


Is there any predictor for relapse after treatment withdrawal in autoimmune hepatitis patients in the real life?

International Journal of
Immunopathology and Pharmacology
Volume 36: 1–7
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/03946320221077860
journals.sagepub.com/home/iji
SAGE

Bilger Çavuş¹ , Filiz Akyuz¹, Raim İliaz¹, Alp Atasoy, Umit Akyuz², Kadir Demir¹, Fatih Besisik¹ and Sabahattin Kaymakoglu¹

Abstract

Backgrounds and Aims: In autoimmune hepatitis, there are uncertainties about whether to discontinue the treatment, when the treatment should be discontinued, and the risks of relapse in the cases where remission is achieved with immunosuppressive therapy. In this study, patients with AIH, whose immunosuppressive treatments were discontinued, were evaluated for the rates of remission and the risk of relapse.

Materials and Methods: A total of 119 patients, who were diagnosed with AIH based on the AIHG scoring systems between 1990 and 2015, were evaluated. Patients were receiving standard azathioprine and steroid therapy. The treatment was discontinued in patients, who had been receiving treatment for at least 2 years, who had no clinical complaints, and whose aminotransferases were normal and when an increase occurred in AST values more than two times the normal after the treatment was interrupted, the case was considered as a relapse.

Results: Among the patients, 83% ($n = 99$) were women. When the patients were diagnosed with AIH, their mean age was 36 ± 16 (8–79) years; 70.6% ($n = 84$) were type 1, 3.4% ($n = 4$) type 2, and 26% ($n = 31$) were autoantibody-negative AIH. At the time of discontinuation, liver biopsy was performed in 8 of the patients and minimal-mild abnormalities were detected. Patients whose treatment was discontinued received treatment for an average of 101 ± 75 (range: 24–280, median: 68.5) months; and, they were followed up for an average of 19 (1–110) months during the period without medication. Relapse occurred in 67% ($n = 12$) of the patients with drug withdrawal. Relapse occurred within the first 12 months in 67% of these patients ($n = 8$) and developed with an acute hepatitis attack in 42%. None of the clinical, laboratory, and histological data were found to be effective on relapse.

Conclusion: In patients with AIH, relapse occurs in two-thirds of patients within an average of 19 month after the discontinuation of the medication. Most relapses occur at the early period and they are accompanied by an acute hepatitis attack.

Keywords

Autoimmune hepatitis, treatment withdrawal, cirrhosis

Introduction

Autoimmune hepatitis (AIH) is an inflammatory disease of the liver whose pathogenesis has not yet been clearly determined and that has genetic, environmental, and immune

¹Istanbul University, Istanbul Faculty of Medicine, Department of Gastroenterology, İstanbul, Turkey

²Fatih Sultan Mehmet Educational and Research Center, İstanbul, Turkey

Corresponding author:

Filiz Akyuz, Istanbul University, Istanbul Faculty of Medicine, Department of Gastroenterohepatology, Capa-Istanbul, Beyazit, 34452, Fatih/Istanbul 34390, Turkey.
Email: filizakyuz@hotmail.com



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

mechanisms contributing to its etiology.¹ AIH is present in multiple locations with varying frequency; however, it is a heterogeneous disease, which can be seen all over the world, affecting all age groups and both genders, in most cases as a pediatric disorder from infancy to adolescence, with a greater frequency in females.² The clinical presentation of AIH can range from asymptomatic disease to acute hepatitis, fulminant hepatitis, and cirrhotic stage. Therefore, clinical or laboratory findings would not be sufficient in the diagnostic approach to AIH, which can develop in different clinical pictures.^{3,4} Various scoring systems have been developed along with clinical findings in the diagnosis of AIH.⁵ AIH is classically divided into two groups based on the presence of autoantibodies. Type I AIH is based on the presence of anti-smooth muscle antibodies (ASMA); the presence of Type II AIH is based on the presence of anti-liver/anti-kidney microsome (anti-LMK) type 1 or anti-liver cytosol (anti-LC) type 1 antibodies.^{6,7}

