

International consensus for the treatment of autoimmune pancreatitis



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ABSTRACT

Background and aims: The International Consensus Diagnostic Criteria (ICDC) for AIP has proposed two distinctive type of AIP, type 1 and type 2, and enabled us first to differentiate two types of AIP each other. By initial steroid treatment for induction of remission, remission can be successfully induced in almost all subjects with type 1 and type 2 AIP. As relapse rate in type 1 AIP is significantly higher than in type 2 AIP, there has been ongoing debate on how to treat effectively relapse of type 1 AIP.

Methods: By a modified Delphi approach, a panel of international experts has proposed an international consensus on the treatment of AIP after intense discussion and deliberation during an international consensus symposium of the International Association of Pancreatology (IAP) 2016.

Results: Individual statements for nine clinical questions with recommendation levels and the therapeutic strategy have been proposed.

Conclusion: The recommendations are based on the available evidence, and eastern and western experts' opinions to find standard treatment of AIP worldwide. These recommendations can be tailored according to the local expertise and context in the management of individual patients.

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1. Introduction

Autoimmune pancreatitis (AIP) is a distinct form of pancreatitis characterized clinically by frequent presentation with obstructive jaundice with or without a pancreatic mass, histologically by a lymphoplasmacytic infiltrate and fibrosis, and therapeutically by a dramatic response to steroids [1]. The International Consensus Diagnostic Criteria (ICDC) for AIP has proposed two distinctive type of AIP, type 1 and type 2, and enabled us first to differentiate two

types of AIP from each other [1]. Recently, type 1 AIP has been defined as a pancreatic manifestation of IgG4-related disease [2,3].

In an international multicenter retrospective study using more than one thousand cases, 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 ($p = 0.01$) [4]. By initial steroid treatment for induction of remission, remission has been successfully induced in almost all subjects with type 1 and type 2 AIP. The patients with type 1 who received intervention (either steroids or surgery) showed higher remission rates (90–99.2%) compared with those who did not receive it (55.2–74%) [4,5]. On the other hand, initial remission rates were similar in patients with type 2 AIP who received intervention compared with conservative

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management (83.5% vs 66.7%, respectively, $p = 0.29$) [4]. Relapse rate in type 1 AIP (31%) is significantly higher than in type 2 AIP (9%) [4–8]. Due to the high relapse in type 1 AIP, the concepts of induction of remission and maintenance of remission have been proposed.

There has been ongoing debate on how to treat the patients with AIP. Questions that need consensus include: Who should be treated? In patients with obstructive jaundice who needs biliary drainage before treatment of AIP? What is the induction regimen for steroid treatment? When to taper and when to stop initial steroid treatment? Who needs and who does not need maintenance treatment? How to treat relapsing patients?

To achieve the international consensus for treatment of AIP, the international consensus symposium was organized in the 20th meeting of the International Association of Pancreatology (IAP) on the 4th–7th July 2016 held in Sendai, Japan. The moderators selected eastern and western expert panels based on previous international meetings and discussions through email or physical meetings for AIP. Prior to the consensus meeting, the panels extracted the specific clinical questions and statements for treatment of AIP from the literature by PubMed search (1963–2016). Most of the evidence levels of the specific clinical statements and a secondary database were still lower than grade III as proposed by the Agency for Health Care Policy and Research in 1993. Therefore, we have developed the consensus guidelines for treatment of AIP by modified Delphi approach. To establish consensus, a panel of international experts has proposed 9 clinical questions and statements on the treatment of AIP after intense discussion and deliberation during the symposium. The recommendations are based on the available evidence, and eastern and western experts' opinions to find standard treatment of AIP worldwide. Because available clinical evidence regarding the management of AIP is limited, we could not set a suitable recommendation level for some clinical statements according to an evidence based system such as GRADE system. We evaluated some as “strongly recommendable”, (level A) or “strongly unrecommendable (level D)”, and “ordinarily recommendable” (level B), “unrecommendable” (level C), or “conflicting benefits and harms” (level I) according to the grading proposed by United States Preventive Services Task Force [9]. These recommendations can be tailored according to the local expertise and context in the management of individual patients.

2. Clinical questions (CQs), consensus statements and descriptions for the treatment of AIP

2.1. CQ-1. What are the indications for treatment of AIP?

2.1.1. Consensus statements

A. “Symptomatic patients as follows are indication for treatment”: (level B).

- Pancreatic involvement: e.g., obstructive jaundice, abdominal pain, back pain.
- Other organ involvement (OOI): e.g., Jaundice due to bile duct stricture.

