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Our Autoimmune Hepatitis Patients: Single Center Experience

Otoimmün Hepatit Hastalarımız, Tek Merkez Deneyimi

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ABSTRACT

Introduction: Autoimmune hepatitis (AIH) is a form of chronic hepatitis of unknown etiology characterized by autoimmunological properties and circulating autoantibodies. It can be treated after early diagnosis and often requires a great effort during diagnosis and regular follow-up. In Turkey, the number of studies examining AIH patients from the point of diagnosis to treatment is very low. We retrospectively evaluated patients diagnosed with AIH in the last 10 years.

Methods: Between 2009 and 2019, AIH patients who were diagnosed in our hospital or applied for ongoing treatment were evaluated retrospectively from the hospital information system. Patients who responded were invited to the clinic and missing data were added.

Results: A total of 48 patients (10 males and 38 females) aged 18-73 years (44.8±14.8 years) were evaluated. Four patients (8.3%) were asymptomatic. In the pre-treatment evaluation, cirrhosis occurred in 31% of patients, acute hepatitis in 21% of patients, and chronic hepatitis in 39% of patients. Type 1 AIH was observed in 81.2% of patients, 4.2% had type 2 AIH, and 14.6% demonstrated autoantibody negative AIH. A total of 35.4% of patients (n=17) had overlap syndrome accompanied by biliary tract damage. A total of 68.8% of patients with type 1 AIH had antinuclear antibody, 41.7% were positive for anti-smooth muscle antibody, and 31.3% were positive for both autoantibodies. A total of 33.3% of patients had non-hepatic disease. The treatment response rates were: 68.8% (complete); 18.7% (partial); and 12.5% (non-responders). Of the patients with a mean follow up of 3.54±2.63 years, 37 patients continued the treatment.

Conclusion: Our data demonstrated similar findings to previously published literature in terms of the ratio of female-to-male presentation, type 1, type 2 rates, rate of concomitant non-hepatic autoimmune disease, and response to treatment. They were different in terms of the low number of asymptomatic patients, lower percentage autoantibodies, and high proportion of overlap syndrome.

Keywords: Autoimmune hepatitis, autoantibody, primary biliary cholangitis, cirrhosis

ÖZ

Amaç: Otoimmün hepatit (OIH) dolaşan otoantikorlar, otoimmünolojik tabloyla karakterize etiyolojisi bilinmeyen bir kronik hepatittir. Erken tanı ile çoğu kez tedavi edilebilen, tanısında birden çok değerin kullanıldığı, düzenli takip gerektiren bir hastalıktır. Ülkemizde OIH hastalarını tanısından tedaviye yanıtına kadar inceleyen çalışma sayısı yok denecek kadar azdır. Son 10 yılda OIH tanısı alan hastalarımızı retrospektif olarak değerlendirdik.

Yöntemler: 2009 ile 2019 yılları arasında kliniğimizde tanı almış veya takip amacıyla başvurmuş OIH hastaları, retrospektif olarak hastane bilgi sisteminden geriye dönük olarak değerlendirildi. Ulaşabilen hastalar kliniğimize davet edilerek, elde olmayan bazı tetkikleri eklendi.

Bulgular: 18-73 yaş arası (44,8±14,8 yıl) toplam 48 hasta (10 erkek ve 38 kadın) değerlendirildi. Dört hasta (%8,3) asemptomatik idi. Tedavi öncesi değerlendirmede hastaların %31'i siroz, %21'i akut hepatit, %39'u kronik hepatit idi. %81,2'si tip 1 OIH, %4,2'si tip 2 OIH iken %14,6'sında ise otoantikor negatif OIH saptandı. Hastaların %35,4'ünde (n=17) ise safra yolları hasarının eşlik ettiği overlap sendromu mevcut idi. Tip 1 OIH hastaların %68,8'inde antinükleer antikor, %41,7'sinde anti düz kas antikoru pozitifliği var iken her iki otoantikor pozitif olan hasta sayısı oranı %31,3 idi. %33,3'ünde karaciğer dışı hastalık mevcut idi. Tedaviye yanıt oranları tam yanıt %68,8, kısmi yanıt %18,7, yanıtsız hasta oranı ise %12,5 idi. Ortalama takip süresi 3,54±2,63 yıl olan hastaların halen 37'si tedaviye devam etmekte idi.

