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Autoimmune Hepatitis in Cuban Patients: A Retrospective Analysis of Clinical and Histological Profiles, Treatments, and Outcomes

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ABSTRACT

Background: Population-based studies on the clinical course and prognosis of autoimmune hepatitis (AIH) from Caribbean countries are limited.
Objective: The aim of this study was to provide information regarding the clinical and laboratory findings, histological profile, treatments, and outcomes of patients with AIH with long-term follow-up in a tertiary referral center.
Methods: A retrospective study was performed at the National Institute of Gastroenterology in Havana, Cuba, by enrolling 82 patients with a well-documented, long-term clinical course of AIH. Clinical and laboratory findings, histological profiles, treatments, and outcomes were analyzed.
Results: At diagnosis, 73 (89%) patients had AIH type 1, 84.1% were women, and their median age was 46.5 years (range, 17–79 years). The median follow-up period was 84 months (interquartile range, 12–276 months). Clinical onset was mild or subclinical in 72% of patients and asymptomatic in 12.2%. At diagnosis, the Hennes's median score was 6 (range, 3–8). Complications were seen in 44 (53.6%) patients, 42 (51.2%) with liver-related complications and 9 (10.9%) without liver-related complications. Cirrhosis was present at diagnosis in 32 (39%) patients. Cirrhosis was subsequently diagnosed in the other 28 patients who were not cirrhotic at diagnosis, over a median follow-up of 12 (IQR, 2-84) months. During follow-up, 6 patients died (7.3%). Cumulative survival at 5 and 10 years was 98.4% and 89%, respectively. A complete biochemical response was achieved in 79% of patients in a mean (SD) of 11.7 (11.6) months. Side effects due to treatment were reported in 76 (92.7%) patients, and no pretreatment factors were found to predict treatment response.
Conclusions: These Cuban patients with AIH had acceptable disease remission rate and a prompt treatment response. Although most patients had advanced-stage liver disease at diagnosis or developed during follow-up, the cumulative survival rate was high when patients were receiving and complying with treatment.

Introduction

Autoimmune hepatitis (AIH) is an inflammatory disease of the liver caused by an aberrant immune response directed against liver tissue. The exact pathogenesis of the aberrant immune response in the liver is unknown; however, it is likely to be a combination of a genetic predisposition and environmental triggers. Appropriate

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diagnosis and treatment often have a dramatic effect on patient well-being and long-term prognosis.[1]

Previous studies on the natural history of this relatively rare disease have often included different cohorts, typically from tertiary institutions, and therefore data can be difficult to interpret and generalize.[2–5] Despite the available guidelines, management of AIH is based on expert opinion rather than on high-quality evidence. Moreover, there is wide variation in the management of patients with AIH, even among the highest-level experts in the field.[6,7] The majority of studies on the epidemiology and natural history of AIH have been performed in developed countries. Thus, data from developing and resource-constrained countries are urgently needed to increase our understanding of this disease.[8–10]

A prospective Cuban study among 106 patients with autoimmune liver diseases identified AIH as the most common condition in 56 patients, 6% followed by primary biliary cholangitis in 20 patients, 7%, but it does not provide enough information about AIH and its differential characteristics, which range from the diagnosis to treatment and outcomes.[11] The authors of this study aimed to provide details about the clinical and laboratory findings, histological profile, treatments, and outcomes of patients with AIH in a tertiary referral center in a long-term follow-up study. The data will expand the knowledge of this disease in Cuba and Latin America.

Materials and Methods

Study design and setting

This is a retrospective study performed to assess the outcomes of patients with a well-documented diagnosis of AIH and a long-term clinical course at a tertiary care academic center (National Institute of Gastroenterology, Havana, Cuba). Diagnoses were made according to recommendations of the Simplified International AIH Criteria Group, 2008.[12] Patients diagnosed between 1995 and 2018 were followed up until 2019.

The data were collected from clinical charts that were available at the Department of Hepatology, and all patients were evaluated following the department's protocol for autoimmune liver diseases.[13]

Participants

Eighty-two patients were recruited with uncertain diagnostic criteria of AIH or inadequate follow-up or with diagnoses of HIV infection, viral hepatitis B or C, alcohol abuse, use of potentially hepatotoxic drugs, ischemic liver disease, alpha-1 antitrypsin deficiency, hemochromatosis, or Wilson's disease, all of which were excluded from the study.

All patients were evaluated weekly during the first 3 months of diagnosis; and at 6, 9, 12, and 24 months or until the end of the follow-up period.

All patients submitted serum to a laboratory according to medical criteria (liver panel test) comprising hematological, biochemical, serological, and immunologic studies performed according to Good Clinical Practice procedures for clinical trials and were certified by the national regulatory authority. The study was approved by our institutional ethics committee (IGE–2017-04).

