Journal of Clinical and Translational Hepatology **2024** vol. 12(10) | 878–885
DOI: 10.14218/JCTH.2024.00193

Review Article

Advances in the Treatment of Autoimmune Hepatitis

Zelu Meng and Yida Yang*

State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, National Medical Center for Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Department of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

Received: June 12, 2024 | **Revised:** September 03, 2024 | **Accepted:** September 05, 2024 | **Published online:** September 24, 2024

Abstract

Autoimmune hepatitis (AIH) is a chronic, progressive inflammatory liver disease caused by autoimmune reactions, with an unknown etiology. If left untreated, it can progress to cirrhosis, liver failure, or even death. While most patients respond well to first-line treatments, a significant number experience poor responses or intolerance, requiring the use of second- or third-line therapies. Ongoing research into the pathogenesis of AIH is leading to the development of novel therapeutic approaches. This review summarized recent advancements in the treatment of AIH both domestically and internationally.

Citation of this article: Meng Z, Yang Y. Advances in the Treatment of Autoimmune Hepatitis. J Clin Transl Hepatol 2024;12(10):878–885. doi: 10.14218/JCTH.2024.00193.

Introduction

Autoimmune hepatitis (AIH) is a chronic, progressive inflammatory liver disease driven by an autoimmune reaction in which the immune system attacks liver tissue, leading to inflammation and damage. The clinical features of AIH include elevated serum transaminases of varying degrees, hypergammaglobulinemia, positive serum autoantibodies, and histological evidence of interface hepatitis, characterized by lymphocytic and plasma cell infiltration. The global annual incidence and prevalence of AIH are 1.37/100,000 and 17.44/100,000, respectively.[1] AIH can occur across all age groups and ethnicities[2] but is most prevalent in individuals aged 40 to 70 years[3] and is more common in middle-aged women.[4,5] The exact cause of AIH remains unknown but is thought to involve a combination of genetic predisposition and environmental factors. Without early diagnosis and treatment, AIH can progress to cirrhosis, liver failure, and even death.[6] This review summarizes the current advancements in AIH treatment research.

Keywords: Hepatitis, Autoimmune; Immunosuppression; Treatment; Management; Update; Remission Induction; Long-term Prognosis.

***Correspondence to:** Yida Yang, Department of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, 79 Qingchun Rd, Hangzhou, Zhejiang 310003, China. ORCID: https://orcid.org/0000-0002-9673-0969. Tel: +86-571-87236731, Fax: +86-571-87236755 E-mail: yidayang65@zju.edu.cn

Indications for treatment

Research indicates that immunosuppressive treatment in AIH patients can improve liver function, alleviate symptoms, extend survival time, and promote fibrosis regression, even in cases of cirrhosis.[7,8] Untreated AIH patients are at risk of developing advanced fibrosis, cirrhosis, and ultimately hepatic decompensation.

Therefore, guidelines from China, Europe, and the United States all recommend initiating immunosuppressive therapy for patients with active AIH (serum aminotransferase levels ≥ 3× the upper limit of normal [ULN], IgG ≥ 1.5× ULN, and/or moderate to severe interface hepatitis). The treatment regimen and drug dosage can be adjusted based on disease activity.[9,10] For patients with inactive or mild inflammatory activity (serum aminotransferase levels < 3× ULN, IgG < 1.5× ULN, and/or mild interface hepatitis), especially the elderly, the benefits and risks of immunosuppressive treatment should be carefully weighed for individualized management.[6,9,10] Patients for whom immunosuppressive therapy is not immediately initiated must be monitored every three to six months, with treatment administered if significant clinical symptoms or inflammatory activity are observed.[6,9,10]

Immunosuppressive treatment should continue for at least two years after achieving complete biochemical remission, which is defined by the normalization of serum transaminases and IgG levels. A liver biopsy is recommended before discontinuing treatment to confirm remission, and liver functions should be closely monitored after discontinuation to detect relapse promptly.

Despite some patients maintaining remission after discontinuation,[11] research has shown that the majority experience disease relapse after stopping medication. Muratori *et al*.[12] found that 23 AIH patients in complete remission all relapsed within 10 months of discontinuing very low doses of steroids. Similarly, a study by Gerven *et al*.[13] found that among 131 patients with complete remission, the relapse rate exceeded 80% within three years of stopping immunosuppressive therapy. Since multiple relapses are associated with a poorer prognosis, some researchers believe it may be safer to prolong maintenance treatment in complete responders with low-dose drugs indefinitely, regardless of liver function tests and biopsy results. In the vast majority of such patients, this approach—virtually devoid of significant side effects—was successful in controlling liver inflammation and halting disease progression. Thus, whether patients who meet the criteria for medication withdrawal should stop maintenance treatment remains a topic for further research and discussion.

Treatment

First-line treatment

The goal of first-line treatment is to alleviate symptoms, prevent disease progression, achieve biochemical remission, and reduce complications. Ideal biochemical remission is defined as the normalization of serum transaminases (ALT, AST) and IgG levels.[6,9,10]

Predniso(lo)ne and azathioprine (AZA)

For untreated adult AIH patients who are not experiencing an acute severe flare-up or cirrhosis, predniso(lo)ne combined with AZA or predniso(lo)ne alone has long been considered the first-line treatment. The Chinese guidelines for the diagnosis and treatment of autoimmune hepatitis (2021)[6] recommend predniso(lo)ne combined with AZA as the initial first-line treatment. Predniso(lo)ne is used to induce remission, while AZA is used for maintenance therapy. The initial dose of predniso(lo)ne is 0.5–1 mg/kg/day (typically 30–40 mg/day), with an induction regimen of 30 mg/day for the first week, 20 mg/day for two weeks, and 15 mg/day for four weeks. Once the predniso(lo)ne dose is below 15 mg/day, it should be reduced gradually by 2.5 mg/day until a maintenance dose of 5–10 mg/day is achieved. During the maintenance phase, predniso(lo)ne can even be discontinued, with AZA 50 mg/day used alone. The American Association for the Study of Liver Diseases (hereinafter referred to as AASLD) guidelines (2019)[9] recommend either predniso(lo)ne alone (40–60 mg/day) or predniso(lo)ne (20–40 mg/day) combined with AZA (50–150 mg/day) as the first-line treatment, with biochemical tests conducted every one to two weeks. The European Association for the Study of the Liver guidelines (2015)[10] suggest an initial predniso(lo)ne dose of 0.5–1 mg/kg/day, adding AZA (50 mg/day) after two weeks, with dosage adjustments based on toxicity and response until a maintenance dose of 1–2 mg/kg is achieved. Combining predniso(lo)ne with AZA significantly reduces the required predniso(lo)ne dose and its side effects, making this approach suitable for postmenopausal women and patients with osteoporosis or diabetes. However, AZA as a first-line treatment is contraindicated in cholestatic patients due to the increased risk of hepatotoxicity.

