OVERVIEW OF CLINICAL PRESENTATION AND DIAGNOSIS OF AUTOIMMUNE HEPATITIS IN A SINGLE, REFERRAL CENTER

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ABSTRACT

BACKGROUND AND AIMS: The diagnosis of autoimmune hepatitis (AIH) is often difficult because of the large heterogeneity of its clinical, laboratory and histological features and the absence of a specific diagnostic test. This study aims to determine the demographic, clinical, biochemical and serological characteristics and histological findings of AIH and to what extent they correspond to the International Autoimmune Hepatitis Group (IAIHG) diagnostic criteria.

METHODS: Retrospective analysis of the adult patients diagnosed as AIH at our clinic from January 2005 to December 2013 was performed. Demographic, laboratory, clinical and histological data of the patients were collected and a score was calculated for each patient based on the IAIHG revised and simplified scoring system. Only pretreatment scores were analyzed.

RESULTS: 57 patients were diagnosed as AIH on clinical grounds (mean age: 50 years, range: 19-74), from which 82.5% were women. 49.1% were asymptomatic, 10.5% had acute hepatitis, and 40.3% had chronic liver disease. The most common symptoms at presentation were fatigue (24.6%), icterus (21.1%) and dark urine (19.3%). 28.1% of patients had cirrhosis at presentation. Elevated IgG levels were detected in 75% of cases. ANA, ASMA, ALKM and pANCA were positive in 75.0%, 54.5%, 6.5% and 25.0% of patients respectively. Liver biopsy was performed in 42.1% of the patients. 84% of patients diagnosed with AIH according to clinical judgment of the treating physician were also diagnosed with AIH according to the revised and simplified criteria.

CONCLUSIONS: The majority of patients satisfy the original or simplified criteria and these criteria are useful in the diagnosis.

Keywords: Autoimmune hepatitis, Scoring systems, Diagnosis, Clinical presentation, Laboratory features

INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease that is characterized by hypergammaglobulinemia with selectively elevated IgG, presence of autoantibodies and interface hepatitis on histological examination (1). AIH occurs predominantly in women and affects all age groups (2). The annual incidence of AIH in Europe is 1.9 cases per 100,000 with a point prevalence of 16.9 per 100,000 population (3). The absence of specific diagnostic markers in AIH patients may make a correct and timely diagnosis difficult. The International

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Received: April 3, 2014

Accepted: June 4, 2014

al Autoimmune Hepatitis Group (IAIHG) proposed the diagnostic criteria for AIH and a diagnostic scoring system in 1993, which were subsequently revised in 1999. The revised 1999 criteria evaluated up to 12 parameters to classify patients as having “definite AIH”, “probable AIH” or “not AIH” (4). Despite a high degree of sensitivity and specificity, these criteria are considered complicated and not useful in everyday practice. In 2008, the IAIHG published a simplified system for the diagnosis of AIH which is less complex and easier to use in clinical practice. This system takes into account only four parameters: autoantibodies, IgG concentration, exclusion of viral hepatitis and histological criteria (5). The simplified scoring system detects fewer cases of AIH than the original system (lower sensitivity, 95% vs. 100%), but it has higher specificity (90% vs. 73%) and accuracy (92% vs. 82%). The revised original scoring system performs better in patients with few or atypical features of AIH, and the simplified system is better at excluding the diagnosis in diseases with concurrent immune manifestations (6). The aim of this study was to evaluate the clinical features of AIH and the utility of IAIHG scoring systems for its diagnosis.

PATIENTS AND METHODS

Study population and data collections

All patients diagnosed with AIH from 2005 to 2013 were evaluated for clinical and laboratory parameters and compared with the revised and simplified IAIHG diagnostic criteria. The medical records of patients were reviewed using data at the time of first admission of each patient in our center. The following information was recorded:

1. Demographic characteristics, onset type of disease, symptoms at presentation, duration of symptoms or other evidence of liver disease, presence of concurrent autoimmune diseases.
2. Serologic and biochemical evaluation, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (γ -GT), alkaline phosphatase (ALP), total protein, albumin, total and direct bilirubin, erythrocyte sedimentation rate, prothrombin time, platelet count, cholinesterase, total cholesterol, serum immunoglobulins (IgA, IgG, IgM). Antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), anti-

liver kidney microsomal antibodies (ALKM), perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) and antimitochondrial antibodies (AMA) were evaluated using indirect immunofluorescence. A titer of $\geq 1:80$ for ANA and 1:20 for ASMA, ALKM, pANCA and AMA was considered to be positive. All patients were negative for HBsAg and anti-HCV and the other known causes of chronic liver disease were ruled out using appropriate tests.

