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SPECIAL ARTICLE

Amendment of the Japanese Consensus Guidelines for Autoimmune Pancreatitis, 2013 III. Treatment and prognosis of autoimmune pancreatitis

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Abstract The standard treatment for autoimmune pancreatitis (AIP) is steroid therapy, although some patients improve spontaneously. Indications for steroid therapy in AIP patients are symptoms such as obstructive jaundice, abdominal pain, back pain, and the presence of symptomatic extrapancreatic lesions. Prior to steroid therapy, obstructive jaundice should be managed by biliary drainage, and blood glucose levels should be controlled in patients with diabetes mellitus. The recommended initial oral prednisolone dose for induction of remission is 0.6 mg/kg/day, which is administered for 2–4 weeks. The dose is then tapered by 5 mg every 1–2 weeks, based on changes in clinical manifestations, biochemical blood tests (such as liver enzymes and IgG or IgG4 levels), and repeated imaging findings (US, CT, MRCP, ERCP, etc.). The dose is tapered to a maintenance dose (2.5–5 mg/day) over a period of 2–3 months. Cessation of steroid therapy should be based on the disease activity in each case. Termination of maintenance therapy should be planned within 3 years in cases with radiological and serological improvement. Re-administration or dose-up of steroid is effective for treating AIP relapse. Application of immunomodulatory drugs is considered for AIP patients who prove resistant to steroid therapy. The prognosis of AIP appears to be good over the short-term with steroid therapy. The long-term outcome is less clear, as there are many unknown factors, such as relapse, pancreatic exocrine or endocrine dysfunction, and associated malignancy.

This article is the third of a three-article series on the Japanese consensus guidelines. The first and second articles are available at doi: (doi:10.1007/s00535-014-0942-2) and (doi:10.1007/s00535-014-0944-0), respectively. The members of the Working Committee are listed in the "Appendix" in the text.

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CQ-III-1. Do AIP patients improve spontaneously?

- Some AIP patients improve spontaneously.

Description Swelling of the pancreas or irregular narrowing of the main pancreatic duct improves spontaneously without steroid therapy in some autoimmune pancreatitis (AIP) patients. In studies by Wakabayashi et al. [1], pancreatic swelling was alleviated in 9 (24 %) of 37 AIP patients with only conservative therapy, and of these, narrowing of the main pancreatic duct also improved after 3–60 months in 4 patients, remained unchanged in 3 patients, and worsened in 2 patients. It has been reported that most AIP cases that improved spontaneously did not have bile duct stenosis [2, 3]. Kamisawa et al. [2] noted that, among 21 AIP patients, spontaneous improvement was detected in 2 non-jaundiced patients (10 %). Kubota et al. [3] compared the clinicopathological parameters in 8 AIP patients with remission in the absence of steroid therapy and 12 patients with remission after steroid therapy, and found an association between remission in the absence of steroid therapy and seronegative findings for IgG4, absence of obstructive jaundice, absence of diabetes mellitus, and the presence of focal pancreatic swelling.

Ozden et al. [4] reported an AIP patient who showed spontaneous regression of biliary obstruction 2 months after biliary drainage, and the drainage catheter was removed. Araki et al. [5] reported the natural course of an AIP patient in whom a mass in the uncinate process of the pancreas spontaneously decreased in size and disappeared after 9 months; conversely, however, the mass in the tail increased in size.

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CQ-III-2. What are the indications for steroid therapy in AIP patients?

- Indications for steroid therapy in AIP patients are symptoms such as obstructive jaundice, abdominal pain, back pain, and the presence of symptomatic extrapancreatic lesions. (Level of recommendation: A)

Description According to the nationwide survey by the Research Committee of Intractable Pancreatic Disease supported by the Japanese Ministry of Health, Labour and Welfare [6], three-quarters of all AIP patients received steroid therapy. The remission rate of steroid-treated AIP was 98 %, which was significantly higher than that of patients without steroid therapy (88 %), and the treatment duration necessary to achieve remission averaged 98 days in steroid-treated patients, which was significantly shorter than the average 142 days in patients without steroid therapy. In 2013, an international multicenter study of the long-term outcomes of AIP was performed using data from 1,064 AIP patients (type 1, $n = 978$; type 2, $n = 86$) treated at 23 institutes in 10 countries [7]. Data from the study noted that remission was successfully induced in almost all patients with type 1 (99.6 %, 681/684) and type 2 (92.3 %, 48/52) AIP. Based on these findings, steroid therapy appeared to be a standard treatment for AIP.