Thiopurine methyltransferase (TPMT) is an enzyme involved in AZA metabolism. Measuring TPMT activity can help predict AZA toxicity. Guidelines[9,10] recommend TPMT testing before initiating AZA therapy in AIH patients. For patients with TPMT deficiency, a predniso(lo)ne monotherapy regimen may be used. However, even with TPMT testing, all patients starting AZA therapy must be closely monitored to minimize side effects and drug toxicity. In practice, this monitoring may not always be feasible.

A study[14] involving 451 adult AIH patients divided them into high-dose predniso(lo)ne (0.50 mg/kg/day, n = 281) and low-dose predniso(lo)ne (< 0.50 mg/kg/day, n = 170) treatment groups. After one year of treatment, the overall biochemical remission rates were similar between the two groups (76.2% vs. 77.6%), indicating that low-dose steroid therapy can also effectively induce remission of AIH while significantly reducing steroid side effects. However, further research is needed to confirm these findings.

Additionally, research[12] has shown that in AIH patients with complete biochemical remission, maintaining treatment with the minimum dose of steroids (2–4 mg daily or even every other day) seems to protect against the progression of liver disease.

Budesonide

Budesonide is a second-generation glucocorticoid with a hepatic first-pass clearance rate of nearly 90%. Its primary sites of action are the liver and intestines, resulting in relatively mild systemic side effects.[6] In cases of non-severe acute or chronic AIH, budesonide is an effective alternative to predniso(lo)ne for induction treatment.[15] However, budesonide is not recommended for patients with cirrhosis due to the loss of its first-pass effect advantage caused by portosystemic shunting. A multicenter retrospective study[16] conducted in Spain compared 105 early AIH patients treated with budesonide as first-line therapy to 276 patients treated with predniso(lo)ne. The median time to biochemical response was 3.1 months in the budesonide group and 4.9 months in the predniso(lo)ne group, with a significantly higher biochemical response rate in the predniso(lo)ne group (87% vs. 49%, $p < 0.001$). Among patients with transaminase levels less than twice the upper limit of normal, the biochemical response rates were similar between the two treatment groups. This indicates that while budesonide is effective in treating AIH, its efficacy appears to be inferior to predniso(lo)ne. It can be considered as a first-line treatment option for AIH in patients with mild flare-ups.

In a recent retrospective study on AIH patients in the United States,[17] it was found that budesonide use as a treatment option was uncommon. During a follow-up period of at least two years, less than 5% of patients used budesonide as a first-line treatment, suggesting that most American AIH patients were only temporarily exposed to budesonide and did not consider it a primary treatment strategy. Therefore, although budesonide can reduce the adverse effects associated with prednisone and serve as an alternative first-line therapy, its use as a first-line treatment in real-life practice remains low.

Second-line treatments

Second-line treatments are indicated for patients who experience nonresponse, insufficient response, or intolerance to first-line therapy. Nonresponse is defined as a less than 50% decrease in serum transaminases within four weeks after the initiation of treatment, occurring in 7% to 9% of adults.[9] Insufficient response refers to the lack of complete biochemical response (normalization of serum transaminases and IgG levels) after six months of treatment. Intolerance to treatment refers to any adverse events that lead to the discontinuation of the drug. Muratori *et al*.[12] found that 36 (54.5%) of 66 partial or non-responders experienced progression of liver disease despite intensive conventional immunosuppression, highlighting the urgent need for second-line treatments. Second-line therapies for AIH include mycophenolate mofetil, calcineurin inhibitors (cyclosporine A, tacrolimus), purine synthesis inhibitors (allopurinol, 6-mercaptopurine, 6-thioguanine), and methotrexate etc.

Mycophenolate mofetil (MMF)

MMF is a derivative of mycophenolic acid and inhibits the proliferation of T and B lymphocytes by interfering with inosine monophosphate dehydrogenase.[18] MMF is the most widely used alternative immunosuppressant in patients with an inadequate response to first-line therapy.

A meta-analysis[19] of 309 patients found that the overall response rate to MMF was 82% in patients intolerant to AZA and 32% in those unresponsive to AZA. Compared to non-responsive patients, those who started MMF treatment due to

intolerance to standard therapy had a higher response rate. Additionally, AIH patients showed good tolerability to MMF, with a lower discontinuation rate due to side effects.

A multicenter, randomized controlled trial[20] showed that in treatment-naïve AIH patients, MMF combined with predniso(lo)ne achieved a higher biochemical remission rate at 24 weeks and better tolerance compared to the combination of AZA and predniso(lo)ne. MMF combined with predniso(lo)ne may be considered a first-line treatment option to achieve biochemical remission in AIH, though more evidence is needed. The most common side effects of MMF include gastrointestinal symptoms such as nausea, vomiting, diarrhea, and pancytopenia,[19] which should be monitored during treatment.

Calcineurin inhibitors

Calcineurin inhibitors (CNIs), including cyclosporine A (CsA) and tacrolimus (TAC), inhibit lymphocyte proliferation and interfere with T-cell-mediated responses, thereby reducing liver inflammation in AIH patients.[18]

A small retrospective study[21] of 33 AIH patients treated with CNIs showed that 10 out of 17 (59%) patients treated with CsA and 6 out of 16 (38%) patients treated with TAC achieved complete biochemical remission without significant adverse effects. This indicates that CNI treatment is safe, moderately effective, and well-tolerated.