Variables, data sources, and measurement

Patients were categorized into 1 of 3 distinct patterns of AIH clinical presentation: asymptomatic (absence of symptoms with only occasional abnormal liver tests), acute disease (<30 days from onset of symptoms, including jaundice, fatigue, drowsiness, or fever with marked alterations in serum liver function test) this pattern included severe hepatitis and acute liver failure, mild or subclinical onset (mild symptoms of illness, that may include progressive fatigue, malaise, anorexia, weight loss, jaundice, pruritus, or clinical manifestations of established cirrhosis), or any other chronic nonspecific symptoms for at least 6 months.

Decompensated cirrhosis was defined as the presence of among the following features: variceal hemorrhage, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, jaundice, low serum albumin concentration (<35 g/L), or prolonged prothrombin time (>15 seconds or international normalized ratio >1.5).

The presence of concurrent autoimmune disorders, including arthritis, nonspecific arthralgias with inflammation, thyroid disease, systemic lupus erythematosus, ulcerative colitis, rheumatoid arthritis, and glomerulonephritis, was recorded. A family history of autoimmune disease was determined by querying the patients with regard to first-degree relatives with known autoimmune diseases.

The laboratory tests included red and white blood cell counts (eg, platelets, hemoglobin, and hematocrit), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and other biochemical parameters. All laboratory tests were performed in the clinical laboratory of the National Institute of Gastroenterology, using routine validated methods. The upper limit of normal (ULN) ranges of AST and ALT used was provided according ALT 4+1 test validated available by HELFA diagnostic (https://es.scribd.com/document/383145547/Catalogode-Tecnicas-HELFA). Hematological tests were performed using the BC-3200 Auto Hematology Analyzer (Mindray, Shenzhen, China) and biochemical parameters were measured using the Cobas C311 Clinical Chemistry Analyzer (Roche, Basel, Switzerland). International normalized ratios were also determined. Triiodothyronine, thyroxine, and thyroid-stimulating hormone levels were measured by radioimmunoassay.

The patients had negative findings for viral hepatitis serology, as determined using ELISA and confirmed using reverse transcription polymerase chain reaction for hepatitis B and C virus. Blood levels of hepatitis B and hepatitis C virus were quantified using Cobas Amplicor version 2.0 (Roche). In patients with an acute presentation, serologic tests for hepatitis A virus and hepatitis E virus were also performed. The presence of Wilson's disease was determined by basal 24-hour urine copper and ceruloplasmin tests, and the presence of hemochromatosis was assessed by a combination of transferrin saturation test ≥45% and serum ferritin above the ULN. HFE genotype (mutation analysis) was also performed only in the case that previous tests were abnormal.

Immunoglobulins G (IgG) and IgM were quantified using the reference values 6.80 to 14.45 g/L for IgG and 0.34 to 0.91 g/L (men) or 0.40 to 0.95 g/L (women) for IgM. Immunoglobulin levels were measured using a turbidimetric method (Roche diagnostics GmbH, Mannheim, Germany, specific for the Cobas C311 instrument).

Patients were tested at presentation for antinuclear autoantibodies, antismooth muscle antibodies, and antimitochondrial antibodies, using indirect immunofluorescent staining of rat liver, kidney, and stomach sections (1:40 dilution). Furthermore, antimicrosomal liver and kidney type 1 antibodies (positive = 15 IU/mL) and antimitochondrial M2 antibodies (positive = 10 IU/mL) were quantified in patients with antimitochondrial antibody-positive indirect immunofluorescent staining results. Autoantibodies were quantified using commercial enzyme-linked immunosorbent assays (#ORG-516 and #ORG-253; Orgentec, Mainz, Germany). Tests for other highly specific autoantibodies, like soluble liver antigen/liver pancreas and liver-cytosolic type 1 were not available.

At the time of diagnosis and during the follow-up period, the results of upper abdominal ultrasounds and upper gastrointestinal tract endoscopic examinations were also reviewed. The presences of esophageal or gastric varices and/or portal hypertensive gastropathies were determined to diagnose decompensated

portal hypertension. Patients nonresponsive to immunosuppressive drugs (incomplete or delayed) with increased serum alkaline phosphatase or gamma-glutamyltransferase level are indicated of an alternative diagnosis (eg, overlap syndrome) hence cholangiography was available to perform endoscopic retrograde cholangiopancreatography because magnetic resonance cholangiography was not available.

Before initiating immunosuppressive treatment, a liver biopsy was performed in 72 (87.8%) patients via percutaneous needle biopsy using a Menghini needle. The mean (SD) measurement of all biopsies with a single pass of more than 8 portal tracts in size, as measured after fixation and before paraffin embedding, were 1.85 (0.32) cm and 1.1 (0.3) mm in diameter, respectively. Liver tissue specimens were inspected via hematoxylin eosin and Masson's trichrome staining in all cases. Histological features were recorded and divided into the following 3 categories:[14] typical, when interface hepatitis with lymphocytic or lymphoplasmacytic portal inflammatory infiltrates extending into the lobule, hepatocyte rosette formation, and emperipolesis were present; compatible, when all 3 features were not present (chronic hepatitis with lymphocytic infiltration, without all the features considered typical); and atypical, when there was incomplete evidence of AIH or an alternative diagnosis. Histologic report included the degree of fibrosis and cirrhosis at initial biopsy if it was present.

