ORIGINAL ARTICLE

Randomised controlled trial of long-term maintenance corticosteroid therapy in patients with autoimmune pancreatitis

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ABSTRACT

Objective Corticosteroid has been established as the standard therapy for autoimmune pancreatitis (AIP), but the requirement for maintenance corticosteroid therapy is controversial. We conducted a randomised controlled trial to clarify the efficacy of maintenance corticosteroid therapy in patients with AIP.

Design We conducted a multicentre, tertiary setting, randomised controlled trial. After the induction of remission with the initial oral prednisolone (PSL) treatment, maintenance therapy with PSL at 5–7.5 mg/day was continued for 3 years or withdrawn at 26 weeks. The primary endpoint was relapse-free survival over 3 years and the secondary endpoint was serious corticosteroid-related complications. All analyses were performed on an intention-to-treat basis.

Results Between April 2009 and March 2012, 49 patients with AIP were randomly assigned to the maintenance therapy group (n=30) or the cessation group (n=19). Baseline characteristics were not different between the two groups. Relapses occurred within 3 years in 11 out of 19 (57.9%) patients assigned to the cessation group, and in 7 of 30 (23.3%) patients in the maintenance therapy group. The relapse rate over 3 years was significantly lower in the maintenance therapy group than that in the cessation group (p=0.011). The relapse-free survival was significantly longer in the maintenance therapy group than that in the cessation group (p=0.007). No serious corticosteroid-related complications requiring discontinuation of PSL were observed.

Conclusions Maintenance corticosteroid therapy for 3 years may decrease relapses in patients with AIP compared with those who discontinued the therapy at 26 weeks.

Trial registration number UMIN000001818; Results.

Significance of this study

What is already known on this subject?

- Corticosteroid has been established as the standard therapy for patients with autoimmune pancreatitis (AIP).
- There is no consensus regarding the requirement for maintenance corticosteroid therapy.
- Retrospective studies showed that maintenance therapy might reduce the incidence of relapses compared with those who discontinued the therapy.

What are the new findings?

- The relapse rate was lower and the relapse-free survival was longer in patients with AIP who received the maintenance corticosteroid therapy for 3 years compared with those who discontinued the therapy at 26 weeks.
- Maintenance corticosteroid therapy may reduce relapses in patients with AIP.

How might it impact on clinical practice in the foreseeable future?

- Maintenance corticosteroid therapy for 3 years would be an option to decrease relapses in patients with AIP, especially those with high disease activity.
- Further studies based on the International Consensus Diagnostic Criteria would be warranted to confirm our findings in larger series.

INTRODUCTION

Autoimmune pancreatitis (AIP), the disease entity first proposed by Yoshida *et al* in 1995,[1] is a rare type of pancreatitis with a hypothesised autoimmune mechanism (two to four for review). The latest nationwide epidemiological survey estimated the total number of patients with AIP in Japan in 2011 as 5745, with an overall prevalence

rate of 4.6 per 100 000 population.[5] AIP has several distinct clinical, serological and morphological characteristics; it frequently presents with obstructive jaundice and increased serum immunoglobulin (Ig) G4.[2–4] It has two distinct phenotypes, termed type 1 and type 2. Histologically, lymphoplasmacytic sclerosing pancreatitis is a characteristic feature of type 1 AIP, whereas idiopathic duct-centric chronic pancreatitis and granulocytic epithelial lesions are characteristic of type 2 AIP.[2–4] Type 1 AIP is currently regarded as a pancreatic manifestation of a systemic IgG4-related disease.[6 7] AIP responds dramatically to corticosteroid therapy.[1–4 8–10] In an international retrospective multicentre study, 681/684 (99.6%) patients with type 1 AIP and 48/52 (92.3%) patients with type 2 AIP achieved clinical remission by the initial treatment with corticosteroid.[9] Corticosteroid has been established as the standard therapy for the treatment of patients with AIP,[8–12] and a rapid response to the corticosteroid treatment is included in the International Consensus Diagnostic Criteria (ICDC) for AIP.[13] But the benefit of universal and prolonged maintenance corticosteroid therapy has not been established, and the requirement for maintenance therapy is controversial.[8–12 14] In Europe and North America, corticosteroid therapy is discontinued after successful induction of remission to minimise cumulative corticosteroid exposure.[9–11 14] One standard protocol is administration of oral prednisolone (PSL) for 4 weeks followed by tapering of 5 mg each week until being discontinued after 11 weeks.[14] In Japan, long-term maintenance therapy with low-dose corticosteroid is preferred.[8 12] In a retrospective multicentre study from Japan, 10/38 (26%) of the cases relapsed during the maintenance treatment with PSL at more than 5 mg/day, and this was significantly lower than the relapse rate of 14/26 (54%) in patients who discontinued the therapy.[15 16] Another retrospective study from Japan showed that the relapse rate was lower in patients with AIP receiving the corticosteroid maintenance therapy than in those with no maintenance therapy (23% (63/273) vs 34% (35/104); p=0.048)[8] Based on these studies, the Japanese guidelines for the management of AIP recommended maintenance therapy for up to 3 years to prevent relapses.[12] Until now, however, there is no clear high-level evidence that maintenance corticosteroid therapy provided beneficial outcomes after remission. To clarify this issue, we conducted a randomised controlled trial to assess the efficacy of maintenance therapy in patients with AIP.

