sciendo

PROCEEDINGS OF THE LATVIAN ACADEMY OF SCIENCES. Section B,
Vol. 78 (2024), No. 4 (751), pp. 275–282.

DOI: 10.2478/prolas-2024-0038

Original Paper

CLINICAL FEATURES, TREATMENT CHALLENGES AND OUTCOMES OF PATIENTS WITH AUTOIMMUNE HEPATITIS: FIVE YEARS EXPERIENCE IN RĪGA EAST UNIVERSITY HOSPITAL

Elīna Vašuka[1,#], Vita Novika[1], Sniedze Laivacuma[1,2], Angelika Krūmiņa[2], and Indra Zeltiņa[1,2]

[1] Rīga East University Hospital, 2 Hipokrāta Str., Rīga, LV-1038, LATVIA

[2] Department of Infectology, Rīga Stradiņš University, 16 Dzirciema Str., Rīga, LV-1007, LATVIA

[#] Corresponding author, elina.vasuka@gmail.com

Communicated by Aivars Lejnieks

Autoimmune hepatitis is an inflammatory disease of the liver of unknown aetiology that can progress to liver cirrhosis and end-stage liver failure. The clinical presentation is often acute hepatitis, but can be insidious or completely asymptomatic. It is characterised by an increase in serum transaminases and immunoglobulin G, an inflammatory liver histology, and the presence of circulating autoantibodies. An autoimmune hepatitis diagnosis justifies lifelong treatment in most patients to prevent the development of cirrhosis and end-stage liver disease. The cornerstone of treatment is steroid induction therapy followed by maintenance therapy with azathioprine, which is effective in most cases. Treatment should be optimised to reach these aims with a minimum of side effects. To achieve optimal results, individual treatment regimens and compromises between treatment aims and personal choices are needed. The aim of the study was to collect data on the clinical course, therapy, and results of autoimmune hepatitis, on the compliance of treatment choice with the criteria for starting therapy. A retrospective cohort study was conducted using data from the Rīga Eastern University Hospital Archives for the period 2019–2023. The study group consisted of 37 patients diagnosed with autoimmune hepatitis who were hospitalised or consulted in an outpatient clinic during the above period. Information relating to the patient's electronic medical records were obtained and no additional sources were used. In the study, it was found that the clinical and diagnostic criteria of autoimmune hepatitis in Rīga Eastern Clinical University Hospital over a five-year period usually correspond to the generally accepted diagnostic principles, but the therapeutic approach does not always correspond to the guidelines, especially regarding the duration of therapy.

Keywords: *diagnostic, rare liver diseases, prognosis, autoimmunity.*

INTRODUCTION

Autoimmune hepatitis (AIH) is a rare autoimmune inflammatory liver disease, characterised by circulating autoantibodies, an increased concentration of IgG, and nonspecific but distinctive histological characteristics (European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis, 2015). Previously defined as affecting young women, Autoimmune hepatitis is now considered a disease affecting both sexes and all ages worldwide (Trivedi and Hirschfield, 2021). The combined annual incidence and prevalence worldwide are 1.37 and 17.44 per 100,000 people, respectively. The pooled annual incidences for the European population are 1.37 per 100,000. The pooled prevalences for the European population are 19.44 per 100,000 (Lv *et al.,* 2019). As mentioned

before, AIH occurs at all ages and within all ethnic groups and can be variable by race and ethnicity. According to the American Association for the Study of Liver Diseases (AASLD) guidelines, Alaskan Natives have a high frequency of icterus at presentation, Hispanics are more commonly present with cirrhosis, and African Americans have accelerated progression of the disease and a higher rate of recurrence after LT compared to other races (Gatselis *et al*., 2015). The female sex is still more affected in adults (71%–95% women) and children (60%–76% girls) (Czaja *et al*., 1993; Gregorio *et al*., 1997).

AIH is a complex disease that requires the interplay between genetic, epigenetic, immunologic, and environmental factors. A rare exception is the form associated with an autosomal recessive mutation in the autoimmune regulator gene on chromosome 21q22.3, which has been associated with autoimmune polyglandular syndrome type 1 (APS 1) (Nagamine *et al.*, 1997). Environmental exposures play more important role than genetics in shaping the immune repertoire, and specific environmental factors, such as viral infections or xenobiotic exposures, can act as environmental triggers for loss of self-tolerance to autoantigens in susceptible people (Volk and Reau, 2021).

There are two types of AIH depending on the autoantibodies present. Type 1 is characterised by antinuclear antibody (ANA) and/or smooth muscle antibody (SMA) / antiactin antibodies, and type 2 is characterised by antibodies to type 1 liver kidney microsome (antiLKM1), usually in the absence of ANA and SMA (Table 1). It is important to mention that up to 20% of cases may be negative for ANA, SMA, and LKM1 autoantibodies, despite the presence of other characteristic features of AIH, and are referred to as as seronegative AIH. Classification of AIH into types assists in management and aids in predicting outcomes in children, but it can be less informative in adults (Volk and Reau, 2021).

The diagnosis of autoimmune hepatitis remains challenging due to nonspecific serologic markers and a sometimes difficult clinical picture, ranging from asymptomatic disease to fulminant liver failure (Rahim *et al*., 2020).

