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PANCREATOBILIARY

Type 1 Autoimmune Pancreatitis in Europe: Clinical Profile and Response to Treatment

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Abbreviations used in this paper: AIP, autoimmune pancreatitis; CI, confidence interval; ICDC, International Consensus Diagnostic Criteria; IQR, interquartile range; NOS, not-otherwise-specified; OR, odds ratio.

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BACKGROUND & AIMS: **Autoimmune pancreatitis (AIP) is an immune-mediated disease of the pancreas with distinct pathophysiology and manifestations. Our aims were to characterize type 1 AIP in a large pan-European cohort and study the effectiveness of current treatment regimens.**

METHODS: **We retrospectively analyzed adults diagnosed since 2005 with type 1 or not-otherwise-specified AIP in 42 European university hospitals. Type 1 AIP was uniformly diagnosed using specific diagnostic criteria. Patients with type 2 AIP and those who had undergone pancreatic surgery were excluded. The primary end point was complete remission, defined as the absence of clinical symptoms and resolution of the index radiologic pancreatic abnormalities attributed to AIP.**

RESULTS: **We included 735 individuals with AIP (69% male; median age, 57 years; 85% White). Steroid treatment was started in 634 patients, of whom 9 (1%) were lost to follow-up. The remaining 625 had a 79% (496/625) complete, 18% (111/625) partial, and 97% (607/625) cumulative remission rate, whereas 3% (18/625) did not achieve remission. No treatment was given in 95 patients, who had a 61% complete (58/95), 19% partial (18/95), and 80% cumulative (76/95) spontaneous remission rate. Higher (≥0.4 mg/kg/day) corticosteroid doses were no more effective than lower (<0.4 mg/kg/day) doses (odds ratio, 0.428; 95% confidence interval, 0.054–3.387) and neither was a starting dose duration >2 weeks (odds ratio, 0.908; 95% confidence interval, 0.818–1.009). Elevated IgG4 levels were independently associated with a decreased chance of complete remission (odds ratio, 0.639; 95% confidence interval, 0.427–0.955). Relapse occurred in 30% of patients. Relapses within 6 months of remission induction were independent of the steroid-tapering duration, induction treatment duration, and total cumulative dose.**

CONCLUSIONS: **Patients with type 1 AIP and elevated IgG4 level may need closer monitoring. For remission induction, a starting dose of 0.4 mg/kg/day for 2 weeks followed by a short taper period seems effective. This study provides no evidence to support more aggressive regimens.**

Keywords: Autoimmune Pancreatitis; IgG4-Related Disease; IgG4-Related Pancreatitis.

Autoimmune pancreatitis (AIP) is an immune-mediated disease of the pancreas.[1] Currently, 2 subtypes have been established.[1] Type 1 AIP is the pancreatic manifestation of IgG4-related disease.[2] Type 2 AIP is known as idiopathic duct-centric pancreatitis and is limited to the pancreas.[3] Type 1 is more common than type 2, and represents more than 90% of patients diagnosed with AIP.[4] Type 2 AIP might be overlooked, because there is no serologic marker available, making a histologic specimen essential for a definite diagnosis.

Several diagnostic scoring systems have been proposed during the past few decades, based on a combination of clinical, radiologic, serologic, and pathologic characteristics, until eventually the International Consensus Diagnostic Criteria (ICDC) were developed.[1] Besides type 1 and type 2 AIP, the ICDC defines a third group of individuals who do not fulfill the criteria for either type, the so-called not-otherwise-specified (NOS) AIP.[1]

The standard therapy for AIP is steroids,[5] with a very high response rate (>95% of cases).[4,6,7] Consensus

guidelines recommend treatment with an initial dose of prednisone 0.6–1.0 mg/kg/day with a minimum of 20 mg/day, for 2–4 weeks, to induce remission. Afterward, it is recommended to gradually taper the dose, with a total treatment duration of at least 12 weeks.[5,8] As an alternative to steroids, several studies have shown good results for rituximab, albeit in small numbers of patients.[9–11] After inducing remission of the disease, relapses are seen in around 30% of patients with type 1 AIP, and only in 9% of patients with type 2.[4] For relapses, it is recommended to readminister steroids.[5] However, the level of evidence supporting the previously mentioned treatment recommendations is generally low.[5,8] Data on the optimal treatment regimen are limited, almost exclusively retrospective, and large-scale studies are scarce, mostly because AIP is a rare disease.

In Japan, its annual incidence is estimated at 3.1 per 100,000 per year.[12] In Europe, this is thought to be even lower, possibly 0.29 per 100,000 per year.[13] In the United States, its exact incidence is unknown but may be comparable, because the incidence of any manifestation of IgG4-related disease is estimated at 1.20 per 100,000 per year.[14] The difference in incidence between Japan and the Western world might partially be explained by higher awareness of AIP in Asia, where it was first described as a distinct disease. This is illustrated by the increase in registered incidence in Japan, from 0.71 per 100,000 in 2002 to 3.1 in 2016.[12,15] European populations might differ in disease characteristics and treatment response, but have been reported on only in small single-country cohort studies of up to 160 patients,[10] and in international studies combined with Asian and North American patients.[4,16,17]

Our primary objectives were: to describe the clinical profile of a large pan-European cohort of patients with type 1 AIP; and to compare the effectiveness of different steroid treatment regimens. Our secondary objectives were: to identify factors associated with successful remission induction; and to compare the effectiveness of steroids and rituximab in treating relapse of disease.

What You Need to Know

Background

Type 1 autoimmune pancreatitis is a rare immune-mediated disease. There are no large-scale studies in European patients, and evidence on the optimum steroid treatment regimen is lacking.

Findings

Induction of complete remission occurred irrespective of the starting dose or starting dose duration. Early relapse occurred irrespective of the steroid tapering duration, induction treatment duration, and total cumulative dose.

Implications for patient care

To achieve complete remission, a steroid starting dose of 0.4 mg/kg/day with a minimum of 20 mg, for 2 weeks, followed by a tapering regimen less than 12 weeks was effective. We found no evidence to support a higher starting dose, longer starting dose duration, or long taper period.

Methods

Study Design and Setting

This study is part of the PrescrAIP study (A Pan-European Study on Current Treatment Regimens of Auto-Immune Pancreatitis).[18] The PrescrAIP study is a retrospective, observational cohort study performed in 42 European university hospitals. The study received institutional review board approval as required by the respective national laws and regulations, and was performed according to the declaration of Helsinki.

Population and Data Collection

The PrescrAIP study protocol has been published in detail previously.[18] The PrescrAIP database includes all adults presumed to have AIP since 2005. Data were retrospectively collected from the hospitals' medical records by use of a REDCap-based electronic case record form, including variables on demography and epidemiology, disease characteristics (radiologic, laboratory, and clinical), treatment (type, dose, duration), and clinical outcomes. For data entry, a definition of the type of AIP or the use of specific diagnostic criteria was not a prerequisite. Instead, to minimize heterogeneity between centers, all patients were centrally and uniformly classified according to the diagnostic criteria most often used in Europe: U-AIP,[19,20] HISORt,[21] revised HISORt,[22] and the ICDC.[1] For the current analysis, we excluded all patients who met none of these diagnostic criteria. Second, we excluded patients with type 2 AIP (as diagnosed through the ICDC), because the diagnosis could not be histologically confirmed in most cases due to the retrospective nature of the study. Third, we excluded patients who underwent partial or total surgical resection of the pancreas. Lastly, any double inclusion of patients at multiple study centers was corrected for by cross-referencing based on date of birth, sex, and date of first symptoms.

Study End Points

The primary end point was complete remission of disease (defined as the absence of clinical symptoms and resolution of the index radiologic pancreatic abnormalities attributed to AIP). Partial remission was defined as either the absence of symptoms or resolution of radiologic abnormalities, but not both.