Another prospective randomized trial[22] involving 50 children compared standard therapy with CsA treatment, showing that CsA was as effective as standard therapy in inducing remission in children with AIH, although the time to biochemical remission was shorter in the standard treatment group. This suggests that CsA can be used as a second-line treatment in AIH patients, though further studies are needed to confirm this.

A meta-analysis[23] evaluated the efficacy and safety of TAC and MMF in treating AIH patients, showing overall biochemical remission rates of 68.9% for TAC and 59.6% for MMF. In patients intolerant to standard treatment, the biochemical remission rates were 56.6% for TAC and 73.5% for MMF, while in non-responders, the rates were 59.1% for TAC and 40.8% for MMF. This suggests that TAC can be used as a second-line treatment, particularly in patients who respond poorly to MMF. Additionally, a 2021 multicenter study in Spain[24] found that 18 out of 23 AIH patients (78%) achieved biochemical remission with TAC, with only one patient discontinuing TAC due to severe neurotoxicity and ototoxicity. This indicates that TAC is an effective and well-tolerated second-line treatment for AIH patients.

Purine synthesis inhibitors

AZA is a purine antimetabolite with cytotoxic properties. AZA is converted into 6-mercaptopurine (6-MP), which is partially inactivated through methylation catalyzed by TPMT to form 6-methylmercaptopurine, or through oxidation by xanthine oxidase to form 6-thiouric acid. However, 6-MP can also enter the immunosuppressive pathway and be converted into 6-thioinosinic acid by hypoxanthine-guanine phosphoribosyl transferase. 6-thioinosinic acid can then be methylated by TPMT into 6-methyl-thioinosine monophosphate or converted by inosine-monophosphate dehydrogenase into 6-thioguanine nucleotides (6-TGN). The immunosuppressive effects of AZA are primarily mediated by 6-TGN and 6-methyl-thioinosine monophosphate, which are incorporated into DNA and RNA, inhibiting purine nucleotide formation and leading to cell apoptosis (Fig. 1).[18]

Allopurinol

Allopurinol, a xanthine oxidase inhibitor, blocks the conversion of 6-MP into 6-thiouric acid, shifting the metabolism of AZA toward 6-TGN (Fig. 1).[25] A study[26,27] involving AZA-refractory or AZA-intolerant AIH patients treated with allopurinol combined with AZA showed biochemical improvement in all eight participants, with reductions or normalization of ALT levels and sustained long-term improvement in seven patients. Additionally, approximately 80% of patients effectively bypassed the side effects caused by AZA. These findings suggest that allopurinol can be an effective and relatively safe alternative immunosuppressive therapy.[25]

6-MP

A retrospective analysis of 22 AIH patients treated with 6-MP in Europe[28] found that out of 20 patients previously intolerant to AZA, 15 (75%) responded to 6-MP treatment: eight achieved complete remission, seven achieved partial remission, and five switched to other immunosuppressive regimens due to intolerance to 6-MP. The two patients with insufficient response to AZA also did not respond to 6-MP. This study suggests that 6-MP can be an effective second-line treatment for AIH patients who are intolerant to AZA.

6-Thioguanine (6-TG)

6-TG is enzymatically converted to 6-TGN, an active metabolite of AZA, but bypasses the metabolic step that produces the hepatotoxic metabolite 6-methylmercaptopurine.[18] A study from France[29] described the outcomes of 17 AIH patients who failed previous AZA therapy and were treated with 6-TG. Of these, 16 (94%) achieved normalization of serum transaminases within three months, 11 (64%) maintained a sustained biochemical response, while four (23%) relapsed, and two discontinued treatment due to adverse effects. This suggests that 6-TG can be a viable second-line treatment option for AZA-intolerant patients.

Methotrexate (MTX)

MTX, a classical immunosuppressant, inhibits folic acid reductase activity, blocking the synthesis of tetrahydrofolate and thereby inhibiting DNA replication and synthesis. It is widely used in autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. In a small study,[30] six out of 11 AIH patients (54.5%) treated with MTX achieved complete biochemical response within 36 months, most within 12 months, while five patients discontinued due to poor efficacy. Although MTX may have a role in AIH treatment, its efficacy appears lower compared to other second-line therapies, and further validation is needed. Given its inherent hepatotoxicity, its use must be carefully considered.

Third-line treatment

For AIH patients who fail first- and second-line therapies, reevaluation of the diagnosis is necessary, and third-line treatments may be initiated. Currently, third-line treatments include biologic medications such as rituximab, infliximab, and belimumab. In September 2023, a study[31] analyzed clinical data from 25 AIH patients treated with various biologics for different reasons, collected via an online questionnaire. The study found that biologic therapy normalized ALT levels in most patients and effectively controlled extrahepatic autoimmune diseases, although relapses were more common among patients treated with belimumab. This study provides valuable insights into the safety and efficacy of biologics in AIH patients.