There is an AASLD developed allgorithm available to help medical practitioners navigate their decision based on the autoantibody pattern shown in Fig. 1.

Summary of the criteria for the diagnosis of autoimmune hepatitis, on which the 1999 International Autoimmune Hepatitis Group (IAIHG) diagnostic score was based on the criteria shown in Table 2.

Clinical manifestations of AIH:

1. Symptomatic

Most patients with AIH have nonspecific chronic symptoms (fatigue, malaise, arthralgia, or amenorrhoea). Fatigue is the main complaint in 85% of patients, and jaundice can be present. The presence of pruritus or hyperpigmentation is inconsistent with the diagnosis, and weight loss may suggest serious complications (malignancy). Physical signs are usually absent, except signs of advanced chronic liver disease (spider nevi, caput medusa, splenomegaly, ascites, and palmar erythema) or manifestations of extrahepatic autoimmune disease (vitiligo, inflammatory bowel disease (IBD)) (Alvarez et al.,1999).

2. Asymptomatic

AIH is asymptomatic in 25%–34% of patients. Asymptomatic patients can achieve spontaneous laboratory improvement (12%), may have histological findings similar to those of symptomatic patients, frequently develop symptoms within 2 to 120 months (mean interval, 32 months; 26%–70%), and experience a 10–year survival that is less than that of treated patients with more severe disease (67% versus 98%). The absence of symptoms should not discour-

Table 1. Characteristics of type 1 and type 2 autoimmune hepatitis (AIH)

Features	Type 1 AIH	Type 2 AIH
Frequency	Adults in the US, 96%	US children, 9%–12%; UK children, 38%
Age at presentation	Peripubertal and adults	Usually under 14 years of age.
Mode of presentation	Chronic symptoms common; ascites or GI bleeding rare; asymptomatic in 25%–34%; acute in 25%–75%; acute severe in 2%–6%	Acute onset (~40%); acute liver failure possible; frequent relapse
Laboratory characteristics	Hypergammaglobulinemia	IgA levels may be reduced
Autoantibodies	ANA; SMA, anti-actin; SLA	Anti-LKM1; [Anti-LC1, Anti-LKM3]
Concurrent immune diseases	Autoimmune thyroiditis; rheumatic diseases; IBD	Autoimmune thyroiditis; diabetes mellitus; vitiligo
Autoimmune overlap with PSC (ASC in children)	Common in children; atypical pANCA positive	Rare; atypical pANCA negative
Overlap with PBC	Seen in adults (not children)	Not reported
Cirrhosis at presentation	Adults, 28%–33% (especially elderly); children, !%	Rare
Remission after drug withdrawal	Possible	Rare, usually need long-term immunosuppression

ANA, antinuclear antibody; SMA, smooth muscle antibody; SLA, soluble liver antigen; LKM1, type 1 liver kidney microsome; pANCA, perinuclear anti-neutrophil cytoplasmic antibodies

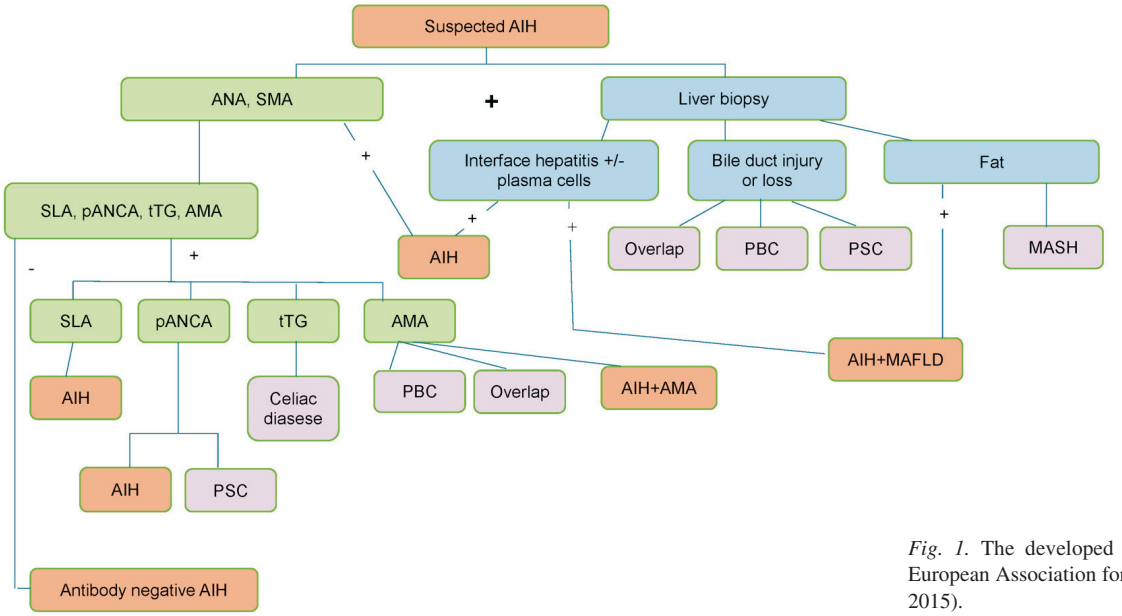

Fig. 1. The developed AASLD algorithm (after European Association for the Study of the Liver…, 2015).

