suspicion of cancer who proved not to have cancer. When the clinical profiles of patients with these two histological entities were compared, they were distinctly different (table 3).[5–9 24 32 57 78] There is also a difference in the prevalence of the two subtypes. Type 2 AIP appears to be relatively common in the USA and Europe but rare in East Asia; nevertheless, patients with type 1 AIP outnumber those with type 2 AIP even in Western countries.[5 8 32 78] However, since definitive diagnosis of type 2 AIP requires pancreatic histology, under-recognition of type 2 AIP is

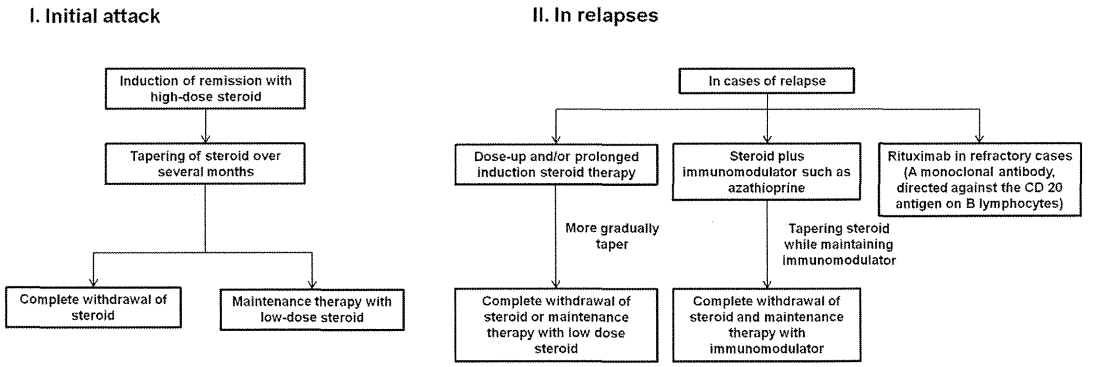

Figure 3 Current practice in the treatment of type 1 autoimmune pancreatitis.

Table 3 Differences in clinical profiles between type 1 and type 2 AIP

	Type 1 AIP	Type 2 AIP
Synonym	Lymphoplasmacytic sclerosing pancreatitis AIP without GEL	Idiopathic duct-centric chronic pancreatitis AIP with GEL
Epidemiology	Asia>USA, Europe	Europe>USA>Asia
Age at diagnosis	Old	Young
Gender distribution	Striking male predominance	Equal or small difference
Clinical presentation	Obstructive jaundice (painless)	Obstructive jaundice (painless) Abdominal pain/acute pancreatitis
Serum IgG4 level	Often elevated	Normal
Other organ involvement	Proximal bile duct, salivary gland, kidney, retroperitoneum	Not seen
Association with ulcerative colitis	Occasionally	Common
Steroid responsiveness	Excellent	Excellent
Recurrence	Common	Rare

AIP, autoimmune pancreatitis; GEL, granulocytic epithelial lesion.

far more likely than that of type 1 AIP. For example, there are numerous case reports and case series of 'idiopathic fibrosing pancreatitis' in children. The profile of this entity is suspiciously similar to that of type 2 AIP; it occurs in young patients, often presents with painless obstructive jaundice, is sometimes associated with inflammatory bowel disease, and can resolve spontaneously. A review of the pancreatic histopathology of these patients by a pathologist familiar with AIP will help resolve the issue of whether this entity is the same as type 2 AIP.