B. “Asymptomatic patients as follows are indication for treatment”: (level B).

- Pancreatic: Persistent pancreatic mass on imaging.
- OOI: Persistent liver test abnormalities in a patient with associated IgG4-related sclerosing cholangitis (IgG4-SC).

2.1.2. Description

As some AIP patients (about 10–25%) improve spontaneously without intervention or steroid treatment [4–13], “watchful waiting” may be appropriate in most of asymptomatic patients. The Japanese consensus guidelines [13] recommend that indications for steroid therapy in AIP patients are symptoms such as obstructive jaundice, abdominal pain, back pain, and the presence of symptomatic OOs. Similarly, the international consensus treatment for IgG4-RD also recommend steroid treatment for subclinical lesions leading to severe, irreversible sequelae in the biliary tree, kidney, aorta, mediastinum, retroperitoneum, mesentery, and other organs [14]. For urgent treatment, proximal biliary strictures inducing superimposed infectious cholangitis, irreversible hepatic fibrosis and cirrhosis in addition to pancreatic involvement leading to irreversible pancreatic exocrine and endocrine failure are preferable for indication [13,14].

2.2. CQ-2. What is the best approach to induction of remission?

2.2.1. Consensus statements

- “For induction of remission, steroid is the first-line agent in all patients with active untreated AIP, unless if there are contraindications to steroid use.” (level A).
- “In those with contraindications to steroid treatment, rituximab can induce remission as single agent.” (level B).
- “Except for rituximab, other steroid-sparing such as thiopurines are poorly effective as single agents for induction of remission.” (level C).

2.2.2. Description

Most experts usually use steroid as the first-line agent for induction of remission in all patients with active untreated AIP, if no contraindications to steroid [1,5–14]. Steroid treatment achieved high remission rates in the Japanese national study (98% in steroid treated AIP patients vs 88% in untreated ones) and the international multicenter study for AIP (99.6% in type 1 ($n = 684$) and 92.3% in type 2 ($n = 52$)) [5].

In most cases of obstructive jaundice or OOs inducing organ dysfunction such as renal dysfunction, faster treatment may induce more complete remission with fewer long-term complications [14,15].

An alternative administration with steroid mini-pulse treatment (2 course of methyl-prednisolone 500 mg \times 3 days with 4days interval) may be more useful for induction of remission in refractory cases [5,16,17,18].

Evaluations of steroid effects by imaging and serological examinations are recommended within 1–2 weeks after starting steroid treatment [13]. The Korean prospective study suggested estimation of “a two weeks steroid trial” was the most appropriate to differentiate AIP from pancreas cancer in difficult cases after non conclusive complete workup [19]. Therefore, in cases of poor response to steroid, reevaluation of the diagnosis including pancreatic cancer is needed.

When glucocorticoid monotherapy ultimately fails to induce remission or control the disease and long-term glucocorticoid toxicities pose a high risk to patients, rituximab can induce remission as single agent [20,21]. However, other than rituximab, immune-modulators such as thiopurines are poorly effective as single agents for induction of remission. Early studies reported high rates of maintaining remission in relapsing AIP using immune-modulators such as thiopurines (azathioprine and 6-mercaptopurine), and mycophenolate mofetil [22–24]. However, in a larger case series, the relapse-free survival was similar when

relapse patients were treated with corticosteroids and an immune-modulator compared with corticosteroids alone without maintenance treatment [25]. Although rituximab is preferably recommended as an alternative use in those with contraindications to steroid treatment, steroid-sparing agents such as immune-suppressive agents can be used when rituximab is unavailable [13].

2.3. CQ-3. Is biliary drainage needed in obstructive jaundice before treatment?

2.3.1. Consensus statements

- “Biliary drainage is useful to prevent biliary infection and use of brushing and cytology can differentiate IgG4-SC from biliary malignancy.” (level B).
- “In some cases of mild jaundice without signs of infection, steroid treatment alone can be performed safely without biliary stenting.” (level B).

2.3.2. Description

The Japanese clinical guidelines recommend biliary drainage with biopsy or cytology in patients with obstructive jaundice, and control of blood glucose levels in patients with diabetes mellitus before steroid induction therapy [13]. On the other hand, the international multicenter study showed that some patients with jaundice did not necessarily require biliary stent placement (71% of type 1 and 77% of type 2 AIP) to achieve remission [4]. In the Japanese 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 \pm SD)] and those treated with biliary drainage and steroids (0.60 ± 0.17 mg/kg/day) [5]. In some cases of mild jaundice without signs of infection, steroid treatment alone can be performed safely without biliary stenting [26].