The secondary study end point was relapse of the disease (defined as the recurrence of symptoms and/or the redevelopment of radiologic abnormalities) after

initial induction of remission. Relapse within 6 months of remission after steroid treatment was considered a failure of the tapering regimen.[18]

Statistical Analysis

We assessed differences in patient and disease characteristics using the independent samples t-test, Mann-Whitney *U* test, chi-square, and Fisher exact test. For the analysis of the primary end point after induction treatment, we divided patients in groups according to international consensus treatment recommendations.[5,8] The groups were based on the steroid starting dose (absolute dose: <20, 20–39, 40–59, or 60–79 mg/day; and relative dose: <0.6, 0.6–0.8, or >0.8 mg/kg body weight/day), starting dose duration (1–2, 3–4, or >4 weeks), tapering duration (<6 weeks, 6–10 weeks, or >10 weeks), remission induction treatment duration (<12 or ≥12 weeks), and total cumulative dose (<25 or ≥25 mg/kg). We compared the primary and secondary end points and corrected for confounders using multivariable logistic regression analysis. A time-to-event analysis with a Kaplan-Meier curve was impossible to conduct because the underlying assumption that censoring of patients occurred at random could not be met. We also analyzed the primary end point after relapse treatment, comparing steroid treatment with rituximab. A *P* value of < .05 (2-sided) was considered statistically significant. Statistical analysis was performed using Statistical Package for the Social Sciences 23 (IBM Corporation, Armonk, NY).

Results

Study Population

A total of 1079 adults were registered in the PrescrAIP database. We excluded 344 patients because of not meeting any of the diagnostic criteria (177), a classification as probable (10) or definitive (9) type 2 AIP according to the ICDC, or having undergone pancreatic surgical resection (148). The remaining 735 type 1 AIP and type NOS patients were included in the analysis (69% male; median age, 57 years; interquartile range [IQR], 27; 85% White). Detailed patient and disease characteristics with stratification on remission induction treatment are shown in Table 1. Supplementary Table 1 shows the cohort characteristics stratified on fulfillment of the different diagnostic criteria.

Remission Induction Treatment Choice

Supplementary Figure 1 illustrates the treatment strategies and outcomes within the cohort (the timeline of the disease course and treatment duration were not incorporated in the figure). At diagnosis, 631 (86%) patients underwent remission induction treatment with steroids, 2 (0.3%) patients underwent rituximab treatment, and 95 (13%) initially underwent no treatment (of which 3 eventually switched to steroids, resulting in 634 [86%] patients under steroid remission induction treatment). The reason to choose rituximab as initial therapy was a contraindication for steroids in both patients. They both received 2 doses of 1000 mg 2 weeks apart and reached remission (100%).

For those initially not treated, reasons to withhold treatment were: spontaneous relief of symptoms in 70 (74%) patients; diabetes mellitus in 3 (3%); a contraindication for steroids in 2 (2%); and unreported in 5 (5%) patients. Spontaneous remission was reached completely in 58 (61%, Supplementary Figure 1), partially in 18 (20%), and not at all in 3 (3%) patients. Sixteen patients were lost to follow-up.

Patients initially selected for treatment with steroids were compared with patients initially not undergoing treatment. At baseline, they more often had symptoms (96% vs 92%; $P = .032$; Table 1), presented with obstructive jaundice (56% vs 27%; $P < .001$), or had other organ involvement (47% vs 28%; $P = .001$). They also more often had histology available (37% vs 22%; $P = .015$).

Steroid Treatment Effectiveness

Of the 634 steroid-treated patients, 454 (72%) reached complete remission at the first evaluation, 149 (24%) partial remission (cumulative remission 95%; 603/634), and 24 (4%) did not reach remission at the first evaluation. Seven (1%) were lost to follow-up at this point. The 149 patients with partial remission either: continued on steroids (92; 62%); were switched to azathioprine (21; 14%), rituximab (5; 3%), methotrexate (2; 1%), or another treatment (9; 6%); or were lost to follow-up (20; 13%). After changing treatment, the remission rate was 65% (61% for steroids, 72% for azathioprine, 100% for rituximab, 100% for methotrexate).

The 24 individuals who did not reach remission under initial steroid therapy either continued on steroids (10; 42%); switched to azathioprine (7; 29%), rituximab (3; 13%), or another treatment not specified (2; 8%); or were lost to follow-up (2; 8%). In this group the remission rate after treatment change was 50% (40% for steroids, 29% for azathioprine, and 100% for rituximab). In the combined group of 173 patients with either partial or no remission, the remission rates after treatment change were 61% (62/102) for continuing steroids, 61% (17/28) for azathioprine, 100% (8/8) for rituximab, and 100% (2/2) for methotrexate.

Overall, of the 634 patients who started steroid treatment, 9 (1%) individuals had been lost to follow-up at some point. Of the remaining 625 patients, 496 (79%) eventually reached complete remission under steroid monotherapy, 111 (18%) reached partial remission (cumulative remission 97%; 607/625), and 18 (3%) no remission.

Risk Factors for Not Reaching Complete Remission

When analyzed in the entire cohort (N = 735), an elevated IgG4 level was independently and inversely

Table 1. Characteristics of Patients With Type 1 AIP Stratified on Remission Induction Treatment at Diagnosis

	Total (N = 735)	Steroid treatment (n = 631)	No treatment (n = 95)	*P* value
Patient characteristics				
Male sex	509 (69)	444 (70)	62 (65)	.313
Age, median (IQR), *y*	57 (27)	57 (26)	54 (27)	.834
White	626 (85)	537 (85)	81 (85)	.322
BMI, mean (SD)	25 (4)	25 (5)	25 (3)	.704
Smoking, ever	276 (38)	231 (37)	42 (44)	.194
Alcohol use, ever	230 (31)	196 (31)	32 (34)	.673
History of acute pancreatitis	102 (14)	82 (13)	17 (18)	.179
History of IBD	73 (10)	61 (10)	10 (11)	.784
History of other autoimmune disease	122 (17)	100 (16)	19 (20)	.319
Diabetes mellitus	213 (29)	186 (30)	25 (26)	.533
Pancreatic exocrine insufficiency	190 (26)	160 (25)	27 (28)	.632
Blue collar worker	246 (34)	217 (34)	26 (27)	.975
Symptoms				
None (incidental finding)	32 (4)	23 (4)	8 (8)	.032
Obstructive jaundice	381 (52)	352 (56)	26 (27)	< .001
Abdominal pain	471 (64)	400 (63)	63 (66)	.580
Anorexia	84 (11)	76 (12)	8 (8)	.390
Weight loss	270 (37)	241 (38)	28 (30)	.101
Diarrhea	82 (11)	74 (12)	6 (6)	.158
Malaise	85 (12)	76 (12)	8 (8)	.390
Nausea	68 (9)	59 (9)	9 (10)	1.000
Night sweats	20 (3)	17 (3)	3 (3)	.737
Acute pancreatitis	76 (10)	54 (8)	20 (21)	< .001
Radiology				
Parenchymal enlargement	653 (89)	560 (89)	85 (90)	1.000
Diffuse	364 (50)	312 (49)	47 (50)	
Segmental	289 (39)	248 (39)	38 (40)	
Rim-like enhancement	125 (17)	112 (18)	12 (13)	.429
Focal mass	231 (31)	201 (32)	30 (32)	.551
Narrowing of main pancreatic duct	224 (31)	204 (32)	27 (28)	.750
Diffuse	57 (8)	53 (8)	3 (3)	
Long (one-third length)	66 (9)	58 (9)	8 (8)	
Segmental	101 (14)	86 (14)	15 (16)	
Other organ involvement				
Yes	329 (45)	297 (47)	27 (28)	.001
Orbit	12 (2)	11 (2)	2 (2)	
Bilateral salivary glands	54 (7)	49 (8)	5 (5)	
Thyroid	13 (2)	12 (2)	2 (2)	
Pulmonary	38 (5)	36 (6)	3 (3)	
(Peri)aorta	17 (2)	14 (2)	1 (1)	
Retroperitoneal fibrosis	24 (3)	22 (4)	0 (0)	
Sclerosing cholangitis/biliary tree	262 (36)	240 (32)	19 (20)	
Renal	49 (7)	46 (7)	2 (2)	
Serology				
IgG4 > 1x ULN	440 (60)	385 (61)	51 (54)	.538
IgG4 > 2x ULN	279 (38)	249 (40)	29 (31)	.226
Pathology				
No	299 (41)	244 (39)	48 (51)	.028
Cytology	182 (25)	154 (24)	26 (27)	.533
Histology (not surgically resected)	254 (35)	233 (37)	21 (22)	.005

NOTE. Data presented as number (%) unless otherwise indicated.
AIP, autoimmune pancreatitis; BMI, body mass index; IBD, inflammatory bowel disease; IQR, interquartile range; SD, standard deviation; ULN, upper limit of normal.