Steroid therapy is effective for extrapancreatic lesions, such as sclerosing cholangitis, as well as the pancreatic lesions in AIP. AIP is frequently associated with stenosis of the bile duct due to sclerosing cholangitis, and obstructive jaundice is a frequent initial symptom. Based on data reported in the nationwide survey, obstructive jaundice is the principal indication for steroid therapy, [2, 6, 8–11] as 91 % of AIP patients with obstructive jaundice underwent steroid therapy [6]. While the severe abdominal pain that occurs in acute pancreatitis is rarely seen in AIP patients, persistent abdominal or back pain in AIP appears to be an indication for steroid therapy [2, 6, 8–10]. In the international study [7], jaundice (63 %, 458/724) was the most common indication for steroid treatment in type 1 AIP patients, and abdominal pain (64 %, 34/53) and inflammatory bowel disease (48 %, 23/53) were major indications for type 2 AIP patients. Associated symptomatic extrapancreatic lesions, such as retroperitoneal fibrosis, interstitial pneumonia, tubulointerstitial nephritis, and hepatic or pulmonary pseudotumor, are indications for steroid therapy [2, 8, 10, 11].

Impaired pancreatic endocrine or exocrine function improved in some AIP patients, suggesting that marked impairment of pancreatic endocrine or exocrine function may be an indication for steroid therapy [8, 11, 12]. Some AIP patients showing diffuse enlargement of the pancreas undergo steroid therapy even when they are asymptomatic

[2, 10]. It may be better to follow up for 1–2 weeks before commencing steroid treatment in order to check for spontaneous regression. In principle, steroid therapy should be performed for patients diagnosed as having AIP, but a facile steroid trial to differentiate AIP from pancreatic cancer should be avoided [13].

CQ-III-3. How do we perform initial steroid therapy?

- Before steroid therapy is begun, jaundice should be managed by biliary drainage in patients with obstructive jaundice, and blood glucose levels should be controlled in patients with diabetes mellitus. The recommended initial oral prednisolone dose for induction of remission is 0.6 mg/kg/day, which is administered for 2–4 weeks and then gradually tapered. (Level of recommendation: A)

Description Prior to initiating steroid therapy, it is important to distinguish AIP from pancreatic or biliary cancer with imaging studies and endoscopic approach [10]. In cases with obstructive jaundice due to bile duct stenosis, endoscopic or transhepatic biliary drainage is performed. Repeated cytologic examination of the bile is performed. After cytologic examination, a plastic stent is sometimes inserted. In the international study [7], biliary stenting was performed in 351 (71 %) of 492 type 1 AIP patients with jaundice. Steroid treatment may be initiated without biliary drainage in cases with mild jaundice. Blood glucose levels should be controlled in patients with diabetes mellitus prior to commencing steroid therapy [9, 10].

The nationwide survey by the Research Committee of Intractable Pancreatic Disease [6] reported an initial oral prednisolone dose of 30 mg/day ($n = 54$) or 40 mg/day ($n = 32$) in 93 AIP patients treated with steroids. The treatment duration necessary to achieve remission in patients treated with an initial prednisolone dose of 30 mg/day averaged 70 days from initial administration, which was not significantly different from those treated with an initial prednisolone dose of 40 mg/day (average 91 days). In AIP patients with obstructive jaundice, there were no significant differences between the initial prednisolone dose administered to patients treated with steroids alone [0.60 ± 0.12 mg/kg/day (mean ± SD)] and those treated with biliary drainage and steroids (0.60 ± 0.17 mg/kg/day). A recent multicenter study showed similar results [10]. Given these findings, an initial oral prednisolone dose of 0.6 mg/kg/day is recommended, gradually tapered after 2–4 weeks [10].

In Western countries, initial prednisolone doses of 50–75 mg/day [14], 40 mg/day [15, 16], and 0.5 mg/kg/day have been reported for treatment of AIP [17]. Matsushita et al. [18] reported that steroid pulse therapy is useful and may prevent unnecessary surgery when oral steroid therapy is not indicated due to the required period for drug tapering.

CQ-III-4. How is the steroid dose tapered?