The uncertainty in the etiopathogenesis of AIH, its clinical course of different ranges, and the need for scoring systems in the diagnosis rather than a single laboratory or clinical finding causes the treatment and management of AIH to be complicated. As with other liver diseases, the aim in the cases of AIH is to prevent the progression of liver injury and stop cirrhosis; therefore, it aims to keep the disease in remission.⁸ The treatment of AIH involves immunosuppressive treatments, particularly steroids and azathioprine. Normalization of liver transaminases and immunoglobulin G and the absence of biochemical remission and histological activity or the presence of minimal hepatitis are also defined as histological remission; however, the factors affecting the achievement of these goals and the ideal duration of the treatment remain uncertain.^{8,9}

In the disease management of AIH, which has complicated etiopathogenesis, different clinical findings, difficulties in diagnosis, and treatment management, we use the experiences we have gained from the literature and our practical observations. In this regard, we aimed to evaluate the clinical and demographic features of the patients with AIH, their treatment processes, remission rates, and the follow-up processes after discontinuation of the treatment.

Materials and methods

Study design

We included 119 patients diagnosed with AIH according to the International Autoimmune Hepatitis Group (IAHG) scoring system¹⁰ at the Istanbul University Istanbul Medical Faculty between 1990 and 2015. The patients' demographic and clinical features, treatment response, and relapse rates were analyzed retrospectively. The Revised Original Score for AIH was used for patients that are included in the study.¹¹

The study was performed following good clinical practice and the Declaration of Helsinki and was approved by the local ethical committee (Ethical Committee of Istanbul Medical University Faculty, Ethical Approval Number: 1536–712).

Treatment withdrawal and relapse criteria

The treatment was discontinued in patients receiving treatment for at least 2 years, who had no complaints and whose aminotransferases were normal. Patients who agreed to a biopsy before the treatment discontinuation and whose biopsies resulted between 0 and 4 according to the hepatitis activity index (HAI)¹²—indicating minimal hepatitis and/or inflammation—were accepted to meet the treatment discontinuation criteria. When an increase occurred in AST values more than two times the normal after the treatment was interrupted, the case was considered as a relapse.

Statistical analysis

The suitability of the data to the normal distribution was tested with the Shapiro–Wilk test. The student's *t*-test was used to compare the properties with normal distribution in two independent groups, and the Mann–Whitney *U* test was used to compare the properties without normal distribution in two independent groups. The relations of quantitative variables were analyzed by Fisher exact and Pearson Chi-square tests. For the descriptive statistics, mean \pm standard deviation, median, and 25–75% cutoff points for numerical variables and number and % values for categorical variables are given. The cumulative relapse rate was estimated by the Kaplan–Meier method, and the log-rank test evaluated the difference between curves. In calculating the sample size of this study, power analysis for each variable was determined by taking at least 80% and type 1 error of 5%. SPSS Windows (version 23.0) was used for statistical analysis, and *p*-values < 0.05 were considered statistically significant.

Results

One-hundred-nineteen patients (83% female, mean age 48 \pm 15.4 years) were included in this study. The mean follow-up period was 86 \pm 69 (3–240) months. The types of AIH were as follows: 70.6% (*n* = 84) type 1, 3.4% (*n* = 4) type 2, and 26% (*n* = 31) autoantibody negative (Figure 1).

In 50% of patients, steroid monotherapy was used for remission induction and 80% of these patients achieved remission (Figure 2) (Table 1).