2.4. CQ-4. What should be the minimum starting dose steroids for induction of remission?

2.4.1. Consensus statements

- “Prednisone with the initial dose of 0.6–1.0 mg/kg/day should be started.” (level A).
- “A minimum of 20 mg/day is generally necessary to induce remission.” (level B).

2.4.2. Description

Both the Japanese consensus for AIP [12] and international consensus for AIP [1] and IgG4-RD [13] recommend that initial oral prednisolone dose for induction of remission is 0.6–1.0 mg/kg/day, which is administered for 2–4 weeks and then gradually tapered.

Administration of high-dose corticosteroid (approximately 30–40 mg/day) results in more rapid and fair induction of remission than conservative management [27]. As a low dose of prednisolone less than 20 mg/day has a limitation of remission rate [13,28,29], a minimum of 20 mg/day is generally necessary to induce remission.

2.5. CQ-5. How to taper steroids?

2.5.1. Consensus statements

- “Usually tapered by 5–10 mg/day every 1–2 weeks until a daily dosage of 20 mg, followed by tapering with 5 mg every 2 weeks.” (level B).
- “Another acceptable regimen is 40 mg/day for 4 weeks followed by taper by 5 mg/week until off.” (level B).
- “Duration of total remission treatment should generally last 12 weeks.” (level A).
- “Very short duration (<4 weeks) of steroid induction treatment with a high dose of steroid ≥ 20 mg is not recommended.” (level C).

2.5.2. Description

Although the regimen of tapering steroid has varied in different studies [14,30], the Japanese experts consensus recommends that after 2–4 weeks at the initial dose, the dose is tapered by 5 mg every 1–2 weeks over 2–3 months 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.) [14]. Many experts usually taper 5–10 mg/day every 1–2 weeks until a daily dosage of 20 mg, followed by tapering with 5 mg every 2 weeks [13,14].

Another acceptable regimen is 40 mg/day for 4 weeks followed by taper by 5 mg/week until off. Duration of induction treatment should generally last 12 weeks and very short duration of steroid induction treatment with high dose steroid ≥ 20 mg (<4 weeks) is not recommended. The goal of induction therapy is to achieve fast and complete remission with avoiding adverse effects of steroid as much as possible. Therefore, steroid therapy should be discontinued based on the disease activity in each case.

2.6. CQ-6. Is maintenance treatment useful to prevent relapse of AIP?

2.6.1. Consensus statements

- “The patients with type 1 AIP having low disease activity before treatment and those with type 2 do not need maintenance treatment.” (level C).
- “After successful induction of remission, maintenance therapy with low-dose glucocorticoids or steroid-sparing agents may be useful in some patients with type 1 AIP”. (level B).

2.6.2. Description

Although there is no high-level evidence regarding maintenance therapy, certain patients benefit from maintenance therapy following a successful course of induction therapy [13–15]. Maintenance therapy may consist of low-dose glucocorticoids or any of the steroid-sparing agents such as immune-suppressive agents or rituximab. Data from Asian countries, mainly Japan (23% of relapsing rate in maintenance group vs 34% in non-maintenance group, $P < 0.05$) [6] and South Korea (33% relapsing in non-maintenance group) [30], have suggested that steroid maintenance monotherapy may prevent relapse after remission. A retrospective Japanese multicenter study ($n = 459$) in which 82% of AIP patients received steroid induction treatment received steroid maintenance monotherapy with a dose of 2.5–7.5 mg/day [5]. In the retrospective international multi-center study, the majority of relapse episodes mainly occurred in steroid-treated AIP patients following steroid discontinuation (67%), as compared to during

steroid taper (15%) or while on maintenance steroid therapy (18%) [5]. In addition to retrospective studies, a recent prospective Japanese multicenter study has shown that steroid maintenance therapy provides beneficial outcomes after remission [31].

Many Japanese experts recommend the use of low-dose (2.5–7.5 mg/day) glucocorticoid maintenance therapy for up to 3 years and cessation of maintenance therapy should be planned in cases with radiological and serological improvement, although it is still debating about the duration of maintenance therapy [13].

In cases of low disease activity such as involvement in the pancreas alone with segmental/focal lesion without any OOs and complete radiological remission with normalized IgG/IgG4 in rapid response to steroid, steroids can be tapered off within 3 months followed by no steroid maintenance. On the other hand, maintenance therapy using low dose of steroid, immune-modulators, or rituximab is recommended in the patients with type 1 AIP showing diffuse enlargement of the pancreas, delayed radiological remission or persistently high serum IgG4 (>2xUNL) after treatment, or more than 2 OOs (≥ 2) or association with proximal IgG4-SC before treatment.

