Original Research

Diagnosis and Treatment of Autoimmune Liver Diseases in a Tertiary Referral Center in Cuba

Marlen Ivón Castellanos Fernández, MD, PhD, MP*,1,
Deyanira la Rosa Hernández, MD, MP2, Diego Enrique Cabrera Eugenio, MD1,
Wilson Palanca, MD1, Zaily Dorta Guridi, MD, PhD, MP3, Licet González Fabián, MD, MCs, MP4

1 Department of Researches, National Institute of Gastroenterology, Havana, Cuba
2 Department of Immunology, National Institute of Gastroenterology, Havana, Cuba
3 Department of Hepatology, National Institute of Gastroenterology, Havana, Cuba
4 Department of Pathology, National Institute of Gastroenterology, Havana, Cuba

ABSTRACT

Background: Autoimmune liver diseases (AILD) comprise a set of entities characterized by tissue damage as a result of the loss of self-tolerance. There are few reports of AILD from Caribbean countries.

Objectives: The aim of our study was to investigate the clinical patterns, laboratory findings, and immunologic features, treatment responses, and prognoses of AILD in adult patients at a Cuban tertiary referral center.

Methods: A prospective study was conducted at the National Institute of Gastroenterology in Havana, Cuba, from May 2012 to April 2016. Clinical, immunologic, and histologic features of autoimmune hepatitis (AIH), primary biliary cirrhosis, AIH/primary biliary cirrhosis overlap syndrome, autoimmune cholangiopathy, and primary sclerosing cholangitis were recorded. Response to therapy was assessed by serum alanine aminotransferase and bilirubin levels at 3, 6, 12, and 24 months after treatment initiation.

Results: Of the 106 patients included in the study, 85.5% were women. The median age at presentation was 47 years. AIH was the most common AILD and was diagnosed in 60 patients (56.6%), 55 of whom had type 1 AIH. Primary biliary cirrhosis was diagnosed in 22 patients (20.7%), overlap syndrome in 16 patients (15%), autoimmune cholangiopathy in 5 patients (4.7%), and PSC in 3 patients (2.8%). Most patients were symptomatic; 48 patients (45.2%) presented with liver cirrhosis, 14.5% of whom had decompensated cirrhosis. Follow-up of treatment was between 6 and 24 months. Prednisone monotherapy was used in 22 AIH patients (36.6%) and a combination of prednisone and azathioprine was used in 28 (46.6%) AIH patients. Response to treatment was seen in 41 AIH patients (68.3%), 33 of whom (55%) had a complete response and 8 of whom (13%) relapsed after 12 months of maintenance therapy. No or incomplete response to treatment was seen in 18 patients (30%). In 46 patients with autoimmune cholestasis, ursodeoxycholic acid was used as monotherapy in 25 patients (54.3%).

Conclusions: The clinical profile of AILD in a sample of the Cuban population is similar to that reported in South areas (Developing countries). AIH was more frequent than PBC, and usually presented with advanced liver disease that responded poorly to treatment.

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Introduction

Autoimmune liver diseases (AILDs), including autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and autoimmune cholangiopathy (AIC), comprise a set of entities characterized by tissue damage as a result of the loss of self-tolerance, often in genetically susceptible individuals. These entities sometimes co-occur or overlap, making it difficult to establish conclusive diagnostic criteria and raising the question of whether they are distinct diseases or variants within a spectrum. AILDs have a low prevalence relative to other liver diseases, such as viral hepatitis, nonalcoholic fatty liver disease, and alcoholic liver disease. Genetic, cultural, environmental, social, racial, and other differences across various geographic regions may be involved in the expression of AILD.1,2
AILD diagnosis is based on histologic abnormalities, clinical and laboratory findings, and the presence of 1 or more characteristic autoantibodies. In routine clinical practice in developing countries, AILD diagnosis often relies upon clinical, biochemical, and histologic criteria alone, because autoantibody studies are often unavailable. Most AILD prevalence estimates have been based on European and US populations. In Cuba and other Caribbean countries, population-based studies of the clinical course, incidence, prevalence, and prognosis of these diseases are scarce.

