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Literature Review

Autoimmune Hepatitis

Fatima Safira Alatas[1], Gryselda Hanafi[1], Lestari Kanti Wilujeng[1], Nielda Kezia Sumbung[1]

[1] Department of Child Health, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Corresponding author:
Fatima Safira Alatas, MD, PhD
safiraalatas@gmail.com

Editor:
Fatima Safira Alatas
Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

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Abstract: Autoimmune hepatitis (AIH) is a condition caused by self-perpetuating immune response towards hepatocytes in liver. In children, AIH may progressed more rapidly compared to adults. Thus, early diagnosis and prompt treatment are the key for successful management of AIH. Five main characteristics of AIH include female predominance, increased IgG or hypergammaglobulinemia, circulatory auto-antibody seropositivity, and hepatitis interface from the histological finding. Liver biopsy is needed to evaluate the degree of damage and to confirm the diagnosis. The standard regiment for AIH include prednisone (or prednisolone) and azathioprine. Other alternative treatments available for non-responder, such as mycophenolate mofetil, tacrolimus, cyclosporine, budesonide, rituximab, and infliximab. AIH treatment is recommended to be taken minimally for 2-3 years before attempting treatment termination.

Keywords: autoimmune hepatitis, children, genetic disorder, diagnosis

Introduction

Autoimmune hepatitis (AIH) is a condition that could occur in children and adults of all ages. AIH is a hepatopathy caused by self-perpetuating immunity toward the liver cells. This condition leads to chronic and progressive inflammation and may eventually lead to irreversible liver damage. The main characteristics of AIH include the histological appearance of hepatitis, female predominance, positive circulatory antibody, presence of hypergammaglobulinemia or increased IgG, and family history of autoimmune disease. The occurrence of AIH in children has been seen to cause a worse impact on children than on adults.[1,2]

Early treatment is the key to preventing the progression of AIH into end-stage liver disease and increasing demand for liver transplantation. Treatment using immunosuppressants in AIH patients without acute and serious manifestation accompanied by encephalopathy has shown satisfactory results. However, there is still no diagnostic test or eligible and reliable criteria to be used as the gold standard

for diagnosing AIH in pediatric patients. Currently, the only diagnostic criteria available are only applicable to adults.[1,2] Thus, through this literature, we aim to summarize the important findings and current knowledge on AIH in children for better understanding and clinical judgment in diagnosing and treating AIH patients.

Epidemiology

AIH can occur at any age and ethnicity, with varying manifestations. The prevalence of AIH in Asia is 12.99 per 100,000 people.[3] Meanwhile, in the United States, the prevalence reached up to 31.2 per 100,000 people.[4] AIH can occur in both adults and children. The prevalence of AIH in females is high[3], with 71%-95% occurring in adults and 60-76% in children. AIH often occurs at the age of 10-30 years and 40-60 years.[2] The ratio of vulnerable sex and age may vary depending on the region.

Genetic Predisposition

AIH is a complex genetic disease. It was influenced by epigenetic, immunological, and environmental. Currently, genetic factor is suspected to be important in determining a person's susceptibility to AIH. Human leukocyte antigen (HLA) has been proposed as the most important genetic factor in AIH. HLA is the main molecule in antigen presentation and is associated with the onset of AIH.[2,3]

In addition, AIH is also proposedly related to non-HLA genetics. It associates with genetic polymorphisms that encode cytotoxic T lymphocyte antigen-4, TNF alpha, Fas, vitamin D receptors, signal transducers, transcription activators 4, TGF beta, IL-23, etc. Dysfunction of genetic products or abnormalities at the genetic level can affect the proliferation and resistance of B cells and auto-reactive T cells. It may affect the regulation of cytokine production, modulation of inflammation, and immune response control.[2]