METHODS

Trial design

A multicentre, randomised controlled trial was performed in patients with AIP. A total of 15 tertiary-care institutions in Japan participated in this study. The recruitment period was initially scheduled from 1 April 2009 to 31 March 2011. However, because sufficient numbers of patients could not be recruited, it was extended for another year to 31 March 2012. The protocol was revised accordingly in March 2011.

Participants

The inclusion criteria at the time of enrolment were as follows: (i) patients diagnosed as having AIP according to the clinical diagnostic criteria for AIP proposed by the Japan Pancreas Society in 2006 (JPS2006),[17] (ii) no history of treatment for AIP, (iii) indication for corticosteroid therapy, (iv) between the ages of 20 and 79 years old, (v) good performance status (score 0–1 defined by the Eastern Cooperative Oncology Group) and (vi) adequate organ function (as defined by an absolute neutrophil count ≥1500/μL; platelets ≥75×10^9/L haemoglobin ≥8 g/dL; aspartate aminotransferase and alanine aminotransferase ≤X3 of the upper limit of normal; serum albumin ≥2.5 g/dL; serum creatinine ≤2.0 mg/dL; absence of significant abnormalities on ECG; and SpO2 ≥94% in room air).

The JPS2006[17] consisted of characteristic radiological findings (diffuse or segmental irregular narrowing of the main pancreatic duct (MPD) and enlargement of the pancreas) as an essential factor in combination with serological findings (elevated serum γ-globulin (>2.0 g/dL), IgG (>1800 mg/dL), IgG4 (>135 mg/dL) or the presence of autoantibodies, such as antinuclear antibodies (>80 folds) and rheumatoid factor (>20 IU/mL)) and/or histopathological findings (marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells in the periductal area, occasionally with lymphoid follicles in the pancreas). Indications for corticosteroid therapy were symptoms such as obstructive jaundice, abdominal pain and back pain, and the presence of symptomatic extrapancreatic lesions.[12 16]

The exclusion criteria were as follows: (i) corticosteroid administration within 3 months for the treatment of other diseases; (ii) poorly controlled infection including active tuberculosis; (iii) chronic hepatitis type B or positive for HBs antigen; (iv) malignant tumour; (v) serious complications (eg, malignant hypertension, severe congestive heart failure, severe coronary artery disease, acute myocardial infarction within 3 months, end-stage liver cirrhosis, poorly controlled diabetes mellitus, severe pulmonary fibrosis, active interstitial pneumonia and active peptic ulcer): (vi) pregnant or lactating women, possibly pregnant women and women who might want to become pregnant; (vii) severe mental disorder; and (viii) judged ineligible by the investigators (eg, difficulty to comprehend or comply with the trial protocol, and difficulty in attending regular consultation). Participants were recruited before the initiation of corticosteroid treatment. Consent interviews were performed individually before the initial corticosteroid treatment, and written informed consent was obtained from all participants. A data and safety monitoring board was established to monitor the study. This study was approved by the institutional review boards of all participating institutions, and registered at the University Hospitals Medical Information Network as number UMIN000001818.

Interventions

Participants were randomised before the initiation of the corticosteroid treatment to induce remission. In the initial treatment, PSL was administered at the dose of 0.6 mg/kg/day, and reduced to a maintenance dose of 5–7.5 mg/day over a period of up to 12 weeks, based on changes in the clinical manifestations, biochemical blood tests and imaging findings, at the discretion of the treating clinician[8] (figure 1). A maintenance PSL dose of 10 mg/day could be considered in cases of high disease activity and body weight. After the achievement of remission, the short-term maintenance treatment continued for 26 weeks. There was no difference in the trial protocol between the two intervention arms until 26 weeks.