- After 2–4 weeks at the initial dose, the dose is tapered by 5 mg every 1–2 weeks based on changes in clinical manifestations, biochemical blood tests (such as liver enzymes and IgG or IgG4 levels), and repeated imaging findings (US, CT, MRCP, ERCP, etc.). The dose is tapered to a maintenance dose over a period of 2–3 months. (Level of recommendation: B)

Description In order to induce remission, after 2–4 weeks at the initial dose, the dose is tapered by 5 mg every 1–2 weeks based on changes in clinical manifestations, biochemical blood tests (such as liver enzymes and IgG or IgG4 levels), and repeated imaging findings (US, CT, MRCP, ERCP, etc.). The dose is tapered gradually to a maintenance dose, usually 5–10 mg/day [6, 9, 10, 19] (Fig. 1, [20]). After 15 mg/day, the dose is tapered more gradually, and the amount of steroid is reduced to a maintenance dose over a period of 3–6 months [10].

At the Mayo Clinic, an initial prednisolone dose of 40 mg/day was administered for 4 weeks, followed by tapering of 5 mg per week (total of 11 weeks of treatment) [15]. As reported by Park et al. [17] in Seoul, the induction dosage of prednisolone was initially administered at 0.5 mg/kg/day for 1–2 months and was gradually reduced by 5–10 mg per month to a maintenance dose, and maintenance therapy was discontinued completely after an average period of 6 months.

Because radiological improvement appears 1–2 weeks after the initiation of steroid therapy, morphological and serological evaluation for effectiveness of therapy should be performed 1–2 weeks after beginning steroid treatment. A poor response to steroid therapy should flag the possibility of pancreatic cancer and the need for re-evaluation of the diagnosis [10].

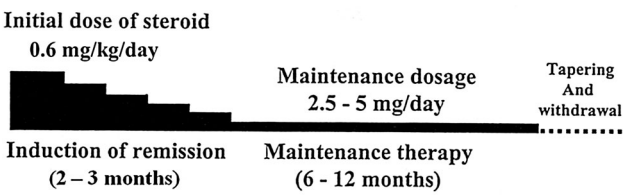

Fig. 1 Regimen of oral steroid therapy for AIP. Reference [34] is partially modified

CQ-III-5. Is maintenance steroid therapy necessary?

- To prevent relapse, maintenance therapy (2.5–5 mg/day) is recommended. (Level of recommendation: B)

Description Although there is no clear high-level evidence and consensus regarding maintenance steroid therapy, steroid treatment in Japan and South Korea is often discontinued after a certain period of maintenance therapy. A multicenter study in Japan [10] reported that 377 (82 %) of 459 steroid-treated AIP patients received maintenance therapy with steroids. A maintenance dose of 5 mg/day of oral prednisolone was most common (63 %), followed by 2.5 mg/day (21 %), 10 mg/day (7 %), and 7.5 mg/day (3 %). Relapse occurred significantly less often during maintenance steroid therapy (23 %, 63/273) than after therapy was discontinued (34 %, 35/104; $p < 0.05$). A report from South Korea [17] showed that 13 (33 %) of 40 AIP patients relapsed when steroid therapy was discontinued after a mean of 6 months of oral prednisolone administration (maintenance dose 2.5–7.5 mg/day). Of the 13 patients who relapsed, 7 had been undergoing maintenance therapy at the time and 6 had already discontinued steroid therapy. In the international study [7], the majority of relapse episodes occurred in steroid-treated AIP patients following steroid discontinuation (67 %), as compared to during steroid taper (15 %) or while on maintenance steroid therapy (18 %).

In contrast, steroid therapy protocol without maintenance therapy is common in American and European countries [7, 21, 22]. At the Mayo Clinic, initial therapy with oral prednisolone of 40 mg/day for 4 weeks is tapered by 5 mg/week and discontinued after 11 weeks [21]. Under this regimen, 16 (53 %) of 30 AIP patients associated with sclerosing cholangitis relapsed during median follow-up of 29.5 months. A group from Pittsburgh [22] also conducted short-term (12-week) steroid treatment without maintenance therapy, and reported that of the 15 patients who displayed complete remission, 9 (60 %) relapsed 8–12 weeks after therapy was discontinued.

The survey by the Research Committee for Intractable Pancreatic Disease [23] reported relapse in 38 (40 %) of 96 AIP patients who underwent maintenance therapy. Of these 38 patients, relapse occurred only in the pancreas in 19 (50 %), only in extrapancreatic lesions in 11 (29 %), and in both lesions in 8 (21 %). The relapse rate for patients during maintenance therapy with prednisolone >5 mg/day was 26 % (10/38), which was significantly lower than the rate (54 %, 14/26) in patients who discontinued maintenance therapy ($p < 0.05$) (Fig. 2, [20]).