Table 2. Criteria for definite and probable autoimmune hepatitis (AIH)

Criteria	Definite AIH	Probable AIH
Normal α-1AT phenotype	Normal α-1AT phenotype	Partial α-1AT deficiency
Normal ceruloplasmin level	Normal ceruloplasmin level	Non-diagnostic ceruloplasmin / copper levels
Normal iron and ferritin levels	Normal iron and ferritin levels	Non-diagnostic iron and/or ferritin changes
No active hepatitis A, B, or C infection.	No active hepatitis A, B, or C infection.	No active hepatitis A, B, or C infection.
Daily alcohol	< 25 g/day	< 50 g/day
No recent hepatotoxic drugs	No recent hepatotoxic drugs	No recent hepatotoxic drugs
Predominant AST/ALT abnormality	Predominant AST/ALT abnormality	Predominant AST/ALT abnormality
γ-globulins or IgG level	> 1.5 times the upper normal limit	Hypergammaglobulinemia of any degree
Autoantibodies	ANA, SMA anti-LKM1 > 1:80 in adults and > 1:20 in children	ANA, SMA, anti-LKM1 > 1:40 in adults; other autoantibodies
AMA negative	AMA negative	
Liver histology	Moderate to severe; No biliary lesions, granulomas, or prominent changes suggestive of another disease	Interface hepatitis moderate to severe; No biliary lesions, granulomas or prominent changes suggestive of another disease

Source: European Association for the Study of the Liver…, 2015; Alvarez *et al*., 1999. Abbreviations see under Table 1. AMA, antimitochondrial antibodies

age treatment (Alvarez *et al*., 1999; Kogan *et al*., 2002; Feld *et al*., 2005).

3. Acute severe hepatitis and ALF

AIH presents with acute onset (duration, < 30 days) in 25% 75% of patients. ALF associated with hepatic encephalopathy occurs in 3%–6% of patients in North America and Europe. Spontaneous exacerbation or superimposed viral, toxic or drug–induced liver injury in previously undiscovered AIH (acute–on–chronic liver disease) must be excluded. ANA are absent or weakly positive in 29%–39% of patients with acute severe AIH, and the serum IgG level is normal in 25%–39%. Histological evaluation is a key diagnostic test: lobular hepatitis, lymphoplasmacytic infiltrate, and interface hepatitis support the diagnosis of acute AIH; and similar characteristics in the presence of cirrhosis suggest exacerbated chronic disease. Unenhanced computed tomography demonstrates heterogeneous hypoattenuated regions within the liver in 65% of patients with acute severe AIH and may be disease–specific (Volk and Reau, 2021).

Fig. 2 shows that the objective of treatment is to induce remission, defined as the normalisation of aminotransferases and IgG, and to maintain remission thereafter. Approximately 10–20% of patients with autoimmune hepatitis do not achieve remission with standard treatment (with Prednisolone, Azathioprine) or develop severe side effects that require discontinuation of treatment. Second-line treatments are defined, but third-line therapies are not always available. For patients with treatment failure, this disease