Outcomes

Complications were classified as 1 of 2 types. Liver-related outcomes were defined as the presence of decompensated cirrhosis, marked as the first occurrence of at least 1 of the following clinical conditions: ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, variceal hemorrhage, or jaundice. Nonliver-related outcomes included other events (eg, cardiovascular, hematological, and nonliver malignancy). Ascites was clinically and/or confirmed by abdominal ultrasound, hepatic encephalopathy was diagnosed in accordance with West Haven criteria for grading from 0 (subclinical) to 4 (coma) and spontaneous bacterial peritonitis was diagnosed when ascites polymorphonuclear leukocyte count was $>250/mm^3$ with or without positive ascites bacterial culture. Upper gastrointestinal bleeding related to esophageal or gastric varices and/or portal hypertensive gastropathy was confirmed by endoscopic examination. Hepatocellular carcinoma (HCC) was included as a liver-related complication, and it was diagnosed according to the Liver Imaging Reporting and Data System criteria.[15] Other clinical events detected at the same time or after the diagnosis of HCC were also considered in the outcome analysis. All clinical outcomes were confirmed by 2 expert hepatologists.

Liver transplantation was considered for patients presenting with acute liver failure, failed treatment, progression to decompensated cirrhosis with a model for end-stage liver disease score >15, or HCC within Milan criteria.[16]

Mortality was defined as death during the follow-up period, as reported in the registry of deaths available from the Department of Medical Records and Health Statistics of the institution. The cumulative survival was analyzed using Kaplan-Meier method, and the duration of follow-up for each patient was recorded. Progression to decompensated cirrhosis during the follow-up period was also recorded. Immunosuppressive therapies response relating to treatment mode, treatment response (therapeutic response to immunosuppressive), withdrawal (ie, removal of treatment or termination of therapy after induction of remission), and drug toxicity (development of toxic effects to corticosteroids or azathioprine) was recorded. Appropriate regimens were taken into account according to the anticipated low tolerance for corticosteroids or azathioprine (AZA). Monotherapy with prednisone (60 mg daily) or a lower dose of prednisone (30 mg daily) plus AZA (50 mg) was used. Prednisone dose was tapered down from 20 mg daily to an individual level sufficient to maintain remission. The dose was reduced by 5 mg every week until it reached 10 mg/d, after which a further reduction of 2.5 mg/wk was made to reach 5 mg daily while maintaining stable clinical and laboratory parameters. Serum ALT, AST, and bilirubin levels were determined at diagnosis; every week after treatment initiation; and at 1, 3, 6, 12, and 24 months until the end of the follow-up period.

Treatment response was considered as a complete biochemical response if serum ALT and/or AST levels dropped to the normal range and IgG levels were in the lower range of normal within 6 to 24 months of starting treatment. Treatment response was considered incomplete if serum ALT and/or AST levels decreased to the normal range after 24 to 36 months of treatment or by the end of follow-up period, if the follow-up period was <36 months. Patients who failed to achieve a reduction in serum ALT or AST levels or who had increased ALT and/or AST levels within 24 months were considered nonresponders. Relapse was defined as an increase in ALT and/or AST levels to more than thrice the ULN and/or an increase in IgG levels to more than 50% of the basal value after withdrawal.

The duration of follow-up during treatment and any other medication being used were recorded. Drug toxicity was considered when intolerable cosmetic changes (including facial rounding, dorsal hump formation, striae, weight gain, acne, alopecia, or facial hirsutism), obesity, symptomatic osteopenia, emotional instability, poorly controlled hypertension, or brittle diabetes occurred. Moreover, hematological symptoms (eg, leucopenia or thrombocytopenia), bone marrow failure, fever, rash, nausea, and other enteric symptoms were considered.

The sample was confirmed after completing an authentic data collection, evaluating the results (per protocol of study) and addressing the potential sources of bias on diagnosis and the outcomes of all clinical charts were reviewed by 2 investigators (MECM and ZDG) trained and qualified to perform this investigation. All medical records (demographic, clinical, biochemical, histological, and treatment data) were collected via an anonymous questionnaire. Dual data entries were done in Excel (Microsoft Corp, Redmond, Washington) datasheets and the results were compared. In the case of disagreement, an expert assessment by one of the authors (MICF) was done. The reliability assessed by interobserver agreement (Kappa index) was 0.89. All patients must have at least 12 months of follow-up. All others simplified diagnostic criteria were mandatory in the case of patient without histological results.