Then, in the patients assigned to the maintenance treatment group, the long-term maintenance treatment at a dose of 5–7.5 mg/day of PSL continued for 3 years. Corticosteroid treatment was discontinued in the patients assigned to the cessation group. They were followed until 3 years from the start of corticosteroid treatment. The patients were instructed to visit the clinics for laboratory tests and imaging studies at least once in every 3 months during the follow-up period.

Outcomes

The primary endpoint was relapse-free survival over 3 years and the secondary endpoint was serious corticosteroid-related

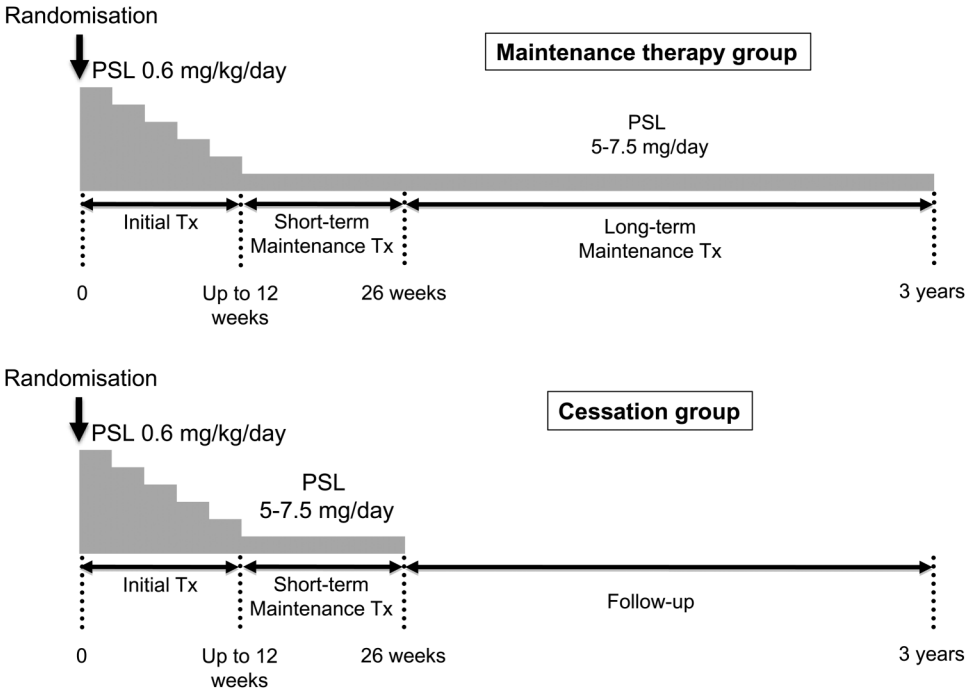


Figure 1 Study design. In the initial treatment, PSL was administered at the dose of 0.6 mg/kg/day, reduced to a maintenance dose of 5–7.5 mg/day over a period of up to 12 weeks and continued until 26 weeks (short-term maintenance therapy). Then, in the patients assigned to the maintenance treatment group, the maintenance treatment at a dose of 5–7.5 mg/day of PSL was continued until 3 years (long-term maintenance therapy). Corticosteroid treatment was withdrawn at 26 weeks in the patients assigned to the cessation group. They were followed until 3 years from the start of corticosteroid treatment. PSL, prednisolone; Tx, therapy.

complications. Primary and secondary endpoints were assessed first by the physicians treating the patients at the time of the events. In the case of relapses and adverse events, the physicians responsible were requested to promptly submit the completed standardised efficacy and safety report form containing information about the clinical course, treatment, complications, biochemical and serological data such as liver enzymes and IgG4 along with imaging findings of abdominal ultrasonography, CT, endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography (MRCP) and 18F-fluorodeoxyglucose positron emission tomography) to the data monitoring centre at Tohoku University. In addition, the efficacy and safety reports were collected at the time of entry, 26 weeks, 1 year, 2 years and 3 years (end of trial) after the start of the initial corticosteroid treatment. All of the efficacy and safety reports and imaging findings collected were reviewed to validate the events including relapses by a co-author (SH) who was blinded to the allocation.