Pathogenesis

The pathogenesis of AIH is a complex cascade triggered by multifactorial factors. The failure of the immune system to inhibit the T cells' autoreactivity towards autoantigens in the liver is proposedly affected by environmental and genetic factors. In general, AIH is primarily caused by three main impairments; the disruption of regulatory cells (particularly Tregs), the inability of the immune system to recognize self-antigen, and the inadequate control of inflammation.[2]

During the conditions requiring hepatic or systemic immune response (consumption of hepatotoxic drugs or viral infections), the dysfunction of T regulatory cells (Tregs) in tolerating the hepatic autoantigens causes the antigen-presenting cells (APC) to be able to present the autoantigens to the T cell receptors (TRC) on naive CD4-positive and CD8-positive T lymphocytes.[2] The activation of CD4-positive and CD8-positive

T cells leads to the series of cytokines productions, which contributes to the development of both CD4 and CD8 into their differentiated and mature forms, particularly CD4 Th1, Th2, Th9, Th17, Tfh, iTreg, as well as CD8 Tregs and CD8 CTLs. CD4 Th1 and CD4 Th9 are known to initiate macrophage activation, while CD Th2 and CD4 Tfh play an important role in the generation and activation of B cells autoantibodies into antibody-secreting plasma cells that produce immunoglobulin G (IgG). Furthermore, CD4 Th17 is seen to generate cytotoxic effect, which also increases the degree of hepatocytes injury due to inflammation.[2]

Normally, the function of CD4 induced Treg (iTreg) alongside other Tregs and Breg is to regulate the inflammation caused by the CD4 Th subsets. However, the defect of CD4 iTregs due to the exposure to specific cytokines may lead to the differentiation of CD4 iTregs to CD4 Th17, which further aggravates the inflammation occurring in the hepatocytes. The presence of CD4 subtypes, and the inability of both CD4-positive and CD8-positive Tregs and Bregs to control the autoreactivity of immune system towards hepatic autoantigen, leads to the prolonged incidence of AIH. Besides the generation of CD4-positive and CD8-positive subtypes, APC also triggers mucosal invariant T (MAIT) cell activation, which also contributes to CD4 iTregs alteration to CD4 Th17. Furthermore, MAIT cells have been seen to exhibit similar trait possessed by CD4 Th1 and Th17.[2]

The increased amount of both humoral and cellular inflammatory components leads to hepatocytes injury as well as the build-up in hepatic portal. Further activation of chemokines and adhesion molecules initiate diapedesis, which causes inflammation in the periportal and lobules. The initiation of the whole cascades results in cytotoxic injury and necroinflammation. Continuous activation of the immune response will induce portal fibrosis, eventually resulting in the end stage liver disease.[2]

Classification

AIH is generally a progressive inflammatory hepatopathy that can develop into end-stage liver disease. There are two types of AIH subtypes depending on the serological profile. People with AIH Type 1 are positive for anti-nuclear antibody (ANA) or anti-smooth muscle antibody (SMA). Meanwhile, those who are classified with AIH Type 2 are positive for anti-liver kidney microsomal type 1 antibody (anti-LKM-1) and/or anti-liver cytosol type 1 antibody (anti-LC-1).[1]

Diagnosis Criteria

AIH is diagnosed based on clinical, biochemical, immunological, and histology features and must not be caused by another liver disease. Typical AIH findings include:[1]

- Higher prevalence in women.

- Increased immunoglobulin G (IgG)/ hypergammaglobulinemia.
- Circulatory auto-antibody seropositivity.
- Hepatitis interface in histological finding.