Clinical presentation

Our understanding of the clinical spectrum of type 2 AIP continues to evolve. From published studies it is clear that the clinical profile of type 2 AIP is sufficiently different from that of type 1 AIP to suggest that it is an entirely different disease entity. The similarities to type 1 AIP are that type 2 can also present with obstructive jaundice and have diffuse pancreatic enlargement on imaging studies and the inflammatory process responds to steroid therapy. However, patients with type 2 are significantly younger than those with type 1, and, as noted above, it may be missed in the really young, as the pancreas is rarely biopsied in that age group. While the majority of patients with type 1 AIP present with obstructive jaundice, those with type 2 are as likely to present with abdominal pain and pancreatitis as with obstructive jaundice. There is an absence of any collateral evidence of AIP, such as elevated serum IgG4 and OOI, evidence that is of great help in non-invasively diagnosing type 1 AIP. Inflammatory bowel disease is more common in type 2 than type 1 AIP, although even type 1 has a higher prevalence of it compared with the general population. Among those not intimately familiar with the literature, the term 'AIP' evokes the profile of an IgG4-associated disease typical of type 1. The indiscriminate use of the same term without subtype specification to describe the two diseases may hamper progress in understanding this uncommon disorder.

Treatment and follow-up

Initial reports of type 2 AIP included only patients who had undergone surgical resection. In such patients no further treatment was required and no relapses were reported. In the limited experience with histologically confirmed and medically treated type 2 AIP, it appears to either spontaneously resolve or respond promptly to steroid therapy (STC, personal experience). When treated with a 3-month tapering course of steroids, relapses are still uncommon.

CONCLUSION

The field of AIP is rapidly evolving. In the past few years the following facts have been recognised. (i) AIP has at least two distinct subtypes, type 1 and 2. (ii) Type 1 AIP is the pancreatic manifestation of a multiorgan syndrome called IgG4-RD. (iii) Relapses in type 1 AIP can be prevented using immunomodulators or biological agents. There is a growing suspicion that, while IgG4 is a useful biomarker for diagnosis of type 1 AIP, it is unlikely that it plays a pathogenetic role in type 1 AIP. (iv) Type 2 AIP is a distinct disease entity that shares some common features with type 1 AIP. While it responds to steroid therapy, relapses are uncommon. (v) The continued use of the term 'AIP' to describe both entities without subtype specification does cause confusion, as the term often evokes a profile of type 1 AIP, which is so deeply entrenched in the literature.

Contributors All authors drafted the manuscript.

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ORIGINAL ARTICLE

Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis

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ABSTRACT

Objective Autoimmune pancreatitis (AIP) is a treatable form of chronic pancreatitis that has been increasingly recognised over the last decade. We set out to better understand the current burden of AIP at several academic institutions diagnosed using the International Consensus Diagnostic Criteria, and to describe long-term outcomes, including organs involved, treatments, relapse frequency and long-term sequelae.

Design 23 institutions from 10 different countries participated in this multinational analysis. A total of 1064 patients meeting the International Consensus Diagnostic Criteria for type 1 (n=978) or type 2 (n=86) AIP were included. Data regarding treatments, relapses and sequelae were obtained.

Results The majority of patients with type 1 (99%) and type 2 (92%) AIP who were treated with steroids went into clinical remission. Most patients with jaundice required biliary stent placement (71% of type 1 and 77% of type 2 AIP). Relapses were more common in patients with type 1 (31%) versus type 2 AIP (9%, p<0.001), especially those with IgG4-related sclerosing cholangitis (56% vs 26%, p<0.001). Relapses typically occurred in the pancreas or biliary tree. Retreatment with steroids remained effective at inducing remission with or without alternative treatment, such as azathioprine. Pancreatic duct stones and cancer were uncommon sequelae in type 1 AIP and did not occur in type 2 AIP during the study period.

Conclusions AIP is a global disease which uniformly displays a high response to steroid treatment and tendency to relapse in the pancreas and biliary tree. Potential long-term sequelae include pancreatic duct stones and malignancy, however they were uncommon during the study period and require additional follow-up. Additional studies investigating prevention and treatment of disease relapses are needed.

Significance of this study

What is already known on this subject?
- Autoimmune pancreatitis (AIP) is a treatable form of chronic pancreatitis that is felt to be responsive to steroid treatment.
- There are few long-term data regarding response to treatment and subsequent disease sequelae.