3. Abdominal ultrasound findings: liver size, spleen size and presence of ascites.

4. Findings at upper gastrointestinal endoscopy: presence of esophageal or gastric varices and/or portal hypertensive gastropathy.

5. Histological findings (if biopsy had been performed).

Statistical analysis

Descriptive statistical analysis was made. Categorical data are expressed as frequencies and percentages and continuous data as medians and ranges or mean $\pm$ SD. Statistical analysis was performed using IBM SPSS, version 21.0.

RESULTS

Study population

A total of 57 patients, diagnosed and treated for AIH in our center within the specified time period were identified. The diagnosis was based on overall assessment of clinical, biochemical, immunological and histological parameters without using a scoring system. Other possible causes of liver disease, such as alcohol, drug induced liver injury, Wilson's disease, $\alpha 1$ antitrypsin deficiency and hemochromatosis, had been carefully excluded by appropriate in-

Figure 1. Age distribution of patients

Table 1. Baseline characteristics of patients

Characteristics	AIH (n = 57)	Median (range)
Age at diagnosis (y), mean $\pm$ SD	50.3 $\pm$ 14.1	54.0 (19.0 – 74.0)
Age $\geq$ 60, n (%)	14 (24.6)	
Age < 60, n (%)	43 (75.4)	
Gender		
Male, n (%)	10 (17.5)	
Female, n (%)	47 (82.5)	
M:F ratio	1 : 4.7	
Body Mass Index (kg/m ²), mean $\pm$ SD	26.9 $\pm$ 4.5	26.8 (19.6-36.1)
Revised AIH score		
Definite, n (%)	7 (12.3)	
Probable, n (%)	39 (68.4)	
Less than probable, n (%)	11 (19.3)	
Pretreatment score, mean $\pm$ SD	12.4 $\pm$ 3.3	13.0 (5.0-19.0)
Simplified AIH Score		
Definite, n (%)	2 (3.5)	
Probable, n (%)	20 (35.1)	
Less than probable, n (%)	35 (61.4)	
Mean observation period (months)	24.0 $\pm$ 41.2	6.0 (0-175.0)
Presentation		
Acute, n (%)	6 (10.5)	
Chronic, n (%)	23 (40.3)	
Asymptomatic, n (%)	28 (49.1)	
Cirrhosis at presentation, n (%)	16 (28.1)	
Child-Pugh score		
A, n (%)	9 (56.3)	
B, n (%)	6 (37.5)	
C, n (%)	1 (6.3)	
Oesophageal varices, n (%)	5/21 (23.8)	
Clinical decompensation at presentation, n (%)	4 (7.0)	
Histological findings		
Interface hepatitis, n (%)	12/23 (52.0)	
Bridging necrosis, n (%)	3/23 (13.0)	
Multilobular necrosis, n (%)	2/23 (8.0)	
Mononuclear cell infiltrate, n (%)	15/23 (65.0)	
Biliary changes, n (%)	8/23 (34.0)	
Steatosis, n (%)	8/23 (34.0)	
No Fibrosis	3/23 (13.0)	
Portal Fibrosis	3/23 (13.0)	
Periportal Fibrosis	4/23 (17.0)	
Bridging Fibrosis	10/23 (43.0)	
Cirrhosis	3/23 (13.0)	
Splenomegaly, n (%)	15 (26.3)	
Hepatomegaly, n (%)	19 (33.3)	
Associated autoimmune diseases, n (%)	15 (26.3)	
Time to diagnosis, months	24.3 $\pm$ 72.3	3.0 (0-457.0)
Overlap syndrome, n (%)	7 (12.3)	

vestigations. The mean age at diagnosis was 50 ± 14 years (range, 19-74 years). 24.6% of patients were older than 60 (Figure 1).