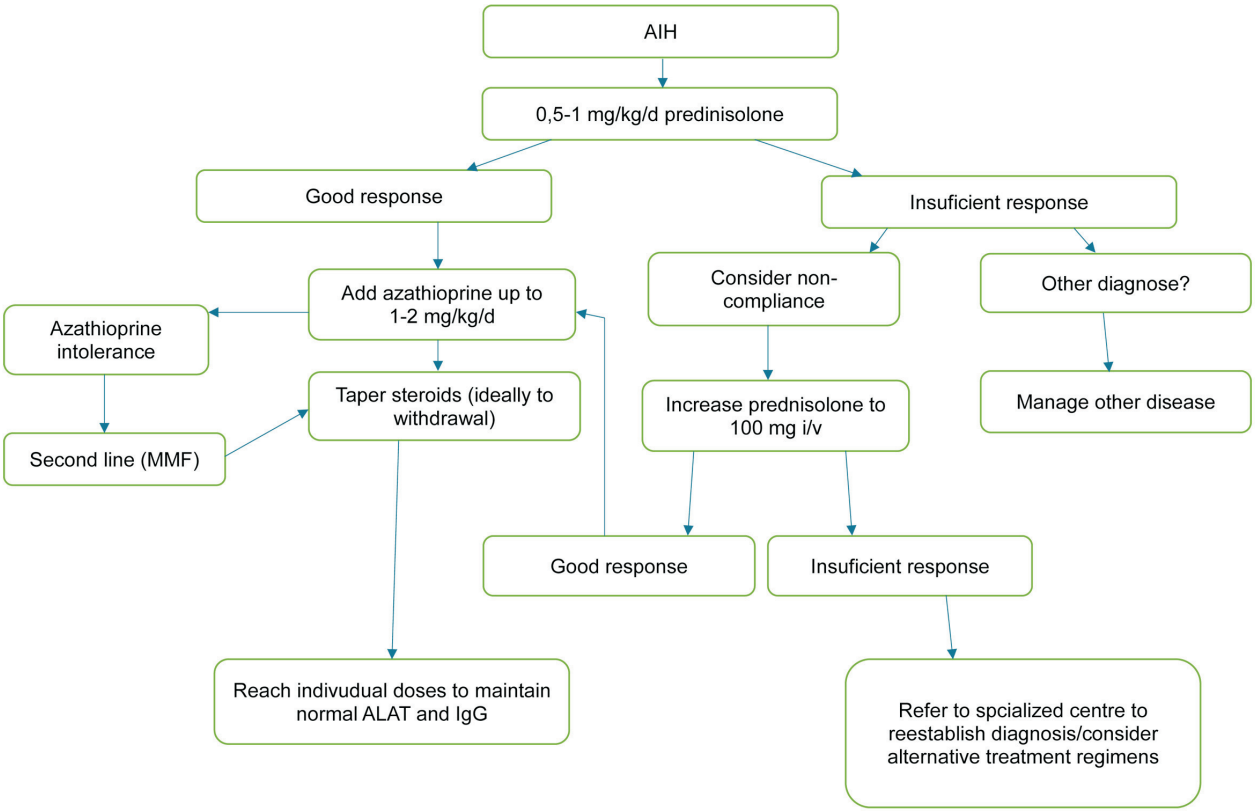

Fig. 2. Therapeutic strategy in autoimmune hepatitis (after European Association for the Study of the Liver…, 2015).

progresses to liver failure, cirrhosis, and premature death. In 2010, there was a trial comparing budesonide with prednisone and it was recommended as an effective alternative for the treatment of non-severe acute or chronic autoimmune hepatitis. The overall results of the trial showed better response to budesonide/azathioprine than to prednisone/azathioprine treatment, the primary end-point being achieved in 60% of patients with budesonide vs 38.8% of those given prednisone (Terziroli *et al*., 2017). In a retrospective study 60 patients with either prednisolone side effects or dependence on a relative high dose of prednisolone were switched to budesonide: the biochemical remission rate at 6 months was 55%, and 25% of the patients needed to be switched back to prednisone due to budesonide side-effects or insufficient response. These findings indicate that budesonide is effective in maintaining remission in patients who have achieved it with prednisone but it is not effective in patients resistant to prednisone, as prednisone and budesonide share the same receptor (Werner *et al*., 2010). However, as later studies show, in the real-life setting, the use of budesonide as first-line treatment is low, and it is generally prescribed to patients with perceived lower disease activity. Budesonide was inferior to prednisone as a first-line drug, but was associated with fewer side effects (Díaz-González *et al*, 2023). Debate on which steroid to use in AIH: whether or not budesonide may be a reasonable alternative for predniso(ol)one treatment, budesonide does not and will not solve the problem of optimizing treatment of AIH. In other immune-mediated diseases, steroids are no longer a mainstay of therapy and only used for the initial therapy in the acute period until more effective and more specific immunosuppressive and immunomodulatory drugs take effect (Steinmann and Lohse, 2023).

The aims of the study were to collect data on the clinical course, therapy, and results of autoimmune hepatitis, the compliance of treatment choice with the criteria for starting therapy.

MATERIALS AND METHODS

Terms used in this paper: AIH – Characteristic histologic abnormalities (lymphoplasmacytic interface hepatitis), elevated AST, ALT, and total IgG (immunoglobulin G), and the presence of one or more characteristic autoantibodies. Acute severe AIH – jaundice, INR > 1.5 < 2, no encephalopathy; no previously recognised liver disease. Acute liver failure (ALF) – INR (international normalised ratio) ≥ 2; hepatic encephalopathy within 26 weeks of the onset of the illness; no previously recognised liver disease. Biochemical remission – normalisation of serum AST, ALT, and IgG levels. Histological remission – absence of inflammation in liver tissue after treatment. Treatment failure – worsening laboratory or histological findings despite compliance with standard therapy. Incomplete response – improvement in laboratory and histological findings that are insufficient to satisfy the remission criteria. Relapse – exacerbation of disease activity after induction of remission and withdrawal of drugs. Treatment intolerance – inability to continue maintenance therapy due to drug-related side effects.

A retrospective cohort study was conducted using data from the Rīga Eastern University Hospital Archives for the period 2019–2023. The study group consisted of 37 patients diagnosed with autoimmune hepatitis who were hospitalised or consulted in an outpatient clinic during the above period. Information relating to the patient's electronic medical records were obtained and no additional sources were used.

Data processing was performed using the SPSS Statistics 29 software. The study group was formed with the help of specific inclusion criteria. Detection was based on clinical, biochemical, saline and histological observations, such as increased levels of aminotransferase, gamma-glutamyltransferase, antinuclear antibodies, immunglobulin G, bilirubin and liver biopsy results. The results of the liver biopsy were of the utmost importance in this study. Additionally, almost all patients received regular follow-up.

RESULTS

In the study, both inpatients and outpatients were included, totalling 37 respondents. Patients were divided by gender: 31 female and 6 male representatives. Additionally, age groups were classified when autoimmune hepatitis was diagnosed. The following results were obtained: two respondents (one male and one female) had < 18 years of age, seven respondents (two males and five females) were in the age group 18-40 years, 14 (three males and 11 females) in the age group of 41–59 years, and 14 respondents (0 males and 14 females) in the age group of 60+ years. The youngest female diagnosed with AIH was 16 years old. The oldest patient was 75 years old at the time of diagnosis. The median age in the female group was 58 years. The youngest male representative at diagnosis was 18 years and the oldest was 58 years. The median age in the male group was 35 years.