Sonuç: Kadın erkek oranı, prezetasyonu, tip 1, tip 2 oranları, eşlik eden karaciğer dışı otoimmün hastalık oranı ve tedaviye yanıt oranları bakımından çalışmamızın literatüre benzer şekilde olduğu görüldü. Asemptomatik hasta oranının düşük olması, otoantikorların daha düşük yüzdede saptanması, overlap sendromunun yüksek olması açısından farklılık göstermekte idi.

Anahtar Kelimeler: Otoimmün hepatit, otoantikor, primer bilier kolanjit, siroz

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Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory disease of the liver that can occur at any age and may progress to cirrhosis if untreated. Females are more frequently affected than males. Difficulties in AIH diagnosis may be observed due to its heterogeneous nature, its prevalence, and the different ways in which AIH presents itself. Diagnosis is based on certain parameters such as the presence of characteristic autoantibodies, which is a specific feature in liver histopathology, abnormal serum globulin levels, and exclusion of other chronic liver diseases (1). The prevalence of AIH varies from 4 to 25 people per 100,000, although it varies among countries (2,3).

The symptoms and signs may occur in a a range from the findings of a normal physical examination to signs of cirrhosis or hepatic failure (e.g., jaundice, ascites, splenomegaly). Patients may be asymptomatic or experience non-specific symptoms such as loss of appetite, nausea, abdominal pain, fatigue, arthralgia, and itching (4). Autoimmunity-related diseases such as celiac disease, rheumatoid arthritis, type 1 diabetes, autoimmune thyroiditis, and ulcerative colitis may accompany AIH. In acute presentation, an increase in aminotransferases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] by 10-20 times the upper limit of the reference range is observed. The AST and ALT to alkaline phosphatase (ALP) ratio is generally <1:5. In patients with chronic symptoms or cirrhosis, the increase in AST and ALT is less pronounced while the ratio of ALP to AST (or ALT) is lower (approximately 1:2) (5). AIH is usually accompanied by hypergammaglobulinemia due to the elevation of immunoglobulin (Ig) G while Ig A and Ig M levels are normal (6). Antinuclear antibodies (ANA) are the most common circulating autoantibodies in AIH and may be the only autoantibodies detectable. Anti-smooth muscle antibodies (ASMA) are more specific but less common in AIH than ANA, especially when present at titers of 1:80 or are greater in adults. Anti-liver-kidney microsomal antibodies (anti-LKM) often occur in patients with type 2 AIH (7). Anti-liver cytosol antibody-1 is a marker of type 2 AIH. These antibodies usually coexist with anti-LKM-1 but may be the only detected autoantibody. Anti-soluble liver antigen/liver pancreatic (anti-SLA/LP) antibodies were found in 10%-30% of adult patients with type 1 AIH (8). Furthermore, different autoantibodies such as anti-actin antibodies, peripheral antineutrophil cytoplasmic antibodies, and anti-DNA antibodies may be found in some patients. Although liver histology is not specific, histopathological changes such as interface hepatitis (with lymphoplasmacytic infiltration rich in plasma cells), hepatocyte rosette formation, and zone 3 necrosis (central perivenulitis) support the diagnosis.