These findings suggest that maintenance steroid therapy is effective in preventing AIP relapse. As the anti-

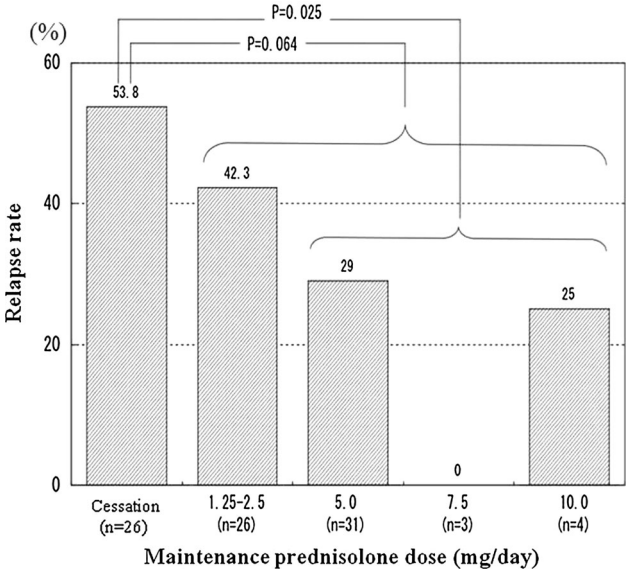

Fig. 2 Relationship between relapse rate of AIP and prednisolone dose during maintenance steroid therapy

inflammatory and immunosuppressive effects of steroids appear to suppress the activity of AIP, maintenance therapy with prednisolone at a minimum of 5 mg/day is recommended. However, as some patients who are not on maintenance therapy do not relapse, and some patients relapse during steroid tapering [21, 24] or during maintenance therapy with relatively high doses of prednisolone, it is important to evaluate disease activity in the patient in order to determine the indications for maintenance therapy. The Research Committee of Intractable Pancreatic Disease compared the clinical features of patients with and without relapse, and reported that the clinical features of patients who tended to relapse included pancreatic enlargement of more than one-third of the entire pancreas, association with extrapancreatic lesions diagnosed by Gallium scintigraphy, and association with extrapancreatic sclerosing cholangitis [23]. The presence of diffuse enlargement of the pancreas [3, 25], elevation of serum IgG4 levels [19], and proximal extrahepatic/intrahepatic strictures [7, 21, 26] have been reported to be predictive of relapse in AIP patients, and maintenance therapy is indicated for these patients.

CQ-III-6. When should steroid therapy be discontinued?

- Steroid therapy should be discontinued based on the disease activity in each case. (Level recommendation: B)
- Cessation of maintenance therapy should be planned within 3 years in cases with radiological and serological improvement. (Level of recommendation: B)

Description There is no consensus regarding duration of steroid therapy in AIP patients. As described in the previous section, maintenance therapy is frequently continued for the relative long-term in Japan. In a Japanese multicenter study [10], the cumulative rate of relapse ($n = 99$) after initiating steroid therapy was 56 % at 1 year, 76 % at 2 years, and 92 % after 3 years.

According to the survey by the Research Committee of Intractable Pancreatic Diseases [23], most patients relapsed within 3 years of the initiation of steroid therapy (Fig. 3, [20]). The incidence of relapse was higher in cases where therapy was discontinued after 3 years than during maintenance therapy. There were no differences in the period of steroid therapy between relapsed cases (12.8 ± 8.9 months, 1–30 months, $n = 14$) and non-relapsed cases (13.5 ± 10.5 months, 1–31 months, $n = 11$) after discontinuation of steroid therapy.

The efficacy of a certain duration of maintenance steroid therapy has been demonstrated from the perspective of improvements in pancreatic exocrine function: when oral prednisolone was administered for 1 year at 5 mg/day, although no changes were observed in the amount of pancreatic juice with secretin test, mean bicarbonate concentration improved within 3 months and the amount of pancreatic enzyme secretion improved within a year [27]. However, as AIP patients are typically elderly and are at high risk of developing steroid-related complications such as osteoporosis and diabetes mellitus, discontinuation of steroid treatment should be attempted. Cessation of maintenance therapy should be planned within 3 years in cases with radiological and serological improvement. When treatment is discontinued, it is necessary to evaluate disease activity, and patients should be followed up for relapse of AIP [10, 23].