associated with reaching complete remission (66% of those with elevated levels reached complete remission vs 76% of those without; odds ratio [OR], 0.613; 95% confidence interval [CI], 0.409–0.917; Table 2 and Figure 1). A subgroup analysis was performed in the 95 initially untreated patients and the 631 initially steroid-

Table 2. Regression Analysis of Factors Associated With Reaching Complete Remission (N = 735)

	OR (95% CI)	
	Univariable	Multivariable
Male sex	0.944 (0.659–1.353)	—
Age, *y*	0.994 (0.984–1.003)	—
BMI	1.014 (0.966–1.065)	—
History of IBD	0.718 (0.426–1.211)	—
History of other autoimmune disease	1.165 (0.742–1.830)	—
Acute pancreatitis at presentation	0.605 (0.367–0.998)	0.575 (0.325–1.018)
Jaundice at presentation	1.176 (0.846–1.634)	—
Weight loss at presentation	0.720 (0.514–1.009)	—
Parenchymal enlargement	1.248 (0.703–2.213)	—
Focal mass	0.849 (0.596–1.212)	—
Rim-like enhancement	0.820 (0.531–1.268)	—
Any other organ involvement	0.560 (0.401–0.782)	0.552 (0.291–1.046)
IgG4-related sclerosing cholangitis	0.618 (0.440–0.868)	1.093 (0.578–2.066)
IgG4 level > 1x ULN	0.572 (0.386–0.848)	0.613 (0.409–0.917)
Histology available	1.050 (0.742–1.484)	—

BMI, body mass index; CI, confidence interval; IBD, inflammatory bowel disease; OR, odds ratio; ULN, upper limit of normal.

treated patients; the results are reported in Supplementary Tables 2 and 3 in the supplementary information.

Steroid Starting Dose and Duration

The median prednisone starting dose was 40 mg (IQR, 10 [range, 10–180]); translating to a median dose of 0.6 mg/kg/day (IQR, 0.3 [range, 0.1–2.1]). Patients were treated with the starting dose for a median of 3 weeks (IQR, 2 [range, 1–44]). Detailed patient and disease characteristics per treatment regimen group are shown in Supplementary Table 4. The number of patients per regimen group and their remission rates are shown in Figure 2. After adjustment for confounders, the only independent association with induction of complete remission was found for a dose of 20–39 mg/day when compared with 40–59 mg/day (adjusted OR, 1.873; 95% CI, 1.009–3.477). The group receiving a starting dose <20 mg/day included only 8 patients and therefore could not be properly statistically compared with higher dose groups. Overall, the results did not show a linear relationship between induction dose and remission rate, because high doses were not superior to medium doses (both for the absolute and relative to body weight dose groups; Figure 2 and Table 3).

Steroid-Tapering Regimen, Treatment Duration, and Cumulative Dose

Steroid therapy was tapered (to either maintenance therapy or complete stop) over a median period of 7 weeks (IQR, 6). The median remission induction treatment duration was 11 weeks (IQR, 8). Patients were treated with a median total cumulative dose of 26 mg/kg (IQR, 19). Of the 493 patients who reached complete remission under only steroid therapy, 45 (9%) experienced a relapse within 6 months of remission induction. There were no differences in this outcome depending on the taper period, remission induction treatment duration, or total cumulative dose (percentage per group and full results in Table 4). The only factors independently associated with fewer relapses within 6 months of remission induction were having parenchymal enlargement (OR, 0.390; 95% CI, 0.167–0.910) and being treated with (any type of) maintenance therapy (4% vs 14%; OR, 0.299; 95% CI, 0.120–0.740; Supplementary Table 5).

Relapse Treatment

The median follow-up was 30 months (IQR, 51 [range, 0–240]) for the entire cohort (N = 735) and 31 months (IQR, 49 [range, 0–240]) for the 587 individuals who reached remission of disease. Of these 587 individuals, 176 (30%) experienced 1 or more relapses, at a median of 15 months (IQR, 26 [range, 1–146]) after diagnosis. The relapse rate was lower in patients treated with (any type of) maintenance therapy (25% vs 37%; $P = .002$). Relapses were treated with steroids (117; 67%), rituximab (30; 17%), another therapy (19; 11%), not at all (5; 3%), or unknown (5; 3%). There was no

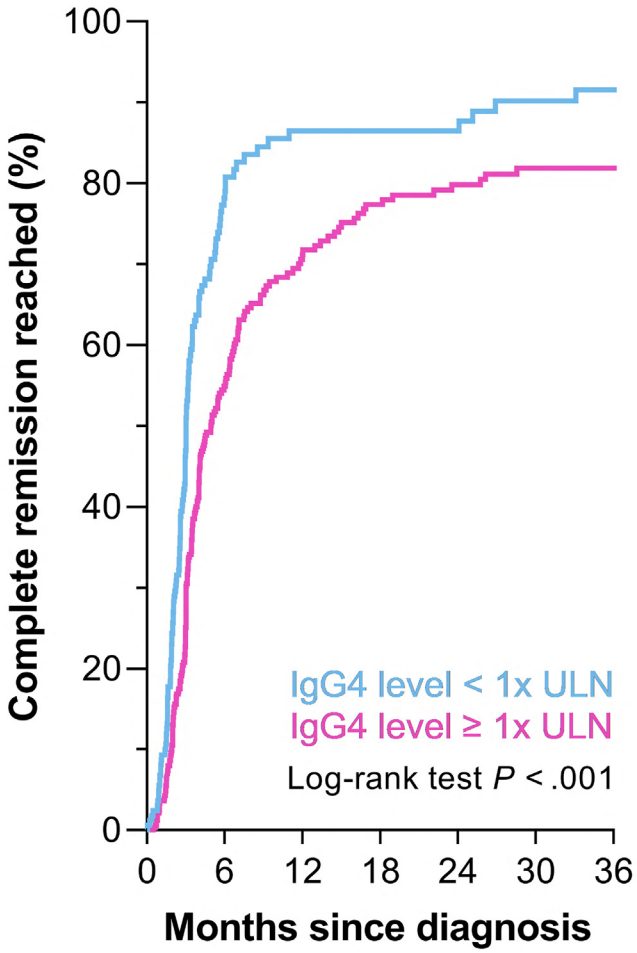

Figure 1. Complete remission stratified on elevation of IgG4 level. ULN, upper limit of normal.

difference between steroid and rituximab treatment in reaching complete remission of the relapse (78% vs 73%; $P = .450$). Full details of relapse treatment are described and shown in the supplementary information (Supplementary Table 6).

Discussion

Because of the relative rarity of AIP, large cohorts from which the optimum treatment regimen can be deduced, are lacking. We now describe the largest study on European patients with type 1 AIP and the second largest AIP study worldwide. Compared with formerly reported large (combined) cohorts from Japan, Korea, Taiwan, China, India, and the United States,[4,6,16,17,23,24] European patients with type 1 AIP seem to be younger (57 vs the reported 60–65 years) and less often male (69% vs 71%–90%), in line with a previous study by Kamisawa et al.[16] Patients' clinical presentation (eg, the proportions presenting with jaundice, weight loss) was comparable with that of Asian patients, although Asian cohorts have shown considerable heterogeneity in this aspect.[16,17,24] Radiologic characteristics were also similar to previously reported cohorts. European patients had other organ involvement in 45%, which is the same as Asian patients, but lower than that reported in North Americans (75%).[16,23] IgG4 levels were elevated in 60% of our patients, whereas most, but not all, studies in North American and Asian cohorts have reported higher numbers (range, 44%–87%).[16,17,23,24]

The treatment choices at diagnosis in our cohort correspond very well with those reported in earlier studies. Excluding those not meeting diagnostic criteria, 17% underwent surgical resection (this group was excluded from analysis), 71% steroid treatment, and 11% initially no treatment, as compared with 14%, 74%, and 7% in the international analysis by Hart et al,[4] and 13%, 73%, and 0%–16% in the combined Asian analysis by Kamisawa et al.[16] Reasons to initiate steroid treatment were the presence of symptoms, obstructive jaundice, and other organ involvement. This is in line with a recent study by Kubota et al,[25] with the European and international consensus treatment guidelines,[5,8] and in accordance with guidelines for IgG4-related disease in other organs.[26] In our analysis, an elevated serum IgG4 level was inversely associated with reaching complete remission, confirming another, earlier study by Kubota et al.[27] Currently, an elevated IgG4 level is not an indication for steroid treatment because of lack of evidence.[5,8] However, based on these results, high IgG4 levels might identify patients unlikely to reach complete remission, and that might require closer monitoring during remission induction treatment.

