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Original article

Obstructive jaundice in autoimmune pancreatitis can be safely treated with corticosteroids alone without biliary stenting

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ABSTRACT

Objective: Autoimmune pancreatitis (AIP) responds dramatically to corticosteroids treatment. We reviewed our experience to determine the safety and effectiveness of treating obstructive jaundice in definitive AIP with corticosteroids alone without biliary stenting.
Methods: From our AIP database, we retrospectively identified type 1 AIP subjects whose jaundice was treated with corticosteroids alone without biliary stenting. Their medical records were reviewed and clinical data were evaluated to determine the outcomes.
Results: Fifteen AIP subjects (87% male, mean age 68.4 years) were treated with corticosteroids at initial presentation (n = 8), first (n = 5) or subsequent (n = 2) relapse. Mean values (upper limit of normal, ULN) of liver tests prior to corticosteroids were aspartate aminotransferase (AST) 203.5u/l (4 × ULN), alanine aminotransferase (ALT) 325.8u/l (6 × ULN), alkaline phosphatase (ALP) 567.4u/l (5 × ULN), and total bilirubin (TB) 5.9 mg/dl (5.9 × ULN). At first follow-up (mean 4 days) the decrease was 54.9% for AST, 51.6% for ALT, 33% for ALP and 47.2% for TB (all $p < 0.05$). After 15–45 days, all patients had normal AST, 3/15 had ALT > 1.5 × ULN, 1/15 had ALP > 1.5 × ULN, 1/15 had TB > 1.5 × ULN. No patient required biliary stent placement, or developed cholangitis or other infectious complications during steroid treatment.
Conclusion: Under the supervision of an experienced pancreatologist and with close monitoring of patients, obstructive jaundice secondary to definitive AIP can be safely and effectively managed with corticosteroids alone, without the need for biliary stenting.

Introduction

Reports of steroid-responsive obstructive jaundice were described in the early 1950s, and the possibility of a pancreatic disease of autoimmune etiology was first postulated by Sarles et al., in 1961 [1], [2]. However, the term autoimmune pancreatitis (AIP) was not introduced until decades later in a review of the etiology and classification of chronic pancreatitis [3]. Shortly thereafter, Yoshida et al. described the first clinical cohort, including serological abnormalities and steroid responsiveness, of what we currently refer to as type 1 autoimmune pancreatitis [4].

AIP is a distinctive chronic condition of pancreas, presumably caused by an autoimmune process. It is a fibro-inflammatory disease with lympho-plasmacytic infiltration and peculiar storiform fibrosis that can cause multi-organ dysfunction. Type 1 AIP is considered to be the pancreatic manifestation of IgG4-related disease with elevated serum IgG4, and abundant IgG4-positive cell

Abbreviations: AIP, autoimmune pancreatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ERCP, Endoscopic retrograde cholangiopancreatography; TB, total bilirubin.

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infiltration in the pancreas and other organs. It is the most common form worldwide, accounting for almost all cases in Japan and Korea and more than 80% of cases in Europe and the United States [5,6]. Type 2 AIP is a pancreas-specific disorder without any association with IgG4. Both types respond rapidly to steroid treatment [6]. Approximately 75% of patients with type 1 AIP patients present with obstructive jaundice, for which the vast majority (71%) undergo ERCP with biliary stenting [6]. As steroid treatment may potentially trigger or worsen cholangitis, obstructive jaundice in AIP has historically been managed by endoscopic or percutaneous transhepatic biliary drainage before steroid administration. However, since AIP responds promptly to corticosteroids, we have recently been treating obstructive jaundice in those with definitively diagnosed AIP and in which close clinical follow-up can be ensured with corticosteroids alone (i.e., without biliary stenting). Herein, we report on the safety and effectiveness of treatment of obstructive jaundice with corticosteroids alone in definitive AIP.

Methods

This study was approved by the Institutional Review Board at Mayo Clinic Rochester. We reviewed a prospectively maintained AIP database through December 2014 to identify subjects with jaundice secondary to type 1 AIP [7]. A total of 15 subjects were identified whose jaundice was managed exclusively with corticosteroids without biliary stenting and whose laboratory data were available within 2 weeks of start of steroid therapy. The diagnosis of AIP was made according to the International Consensus Diagnostic Criteria for AIP [8]. Among these subjects, 8 were treated at initial presentation, 5 at 1st, 1 at 2nd and 1 at 3rd relapse.