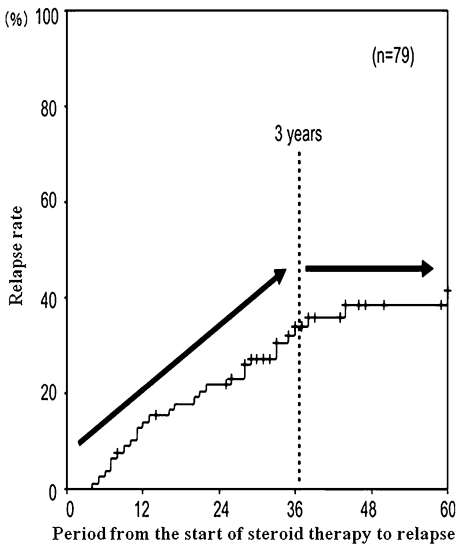

Fig. 3 Relapse rate of AIP and period from the start of steroid therapy to relapse

CQ-III-7. Is early prediction of AIP relapse possible?

- Elevated serum IgG4 levels or elevated immune complexes are useful early predictors of AIP relapse. (Level of recommendation: B)

Description In a Japanese multicenter study [10], patients for whom serum IgG4 levels did not normalize after initiation of steroid therapy showed a significantly greater rate of AIP relapse (30 %, 34/115) than those in whom serum IgG4 levels had normalized (10 %, 7/69). Moreover, 37 (69 %) of 54 relapsed patients showed that serum IgG4 levels elevated again prior to relapse. In addition to serum IgG4 levels, circulating immune complexes (monoclonal rheumatoid factor method) have been reported as useful early predictors of relapse [28].

CQ-III-8. How are AIP relapses treated?

- Re-administration or dose-up of steroid is effective for treating AIP relapses. (Level of recommendation: A)
- In most relapsed AIP cases, remission can be achieved with the same prednisolone dose as the initial dose, although it may be necessary to taper more gradually. (Level of recommendation: B)
- Application of immunomodulatory drugs is considered for AIP patients who prove resistant to steroid therapy. (Level of recommendation: B)

Description In most relapsed AIP cases, remission can be achieved with re-administration or dose-up of steroid. In a Japanese multicenter study [10], most patients who relapsed were able to achieve remission again (97 %, 91/94) by increasing prednisolone doses (60 mg/day in 5 % of patients, 40 mg/day in 23 %, 30 mg/day in 47 %, and 20 mg/day in 11 %). In addition, in all 32 patients who were in remission without the use of steroids for initial therapy but subsequently relapsed, remission was achieved with steroid therapy. In the international study [7], remission was successfully induced using steroids in 201 (95 %) of 210 relapsed type 1 AIP patients.

One studied approach to the administration of steroid therapy after relapse was to gradually decrease the dose at a slower rate compared to initial therapy [19, 24]. However, in 11 relapsed patients in whom prednisolone dosage was gradually reduced, 4 of the patients reportedly relapsed again ([21]. Pulse steroid therapy is

another method that has been studied in patients who relapsed. Matsushita et al. [18] conducted studies of mini-pulse therapy with methylprednisolone (500 mg/day, 3 days/week, 2 cycles) in patients who experienced recurrence with obstructive jaundice due to sclerosis of the bile duct, demonstrating marked improvements in biliary stricture and subsequent lowering of steroid maintenance doses.

In Western countries, immunomodulatory drugs have recently been introduced in AIP patients who had relapsed or who were resistant to steroid therapy [7, 21, 29]. A study from the Mayo Clinic [21 on the administration of 2–2.5 mg/kg/day of azathioprine (Imuran®, Azanin®) or 1,500 mg/day of mycophenolate mofetil (CellCept®) in 7 patients with AIP and sclerosing cholangitis who had relapsed once or twice, or with IgG4-related sclerosing cholangitis without AIP, reported that no relapse was observed (median observation period 6 months; range 2–19 months). In 2 of the 7 patients, low doses of azathioprine (50 mg/day) and mycophenolate mofetil (1,000 mg/day) were administered initially, but both patients relapsed.

A report from the United Kingdom [29] described the use of steroid therapy in 28 AIP patients and found that 13 patients with sclerosing cholangitis relapsed (5 patients relapsed during maintenance steroid therapy and 8 patients relapsed after steroid discontinuation). Prednisolone dose was increased (20–30 mg/day) in all 13 of the patients who relapsed, and 10 patients also received azathioprine (1–2 mg/kg/day). Remission was subsequently achieved in 12 patients. However, after second remission, 1 of 7 patients who underwent azathioprine monotherapy and 2 of 3 patients who underwent maintenance therapy with concomitant azathioprine and steroid relapsed again.