There was a female predominance (82.5%). Overlap syndromes were present in 7 (12.3%) patients (6 AIH with primary biliary cirrhosis and 1 AIH with primary sclerosing cholangitis). Patient's characteristics are described in Table 1.

Clinical presentation

28 of 57 patients (49.1%) were asymptomatic at initial presentation. At diagnosis, 16 patients (28.1%) had cirrhosis and 4 (7.0%) had clinical decompensation. Acute presentation was observed in 6 (10.5%) and was defined as the presence of recent onset (< 30 days) symptoms in conjunction with ALT levels higher than 10 times the ULN.

The most common symptoms and signs at presentation were as follows: fatigue (24.6%), jaundice (21.1%), dark urine (19.3%), right upper side pain and discomfort (14.0%), pruritus (14%), abdominal discomfort (12.3%), loss of appetite (10.5%), abdominal distension (7.0%), edema (7.0%), nausea (5.3%), arthralgia (3.5%), weight loss (3.5%) and fever (1.8%) (Table 2).

Table 2. Clinical symptoms and signs at presentation

Symptoms	n (%)
Asymptomatic	28 (49.1)
Fatigue	14 (24.6)
Jaundice	12 (21.1)
Dark urine	11 (19.3)
Right upper side pain and discomfort	8 (14.0)
Pruritus	8 (14.0)
Abdominal discomfort	7 (12.3)
Loss of appetite	6 (10.5)
Abdominal distension	4 (7.0)
Edema	4 (7.0)
Nausea	3 (5.3)
Weight loss	2 (3.5)
Arthralgia	2 (3.5)
Fever	1 (1.8)

There was a mean delay of 24 months (range 0-457) from the first biochemical abnormalities or

symptoms to the diagnosis of AIH. Patients were followed up for a mean of 24 ± 41 months. The most common complications during the follow-up period are listed in Table 3.

Table 3. Complications of chronic liver disease in the AIH cohort (n = 57)

Complications	n (%)
Coagulant function abnormality	9 (15.8)
Esophageal varices	8 (14.0)
Hypoalbuminemia	8 (14.0)
Hypersplenism	6 (10.5)
Ascites	5 (8.8)
Variceal bleeding	0
Spontaneous bacterial peritonitis	0
HCC	1 (1.8)
Liver transplantation	0
Death	4 (7.0)

Associated autoimmune diseases

15 (26.3%) were diagnosed with concurrent extrahepatic autoimmune diseases. Among the 15 patients, autoimmune thyroiditis was the most common disorder - 7 patients (46.7%). Rheumatoid arthritis was present in 3 patients (20.0%), celiac disease in 3 (20.0%), ulcerative colitis in 1 (6.7%) and Raynaud's syndrome in 1 (6.7%).

Biochemical and serological characteristics of AIH

50% of patients had dominant cytolytic pattern (ALAT / ALP ratio > 1 (both xULN)) and 50% of patients had dominant cholestatic pattern (ALAT / ALP ratio < 1 (both xULN)). ANA, ASMA, ALKM and pANCA were positive in 75.0%, 54.5%, 6.5% and 25.0% of patients, respectively, at some point during the course of their disease. Simultaneous seropositivity for ASMA/ANA occurred in 16, ANA/pANCA in 5 and ALKM/ASMA and/or ANA in 3 patients. 15 (75.0%) of our patients demonstrated elevated IgG levels. 37 patients didn't have determinations of serum levels of immunoglobulins. Further serological and biochemical data are shown in Table 4.