Azathioprine, 6-mercaptopurine, mycophenolate, mofetil, and cyclosporine were used in the others for maintenance and second-line therapy. The remission rate was higher in pre-cirrhotic patients compared to the cirrhotic patients in maintenance treatment (78% vs 54%; *p* = 0.007). During the

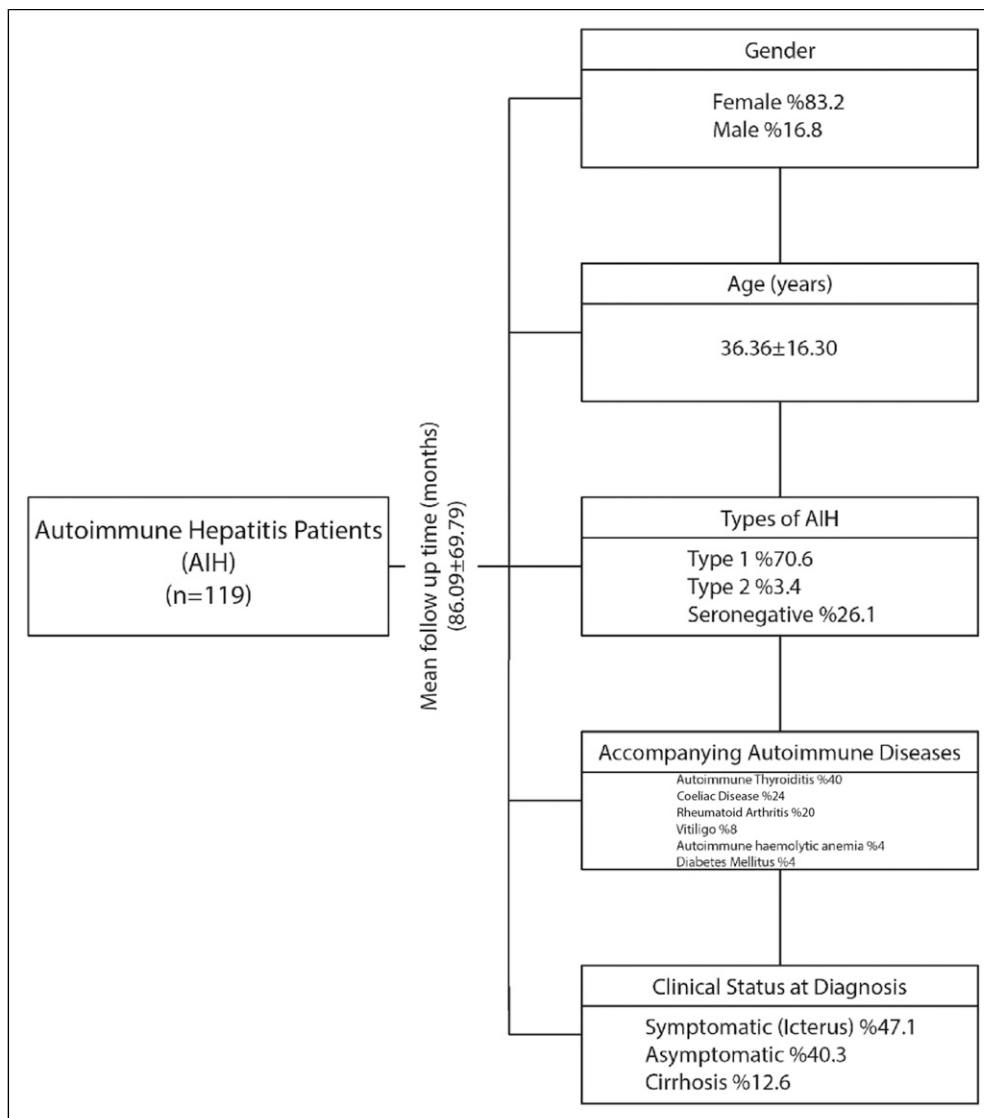


Figure 1. Patients’ characteristics in the study group.

follow-up, 15 patients became cirrhotic. Treatment was discontinued in 18 patients (three compensated cirrhosis). Liver biopsy was performed in eight patients whose treatment was withdrawn, and it revealed no portal inflammation, and relapse occurred in four patients. The mean treatment duration was 101 ± 75 months (24–280) before treatment withdrawal. The relapse rate was 67% ($n = 12$) in patients with drug withdrawal. Relapse occurred within an average of 19 months after the treatment withdrawal. We could not find any predictors for relapse (Table 2).