The rate of spontaneous remission in untreated patients is derived from small cohorts or from larger studies with different or unknown definitions of remission.[4,24] Other studies reported untreated patients together with operated patients.[6] The study best suited for comparison with ours is the one by Kubota et al,[25] who used the same definition and analyzed 97 untreated Japanese patients with type 1 AIP with elevated IgG4 levels. Their reported spontaneous complete remission rate was 56%, very similar to our 61%. Therefore, asymptomatic patients, without obstructive jaundice and other organ involvement, seem to form a subgroup in which spontaneous remission can be awaited.

The rate of complete remission after corticosteroid treatment in our cohort was 79%. On first glance this seems substantially lower than the 98% reported in Japanese patients (same definition of remission),[6,25] 96% in Chinese patients (unknown definition),[24] and 99.6% in the international analysis (unknown definition),[4] and might imply that European patients are less responsive to corticosteroid treatment. Most likely, however, methodologic differences that can only be partially resolved in our dataset, such as the time point of assessment of remission (not defined in most studies), or the strictness of assessing the resolution of clinical and radiologic signs, can explain the observed differences. When comparing the existing literature with our cumulative remission rate (97%), there does not seem to be a

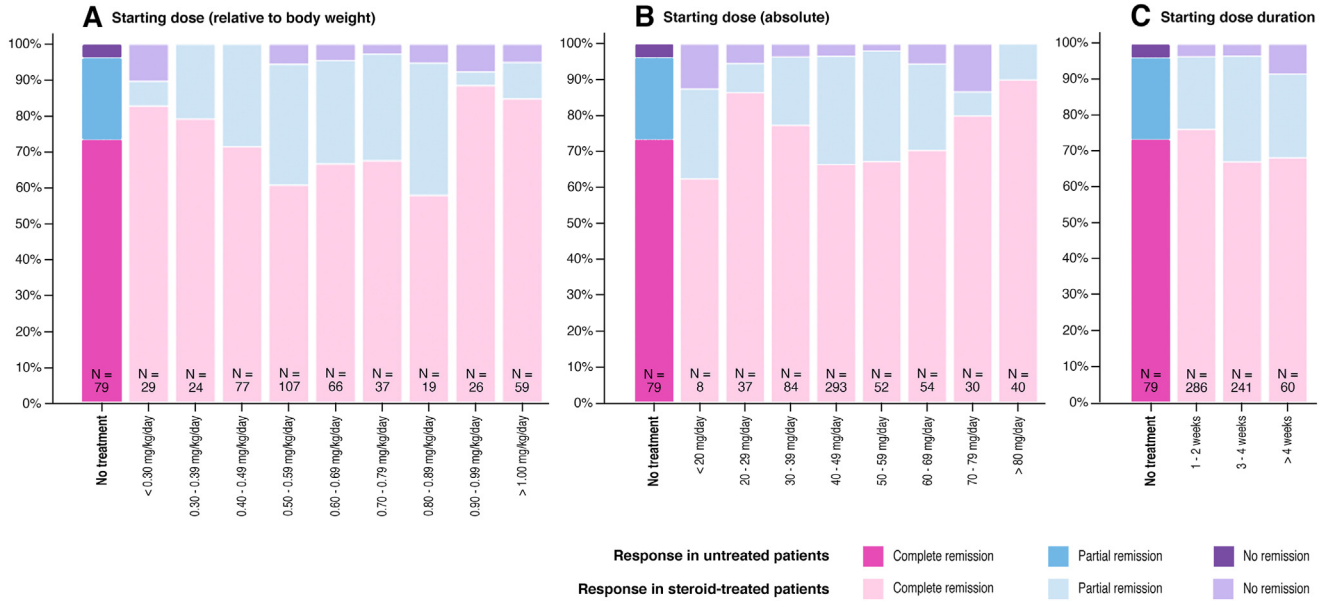

Figure 2. (*A–C*) Remission rates stratified for the different steroid remission induction treatment regimens or no treatment. Complete remission: absence of clinical symptoms and resolution of index radiologic pancreatic abnormalities attributed to autoimmune pancreatitis. Partial remission: either absence of symptoms or resolution of radiologic abnormalities. No remission: neither of the 2.

difference. However, 2 Italian studies with 74 and 86 nonsurgical patients with AIP type 1 or NOS (not included in our current cohort) reported corticosteroid remission rates (same definition in 1 study, undefined in the other) of 84% and 91%,[7,28] suggesting that European patients may indeed respond less well to treatment.

Higher steroid dosages did not result in higher remission rates, and neither did a longer duration of the starting dose, both observations in line with the few earlier studies.[6,29] Consensus treatment guidelines recommend a starting dose of at least 0.6 mg/kg/day, for up to 4 weeks.[5,8] The results of our current analysis indicate that a dose of 0.4 mg/kg/day for 2 weeks is equally effective in reaching remission in general. This would open the opportunity to reserve higher dosages and longer starting dose durations for patients at risk of not reaching remission.

Regarding the tapering of the starting dose, guidelines recommend to do this over at least 8–12 weeks,[30] 12 weeks,[5] or 12–24 weeks.[8] In our analysis, only 45 of 493 (9%) patients who reached remission under steroid therapy relapsed within 6 months of remission. Early relapse was not associated with the tapering duration, remission induction treatment duration, or cumulative

Table 3. Regression Analysis of the Effectiveness of Steroid Treatment Regimens in Inducing Complete Remission (N = 631)

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Starting dose (relative to body weight)		
Per mg/kg/day (as continuous variable)	1.686 (0.698–4.073)	0.428 (0.054–3.387)
<0.6 vs 0.6–0.8 mg/kg/day	1.071 (0.657–1.745)	1.367 (0.742–2.519)
0.6–0.8 vs >0.8 mg/kg/day	0.483 (0.254–0.917)	1.071 (0.437–2.627)
Starting dose (absolute)		
Per mg/day (as continuous variable)	1.010 (0.999–1.022)	1.000 (0.972–1.028)
<20 vs >20 mg/day	0.647 (0.153–2.738)	[b]
<20 vs 20–39 mg/day	0.412 (0.092–1.847)	[b]
20–39 vs 40–59 mg/day	2.021 (1.226–3.331)	1.873 (1.009–3.477)
40–59 vs 60–79 mg/day	0.710 (0.415–1.212)	1.106 (0.535–2.284)
Starting dose duration		
Per wk (as continuous variable)	0.941 (0.876–1.012)	0.908 (0.818–1.009)
1–2 wk vs 3–4 wk	1.563 (1.066–2.292)	1.813 (0.996–3.302)
3–4 wk vs >4 wk	0.950 (0.518–1.743)	1.143 (0.455–2.868)

CI, confidence interval; OR, odds ratio.
[a]Adjusted for the starting dose; starting dose duration; age; acute pancreatitis at presentation; jaundice at presentation; weight loss at presentation; rim-like enhancement; any other organ involvement; IgG4 level > 1x upper limit of normal.
[b]The group of <20 mg/day was of insufficient size for multivariable regression analysis.

Table 4. Regression Analysis of the Effectiveness of Steroid-Tapering Regimens in Preventing Relapse Within 6 Months of Remission Induction (N = 493)

	Early relapse, %	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Tapering duration			
Per wk (linear effect)		0.973 (0.916–1.033)	1.048 (0.812–1.352)
<6 vs 6–10 wk	9 vs 15	0.597 (0.244–1.457)	0.428 (0.120–1.529)
6–10 vs >10 wk	15 vs 10	1.508 (0.746–3.050)	0.498 (0.122–2.031)
Total remission induction treatment duration			
Per wk (linear effect)		0.973 (0.922–1.026)	0.922 (0.711–1.194)
<12 vs ≥12 wk	13 vs 11	1.256 (0.660–2.389)	1.004 (0.291–3.463)
Total cumulative dose			
<25 vs >25 mg/kg	14 vs 11	1.264 (0.608–2.631)	1.214 (0.472–3.120)
<20 vs 20–30 mg/kg	11 vs 15	0.728 (0.287–1.843)	0.809 (0.266–2.457)
20–30 vs >30 mg/kg	15 vs 12	1.338 (0.565–3.170)	1.277 (0.416–3.917)

CI, confidence interval; OR, odds ratio.
[a]Adjusted for the tapering duration; remission induction treatment duration; total cumulative dose; presenting with acute pancreatitis; IgG4 level > 1x upper limit of normal; treatment with maintenance therapy.

dose. In the study by Kamisawa et al[6] as well, 32 out of 451 (7%) patients relapsed within 6 months of steroid therapy, and there was no correlation between the relapse rate and the initial steroid dose. Therefore, there is no evidence to support a long tapering regimen over a short one, before continuing on a low-dose steroid maintenance therapy.