There is still no gold standard to establish AIH diagnosis. The International Autoimmune Hepatitis Group has reviewed the scoring system to determine probable or definitive AIH. However, the scoring system is found to be applicable to pediatric cases of AIH. A liver biopsy is needed to confirm the diagnosis and evaluation of the degree of liver damage.[1]

Clinical Manifestation

In general, the clinical manifestation of AIH is divided into five features, including:[1]

1. Manifestations are similar to acute viral hepatitis symptoms include malaise, nausea/vomiting, anorexia, joint and abdominal pain, followed by symptoms of bile duct obstruction (jaundice, dark urine, and pale stools).
2. Acute liver failure with hepatic encephalopathy (grade II to IV) occurred within 26 weeks after the symptoms first appeared; INR≥2; with no history of liver disease before.
3. Non-specific symptoms that indicate dangerous onset (progressive fatigue, relapsing jaundice, amenorrhea, headache, anorexia, joint and abdominal pain, diarrhea, weight loss) appeared for six months until several years before diagnosis.
4. Complications of cirrhosis and port hypertension (hematemesis of esophageal/ gastric varicose veins, diathesis bleeding, splenomegaly), without a history of jaundice or liver disease
5. Hepatic aminotransferases increase with no signs or symptoms.

Additional/Pathological Examination

- *Autoantibodies*

  A positive autoantibody must be present in the diagnosis of AIH. Autoantibodies associated with AIH include ANA, SMA, anti-MFI1, anti-LC-1, and anti-mitochondrial antibody (AMA). In adults, the autoantibodies test result is positive when the autoantibodies are found after ≥1:40 dilution. Meanwhile, the positive result in children is concluded with the presence of autoantibody after a dilution of ≥1:20 for ANA and SMA or ≥1:10 for anti-LKM1.[1]
- *Histological features*

  Enforcement of the diagnosis of AIH should be accompanied by an additional examination of liver biopsy and compatible histological findings. However, there are still no specific histological findings for AIH. AIH should be considered if there are some of the following histological findings below:[2]

a. The histological finding of the hepatitis interface. It is usually accompanied by infiltration of plasma cells and lobular hepatitis.
b. Emperipolesis. Emperipolesis can be found in 65% of patients with AIH. Emperipolesis is the penetration of the whole cell into another cell, with both cells retaining their viability. Besides emperipolesis, hepatocyte rosette also can be found in 33% of patients.
c. Cirrhosis features. The features are found in 28-33% of adult patients and 38% of pediatric patients. The description of cirrhosis with multilobular necrosis or bridging necrosis is important to rule out differential diagnoses and determine the severity of inflammation or indicate fibrosis.
d. In AIH with ALF, the hallmark consists of 4 important features: central perivenulitis, plasma cell-enriched inflammatory infiltrate, massive hepatic necrosis, and lymphoid follicles. It primarily occurs in the centrilobular zone.

Table 1. The comparison of clinical features between the two types of AIH[1,2]

	AIH 1	AIH 2
Age distribution	Occurring at all age, peaks during childhood/adolescence and adulthood.	Present at younger age, including infant. Mainly in children and young adults.
Symptoms	Chronic symptoms Rare sign of portal hypertension	Acute onset Higher tendency to present as ALF Frequent relapse Rare presentation of cirrhosis
Laboratories	IgG usually elevated (hypergammaglobulinemia)	Partial IgA deficiency (40%)
Autoantibodies	ANA, SMA, anti-actin, SLA	Anti-LKM1, Anti-LC1, Anti-LKM3
Comorbid immune disease	Autoimmune thyroiditis Rheumatic disease IBD	Comorbid immune disease Diabetes Mellitus Vitiligo Adisson disease
Response towards therapy	Possible remission after drug withdrawal	More refractory to eventual treatment, need long-term immunosuppressive

Management of Autoimmune Hepatitis

The aims of AIH management are to achieve remission, reduce liver inflammation, improve symptoms, and prolong life expectancy.[1,6] According to ESPGHAN 2018, remission among the pediatric population is defined as clinical recovery marked by normalization of transaminase and IgG levels, negative or very low titer for autoantibodies including ANA or SMA (<1:20) and anti-LKM-1 and anti-LC-1 (<1:10), and histological resolution of the inflammation.[1] Although improvement of

histological findings can be found in 95% of patients after approximately 4 years of effective treatment. This resolution succeeds late after the clinical, biochemical, and immunological remission.[1] Clinical remission may be assumed if biopsy could not be conducted.