What are the new findings?
- Disease relapses are common after steroid discontinuation, and typically occur in the pancreas and/or biliary tract.
- Pancreatic duct stones are relatively uncommon, but are seen more frequently in patients with at least one disease relapse.
- The occurrence of incident cancers following AIP diagnosis appears to be uncommon.

How might it impact on clinical practice in the foreseeable future?
- Since disease relapses are common, additional studies are needed to compare different treatment strategies for maintaining disease remission.
- Further investigations are needed to understand if the risk of cancer is increased compared with the general population.

INTRODUCTION

Autoimmune pancreatitis (AIP) is a unique form of chronic pancreatitis with characteristic histological features, frequent elevations of serum IgG4 levels and a predictable response to steroid therapy. Although the identification of a steroid-responsive form of chronic pancreatitis was initially reported in 1995 by Yoshida *et al*, there was minimal progress in understanding this disease until a serum biomarker (IgG4 antibody) was identified by Hamano *et al*.[1 2] Over the last decade significant progress has been made in understanding this disease, including identification of two distinct histological subtypes, with different clinical phenotypes (termed type 1 and type 2 AIP), incorporation of seemingly unrelated diseases within the spectrum of IgG4-related disease (of which AIP is the pancreas manifestation) and treatment of refractory patients with rituximab.[3–6]

Despite these advances, many questions remain unanswered. Although patients respond initially to steroid therapy, many patients will develop disease relapse either during steroid taper or following

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steroid discontinuation. Reported rates of disease relapse have ranged from 15–60% in various series.[4 7–10] Although there is general agreement that steroids are the ideal initial treatment, there is no clear consensus regarding treatment for disease relapses.

Due to the recent recognition of patients with this condition, the long-term sequelae of the disease are largely unknown. Follow-up data are recently becoming available, permitting the present analysis. In an effort to better understand these knowledge gaps we set out to perform an international analysis of patients with type 1 and type 2 AIP. One previous study evaluated the distribution of AIP subtypes worldwide, however multiple diagnostic criteria were used based on the country of origin.[11] Recently a multinational group met and agreed upon diagnostic criteria, termed International Consensus Diagnostic Criteria (ICDC).[12] This classification scheme categorises diagnostic evidence into one of two levels of confidence in the following categories: pancreatic parenchymal imaging, imaging of the pancreatic duct (ie, endoscopic retrograde pancreatogram), serum IgG4 level, other organ involvement of IgG4-related disease, histology of the pancreas (from core biopsy or resection) and response to steroid treatment. We specifically set out to gain additional understanding of the current burden of AIP at several large, academic institutions using the ICDC, and to describe the long-term outcomes of this disease including organs involved, treatments, relapse frequency and long-term sequelae.

METHODS

A total of 31 institutions were invited to participate in this study on the basis of their scientific merit in this field, or established experience in management of AIP; ultimately 23 institutions from 10 different countries participated. The Tokyo Metropolitan Komagome Hospital in Japan and Mayo Clinic in the USA served as the coordinating centres. The study was approved by the institutional review board of Tokyo Metropolitan Komagome Hospital and was in compliance with the Declaration of Helsinki.

In centres with existing patient databases, patient follow-up data were updated and retrieved. If data were not available, investigators retrospectively reviewed paper and/or electronic medical records or contacted patients by telephone for data collection. Each centre independently reviewed histological, radiographic, and clinical records of subjects with suspected AIP. Subjects classified as either definite or probable type 1 or type 2 AIP according to the ICDC were selected for this study (see online supplementary tables S1–S4).[12] The two subtypes are definitively distinguished based on their histology in which type 1 AIP (also known as lymphoplasmacytic sclerosing pancreatitis) demonstrates lymphoplasmacytic infiltration, obliterative phlebitis, storiform fibrosis and abundant IgG4-postive cells, while type 2 AIP (also known as GEL+ pancreatitis or idiopathic duct-centric chronic pancreatitis) shows granulocytic infiltration of the duct wall (termed GEL) and absent or minimal IgG4-postive cells. Additionally, type 2 AIP patients are unlikely to have serum IgG4 elevation or other organ involvement. Site data through 1 January 2012 were compiled using a standardised data collection form, then submitted to the lead investigator (TK) for analysis.