Almost 90% of AIH patients have type 1 AIH. Positive autoantibodies such as ANA, ASMA or anti-SLA/LP with HLA DR3, DR4 and DR13. Unresponsiveness to treatment is rare but post-treatment relapse and duration of treatment vary (9). Type 2 AIH occurs in approximately 10% of patients and is associated with HLA DR3 and DR7. Type 2 AIH is more common in children and young adults and has a more severe course and resistance to treatment than type 1 AIH (10). Type 3 AIH (anti-SLA/LP often accompanied by anti-Ro52 positivity) is rare while type 1 AIH has a similar but worse prognosis. Some authorities and guidelines accept it as if type 1 AIH. Autoantibody-negative AIH (or cryptogenic hepatitis) may also occur. Here, the response to treatment supports the diagnosis (4). Diseases such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) may accompany AIH. In these cases, overlap syndrome is observed. In patients with AIH/PBC overlap, histology may refer to AIH, serology may refer to PBC or histology may refer to PBC, serology may refer to AIH (11). In AIH/PSC overlap, serological and histological features are similar to those observed in AIH. When examined using imaging techniques, PSC has characteristic features. Survival rates were decreased in patients with overlap compared to AIH patients (12). It is necessary to differentiate drug-induced AIH from drug-induced liver damage, which differs in patophysiology. Corticosteroids and azathioprine are mainly used in treatment (4,10). In overlap syndromes, ursodeoxycholic acid (UDCA) may be added to the treatment regime. With early diagnosis and effective treatment, the disease can stabilize, fibrosis can regress histologically, and cirrhosis can be halted (6).

In Mersin University Hospital, Department of Gastroenterology, we investigated certain parameters such as the type of AIH that patients were diagnosed with and treated for over the last 10 years, their presentation at the time of diagnosis, the percentage of overlap syndrome, the types of given treatments, and the response of patients to treatment.

Methods

In our clinic, adult patients with AIH, who had been diagnosed over the last 10 years or who were continuing their follow-up, were retrospectively identified from the hospital information system. Complete blood counts; liver function tests; and measures of albumin, total protein, immunoglobulins, prothrombin time, alpha-1-antitrypsin, ferritin, copper, and ceruloplasmin were made in the biochemistry laboratory of Mersin University Hospital. The serology of hepatitis A, B, and C, cytomegalovirus, and the Epstein-Barr virus were examined in the microbiology laboratory of our hospital. ANA, ASMA, anti-LKM, anti-SLA/LP, and anti-mitochondrial antibody (AMA) were investigated by using an indirect immunofluorescence method in the microbiology laboratory of our hospital. Values above 1/40 for each antibody were considered positive. The sizes of the liver and spleen and the parenchymal status of all cases were examined using abdominal ultrasonography. Endoscopy was performed in patients with an enlarged spleen and/or cirrhosis.

The diagnosis of AIH was made according to the simplified scoring system published by the International Autoimmune Hepatitis Group (2008), which includes four basic components: autoantibody presence, Ig level, histopathology and viral hepatitis status (13). If the total score was 6, AIH was possible. On the other hand, if the total score was ≥7, definite AIH was diagnosed. The AIH subtypes were classified as follows: type 1, positive for ANA and/or ASMA; type 2, positive for LKM-1; type 3, positive for anti-SLA; autoantibody negative, negative for autoantibodies. The diagnosis of AIH was accepted as an overlap syndrome if there was associated biliary tract damage, enzyme height in a cholestatic pattern, and/or AMA positivity in histology. Magnetic resonance cholangiopancreatography (MRCP) was performed to rule out the possibility of PSC in suspected patients.

A total of 173 patients were evaluated. Fifty-six of these patients presented with incomplete data, 28 patients did not undergo regular follow-up, 13 patients refused biopsy, 11 patients demonstrated only

biliary changes in histology, and 17 patients had a simplified AIH score <6, and they were excluded from the study (Figure 1). A total of 48 patients were included in the study. This study was approved by the Ethics Committee of Mersin University (decision no: 2019/750).

Histological Evaluation

Before the treatment, liver biopsy was performed with a 16-g Menghini type needle under ultrasound guidance in Mersin University Hospital, Department of Gastroenterology and histopathological evaluation was carried out by medical pathology specialists in our hospital. Patients who underwent biopsy at the external center were asked for their preparations and were re-evaluated in our pathology unit. Pathological diagnoses were made according to pre-determined criteria (14).