Rituximab (anti-CD20 antibody) has also been successfully used to treat AIP patients with sclerosing cholangitis who showed resistance to or side effects from treatments including steroid, azathioprine, mycophenolate mofetil, 6-mercaptopurine, and methotrexate [30, 31]. Inhibition of AIP relapse in these cases indicates results that were anticipated from the pathophysiological condition of AIP and the mechanism of action of the drugs. Reports from Japan have also described the use of immunomodulatory drugs to treat AIP complications [32]. While the use of immunomodulatory drugs as second-line therapy for AIP patients who repeatedly relapse or who are resistant to steroid therapy is expected to become increasing significant, these drugs are associated with serious side effects and should be considered with caution. Randomized controlled studies are needed to investigate the use of immunomodulatory drugs in the treatment of patients who relapse.

CQ-III-9. Do pancreatic exocrine and endocrine functions improve after steroid therapy in AIP patients?

- Pancreatic exocrine and endocrine functions improve after steroid therapy in some AIP patients. Many AIP patients with type 2 diabetes mellitus before AIP onset showed worsening of diabetes mellitus control after steroid therapy. (Level of recommendation: C)

Description Many AIP patients have associated pancreatic exocrine and endocrine dysfunction [2, 12, 24, 33–35]. Steroid therapy has been reported to improve pancreatic exocrine and endocrine function in 38 % [24] to 50 % [34] and 25 % [24] to 45 % [34] of AIP patients, respectively. One suggested mechanism posits that steroid suppresses lymphoplasmacytic cell infiltration and fibrosis, permitting the attenuation of blood flow [35] and further regenerating islet cells by suppression of cytokine production [36]. A recent study of activity in pancreatic tissue before and after steroid therapy in AIP patients revealed regeneration of acinar cells during steroid treatment, suggesting that acinar cell regeneration may be associated with CD133-positive pancreatic progenitor cells [27].

Diabetes mellitus (DM) control was shown to worsen in 75 % of AIP patients with type 2 diabetes mellitus before AIP onset after steroid therapy [34]. As DM has been reported to develop in some AIP patients after steroid therapy [33, 34], the occurrence of DM should be taken into consideration in patients who continuously undergo steroid therapy.

CQ-III-10. Is the prognosis of AIP good with steroid therapy?

- The prognosis of AIP appears to be good over the short-term with steroid therapy. (Level of recommendation: B)
- The long-term outcome is less clear, as there are many unknown factors, such as relapse, pancreatic exocrine or endocrine dysfunction, and associated malignancy. (Level of recommendation: I)

Description Several Japanese studies have been conducted to determine the rate of relapse in patients who received steroid therapy, with mean observation periods ≥40 months [24, 26, 37]. Kamisawa and Okamoto [37] reported a 5.6 % rate of relapse, while Nishino et al. [24] reported a rate of 33.3 %. In addition, Hirano et al. [26] investigated the occurrence of adverse events with and without steroid therapy, and demonstrated that adverse events, including relapse, occurred in 31.6 % of patients who received steroid therapy (mean observation period

41 months) and 69.6 % in those who did not (mean observation period, 61 months). Further, various Japanese reports since 2009 have described the long-term clinical course [10, 28, 38]. In one study, Uchida et al. [38] showed relapse in 2 patients (16.7 %) during maintenance steroid therapy, with a mean observation period of 40.8 months. They also reported on the outcome of all 21 patients, indicating that pancreatic cancer and pancreatic cyst developed after 4 years and 2 months and after 2 years, respectively, each in 1 patient. Progression to chronic pancreatitis was reported in 3 patients.

Kamisawa et al. [10] analyzed 563 AIP patients at 17 Japanese institutions, showing relapse in 110 (24.4 %) of 451 patients who underwent steroid therapy and in 32 (41.6 %) of 77 patients who did not undergo therapy. With regard to relapse during maintenance therapy, the rate of relapse in patients who discontinued maintenance therapy was 33.7 % (35/104 patients). In contrast, patients who continued maintenance therapy exhibited a significantly lower rate of relapse, at 23.1 % (63/273). Kawa et al. [28] found that 17 (40.5 %) of 42 patients who received steroid therapy relapsed during a mean observation period of 72 months. Furthermore, pancreatic calcification appeared to be present in 17.6 % (9/51), suggesting that this calcification is common in patients who relapse (7/21 patients, 33.3 %; patients who did not relapse, 6.7 %). They also reported that pancreatic calcification was associated with AIP relapse, with some AIP patients relapsing several times and transitioning to a normal type of chronic pancreatitis. In an analysis of a nationwide Japanese survey, Nishimori et al. [9] found that the rate of relapse was significantly higher among patients exhibiting biliary stricture. This finding was recently corroborated by domestic and international studies after it was reported that biliary stricture may be clinically predictive of relapse [7, 21, 22, 26].