Statistical Analysis

Statistical Package for Social Sciences for Windows version 24.0 (IBM-SPSS Inc, Armonk, New York) was used for statistical analyses. The means, SDs, medians, ranges, and frequencies were calculated. Categorical variables were assessed using χ^2 test or Fisher exact test. The Kolmogorov-Smirnov test was used to assess the normal distribution of data. Logistic regression was used to identify associations between the AIH type 1 and AIH type 2 groups and all categorical variables (ie, sex, clinical presentation, concurrent immune disease, and histological features). Odds ratios were determined with 95% CIs. The Mann-Whitney *U* test was used to compare continuous variables between different groups, and the significance level was set at $P \leq 0.05$.

Cumulative survival was analyzed by the standard Kaplan-Meier method using an estimation of the cumulative proportion of patients who survived up to the analyzed time, with SEs. Differences in cumulative survival between patients with cirrhosis and those without cirrhosis at initial presentation were analyzed using the log-rank test. The loss to follow up was treated as

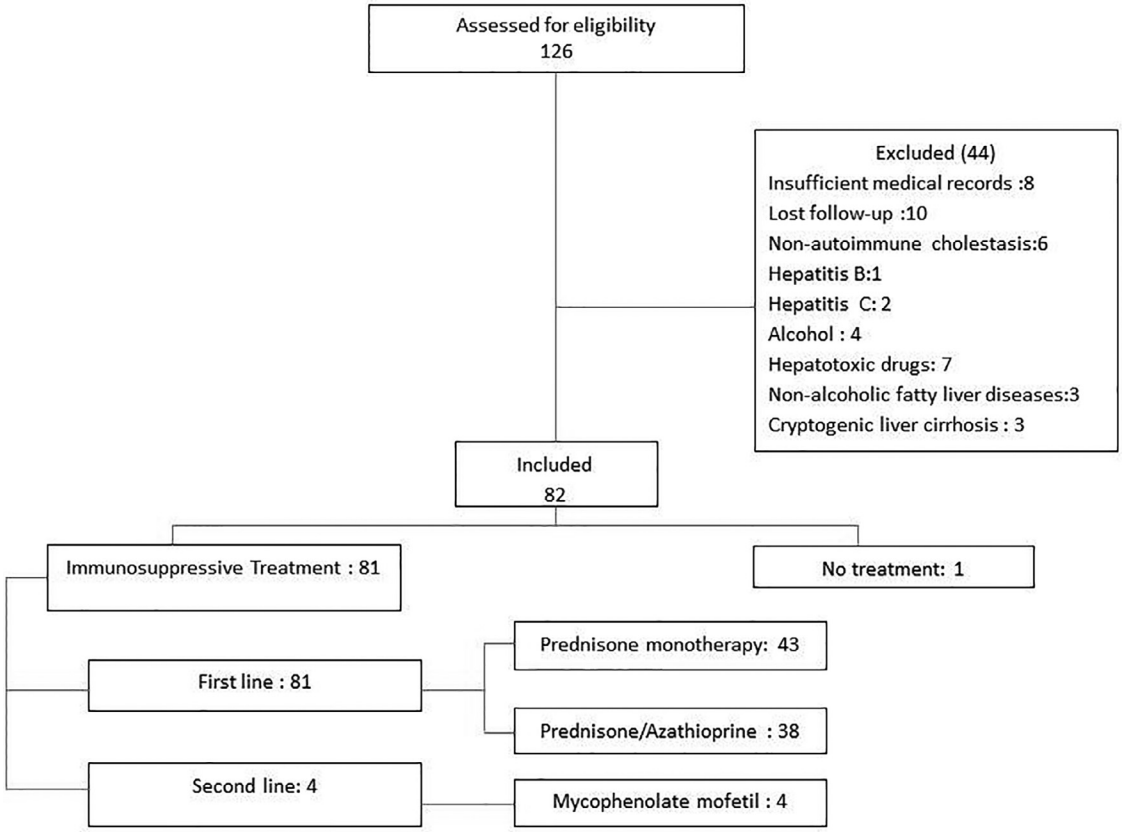


Figure 1. Flow of patients through the study according to treatment received.

censoring event. If there were missing values, statistical analysis was performed with available data. Stepwise multiple regression analysis was performed with incomplete/nonresponders as dependent variable. Clinical and/or laboratory parameters were considered as independent variables.

A literature search including other local studies of AIH was done on PubMed, ClinicalKey, EMBASE, SCIELO, and BVSCUBA (http://bvscuba.sld.cu/) from 1976 to 2019 using the terms *autoimmune hepatitis in Cuba*, *autoimmune liver diseases in Cuba*, and the combinations of *Autoimmune hepatitis in Cuba* OR *Autoimmune liver diseases in Cuba* AND the following terms: *clinical profile*, *diagnoses*, and *treatment*.