Evaluation of Response to Treatment

According to serum ALT and AST and/or Ig G levels, cases that returned to normal values within 6-12 months and cases that were clinically asymptomatic were evaluated as a complete response. Cases that did not return to normal within 12 months but decreased according to baseline level were evaluated as a partial response. Cases that did not demonstrate any decrease during the two-year follow-up were considered non-responsive. If the increase in ALT and AST levels after receiving treatment, or discontinuation of treatment was greater than three times the normal values, this was classed as a relapse.

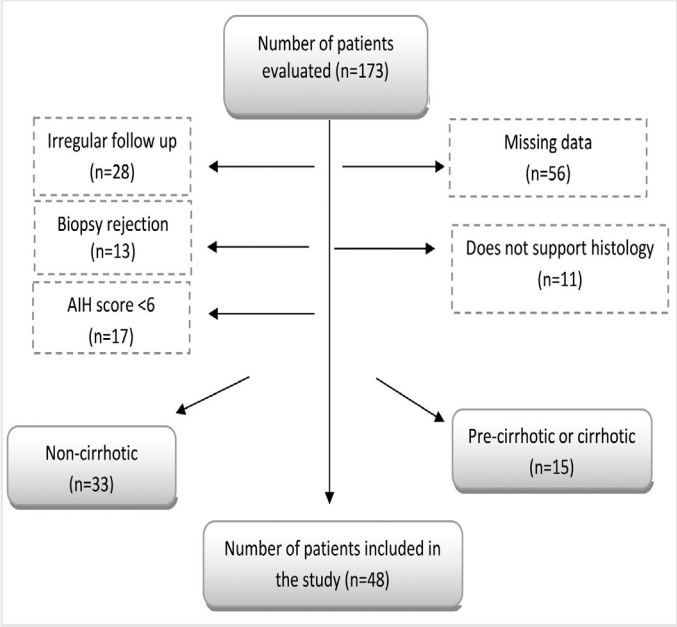

Figure 1. Patient selection (autoimmune hepatitis)

Statistical Analysis

Continuous variables were reported as mean ± standard deviation, and categorical variables were reported as percentages. A student's t-test and a Mann-Whitney test were used for continuous variables and a chi-square test was used for categorical variables. SPSS 20.0 for Windows (IBM Corporation, Armonk, New York, USA) was used to perform the statistical analyses.

Results

The study included 48 patients. Ten patients (20.8%) were male and 38 patients (79.2%) were female. The mean age was 44.8±14.8 years (range: 18-73 years). The period between symptomatic onset and patient diagnosis was 7.51±7.8 months. The main symptoms and signs at admission were fatigue (86%), mild abdominal pain (46%), pruritus (27%), muscle pain (25%), jaundice (14%), and ascites (10%). Diarrhea and fever were present in several cases. Four patients (8.3%) were asymptomatic and transaminase elevation was detected in screening tests. These patients were diagnosed with AIH due to the persistence of this elevation during follow-up. In the pre-treatment evaluation, cirrhosis or pre-cirrhosis was detected while 31.3% of patients and 68.7% of patients were non-cirrhotic. A total of 33% of patients who were non-cirrhotic presented with acute hepatic attack, which was also observed in 40% of cirrhotic patients (Table 1).

Biopsy was not performed in a patient who was cirrhotic due to refusal of the patient and a risk of complications. This patient was ANA and ASMA positive and demonstrated high transaminases, and other etiologic factors were excluded. This patient was diagnosed as having type 1 AIH and treatment was initiated. Biopsy was performed in 47 patients. Cirrhosis or pre-cirrhosis was detected by biopsy in eight patients whose conditions were classified as non-cirrhotic before the histologic evaluation. Interface hepatitis was detected in 45 patients (96%), plasmocytic infiltration in 39 patients (83%), and rosette formation in six patients (12.7%). AIH-compatible histology was not detected in one patient, but the patient had a simplified AIH score of 6. This patient was diagnosed with AIH and treatment was initiated. A complete response

Table 1. Gender complaints, presentation and histological characteristics of the patients