Acute hepatitis attack was observed in five patients; none of them experienced a liver failure during the relapse. Death and liver transplantation were similar between treatment withdrawn patients and maintenance treatment ($p > 0.05$). On the other hand, cirrhosis and decompensation rates were

higher in the treatment withdrawal group (36%/33% vs 8%/4%) during the follow-up period.

Discussion

AIH constitutes an interesting hepatology disease group with uncertainty in its etiopathogenesis and complex treatment routes.

In epidemiological studies conducted in this area, AIH was reported in the female with 75% and 80% was Type 1 AIH.^{13–16} In our study, 83% of our patient group was female, and 70.6% of them were identified to have type 1 AIH. In a study by Sonthalia et al.,¹⁵ 25% of 125 patients diagnosed with AIH were classified as seronegative OIH. In a study of 120 patients, the rate of remission with a steroid alone or with

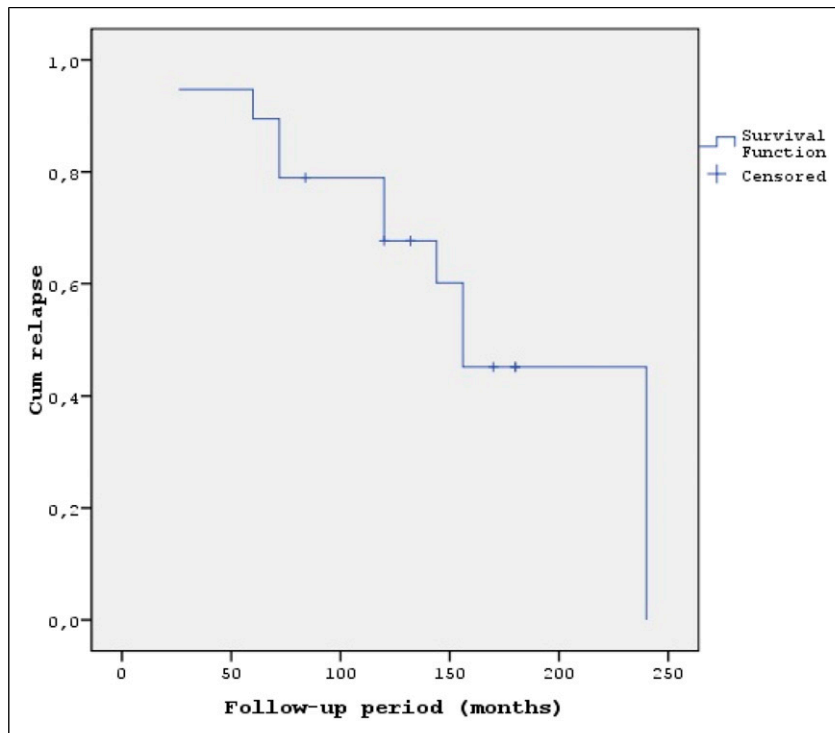


Figure 2. The relapse rate observed in the follow-up after discontinuation of the drug.

Table 1. Demographic and clinical findings of patients according to maintenance treatment and treatment withdrawal.

	Maintenance treatment <i>n</i> = 101	Drug withdrawal <i>n</i> = 18	<i>p</i> value
Age (years)	48.17 ± 16.39	47.99 ± 15.41	0.838
Female/male (n)	84/17	15/3	0.986
Other autoimmune disorders (%)	23.5	24.4	0.936
Cirrhosis (%)	48	33	0.268
ALT (IU/L)	392.28 ± 490.91	368.17 ± 324.64	0.455
AST (IU/L)	438.54 ± 490.11	354.89 ± 292.17	0.924
Gamma globulin (g/L)	3 ± 1.4	3.4 ± 1.3	0.259
Mean follow-up (months)	76 ± 66	140 ± 62.9	<0.001
ANA, SMA, LKM, P ANCA, (%)	24/16/5/7.9	27/22/0/11	0.874
Autoantibody negativity (%)	28.6	27.8	
During the follow-up (%)	8.2/4	36.4/33.3	0.103
Cirrhosis/Decompensated			
Death (n)	4	1	—
Liver transplantation (n)	1	0	—