Definitions

Remission

Remission was defined as the disappearance of clinical symptoms and resolution of the pancreatic and/or extrapancreatic manifestations on imaging studies.[8]

Relapse

Relapse in the pancreas was defined as diffuse or segmental reswelling of the pancreas and renarrowing of the MPD compared with those in the remission state (as assessed by endoscopic retrograde cholangiopancreatography and/or MRCP). Relapses outside the pancreas were defined as extrapancreatic lesions such as sclerosing cholangitis, retroperitoneal fibrosis and dacryoadenitis/sialadenitis with the need to resume or increase the dose of PSL. Biliary relapse was diagnosed based on cholangiography showing segmental/multiple strictures of bile ducts, along with increased hepatobiliary enzymes. Other extrapancreatic lesions were diagnosed based on physical evidence (eg, salivary gland enlargement) and/or radiological evidence. Biochemical and serological recurrences such as increased liver enzymes and IgG4 alone were not considered relapse.[8]

Adverse events and complications

We defined serious adverse events as death, hospital admission or persistent incapacity. Serious complications were defined as adverse events that might have been related to the corticosteroid treatment such as serious infection, psychosis, avascular necrosis of the femoral head, lumbar vertebral fracture and diabetes requiring the discontinuation of corticosteroids.

The change of glucose tolerance was evaluated as previously described.[18] A decrease in the required dose of insulin in patients treated with insulin, or a decrease of HbA1c by more than 0.5% in patients treated with diet therapy or oral antidiabetic agents was judged as an improvement in glucose tolerance. An increased dose of insulin or an increased HbA1c level by more than 0.5% in patients treated without insulin was considered an exacerbation. The other patterns were judged as no change.

Sample size

A power analysis was performed to assess the required sample size and to avoid a type II error. Based on a multicentre study in Japan showing that relapsed occurred in 10/38 (26%) of the cases during maintenance treatment with PSL at more than 5 mg/day and in 14/26 (54%) of the patients who discontinued the therapy,[15 16] it was assumed that maintenance corticosteroid treatment reduced the incidence of relapses from 50% to 25%.

With α of 0.05 and power at 80%, the calculated required sample size was 66 patients for each group. Interim analyses of the primary and secondary endpoints were scheduled at 24, 36 and 48 months after the start of the trial. The interim analysis was conducted by a co-author (SH), who was blinded to the allocation.

Randomisation

Participants were randomised just before the initiation of the corticosteroid treatment to induce remission. Randomisation was done centrally by a co-author (IT). The enrolled patients were randomised in a 1:1 ratio to the maintenance corticosteroid therapy group or the cessation group. Randomisation was stratified for study sites, age (<60 or ≥60 years old) and gender. The size of each block was four cases. We assigned a number for each of the six allocated blocks, with the maintenance therapy group as A and the cessation group as B: AABB=1, ABAB=2, ABBA=3, BBAA=4, BABA=5 and BAAB=6. Then, we assigned the allocation sequence for each stratum by using a random number table. Allocation codes were kept in sealed envelopes that were sent to the principle investigator of this clinical trial, and then transferred to the investigators at each study site before randomisation. Allocation could not be masked for patients and their clinicians. The initial corticosteroid treatment was to be started within 15 days of the randomisation.

Statistical methods

All analyses were performed on an intention-to-treat basis. Data are shown as mean±SD. Continuous variables were compared using Student's t-test. χ^2 test or Fisher's exact test was appropriately used for the comparison of proportions. The Kaplan-Meier survival analysis and a Cox proportional hazards model were used to compare the length of time without a relapse and to calculate the HR along with the 95% CI. We included the data of allocation (the maintenance therapy group or the cessation group) in the Cox proportional hazards model, while no other covariates were included. Statistical analyses were performed using the SPSS V.17.0 statistical analysis software (SPSS, Chicago, Illinois, USA) and the R software V.3.2.4 (http://www.r-project.org). A two-sided p value of <0.05 was considered statistically significant.

RESULTS

Enrolment, baseline characteristics and interventions

By the end of March 2012, 131 patients with AIP diagnosed according to the JPS2006 were assessed for eligibility. Eighty-two patients were excluded, and 49 patients were enrolled (figure 2). Among the 49 patients, 44 patients were diagnosed as definitive, 3 patients as probable and 2 patients as AIP-not otherwise specified according to the ICDC. Thirty patients were randomly assigned to the maintenance therapy group, and 19 patients were assigned to the cessation group. For randomised allocation, 31 blocks were generated but only 3 (9.7%) blocks were filled with four cases. Otherwise, 21 blocks contained only one case, 5 blocks contained two cases and 2 blocks contained three cases. The baseline characteristics of the patients were not different between the two groups (table 1). Known risk factors for disease relapse including proximal biliary involvement[9 14] and presentation with diffuse pancreatic enlargement[19 20] were not different between the two groups. Twenty-six of the 49 patients had diabetes mellitus at the enrolment; blood glucose levels were controlled using insulin in 10 patients and using oral antidiabetic medicines in 9 patients. Remission was induced in all of the 49 patients within 12 weeks from the start of PSL administration. The short-term maintenance doses of PSL after the induction of remission were not different between the maintenance therapy group (5.42 ±1.15 mg/day; mean±SD) and the cessation group (5.53 ±1.34 mg/day; mean±SD) (p=0.76).