The aim of this study was to investigate the clinical patterns, laboratory findings, immunologic features, treatment responses, and prognoses of adult patients with AILD treated at a tertiary referral center in Cuba.

Materials and Methods

A prospective study was conducted at the National Institute of Gastroenterology, Havana, Cuba, between May 2012 and April 2016. The study was approved by the institutional ethics committee. Written informed consent was obtained from patients before study enrollment. A total of 8320 adult patients were admitted to the outpatient clinic during the study period. A total of 130 patients were recruited, 106 of whom satisfied the inclusion criteria for their particular diagnosis (Table I and Figure 1). Six patients with AILD did not meet inclusion criteria. AIH diagnosis was based on the simplified International Autoimmune Hepatitis Criteria Group 2008 criteria. The diagnostic criteria for PBC, AIC, and PSC were based on the practice guidelines of the American Association for the Study of Liver Diseases. The Chazouillières criteria were used for the diagnosis of AIH/PBC overlap syndrome. Patients were excluded from the analysis if evidence of AILD diagnosis was insufficient or if their medical records were incomplete due to poor follow-up. Exclusion criteria also included pregnancy, HIV infection, hepatitis B or C virus infection, alcohol consumption, use of potentially hepatotoxic drugs, neoplastic disease, and liver ischemic diseases.

All laboratory analyses were performed under the internal organization rules and procedures for the development of clinical trials (Good Clinical Practice), which receive external quality control by the Cuban national regulatory authority, Center for State Control of Medicines, Equipment, and Medical Devices. Patient information was obtained from medical records available from the hepatology department. All patients were evaluated according to the AILD protocol of the Department of Hepatology at National Institute of Gastroenterology.

Study Variables

Mode of Presentation

Patients were categorized into 1 of 4 distinct patterns of AILD presentation: asymptomatic (absence of symptoms with only occasional abnormal liver tests), acute disease (≤ 30 days onset of symptoms, including jaundice, fatigue, drowsiness, or fever, with marked alterations in serum liver function test), insidious onset (mild symptoms of illness for at least 6 months, including progressive fatigue, malaise, anorexia, weight loss, jaundice, or pruritus), or liver cirrhosis (clinical manifestations of established liver cirrhosis). Decompensated cirrhosis was defined as the presence of 1 of the following features: ascites, variceal bleeding, hepatic encephalopathy, bacterial peritonitis, low serum albumin (< 35 g/L), and prolonged prothrombin time (> 15 seconds).

Concurrent Autoimmune Disorders

We recorded the presence of concurrent arthritis (ie, non-specific arthralgia with inflammation) or a confirmed diagnosis of other autoimmune diseases (eg, thyroid disease, rheumatoid arthritis, glomerulonephritis, systemic lupus erythematosus, ulcerative colitis, and others).

| Table I | Definitions used for each autoimmune liver disease. |
|---------|-----------------------------------------------------|
| Primary biliary cirrhosis | The diagnosis can be established when 2 of the following three criteria are met:  
✓ Biochemical evidence of cholestasis based mainly on alkaline phosphatase elevation  
✓ Presence of AMA  
✓ Histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts |
| Autoimmune cholangiopathy (AMA-negative PBC) | ✓ Biochemical evidence of cholestasis based mainly on alkaline phosphatase elevation  
✓ Histologic evidence of nonsuppurative destructive cholangitis, presence of granulomas and destruction of interlobular bile ducts  
✓ AMA-negative, but ANA and ASMA may be present |
| Primary sclerosing cholangitis | ✓ Cholestatic biochemical profile  
✓ Cholangiography endoscopic retrograde cholangiography shows characteristic bile duct changes with multifocal strictures and segmental dilations  
✓ Secondary causes of sclerosing cholangitis excluded  
✓ Patients who present with clinical, biochemical, and histologic features compatible with PBC, but have a normal cholangiogram, were classified as small-duct PSC |
| Overlap syndrome AIH/PBC | AIH (2 out of 3 criteria)  
1. Alanine aminotransferase levels > 5 × ULN  
2. Serum immunoglobulin G levels > 2 × ULN or a positive test for AMA  
3. Liver biopsy showing moderate or severe periportal or periseptal lymphocytic piecemeal necrosis PBC (2 out of 3 criteria)  
PBC (2 out of 3 criteria)  
1. Alkaline phosphatase levels > 2 × or γ-glutamyltransferase levels > 5 × ULN  
2. Positive test for AMA  
3. Liver biopsy specimen showing florid bile duct lesions |
| Autoimmune hepatitis | Simplified International Autoimmune Hepatitis Criteria Group 2008 |