Ultrasound

Abdominal ultrasound examination was performed in all patients. Splenomegaly was found in 15

Table 4. Serological, biochemical and histological findings in patients with AIH

Parameter	Mean $\pm$ SD	Median (range)
Biochemical and hematological values		
AST (IU/L)	158 $\pm$ 193	86 (16-872)
ALT (IU/L)	196 $\pm$ 304	71 (12-1399)
γ -GTP (IU/L)	(212 $\pm$ 256)	90 (14-1308)
Alkaline phosphatase (IU/L)	431 $\pm$ 769	199 (35-5075)
Total bilirubin (μ mol/l)	31 $\pm$ 43	15 (7-244)
Direct bilirubin (μ mol/l)	23 $\pm$ 33	14 (2-147)
Total protein (g/l)	73 $\pm$ 10	72 (32 – 107)
Albumin (g/L)	37 $\pm$ 6	38 (19-49)
Erythrocyte sedimentation rate (mm/hr)	34 $\pm$ 27	30 (3-120)
Platelet count ($\times 10^9$)	236 $\pm$ 110	224 (42-572)
Prothrombin time (%)	89 $\pm$ 26	88 (22 – 140)
Creatinine (μ mol/l)	82 $\pm$ 36	76 (46-295)
Total cholesterol (mmol/l)	5.1 $\pm$ 1.8	4.9 (2.32 – 11.7)
Cholinesterase	7243 $\pm$ 3377	6904 (1010-14742)
Serum globulin or IgG above normal, n (%)		
IgA (g/l)	2.8 $\pm$ 1.2	2.5 (0.98 – 6.37)
IgG (g/l)	19.4 $\pm$ 6.8	20 (7.5 – 33.2)
IgM (g/l)	1.6 $\pm$ 0.8	1.5 (0.43 – 3.1)
Autoantibody profile		
ANA positive, n (%)	42/56 (75)	
SMA ($\geq 1:40$), n (%)	30/55 (54.5)	
Both ANA and SMA pos.; n (%)	16/55 (29.0)	
LKM positive, n (%)	3/46 (6.5)	
pANCA, n (%)	6/24 (25)	
AMA positive, n (%)	7 (12.5)	

patients (26.3%), hepatomegaly in 19 patients (33.3%) and ascites in 4 (7.0%).

Upper gastrointestinal endoscopy

Upper gastrointestinal endoscopy was performed before the start of treatment in 21 patients (36.8%) – esophageal varices were observed in 5 (23.8%) of them and 6 (28.5%) had portal hypertensive gastropathy.

Histological findings

Liver biopsy was performed in 24 (42.1%) patients. Liver histology showed interface hepatitis in 52%, bridging necrosis in 13.0%, multilobular necrosis in 8%, mononuclear cell infiltration in 65.0%, biliary changes (ductular proliferation or bile duct injury and loss) in 34.0%. Bridging fibrosis and cirrhosis were present in liver biopsies of 43.0% and 13.0% respectively.

Application of the scoring systems

48 (84%) of our patients satisfy either the original or the simplified criteria. The remaining 16% did not satisfy these criteria, most likely due to insufficient data recording at diagnosis (absence of serum IgG assessments and/or lack of histological examination). According to the revised IAHG criteria, 12.3% of cases had a definite diagnosis of AIH, 68.4% of cases had a probable diagnosis and 19.3% of cases had no AIH. By the simplified scoring system, 2 (3.5%) were diagnosed as “definite” AIH, 20 (35.1%) as “probable” and 35 (61.4%) as “non-diagnostic”.

DISCUSSION

Our study of all patients with AIH confirms some of the previous findings on AIH, including

peak incidence around the age of 50 years (7-11), female predominance (females 72.0 – 94.0 %) (7-21), frequency of overlap syndromes (22). In agreement with Chen et al. 24.6% were aged ≥ 60 indicating that AIH should be considered in the differential diagnosis also in the elderly (23). 10.5% of our patients had acute hepatitis, which is lower than reported in previous studies (27.0 – 46.4%) (9,12,16,18,19,21,24). 49.1% were asymptomatic at diagnosis. In recent studies 30.6 – 52.6% were symptom free at presentation (7,9,12,16,17). Fatigue and jaundice were most common among the various manifesting symptoms. It was consistent with the studies in other countries (7,14,19,25). Our finding that 28.1% of the AIH patients had already developed cirrhosis at the time of diagnosis is in agreement with previous reports (12,14,20). It indicates that the disease usually has a prolonged asymptomatic course and has gone unrecognized for a considerable period of time prior to diagnosis. In our study 26.3% were diagnosed with concurrent extrahepatic autoimmune diseases and they were all female. In earlier studies concomitant autoimmune disorders were found in 21.0 – 57.1% (7-9,11-19, 21,24,26-28) with the most prevalent disease being autoimmune thyroiditis (9,15,19,27,28). ANA was positive in 75% of the patients, SMA in 54.5%. In similar studies the range of antibody positivity was: ANA 54.5 – 94.2% (8,9,11,21,24,26), SMA 21.2 – 64.0% (9,21,26). Our findings are mostly in the reported ranges. It has been reported that anti-SLA are highly specific for the diagnosis of autoimmune hepatitis and their estimation may be useful in identifying patients with AIH. pANCA are not specific, but are commonly present.