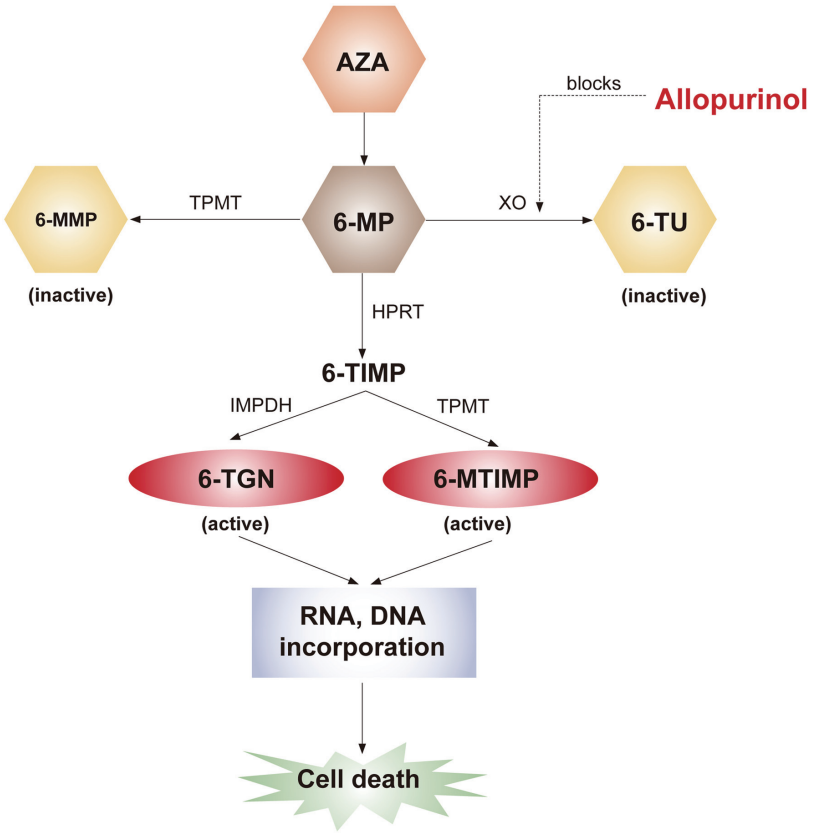

Fig. 1. Metabolites and pharmacokinetics of azathioprine. AZA, azathioprine; 6-MP, 6-mercaptopurine; TPMT, thiopurine methyltransferase; 6-MMP, 6-methyl-mercaptopurine; XO, xanthine oxidase; 6-TU, 6-thiouric acid; HPRT, hypoxanthine-guanine phosphoribosyl transferase; 6-TIMP, 6-thioinosine monophosphate; IMPDH, inosine-monophosphate dehydrogenase; 6-TGN, 6-thioguanine nucleotides; 6-MTIMP, 6-methyl-thioinosine monophosphate; RNA, Ribonucleic acid; DNA, Deoxyribonucleic acid.

Rituximab

Rituximab is a monoclonal antibody targeting the CD20 receptor on the cell surface. A study by the International Autoimmune Hepatitis Group[32] involving 22 AIH patients treated with rituximab and followed for 24 months found that patients tolerated rituximab well, with significant biochemical improvements and disease stabilization. Predniso(lo)ne dosage was reduced in 62% of patients, and 71% experienced no AIH flare-ups. This suggests that rituximab can be effective for some AIH patients, but it can also lead to serious side effects, such as infections and hematologic or lymphatic abnormalities.

Infliximab

Infliximab is a tumor necrosis factor (TNF)-α inhibitor widely used in autoimmune diseases such as inflammatory bowel disease. A study[33] of 11 refractory AIH patients found that infliximab treatment reduced hepatic inflammation, as evidenced by lower serum transaminase and immunoglobulin levels, though seven patients developed infections. Additionally, studies[34] have found that infliximab can induce drug-induced AIH-like liver injury, so its use requires careful monitoring of liver function and other relevant indicators.

Belimumab

Belimumab is a B-cell activating factor inhibitor proven effective in systemic lupus erythematosus and other systemic autoimmune diseases. A study[35] on two refractory AIH patients treated with belimumab as third-line therapy showed that both patients achieved complete biochemical remission while maintaining low-dose corticosteroids, with no adverse events observed. This suggests that belimumab may be a promising option for treating AIH patients.

In addition, ongoing trials are investigating treatments such as tocilizumab, ustekinumab, sirolimus, and JAK/STAT pathway inhibitors in AIH patients.

Liver transplantation (LT)

LT is indicated for AIH-related liver failure or decompensated cirrhosis.[6,10]

Reports[36] indicate that approximately 10% of AIH patients will require LT during their lifetime. A long-term study[37] of 74 AIH patients who underwent LT found one-year, three-year, five-year, and 10-year survival rates of 91%, 89%, 87%, and 82%, respectively, with graft survival rates of 89%, 88%, 86%, and 76%, respectively. Another long-term nationwide study[38] in France, spanning 30 years, also demonstrated excellent survival rates for AIH patients and their grafts post-LT.

Post-LT AIH patients often receive low-dose corticosteroids (predniso(lo)ne) combined with immunosuppressants,[39] as this regimen reduces AIH recurrence, lowers rejection rates, and increases graft survival while minimizing corticosteroid side effects.[40–43] However, the 2019 AASLD guidelines[9] suggest that glucocorticoids are not significantly effective in

post-LT AIH patients and recommend gradual discontinuation of glucocorticoids after LT.

Microbiome therapy

The human gastrointestinal tract hosts a vast microbial ecosystem, comprising trillions of microorganisms, including bacteria, fungi, and viruses, collectively known as the gut microbiota. These microorganisms play crucial roles in biosynthesis, metabolism, and immunity.[44] Research is increasingly focusing on the close relationship between AIH and the gut microbiota. Exploring this relationship further may elucidate the mechanisms of AIH and uncover new targets for diagnosis and treatment.

Mechanism of Gut Microbiota and AIH

Approximately 75% of the liver's blood supply comes from the portal vein, continuously exposing the liver to various antigens and toxins derived from the gut. Under normal conditions, the intestinal mucosal barrier prevents gut microbiota and their metabolites from entering the portal system, and the liver can clear small amounts of microbes entering the portal vein. However, in pathological states like AIH, intestinal mucosal permeability changes, allowing large amounts of gut microbiota and their metabolites to translocate through the portal system to the liver. This induces activation of hepatic immune cells and fosters a pro-inflammatory environment. Consequently, this affects T lymphocytes' recognition of self-antigens, impairs organ-specific immune tolerance, and ultimately leads to AIH.

Gut Microbiota-Related Therapeutic Approaches

Probiotics/prebiotics

A study[45] treating AIH mice with a mix of Bifidobacterium and Lactobacillus probiotics found that these probiotics inhibited inflammatory cell differentiation, promoted the differentiation of regulatory T cells (Tregs) for immune tolerance, improved intestinal barrier function, increased the abundance of intestinal flora in AIH mice, prevented the translocation of lipopolysaccharides to the liver, and reduced the production of inflammatory cytokines, thereby promoting AIH remission. Additionally, prebiotics such as fructooligosaccharides are indigestible food components that promote the growth of beneficial gut bacteria and play important roles in regulating the gut microbiota and improving immune regulatory functions.