the combination of azathioprine and the steroid was reported to be 74–80%.^{17–19} Similarly, the rate of achieving remission with steroid induction alone was 80% in our patient group. While the criteria that were effective in obtaining remission in patients with AIH were evaluated in previous studies, it was stated that the rates of obtaining remission in patients, who were cirrhotic at the time of diagnosis, were worse.^{20,21}

It remains unclear which AIH patients should discontinue treatment, how long the follow-up period should

be after discontinuation, what are the relapse rates and relapse times. There are few original studies about the discontinuation of treatment in AIH, and the previous studies were mostly based on retrospective analysis.²² Czaja et al.²³ demonstrated that 46% of the patients required treatment again within an average of 7 ± 1 months after discontinuation of the treatment. In a compilation study, in which treatment without follow-up in AIH was evaluated, it was reported that in studies with long-term follow-up involving a

Table 2: Comparison of patients' characteristics after treatment withdrawal.

	Relapse after drug withdrawal n = 12 (67%)	No relapse after drug withdrawal n = 6 (33%)	p value
Age (years)	49.17 ± 15.96	46.17 ± 18.61	0.616
Female/male (n)	10/2	5/1	0.999
Other autoimmune disorders (%)	27.3	16.7	0.622
Initial symptom Asymptomatic/Symptomatic (%)	41.7/58.3	50/50	0.737
Initial ALT (IU/L)	335.75 ± 285.49	433 ± 414.08	0.682
Initial AST (IU/L)	315.92 ± 282.87	432.83 ± 321.34	0.385
Initial gamma globulin (g/L)	3.00 ± 1.00	4.50 ± 1.80	0.267
AIHG score	15.00 ± 4.04	14.2 ± 3.03	0.639
Duration time of ALT normalization (month)	3.09 ± 2.81	1.60 ± 0.89	0.377
Duration time of gamma globulin normalization (month)	16.25 ± 8.5	7.00 ± 1.73	0.057
Mean follow-up (months)	137.17 ± 73.78	146.33 ± 37.74	0.553
ANA, SMA, both ANA/SMA, autoantibody negativity (%)	33.3/16.7/16.7/33.3	16.7/33.3/33.3/16.7	0.615
Before withdrawal ALT(IU/L)	21.20±6.91	16.80±4.09	0.151
Before withdrawal AST(IU/L)	22.20±4.09	19.20±3.27	0.310
Before withdrawal gamma globulin (g/L)	1.20±0.01	1.27±0.28	0.999
Time until withdrawal (month)	80.60±62.84	135.67±86.65	0.220

minimum of 3 years, the rate of patients, who were under follow-up without treatment and who did not require further treatment, varied between 19% and 40%.²⁴ In the literature, different periods have been referred to as late relapse, even up to 20 years. However, close follow-up has been recommended for patients within the first 1-year after the drug discontinuation in terms of biochemical and clinical parameters.^{25,26} In a study involving 131 patients with AIH, van Gerven et al.²⁷ stated that 59% of the patients required treatment 1 year after the drug was discontinued, 73% required treatment after 2 years, and 81% required treatment after 3 years. We also found the relapse rate as 67% in our patient group and observed that the relapse occurred in an average of 19 months, which was a high rate similar to the findings present in the literature. On the other hand, John et al.²⁸ found that worsening occurred in 25% of patients during the follow-up period of 11.4 ± 1 months after discontinuation of treatment in a group of 34 patients. The fact that this exacerbation rate was lower compared to our patient group and the current literature is believed to be associated with the selectiveness of the criteria for inclusion in the study, homogenous distribution of the treatment protocols of the patient group, and the lower ages of diagnosis compared to our patient group. It is reported that de novo cirrhosis could develop in AIH despite treatment with a probability of 18%.² In our study, the rate of cirrhosis development in treated patients was 8.2%; however, this rate was found to be 36.4% in the discontinued group.