AIH is a difficult clinical diagnosis, as there is no pathognomonic clinical, laboratory or histological features and the condition can mimic almost any form of acute or chronic liver disease. Most patients in the present study were accurately diagnosed according to the IAIHG revised and simplified scoring systems. Thus, these criteria are useful tools that facilitate diagnosis. Furthermore they can help assure comparability of patient groups reported from different study centers. In our study 16% of the patients failed to meet the diagnostic criteria of IAIHG, mainly due to lack of laboratory or histological data at diagnosis required for calculating scores for both diagnostic criteria. In recent studies 28.5% and 5.0%

of cases did not meet either diagnostic criteria of AIH (9,25). We agree with the suggestion that due to its convenience the simplified scoring system could be used as the primary diagnostic tool in suspected cases of AIH. The revised scoring system could be applied to enhance the diagnosis of AIH in cases that are unrecognized by the simplified criteria (with few features of AIH) (8,29).

In conclusion, the clinical features of patients with AIH are comparable to those described in the literature. Our data are consistent with those previously reported, showing that international diagnostic scoring systems are useful and should be used as an adjunct to the clinical judgment to ensure a correct diagnosis of patients with AIH.

REFERENCES

1. Czaja AJ, Manns MP. Advances in the diagnosis, pathogenesis, and management of autoimmune hepatitis. *Gastroenterology*. 2010;139:58-72 e54.
2. Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, et al. Diagnosis and management of autoimmune hepatitis. *Hepatology*. 2010;51:2193-2213.
3. K. M. Boberg EAJJ. Incidence and Prevalence of Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis, and Autoimmune Hepatitis in a Norwegian Population. *Scandinavian journal of gastroenterology*. 1998;33:99-103.
4. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. *Journal of hepatology*. 1999;31:929-938.
5. Hennes EM, Zeniya M, Czaja AJ, Pares A, Dalekos GN, Krawitt EL, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology*. 2008;48:169-176.
6. Czaja AJ. Performance parameters of the diagnostic scoring systems for autoimmune hepatitis. *Hepatology*. 2008;48:1540-1548.
7. Kil JS, Lee JH, Han AR, Kang JY, Won HJ, Jung HY, et al. Long-term treatment outcomes for autoimmune hepatitis in Korea. *Journal of Korean medical science*. 2010;25:54-60.
8. Li Y, Peng M, Gong G. Evaluation of the revised versus the simplified scoring system in patients with autoimmune hepatitis. *Experimental and therapeutic medicine*. 2014;7:131-136.