Medical records were reviewed to record liver tests aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (TB) before and after corticosteroids. Changes on cross-sectional imaging studies and treatment-related adverse events (e.g., cholangitis, infectious complications and worsening hyperglycemia) were also recorded. The initial oral prednisone dose was 40 mg/day (n = 12, 80%), 30 mg/day (n = 2, 13.3%), and 20 mg/day (n = 1, 6.7%). The initial dose was administered for 4 weeks in all cases, and then gradually tapered by 5 mg every 1–2 weeks. Data were analyzed using Prism statistical software (GraphPad Software, Inc., La Jolla, CA) and variables were compared using Fisher's t test. A p-value of less than 0.05 was considered statistically significant.

Table 2
Mean liver test abnormalities prior to and following a short course of corticosteroids (median 4 days, range 1–14 days) in 15 patients with type 1 AIP and jaundice.

	Pre-steroids	Post-steroids	%decrease	Reference	p-value
AST (U/L)	203.5 ± 157.4	56.4 ± 28.7	54.9 ± 36.3	8–43	0.001
ALT (U/L)	325.8 ± 160.1	148.4 ± 61.8	51.6 ± 24.9	7–45	<0.001
ALK (U/L)	567.4 ± 435.9	313.3 ± 168.2	33.02 ± 25.2	46–118	0.044
TB (mg/dl)	5.9 ± 2.4	3.4 ± 2.7	47.25 ± 27.5	≤1.2	0.012
DB (mg/dl)	4.2 ± 2.4	2.7 ± 1.5	46.36 ± 19.1	0.0–0.3	0.050

Results

Patient characteristics

As is typical of type 1 AIP, the majority of treated patients were male (13/15) and the mean age at time of diagnosis was 68.4 ± 14.8 (range 44–93 years). All patients presented with jaundice, eight with abdominal pain, seven with fatigue, six with pancreas mass, 1 with renal involvement and 1 with parotid gland enlargement. Eight patients were treated at initial presentation and seven were treated at their relapse. Among those treated with steroids for their relapse, five had previously had biliary stenting and one underwent Whipple procedure during their initial presentation. Patient demographics of initial presenters are summarized in Table 1. In these eight patients, CT scan was performed in all and 6/8 had diffuse pancreas enlargement; 2/8 had localized pancreas mass; 3/8 had a capsule –like rim, 6/8 had distal-bile duct stricture with associated intra- and extra-hepatic duct dilation. Four patients (4/8) had EUS and 3 showed typical AIP features and pathology either suggestive or consistent with AIP. One patient had abnormal CT scan of kidney cortex and biopsies of the kidney suggested IgG4 associated tubulointerstitial nephritis. 6/8 had elevated IgG4; 5/8 had elevated IgG4 and typical CT images of AIP (Table 1).

Liver tests rapidly improve after corticosteroid treatment in AIP patients

CT scan of the abdomen showed all patients had distal common bile duct stricture and one patient had intrahepatic biliary stricture

Table 1
Clinical details of 8 newly diagnosed AIP patients.

Patient	Age	Sex	Initial presentation	IgG4 (mg/dl)	CT scan	EUS	Pathology	Prednisone dose (mg/day)
1	76	M	Painless jaundice; weight loss	341	Pancreas head fullness; Distal bile duct stricture, intra- and extra-hepatic ductal dilation.	Consistent with AIP	Suggestive of AIP	40
2	59	M	New DM, weight loss	228	Diffuse pancreas enlargement with a capsule-like rim; Distal bile duct stricture, moderate intra- and extra-hepatic bile duct dilation.			20
3	44	M	Painless jaundice	109	Enlarged pancreas, distal bile duct stricture, mild intra- and extra-hepatic bile duct dilation.	Consistent with AIP	Suggestive of AIP	40
4	79	M	Obstructive jaundice	121	Diffuse pancreas enlargement; distal bile duct stricture, mild intra- and extra-hepatic biliary ductal dilation.	Pancreas head irregular hypoechoic mass; Not typical for AIP	Atypical; No increase in plasma cells	40
5	59	F	Obstructive jaundice	244	Pancreatic mass and distal common bile duct stricture; capsule rim			40
6	85	M	Obstructive jaundice, weight loss	1290	Diffuse pancreas enlargement; mild distal bile duct stricture, dilatation of the intra- and extra- hepatic bile ducts.			30
7	57	M	Obstructive jaundice	1820	Diffuse pancreas enlargement with a thin rim	Typical for AIP	Consistent with AIP	40
8	43	M	Left flank and epigastric pain	456	Diffusely pancreas enlargement; mild distal bile duct stricture; moderate bile duct dilatation; multiple small perfusion defects in the cortex of the kidneys		IgG4-related tubulointerstitial nephritis	40