A recent study by Liwinski *et al*.[46] observed significant changes in the gut microbiota (GM) of AIH patients, noting that a reduction in Bifidobacterium was associated with a failure to achieve remission. Therefore, assessing the GM alternations during different AIH stages (diagnosis, remission, relapse) and outcomes (responder, non-responder, disease progression) may reveal new therapeutic strategies. These findings could support the use of probiotics to maintain a healthy GM state after achieving remission with standard immunotherapy, to prevent disease relapse, or to use probiotics as adjunctive therapy in non-responsive AIH patients to prevent disease progression.

Fecal microbiota transplantation (FMT)

FMT involves transplanting fecal microbiota from a healthy donor into the patient's gut to restore the balance of gut microbiota. Recent studies have shown that FMT has potential in treating AIH.

Research[47] found that AIH mouse models exhibited significant liver inflammation and imbalances in follicular regulatory T cells and follicular helper T cells. Therapeutic FMT in AIH mice significantly reduced liver injury, improved the balance of follicular regulatory T cells and follicular helper T cells in the spleen, decreased serum ALT, AST, and TBIL levels, and effectively restored gut microbiota dysbiosis in AIH mice.

However, current studies on FMT in AIH are limited and remain at the preclinical stage. Further research and clinical trials are needed to determine the specific mechanisms and long-term effects of FMT in AIH treatment.

Bacteriophage

Bacteriophages are an important component of gut viruses and may have potential therapeutic effects in AIH patients.

Bacteriophages can regulate the immune system by interacting with host cells, affecting immune cell activity, promoting immune tolerance, and reducing autoimmune responses. They can also be engineered to carry specific gene sequences encoding antibodies or other therapeutic proteins targeting AIH-related autoantigens. Introducing these bacteriophages into patients could allow them to release therapeutic molecules in the liver, specifically modulating immune responses. Additionally, bacteriophage therapy might induce an immune system response by mimicking infection, thereby re-regulating the immune system and alleviating AIH symptoms or improving disease progression.[48]

While these potential therapies are promising, more research is needed to determine their true efficacy and safety in AIH treatment.

New experimental drugs

Interleukin (IL)-2: IL-2 is a crucial immunomodulatory factor that promotes the growth, differentiation, and survival of T cells. Low-dose IL-2 has demonstrated therapeutic efficacy in various autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and ankylosing spondylitis.[49–51] Research by Graßhoff *et al*.[52] found that low-dose IL-2 therapy increases the number and function of Tregs, which may help alleviate symptoms and liver inflammation in AIH patients. Buitrago *et al*.[53] reported that combined IL-2/anti-IL-2 therapy restored the balance of intrahepatic Tregs and effector T cells, improving the disease course in AIH mice. This suggests that IL-2 therapy may have the potential to reestablish immune tolerance in AIH patients.

Although some studies have shown positive effects of IL-2 treatment in AIH patients, further investigation is needed to confirm its long-term efficacy and safety.

Tregs: Tregs are a specialized subset of T cells that have been recognized as a fundamental group of lymphocytes responsible for maintaining immune homeostasis and preventing autoimmune diseases.[54] A systematic review and meta-analysis[55] on the changes in Treg proportions in the peripheral blood of AIH patients revealed that Treg proportions among CD4 T cells and PBMCs were decreased in AIH patients compared with healthy controls. These changes in Treg number and function play a significant role in AIH liver injury. Consequently, many experts believe that Treg therapy could be potentially curative for AIH.

A proof-of-concept study[56] reported that nearly a quarter of reinfused Tregs homed to and resided in the liver, supporting further investigation of Treg infusion in AIH. Additionally, research[57] found that the use of erythropoietin in stable AIH patients can increase overall Tregs, thereby improving the prognosis of AIH patients. These findings provide a foundation for the future use of Tregs as a therapeutic option for AIH patients.

Preimplantation factor (PIF): PIF is a polypeptide secreted by viable embryos that promotes maternal immune tolerance. A randomized, double-blind, placebo-controlled clinical trial[58] randomly assigned 18 AIH patients into three groups of six, each receiving different doses (0.1, 0.5, 1.0 mg/kg) of synthetic PIF or a matching placebo. Results showed that all 18 patients completed the trial successfully, with good tolerance across all dosage groups and no significant clinical adverse events. However, no significant reduction in ALT and AST levels was observed in PIF-treated patients compared to the placebo group. This suggests that while PIF is safe and well-tolerated in AIH patients, further research is needed to explore its long-term efficacy and optimal dosing.

Ginsenosides: Ginsenosides, the main active components in ginseng, can inhibit the expression of TNF-α and IL-6, exhibiting significant anti-inflammatory effects.[59] Ginsenosides also enhance the number and function of Tregs, strengthening immune regulation.[60] They have been widely studied for treating various diseases, including cancer, diabetes, cardiovascular diseases, and neurodegenerative diseases.[61] Recent studies have begun to explore their potential therapeutic effects in autoimmune diseases, including AIH. However, more clinical and experimental research is needed to verify the specific efficacy of ginsenosides in AIH. If future studies confirm their effectiveness and safety, ginsenosides could become a new adjunctive treatment, helping to improve patient outcomes.

Treatment in special populations

Pregnant women

Studies[62–66] show that AIH is more common in female patients, with 7–33% experiencing disease flare-ups or relapses during pregnancy and 30–50% relapsing postpartum. It is recommended to continue maintenance doses of predniso(lo)ne and AZA throughout pregnancy and the preconception period to reduce the risk of relapse and hepatic decompensation. Women with cirrhosis who are pregnant or planning to conceive within a year should undergo endoscopic variceal screening and banding treatment before conception or in the second trimester. MMF should be avoided during pregnancy due to its association with early miscarriage and birth defects (e.g., ear and heart defects). Women should be informed of these risks before initiating MMF therapy. AIH female patients should be closely monitored for six months postpartum to prevent relapse.