Strengths of our study are its size (the largest European cohort to date and the second largest worldwide), the central and uniform use of diagnostic criteria, and homogeneity of the cohort after excluding patients who underwent pancreatic surgery and type 2 AIP patients. Additionally, because of the cohort's large size we were able to correct our results for potential confounders of treatment effectiveness, such as age, acute pancreatitis at presentation, other organ involvement, and elevated IgG4 levels. Limitations of this study are its retrospective nature, the substantial number of patients lost to follow-up (20%), and the possible heterogeneity in the definition of remission and the time point of remission assessment. This, and such factors as distinct interpretations of clinical symptoms in the medical centers, might explain the observed lower cumulative remission rates in Europeans that otherwise might be caused by lower responsiveness to steroid treatment. Furthermore, demographic comparisons between European and Asian or North American AIP cohorts lack statistical assessment because no direct data-level comparison is possible. Lastly but importantly, we selected patients who met any of the diagnostic criteria used in Europe during the study period to avoid unnecessary exclusion of patients with AIP. This choice leaves room for discussion, because the U-AIP do not differentiate between type 1 and type 2, potentially influencing our results by wrongfully including type 2 patients. We have mitigated this by excluding all patients who met the ICDC criteria for type 2. In the final analyzed cohort, there were 106 patients who met the U-AIP criteria but not the ICDC criteria (for either type 1, NOS, or type 2) and thus remained unclassified. We performed a sensitivity analysis excluding this group and found no meaningful differences in the primary study outcomes (results presented in the supplementary information [Supplementary Tables 7–9]), leaving the conclusions of the study intact.

In conclusion, our findings indicate that European patients with type 1 AIP might be demographically different from Asian and North American patients with AIP, with a younger age of onset and lower male/female ratio. However, other aspects can be harmonized with existing studies in other populations, because clinical presentation, radiologic characteristics, and other organ involvement seem comparable. In contrast, Europeans seem to respond slightly less well to steroid treatment than do Asian patients. Elevated IgG4 levels may be useful as a predictor for not reaching complete remission. Regarding treatment effectiveness, a steroid starting dose of 0.4 mg/kg/day with a minimum of 20 mg, for 2 weeks, followed by a tapering regimen less than 12 weeks, was shown to be equally effective as higher doses in our study. For achieving disease remission, we provide no evidence to support high dosages, long starting dose durations, or a long tapering regimen.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2023.12.010.

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Conflicts of interest

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Supplementary Material

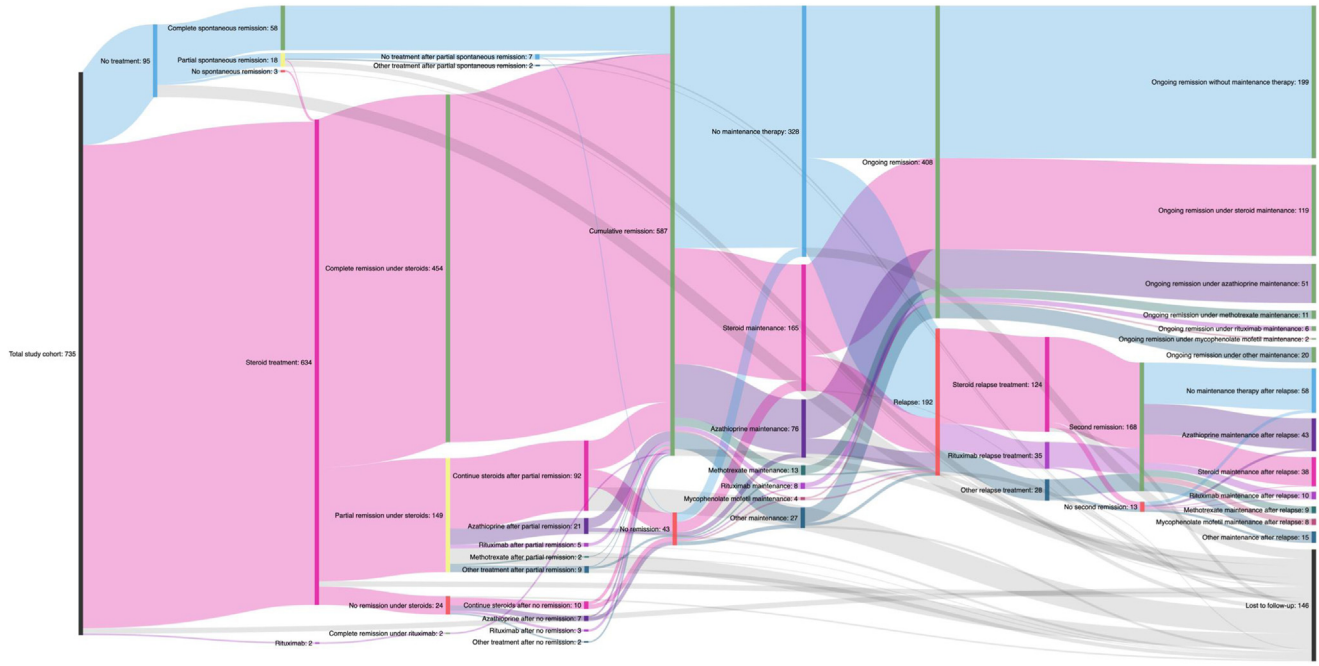
Risk Factors for Not Reaching Complete Remission in Subgroup Analysis

When potential risk factors were analyzed in the subgroup of 95 patients who were initially untreated, presenting with weight loss was associated with a lower likelihood to spontaneously reach complete remission (OR, 0.167; 95% CI, 0.055–0.508; no multivariable analysis performed; Supplementary Table 2). In the subgroup of 631 patients who were initially selected for steroid therapy, presenting with acute pancreatitis (OR, 0.463; 95% CI, 0.242–0.884) and an elevated IgG4 level (OR, 0.639; 95% CI, 0.427–0.955) were independently and inversely associated with complete remission. Also in this group, any other organ involvement and IgG4-related sclerosing cholangitis were not independent predictors (Supplementary Table 3).

Relapse Treatment

The 587 individuals who reached remission of disease (initially or after a treatment change) were followed for a median of 31 months (IQR, 49; range, 0–240). The overall relapse rate was 30% (176 of 587), occurring at a median of 15 months (IQR, 26; range, 1–146) after diagnosis. One hundred and eight (18%) patients had 1 relapse, 56 (10%) experienced multiple relapses (median, 2; IQR, 1; range, 2–8), and 12 (2%) patients had an unknown number of relapses. The relapse rate in patients untreated at diagnosis was 15%, versus 33% in patients who initially started on steroids ($P = .003$). The relapse rate was also lower in patients treated with any type of maintenance therapy (25% vs 37%; $P = .002$).

Relapses were treated with steroids (117; 67%), rituximab (30; 17%), another therapy (19; 11%), not at all (5; 3%), or unknown (5; 3%). The other therapy options included combinations of azathioprine, methotrexate, tacrolimus, mycophenolate-mofetil, 6-mercaptopurine, budesonide, cyclophosphamide, or surgery in 1 case. Details of the steroid and rituximab treatment regimens are shown in Supplementary Table 6. There was no difference between the 2 treatments in reaching complete remission (78% vs 73%; $P = .450$).



Supplementary Figure 1. Descriptive flow-chart of the cohort's treatment strategies and outcomes.