Gender		Complaints		Presentation		Histology	
Male	20.8%	Weakness	86%	Cirrhosis or pre-cirrhotic	31%	Interface hepatitis	96%
Female	79.2%	Abdominal pain	46%	Acute hepatitis	21%		
		Itching	27%	Chronic hepatitis	39%	Plasmocytic infiltration	83%
		Muscle pains	25%	Asymptomatic	9%	Rosette formation	12.7%
		Jaundice	14%	Fulminant liver failure	0%	Biliary tract changes	41.6%
		Ascites	10%			None	2.1%
		Fewer	8.3%				
		Asymptomatic	8.3%				

to treatment was achieved in this patient. Biliary duct changes were detected by histology on biopsies from 20 patients. Three patients were AMA negative and normal cholestatic enzymes were not accepted as representing overlap syndrome (Table 1).

In the pre-treatment evaluation, 81.2% of patients were diagnosed with type 1 AIH, 4.2% were diagnosed with type 2 AIH, and 14.6% were diagnosed with autoantibody negative AIH. A total of 68.8% of patients diagnosed with type 1 AIH were positive for ANA, 41.7% were ASMA positive, and 31.3% were both ANA and ASMA positive. A total of 35.4% of patients (n=17) had overlap syndrome with PBC. AMA was positive in 12 out of 17 patients (70.5%) with PBC. Histopathologic examination of AMA-negative patients showed bile duct damage and high cholestatic enzymes. In these patients, PSC was excluded by MRCP. Two patients who were AMA positive were not considered to have overlap syndrome because of the absence of bile duct changes and the normal range of cholestatic enzymes. No difference was observed between the cirrhotic and non-cirrhotic groups in terms of the type of AIH ($p>0.05$). Hepatitis B (HBV) was detected in two patients at the time of diagnosis, one of whom was cirrhotic. The HBV DNA of these patients was below 2000 IU/mL and hepatitis D antigen was negative. Both ANA and ASMA autoantibodies were detected in these patients, who also presented with acute hepatitis. Hepatitis C and HIV were not detected in any of the patients. In the non-cirrhotic group, albumin and platelet counts were high. In the cirrhotic group, ALP, total bilirubin and international normalized ratio levels were high ($p<0.05$). Data from all patients are presented in Table 2.

When we evaluated the accompanying diseases [diabetes mellitus (DM) in five patients, Hashimoto's thyroiditis in five patients, hypertension

Table 2. Demographic and laboratory patient data (prior to treatment)

		Total group (n=48)	Non-cirrhotic group (n=33)	Pre-cirrhotic and cirrhotic group (n=15)	p
Age (years)		44.8±14.8 49.3±9.82	45.7±13.6	42.6±17	0.253
Gender (female)		38 (79.2%)	25 (76%)	13 (86.7%)	0.389
AIH	Type 1 (%)	39 (81.2%)	27 (81.8%)	12 (80%)	0.881
	Type 2 (%)	2 (4.2%)	1 (3%)	1 (6.7%)	0.558
	Type 3 (%)	0	0	0	-
	Autoantibody negative	7 (14.6%)	5 (15.2%)	2 (13.3%)	0.676
Overlap syndrome (%)		17 (35.4%)	10 (30.3%)	7 (46.7%)	0.272
ANA positivity (%)		33 (68.8%)	24 (72.8%)	9 (60%)	0.379
ASMA positivity (%)		20 (41.7%)	14 (42.4%)	6 (40%)	0.874
Anti-LKM positivity (%)		2 (4.2%)	1 (3%)	1 (6.7%)	0.558
IgG		1.89±0.61	1.73±0.51	2.22±0.68	0.004
HBV positivity (%)		2 (4.2%)	1 (3%)	1 (6.7%)	0.558
HCV positivity (%)		0	0	0	-
ALT (U/L)		320±301	341±323	276±239	0.249
AST (U/L)		312±323	274±277	393±395	0.124
GGT (U/L)		188±146	170±131	228±165	0.107
ALP (U/L)		189±149	163±128	245±173	0.041
FBG		107±37	103±40	118±27	0.103
Creatinine (mg/dL)		0.64±0.16	0.66±0.18	0.62±0.11	0.227
Albumin (g/dL)		3.68±0.63	3.83±0.60	3.39±0.56	0.005
Total protein (g/dL)		7.42±1.17	7.39±1.33	7.51±0.65	0.371
Total bilirubin (mg/dL)		2.32±2.68	1.79±2.26	3.47±3.13	0.024
INR		1.13±0.25	1.08±0.22	1.23±0.25	0.025
Plt (x 10^3/µL)		222±82	257±71	146±49	0.000
HCT (%)		37.5±5.38	37.8±5.35	36.9±5.3	0.312
Wbc (µL)		7254±2623	7916±2550	5800±2152	0.004