When evaluating the final status of autoimmune hepatitis diagnose, patients were divided into two small groups – partially confirmed diagnosis and confirmed diagnosis. The following data were obtained: eight (21.6%) patients had a partially confirmed diagnosis, consisting of two males and six females, and 29 (78.4%) patients had a confirmed diagnosis, consisting of four males and 25 females. During the selection process, it was found that autoimmune hepatitis was the primary diagnosis of 25 (67.6%) respondents, while it was a secondary diagnosis in 12 (32.4%) patients.

A liver biopsy was not performed in six respondents, data were missing for one respondent, and biopsy was performed for 30 respondents. The main reason for lack of a liver biopsy was coagulation disorders — for six respondents. Table 3 shows the results of histology — findings corresponding to autoimmune hepatitis were found in 14 respondents, findings corresponding to chronic autoimmune hepatitis were found in three respondents, but characteristic morphological features of autoimmune hepatitis were not detected in histology for three respondents. Autoimmune hepatitis could be completely excluded in five respondents. There were five respondents who underwent a biopsy, but histology results were not available.

Table 3. Hystology data

Histology	Count
Morphology consistent with AIH	14
Not performed due to coagulation disorders	6
AIH cannot be completely ruled out.	5
No convincing morphological signs characteristic of AIH were found in the material examined.	3
Chronic AIH	3
No data	1
Histology results are not available	5
Total	37

AIH, autoimmune hepatitis

ANA IgG autoantibodies were also evaluated in the respondents against various nuclear components, which are found in systemic autoimmune diseases. Of the 37 medical records analysed, ANA IgG was analysed in 33 respondents – autoantibodies were negative in five respondents and positive in 28 respondents, with no data available for four respondents. Furthermore, confirmed or partially confirmed diagnosis of autoimmune hepatitis was evaluated for possible correlation with ANA IgG autoantibodies. In the case of a partially confirmed AIH diagnosis, ANA IgG autoantibodies were negative for one respondent and positive for four respondents. In the case of confirmed diagnosis of AIH, ANA IgG autoantibodies were negative for four respondents and positive for 24 respondents.

The medical records of the respondents were also examined for ALAT, ASAT, GGT and bilirubin levels. ALAT and ASAT levels were evaluated both before and dynamically after therapy initiation. Unfortunately, it was not possible to determine when control analyses were prescribed after therapy initiation because there were cases in which ALAT and ASAT were evaluated approximately a month after therapy initiation, as well as cases in which control was performed several years after therapy initiation. Elevated ALAT levels often served as the first step in defining the diagnosis because patients did not have specific complaints. ALAT levels were analysed in 33 respondents before starting therapy, with a median of 551 U/l, a minimum of 25 U/l and a maximum of 6230 U/l. ALAT was analysed in 29 respondents after starting therapy, with a median of 53 U/l, a minimum of 9 U/l and a maximum of 1055 U/L. ASAT levels were analysed in 26 respondents before starting therapy, with a median of 396.5 U/l, a minimum of 55 U/l, and a maximum of 2542 U/l. ASAT was analysed in 14 respondents after initiation of therapy, with a median of 39 U/l, a minimum of 12 U/l and a maximum of 2163 U/l. GGT levels were analysed in 26 respondents before starting therapy, with a median of 135.5 U/l, a minimum of 43 U/l and a maximum of 685 U/l. GGT was analysed in 20 respondents after starting therapy, with a median of 35.5 U/l, a minimum of 13 U/l, and a maximum of 387 U/l. Bilirubin levels were deter-

mined for the patients, but only pretherapy initiation levels were included in the study, with a median of 66 mkmol/l, a minimum of 7 mkmol/l and a maximum of 283 mkmol/l.

Regarding the administration of therapy, three medications were used in this retrospective study: prednisolone, azathioprine, and medrol. Prednisolone was received by 33 respondents, not received by three respondents, and there were no data for one respondent. Azathioprine was received by 24 respondents, not received by 12 respondents, and there was no data for one respondent. Medrol was received by two respondents, not received by 34 respondents, and there was no data for one respondent. 22 respondents received a combination of prednisolone and azathioprine.

All patients with autoimmune hepatitis had high levels of transaminases and GGT. Not all patients received immunosuppressive therapy, as one patient in this group avoided treatment for fear of side effects of treatment. The duration of immunosuppressive treatment was generally shorter than traditionally accepted and patients chose to discontinue therapy without specifying specific reasons.

DISCUSSION

Autoimmune hepatitis is thought to be a diagnosis of exclusion; therefore, testing for the most likely aetiology, such as viral hepatitis, toxic substance (e.g., hepatotoxic medication, alcohol, narcotic substances) that caused liver damage, Wilson's disease, etc., is essential.