Supplementary Table 1. Cohort Characteristics Stratified on Meeting Diagnostic Criteria

	HISORt (n = 374)	Revised HISORt (n = 320)	ICDC definitive type 1 (n = 538)	ICDC probable type 1 (n = 27)	ICDC not otherwise specified (n = 8)	U-AIP (n = 630)	Meets ≥1 criteria (N = 735)
Patient characteristics							
Male sex	274 (73)	301 (73)	376 (70)	17 (63)	5 (63)	440 (70)	509 (69)
Age, median (IQR), *y*	60 (22)	59 (25)	57 (26)	58 (27)	37 (31)	52 (27)	57 (27)
White	317 (85)	357 (86)	459 (85)	19 (70)	6 (75)	541 (86)	626 (85)
BMI, mean (SD)	25 (4)	25 (4)	25 (4)	25 (5)	23 (3)	25 (4)	25 (4)
Smoking, ever	131 (35)	143 (35)	186 (35)	8 (30)	8 (30)	233 (37)	276 (38)
Alcohol use, ever	111 (30)	121 (29)	168 (31)	7 (26)	2 (25)	190 (30)	230 (31)
History of acute pancreatitis	31 (8)	46 (11)	71 (13)	4 (15)	4 (50)	85 (14)	102 (14)
History of IBD	21 (6)	54 (13)	58 (11)	3 (11)	0 (0)	62 (10)	73 (10)
History of other autoimmune disease	67 (18)	78 (19)	85 (16)	9 (33)	1 (13)	109 (17)	122 (17)
Diabetes mellitus	126 (34)	119 (29)	154 (29)	12 (44)	1 (13)	184 (29)	213 (29)
Pancreatic exocrine insufficiency	98 (26)	114 (28)	142 (26)	5 (19)	1 (13)	167 (27)	190 (26)
Blue collar worker	141 (38)	151 (36)	182 (34)	7 (26)	1 (13)	208 (33)	246 (34)
Presenting symptoms							
Obstructive jaundice	235 (63)	256 (62)	303 (56)	13 (48)	2 (25)	335 (53)	381 (52)
Abdominal pain	208 (56)	240 (58)	336 (63)	17 (63)	8 (100)	399 (63)	471 (64)
Anorexia	50 (13)	53 (13)	67 (13)	5 (19)	0 (0)	72 (11)	84 (11)
Weight loss	137 (37)	161 (39)	210 (39)	11 (41)	2 (25)	226 (36)	270 (37)
Diarrhea	40 (11)	56 (14)	69 (13)	1 (4)	0 (0)	74 (12)	82 (11)
Malaise	46 (12)	54 (13)	67 (13)	2 (7)	0 (0)	74 (12)	85 (12)
Nausea	37 (10)	44 (11)	54 (10)	1 (4)	0 (0)	58 (9)	68 (9)
Night sweats	10 (3)	15 (4)	17 (3)	0 (0)	1 (13)	17 (3)	20 (3)
Acute pancreatitis	23 (6)	35 (8)	52 (10)	2 (7)	2 (25)	62 (10)	76 (10)
None (incidental finding)	20 (5)	19 (5)	22 (4)	1 (4)	0 (0)	26 (4)	32 (4)
Radiologic findings							
Parenchymal enlargement	313 (84)	394 (95)	519 (97)	23 (85)	5 (63)	594 (94)	653 (89)
Diffuse	171 (46)	296 (71)	364 (68)	0 (0)	0 (0)	325 (52)	364 (50)
Segmental	142 (38)	98 (24)	155 (29)	23 (85)	5 (63)	269 (43)	289 (39)
Rim-like enhancement	65 (17)	91 (22)	110 (20)	2 (7)	1 (13)	110 (18)	125 (17)
Focal mass	135 (36)	115 (28)	144 (27)	15 (56)	2 (25)	200 (32)	231 (31)
Narrowing of main pancreatic duct[a]	120 (32)	130 (31)	203 (38)	10 (37)	8 (100)	211 (34)	224 (31)
Diffuse	29 (8)	34 (8)	55 (10)	0 (0)	0 (0)	54 (9)	57 (8)
Long (one-third length)	28 (8)	39 (9)	66 (12)	0 (0)	0 (0)	58 (9)	66 (9)
Segmental	55 (15)	50 (12)	77 (14)	9 (33)	8 (100)	89 (14)	101 (14)
Other organ involvement							
Yes	173 (46)	209 (50)	261 (49)	8 (30)	0 (0)	285 (45)	329 (45)
Orbital	7 (2)	7 (2)	8 (2)	1 (4)	0 (0)	10 (2)	12 (2)
Bilateral salivary gland	28 (8)	39 (9)	44 (8)	2 (7)	0 (0)	53 (8)	54 (7)
Thyroid	7 (2)	8 (2)	9 (2)	2 (7)	0 (0)	12 (2)	13 (2)
Pulmonary	29 (8)	29 (7)	31 (6)	1 (4)	0 (0)	34 (5)	38 (5)
(Peri)aorta	13 (4)	12 (3)	15 (3)	0 (0)	0 (0)	15 (2)	17 (2)
Retroperitoneal fibrosis	13 (4)	17 (4)	19 (4)	0 (0)	0 (0)	20 (3)	24 (3)
Sclerosing cholangitis/biliary tree	136 (36)	171 (41)	215 (40)	6 (22)	0 (0)	225 (36)	262 (36)
Renal	35 (9)	36 (9)	44 (8)	1 (4)	0 (0)	46 (7)	49 (7)
Serology							
IgG4 >1x ULN	293 (78)	302 (73)	329 (61)	19 (70)	0 (0)	404 (64)	440 (60)
IgG4 >2x ULN	190 (51)	205 (49)	225 (42)	0 (0)	0 (0)	253 (40)	279 (38)
Pathology							
No	106 (28)	155 (37)	216 (40)	8 (30)	5 (63)	248 (39)	299 (41)
Cytology	82 (22)	98 (24)	134 (25)	6 (22)	1 (13)	160 (25)	182 (25)
Histology (not surgically resected)	186 (50)	162 (39)	188 (35)	13 (48)	2 (25)	222 (35)	254 (35)

NOTE. Data presented as number (%) unless otherwise indicated. Patients can meet multiple diagnostic criteria, but not multiple classifications within the ICDC. Diagnostic criteria: HISORt, revised HISORt, ICDC, and U-AIP.

BMI, body mass index; IBD, inflammatory bowel disease; IQR, interquartile range; SD, standard deviation; ULN, upper limit of normal.

[a]Subtotals may not add up because of missing data on the type of main pancreatic duct narrowing.

Supplementary Table 2. Regression Analysis of Factors Associated With Reaching Complete Remission Among Untreated Patients (N = 95)

	OR (95% CI)
Male sex	1.169 (0.416–3.288)
Age, *y*	0.984 (0.955–1.014)
BMI	0.970 (0.817–1.152)
History of IBD	0.500 (0.126–1.986)
History of other autoimmune disease	0.924 (0.284–3.004)
Acute pancreatitis at presentation	2.286 (0.592–8.827)
Jaundice at presentation	0.652 (0.209–2.040)
Weight loss at presentation	0.167 (0.055–0.508)
Parenchymal enlargement	4.235 (0.861–20.833)
Focal mass	1.638 (0.540–4.968)
Rim-like enhancement	0.480 (0.126–1.831)
Any other organ involvement	0.893 (0.293–2.724)
IgG4-related sclerosing cholangitis	1.039 (0.291–3.711)
IgG4 level >1x ULN	0.538 (0.165–1.753)
IgG4 level >2x ULN	0.371 (0.121–1.141)
Histology available	0.652 (0.209–2.040)

BMI, body mass index; CI, confidence interval; IBD, inflammatory bowel disease; OR, odds ratio; ULN, upper limit of normal.