Prior to treatment, 4 patients had TB between 1–2 × ULN, 5 patients had TB 2–5 × ULN and 6 patients had TB more than 5 × ULN. The mean value (+/− SD) of liver test values prior to steroid treatment were as follows: AST 203.5 ± 157.4 u/l (4 × ULN), ALT 325.8 ± 160.1 u/l (6 × ULN), ALP 567.4 ± 436.0 u/l (5 × ULN), and TB 5.9 ± 2.4 mg/dl (5.9 × ULN) (Table 2). Follow-up liver tests at a mean of 4 days (range 1–14 days) after starting prednisone showed rapid reduction of all liver tests: the decrease was 54.9 ± 36.3% for AST, 51.6 ± 25% for ALT, 33 ± 25.2% for ALP and 47.2 ± 27.5% for TB (Table 2). Fifteen to forty-five days after corticosteroids treatment, all patients had normal AST, 3 patients had ALT more than 1.5 × ULN, one patient had ALP more than 1.5 × ULN and only one patient had TB more than 1.5 × ULN (Fig. 1). The mean values of liver tests were as follows: AST 0.83 × ULN, ALT 1.06 × ULN, ALP 0.80 × ULN and TB 0.79 × ULN (Fig. 2). No patients required endoscopic or percutaneous biliary stenting.

Steroid-related complications

Six (40%) patients were diabetic prior to the start of corticosteroids; 4 patients were treated with insulin, 1 patient was treated with metformin and 1 patient was on no treatment. The mean