It was believed that this could be due to the continuation of the inflammation in the discontinued group, in which 42% of the patients who experienced relapse after discontinuation of the drugs had presented with acute hepatitis. The patient groups with a lower risk of relapse after

discontinuation of the treatment for AIH have been indicated in the literature as the patient groups who were not in the cirrhotic stage, had type 1 AIH, were over the age of 40, had normal levels of IgG, did not have any coexisting autoimmune diseases, and who remained in remission for at least 2 years after achieving rapid remission.^{1-3,26-28} In our study, 56.3% of the patients with drug withdrawal had liver biopsy just before the drug was discontinued, and although the patients were in remission histologically, the relapse rate was found to be as high as 40% in these patients who were found to be in remission by liver biopsy. Although EASL guidelines emphasize that histologically being in remission before drug withdrawal in AIH reduces the recurrence rate, in some studies, as in a study by Czaja et al., they indicate that there was no histological difference between the relapse group and the no relapse group.^{8,29} Therefore, as in our study, although patients are histologically in remission, they may not predict the risk of relapse in AIH. A prospective observational study by van den Brand et al. investigated the predictive value of histological remission after successful drug discontinuation in 17 patients with non-cirrhotic AIH evaluated by liver biopsy. They showed that eight of 12 patients with an ISHAK score <3 remained in remission at 62 months of follow-up. They also searched for indicators of relapse in their study and could not find any indicators similar to those in our study.³⁰ AIH constitutes a rare disease group in the field of hepatology. Therefore, the studies and case presentations in this field are important in terms of the literature. However, comprehensive studies cannot be carried out in this field due to the difficulty of establishing and managing homogeneous groups in terms of diagnosis and treatment approach.

The definition of relapse in patients with autoimmune hepatitis can be based on some different criteria. In our study, we defined relapse as an AST value two times higher than the upper limit of normal. However, in different studies in the literature, a serum ALT level 3 times higher than the upper limit of normal and/or an IgG serum level >20 g/L or an AST level 3 times higher than normal have been defined as relapse.^{31,32} For this reason, it is necessary to consider the criteria for relapse while evaluating the relapse rates in different studies. Since there is no single accepted definition of relapse, it is difficult to interpret the prognosis by revealing the increase in liver transaminases based on the criteria, but our study presents descriptive data in terms of relapse to the literature rather than data related to prognosis.

Limitations of our study, like other studies in the literature in this field, include the retrospective nature of the study, the inability to establish homogeneous groups in terms of diagnosis and treatment, and the low number of patients. Also, the fact that not every patient whose drug was discontinued could be evaluated with liver biopsy and the fact that we evaluated with gamma globulin instead of IgG levels, which we are more accustomed to in the literature, constitute the limiting aspects of the study. The small sample size of our study prevents us from strong implications for relapse and prognosis after drug withdrawal. Nevertheless, we hope that this study, which was presented because of a long period of patient follow-up and containing real-life data, would contribute to the literature in this regard.

Due to the long-term side effects of steroid and azathioprine treatment, which form the basis of the treatment in AIH, it has been necessary to reveal the criteria for termination of drug treatment. Regarding AIH, EASL's 2015 and AASLD's 2019 guidelines recommend at least 2 or 3 years of remission as treatment discontinuation criteria, respectively, and according to EASL, the condition of full remission is required clinically, biochemically, and histologically, although it is known that most patients cannot achieve this condition.^{8,33} Therefore, with this study, we investigated whether it is possible to discontinue drugs, which is one of the main difficulties in the treatment of AIH, which affects especially the young age group. We found that the relapse rate after drug discontinuation is as high as 67%.