In general, liver biopsy and histological verification are the most important criteria to confirm the diagnosis. Unfortunately, this is not always possible. In our study, in seven of 37 cases, liver biopsy was not possible due to hypocoagulation. Therefore, the question that arises is whether biopsies are always necessary in cases where AIH clinical and laboratory criteria are fulfilled. According to generally known recommendations, an autoimmune hepatitis scoring system is available (Hennes *et al*, 2008). Applying this system, it is possible to calculate the likelihood of AIH. Subsequently, it can be used as a basis for prescribing therapy. Furthermore, even if a biopsy is performed, it does not always guarantee a histological confirmation of AIH, particularly in cases where the biopsy is performed during the first three months from the onset of the symptom (Weiler-Normann and Lohse, 2014). In our study, in three of 29 liver biopsy cases, AIH was not histologically confirmed. Despite this, immunosuppressive therapy was started.

Interestingly, in our study, a clear predominance of females was observed. This is in agreement with the results of other studies (Mann *et al*., 2010). This large difference can potentially be attributed to hormonal differences between the two genders. For example, estrogen is mentioned as one of the hormones that could be involved in autoimmune process development in different AI diseases; however, this aspect is not completely elucidated yet. Autoimmune diseases in which estrogen has a clear negative association have been described. For example, in systemic lupus erythematosus (SLE), it is believed to stimulate the progression of autoimmune processes (Moulton, 2018). On the other hand, estrogen's role in autoimmune hepatitis has not been examined yet. Based on our results on the patient's age at which autoimmune hepatitis was first diagnosed, the prevalence of the disease was higher in age groups 41–59 and > 60 years age groups. Physiological changes in estrogen levels in premenopause and menopause (WHO, 2024) in addition to other unknown predisposing factors, could result in the development of autoimmune hepatitis. During perimenopause and menopause, estrogen levels are decreased; therefore, its potential protective role decreases, and subsequently the risk of developing AIH increases. However, additional research is necessary to confirm the role of estrogen in the pathogenesis of AI hepatitis.

In most cases, after starting prednisolone therapy, a clinical and biochemical improvement can be observed. To avoid long-term glucocorticoid therapy and its potential side effects, Azathioprine (AZA) is added to disease maintenance therapy. In the present study, most of the patients also received the combination of both medications; however, neither the activity of the enzyme thiopurine methyltransferase (TPMT) nor its metabolites 6-thioguanine nucleotide (6-TGN) and 6-mercaptopurine (6-MP) were tested. Studies have shown that Azathioprine genetic polymorphisms, which determine the activity of 6-TGN and 6-MP metabolites, reveal whether the patient could and, if so, to what extent he/she develops intolerance to AZA and has side effects. It has been noted that determining the AZA genetic polymorphism is a step towards personalised medicine, which in turn results in better drug efficacy and biochemical marker improvement (Candels *et al*., 2021). Furthermore, in cases where treatment is considered ineffective, 6-TGN and 6-MP should be evaluated because they could help to understand the root cause. For example, if the level of both metabolites is low, a dose adjustment is necessary. However, if the level of both factors is very low, it could indicate that the medicine is used incorrectly. However, if 6-TGN is low but 6-MP is high, treatment optimisation should be considered. A potential option is to add allopurinol and reduce the dosage of AZA (Lohse *et al*., 2020).

Most of the patients (32 out of 37) received combined treatment with prednisolone and AZA, which is consistent with international guidelines and generally accepted recommendations. However, even first-line therapy has its variations, for example, discontinuing the use of prednisolone but continuing the use of AZA. There are cases in which both medications are continued; however, efforts are made to ensure that the dose of prednisolone remains as low as possible, with the disease remaining serologically, biochemically and clinically in remission.

When evaluating the most recent trends in treatment and their potential risks, including prednisolone side effects, the incorporation of second-line treatment drugs, such as 6-MP or mycophenolate mofetil, in AIH treatment is still relevant. In the case of AZA and 6-MP intolerance, it is possible that

the use of mycophenolate mofetil will also not lead to disease remission. Therefore, it is recommended to measure the 6-TGN concentration to determine the appropriate dose of medication. The addition of allopurinol in medication could be possible; however, the risk of bone marrow suppression should be considered (Hennes *et al*., 2008). In some rare specific cases, third-line therapy could be considered, although it is mostly experimental and thus requires accurate evaluation and follow-ups. Furthermore, it should start in multidisciplinary centres where multidisciplinary care can be ensured. In our study, first-line treatment due to side effects was discontinued in three cases. The first patient was a young male with severe osteoporosis. Considering that clinically and biochemically AIH remained in remission, immunosuppressive therapy was not reinitiated. The remaining two patients had severe side effects from prednisolone and AZA; therefore, treatment was changed to monotherapy with budesonide (Efe *et al*., 2011), although there are no data on how the treatment was implemented or the effect.

Unfortunately, in our study group, due to side effects of therapy, nonadherence to treatment was highly prevalent. Instead of scheduling an appointment with their hepatologist to adjust treatment, patients discontinued treatment on their own. A potential cause could be the high workload of hepatologists, which results in long waiting lists.

ETHICS

Ethical approval for this study was obtained from Rīga East Clinical University Hospital Medical and Biomedical Research Ethical Committee.

CONCLUSION

The clinical and diagnostic criteria for autoimmune hepatitis generally comply with accepted diagnostic principles, but the therapeutic approach does not always comply with the guidelines, especially with respect to the choice of medication, initiation time, and duration of therapy.