Supplementary Table 3. Regression Analysis of Factors Associated With Reaching Complete Remission Among Patients Treated With Prednisone (N = 631)

	OR (95% CI)	
	Univariable	Multivariable
Male sex	0.889 (0.603–1.312)	—
Age, *y*	0.994 (0.984–1.004)	—
BMI	1.015 (0.965–1.068)	—
History of IBD	0.782 (0.439–1.392)	—
History of other autoimmune disease	1.225 (0.744–2.015)	—
Acute pancreatitis at presentation	0.481 (0.272–0.852)	0.463 (0.242–0.884)
Jaundice at presentation	1.262 (0.888–1.793)	—
Weight loss at presentation	0.837 (0.585–1.197)	—
Parenchymal enlargement	1.044 (0.557–1.955)	—
Focal mass	0.781 (0.536–1.138)	—
Rim-like enhancement	0.899 (0.564–1.435)	—
Any other organ involvement	0.520 (0.363–0.744)	0.513 (0.260–1.012)
IgG4-related sclerosing cholangitis	0.585 (0.408–0.838)	1.116 (0.570–2.189)
IgG4 level >1x ULN	0.585 (0.385–0.889)	0.636 (0.413–0.978)
IgG4 level >2x ULN	0.727 (0.503–1.052)	—
Histology available	1.100 (0.763–1.586)	—

BMI, body mass index; CI, confidence interval; IBD, inflammatory bowel disease; OR, odds ratio; ULN, upper limit of normal.

Supplementary Table 4. Cohort Characteristics Stratified on Treatment Regimen

	Starting dose			Starting dose duration			Tapering duration		
	<0.6 mg/kg/day (n = 240)	0.6–0.8 mg/kg/day (n = 108)	>0.8 mg/kg/day (n = 100)	1–2 wk (n = 287)	3–4 wk (n = 244)	>4 wk (n = 61)	<6 wk (n = 107)	6–10 wk (n = 199)	>10 wk (n = 180)
Patient characteristics									
Male sex	180 (75)	69 (64)	61 (61)	201 (70)	175 (72)	43 (71)	67 (63)	148 (74)	136 (76)
Age, median (IQR), *y*	60 (24)	58 (28)	49 (25)	58 (28)	54 (28)	60 (14)	47 (37)	60 (24)	58 (21)
White	202 (84)	88 (82)	85 (85)	241 (84)	208 (85)	52 (85)	96 (90)	172 (86)	147 (82)
BMI, mean (SD)	26 (5)	23 (3)	25 (4)	26 (5)	25 (4)	24 (3)	24 (5)	25 (5)	25 (4)
Smoking, ever	103 (43)	40 (37)	22 (22)	99 (35)	90 (37)	28 (46)	46 (43)	68 (34)	75 (42)
Alcohol use, ever	106 (44)	31 (29)	12 (12)	87 (30)	69 (28)	32 (53)	40 (37)	71 (36)	54 (30)
History of acute pancreatitis	27 (11)	14 (13)	13 (13)	40 (14)	34 (14)	4 (7)	28 (26)	20 (10)	18 (10)
History of IBD	15 (6)	15 (14)	18 (18)	31 (11)	22 (9)	4 (7)	13 (12)	12 (6)	17 (9)
History of other autoimmune disease	36 (15)	10 (9)	27 (27)	57 (20)	29 (12)	8 (13)	17 (16)	26 (13)	23 (13)
Diabetes mellitus	83 (35)	35 (32)	19 (19)	89 (31)	63 (26)	24 (39)	24 (22)	69 (35)	52 (29)
Pancreatic exocrine insufficiency	80 (33)	20 (19)	10 (10)	78 (27)	50 (21)	20 (33)	28 (26)	54 (27)	48 (27)
Blue collar worker	74 (31)	41 (38)	51 (51)	103 (36)	73 (30)	23 (38)	22 (21)	56 (28)	75 (42)
Presenting symptoms									
Obstructive jaundice	130 (54)	51 (47)	76 (76)	180 (63)	111 (46)	38 (63)	40 (37)	100 (50)	99 (55)
Abdominal pain	154 (64)	72 (67)	67 (67)	175 (61)	164 (67)	37 (61)	80 (75)	129 (65)	108 (60)
Anorexia	36 (15)	13 (12)	5 (5)	22 (8)	36 (15)	15 (25)	9 (8)	25 (13)	28 (16)
Weight loss	120 (50)	44 (41)	16 (16)	106 (37)	76 (31)	40 (66)	31 (29)	87 (44)	76 (42)
Diarrhea	35 (15)	15 (14)	11 (11)	40 (14)	26 (11)	6 (10)	14 (13)	25 (13)	21 (12)
Malaise	41 (17)	12 (11)	8 (8)	37 (13)	23 (9)	13 (21)	14 (13)	24 (12)	19 (11)
Nausea	24 (10)	13 (12)	8 (8)	17 (6)	27 (11)	14 (23)	6 (6)	16 (8)	33 (18)
Night sweats	5 (2)	3 (3)	6 (6)	10 (4)	7 (3)	0 (0)	5 (5)	6 (3)	4 (2)
Acute pancreatitis	17 (7)	9 (8)	6 (6)	29 (10)	16 (7)	5 (8)	18 (17)	12 (6)	14 (8)
None (incidental finding)	5 (2)	8 (7)	1 (1)	8 (3)	13 (5)	1 (2)	2 (2)	9 (5)	11 (6)
Radiologic findings									
Parenchymal enlargement	210 (88)	99 (92)	91 (91)	252 (88)	218 (89)	55 (90)	93 (87)	181 (91)	156 (87)
Diffuse	117 (49)	51 (47)	64 (64)	142 (50)	110 (45)	36 (59)	37 (35)	99 (50)	89 (49)
Segmental	93 (39)	48 (44)	27 (27)	110 (38)	108 (44)	19 (31)	56 (52)	82 (41)	67 (37)
Rim-like enhancement	56 (23)	15 (14)	4 (4)	32 (11)	59 (24)	17 (28)	14 (13)	43 (22)	40 (22)
Focal mass	69 (29)	34 (32)	31 (31)	86 (30)	84 (34)	24 (39)	32 (30)	60 (30)	68 (38)
Narrowing of main pancreatic duct[a]	81 (34)	29 (27)	37 (37)	98 (34)	80 (33)	23 (38)	38 (36)	64 (32)	67 (37)
Diffuse	23 (10)	9 (8)	10 (10)	27 (9)	18 (7)	6 (10)	9 (8)	17 (9)	17 (9)
Long (one-third length)	21 (9)	7 (7)	8 (8)	25 (9)	25 (10)	7 (12)	11 (10)	16 (8)	25 (14)
Segmental	34 (14)	12 (11)	18 (18)	39 (14)	37 (15)	10 (16)	17 (16)	27 (14)	27 (15)

Supplementary Table 4. Continued

	Starting dose			Starting dose duration			Tapering duration		
	<0.6 mg/kg/day (n = 240)	0.6–0.8 mg/kg/day (n = 108)	>0.8 mg/kg/day (n = 100)	1–2 wk (n = 287)	3–4 wk (n = 244)	>4 wk (n = 61)	<6 wk (n = 107)	6–10 wk (n = 199)	>10 wk (n = 180)
Other organ involvement									
Yes	126 (53)	48 (44)	26 (26)	122 (43)	111 (46)	37 (61)	41 (38)	100 (50)	98 (54)
Orbital	1 (0)	1 (1)	3 (3)	6 (2)	2 (1)	2 (3)	1 (1)	3 (2)	4 (2)
Bilateral salivary gland	20 (8)	12 (11)	1 (1)	27 (9)	15 (6)	5 (8)	7 (7)	23 (12)	14 (8)
Thyroid	5 (2)	2 (2)	1 (1)	9 (3)	1 (0)	2 (3)	3 (3)	6 (3)	1 (1)
Pulmonary	14 (6)	6 (6)	6 (6)	17 (6)	13 (5)	6 (10)	6 (6)	11 (6)	13 (7)
(Peri)aorta	4 (2)	4 (4)	1 (1)	7 (2)	4 (2)	3 (5)	1 (1)	7 (4)	5 (3)
Retroperitoneal fibrosis	8 (3)	6 (6)	0 (0)	7 (2)	8 (3)	4 (7)	2 (2)	5 (3)	8 (4)
Sclerosing cholangitis/biliary tree	102 (43)	37 (34)	17 (17)	97 (34)	89 (37)	32 (53)	33 (31)	82 (41)	80 (44)
Renal	22 (9)	3 (3)	7 (7)	17 (6)	20 (8)	7 (12)	3 (3)	16 (8)	20 (11)
Serology									
IgG4 >1x ULN	153 (64)	65 (60)	54 (54)	183 (64)	142 (58)	41 (67)	46 (43)	139 (70)	119 (66)
IgG4 >2x ULN	104 (43)	44 (41)	24 (24)	119 (42)	94 (39)	25 (41)	21 (20)	99 (50)	87 (48)
Pathology									
No	109 (45)	41 (38)	19 (19)	89 (31)	102 (42)	26 (43)	53 (50)	76 (38)	75 (42)
Cytology	71 (30)	34 (32)	8 (8)	71 (25)	59 (24)	17 (28)	26 (24)	66 (33)	42 (23)
Histology (not surgically resected)	60 (25)	33 (31)	73 (73)	127 (44)	83 (34)	18 (30)	28 (26)	63 (35)	63 (35)

NOTE. Data presented as number (%) unless otherwise indicated. Adjacent grey arced cells indicate a statistically significant difference between the 2 columns. Groupings do not add up to the same totals in each category because of missing data in the categorizing variables.