Definitions

For the purposes of this study, proximal biliary was defined as involvement of either intrahepatic bile ducts or the extrahepatic common bile duct proximal to the head of the pancreas. When it occurred in the context of type 1 AIP it was referred to as IgG4-related sclerosing cholangitis (IgG4-related SC)). On the other hand, distal biliary disease referred to disease isolated to the intrapancreatic portion of the common bile duct. Serum IgG4 values vary depending on the assay used, so normal levels were recognised as those less than the upper limit of normal for the lab where the test was performed. Pancreatic duct stones were identified with the use of either cross-sectional imaging or endoscopic retrograde pancreatography.

Treatment regimens

A wide variety of steroid regimens were employed for induction and maintenance of remission. For the initial dose of steroids, all centres used either a weight-based strategy (0.6 mg/kg/day of prednisolone) or fixed-dose regimen (30–40 mg/day) that were roughly equivalent for treatment of a 70 kg individual. Tapering strategies ranged from 5–10 mg decrease every 1–2 weeks. All Asian centres (n=10) used a maintenance strategy of low-dose (2.5–5 mg/day) prednisolone, which was continued for anywhere from 6 months to 3 years. In general, the European and North American groups tapered the steroids off within 3 months and did not provide maintenance doses of steroids. Multiple centres elected to use immunomodulator drugs instead of low-dose steroids for maintenance therapy (n=5). In the four centres treating more than five subjects with this strategy, azathioprine (2 mg/kg/day) was the preferred agent and was used for a variable duration of time (1–3 years).

Many patients initially underwent surgery either due to the absence of typical features of AIP or clinical presentation prior to the recognition of AIP as a disease entity. Surgeries were performed for resection of mass-forming lesions (ie, pancreaticoduodenectomy or distal splenectomy) or palliative bypass (ie, gastrojejunostomy) for those with an apparently unresectable cancer. Surgery was not intentionally performed as primary treatment for AIP. A number of patients were treated conservatively, without the use of steroids or surgery. Supportive care was provided for a variety of reasons including asymptomatic disease, severe comorbid disease (eg, metastatic cancer) or patient preference.

Statistical analyses

Continuous variables were compared using Student t test, χ^2 test and Fisher's exact t test (when one or more expected cell frequencies were <5) were used for comparison of proportions. A p value <0.05 was considered statistically significant.

RESULTS

AIP subject characteristics

A total of 1064 subjects were identified, 978 with type 1 AIP and 86 with type 2 AIP. The average age of subjects at diagnosis was 61.4 and 39.9 years for type 1 and type 2 subjects, respectively. The proportion of males was 77% in type 1 subjects and 55% in type 2 subjects ($p<0.001$). The proportion of patients diagnosed with type 2 AIP was lower in Asian countries (3.7%) compared with European (12.9%, $p<0.001$) and North American (13.7%, $p<0.001$) countries (figure 1).

Treatment response

The majority (74%) of subjects with type 1 AIP were initially treated with steroids, rather than surgical or conservative treatments, in comparison with type 2 subjects in which only 62% were treated with steroids ($p=0.01$). Remission was successfully induced in almost all subjects with type 1 and type 2 AIP (table 1). The per cent of subjects achieving remission was higher in type 1 subjects who received intervention (either