AIH = autoimmune hepatitis; AMA = antimitochondrial antibody; ANA = antinuclear antibody; ASMA = antismooth muscle antibody; PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis; ULN = upper limit of normal.
Family History of Autoimmune Disease

A positive or negative family history of autoimmune disease was determined by patient response to questioning about relatives with known autoimmune disease.

Laboratory Features

Red blood cells, white blood cells, platelets, hemoglobin, and hematocrit were quantified using the ABX Micros 60 hematologic analyzer (ABX Diagnostics, Montpellier, France). Bilirubin, γ-glutamyl transferase, alanine aminotransferase (ALT), aspartate aminotransferase, alkaline phosphatase, albumin, total proteins, glycemia, creatinine, triglycerides, and total cholesterol were determined in the clinical laboratory of the National Institute of Gastroenterology using routine validated methods (Hitachi 902 Clinical Chemistry Analyzer, Roche Holdings AG, Basel, Switzerland).

Hepatitis serology was performed in all patients by ELISA and reverse-transcription polymerase chain reaction for hepatitis B virus and hepatitis C virus. Viral load was quantified using commercially available kits (COBAS Amplicor version 2.0 for hepatitis B virus and hepatitis C virus; Roche). In patients with an acute presentation, serologic tests for hepatitis A virus and hepatitis E virus were also performed. Presence of Wilson’s disease was determined by 24-hour urine copper, ceruloplasmin, and serum copper levels. Presence of hemochromatosis was assessed by transferrin saturation test.

The results of upper abdominal ultrasounds performed at the time of diagnosis were also reviewed. Upper gastrointestinal endoscopic examinations were obtained at presentation even in the absence of bleeding history. Presence of esophageal or gastric varices and/or portal hypertensive gastropathy was considered as diagnostic of decompensated portal hypertension. Magnetic resonance cholangiography was not available. For patients with high suspicion of PSC, endoscopic retrograde cholangiopancreatography was done and the results were included.

Immunologic Data

Levels of immunoglobulins G and M were quantified by a turbidimetric method (Biomediche Technology, specific for the Hitachi 902 supported by Roche Diagnostics (Roche Hitachi 902 Chemistry Analyzer)). Reference values were: immunoglobulin G (6.80–14.45 g/L) and immunoglobulin M (0.34–0.91 g/L [men] and 0.40–0.95 g/L [women]).

Autoantibodies

Presence or absence of serum antinuclear autoantibodies (ANA), antismooth muscle antibodies (ASMA), and antimitochondrial antibodies (AMA) was determined by indirect immunofluorescence (IIF) on rat liver, kidney, and stomach sections (1:40 dilution). In patients with AMA-positive IIF, antimitochondrial M2 antibodies (AMA-M2, positive = 10 IU/mL) and antimicrosomal liver and kidney type 1 antibodies (positive = 15 IU/mL) were quantified using commercial ELISA assays (#ORG-516 and #ORG-253; Orgentec, Mainz, Germany). Antineutrophil cytoplasmic antibodies (positive > 1.0 IU/mL) were quantified by ELISA (#ORG-530; Orgentec).