Conclusion

In conclusion, in patients with AIH, relapse occurs in two-thirds of patients within an average of 1.5 years after discontinuing the drugs. Most relapses occur at the early period, and an acute hepatitis attack can accompany them. In the follow-up of AIH, the balance of benefit and loss of discontinuing the drugs should be well evaluated.

Authors contributions

FA designed the research and BÇ and FA wrote the paper. Rİ, AA, and ÜA were responsible for data collection and analysis. KD, FB, and SK were responsible for critical revision of the manuscript for important intellectual content. FA, mentor and primary investigator, was responsible for the study concept and design, critical revision of the manuscript for important intellectual content, and study supervision.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics approval

This was a retrospective chart review, and the approval of the local ethical committee was acquired. Ethical Approval Number: 1536-712.

Informed consent

This was a retrospective chart review, and the approval of the local ethical committee was acquired.

ORCID iD

Bilger Çavuş  <https://orcid.org/0000-0003-2203-4255>

References

1. Assis DNMD (2020). Immunopathogenesis of autoimmune hepatitis clinical liver disease, *Clinical Liver Disease* 15(3): 129–132.
2. Harrison L (2019) Dermot gleeson Stopping immunosuppressive treatment in autoimmune hepatitis (AIH): is it justified (and in whom and when)? *Liver International* 39: 610–620.
3. Albert J (2016) Czaja diagnosis and management of autoimmune hepatitis: current status and future directions. *Gut and Liver* 10(2): 177–203.
4. Sucher E, Sucher R, Gradistanac T et al. (2019) Stefan schneeberger and thomas berg autoimmune hepatitis—immunologically triggered liver pathogenesis—diagnostic and therapeutic strategies. *Journal of Immunology Research* 2019: 9437043.
5. Jiang YZ and Ying H (2015). Autoimmune hepatitisUnveiling faces. *Journal of Digestive Diseases* 16: 483–488.
6. Ian GM (2002) Definition and classification of autoimmune hepatitis. *Seminars in Liver Disease*, 22(4): 317–324
7. Dalekos GN, Koskinas J and Papatheodoridis GV (2019) Hellenic association for the study of the liver clinical practice