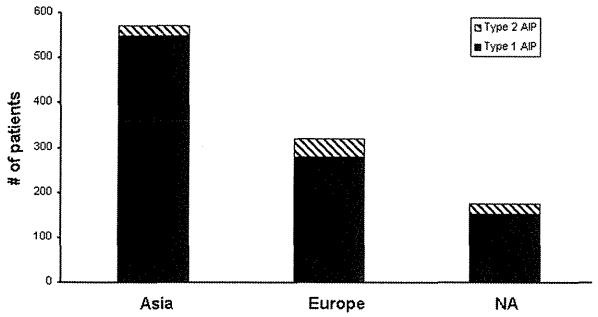

Figure 1 Regional distribution of type 1 and type 2 autoimmune pancreatitis based on the country of diagnosis. NA, North America.

steroids or surgery) (99.2%) compared with those who were managed conservatively (55.2%, p<0.001). However, initial remission rates were similar in patients with type 2 AIP who received intervention compared with conservative management (83.5% vs 66.7%, respectively, p=0.29). Interestingly many of the patients who underwent palliative surgical bypass achieved successful clinical remission; however the total number of cases was small. Initial treatment strategies and indications for treatment and concurrent therapies used in those receiving steroid treatment are also shown in table 1. Treatment for diabetes mellitus was given to a minority of patients prior to steroid treatment. However, biliary stenting was performed for most subjects presenting with jaundice. In subjects with type 1 AIP, jaundice (63%) was the most common indication, followed by abdominal pain with or without biochemical pancreatitis. In those with type 2 AIP, abdominal pain and inflammatory bowel disease were major indications.

In subjects with type 1 AIP and abnormal serum IgG4 levels (n=446) prior to steroids, the serum level decreased in 427 (95.7%) subjects and returned to within normal limits for 204 (45.7%). Of 609 type 1 AIP subjects with pancreatic enlargement at the time of diagnosis, the parenchyma appeared normal in 400 (65.7%), atrophic in 173 (28.4%) and persistently enlarged in 35 (5.9%) subjects following steroid treatment. In contrast, 50 type 2 AIP subjects had pancreatic enlargement at diagnosis. Following treatment the appearance returned to normal in the majority (43/50, 86%) with progression to atrophy in the remaining seven subjects.

Relapse data

Of the 978 subjects with type 1 disease, a total of 302 (31%) subjects experienced at least one disease relapse during the study period, compared with 8 (9%, p<0.001) subjects with type 2 AIP (table 2). The vast majority of relapse episodes occurred in steroid treated subjects following steroid discontinuation (67%), as compared with during the steroid taper (15%) or while on maintenance steroids (18%). Most relapses occurred in the biliary system or pancreas for type 1 AIP, while relapses in type 2 AIP were limited to the pancreas.

Table 1 Initial treatment strategies and treatment details for those treated with steroids

	Type 1 AIP (n=901†)		Type 2 AIP (n=85†)		
	Successful remission, n	%	Successful remission, n	%	
Initial treatment					
Steroids	681/684	99.6	48/52	92.3	
Surgical resection	125/127	98.4	17/25	68.0	
Palliative surgical bypass	22/23	95.7	1/2	50.0	
Conservative	37/67	55.2	4/6	66.7	
	Type 1 AIP (n=724)		Type 2 AIP (n=53)		
	n	%	n	%	p Value*
Indications for steroid treatment					
Jaundice	458	63	13	25	<0.001
Pancreatitis/abdominal pain	198	27	34	64	<0.001
Abnormal imaging (diffuse pancreatic enlargement, pancreas mass)	71	10	0	–	0.01
Salivary gland enlargement	49	7	0	–	0.04
Diagnostic steroid trial	46	6	4	8	0.77
Retroperitoneal fibrosis	17	2	0	–	0.62
IgG4-related renal disease	9	1.2	0	–	0.99
Lymphadenopathy	6	0.8	0	–	0.99
IgG4-related lung disease	4	0.6	0	–	0.99
Inflammatory bowel disease	1	0.1	23	48	<0.001
Other (hyperglycaemia, weight loss, etc)	20	3	0	–	
Diabetes management					
Oral medications	99/596	17	6/46	13	0.53
Insulin therapy	136/596	23	4/46	9	0.03
Endoscopic management (for subjects with jaundice)					
Biliary stent placement	351/492	71	10/13	77	0.77

*p Values represent comparison of proportions between patients with type 1 and type 2 AIP using χ^2 and Fisher's exact t test, when appropriate.
†Seventy-seven subjects with type 1 AIP and one subject with type 2 AIP are not displayed in the table due to pending response to treatment at study closure.
AIP, Autoimmune pancreatitis.