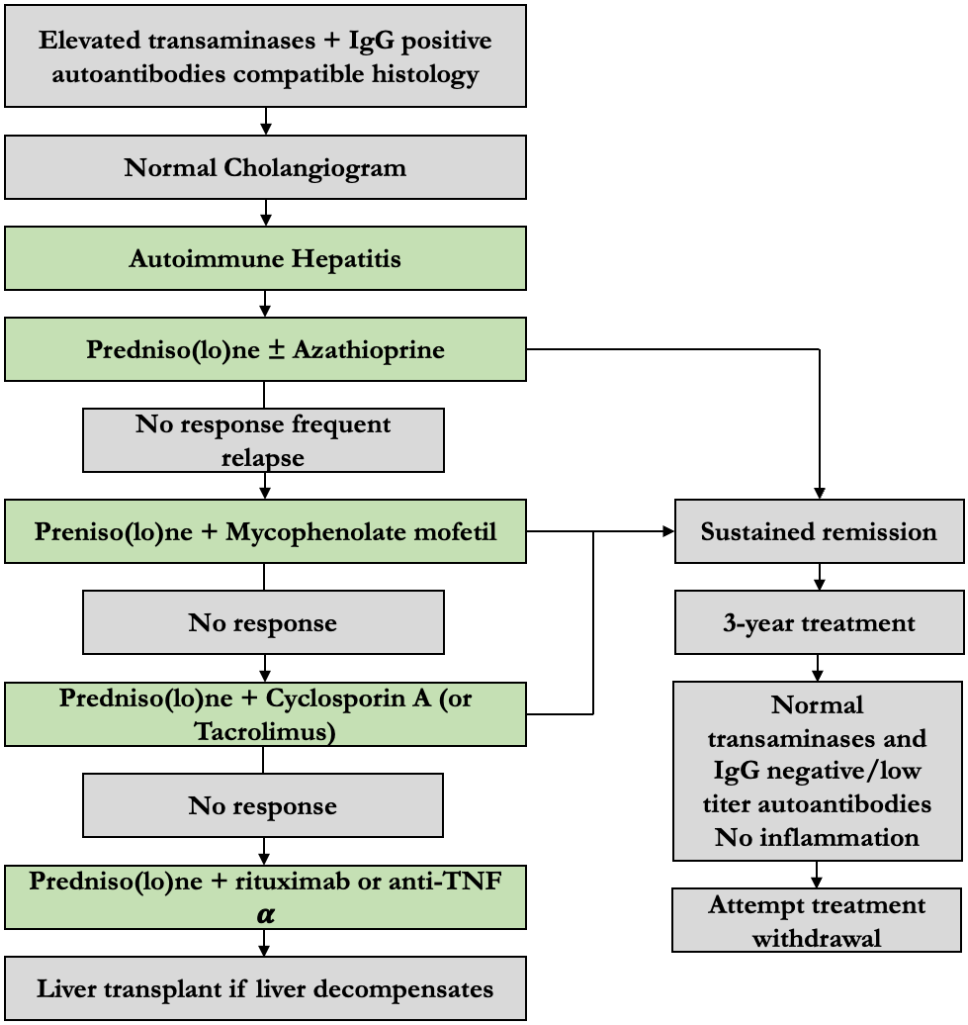

Figure 2. Flow chart for treatment for autoimmune hepatitis (Modified from Mieli-Vergani et al).[1]

As the treatment begins, patient with the sudden increase in serum aminotransferase levels following remission is categorized as relapse. This is a common occurrence in approximately 40% of patients, especially adolescents. The treatment for AIH should be given promptly in all children to prevent progression to end-stage liver disease. AIH usually responds well to immunosuppressive therapy in all degrees of liver impairment, with a remission rate of 90%. The flowchart for treatment for AIH could be seen in **Figure 2**.