In reports from overseas, Ryu et al. [39] summarized AIP cases from 16 South Korean institutions and demonstrated that 10 (14.9 %) of 67 patients relapsed during a mean observation period of 20 months. Ghazale et al. [21] showed relapse in 16 (53.3 %) of 30 patients who received steroid therapy during a median observation period of 29.5 months. Sahani et al. [40] found pancreatic atrophy in 5 (38.5 %) of 13 patients. Sandanayake et al. [29] showed relapse in 8 (34.8 %) of 23 patients who received steroid therapy during a mean observation period of 27.3 months, and all 8 of these patients displayed extrapancreatic lesions or bile duct lesions at the time of diagnosis. Raina et al. [22] found that 9 (60.0 %) of 15 patients who received steroid therapy relapsed during a mean observation period of 12.8 months, and that the relapse occurred in 8–12 weeks. Frulloni et al. [41] found that 25.3 % (22/87) of patients relapsed during a mean observation period of 7.4 ± 5.5 years, and that focal AIP was more likely to relapse than diffuse AIP. They also found pancreatic calcification in 11.5 % (10/87) of patients, and reported 3 deaths during the course (due to pancreatic cancer, systemic metastasis of adenocarcinoma of unknown origin, and traffic accident). In addition, a report from India showed that relapse was not detected during an observation period of 6–8 months [42]. In the international study [7], 245 (36 %) of 684 steroid-treated type 1 AIP patients experienced at least one disease relapse, compared with 8 (15 %) of 52 type 2 AIP patients ($p < 0.001$). Most relapses occurred in the biliary system (51 %) or pancreas (43 %) for type 1 AIP, while relapses in type 2 AIP were limited to the pancreas. Pancreatic calcification was more likely to occur in type 1 AIP patients with at least one relapse (14 %) compared with those who had never experienced relapse (4 %, $p < 0.001$).

As described above, AIP responds well to steroids on a short-term basis, with the potential for high rates of remission [23]. From the perspective of AIP prognosis, the rate of relapse was high in patients who did not receive steroid therapy, although relapse was observed in 20–40 % of those undergoing steroid therapy and 20–30 % of those undergoing maintenance therapy. In addition, an increasing number of reports describe pancreatic atrophy and pancreatic stones as long-term complications, so the prognosis is not necessarily satisfactory. Ko et al. [27] recently reported improvements in pancreatic function and histology after steroid therapy, but further investigation is necessary with regard to long-term pancreatic function.

CQ-III-11. Is there any relationship between AIP and pancreatic cancer?

- There are a few papers reporting an AIP case developing pancreatic cancer, but it is unclear whether there is a relationship between AIP and pancreatic cancer. (Level of recommendation: I)

Description Chronic pancreatitis has been reported as one of the risk factors for pancreatic cancer [43]. Reports also indicate that some AIP patients developed pancreatic atrophy or pancreatic stones [7, 28, 37, 44]. AIP occurred predominantly in elderly males. As steroid therapy is immunosuppressive, it is necessary to investigate whether there is an association with pancreatic cancer and other malignancies in AIP patients on long-term steroid treatment. Periodic checks of serum tumor markers should be performed during follow-up.

There have been 9 recent papers reporting AIP cases developing pancreatic cancer [45–53]. The locations of these cancers were head ($n = 2$), body ($n = 4$), tail ($n = 2$), and whole ($n = 1$) of the pancreas. The male-to-female ratio was 8:1, and average age was 69.3 (59–80) years. Five pancreatic cancers were diagnosed simultaneously with AIP, and the other 4 cancers were diagnosed from 3 to 13 years after the onset of AIP. Elevation of serum tumor markers triggered diagnosis of pancreatic cancer in some cases [50, 54]. Reported rates of associated pancreatic cancer with AIP were 2.4 % [26], 5.6 % [54], 10 % [3], and 3.3 % [21]. A report from China [55] described no progression of pancreatic cancer in AIP patients during a mean observation period of 46 months.

Interestingly, in an investigation of K-ras mutations in gallbladder and pancreas tissues obtained from AIP patients, Kamisawa et al. [56] demonstrated significant K-ras mutation in the pancreatic and biliary regions. While these results suggest that AIP may be a risk factor for pancreatic and bile duct cancer, patients with pancreatic cancer have also been reported as displaying histological similarities to those with lymphoplasmacytic sclerosing pancreatitis (LPSP) around the pancreatic cancer [57]. Therefore, a thorough histopathological investigation is necessary to ensure accurate diagnosis of pancreatic cancer.