- guidelines: autoimmune hepatitis. *Annals of Gastroenterology* 32(1): 1–23.
8. European Association for the Study of the Liver (2015) EASL clinical practice guidelines: autoimmune hepatitis *Journal of Hepatology* 63: 971–1004.
 9. Gleeson D (2011). Heneghan British Society of Gastroenterology (BSG), michael aguidelines for management of autoimmune hepatitis *Gut* 60: 1611–1629. DOI: [10.1136/gut.2010.235259](https://doi.org/10.1136/gut.2010.235259).
 10. Alvarez F, Berg PA, Bianchi FB, et al. (1999) Donaldson international autoimmune hepatitis group report: review of criteria for diagnosis of autoimmune hepatitis. *Journal of Hepatology* 31: 929938.
 11. Czaja AJ (2008) Performance parameters of the diagnostic scoring systems for autoimmune hepatitis. *Hepatology* 48(5): 1540–1548.
 12. Desmet VJ., Gerber M, Hoofnagle JH, et al. (1994) Scheuer classification of chronic hepatitis: diagnosis, grading and staging. *HEPATOLOGY* 19: 1513–1520.
 13. Francque SS, Vonghia L, Albert R et al. (2012) Epidemiology and treatment of autoimmune hepatitis *Hepatic Medicine* 4: 1–10.
 14. Manns MP and Vergani D (2009) Autoimmune hepatitis. *Seminars in Liver Disease* 29: 239–240.
 15. Sonthalia N, Rathi P, Jain S, et al. (2016) Sunil pawar, qais contractor seronegative autoimmune hepatitis presents with more severe disease but has similar outcomes as compared to seropositive patients. *Journal of Clinical and Experimental Hepatology* 6(S1): S74–S102
 16. Michael P (2014) Manns and richard taubert treatment of autoimmune hepatitis. *Clinical Liver Disease* 3(1).
 17. Roberts SK, Therneau TM and Czaja AJ (1996) Prognosis of histological cirrhosis in type 1 autoimmune hepatitis. *Gastroenterology* 110: 848–857.
 18. Piccoli BTB, Mieli-Vergani G and Vergani D (2017) Autoimmune hepatitis: standard treatment and systematic review of alternative treatments. *World Journal of Gastroenterology* 23(33): 6030–6048.
 19. Summerskill WH, Korman MG, Ammon HV et al. (1975) Prednisone for chronic active liver disease: dose titration, standard dose, and combination with azathioprine compared. *Gut* 16: 876–883.
 20. Muratori P., Lalanne C., Bianchi G., et al. (2016) Predictive factors of poor response to therapy in autoimmune hepatitis. *Digestive and Liver Disease* 48: 1078–1081.
 21. Sandusadee N and Sukeepaisarnjaroen W (2020) Tanita sutthichaimongkol prognostic factors for remission, relapse, and treatment complications in type 1 autoimmune hepatitis. *Heliyon* 6: e03767.
 22. Gerd Bouma Carin M and Nieuwkerk V (2015) Treatment withdrawal in autoimmune hepatitis. *Digital Distribution* 33(suppl 2): 88–93.
 23. Czaja AJ, Ludwig J, Baggenstoss AH et al. (1981) Corticosteroid-treated chronic active hepatitis in remission: uncertain prognosis of chronic persistent hepatitis. *New England Journal of Medicine* 304: 5–9.
 24. Czaja A. J. (2014) Review article: permanent drug withdrawal is desirable and achievable for autoimmune. *Alimentary Pharmacology & Therapeutics* 39: 1043–1058. hepatitis
 25. Weiler-Normann C and Ansgar W (2013). Lohse Autoimmune hepatitis: A life-long disease. *Journal of Hepatology* 58: 5–7
 26. Hartl J, Rosa M, Zachou K, et al. (2020) Features and outcome of AIH patients without elevation of IgG. *JHEP Reports* 2: 100094.
 27. van Gerven NM.F., Verwer BJ., Witte BI., et al. (2013) Relapse is almost universal after withdrawal of immunosuppressive medication in patients with autoimmune hepatitis in remission. *Journal of Hepatology* 58: 141147.
 28. Guirguis J, Alonso Y, Lopez R. et al. (2018) Well-controlled autoimmune hepatitis treatment withdrawal may be safely accomplished without liver-biopsy guidance. *Gastroenterology Report* 6(4): 284–290.
 29. Czaja AJ. and Herschel A (2003) Carpenter Histological features associated with relapse after corticosteroid withdrawal in type 1 autoimmune hepatitis. *Liver Int* 23(2): 116–123.
 30. van den Branda FF, Romee Snijdersa JALM, de Boera YS, et al. (2021) Drug withdrawal in patients with autoimmune hepatitis in long-term histological remission: a prospective observational study. *European Journal of Internal Medicine* 90: 30–36.
 31. Trivedi PJ., Hubscher SG., Heneghan M, et al. (2019) Hirschfield grand round: Autoimmune hepatitis. *Journal of Hepatology* 70: 773–784.
 32. van Gerven NM.F., Verwer BJ., BirgitWitte I., et al. (2013) Relapse is almost universal after withdrawal of immunosuppressive medication in patients with autoimmune hepatitis in remission. *Journal of Hepatology* 58: 141–147.
 33. Mack CL., Adams D, Assis DN., et al (2020) *Czaja Diagnosis and Management of Autoimmune Hepatitis in Adults and Children: 2019 Practice Guidance and Guidelines from the American Association for the Study of Liver Diseases*. Hepatology.