Results

Clinical data

Of 126 individuals examined for eligibility, 82 were included in the study after completing follow-up and analyses. Insufficient medical records and loss to follow-up, limited the inclusion of 18 patients. The remaining 26 patients with other diagnosis were excluded. Eighty-one patients received immunosuppressive treatment and 1 patient was not treated (Figure 1). The median follow-up period was 84 months (interquartile range [IQR], 12–276 months)

The demographic, clinical, and histological data at presentation are summarized in Table 1. Of 82 patients included in the study, 73 (89%) had AIH type 1 and 9 (11%) had AIH type 2. Cirrhosis was present at diagnosis in 32 (39%) patients. The most concurrent immune diseases were systemic lupus erythematous (n = 10; 12.1%); type 1 diabetes (n = 9; 10.9%); rheumatoid arthritis, thyroid disease, and vasculitis (n = 4 each; 4.8%); ulcerative colitis (n = 3; 3.6%), Sjogren and thrombocytopenic purpura (n = 2 each; 2.4%); and scleroderma and glomerulonephritis (n = 1 each; 1.2%). Some patients had more than 1 disease.

The mean IgG level in patients with AIH was 1.4-fold higher than the ULN. Ten patients did not undergo liver biopsy because they had uncorrectable coagulopathy, severe thrombocytopenia, decompensated cirrhosis at the time of diagnosis, or refused the procedure. In 2 cases, the liver tissue sample was not useful. Seven patients underwent more than 1 biopsy during follow-up to document disease activity as a signal or as a criterion for therapy cessation after 2 years in cases of clinical and biochemical remission. All available liver biopsy findings were reviewed by 2 expert pathologists (BVGO and LGF) with very good interobserver agreement. (Kappa index >0.8)

Patients had a median AIH Hennes score of 6 (range, 3–8). Patients with AIH type 2 were better classified as definitive by a simplified score of 8 (range, 6–8), whereas patients with AIH type 1 had 6 (range, 3–8) ($P = 0.001$). The logistic regression was not identified demographically, clinically, or histologically, minding the differences between patients with AIH type 1 and AIH type 2.

Outcomes

During follow-up, 51 complications were seen in 44 (53.6%) patients, 42 (51.2%) with liver-related complications, and 9 (10.9%) without liver-related complications (Table 2). Nineteen patients (43.1%) had more than 1 complication. Cirrhosis was diagnosed (based on clinical, laboratory, and imaging findings) or histological in 28 (34.1%) patients over a median of 12 months (IQR, 2–84 months) (that were not cirrhotic at diagnosis) and 19 patients (23.2%) developed clinical decompensation. Variceal hemorrhage was the most common complication (n = 10; 12.2%) requiring therapeutic endoscopy, followed by ascites (n = 8; 9.8%),

Table 1
Demographic, clinical and histological data at presentation of autoimmune hepatitis (n = 82).

Parameter	Total
Age,* y	46.5 (17–79)
Gender†	
Female	69 (84.1)
Male	13 (15.9)
Clinical presentation	
Asymptomatic†	
Yes	10 (12.2)
No	72 (87.8)
Acute disease†	
Yes	13 (15.8)
No	69 (84.2)
Mild or subclinical†	
Yes	59 (72.0)
No	23 (28.0)
Concurrent immune disease†	
Yes	31 (37.8)
No	51 (62.2)
IgG‡	21.2 (9.4)
IgM‡	1.4 (1.4)
Histological features†	
Typical	64 (78.0)
Compatible	8 (22.0)
AIH simplified score*§	6 (3–8)

AIH = autoimmune hepatitis; IgG = immunoglobulin G; IgM = immunoglobulin M.
* Median (min–max).
† Values are presented as n (%).
‡ Values are presented as mean (SD).
§ See reference 12.

Table 2
Outcomes of patients with autoimmune hepatitis.

Parameter	Patient result*
Patients with complications	44 (53.6)
Liver-related outcomes	42 (51.2)
Progression to liver cirrhosis	28 (34.1)
Progression to decompensated cirrhosis	19 (23.2)
Variceal hemorrhage	10 (12.2)
Ascites	8 (9.8)
Hepatic encephalopathy	3 (3.7)
Hepatocellular carcinoma	2 (2.4)
Nonliver-related outcomes	9 (10.9)
Vasculitis	4 (4.9)
Immune thrombocytopenic purpura	1 (1.2)
Cancer†	2 (2.4)
Deep vein thrombosis	1 (1.2)
Ulcerative colitis	1 (1.2)
Transplant criteria	17 (20.7)
Death	6 (7.3)

* Values are presented as n (%). Fifty-one events were seen, 19 (43.1%) patients had more than 1 complication.
† Colon and breast.

encephalopathy (n = 3; 3.7%), and HCC (n = 2; 2.4%). Vasculitis (n = 4; 4.9%) was the most frequent nonliver-related complication. One patient had colon cancer and another had breast cancer.