The standard treatment usually consists of corticosteroids (usually prednisone or prednisolone and azathioprine (**Table 1**). Some of the roles of corticosteroid in AIH is (1) binding with the cytoplasmic receptor, translocation to the nucleus, and interacting with the specific DNA sequences present at regulatory sites in some genes; (2) inhibiting T-lymphocyte activation and proliferation, and (3) inhibits the synthesis of proinflammatory cytokines (e.g., IL-2 and IL-6). Conventionally, the treatment for AIH consists of predniso(lo)ne with starting dose of 2 mg/kg/day, maximum dose of 60 mg/day, gradually decreasing after 4-8 weeks with the resolution of the serum transaminases. The maintenance dose is 2.5 to 5 mg/day.[1,6]

Table 2. Standard regimen for autoimmune hepatitis.[1,2,6-10]

Drug	Recommended dose	Mechanism of action	Side effects
Predniso(lo)ne	**Initial dose:** 2 mg/kg/day Max dose: 60 mg/day **Maintenance dose:** 0.1-0.2 mg/kg/day or 2.5 – 5 mg/day	• Binds to cytoplasmic receptors, translocates to the nucleus, and interacts with specific DNA sequences that are present at regulatory sites in certain genes. • Inhibits T-lymphocyte activation and proliferation • Inhibits the synthesis of pro-inflammatory cytokines such as IL-2 and IL-6	• Cosmetic (moon face, Cosmetic (moon face, hirsutism, alopecia, dorsal hump, striae) • Systemic (weight gain, glucose intolerance, hypertension, fatty liver, osteoporosis, vertebral compression, cataract, glaucoma, opportunistic infection) • Quality of life (emotional instability, psychosis, depression, and anxiety)
Azathioprine (AZA)	**Initial dose:** 1-2 mg/kg/day **Maintenance dose:** 1-2 mg/kg/day if required OR **Maintenance dose for azathioprine monotherapy (AIH-1):** 1.2-1.6 mg/kg/day	• The exact mechanism is unclear • Might be linked to nucleic acid synthesis supression	• Hematology (mild cytopenia, severe leukopenia or bone marrow failure) • Gastrointestinal (nausea, vomiting, pancreatitis) • Neoplastic (non-melanoma skin cancer) • Cholestatic liver damage (rare)

Azathioprine is needed in about 85% of AIH children. However, the exact timing to start azathioprine may differ according to the center. Some centers start azathioprine only when corticosteroid monotherapy fails to induce remission or if a serious side effect occurs while others might start after 2 weeks of corticosteroid therapy or even begin the azathioprine regimen with corticosteroid therapy. The starting dose of azathioprine is 1-2 mg/kg/day, increased gradually if the decline of serum aminotransferase reaches plateau.

Alternative Treatment

Some patients who are non-responder to the conventional treatment may be given alternative AIH treatments to induce remission. In addition, some physicians choose this alternative treatment in an attempt to reduce steroid side effects or intolerant to conventional therapy. **Table 3** shows some of the alternative treatments that can be used in treating children with AIH.

Mycophenolate mofetil (MMF) is one of the more commonly used drugs for the treatment of AIH. MMF is the prodrug of the mycophenolic acid and is used with a dose of 20 mg/kg, twice daily with predniso(lo)ne. In case of MMF intolerance, calcineurin inhibitors should be considered. Tacrolimus and cyclosporin A are some of the proposed drugs for induction of remission. Previous study showed that tacrolimus monotherapy is not enough for complete remission of AIH. However, it allows smaller dose administration of prednisolone and azathioprine and thus, reducing the adverse reaction.