Table 2 Distribution of disease relapse episodes according to initial treatment strategies, and location and frequency for those treated with steroids

	Type 1 AIP		Type 2 AIP	
	Relapse, n	%	Relapse, n	%
Initial treatment				
Steroids	245/684	35.8	8/52	15.3
Surgical resection	35/116	30.2	0/25	0
Palliative surgical bypass	11/23	47.8	0/2	0
Conservative	11/57	19.3	0/6	0
Disease relapses following steroid treatment				
Location of relapse	n=245 episodes		n=8 episodes	
Biliary system	124	50.6	–	–
Pancreas	107	42.9	8	100
Salivary	18	7.3	–	–
Lung	11	4.5	–	–
Lymphadenopathy	4	1.6	–	–
Renal	3	1.2	–	–
Other (RPF or NOS)	13	5.3	–	–
Frequency per subject				
One relapse	189	77.1	8	100
Two relapses	39	15.9	–	–
Three relapses	13	5.3	–	–
≥4 relapses	4	1.6	–	–

AIP, Autoimmune pancreatitis; RPF, retroperitoneal fibrosis; NOS, not otherwise specified.

Table 3 Cumulative frequency of malignancies in type 1 AIP subjects

Cancer type	Subjects, n
Gastric	11
Lung	9
Prostate	7
Colon	5
Pancreatic	5
Oesophageal	4
Cholangiocarcinoma	3
Leukaemia	3
Ovarian	2
Renal	2
Other*	6

*Other cancers with only one reported case include: testicular, gastrointestinal stromal tumour, breast, bladder, hepatocellular and adenocarcinoma of unknown primary.
AIP, Autoimmune pancreatitis.

Predictors of relapse

The proportion of subjects having a relapse was similar in those with persistently abnormal IgG4 levels following steroids compared with those with a normal level (32.7% vs 31.4%, respectively, p=0.77). Likewise, the proportion of subjects with at least one relapse was similar regardless of whether they initially had diffuse (42/440, 32.3%) or focal pancreatic parenchymal enlargement (92/285, 32.3%, p=0.99). In contrast, 96/171 (56.1%) subjects with IgG4-related SC had at least one relapse, while only 142/551 (25.7%) subjects without IgG4-related SC had a relapse (p<0.001). The rates of relapse were similar in those with and without distal biliary disease (33.9% vs 31.1%, respectively, p=0.44). Since there were very few relapse episodes in subjects with type 2 AIP, a meaningful comparison of risk factors for relapse could not be completed.

Treatment for disease relapse

Steroids were the most commonly used treatment for managing disease relapse in type 1 AIP, and inducing remission was successful in 201/210 (95%) of subjects. The addition of azathioprine was used for 68 subjects with successful induction in 56 (85%). Medications used in other subjects (n=18) included mycophenolate mofetil (n=8), cyclosporine (n=3), methotrexate, 6-mercaptopurine, cyclophosphamide and rituximab. Successful remission was achieved in 12 (86%) of these subjects with follow-up.

Long-term sequelae in type 1 AIP

Pancreatic duct stones were uncommonly seen occurring in 46/659 (7%) subjects with follow-up imaging permitting evaluation for stone disease. Pancreatic duct stones were more likely to occur in subjects with at least one relapse, compared with those who had never had a relapse (14.4% vs 4.0%, respectively, p<0.001).