Seventeen patients were referred to a liver transplant center because of treatment failure and progression to decompensated cirrhosis. During the follow-up, 6 patients died. Five of these patients died following hepatic decompensation events (2 with variceal bleeding episode, 2 with hepatic encephalopathy, and 1 with HCC). Colon cancer with metastasis was the nonliver-related cause of death in 1 patient. The overall mortality of patients in this study was 7.3%. The median survival time was 216 months (IQR, 49.2–382.7 months) (equivalent to 18 years). During the follow-up period, the first patient death was recorded at 60 months (5 years). The10-year cumulative survival of patients with AIH was 89.7% (Figure 2). There was no difference in cumulative survival until the initial presentation of cirrhosis or noncirrhosis (log-rank test $P = 0.222$). The median time of follow-up of 32 cirrhotic patients at diagnosis was 90 months (IQR, 12–216 months), of whom 14 (43.7%) had 1 or more complications with 4 (28.5%) deaths. All patients without complications survived.

The long-term follow-up between those cirrhotic patients at diagnosis with complications were 96 months (IQR, 20–216 months) and those without complications was 78 months (IQR, 12–168 months), there was no difference between the groups ($P = 0.610$). Also, the survival Kaplan-Meier curves were not different (Log-rank Mantel Cox test $P = 0.081$).

Treatment

One patient with biopsy-proven AIH was not treated owing to persistently normal liver enzyme levels. The overall mean (SE) duration of treatment during follow-up was 69.3 (37.2) months. Patients who started with prednisone monotherapy had 66.1 (38.7) months of treatment, whereas those who started with prednisone plus AZA had 73.0 (35.5) months of treatment. The group of patients who started with prednisone only (n = 12; 28%) maintained the same treatment until the end of the study period. Meanwhile, AZA was added during the follow-up of 4 weeks (range, 4–60 weeks) in 29 (67.4%) patients. Mycophenolate mofetil was introduced in 4 (5%) patients, at a dose of 2 g daily orally (1 g twice per day tapered down to 0.5 g daily), because of a failure to respond to standard treatment, with frequent relapses (Table 3).

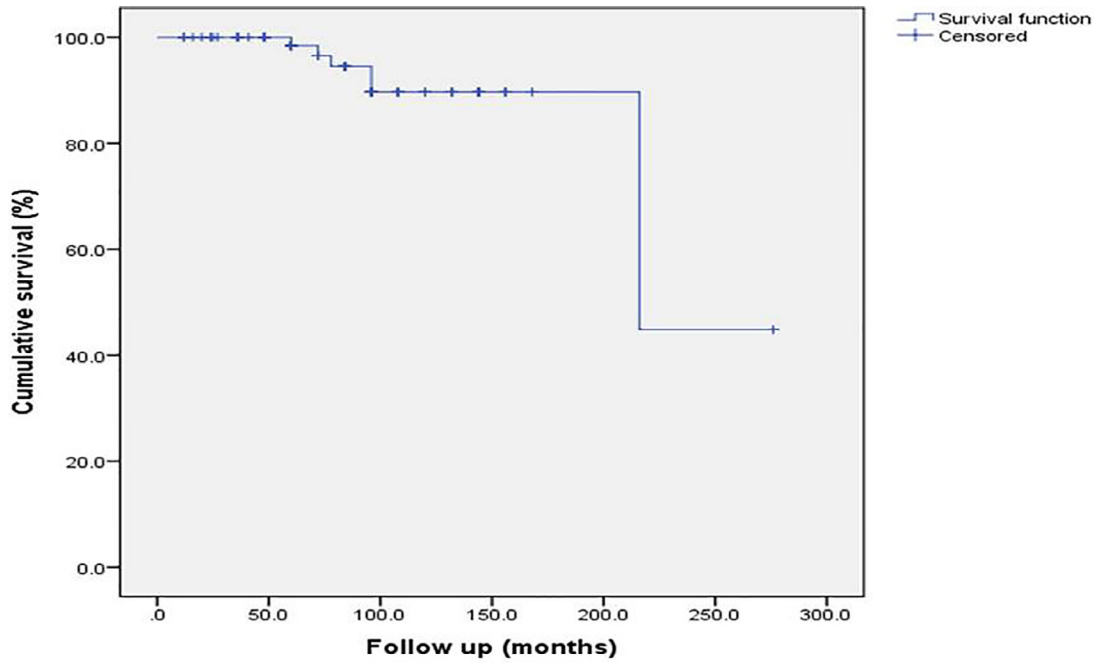
Remission or complete biochemical response was achieved in 79% of patients in <1 year (11.7±11.6 months) with no differences according to the initial mode of treatment. The median time to achieve biochemical remission was less for those patients who were treated with prednisone only as initial therapy (9.0 [9.0] months vs prednisone plus AZA group 15.0 [13.5] months; $P = 0.023$).