Elderly patients

AIH patients over 60 years old account for 20–25% of adult cases and often have few or no symptoms but frequently present with other autoimmune diseases.[67–70] For elderly patients, a combination of predniso(lo)ne and AZA is recommended, with indications and dosages similar to those for younger patients. Combined therapy can reduce steroid doses, minimizing steroid-related adverse effects, especially in patients with existing osteoporosis or poorly controlled diabetes. TPMT activity should be assessed before AZA administration to reduce the incidence of severe bone marrow suppression and other complications.[9,70]

Children

The annual incidence of pediatric AIH is 0.23–0.4 cases per 100,000, peaking around 10 years of age. Immediate initiation of immunosuppressive therapy is essential upon AIH diagnosis in children to avoid delaying treatment and worsening the prognosis.[6]

Guidelines[6,9,10] recommend an initial predniso(lo)ne dose of 1–2 mg/kg/day for children, not exceeding the adult maximum dose (40–60 mg/day), with gradual tapering after four to eight weeks as serum transaminase levels decrease. The maintenance dose is 2.5–5.0 mg/day. Generally, glucocorticoids combined with AZA are recommended, with a two-week glucocorticoid trial before starting AZA to assess efficacy and evaluate TPMT polymorphisms to prevent severe bone marrow suppression. The starting AZA dose is 0.5 mg/kg/day, with a maximum dose of 2.0 mg/kg/day. Additionally, guidelines suggest budesonide combined with AZA as first-line therapy for children without cirrhosis, with mild symptoms, or when steroid side effects are a concern. For children with complex conditions or intolerance or nonresponse to standard therapy, second- and third-line therapies such as MMF or TAC are recommended.

In clinical practice, there are some drug-resistant or seronegative pediatric AIH patients. In these cases, there may be potential genetic variations affecting immune regulation.[71–73] Therefore, early genetic testing and analysis should be conducted to facilitate more targeted immunotherapy.

A case report from England[71] described a 21-month-old girl diagnosed with type II AIH who did not respond well to predniso(lo)ne, AZA, and MMF, exhibiting STAT overactivation. Following the administration of the JAK inhibitor baricitinib, the child showed normalization of transaminases, reduction in spleen size, and improved liver biopsy pathology results within a short period. Additionally, Hegarty and Pandurangi *et al*.[72,73] reported cases of AIH in children with TNFAIP3 gene mutations in the UK and the USA. These children achieved biochemical remission with standard AIH treatments and showed resolution of extrahepatic inflammation with JAK inhibitor therapy. These findings demonstrate the promising therapeutic effects of JAK inhibitors for specific forms of AIH in children.

Conclusions

The etiology of AIH is complex and not yet fully understood. It can occur in individuals of all ages, genders, and races, with clinical manifestations influenced by genetic, environmental, and socioeconomic factors, resulting in significant clinical heterogeneity. Therefore, selecting appropriate, effective, and low-side-effect treatment regimens remains a challenge. Most patients respond well to first-line treatments. However, if predniso(lo)ne and AZA fail to effectively alleviate symptoms and liver inflammation, second- and third-line therapies, such as MMF, TAC, and biologics, have proven to be effective options. With further research into the gut-liver axis, gut microbiota-targeted therapies like probiotics and FMT are also showing promise in AIH treatment. Advances in understanding the pathogenesis have led to the development of new treatments such as IL-2, PIF, and Tregs. In summary, the optimal treatment plan for AIH patients should be individualized to slow disease progression, reduce side effects, and improve treatment efficacy and quality of life.

Funding

None to declare.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Manuscript writing (ZM); Manuscript writing guidance and revision (YY). All authors have approved the final version and publication of the manuscript.

References

[1] Lv T, Li M, Zeng N, Zhang J, Li S, Chen S, *et al*. Systematic review and meta-analysis on the incidence and prevalence of autoimmune hepatitis in Asian, European, and American population. J Gastroenterol Hepatol 2019;34(10):1676–1684. doi:10.1111/jgh.14746, PMID:31146297.

[2] Czaja AJ. Global Disparities and Their Implications in the Occurrence and Outcome of Autoimmune Hepatitis. Dig Dis Sci 2017;62(9):2277–2292. doi:10.1007/s10620-017-4675-y, PMID:28710658.

[3] Bischoff S, Yesmembetov K, Antoni C, Sollors J, Evert M, Ebert M, *et al*. Autoimmune Hepatitis: a Review of Established and Evolving Treatments. J Gastrointestin Liver Dis 2020;29(3):429–443. doi:10.15403/jgld-2667, PMID:32919424.

[4] Takahashi A, Arinaga-Hino T, Ohira H, Torimura T, Zeniya M, Abe M, *et al*. Autoimmune hepatitis in Japan: trends in a nationwide survey. J Gastroenterol 2017;52(5):631–640. doi:10.1007/s00535-016-1267-0, PMID:27722997.

[5] Kim BH, Choi HY, Ki M, Kim KA, Jang ES, Jeong SH. Population-based prevalence, incidence, and disease burden of autoimmune hepatitis in South Korea. PLoS One 2017;12(8):e0182391. doi:10.1371/journal.pone.0182391, PMID:28771543.

[6] Chinese Society of Hepatology, Chinese Medical Association. Guidelines on the dagnosis and management of autoimmune hepatitis (2021). Zhonghua Gan Zang Bing Za Zhi 2022;30(5):482–492. doi:10.3760/cma.j.cn112138-20211112-00796-1.

[7] Lamers MM, van Oijen MG, Pronk M, Drenth JP. Treatment options for autoimmune hepatitis: a systematic review of randomized controlled trials. J Hepatol 2010;53(1):191–198. doi:10.1016/j.jhep.2010.01.037, PMID:20400196.

[8] Hartl J, Ehlken H, Sebode M, Peiseler M, Krech T, Zenouzi R, *et al*. Usefulness of biochemical remission and transient elastography in monitoring disease course in autoimmune hepatitis. J Hepatol 2018;68(4):754–763. doi:10.1016/j.jhep.2017.11.020, PMID:29180000.

[9] Mack CL, Adams D, Assis DN, Kerkar N, Manns MP, Mayo MJ, *et al*. 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 2020;72(2):671–722. doi:10.1002/hep.31065, PMID:31863477.

[10] European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol 2015;63(4):971–1004. doi:10.1016/j.jhep.2015.06.030, PMID:26341719.