The use of cyclosporin in a study in Croatia provided new insight into the use of the drug for AIH. Remission was successfully achieved in treatment-naïve children who used cyclosporine A monotherapy for 6 months, and continued with conventional prednisone and azathioprine. The cyclosporine was discontinued after one month. Unfortunately, there was no clear explanation if this protocol has any advantage compared to the conventional treatment.[1,2]

Budesonide is an ideal "topical" liver treatment as the drug has hepatic first-pass clearance of more than 90% upon oral ingestion with fewer side effects than the traditional predniso(lo)ne. However, budesonide cannot be used in children with cirrhosis, which accounts for a large percentage of AIH patients. Rituximab and Infliximab have been reported to be effective in treating refractory AIH. However, their use should be evaluated carefully due to serious potential side effects of immunosuppression.[1,2]

Stopping Treatment

Current guidelines recommend that AIH treatment commences for at least 2 to 3 years before attempting to withdraw the treatment. In addition, ending the therapy should only be considered only if the transaminase and IgG levels have returned to normal limit and auto-antibody becomes very low or even negative for at least one year. If possible, liver biopsy should be repeated to ensure microscopic resolution of the inflammation, which might herald relapse.[1,2]

Table 3. Alternative regimen for autoimmune hepatitis.[1,2,6-10]

Drug	Recommended dose	Side effects
Mycophenolate mofetil (MMF)	20-40 mg/kg, twice daily with predniso(lo)ne	• Teratogenic • Gastrointestinal disturbance
Tacrolimus	0.1 mg/kg/day up to 1-8 mg/day	• Systemic (headache, tremor, paresthesia, insomnia, renal impairment) • Serum electrolyte disorders (hyperkalemia) • Hypercholesterolemia, hypertriglyceridemia, hyperlipidemia • Psychiatric disorders (mood changes, anxiety) • GI disorders (nausea, vomiting, GI bleeding) • CNS disorders (CNS hemorrhage, coma, paralysis, amnesia, speech abnormalities, dizziness, confusion) • Others (ECG abnormalities, uterine bleeding, pancytopenia, etc)
Cyclosporine	4-10 mg/kg/day in 3 divided doses	• Significant (infections, gingival hyperplasia, nephrotoxicity, hypertension) • Blood and lymphatic system disorders (anemia, leukopenia, thrombocytopenia) • Eye disorders (eye pain, burning/foreign body sensation, visual disturbance) • GI disorders (nausea, vomiting, diarrhea, abdominal pain, dyspepsia) • Immune system disorders (angioedema) • CNS disorders (seizures, encephalopathy, tremor, headache, paresthesia) • Others (hematuria, hirsutism, rash, dermatitis, flushing, etc)
Budesonide	6-9 mg/day in 3 divided doses	• Significant (adrenal suppression, immunosuppression, growth retardation, hyperglycemia, fluid retention) • GI disorders (nausea, abdominal pain, abdominal distension, dyspepsia, dry mouth) • CNS disorders (headache, dizziness, tremor) • Others (palpitation, fatigue, malaise, hypokalemia, myalgia, menstrual disorders)

Table 3. Alternative regimen for autoimmune hepatitis (continued).[1,2,6-10]

Drug	Recommended dose	Side effects
Rituximab	375 mg/m^2/week for 4 weeks, repeat according to patient's response	• Cardiovascular disorders (arrhythmia, cardiogenic shock) • Blood and lymphatic system disorders (pancytopenia, agranulocytosis) • CNS disorders (paresthesia, hypoesthesia, dizziness, migraine, sciatica) • GI disorders (nausea, vomiting, diarrhea, abdominal pain, stomatitis, constipation, GERD) • Metabolic disorders (hyperglycemia, hypocalcemia, hypercholesterolemia, anorexia) • Psychiatric disorders (depression, anxiety, insomnia, agitation) • Others (hypertension, flushing, respiratory tract infections)
Infliximab	5 mg/kg; 4 infusions in 4 weeks interval	• Opportunistic infections • GI disorders (nausea, vomiting, diarrhea, abdominal pain) • Hepatic manifestations (acute liver failure, jaundice, cholestasis) • Blood and lymphatic system disorders (leucopenia, thrombocytopenia, pancytopenia) • Others (hypotension, chill, fever, dyspnea, exacerbation of demyelinating disorders)

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