Liver Biopsy Findings

The following liver biopsy findings were considered indicative of AIH: Presence of interface hepatitis lymphoplasmacytic infiltrate of portal tracts, presence of rosettes of hepatocytes, abnormal bile ducts (including inflammation, proliferation, or ductopenia), and liver cirrhosis. All available liver biopsy results were reviewed by 2 expert pathologists (BVGO and LGF) with very good interobserver agreement (κ index > 0.8).

Response to Therapy

The following data were collected from chart reviews: mode of treatment, treatment response, and treatment withdrawal.
ALT and serum bilirubin levels were determined at diagnosis; at 3, 6, 12 and 24 months after treatment-initiation; and at the end of the follow-up period. Response to treatment in AIH patients was considered complete if serum ALT dropped to the normal range (< 49 U/L) within 6 to 24 months of treatment. Treatment response was considered incomplete if serum ALT decreased to the normal range after 24 months of treatment or by the end of follow-up period if the follow-up period was < 2 years. Patients who failed to achieve reduction of serum ALT or who had an ALT elevation within 24 months were considered non-responders. Relapse was defined as an elevation of ALT to above normal or to the pretreatment level after an initial decrease. Duration of follow-up for each patient was recorded. Progression to decompensated cirrhosis during the follow-up period was recorded. Others drugs used for autoimmune cholestasis were recorded.

Outcome
Mortality was defined as death during the follow-up period as reported in registry of deaths available in the Department of Medical Records and Health Statistics of the institution.

Statistical Analysis
The variables were recorded and processed in a database created in the Statistical Package for Social Sciences for Windows version 21.0 (IBM-SPSS Inc, Armonk, NY). The means, SDs, medians, ranges, and frequencies were calculated in SPSS. Categorical variables were assessed by χ² test. An alpha value of 0.05 was used to determine statistical significance. The estimated prevalence rate of each specific disease was calculated as [(the number of patients with AILD/disease population in the study period) × 100].

Results

Baseline Characteristics
A total of 106 patients were included in the analysis (Figure 1). The median age at presentation was 47 years (range = 18–72 years). Seventy-two patients (68%) were aged > 40 years: 22 (20.8%) were between ages 40 and 49 years, 18 (17%) were between ages 50 and 59 years, and 32 (30.2%) were aged > 60 years. Ninety-one patients (85.8%) were women.

The most common AILD diagnosed in this patient population was AIH (60 patients [56.6%]). Among all patients, 22 (20.7%) were diagnosed with PBC, 16 (15%) with AIH/PBC overlap syndrome, 5 (4.71%) with AIC, and 3 (2.8%) with PSC. Among 8320 patients admitted during the study period, the prevalence of AILD was 1.34%. AIH occurred in 0.7% of admitted patients, PBC in 0.2%, AIH/PBC overlap syndrome in 0.1%, AIC in 0.06%, and PSC in 0.03%.

Clinical Profile of AILD
The clinical, immunologic, and histologic features of each AILD are summarized in Table II.

At the time of AIH diagnosis, the median age was 43.5 years. Liver cirrhosis was the most common mode of AIH presentation, occurring in 28 of 60 (46.6%) patients, 5 (8.3%) of whom had decompensated cirrhosis with ascites (3 patients) or variceal bleeding (2 patients). Insidious onset was the second most common mode of AIH presentation. More than 50% of patients had a concurrent autoimmune disease, and 20% had a family history of autoimmune disease. In patients with AIH, the main immunologic findings were positivity for ANA and ASMA autoantibodies. Serum immunoglobulin G levels were more than 2 times the upper limit of normal in 39 patients and between 1.1 and 2 times the upper limit of normal in 21 patients. Fifty-five patients (91.6%) had type 1 AIH. Only 5 cases of type 2 AIH (antimicrosomal...