The most frequently occurring cancers during follow-up were gastric, lung and prostate (table 3). Importantly, pancreatic cancer was diagnosed in five male patients at a median age of 77 years (range 65–80) at the time of cancer diagnosis. All cancers were diagnosed more than 3 years following AIP diagnosis with the exception of one patient. His cancer was diagnosed 9 months following AIP diagnosis, which was made on the basis of diffuse pancreatic enlargement and elevation of serum IgG4 more than twice the upper limit of normal (definitive histology for type 1 AIP was confirmed on the resected pancreatic specimen). In the two patients with serum IgG4 levels obtained at the time of cancer diagnosis, it was mildly (1–2×upper limits) elevated. Eight (73%) of the subjects with gastric cancers were from study sites located in Japan or Korea, and risk factors for gastric cancer were not reported. No subjects with type 2 AIP developed an incident cancer or pancreatic duct stone during the study period.

DISCUSSION

This study represents the largest, multinational analysis of patients with type 1 and type 2 AIP diagnosed according to ICDC and provides insights into treatment strategies and potential long-term sequelae. Previously noted differences in clinical profiles of type 1 and type 2 AIP, including age and gender differences, were confirmed in this study.[4 11] Type 2 AIP represented a smaller proportion of AIP in Asian countries compared with European and North American countries.

Types 1 and 2 were highly-responsive to steroid treatment; however disease relapses were common in type 1, especially in those with proximal biliary disease (ie, IgG4-related SC). Most patients who required steroid therapy had predominantly pancreatobiliary disease manifestations (jaundice, abdominal pain or abnormal pancreas imaging). Although most subjects with jaundice required biliary intervention prior to steroid therapy, the need for diabetes treatment was unexpectedly low. The remission rate of treating patients following disease relapse remained high. Pancreatic duct stones were relatively uncommon, but occurred more frequently in patients with at least one disease relapse. A number of cancers occurred and further studies are needed to understand whether this represents a true

increased risk for malignancy in subjects with AIP or is due to older age of type 1 patients and ascertainment bias as patients with AIP have extensive diagnostic studies and close follow-up.

Our present compilation of more than 1000 patients is the largest to date, and the number of institutions required to reach this enrolment illustrates the rarity of this disease. Since the landmark discovery that elevated serum IgG4 levels are associated with AIP the number of newly diagnosed cases of AIP has increased dramatically.[2] The disease spectrum of IgG4-related disease, which encompasses AIP and IgG4-related SC, continues to expand also contributing additional diagnoses. It is more likely that the increasing recognition of the diseases is due to its increased awareness rather than true increase in incidence of the disease.

Since its initial description by Yoshida *et al*, type 1 AIP has been recognised as a steroid-responsive disease.[1] The current study shows that both types of disease are characterised by very high remission rates with steroid therapy, suggesting that the diagnosis must be reconsidered in those who do not respond to steroids. Although a noteworthy proportion (55%) of patients initially managed conservatively had spontaneous disease remission, this rate was inferior to that in patients who were treated with steroids or surgery (99% remission rate). Since inflammatory pancreatic and biliary disease can progress to irreversible pancreatic insufficiency and secondary biliary cirrhosis, we feel early treatment is advisable, even in the absence of rigorous evidence-based medicine demonstrating that steroid treatment alters the natural history of AIP. In the absence of a validated induction regimen variation in steroid dosing is inevitable, but despite this remission rates were universally high across all centres. Most patients required treatment for jaundice, abdominal pain or abnormal pancreatic imaging. Interestingly, although most patients with jaundice required endoscopic biliary stenting prior to steroids, less than half of patients required treatment for diabetes. Smaller series have shown an interesting, paradoxical improvement in glycaemic control after steroid therapy, presumably due to recovered pancreatic endocrine function with treatment.[13 14] This finding, experienced anecdotally by many of the authors, led to the withholding of diabetes treatment for some patients with hyperglycaemia. Nonetheless, it is important to monitor blood sugars during steroid treatment to recognise and prevent hyperglycaemia-related morbidity.