REFERENCES

Alvarez, F., Berg, P. A., Bianchi, F. B., Bianchi, L., Burroughs, A. K., Cancado, E. L. *et al.* (1999). International autoimmune hepatitis group report: Review of criteria for diagnosis of autoimmune hepatitis. *J. Hepatol.,* **31**, 929–938.

Bolia, R., Goel, A., Srivastava, A. (2021). Systematic review and meta-analysis of thiopurine metabolite levels and biochemical remission in autoimmune hepatitis. *Ther. Drug Monit*., **43** (5), 609–616. DOI: 10.1097/FTD.0000000000000848.

Candels, L. S., Rahim, M. N., Shah, S., Heneghan, M. A. (2021). Towards personalised medicine in autoimmune hepatitis: Measurement of thiopurine metabolites results in higher biochemical response rates. *J. Hepatol*., **75** (2), 324–332. DOI: 10.1016/j.jhep.2021.03.023.

Czaja, A. J., Carpenter, H. A., Santrach, P. J., Moore, S. B., Taswell, H. F., Homburger, H. A. (1993). Evidence against hepatitis viruses as important causes of severe autoimmune hepatitis in the United States. *J. Hepatol*., **18**, 342–352.

Díaz-González, Á., Hernández-Guerra, M., Pérez-Medrano, I., Sapena, V., Riveiro-Barciela, M., Barreira-Díaz, A., Gómez, E., Morillas, R. M,, Del Barrio, M., Escudé, L., *et al.* (2023). ColHai Registry. Budesonide as first-line treatment in patients with autoimmune hepatitis seems inferior to standard predniso(lo)ne administration. *Hepatology*, **77** (4), 1095–1105. DOI: 10.1097/HEP.0000000000000018.

Efe, C., Ozaslan, E., Kav, T., Purnak, T., Shorbagi, A., Ozkayar, O., Berlot, A. H., Sökmensuer, C., Muratori, P. (2012). Liver fibrosis may reduce the efficacy of budesonide in the treatment of autoimmune hepatitis and overlap syndrome. *Autoimmun Rev*., **11** (5), 330–334. DOI: 10.1016/j.autrev.2011.09.006.

European Association for the Study of the Liver (2015). EASL Clinical Practice Guidelines: Autoimmune hepatitis. *J. Hepatol.,* **63**, 971–1004. DOI:10.1016/j.jhep.2015.06.030 pmid:26341719

Feld, J. J., Dinh, H., Arenovich, T., Marcus, V. A, Wanless, I. R., Heathcote, E. J. (2005). Autoimmune hepatitis: Effect of symptoms and cirrhosis on natural history and outcome. *Hepatology*, **42**, 53–62.

Gatselis, N. K., Zachou, K., Koukoulis, G. K., Dalekos, G. N. (2015). Autoimmune hepatitis, one disease with many faces: Etiopathogenetic, clinico–laboratory and histological characteristics. *World J. Gastroenterol*., **21**, 60–83.

Gregorio, G. V., Portmann, B., Reid, F., Donaldson, P. T., Doherty, D. G., McCartney, M., *et al.* (1997). Autoimmune hepatitis in childhood: A 20–year experience. *Hepatology*, **25**, 541–547.

Hennes, E. M., Zeniya, M., Czaja, A. J. *et al.* (2008). International Autoimmune Hepatitis Group. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology*, **48**,169–176. DOI: 10.1002/hep.22322.

Kogan, J., Safadi, R, Ashur, Y., Shouval, D., Ilan, Y. (2002). Prognosis of symptomatic versus asymptomatic autoimmune hepatitis: A study of 68 patients. *J. Clin. Gastroenterol*., **35**, 75–81.

Lohse, A. W., Sebode, M., Jørgensen, M. H., Ytting, H., Karlsen, T. H,, Kelly, D., Manns, M. P., Vesterhus, M. (2020). European Reference Network on Hepatological Diseases (ERN RARE-LIVER); International Autoimmune Hepatitis Group (IAIHG). Second-line and third-line therapy for autoimmune hepatitis: A position statement from the European Reference Network on Hepatological Diseases and the International Autoimmune Hepatitis Group. *J. Hepatol.,* **73** (6), 1496–1506. DOI: 10.1016/j.jhep.2020.07.023.

Lv, T., Li, M., Zeng, N., *et al.* (2019). Systematic review and meta-analysis of the incidence and prevalence of autoimmune hepatitis in the Asian, European, and American population. *J. Gastroenterol. Hepatol*., **34**, 1676–1684. DOI: 10.1111/jgh.14746.

Manns, M. P., Czaja, A. J., Gorham, J. D., Krawitt, E. L., Mieli-Vergani, G., Vergani, D., Vierling, J. M. (2010). American Association for the Study of Liver Diseases. Diagnosis and management of autoimmune hepatitis. *Hepatology*, **51** (6), 2193–2213. DOI: 10.1002/hep.23584.

Moulton, V. R. (2018). Sex hormones in acquired immunity and autoimmune disease. *Front. Immunol*., **9**, 2279. DOI: 10.3389/fimmu.2018.02279.

Nagamine, K., Peterson, P., Scott, H. S., Kudoh, J., Minoshima, S., Heino, M, *et al.* (1997). Positional cloning of the APECED gene. *Nat. Genet*., **17**, 393–398.