The distribution of the long-term maintenance PSL dosage in patients assigned to the maintenance therapy group was 10 mg/day in one patient, 7.5 mg/day in 3 patients and 5 mg/day in 21 patients. In five patients, the maintenance treatment was conducted at 2.5 mg/day. Because all analyses were performed on an intention-to-treat basis, these five cases were also included in the analysis. During the 3-year follow-up period, two patients

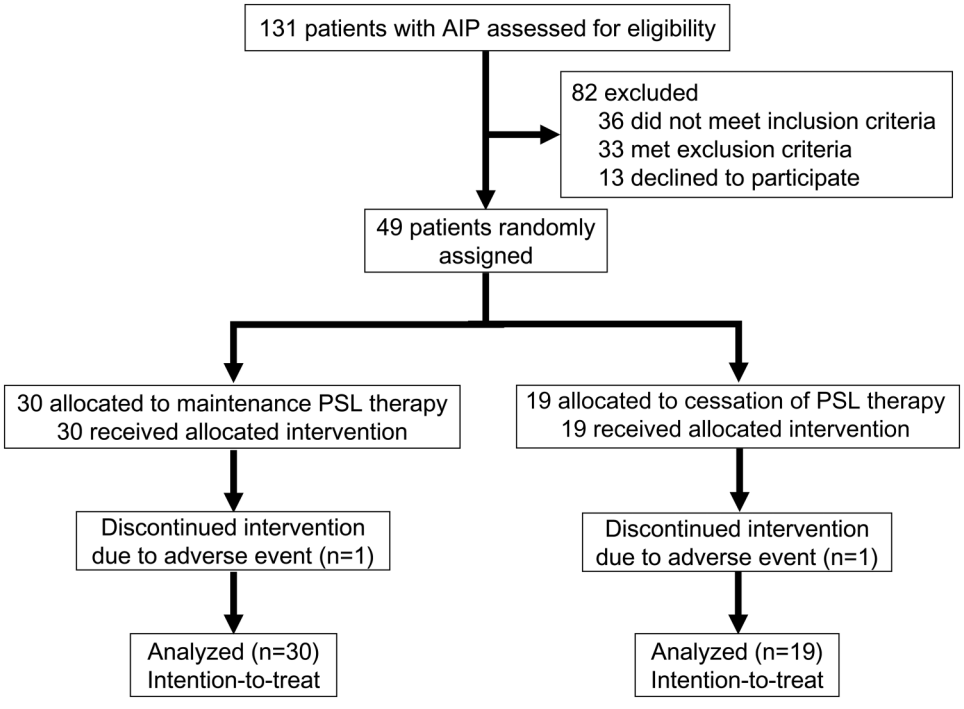


Figure 2 CONSORT 2010 Flow Diagram. One hundred thirty-one patients with autoimmune pancreatitis (AIP) diagnosed according to the JPS2006 were assessed for eligibility. Eighty-two patients were excluded, and 49 patients were enrolled. Thirty patients were randomly assigned to the maintenance therapy group, and 19 patients were assigned to the cessation group. Two patients (one in the maintenance treatment group and one in the cessation group) discontinued intervention due to adverse events. Forty-nine patients were analysed on an intention-to-treat basis. PSL, prednisolone.