AIH: autoimmune hepatitis, ALP: alkaline phosphatase, ALT: alanine aminotransferase, ANA: anti-nuclear antibody, ASMA: anti-smooth muscle antibody, AST: aspartate aminotransferase, FBG: fasting blood glucose, GGT: gamma glutamyl transpeptidase, HBV: hepatitis B virus, HCV: hepatitis C virus, HCT: hematocrit, IgG: immunoglobulin G, INR: international normalized ratio, LKM: liver-kidney microsomal antibody; Plt: platelet, wbc: white blood cell

(HT) in two patients, asthma in two patients, hypoparathyroidism in one patient, impetigo, diabetes insipidus, ulcerative colitis, Parkinson's disease, Guillain-Barre syndrome and coronary artery disease (CAD)] (Table 3), two of these patients had DM and hypothyroidism, one had DM and HT, one had hypothyroidism and hypoparathyroidism, and one had DM and CAD. No accompanying- extrahepatic disease was detected in 66.7% of patients.

Treatment was initiated with a combination of steroids (methylprednisolone and prednisolone), azathioprine (AZA), and UDCA (Table 4). Induction therapy was started with steroids (0.5-1 mg/kg), UDCA (15-25 mg/kg), and AZA (50 mg daily). For remission therapy, the steroid dose was adjusted (5-10 mg daily) and the AZA dose was adjusted (1.5 mg/kg) while the UDCA dose was unchanged. Twenty-nine of the patients were administered a steroid + AZA. Eleven patients were administered steroid + AZA + UDCA. Five patients (12.5%) who received this treatment were unresponsive. Of the five unresponsive patients, two responded to mycophenolate mofetil treatment while three were unresponsive despite different treatments being used. One of the three unresponsive patients had type 2 AIH with cirrhosis, developed sepsis and pancytopenia, and died. In another patient, cirrhosis developed. This patient died of esophageal variceal bleeding. The third unresponsive patient had liver transplantation and is now stable. Only AZA treatment could be administered in a cirrhotic patient who could not receive steroid treatment. Although other treatments were tested in this patient, the patient died within a year due to hepatic cirrhosis. In the seven patients who could not use AZA due to intolerance and hyperbilirubinemia, steroid treatment (plus UDCA in six cases) was administered. No patients were unresponsive to this regime. A complete response was observed in 68.8% of patients, a partial response was observed in 18.7% of patients, and 12.5% of patients were unresponsive (Table 4). One of the 17 patients with AIH-PBC was unresponsive while four demonstrated a partial response.

Table 3. Accompanying -extrahepatic diseases

Diseases	%
Diabetes mellitus	10.4
Hashimoto's thyroiditis	10.4
Hypertension	4.2
Asthma	2.1
Hypoparathyroidism	2.1
Impetigo	2.1
Diabetes insipidus	2.1
Guillain-Barre syndrome	2.1
Ulcerative colitis	2.1
Coronary artery disease	2.1
Parkinson's disease	2.1

One patient who received AZA developed lymphadenopathy in the neck and abdomen during follow-up, leading to treatment discontinuation. Lymph node excision was performed, and lymphoma was excluded. This patient relapsed after the discontinuation of treatment but went on to achieve a complete response with budesonide. Side effects such as weight gain, osteoporosis, and hyperglycemia developed in 13 patients (27%) while side effects such as skin rashes, cataracts, and fibromyalgia were noted in five patients (10.4%). These observations were most frequently observed in patients administered steroids. With a mean follow-up of 3.54±2.63 years, a healthy relapse rate could not be evaluated because 37 patients (77%) were still on treatment. Eleven patients whose treatments were discontinued had an average therapy time of 4.81±1.2 years. Four of these patients developed recurrence after treatment. The first treatment was started again for these patients. No patients who demonstrated a complete response showed loss of response to treatment during the treatment period.