### Table II
Clinical, immunologic, and histologic features at presentation of autoimmune liver diseases, Institute of Gastroenterology, Havana, Cuba, 2012–2016.

| Parameter                              | AIH  | Overlap | PBC  | AIC  | PSC  | Total |
|----------------------------------------|------|---------|------|------|------|-------|
| Median age (y)                         | 43.5 (18–70) | 43 (33–64) | 63 (32–72) | 51 (27–64) | 57 (38–60) | 47 (18–72) |
| % Women                                | 81.7 | 87.5    | 95.5 | 100  | 66.7 | 85.6  |
| Mode of presentation                   |      |         |      |      |      |       |
| Asymptomatic                           | 9 (15) | 2 (12.5) | 3 (13.6) | 0    | 0    | 14 (13.2) |
| Acute disease                          | 7 (11.7) | 2 (12.5) | 0    | 0    | 0    | 9 (8.5)  |
| Insidious onset                        | 21 (35) | 9 (56.3) | 15 (68.3) | 3 (60) | 3 (100) | 51 (48.1) |
| Liver cirrhosis                        | 23 (38.3) | 3 (18.8) | 4 (18.2) | 2 (40) | 0    | 32 (30.2) |
| Concurrent immune disease              | 35 (58.3) | 8 (50)  | 10 (45.5) | 1 (20) | 3 (100) | 57 (52.8) |
| Family history of autoimmune disease   | 12 (20) | 2 (12.5) | 6 (27.3) | 1 (20) | 2 (66.7) | 23 (21.7) |
| Autoantibodies                         |      |         |      |      |      |       |
| ANA                                     | 43 (71.7) | 10 (62.5) | 4 (18.3) | 1 (20) | 2 (66.7) | 60 (56.6) |
| ASMA                                    | 39 (65) | 7 (43.8) | 8 (36.4) | 1 (20) | 2 (66.7) | 57 (53.7) |
| AMA                                     | 4 (6.7) | 6 (37.5) | 15 (68.2) | 0    | 0    | 25 (23.5) |
| Anti-LKM1                               | 5 (8.3) | 1 (63)  | 0    | 0    | 0    | 6 (5.6)  |
| pANCA                                   | 1 (1.7) | 1 (63)  | 1 (45) | 0    | 0    | 3 (2.8)  |
| IgG                                     | 19.1 (9.06) | 12.6 (6.4) | 12.1 (5.1) | 10.3 (5.1) | 16.3 (12.3) | 16.4 (8.3) |
| IgM                                     | 3.2 (2.1) | 5.5 (3.1) | 7.6 (5.3) | 14.3 (11.3) | 11.0 (7.1) | 5.1 (5.0)  |
| Liver biopsy                            | 35 (58.3) | 13 (81.3) | 16 (72.7) | 5 (100) | 2 (66.7) | 71 (67)  |
| Interface hepatitis                     | 21 (60.0) | 6 (46.2) | 6 (37.5) | 1 (20.0) | 1 (50) | 35 (49.2) |
| Mononuclear cell infiltrates            | 28 (80.0) | 12 (92.3) | 13 (81.3) | 3 (60) | 1 (50) | 57 (80.3) |
| Rosette                                 | 9 (25.7) | 1 (7.7)  | 2 (12.5) | 0    | 0    | 12 (16.9) |
| Biliary features                        | 3 (8.6) | 7 (53.8) | 14 (87.5) | 5 (100) | 2 (100) | 31 (41.7) |
| Cirrhosis                               | 5 (23.8) | 3 (50)   | 8 (53.3) | 0    | 0    | 16 (35.6) |

AIH = autoimmune hepatitis; AMA = antimitochondrial antibody; ANA = antinuclear antibody; ASMA = antismooth muscle antibody; IgG = immunoglobulin G; IgM = immunoglobulin M; anti-LKM1 = antiliver kidney microsomal antibody; pANCA = perinuclear antineutrophil cytoplasm antibody.

* Values for age, IgG, and IgM are presented as mean (SD), whereas other values are presented as n (%) unless otherwise noted.