BMI, body mass index; IBD, inflammatory bowel disease; IQR, interquartile range; SD, standard deviation; ULN, upper limit of normal.

[a]Subtotals may not add up because of missing data on the type of main pancreatic duct narrowing.

Supplementary Table 5. Regression Analysis of Factors Associated With Relapse Within 6 Months of Remission Induction With Prednisone Therapy Only (N = 493)

	Univariable OR (95% CI)
Male sex	1.379 (0.676–2.810)
Age, *y*	0.999 (0.982–1.016)
BMI	1.000 (0.916–1.093)
History of IBD	2.032 (0.842–4.905)
History of other autoimmune disease	1.506 (0.709–3.196)
Acute pancreatitis at presentation	2.320 (0.897–5.999)
Jaundice at presentation	0.899 (0.485–1.668)
Weight loss at presentation	1.338 (0.716–2.502)
Parenchymal enlargement	0.390 (0.167–0.910)
Focal mass	0.739 (0.359–1.523)
Rim-like enhancement	1.308 (0.588–2.914)
Narrowing of main pancreatic duct	1.093 (0.570–2.097)
Any other organ involvement	0.940 (0.502–1.763)
IgG4-related sclerosing cholangitis	1.287 (0.679–2.440)
Histology available	0.772 (0.403–1.481)
IgG4 level >1x ULN at diagnosis	0.819 (0.409–1.640)
IgG4 level >2x ULN at diagnosis	1.227 (0.628–2.398)
IgG4 level >1x ULN persisting at remission	0.698 (0.307–1.586)
Maintenance therapy (any type)	0.260 (0.125–0.539)

BMI, body mass index; CI, confidence interval; IBD, inflammatory bowel disease; OR, odds ratio; ULN, upper limit of normal.

Supplementary Table 6. Details of Relapse Treatment

	Steroids (n = 117)	Rituximab (n = 30)
Dose and duration		
Median starting dose, mg/kg/day	0.5 (0.1–1.8)	—
Median starting dose, mg/day	40 (5–125)	
Median starting dose duration, wk	2 (1–36)	—
Dose		
375 mg/m^2	—	3 (10)
1000 mg	—	26 (87)
Number of doses		
<2	—	1 (3)
2	—	24 (80)
>2	—	4 (13)
Interval		
<2 wk	—	1 (3)
2 wk	—	23 (77)
>2 wk	—	4 (13)
Remission		
Complete	91 (78)	22 (73)
Partial	17 (15)	6 (20)
No	5 (4)	2 (7)

NOTE. Data presented as number (%) unless otherwise indicated. Totals may not add up to 100% because of missing data in some variables.

Supplementary Table 7. Sensitivity Analysis Excluding 106 Patients Meeting U-AIP but Not ICDC

	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Starting dose (relative to body weight)		
Per mg/kg/day (as continuous variable)	1.320 (0.531–3.280)	0.291 (0.031–2.691)
<0.6 vs 0.6–0.8 mg/kg/day	1.096 (0.646–1.861)	1.409 (0.728–2.728)
0.6–0.8 vs >0.8 mg/kg/day	0.538 (0.276–1.047)	1.216 (0.471–3.141)
Starting dose (absolute)		
Per mg/day (as continuous variable)	1.009 (0.998–1.021)	1.001 (0.972–1.032)
<20 vs >20 mg/day	0.890 (0.171–4.639)	[b]
<20 vs 20–39 mg/day	0.552 (0.100–3.064)	[b]
20–39 vs 40–59 mg/day	2.077 (1.195–3.611)	2.229 (1.117–4.445)
40–59 vs 60–79 mg/day	0.702 (0.396–1.242)	1.166 (0.532–2.254)
Starting dose duration		
Per wk (as continuous variable)	0.931 (0.862–1.006)	0.897 (0.803–1.003)
1–2 wk vs 3–4 wk	1.734 (1.141–2.637)	1.916 (1.018–3.606)
3–4 wk vs >4 wk	0.957 (0.503–1.820)	1.208 (0.461–3.168)

NOTE: Regression analysis of the effectiveness of steroid treatment regimens in inducing complete remission (N = 552).
CI, confidence interval; OR, odds ratio.
[a]Adjusted for the starting dose, starting dose duration, age, acute pancreatitis at presentation, jaundice at presentation, weight loss at presentation, rim-like enhancement, any other organ involvement, and IgG4 level >1x upper limit of normal.
[b]The group of <20 mg/day was of insufficient size for multivariable regression analysis.

Supplementary Table 8. Sensitivity Analysis Excluding 106 Patients Meeting U-AIP but Not ICDC

	Univariable OR (95% CI)
Male sex	1.437 (0.682–3.062)
Age, *y*	1.002 (0.984–1.020)
BMI	0.980 (0.884–1.085)
History of IBD	2.065 (0.847–5.034)
History of other autoimmune disease	1.531 (0.714–3.284)
Acute pancreatitis at presentation	2.149 (0.765–6.037)
Jaundice at presentation	0.798 (0.419–1.518)
Weight loss at presentation	1.163 (0.605–2.233)
Parenchymal enlargement	0.378 (0.160–0.893)
Focal mass	0.757 (0.355–1.615)
Rim-like enhancement	1.532 (0.676–3.468)
Narrowing of main pancreatic duct	1.069 (0.548–2.086)
Any other organ involvement	0.921 (0.484–1.752)
IgG4-related sclerosing cholangitis	1.214 (0.632–2.334)
Histology available	0.750 (0.382–1.474)
IgG4 level >1x ULN at diagnosis	0.897 (0.423–1.904)
IgG4 level >2x ULN at diagnosis	1.298 (0.646–2.609)
IgG4 level >1x ULN persisting at remission	0.735 (0.319–1.691)
Maintenance therapy (any type)	0.277 (0.132–0.582)

NOTE. Regression analysis of factors associated with relapse within 6 months of remission induction with prednisone therapy only (N = 438).
BMI, body mass index; CI; confidence interval; IBD, inflammatory bowel disease; OR, odds ratio; ULN, upper limit of normal.

Supplementary Table 9. Sensitivity Analysis Excluding 106 Patients Meeting U-AIP but Not ICDC

	Early relapse, %	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Tapering duration			
Per wk (linear effect)		0.975 (0.918–1.035)	1.075 (0.810–1.428)
<6 vs 6–10 wk	7 vs 17	0.378 (0.125–1.145)	0.197 (0.036–1.089)
6–10 vs >10 wk	17 vs 11	1.540 (0.758–3.130)	0.483 (0.119–1.967)
Total remission induction treatment duration			
Per wk (linear effect)		0.974 (0.923–1.027)	0.895 (0.668–1.199)
<12 vs ≥12 wk	14 vs 12	1.224 (0.632–2.369)	0.977 (0.277–3.450)
Total cumulative dose			
<25 vs >25 mg/kg	14 vs 12	1.189 (0.551–2.564)	1.063 (0.390–2.900)
<20 vs 20–30 mg/kg	11 vs 15	0.698 (0.258–1.894)	0.662 (0.204–2.150)
20–30 vs >30 mg/kg	15 vs 13	1.197 (0.483–2.965)	1.042 (0.320–3.391)

NOTE. Regression analysis of the effectiveness of steroid-tapering regimens in preventing relapse within 6 months of remission induction (N = 438).
CI, confidence interval; OR, odds ratio.
[a]Adjusted for the tapering duration; remission induction treatment duration; total cumulative dose; presenting with acute pancreatitis; IgG4 level > 1x upper limit of normal; treatment with maintenance therapy.