Table 1 Baseline characteristics of the patients stratified by the allocation

	Maintenance therapy group (n=30)	Cessation group (n=19)	p Value
Age (mean ±SD)	63.4±7.7	63.1±10.0	0.90
Gender, male (%)	22 (73.3%)	15 (78.9%)	0.74
Diagnosis based on ICDC			0.49
Definitive	26 (86.7%)	18 (94.7%)	
Probable	3 (10%)	0 (0%)	
AIP-NOS	1 (3.3%)	1 (5.3%)	
Parenchymal imaging			0.56
Diffuse	14 (46.7%)	11 (57.9%)	
Segmental/focal	16 (53.3%)	8 (42.1%)	
Ductal imaging			0.30
Long	13 (43.3%)	10 (52.6%)	
Segmental	17 (56.7%)	8 (42.1%)	
Other	0 (0%)	1 (5.3%)	
IgG4 (mg/dL; (mean ±SD))	532.9±617.2	387.3±273.2	0.34
OOIs*			
Cases with OOIs	19 (63.3%)	12 (63.2%)	1.00
Bile duct (proximal)	12 (40.0%)	6 (31.6%)	0.55
Bile duct (distal only)	5 (16.7%)	2 (10.5%)	0.69
Retroperitoneal fibrosis	1 (3.3%)	2 (10.5%)	0.55
Sialadenitis, dacryoadenitis	4 (13.3%)	6 (31.6%)	0.16
Interstitial nephritis	2 (6.7%)	2 (10.5%)	0.64
Diabetes mellitus	14 (46.7%)	12 (63.2%)	0.38

*Including overlapping cases.
AIP-NOS, autoimmune pancreatitis-not otherwise specified; ICDC, International Consensus Diagnostic Criteria; OOIs, other organ involvements.

(one patient in the maintenance therapy group and one in the cessation group) discontinued intervention due to serious adverse events (figure 2). In the maintenance therapy group, one patient was diagnosed as having pancreatic cancer and discontinued intervention at 441 days. The patient received chemotherapy, but died at 898 days and could not complete the 3-year follow-up period. In the cessation group, one patient was diagnosed as having idiopathic thrombocytopenic purpura with the need of readministration of PSL, and discontinued the intervention at 253 days.

Relapse rate

Relapses occurred within 3 years in 11 out of 19 patients originally assigned to the cessation group, and in 7 of 30 patients in the maintenance therapy group. In the maintenance therapy group, the long-term maintenance PSL dosage at the time of relapses was 7.5 mg/day in one patient and 5 mg/day in 4 patients. Two patients stopped taking PSL of their own volition and relapsed. Again, these two cases were also included in the intention-to-treat analysis. Relapses developed in the cessation group at 517±286 days (mean±SD; n=11) and in the maintenance therapy group at 575±287 days (mean±SD; n=7). Relapses occurred in the pancreas in eight cases, outside the pancreas in eight cases and both in and outside the pancreas in two cases. All of the cases with biliary relapses presented increased hepatobiliary enzymes and strictures of the bile ducts on MRCP and/or endoscopic retrograde cholangiopancreatography. The cumulative relapse rates at 1, 2 and 3 years were 3/19 (15.8%), 9/19 (47.4%) and 11/19 (57.9%), respectively, in the cessation group, and 2/30 (6.7%), 5/30 (16.7%) and 7/30 (23.3%), respectively, in the maintenance therapy group. The relapse rate over 3 years was significantly lower in the maintenance therapy group than that in the cessation group (p=0.011; HR: 0.29 (95% CI 0.11 to 0.75)). All relapsed cases were treated with readministration or dose up of PSL and achieved remission, again.

Figure 3 shows the Kaplan-Meier estimates of the relapse-free rates for the two groups. The Kaplan-Meier estimate of the relapse rate at 3 years was 23.8% (95% CI 6.7% to 37.8%) in the maintenance therapy group and 60.9% (95% CI 30.3% to 78.0%) in the cessation group. The relapse-free survival was significantly longer in the maintenance therapy group than that in the cessation group (p=0.007 by a log-rank test).

Serious adverse events

In addition to the two cases described above, two cases in the maintenance therapy group developed serious adverse events. One patient was diagnosed as having early gastric cancer and underwent total gastrectomy. Another patient was diagnosed as having arteriosclerosis obliterans just before the end of the 3-year follow-up period and completed follow-up. All of the serious adverse events were judged as not directly related to the corticosteroid treatment by the data and safety monitoring board.