† Histologic features were calculated on the basis of total biopsies per group (AIH, overlap, PBC, AIC, or PSC).
Table III
Classification of patients with autoimmune hepatitis according to the simplified Hennes criteria, Institute of Gastroenterology, 2012–2016.

| Criteria                        | Score +2 | Score +1 |
|--------------------------------|----------|----------|
| Absence of viral hepatitis     | 60 (100) | 0        |
| Autoantibodies                 | ANA/ASMA | LKM1     |
| Liver histology                | 5 (8.3)  | 32 (53.3)|
| Immunoglobulin G level         | > 2 Upper Limit of normal | 39 (65) |

AIH: autoimmune hepatitis; ANA: antinuclear antibody; ASMA: anti-smooth muscle antibody; LKM1: anti liver kidney microsomal antibody.

Table IV
Response to treatment of patients with autoimmune hepatitis, Institute of Gastroenterology, 2012–2016.

| Alternative treatment |Responders| Nonresponders| Relapsers |
|-----------------------|----------|--------------|-----------|
| Prednisone (n = 22)   | 13       | 8            | 1         |
| Prednisone + AZA (n = 28) | 15     | 7            | 6         |
| Prednisone + UDCA (n = 5) | 2       | 2            | 1         |
| Prednisone + UDCA (n = 1) | 1       | –            | –         |
| UDCA (n – 2)          | 1        | 1            | –         |
| Prednisone + methotrexate (n = 1) | 1        | –            | –         |
| Total (n = 59)        | 33       | 18           | 8         |

AZA = azathioprine; UDCA = ursodeoxycholic acid.

Discussion
Three referral centers in Cuba diagnose and manage adults with AILD. According to the Statistical Yearbook of Health in Cuba, there were a total of 272,930 and 276,250 gastroenterology consultations in 2014 and 2015, respectively.12 Our institution received 6.1% and 6.8% of the gastroenterology consultations from the Cuban population. Disease prevalence estimates based on these data should be made with caution, because multicenter studies with standard methodology and uniform diagnostic criteria are required to establish the actual prevalence of AILD in our country. Despite this limitation, our study is 1 of few to evaluate the clinical features and treatment of AILD in a Cuban population.

AIH is a global disease with different patterns of prevalence and clinical characteristics. Disease onset occurs at younger ages in Africa, Asia, Arabia, India, and South America. In Europe, North America, and Japan, AIH usually occurs at older ages.13 Fallatah et al14 describe a mean age at presentation of 32 years in Arabia, whereas Ngu et al15 reported a relatively higher incidence in the

During the study period, 3 patients died (2 with AIH and 1 with PBC) from complications of cirrhosis (variceal or gastrointestinal bleeding and encephalopathy). Another 3 patients became pregnant, 2 of whom with AIH did not have exacerbations during pregnancy or during the early postpartum period. Another patient with AIC had only an exacerbation of pruritus, which was treated with ursodeoxycholic acid (UDCA).

Treatment
The duration of treatment and follow up was between 6 and 24 months. One patient with AIH was not treated due to persistently normal liver enzymes. Patients with AIH were treated with prednisone monotherapy, UDCA monotherapy, or combination therapy of prednisone plus azathioprine (AZA), UDCA, and/or methotrexate (see Table IV).

The starting dose of prednisone was 30 to 60 mg/d, and maintenance doses were 5 to 15 mg/d. The starting dose of AZA was 50 to 100 mg/d, and maintenance doses were 50 to 75 mg/d. As indicated in Table IV, 41 patients (68.3%) responded to treatment: 33 of the treated patients (55%) (14 with liver cirrhosis) had a complete response and 8 patients (24.2%) relapsed after 12 months of maintenance therapy. Two patients with frequent relapses were treated with mycophenolate mofetil (MMF) 1000 mg daily with a good response. Eighteen patients (30%), 12 of whom had liver cirrhosis, had no or incomplete responses to the treatment. The time to complete response varied from 1 to 12 months. There was no difference in response to treatment at the end of the follow-up period between AIH patients with or without liver cirrhosis (P = 0.194). Three patients responded and stopped after 2 years of uninterrupted treatment without evidence of relapse noted at the end of follow-up. Five patients stopped treatment on several occasions and relapsed. Twenty patients had side effects from prednisone or AZA or both; diabetes was the most common side effect in 8 patients (40%), followed by cosmetic changes (striae, weight gain, and facial hirsutism) in 7 patients (35%), osteopenia in 3 patients, and skin infection in 2 patients.