[11] Liberal R, de Boer YS, Andrade RJ, Bouma G, Dalekos GN, Floreani A, *et al*. Expert clinical management of autoimmune hepatitis in the real world. Aliment Pharmacol Ther 2017;45(5):723–732. doi:10.1111/apt.13907, PMID:28004405.

[12] Muratori P, Granito A, Quarneti C, Ferri S, Menichella R, Cassani F, *et al*. Autoimmune hepatitis in Italy: the Bologna experience. J Hepatol 2009;50(6):1210–1218. doi:10.1016/j.jhep.2009.01.020, PMID:19395113.

[13] van Gerven NM, Verwer BJ, Witte BI, van Hoek B, Coenraad MJ, van Erpecum KJ, *et al*. Relapse is almost universal after withdrawal of immunosuppressive medication in patients with autoimmune hepatitis in remission. J Hepatol 2013;58(1):141–147. doi:10.1016/j.jhep.2012.09.009, PMID:22989569.

[14] Pape S, Gevers TJG, Belias M, Mustafajev IF, Vrolijk JM, van Hoek B, *et al*. Predniso(lo)ne Dosage and Chance of Remission in Patients With Autoimmune Hepatitis. Clin Gastroenterol Hepatol 2019;17(10):2068–2075.e2. doi:10.1016/j.cgh.2018.12.035, PMID:30625402.

[15] Manns MP, Woynarowski M, Kreisel W, Lurie Y, Rust C, Zuckerman E, *et al*. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. Gastroenterology 2010;139(4):1198–1206. doi:10.1053/j.gastro.2010.06.046, PMID:20600032.

[16] Díaz-González Á, Hernández-Guerra M, Pérez-Medrano I, Sapena V, Riveiro-Barciela M, Barreira-Díaz A, *et al*. Budesonide as first-line treatment in patients with autoimmune hepatitis seems inferior to standard predniso(lo)ne administration. Hepatology 2023;77(4):1095–1105. doi:10.1097/HEP.0000000000000018, PMID:36626622.

[17] Bittermann T, Yagan L, Kathawate RG, Weinberg EM, Peyster EG, Lewis JD, *et al*. Real-world evidence for factors associated with maintenance treatment practices among US adults with autoimmune hepatitis. Hepatology 2024. doi:10.1097/HEP.0000000000000961, PMID:38865589.

[18] Vergani D, Terziroli Beretta-Piccoli B, Mieli-Vergani G. A reasoned approach to the treatment of autoimmune hepatitis. Dig Liver Dis 2021;53(11):1381–1393. doi:10.1016/j.dld.2021.05.033, PMID:34162505.

[19] Santiago P, Schwartz I, Tamariz L, Levy C. Systematic review with meta-analysis: mycophenolate mofetil as a second-line therapy for autoimmune hepatitis. Aliment Pharmacol Ther 2019;49(7):830–839. doi:10.1111/apt.15157, PMID:30761563.

[20] Snijders RJALM, Stoelinga AEC, Gevers TJG, Pape S, Biewenga M, Tushuizen ME, *et al*. An open-label randomised-controlled trial of azathioprine vs. mycophenolate mofetil for the induction of remission in treatment-naive autoimmune hepatitis. J Hepatol 2024;80(4):576–585. doi:10.1016/j.jhep.2023.11.032, PMID:38101756.

[21] Roberts SK, Strasser SI, Nicoll AJ, Kemp W, Majeed A, Mitchell J, *et al*. Efficacy and safety profile of calcineurin inhibitor salvage therapy in autoimmune hepatitis. Scand J Gastroenterol 2020;55(11):1309–1317. doi:10.1080/00365521.2020.1821764, PMID:33070650.

[22] Cuarterolo ML, Ciocca M, López S, Araujo M, Álvarez F. Autoimmune Hepatitis in Children: Prednisone Plus Azathioprine Versus Cyclosporine: A Randomized Trial. J Pediatr Gastroenterol Nutr 2020;71(3):376–380. doi:10.1097/MPG.0000000000002776, PMID:32520828.

[23] Abdollahi M, Ekrami NK, Ghojazadeh M, Boezen HM, Somi M, Alizadeh BZ. Tacrolimus and mycophenolate mofetil as second-line treatment in autoimmune hepatitis: Is the evidence of sufficient quality to develop recommendations? World J Gastroenterol 2020;26(38):5896–5910. doi:10.3748/wjg.v26.i38.5896, PMID:33132643.

[24] Ferre-Aracil C, Riveiro-Barciela M, Trapero-Marugán M, Rodríguez-Perálvarez M, Llovet LP, Téllez L, *et al*. Tacrolimus as an Effective and Durable Second-Line Treatment for Chronic Autoimmune Hepatitis: A Multicentric Study. Dig Dis Sci 2021;66(8):2826–2832. doi:10.1007/s10620-020-06569-9, PMID:32860579.

[25] Deswal S, Srivastava A. Role of Allopurinol in Optimizing Thiopurine Therapy in Patients with Autoimmune Hepatitis: A Review. J Clin Exp Hepatol 2017;7(1):55–62. doi:10.1016/j.jceh.2017.01.115, PMID:28348471.

[26] de Boer YS, van Gerven NM, de Boer NK, Mulder CJ, Bouma G, van Nieuwkerk CM. Allopurinol safely and effectively optimises thiopurine metabolites in patients with autoimmune hepatitis. Aliment Pharmacol Ther 2013;37(6):640–646. doi:10.1111/apt.12223, PMID:23347359.

[27] Al-Shamma S, McCrudden R, McLaughlin S. Letter: allopurinol co-therapy is safe and effective in autoimmune hepatitis. Aliment Pharmacol Ther 2013;37(9):919. doi:10.1111/apt.12285, PMID:23551160.

[28] Hübener S, Oo YH, Than NN, Hübener P, Weiler-Normann C, Lohse AW, *et al*. Efficacy of 6-Mercaptopurine as Second-Line Treatment for Patients With Autoimmune Hepatitis and Azathioprine Intolerance. Clin Gastroenterol Hepatol 2016;14(3):445–453. doi:10.1016/j.cgh.2015.09.037, PMID:26492846.