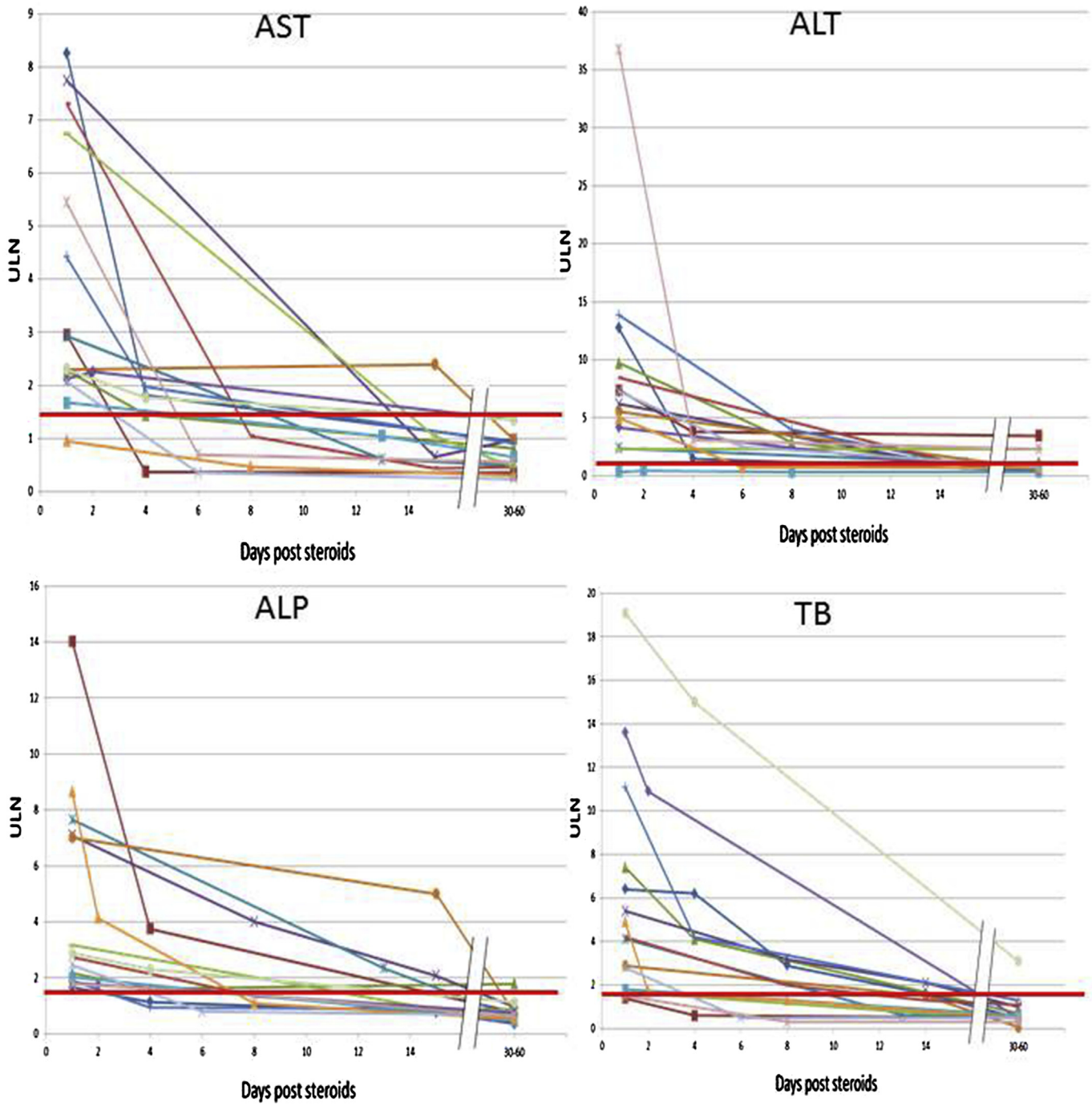

Fig. 1. Line graphs demonstrating the liver test changes in each study subject with type 1 AIP. Dark line indicates 1.5 times ULN of the respective liver test. ULN, upper limits of normal.

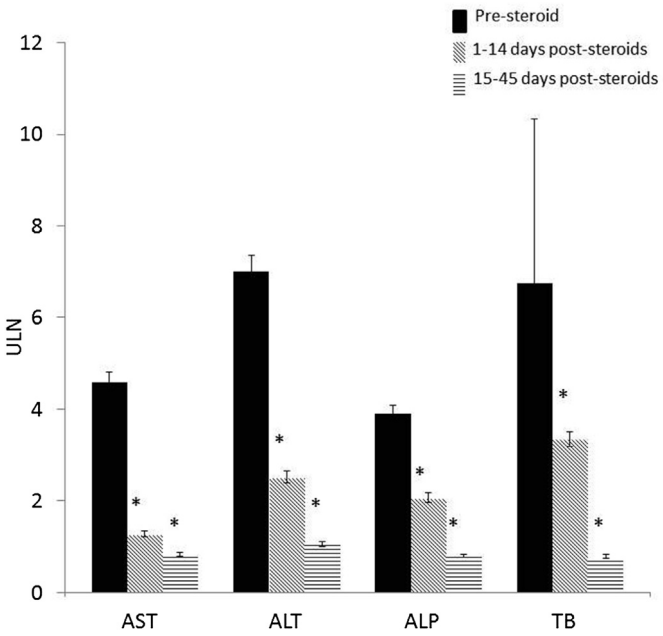

Fig. 2. Mean decrease in liver tests following steroid treatment in 15 patients with type 1 AIP and jaundice. Bars indicate one standard deviation. An asterisk indicates $p < 0.05$.

fasting glucose was 152.4 ± 73.3 mg/dl prior to initiation of corticosteroids and 151.2 ± 68.5 mg/dl after corticosteroids treatment. During steroid treatment, worsening of glucose tolerance occurred in 5 patients, however, all were controlled by oral anti-diabetic medications (n = 1) or insulin (n = 4) therapy. Two patients with hyperglycemia prior to steroid treatment had normal blood glucose after steroid treatment. We did not observe any infectious complications such as pneumonia or cholangitis during steroid treatment.

Radiographic responses

A total of 5 patients had follow-up cross-sectional imaging within 30 days of starting corticosteroids. Improvement in the biliary dilation and pancreatic enlargement was seen in all patients (Fig. 3).

Disease relapses

A total of 5 patients developed a disease relapse within 12 months of starting steroid therapy (45.5%). One patient developed relapse at 3 months, one at 6 months and 3 at 12 months, respectively. Relapses were treated with corticosteroids alone (n = 3), azathioprine (n = 1), and rituximab (n = 1).