Disease relapses in type 1 and type 2 AIP predominantly involve the pancreas and/or biliary system. Cumulative relapse rates could not be accurately calculated since time to event (ie, relapse) data were not available for most patients. However, the relapse rate in this study of 31% falls within the range (15–60%) of that in previous reports. Unfortunately due to the nature of this study, it is not statistically valid to compare relapse rates on the basis of treatment strategies used (eg, with or without maintenance steroids). Due to challenges with study enrolment, a prospective treatment trial to clarify this choice is not expected soon; so the decision must be made on the basis of the provider's familiarity with the treatment strategy, considering the side effect profile, and patients' personal relapse histories and preferences.

For most patients in this study relapses occurred after steroid discontinuation. Patients treated again with steroids continued to respond favourably with a high remission rate. Some patients with relapses were treated with an immunomodulator (most commonly azathioprine or mycophenolate mofetil). These steroid-sparing approaches are attractive to some due to the possibility of avoiding complications from long-term steroid exposure.[6 8 14–16] However, to date no large series have demonstrated either treatment effectiveness or decreased incidence of treatment-related side effects.

Two sequelae identified in other forms of chronic pancreatitis are pancreatic duct stones and pancreatic cancer. So we specifically examined the rates of these complications in this study cohort.[17 18] The occurrence of pancreatic duct stones in this study is low with higher prevalence in those with at least one relapse. Additionally, we report the first systematic collection of malignancies in patients with AIP. Importantly, there were only five cases of pancreatic cancer in this study; however, considering the overall large denominator of AIP patients at risk, limited follow-up and lack of a control population, it is difficult to understand the true clinical significance of this finding. Additional studies with longer follow-up will help refine our understanding of these long-term sequelae.

We estimate that this multinational collaboration of many of the academic foci for AIP permitted analysis of a significant proportion of the world's current AIP population. Our utilisation of the recently developed ICDC permitted study of patients with a unified set of diagnostic criteria. Our data must be interpreted with caution recognising this collaboration could inadvertently introduce heterogeneity in disease on the basis of unknown ethnic differences in the natural history of disease, as well as variations in the standards of care regarding disease evaluation and follow-up.

Although the basic clinical profiles and initial treatment strategies for AIP are generally understood, many questions remain. The importance of steroid treatment at disease onset is commonly accepted, however whether or not one could use a lower steroid dose has not been systematically evaluated and may potentially decrease treatment-related morbidity. The prediction of disease relapse remains inadequate. Except for IgG4-related SC, no clinical factor has been consistently demonstrated to predict subsequent relapse. Finally, it remains unclear whether or not maintenance therapy (using either low-dose steroids or an immunomodulator) actually prolongs relapse-free survival, thereby altering the course of disease.

In summary, in this multinational analysis of more than 1000 patients with AIP we have shown that most patients are treated with steroids for predominantly pancreatobiliary manifestations of their disease. Initial and subsequent treatment responses to steroid therapy are exceedingly high, so the diagnosis should be reconsidered if patients do not respond to steroids. Relapses occur in a substantial proportion of patients and typically involve the pancreas and/or biliary system. Pancreatic duct stones and malignancies are two potential long-term sequelae, which require ongoing surveillance to further understand their full clinical significance. We are hopeful that multinational collaborations, such as the present one, will provide opportunities to better understand this disease, and permit a long-awaited randomised treatment trial.

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SPECIAL ARTICLE

Recommendations for the Nomenclature of IgG4-Related Disease and Its Individual Organ System Manifestations

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Introduction

During the first decade of this century, recognition of a multi–organ system disease known as IgG4-related disease has grown. Serum IgG4 elevation (in some patients) and tissue infiltration with IgG4-positive plasma cells (in essentially all patients) (1–3) are common threads that connect a variety of seemingly disparate conditions observed previously in multiple organs (4). A highly characteristic histopathology and immunohistochemical staining pattern are found in the involved organs (5–7). Japanese investigators recently agreed on the name "IgG4-related disease" for this multifocal disorder (7).

An International Symposium on IgG4-Related

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