Treatment was discontinued in 12 (14.6%) patients. Eight of these patients discontinued treatment after 2 years of normal clinical, biochemical, and histological remission with normal IgG levels. Six patients (75%) relapsed in a median of 30 weeks (IQR, 12–72 weeks) after withdrawal. Two patients discontinued therapy of their own accord and the other 2 patients discontinued because of treatment complications.

The analyses of demographic and clinical parameters as predictive factors of response to therapy are displayed in Table 4. All variables were initially included in the analysis (stepwise logistic regression). None of the variables were related to treatment response in this study.

Side effects due to treatment were reported in 76 (92.7%) patients. These included cosmetic changes (n =55; 67.1%), infection (n = 46; 56.1%), obesity (n = 33; 40.2%), brittle (unstable, labile, or hard to control) diabetes (n=13; 15.9%), and cytopenias (mostly leucopenia and thrombocytopenia) were found in 13 (15.9%), osteopenia (n = 12; 14.6%), fever (n = 6; 7.3%), emotional instability (n = 4; 4.9%), and hypertension (n = 3; 4%). Other, less-common side effects were vertebral compression (n = 4; 4%) and cataracts (n = 1; 1.3%). Bone marrow suppression was not seen in any of the patients.

During the follow-up period between 2012 and 2016, 6 female patients (all with cirrhosis) became pregnant and delivered without complications during gestation or postpartum. All babies were born alive without any birth defects. All mothers continued on their immunosuppressive treatment with prednisone and/or AZA. Prednisone dose was modified pre-emptively 2 weeks before the anticipated time of delivery and maintained throughout the postpartum period. Close monitoring of serum aminotransferases was performed at 3-week intervals for 6 months after delivery, according to previously published guidelines[17] and the recommendations



Months	60	72	78	96	216	276
Survival % (SE)	98.4 (.016)	96.5 (.024)	94.5 (.031)	89.4(.044)	44.8(.318)	44.8(.318)
Patient numbers for each of the time	62	51	47	37	1	0

(SE): standard error

Figure 2. Cumulative survival of patients with autoimmune hepatitis.

Table 3
Treatment outcomes of patients with autoimmune hepatitis.

Parameter	Total(N = 81)	Prednisone(N = 43)	Prednisone/AZA(N = 38)	*P* value
Time to remission,* mo	11.7 (11.6)	9.0 (9.0)	15.0 (13.5)	0.023
Remission†				
Yes	64 (79)	37 (86)	27 (71.1)	0.098
No	17 (21)	6 (14)	11 (28.9)	
Incomplete response†				
Yes	13 (16)	6 (14)	7 (18.4)	0.440
No	68 (84)	37 (86)	31 (81.6)	
Failure†				
Yes	4 (4.9)	0 (0)	4 (10.5)	0.029
No	77 (95.1)	43 (100)	34 (89.5)	
Treatment discontinuation†				
Yes	12 (14.8)	7 (16.3)	5 (13.2)	0.693
No	69 (85.2)	36 (83.7)	33 (86.8)	

AZA = azathioprine.
* Values are presented as mean (SD).
† Values are presented as n (%).

Table 4
Predictive factors of response to therapy in autoimmune hepatitis.

Factor	Incomplete/failure response(n = 17; 20.7%)	Complete response(n = 65; 79.3%)	Odds ratio (95% CI)	*P* value
Age,* y	44.7 (18.5)	45.5 (18.5)	1.00 (0.97–1.03)	0.864
Female†	15 (88.2)	54 (83.1)	0.93 (0.44–1.98)	1.000
Concurrent immune disease†	13 (76.5)	38 (58.5)	1.82 (0.59–5.60)	0.262
Cirrhosis at diagnosis†	8 (47.1)	24 (52.9)	0.51 (0.19–1.36)	0.578
ALT*	207.3 (203.4)	285.4 (339.6)	0.99 (0.99–1.00)	0.680
AST*	256.0 (327.9)	269.8 (203.4)	0.99 (0.98–1.00)	0.496
IgG*	20.4 (9.6)	21.3 (9.4)	0.98 (0.92–1.03)	0.627
IgM*	1.8 (1.9)	1.3 (1.3)	1.23 (0.91–1.66)	0.433
Total bilirubin*	35.9 (85.2)	69.3 (94.3)	0.95 (0.98–1.00)	0.053

AIH = autoimmune hepatitis, ALT = alanine aminotransferase AST = aspartate aminotransferase, IgG = immunoglobulin G, IgM = immunoglobulins M.
* Values are presented as mean (SD).
† Values are presented as n (%).

of the National Maternal–Child Health Program.[18] None of these patients experienced relapse.