In the case of autoimmune cholestasis, UDCA was the most commonly used drug. UDCA monotherapy was used in 25 patients (54.3%) (22 with PBC and 3 with AIC). Patients with overlap syndrome were treated with combination therapy as follows: UDCA plus prednisone in 8 patients (17.3%), UDCA plus AZA plus prednisone in 4 patients (8.6%), and 2 patients (4.3%) also received cholestyramine for itching.

Discussion
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sixth decade of life (ages 50–54 years) in New Zealand. The mean age of AIH presentation in this case series is similar to that reported in the South Sea areas. There is not enough robust epidemiologic data in Cuba to confirm these results. Among the first 100 liver transplant patients at the Medico-Surgical Research Center, Havana, Cuba, the most frequent etiologies of cirrhosis were hepatitis C virus (27%), alcoholic (18%), cryptogenic (13%), and autoimmune (11%).

In a recent study of 46 Cuban patients with AILD, 58.7% of patients were diagnosed with AIH, 17% with overlap syndrome, 13% with PBC, and 11% with PSC.

During the past few decades, there has been an increase in the prevalence of PBC cases reported in Europe and the United States. In India, Choudhuri et al. and Gupta et al. reported an AILD prevalence of 1.7% and 3.43%, respectively, with a higher frequency of AIH (1.5%–2.8%) than PBC (0.1%–0.2%). In contrast, Qiu et al. reported a similar prevalence of AIH in China, but a greater prevalence (23%) of overlap syndrome. Mean age at diagnosis did not differ between these reports. All these results are similar to ours.

Asymptomatic AIH has been reported to occur in between 25% and 45% of patients, but data from a Swedish population study suggests a smaller number (12%) of patients are asymptomatic at the time of diagnosis. Emweluzo et al. also recognized the significance of the persistent elevation in transaminases in patients older than age 18 years. The acute presentation pattern, which is similar to viral hepatitis, has been observed to occur in between 25% to 40% of patients in North America and Europe. We expected to find similar results; however, the acute presentation was seen in only 11.7% of our sample. This is likely an underestimate because patients with acute disease usually first present to an emergency department at primary and secondary care centers. Also, this presentation is commonly recognized in childhood, and children are not seen in our center.

Liver cirrhosis has been reported to be the mode of AIH presentation in 30% to 50% of patients similar to the frequency observed in this investigation. Czaja and Carpenter described a greater frequency of cirrhosis at presentation (33%) in elderly patients.

The presence of a relatively high frequency of cirrhosis in younger patients was striking. It is possible that genetic factors contributed to the frequency of cirrhosis in this sample. It would be interesting to investigate the interaction between genetic factors, geographic area, and mode of AIH expression. Similar to previous reports, thyroid diseases and rheumatoid arthritis were the most common concurrent immune diseases in patients with AIH. These autoimmune diseases are reported relatively frequently in patients with AILD, especially those with AIH. A large number of autoimmune diseases were also found in patients with AIH/PBC overlap syndrome and PBC. Therefore, extended screening for existing autoimmune diseases during the routine assessment of these patients is recommended.

In patients with AIH, similar frequencies of ANA and ASMA were detected by Fallatah et al. Czaja reported 67% positivity for both markers. Positive AMA is the serologic marker of PBC, but 15% of PBC sera are AMA-negative at routine immunofluorescence and are therefore referred to as probable cases. We found a higher proportion of AMA-negative IFF than expected in patients with distinctive histologic findings of PBC (36%). Notably, several of these patients were ANA- and ASMA-positive, suggesting that the laboratory methods used for AMA detection (immunofluorescence) may not be accurate enough. Recently, using 100 PBC IIF AMA-negative sera samples, Bizzaro et al. detected positive results in 43% of samples using newer laboratory methods and recombinant antigens, confirming the hypothesis that the proportion of AMA-negative PBC cases could be significantly minimized by the use of more modern laboratory methods.