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Conflict of interest The authors declare that they have no conflict of interest.

Appendix

The Working Committee of the Japan Pancreas Society (JPS) and the Research Committee for Intractable Pancreatic Disease supported by the Ministry of Health, Labour and Welfare of Japan (RCIPD-MHLWJ):

I. The professional committee for making clinical questions and statements

Chairperson: Kazuichi Okazaki (Department of Gastroenterology and Hepatology, Kansai Medical University)

Co-Chairpersons: Shigeyuki Kawa (Center for Health, Safety and Environmental Management, Shinshu University), Terumi Kamisawa (Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital)

Committee members:

Tetsuhide Ito (Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University), Kazuo Inui (Department of Gastroenterology, Second Teaching Hospital, Fujita Health University), Hiroyuki Irie (Department of Radiology, Faculty of Medicine, Saga University), Takayoshi Nishino (Department of Gastroenterology, Yachiyo Medical Center, Tokyo Women's Medical University), Kenji Notohara (Department of Anatomic Pathology, Kurashiki Central Hospital), Keishi Kubo (Department of Internal Medicine, Shinshu University School of Medicine), Hirotaka Ohara (Department of Community-Based Medical Education, Nagoya City University Graduate School of Medical Sciences), Atsushi Irisawa (Department of Gastroenterology, Fukushima Medical University Aizu Medical Center), Yasunari Fujinaga (Department of Radiology, Shinshu University School of Medicine), Osamu Hasebe (Department of Gastroenterology, Nagano Municipal Hospital), Isao Nishimori (Nishimori Clinic), Shigeki Tanaka (Department of Acupuncture and Moxibusion, Tokyo Ariake University of Medical and Health Sciences)

II. The expert panelist committee for rating statements by the modified Delphi method

Chairperson: Tooru Shimosegawa

Committee members: Kazuichi Okazaki, Shigeyuki Kawa, Terumi Kamisawa, Tetsuhide Ito, Kazuo Inui, Takayoshi Nishino, Hirotaka Ohara, Isao Nishimori, Shigeki Tanaka

III. The Evaluating Committee

Chairperson: Masao Tanaka (Department of Surgery and Oncology, Kyushu University)

1. Committee Members:

Toshimasa Nishiyama (Department of Public Health and Hygiene, Kansai Medical University), Koichi Suda (Department of Pathology, Tokyo-West Tokushukai Hospital), Keiko Shiratori (Department of Gastroenterology, Tokyo Women's Medical University), Kenji Notohara, Keishi Kubo, Hiroshi Yamamoto, Hirotaka Ohara, Atsushi Irisawa, Yasunari Fujinaga, Osamu Hasebe, Shigeki Tanaka

2. Committee Members of the JPS for Autoimmune Pancreatitis:

Kazushige Uchida (Department of Gastroenterology and Hepatology, Kansai Medical University), Atsushi Kanno (Division of Gastroenterology, Tohoku University Graduate School of Medicine), Kensuke Kubota (Department of Gastroenterology, Yokohama City Unicersity), Shigeru Ko (Department of Systems Medicine, Keio University), Junichi Sakagami (Department of Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine), Kyoko Shimizu (Department of Gastroenterology, Tokyo Women's Medical University), Masanori Sugiyama

(Department of Surgery, Kyorin University), Minoru Tada (Department of Gastroenterology, University of Tokyo), Takahiro Nakazawa (Department of Gastroenterology and Metabolism, Nagoya City University), Hirokazu Nishino (Department of Gastroenterology and Hepatology, Jikei University School of Medicine), Hideaki Hamano (Medical Informatics Division and Department of Internal Medicine, Gastroenterology, Shinshu University Hospital), Yoshiki Hirooka (Department of Endoscopy, Nagoya University Hospital), Kenji Hirano (Department of Gastroenterology, University of Tokyo), Atsushi Masamune (Division of Gastroenterology, Tohoku University Graduate School of Medicine), Atsuhiro Masuda (Divison of Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of Medicine), Nobumasa Mizuno (Department of Gastroenterology, Aichi Cancer Center Hospital), Koji Yamaguchi (Department of Surgery 1, University of Occupational and Environmental Health), Hitoshi Yoshida (Division of Gastroenterology, Department of Medicine, Showa University School of Medicine)

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