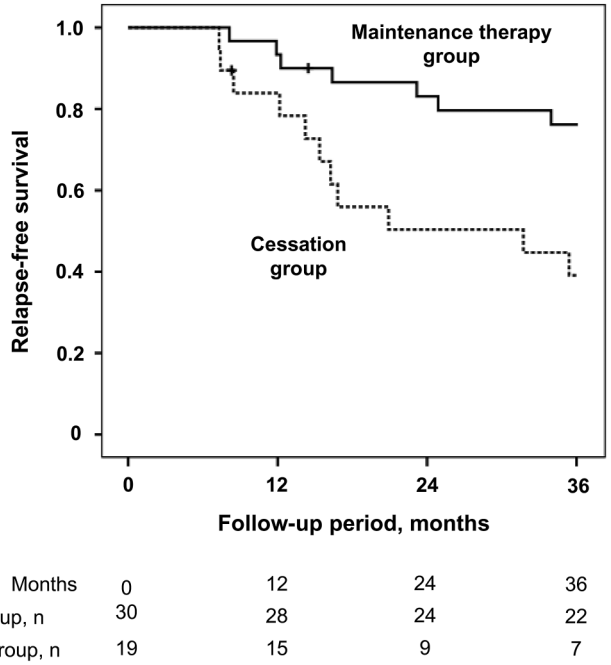
Corticosteroid-related complications

None of the 49 enrolled subjects developed serious infection, lumbar vertebral fracture, avascular necrosis of the femoral head or psychosis during the follow-up. Twenty-three patients did not have diabetes before the administration of PSL. Glucose tolerance could be compared between that at the enrolment and at the end of the 3-year follow-up period or the time of relapse in 46 patients. None of the 21 patients without diabetes at the enrolment developed diabetes. Glucose tolerance was aggravated in 7 patients (3 in the maintenance therapy group and 4 in the cessation group), improved in 8 patients (4 in the maintenance group and 4 in the cessation group) and unchanged in 10 patients (6 in the maintenance group and 4 in the cessation group). Changes in the glucose tolerance did not significantly differ between the maintenance therapy group and the cessation group (p=0.88). There were no deaths attributable to complications from the corticosteroid therapy.

DISCUSSION

We here conducted a randomised controlled trial to clarify whether the maintenance low-dose corticosteroid therapy for a long period decreased relapses in patients with AIP. We set up a 3-year follow-up period because a multicentre study showed that most of the relapses occurred within 3 years.[8 12] We showed that the relapse-free survival was longer in the maintenance therapy group than that in the cessation group. The Kaplan-Meier estimate of the relapse rate at 3 years was 23.8% in the maintenance therapy group and 60.9% in the cessation group. These values were comparable to a previous multicentre study in Japan showing that 10/38 (26.3%) cases relapsed during the maintenance PSL therapy and 12/26 (46.2%) cases did after discontinuing the therapy.[15] To our knowledge, this is the first randomised controlled trial of corticosteroid therapy in patients with AIP. Although it was suggested by retrospective studies,[8 9 16 21] our results showed that maintenance therapy until 3 years might be useful for the prevention of relapses in patients with AIP.

Previous studies showed that many patients who achieved remission relapsed soon after the cessation of corticosteroid treatment.[22 23] In a retrospective study from Pittsburgh, 9 out



Months	0	12	24	36
Maintenance therapy group, n	30	28	24	22
Cessation group, n	19	15	9	7

Figure 3 Kaplan-Meier estimates of the relapse-free survival for the maintenance therapy group and the cessation group. The cumulative relapse-free survival was calculated using the Kaplan-Meier method and compared using a log-rank test. Censored subjects are indicated on the Kaplan-Meier curve as tick marks. The lower chart shows the number of subjects according to the allocation at each time point.

of 15 (60%) patients who achieved complete remission developed relapses within 8–12 weeks after the corticosteroid cessation.[22] In a prospective, but not randomised controlled, study reported from the UK, 48/96 (50%) relapsed at a median time of 4.6 months after stopping the first course of corticosteroid treatment, with two of these patients relapsing while taking steroids.[23] Overall, it was reported that nearly a third of the patients with AIP required maintenance therapy to prevent frequent relapses.[11] In this study, relapses developed in the cessation group at a mean time of 17 months, approximately 11 months after the cessation of PSL treatment. One reason for the relatively longer time to relapses in this study might be that the low-dose corticosteroid maintenance therapy was administered until 26 weeks even in the patients assigned to the cessation group.

Relapses are multifaceted; they may be symptomatic, radiological, serological or histological.[24] The definitions of relapse have varied among previous studies. In the case of a study dealing with IgG4-related cholangitis, relapses were classified as biochemical relapses (increase in liver enzyme levels >2 folds) and (ii) serological relapses (increase in serum IgG4 level >2 folds). Abnormalities on imaging studies were not required to diagnose relapses. Kubota *et al*[20] defined relapses as a recurrence of symptoms with abnormalities on imaging studies, associated with elevations of IgG or IgG4. In this study, biochemical and serological recurrences such as increased liver enzymes and IgG4 alone were not considered relapses, and radiological evidence such as diffuse or segmental reswelling of the pancreas, renarrowing of the MPD and segmental/multiple stricture of the bile ducts were required for the diagnosis of relapse. In addition, all cases were reviewed centrally to validate the diagnosis.