Discussion

This cohort of AIH is the longest duration study reported in Cuba to date. In this sample, AIH type 1 was the most frequent type and most of the patients either already had advanced-stage liver disease at diagnosis or developed it. Patients had high cumulative survival and satisfactory treatment response, but with high frequency of side effects. Similar survival of this disease was observed not only in patients with noncirrhotic AIH, but also in patients who already were cirrhotic at the time of diagnosis even with complications.

The main limitation of this study was data that were not systematically registered and therefore sometimes missing or unavailable. The patients excluded due to loss to follow-up or insufficient medical records could have had diagnosis of AIH, so it was not possible to follow-up their evolution. Also the inaccurate measurements of compliance to therapy could influence the outcomes. The criteria used to establish diagnosis in our patients (from 1999 to 2018) were reliable compared with that used in other studies. Patients who did not undergo liver biopsy at diagnosis met the international criteria for AIH, and no disagreement in the applied scores was observed in the present study. The response to therapy was good, and this remained as the key diagnostic criterion, even if the patient did not attain a score indicating a definitive AIH diagnosis.[19]

The complications of AIH are similar to those of other acute or chronic progressive liver diseases. During follow-up more than half of patients developed complications despite good rate of treatment response. It is not ruled out that the presence of complications may have emerged to noncompliance with standard therapy at some point in the course of the disease. Upper gastrointestinal bleeding was the major liver-related complication, which is similar to a previous report of compensated hepatitis C virus-related cirrhosis in a Cuban population.[20] A variceal bleeding episode was the cause of death in one-third of patients in our study. The 10-year survival rate has been reported to be high, even in untreated patients with mild AIH.[6] The cumulative survival of our treated patients, was similar to that of patients in other studies.[10,21]

Compared with other causes of liver diseases, AIH is an uncommon reason for liver transplantation.[1,17] In Cuba, the most common causes for liver transplantation were hepatitis C and alcoholic liver disease.[22] Despite liver transplantation being an infrequent indication (<10%), owing to the therapeutic advances of immunosuppression,[23] the relatively high percentage of patients undergoing liver transplantation in our study may be related to the restricted accessibility to other therapeutic options because of the high cost. However, even with optimal results after liver transplantation, AIH can recur in the allograft in up to 68% of patients after 5 years.[24] Thus, we agree with Liberal et al[25] that the criteria for prospective studies should focus on these issues and move from expert opinion to evidence-based, personalized care for patients with AIH.

In the absence of a consensus on the maximum period of time to wait before declaring remission in patients with AIH, we based the treatment response on ALT and AST levels. A complete response was considered if ALT and AST levels decreased within the first 24 months of treatment. Similar to other reports, a complete response (biochemical) in our study was achieved in 79% of patients in <1 year. We considered acceptable rate with earlier treatment response. An incomplete response occurred in our patients at a similar frequency to other studies.[17] There are several treatment strategies to induce remission in patients with AIH, and it is difficult to make a decision on the best option for each patient.[26] Thus, it was interesting to observe that the time to remission in patients who began with prednisone at 60 mg/d was shorter than the time to remission in those undergoing combination therapy (prednisone initiated at 30 mg/d plus AZA at 50 mg/d). The beneficial effects on survival were similar between prednisone monotherapy and prednisone plus AZA therapy. However, the influence of a prompt response at delaying the introduction of AZA (approximately 4 weeks) in patients with insufficient medical records to know whether they truly had AIH is not known. The delayed introduction of AZA helps to resolve diagnostic uncertainties and avoids the dilemma of discriminating between AZA-induced hepatotoxicity and a primary nonresponse.[6]

The most appropriate treatment regimen for patients with AIH remains unknown. Budesonide plus AZA may be the most appropriate candidate for the treatment of noncirrhotic patients.[7,27] Unfortunately, budesonide was not available for the treatment of patients in our cohort.

We found no predictive factors of response to therapy in this cohort of patients with AIH similar to other studies. For example, Yoshizawa et al[28] did not find differences related to prognosis, disease severity, sex, liver histology, or presence of cirrhosis among others factors. Ngu et al[29] reported similar results where the histological diagnosis of cirrhosis was not associated with poor prognosis and did not influence the response to initial immunosuppressive treatment. However, Muratori et al,[30] Feld et al,[2] and Kirstein et al,[8] identified the presence of cirrhosis as predictive of poor prognosis and worst treatment response. The reasons for these discrepancies are unknown. Disparities in AIH findings in different studies may be the result of geographical, ethnic, and genetic differences in the studied populations.

Conclusions

The study results cannot be generalizable due to its limitations; nevertheless, this is a valid approach and the data are valuable. These Cuban patients with AIH had an acceptable disease remission rate and a prompt treatment response. Although most patients had advanced-stage liver disease at diagnosis or developed during follow-up, the cumulative survival rate was high when patients were receiving and complying with treatment.

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Conflicts of Interest Statement

The authors have indicated that they have no conflicts of interest regarding the content of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2020.100594.

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