Histologic findings are the key to diagnosis of AILD, although their value has been questioned. When the remaining diagnostic findings are insufficient, liver biopsy can provide essential information in certain situations. However, it is impossible to perform liver biopsy in all cases. Almost 40% of patients with AIH had cirrhosis at the time of diagnosis and it was not possible to perform liver biopsy for multiple reasons. Consistent with our findings, Fallatah et al. reported that it was possible to do a biopsy in only one-third of cases of AIH, because of cirrhosis in advanced stages, ascites, coagulopathy, or patient refusal. Lymphoplasmacytic infiltrate of the portal tracts and interface hepatitis are typical histologic elements of AIH; however, these are reported at variable frequencies.

Interface hepatitis was previously reported in 65% of patients, including patients with overlap AIH-PBC. Choudhuri et al. found this in 72.7%, Bjornsson et al. in 95%, and Gupta et al. and Abdollahi et al. found this in 100% of patients. Furthermore, lymphoplasmacytic infiltrate of portal tracts has been reported between 60% and 91% of patients. Our results are similar. Among the main difficulties that could explain the variable percentages of these findings are specimen size and quality, an inadequate number of portal tracts, and unrepresentative amounts of parenchyma. It is known that sample variability is among the main limitations of liver biopsy.

Based on the available randomized controlled trials, prednisone monotherapy, and prednisone plus AZA combination therapy are both viable induction therapies for treatment-naive AIH patients and relapers. For maintenance therapy, prednisone plus AZA and AZA monotherapy are superior to prednisone monotherapy. The results of this study support the usefulness of these induction therapies but failed to demonstrate the superiority of the combination in maintaining remission because there were no differences among the alternative treatments.

Treatment with prednisone induces clinical, laboratory, and histologic remission in between 70% and 80% of patients within 2 to 3 years. However, about 13% of patients fail to enter remission after 36 months of treatment. Because of the duration of this study, it was impossible to evaluate the response to more than 2 years of treatment; however, the remission rate (68.3%) was lower than reported in international studies. Although the response was higher than found by Fallatah et al. (54.8%), the inadequate response to treatment was also higher than expected (30%), likely because the longest follow-up period was only 24 months, and there was a high frequency of liver cirrhosis. There is a possibility that the indicated pharmacologic therapies have not been the most effective for each patient.

The 13% of patients who failed to enter remission after 36 months of treatment were classified as incomplete responders. The probability of a suboptimal response before treatment is higher in young patients and in patients with a severe presentation or cirrhosis. MMF is widely used in the treatment of AIH as an alternative to the standard regimen, often with good results, in patients with intolerance, treatment failure, or refractory disease. Our 2 patients who failed to respond to standard treatment had a good response to MMF.

UDCA has not been systematically evaluated in AIH, although in early trials patients demonstrated clinical and biochemical improvement. In this study, UDCA was widely used in patients with cholestasis with good results. As expected, most of the treated patients demonstrated some improvement in liver biochemistry.

The results of the study identified some key issues. First, patients with AIILD, particularly AIH, presented in advanced stages where accuracy in diagnostic assessment and therapeutic results were affected. Second, the diagnostic methods, especially of
laboratories, should be more precise, and the treatment should be optimized for each patient using an evidence-based approach. Finally, early referrals to transplant centers must be made for those patients with portal hypertension or synthetic dysfunction who mostly do not comply with the standard treatment.

Conclusions

The clinical profile of AIH was a sample of the Cuban population is similar to that reported in South areas (Developing countries). AIH was more frequent than PBC, and usually presented with advanced liver disease that seemed to respond poorly to treatment. National statistics are needed to facilitate a better understanding of AIH prevalence in patients with chronic liver disease.

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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.

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