9. Kim BH, Kim YJ, Jeong SH, Tak WY, Ahn SH, Lee YJ, et al. Clinical features of autoimmune hepatitis and comparison of two diagnostic criteria in Korea: A nationwide, multicenter study. *Journal of gastroenterology and hepatology*. 2013;28:128-134.
10. Czaja AJ. Comparability of probable and definite autoimmune hepatitis by international diagnostic scoring criteria. *Gastroenterology*. 2011;140:1472-1480.
11. Kim T, Kagihara J, Tsai N, Roytman M. Tu1833 Autoimmune Hepatitis in Hawaii. *Gastroenterology*. 2014;146:S-1008.
12. Garcia-Torres ML, Primo J, Ortuno JA, Martinez M, Anton MD, Zaragoza A, et al. (A clinical study of adult autoimmune hepatitis in Valencia, Spain). *Revista espanola de enfermedades digestivas : organo oficial de la Sociedad Espanola de Patologia Digestiva*. 2008;100:400-404.
13. Werner M, Prytz H, Ohlsson B, Almer S, Bjornsson E, Bergquist A, et al. Epidemiology and the initial presentation of autoimmune hepatitis in Sweden: a nationwide study. *Scandinavian journal of gastroenterology*. 2008;43:1232-1240.
14. Choudhuri G, Somani SK, Baba CS, Alexander G. Autoimmune hepatitis in India: profile of an uncommon disease. *BMC gastroenterology*. 2005;5:27.
15. Floreani A, Niro G, Rosa Rizzotto E, Antoniazzi S, Ferrara F, Carderi I, et al. Type I autoimmune hepatitis: clinical course and outcome in an Italian multicentre study. *Alimentary pharmacology & therapeutics*. 2006;24:1051-1057.
16. Muratori P, Granito A, Quarneri C, Ferri S, Menichella R, Cassani F, et al. Autoimmune hepatitis in Italy: the Bologna experience. *Journal of hepatology*. 2009;50:1210-1218.
17. Jalihal A, Telisinghe PU, Chong VH. Profiles of autoimmune hepatitis in Brunei Darussalam. *Hepatobiliary & pancreatic diseases international : HBPD INT*. 2009;8:602-607.
18. Debbeche R, Maamouri N, Ajmi S, Azzouz MM, Ben Mami N, Dougui MH, et al. (Autoimmune hepatitis in Tunisia. Retrospective multicenter study of 83 cases). *La Tunisie medicale*. 2010;88:834-840.
19. Malekzadeh Z, Haghazali S, Sepanlou SG, Vahedi H, Merat S, Sotoudeh M, et al. Clinical features and long term outcome of 102 treated autoimmune hepatitis patients. *Hepatitis monthly*. 2012;12:92-99.
20. Gronbaek L, Vilstrup H, Jepsen P. Autoimmune hepatitis in Denmark: Incidence, prevalence, prognosis, and causes of death. A nationwide registry-based cohort study. *Journal of hepatology*. 2014;60:612-617.
21. Moura MC, Nunes AT, Pereira E, Araújo JP, Meirinho I, Dias C, et al. 939 Autoimmune Hepatitis in Hospitalized Patients: Case Series Report of Patients Admitted to an Internal Medicine Department. *Journal of hepatology*. 2012;56:S366-S367.
22. Boberg KM, Chapman RW, Hirschfield GM, Lohse AW, Manns MP, Schrupf E, et al. Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. *Journal of hepatology*. 2011;54:374-385.
23. Chen J, Eslick GD, Weltman M. Systematic review with meta-analysis: clinical manifestations and management of autoimmune hepatitis in the elderly. *Alimentary pharmacology & therapeutics*. 2014;39:117-124.
24. Seo S, Toutounjian R, Conrad A, Blatt L, Tong MJ. Favorable outcomes of autoimmune hepatitis in a community clinic setting. *Journal of gastroenterology and hepatology*. 2008;23:1410-1414.
25. Abdollahi MR, Somi MH, Faraji E. Role of international criteria in the diagnosis of autoimmune hepatitis. *World journal of gastroenterology : WJG*. 2013;19:3629-3633.
26. Miyake Y, Iwasaki Y, Sakaguchi K, Shiratori Y. Clinical features of Japanese male patients with type 1 autoimmune hepatitis. *Alimentary pharmacology & therapeutics*. 2006;24:519-523.
27. Teufel A, Weinmann A, Kahaly GJ, Centner C, Piendl A, Worns M, et al. Concurrent autoimmune diseases in patients with autoimmune hepatitis. *Journal of clinical gastroenterology*. 2010;44:208-213.
28. Abe K, Katsushima F, Kanno Y, Takahashi A, Yokokawa J, Ohira H, et al. Clinical features of cirrhosis in Japanese patients with type I autoimmune hepatitis. *Internal medicine (Tokyo, Japan)*. 2012;51:3323-3328.
29. Zachou K, Muratori P, Koukoulis GK, Granito A, Gatselis N, Fabbri A, et al. Review article: autoimmune hepatitis -- current management and challenges. *Alimentary pharmacology & therapeutics*. 2013;38:887-913.