Whereas some patients do not relapse after withdrawal of steroids after remission is achieved, some patients relapse during steroid taper or require relatively high-dose maintenance therapy. Therefore, to determine the indications for maintenance therapy, it is important to evaluate disease activity during induction therapy.

2.7. CQ-7. Can we predict who will relapse?

2.7.1. Consensus statements

- “Risk factors for relapsing remain poorly understood.”
- “Some predictors of relapse include.
 - Remarkably high serum IgG4 levels (such as > x4 UNL) before treatment.
 - Persistently high serum IgG4 levels after steroid treatment.
 - Diffuse enlargement of the pancreas.
 - Proximal type of IgG4-SC.
 - Extensive multi-organ involvement (≥ 2 xOOI) ” (level B).

2.7.2. Description

According to a multicenter study in Japan [5], 56% of 99 relapses after starting steroid therapy relapsed within 1 year, 76% within 2 years, and 92% within 3 years. In an international multicenter study, 302 of the 978 (31%) subjects with type 1 AIP experienced at least one disease relapse, compared with 8 (9%) subjects with type 2 AIP. The vast majority of relapse episodes occurred in steroid-treated subjects following steroid discontinuation (67%), as compared with during tapering of the steroid (15%) or while on maintenance steroids (18%). Most relapses in type 1 AIP occurred in the biliary system or pancreas, while relapses in type 2 AIP were limited to the pancreas [4].

Most of risk factors for relapsing remain poorly understood and require further study. A history of relapse seems to be a strong risk factor for future relapse. In the Japanese national [32,33] and multicenter retrospective [5] studies have suggested that continuously elevated serum IgG4 levels after steroid treatment, and diffuse pancreatic enlargement type or association with OOs including sclerosing cholangitis with obstructive jaundice at diagnosis may be predictors of AIP relapse. In the Japanese multicenter study [1,5,34], patients with continuously high serum levels of IgG4 after steroid therapy showed a significantly high relapse rate (30% vs 10% of patients with normalized serum IgG4). On the other hand, the international study [4] showed similar relapsing rate between in those with persistently abnormal IgG4 levels following steroids

and those with a normal level (32.7% vs 31.4%, respectively, $p = 0.77$), and in initially 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 ($p < 0.001$). A Korean study also reported that relapsed IgG4-SC was characterized by more frequent extrapancreatic and multiple bile duct strictures, increased bile duct segment involvement, thicker bile duct walls, and a less frequent association with autoimmune pancreatitis (AIP) ($P \leq 0.016$) [33]. Therefore, at this moment, association with proximal type of IgG4-SC may be risk factors for relapsing. Moreover, 37 (69%) of 54 relapsed patients showed re-elevation of serum IgG4 levels prior to relapse [5]. In the diagnosis of AIP and IgG4-SC, higher serum IgG4 levels showed higher sensitivity [1,35]. In addition to serum IgG4 levels, circulating immune complexes have been reported as useful early predictors of relapse [36].

2.8. CQ-8. How should relapse be treated ?

2.8.1. Consensus statements

- “Although there is no “gold standard” for treatment in relapse cases, steroid and steroid-sparing agents such as immune-modulators or rituximab are useful. ” (level B)

2.8.2. Description

After steroid-induced remission, steroid-sparing agents (immune-modulators or rituximab) are an alternative approach for maintenance of remission other than steroid. Application of steroid-sparing agents is considered for AIP patients who repeatedly relapse or who are resistant to steroid therapy. These steroid-sparing agents are more commonly used in western countries rather than Asian countries [4].

2.8.3. Steroids

The Japanese consensus guidelines for AIP recommend re-administration or dose-up of steroid in patients who relapse after successful remission induced by initial steroid therapy [13]. 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.

2.8.4. Steroid-sparing agents

Immune-modulators [4,21,25,36–38] or rituximab (anti-CD20 antibodies) [22–25] are used as steroid-sparing agents. Unlike rituximab, immune-modulators are not effective as single agents for induction of remission in relapses. The most studied immune-modulators are thiopurines (azathioprine, 6-mercaptopurine), mycophenolate mofetil, and methotrexate. Thiopurines and mycophenolate require overlap with steroids for 6–8 weeks with disease being in remission at withdrawal of steroids [4,21,25,36]. The international retrospective study showed successful induction in 56 of 68 (85%) relapsing patients by the addition of azathioprine and successful remission with follow-up in 86% of those who received immune-modulators. While the use of immunomodulators as second-line therapy for refractory cases is expected to become increasing significant, these drugs are associated with serious side effects and should be considered with caution [4].