Rahim, M. N., Miquel, R., Heneghan, M. A. (2020). Approach to the patient with acute severe autoimmune hepatitis. *JHEP Rep*., **2**, 100149. DOI: 10.1016/j.jhepr.2020.100149.

Steinmann, S., Lohse, A. W. (2023). Treatment of autoimmune hepatitis: Budesonide does not solve our problems. *Hepatology*, **77** (4), 1071–1073. DOI: 10.1097/HEP.0000000000000183.

Terziroli Beretta-Piccoli, B., Mieli-Vergani, G., Vergani, D. (2017). Autoimmune hepatitis: Standard treatment and systematic review of alternative treatments. **23** (33), 6030–6048. DOI: 10.3748/wjg.v23.i33.6030.

Trivedi, P. J., Hirschfield, G.M. (2021). Recent advances in clinical practice: Epidemiology of autoimmune liver diseases. *Gut*, **70**, 1989–2003. DOI: 10.1136/gutjnl-2020-322362.

Volk, M. L., Reau, N. (2021). Diagnosis and management of autoimmune hepatitis in adults and children: A patient-friendly summary of the 2019 AASLD guidelines. *Clin. Liver Dis.* (Hoboken), **17** (2, 85–89. DOI: 10.1002/cld.1080.

Weiler-Normann, C., Lohse, A. W. (2014). Acute autoimmune hepatitis: Many open questions. *J. Hepatol.,* **61**, 727–729. DOI: 10.1016/j.jhep.2014.06.030.

Werner, M., Wallerstedt, S., Lindgren, S., Almer, S., Björnsson E., Bergquist, A., Prytz, H., Sandberg-Gertzén, H, Hultcrantz, R, Sangfelt, P. (2010). Characteristics and long-term outcome of patients with autoimmune hepatitis related to the initial treatment response. *Scand. J. Gastroenterol*., **45**, 457–467.

WHO (2024). Menopause. https://www.who.int/news-room/fact-sheets/detail/menopause (accessed 11.07.2024).

Received 2 April 2024
Accepted in the final form 13 June 2024

AUTOIMŪNA HEPATĪTA PACIENTU KLĪNISKĀS IZPAUSMES, ĀRSTĒŠANAS IZAICINĀJUMI UN IZNĀKUMI: PIECU GADU PIEREDZE RĪGAS AUSTRUMU KLĪNISKAJĀ UNIVERSITĀTES SLIMNĪCĀ

Pēdējo gadu laikā visā pasaulē pieaug autoimūno saslimšanu skaits, tostarp autoimūna hepatīta gadījumi. Autoimūns hepatīts ir neskaidras etioloģijas iekaisīga aknu slimība, kas neārstēta var progresēt līdz aknu cirozei un hroniskas aknu slimības gala stadijai — aknu mazspējai. Klīniskajā ainā bieži sastopams akūts hepatīts, taču nereti slimības gaita ir bez simptomiem. Parasti konstatē palielinātas aknu transamināzes un imūnglobulīnu G, histoloģiska iekaisuma pazīmes un cirkulējošās autoantivielas. Vairumam autoimūnā hepatīta pacientu nepieciešama mūžilga ārstēšana, lai novērstu slimības progresēšanu. Terapijas stūrakmens parasti ir imūnsupresīva terapija ar prednizolonu un azatioprīnu, kas ir efektīva vairumā gadījumu. Terapijas mērķis ir stabilas remisijas sasniegšana uz iespējami ilgāku laiku, taču korekcijas nereti nākas veikt medikamentu blakņu dēļ. Visai bieži terapijas mērķis sasniedzams, piemērojot individualizētu pieeju, jo, blaknēm ietekmējot dzīves kvalitāti, mazinās pacienta līdzestība. Rīgas Austrumu klīniskajā universitātes slimnīcā veikts retrospektīvs kohorta pētījums par laika periodu no 2019. līdz 2023. gadam. Izmantota 37 pacientu ar autoimūna hepatīta diagnozi medicīniskā dokumentācija — ambulatorās vai stacionāra kartes. Diagnoze autoimūns hepatīts noteikta, balstoties uz vispārpieņemtiem starptautiskiem kritērijiem. Visiem pacientiem bija paaugstināts aknu funkciju raksturojošo transamināžu līmenis. Terapijas shēmās visbiežāk izmantotie medikamenti — prednizolons, azatioprīns un metilprednizolons. Ne visi pacienti saņēma nepieciešamo imūnsupresīvo terapiju, viens atkārtoti atteicās no tās, baidoties no iespējamām blaknēm. Imūnsupresīvās terapijas ilgums lielākoties bija īsāks nekā nozīmēts, jo pacienti izvēlējās terapiju pārtraukt, nenorādot konkrētus iemeslus. Pētījumā tika konstatēts, ka Rīgas Austrumu klīniskajā universitātes slimnīcā piecu gadu laikā autoimūna hepatīta klīniskie un diagnostikas kritēriji parasti atbilst vispārpieņemtajiem diagnostikas principiem, bet terapeitiskā pieeja ne vienmēr atbilst vadlīnijām, īpaši attiecībā uz terapijas ilgumu.