Discussion

Typically obstructive jaundice in AIP is managed with placement of biliary stents. The Japanese Consensus Guidelines for Autoimmune Pancreatitis recommends that "before corticosteroids therapy is begun, jaundice should be managed by biliary drainage in patients with obstructive jaundice (Level of recommendation: A)" [9]. However, our experience suggests that obstructive jaundice secondary to definitive AIP patients can be safely and effectively

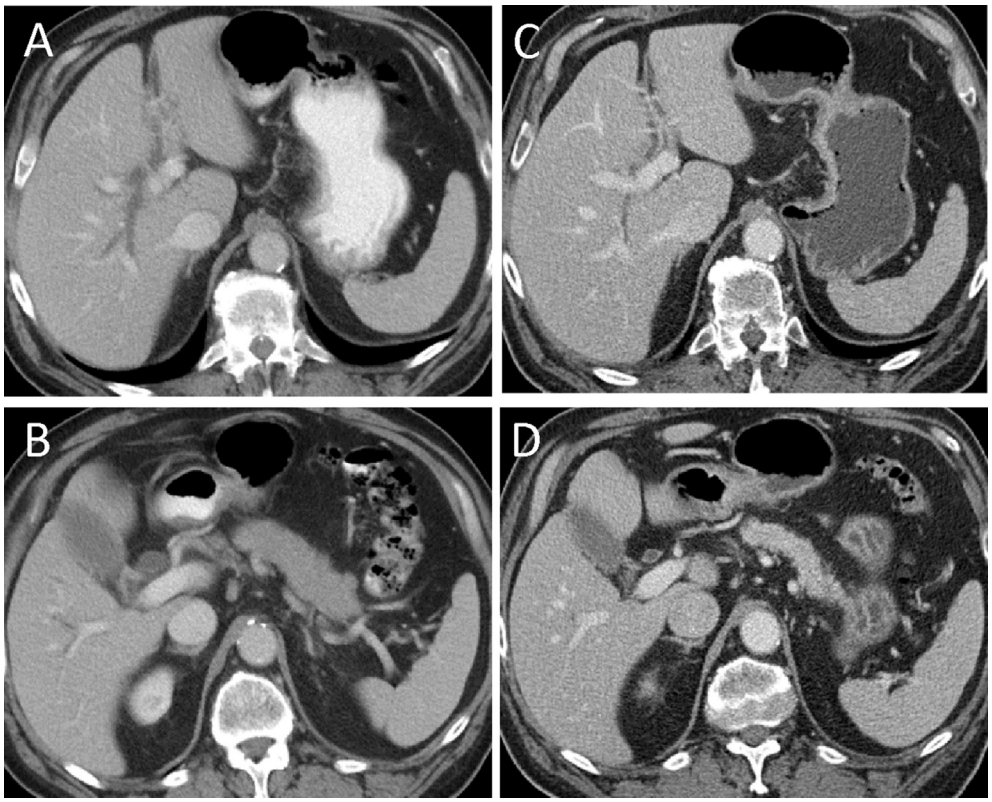

Fig. 3. CT images of a 76-year old man with type 1 AIP who responded promptly to corticosteroids. (A, B) Pre-treatment contrast-enhanced CT showed dilatation of intrahepatic and extrahepatic bile ducts (12 mm) caused by diffusely enlarged pancreas. Pancreatic head was also enlarged (not shown). (C, D) Contrast-enhanced CT obtained 4 weeks after initiation of the steroid treatment, dilatation of intrahepatic and extrahepatic bile ducts (8 mm) and enlargement of pancreas resolved. Pancreas became mildly atrophic.

treated using corticosteroids alone without risk of cholangitis or other infectious complications.

In the current study, 7 out of 8 newly diagnosed AIP can be considered definitive AIP and 1 probable AIP based on the International Consensus Diagnostic Criteria (ICDC) [8]. We observed an ultra-rapid biochemical response to corticosteroids in 15 type 1 AIP patients with obstructive jaundice. The liver test reduced by 30–55% at 4 days (range 1–14 days) after starting prednisone and the majority of patients had normal liver tests 2–6 weeks after corticosteroid therapy (Fig. 1). Contrast-enhanced CT scan showed significant improvement of biliary obstruction and pancreas enlargement (Fig. 3). No patients required biliary stenting and no cases of cholangitis or other infections were observed.