Rituximab has also been successfully used to treat patients with IgG4-RD including type 1 AIP who showed resistance to or side effects from treatments including steroid, and immune-modulators [14,22–25]. Rituximab may be used as single agent even in patients with active disease. However, treatment with steroids for 4–6

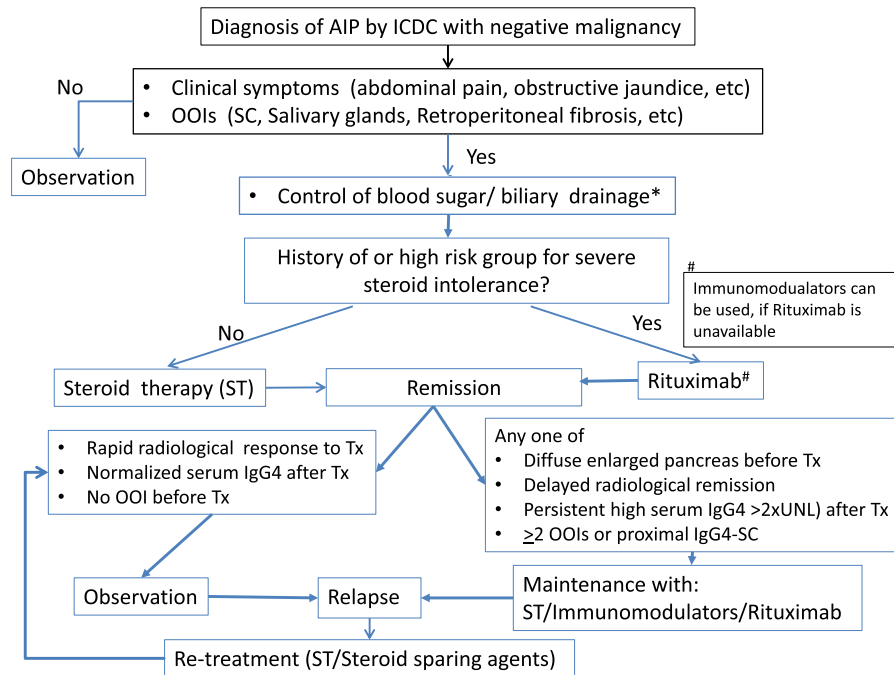


Fig. 1. Therapeutic algorithm for autoimmune pancreatitis.

This algorithm is based on eastern and western experts' opinions to recommend standard treatment of AIP worldwide. As medical insurance systems are different in each country, it can be tailored depending on local expertise. ICDC: International consensus of diagnostic criteria for autoimmune pancreatitis. OOI: other organ involvement. ST: steroid treatment.

weeks may be necessary in jaundiced patients due to delay in onset of action of rituximab [22,25].

Although few, due to strict regulation by medical insurance system, Japanese [38] investigators have also described the use of immune-modulators in refractory cases or those with contraindication to steroids. Experimental data suggest that cyclosporine A and rapamycin may be more effective than azathioprine as steroid alternatives [39]. In patients having occult hepatitis B virus (HBV), HBV can be reactivated by immunosuppressive medications such as using rituximab, immune-moderators, steroid, or anti-cancer agents [40]. The patients with positive anti-HBs or anti-HBc antibody, but negative HBs-antigen, should be monitored with HBV-DNA during immunosuppressive medications [40].

2.9. CQ-9. Is surgical treatment useful?

2.9.1. Consensus statements

- “Although steroid or alternative medications should be initially performed, surgical treatment may be useful in some refractory cases.” (level B)

2.9.2. Description

In some organs of IgG4-RD such as highly fibrotic orbital pseudotumors, surgical debulking may be an option, when surgery is possible [13]. Similarly, a few studies demonstrate that the patients who underwent palliative surgical pancreatic resection or bypass can achieve successful clinical remission and/or rarely relapse [41–43]. Although medical treatment should be more preferable to surgical intervention, surgical intervention may be an option in cases of poor response to medical treatment, in which long-term biliary stenting is necessary due to continuous obstructive jaundice.

2.9.3. Therapeutic algorithm

Based on the above, the experts' panel has proposed an international consensus for a therapeutic algorithm [Fig. 1]. This algorithm is based on eastern and western experts' opinions to recommend standard treatment of AIP worldwide. As medical insurance systems are different in each country, it can be tailored depending on local expertise.

3. Conclusion

The present consensus statements are based on the available evidence, and eastern and western experts' opinions to find standard treatment of AIP worldwide. These recommendations can be tailored according to the local expertise and context in the management of individual patients. Further studies, especially RCT studies for treatment, in addition to validations of consensus recommendations are needed.

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