Discussion

AIH is a preventable liver disease, which requires timely diagnosis and treatment. It is a disease that is difficult to diagnose because it presents with multiple non-specific symptoms and is rare (15). In admission to hospital, patients may show different presentation from asymptomatic presentation to cirrhosis of the liver.

In some previous studies, the ratio of females to males was 3.6:1 (3,12). Similar ratio was found in our study (3.8:1). In previous studies, the rate of asymptomatic AIH was 12%-35% (16,17). In the present study, this rate was 8.3%. The reason for this discrepancy was that the patients included in this study did not have regular follow-up appointments. This meant that asymptomatic enzyme elevation was not monitored by clinicians. Most of the patients that participated in this study had non-specific

Table 4. Drugs used and treatment response rates

Drugs	n (%)	Complete	Partial	Non-responders
Steroid + AZA	29 (60.3%)	n=20	n=5	n=4
Steroid + AZA + UDCA	11 (23%)	n=8	n=2	n=1
Steroid + UDCA	6 (12.5%)	n=4	n=2	n=0
Steroid	1 (2.1%)	n=1	n=0	n=0
AZA	1 (2.1%)	n=0	n=0	n=1
TOPLAM	48 (100%)	n=33	n=9	n=6

AZA: azathioprine, UDCA: ursodeoxycholic acid

symptoms such as fatigue and abdominal pain, and their incidence was consistent with previous studies (18). The detection rate of jaundice was low compared to other studies (19).

At the time of diagnosis, cirrhosis occurred in 31% of patients, which corroborates existing literature (17,20). The rate of acute hepatitis was 21% and the rate of chronic hepatitis was 39%. None of the patients included in this study developed fulminant hepatic failure. In a study carried out over approximately 20 years, 36.3% of patients had chronic hepatitis, 27.9% had acute hepatitis, 2.9% had fulminant hepatic failure, and 41% had cirrhosis (20). There is no typical morphological feature for the diagnosis of AIH. Histological changes include features such as interface hepatitis, rosette formation, zone three necrosis, and plasmocytic infiltration. They are necessary for the diagnosis of AIH (14). We detected interface hepatitis in 45 patients (96%), plasmocytic infiltration in 39 patients (83%), and rosette formation in six patients (12.7%).

In the present study, a total of 81.2% of patients had type 1 AIH, 4.2% had type 2 AIH, and 14.6% had autoantibody negative AIH. A total of 68.8% of patients in the present study with type 1 AIH had ANA, 41.7% were ASMA positive, and 31.3% of patients were tested as positive for both autoantibodies. In a study from Israel, ANA positivity was 79% and ASMA positivity was 56% (20). In another study, 78% of patients were tested as positive for ANA and 69% of patients were tested as positive for ASMA (17). In a study from North America, 96% of AIH patients were tested as positive for ANA, ASMA, or both (21). In these studies, the frequency of type 2 AIH was similar to the present study (approximately 4%). Type 2 AIH is more common in children (15%-20%). In our study, the frequency of autoantibody-negative AIH was found to be 14.6%, which was higher than the literature. However, certain studies conducted before the year 2000 reported that the incidence of seronegative AIH was approximately 10%-15% (22,23). In the autoantibody negative AIH patients enrolled in our study, the simplified AIH score was 6 and all patients responded to a standard treatment. We think that this ratio is remarkable. A limited number of studies were conducted in Turkey and these were usually carried out by pediatricians. In addition, some cases of AIH (e.g., acute hepatitis) may be ANA negative and present with normal Ig G levels in the initial stages (24).