Resolution or improvement of biliary stricture and obstructive jaundice in AIP has been reported previously when treated with steroids. In one report, three out of seven patients had bile duct stricture improved to almost its normal caliber and 4/7 patients had recovery to approximately 30–40% of the normal caliber [10,11]. However, the obstructive jaundice resolved in all 5 patients after steroids treatment. In another study, resolution of biliary stricture was found in 18 out of 30 patients (60%) and improvement of stricture was found in additional 11 (37%) patients [10,11]. In our practice, we have observed rapid resolution or improvement of biliary structure and jaundice in all patients without need for biliary stenting. We believe rapid relief from biliary obstruction from corticosteroids prevents development of cholangitis and obviates the need for ERCP with biliary stent placement or transhepatic drainage for these patients. In addition to avoiding the index procedure, follow-up procedures for evaluation of stent placement and/or removal are unnecessary. Although efforts are made to minimize ERCP-related complications, this remains a relatively high risk procedure, with potential complications including pancreatitis hemorrhage, or perforation [12–15]. Likewise, following placement of a biliary stent complications including stent migration or occlusion may develop. Due to the nature of invasiveness, low cost and effectiveness of corticosteroids on AIP, it is therefore reasonable to consider a steroid therapy alone for obstructive jaundice in AIP patients whose diagnosis is certain or who have relapse following prior confirmed diagnosis of AIP although we have to stress that the steroid treatment should be under the guidance of an experienced pancreatologist and the patient should be monitored closely clinically and biochemically. While it is possible that the stricture in advanced-stage of sclerosing cholangiopathy may not respond to steroid due to its fibrotic nature therapy, we have not yet seen a patient who has needed biliary bypass or long-term endoscopic stenting for obstructive jaundice that is not relieved by medical therapy in AIP.

The mechanism of the ultra-rapid liver test and biliary stricture improvement of AIP is likely multifactorial. An important contributing factor is the bile duct wall inflammation. Studies of surgical resection specimens in patients with AIP have shown inflammatory features in the distal bile duct identical to those seen in the pancreas, including lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis [11,16,17]. Likewise, abundant lymphoplasmacytic infiltration may also be evident in the bile duct biopsies from distal bile duct strictures in AIP, however often cannot be seen due to the small amount of tissue acquired [10]. In addition, many consider the biliary dilation and resultant jaundice a consequence of extrinsic compression from pancreatic enlargement. This certainly contributes, as the enlargement of pancreas has been shown to significantly decrease even after 2 weeks of steroid therapy [18]. “Steroid whitewash” has been previously reported in viral hepatitis, wherein liver tests and patient well-being improve with corticosteroids despite an infectious etiology of the hepatitis [19]. However, it is not known if a similar phenomenon would be seen in response to corticosteroids in obstructive jaundice in AIP.

It is important to recognize that the diagnosis of AIP is challenging and differentiating it from pancreatic cancer and cholangiocarcinoma is crucial. An ultra-rapid steroid trial of 7 days may potentially differentiate AIP from malignancies. Differentiating AIP from pancreatic cancer is an important however difficult task. In our study, AIP patients demonstrated an ultra-rapid response of liver tests to corticosteroids. Therefore, would a “weekend steroid trial” be useful in differentiating AIP from pancreatic cancer? Unfortunately, we are not able to definitively answer that question as we have limited experience with steroid treatment of obstructive jaundice due to causes other than AIP. However, our data are supported by a previous Korean study in which 22 clinically suspected AIP were challenged to 2 weeks of steroid therapy. The steroid response was assessed by improvement of main pancreatic duct narrowing and/or measurable reduction of a pancreas mass. In this study, all patients ($n = 15$) who responded to corticosteroids were diagnosed as having AIP, whereas all patients ($n = 7$) who did not show a response to corticosteroids were confirmed as having pancreatic cancer. Complete resection was possible in all (6/6; 100%), except one individual who refused surgery [18]. However, it should be noted that most patients in this trial underwent ERCP and it is unclear how many had biliary stenting at diagnosis. We recommend in patients with suspicious AIP, especially in cases with indeterminate imaging and not responding to “weekend steroid trial”, ERCP with biopsy should be performed to exclude malignancies.

We observed 45.5% relapse rate after stopping steroids. It is higher than our previously report. However, it still aligns well with the most of published data on AIP relapse (15–60%) [20–23]. It is likely due to the small sample size; higher percentage of patients with diffuse pancreatic swelling which has been shown as a predictor for AIP relapse (HR, 2.00; $P = 0.049$) [23].

Our study is limited by small sample size and lack of long-term follow up. However, it is a proof of principle study showing that obstructive jaundice in AIP can be safely and effectively treated with corticosteroids alone without biliary stenting in a closely monitored setting under the guidance of an experienced pancreatologist.

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Writing assistance

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Author contributions

Chari ST developed the concept. Bi Y, Hart PA, Clain JE, Farnell MB, Gleeson FC, Kendrick ML, Law R, Levy MJ, Pearson RK, Petersen BT, Pisney LD, Smyrk TC, Takahashi N, Topazian MD, Vege SS and Chari ST acquired data. Bi Y, Hart P and Chari ST analyzed data and drafted the manuscript. All authors reviewed and approved the final manuscript.

Conflict of interest

The authors have no conflict of interest to report.

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