Maintenance therapy with corticosteroid for years even at low doses might be associated with treatment-related morbidity in AIP.[25] This is a serious concern because AIP mostly occurs in middle aged to elderly who are at high-risk for the corticosteroid-related complications.[5 26] There are few studies dealing with the threshold of serious corticosteroid-related complications in patients with AIP. Shimizu *et al*[21] reported that the cumulative amount of corticosteroid was significantly higher in patients with serious side effects than in those without (12 645 vs 7322 mg; p=0.041). In the receiver operating characteristic curve analysis, the best cut-off value of cumulative corticosteroid for serious complications was 8694 mg/dL with moderate diagnostic accuracy determined using an area under the curve of 0.711. The cumulative amount of PSL administered during the 3-year maintenance therapy at 5 mg/day of PSL is well below the cut-off value of 8694 mg/dL. The cumulative amount of PSL >10 000 mg, which corresponds approximately to a 5-year maintenance therapy,[21] was a significant risk factor for the development of serious side effects. Importantly, the cumulative amounts of corticosteroid are increased in patients with relapses, because the relapsed cases are treated with readministration or dose up of PSL. Relapse was a significant independent predictive risk factor for serious corticosteroid-related complications in patients with AIP.[21] Some reports have suggested that maintenance therapy longer than 3 years is required to prevent relapses.[21 26] Obviously, the risks of corticosteroid-related complications and of disease relapses should be estimated carefully in each AIP case. For patients who are either intolerant of corticosteroids or have multiple relapses, there are other treatment options, including corticosteroid-sparing immunomodulators and B-cell depletion therapy using rituximab, which might be options to avoid increased cumulative amounts of PSL.[27 28] However, the high medical cost of these drugs might be another important issue.

In this study, one patient was diagnosed as having pancreatic cancer at about 14 months, and one patient as having gastric cancer at about 28 months after the start of corticosteroid therapy. It remains controversial whether AIP is a risk factor for pancreatic cancer.[29–31] In the nationwide survey in Japan,[5] malignant tumours were found in 109 (11.8%) out of 923 patients with AIP during the mean follow-up period of 4.8 years, but only seven cases were pancreatic cancer.[5] Hart *et al*[29] reported that all cancer risk is not higher in patients with AIP than that in the general population. Kamisawa *et al*[30] reported that significant K-ras mutations occur most frequently in the pancreatobiliary regions of patients with AIP. It was also suggested that AIP might have an aspect of paraneoplastic syndrome.[31] Careful examination to detect and differentiate AIP from pancreatic cancer is essential in all patients with AIP.

This study has several limitations and the results should be interpreted with caution. First, the sample size was small. This study was conducted as a research project of the Research Committee of Intractable Pancreatic Diseases in Japan (Principal Investigator: TS) with financial support provided by the Ministry of Health, Labour and Welfare of Japan. Due to the scheduled termination of the research committee in March 2014, we could not further extend the recruiting period to increase the sample size. Second, the numbers were imbalanced between the groups and selection bias might exist. For the allocation, subjects were stratified for study sites, age and gender. Thirty-one blocks were generated for the allocation, but only 3 (9.7%) blocks were filled by four cases. The unbalanced allocation of patients was due to the incomplete recruitment of patients in the remaining 28 blocks. If the subjects had been stratified based on fewer factors, the size of each block would have been smaller and the allocation would have been more balanced. Importantly, the baseline characteristics of the patients were not different between the two groups. Third, AIP was diagnosed based on the JPS2006, because the diagnostic criteria currently used such as the ICDC and the JPS2011 were not proposed at the start of this study. Lastly, allocation could not be masked for patients and their physicians due to the study design. Despite these limitations, our study is the first randomised controlled trial to show that maintenance corticosteroid therapy reduced relapses in patients with AIP. Further studies based on the ICDC would be warranted to confirm our findings in larger series.

In conclusion, our results suggested that maintenance corticosteroid therapy might be effective in reducing relapses. Low-dose maintenance corticosteroid therapy for a long period would be an option to decrease relapses in patients with AIP, especially those with high disease activity and risk of relapse. Further studies on long-term effects of the maintenance therapy as well as identification of biomarkers predicting relapses are needed.

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Randomised controlled trial of long-term maintenance corticosteroid therapy in patients with autoimmune pancreatitis

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