Biliary duct involvement was identified in 35% of patients with AIH in the present study. This rate is higher than that reported in the literature. The prevalence of AIH-PBC is estimated at around 8%-10% (25,26). Previous studies have indicated that regional differences may occur. Studies from the Middle East and the Hispanics found that AIH patients demonstrated a high cholestatic pattern (27,28). In another study, approximately 20% of patients with phosphate buffered saline may have AIH (29). In a study carried out in the United States, AIH coexistence rate with PBC, PSC, and autoimmune cholangitis was 18% while the AIH: PBC ratio was 3.2% (23). Although PSC was excluded in the present study, non-exclusion of autoimmune cholangitis could be a reason for the high PBC ratio. Coexistence of AIH and PSC is more common in children, young adults, and those with ulcerative colitis (30). The patients in the present study were older and did not present with ulcerative colitis (except one patient). Therefore, regional differences may explain the absence of PSC. Five percent of patients were tested as positive for AMA. These patients did not present with bile duct damage when examined by histology (11). This rate was 4% in the present study. Combination therapies including UDCA are recommended for the treatment of overlap syndrome (28). We administered combination therapy to our patients, and only one (6%) was non-responsive, which is similar to that observed in the literature.

The rate of extrahepatic diseases accompanying AIH was 33.3%. Most of these cases were autoimmune diseases (e.g., hypothyroidism, ulcerative colitis). In a study conducted in Italy, the prevalence of non-liver autoimmune disease accompanying AIH was 42%, and autoimmune thyroiditis was common (31). In some studies, the rate of extrahepatic diseases was 29-38% (20,32). Studies have shown that patients with non-liver autoimmune disease do not differ in terms of disease progression and survival (31,33).

In the present study, 68.8% of patients demonstrated a complete response to induction-remission therapy, 18.7% demonstrated a partial response, and 12.5% were non-responsive. In a single-center study on approximately 68 patients with AIH from Israel, 70% of patients receiving steroid and/or AZA treatment demonstrated a complete response, 24% demonstrated a partial response, and 6% were non-responsive (20). In a study of 153 patients with AIH, 12 of whom had overlap syndrome, with a mean follow-up of 88 months, the remission rate was 70% and treatment failed in 13% (34). In this study, the relapse rate was 51%, the mortality rate due to hepatic failure was 7%, and the rate of transplanted patients was 3.2%. In another study involving 125 patients (4% type 2 AIH), 84.7% demonstrated a complete response, 13.3% demonstrated a partial response, and 2% were unresponsive (17). In this study, the relapse rate after treatment was 35%. Ten patients (8%) required liver transplantation. Nine of these patients had cirrhosis before treatment. In the present study, three patients (6%) died from liver cirrhosis and complications. One patient underwent liver transplantation. In our study, the likely cause of the low cirrhosis development rate and low transplantation rate was short-term follow-up. A healthy relapse rate could not be determined because 77% of patients in the present study had ongoing treatment. Of the 11 patients whose treatments were terminated, four patients relapsed within one year. This figure is similar to the literature in terms of the side effects of the drugs used.

Study Limitation

The limitations of our study are that it was designed retrospectively, the number of patients was low, and some data in the past were not available.

Conclusion

We found in our study that although rare papers on the evaluation of AIH patients in Turkey exist in the literature, the female to male ratio, presenting complaints, presentation, histology, incidence of type, concomitant non-hepatic autoimmune disease rate and treatment response rates were similar to those reported before. The patients in the present study differed in terms of the low number of asymptomatic

patients, detection of autoantibodies at lower percentages, and higher overlap syndrome.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Mersin University (decision no: 2019/750)

Informed Consent: Retrospective study. (Verbal consent was obtained from the patients).

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - O.Ö., S.Y.; Concept - O.Ö.; Design - O.Ö.; Data Collection and/or Processing - O.Ö., S.Y.; Analysis and/or Interpretation - O.Ö., S.Y.; Literature Search - O.Ö., S.Y.; Writing Manuscript - O.Ö., S.Y.

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