[29] Legué C, Legros L, Kammerer-Jacquet S, Jézequel C, Houssel-Debry P, Uguen T, *et al*. Safety and Efficacy of 6-thioguanine as a Second-line Treatment for Autoimmune Hepatitis. Clin Gastroenterol Hepatol 2018;16(2):290–291. doi:10.1016/j.cgh.2017.07.032, PMID:28782666.

[30] Haridy J, Nicoll A, Sood S. Methotrexate Therapy for Autoimmune Hepatitis. Clin Gastroenterol Hepatol 2018;16(2):288–289. doi:10.1016/j.cgh.2017.07.003, PMID:28711687.

[31] Terziroli Beretta-Piccoli B, Buescher G, Dalekos G, Zachou K, Geerts A, Semmo N, *et al*. Hepatic safety and efficacy of immunomodulatory drugs used in patients with autoimmune hepatitis. J Autoimmun 2023;140:103113. doi:10.1016/j.jaut.2023.103113, PMID:37716078.

[32] Than NN, Hodson J, Schmidt-Martin D, Taubert R, Wawman RE, Botter M, *et al*. Efficacy of rituximab in difficult-to-manage autoimmune hepatitis: Results from the International Autoimmune Hepatitis Group. JHEP Rep 2019;1(6):437–445. doi:10.1016/j.jhepr.2019.10.005, PMID:32039395.

[33] Weiler-Normann C, Schramm C, Quaas A, Wiegard C, Glaubke C, Pannicke N, *et al*. Infliximab as a rescue treatment in difficult-to-treat autoimmune hepatitis. J Hepatol 2013;58(3):529–534. doi:10.1016/j.jhep.2012.11.010, PMID:23178709.

[34] van Casteren-Messidoro C, Prins G, van Tilburg A, Zelinkova Z, Schouten J, de Man R. Autoimmune hepatitis following treatment with infliximab for inflammatory bowel disease. J Crohns Colitis 2012;6(5):630–631. doi:10.1016/j.crohns.2012.01.017, PMID:22398075.

[35] Arvaniti P, Giannoulis G, Gabeta S, Zachou K, Koukoulis GK, Dalekos GN. Belimumab is a promising third-line treatment option for refractory autoimmune hepatitis. JHEP Rep 2020;2(4):100123. doi:10.1016/j.jhepr.2020.100123, PMID:32671332.

[36] Hoeroldt B, McFarlane E, Dube A, Basumani P, Karajeh M, Campbell MJ, *et al*. Long-term outcomes of patients with autoimmune hepatitis managed at a nontransplant center. Gastroenterology 2011;140(7):1980–1989. doi:10.1053/j.gastro.2011.02.065, PMID:21396370.

[37] Alswat K, Soliman E, Salih I, Bashmail A, Letierce A, Benmousa A, *et al*. Long Term Outcomes of Liver Transplantation For Patients With Autoimmune Hepatitis. Transplant Proc 2021;53(7):2339–2345. doi:10.1016/j.transproceed.2021.07.040, PMID:34474912.

[38] Chouik Y, Chazouillères O, Francoz C, De Martin E, Guillaud O, Abergel A, *et al*. Long-term outcome of liver transplantation for autoimmune hepatitis: A French nationwide study over 30 years. Liver Int 2023;43(5):1068–1079. doi:10.1111/liv.15552, PMID:36825353.

[39] João M, Carvalhana S, Moura M, Freitas LC, Silva A, Figueiredo P, *et al*. Severe acute autoimmune hepatitis: How to early predict who will not respond to corticosteroids and needs urgent liver transplantation? Dig Liver Dis 2022;54(12):1681–1685. doi:10.1016/j.dld.2022.08.035, PMID:36115818.

[40] Krishnamoorthy TL, Miezynska-Kurtycz J, Hodson J, Gunson BK, Neuberger J, Milkiewicz P, *et al*. Longterm corticosteroid use after liver transplantation for autoimmune hepatitis is safe and associated with a lower incidence of recurrent disease. Liver Transpl 2016;22(1):34–41. doi:10.1002/lt.24323, PMID:26335026.

[41] Campsen J, Zimmerman MA, Trotter JF, Wachs M, Bak T, Steinberg T, *et al*. Liver transplantation for autoimmune hepatitis and the success of aggressive corticosteroid withdrawal. Liver Transpl 2008;14(9):1281–1286. doi:10.1002/lt.21525, PMID:18756454.

[42] Pelletier SJ, Nadig SN, Lee DD, Ammori JB, Englesbe MJ, Sung RS, *et al*. A prospective, randomized trial of complete avoidance of steroids in liver transplantation with follow-up of over 7 years. HPB (Oxford) 2013;15(4):286–293. doi:10.1111/j.1477-2574.2012.00576.x, PMID:23458449.

[43] Theocharidou E, Heneghan MA. Con: Steroids Should Not Be Withdrawn in Transplant Recipients With Autoimmune Hepatitis. Liver Transpl 2018;24(8):1113–1118. doi:10.1002/lt.25205, PMID:29893056.
[44] Lynch SV, Pedersen O. The Human Intestinal Microbiome in Health and Disease. N Engl J Med 2016;375(24):2369–2379. doi:10.1056/NEJMra1600266, PMID:27974040.
[45] Zhang H, Liu M, Liu X, Zhong W, Li Y, Ran Y, *et al*. Bifidobacterium animalis ssp. Lactis 420 Mitigates Autoimmune Hepatitis Through Regulating Intestinal Barrier and Liver Immune Cells. Front Immunol 2020;11:569104. doi:10.3389/fimmu.2020.569104, PMID:33123141.
[46] Liwinski T, Casar C, Ruehlemann MC, Bang C, Sebode M, Hohenester S, *et al*. A disease-specific decline of the relative abundance of Bifidobacterium in patients with autoimmune hepatitis. Aliment Pharmacol Ther 2020;51(12):1417–1428. doi:10.1111/apt.15754, PMID:32383181.
[47] Ma L, Song J, Chen X, Dai D, Chen J, Zhang L. Fecal microbiota transplantation regulates TFH/TFR cell imbalance via TLR/MyD88 pathway in experimental autoimmune hepatitis. Heliyon 2023;9(10):e20591. doi:10.1016/j.heliyon.2023.e20591, PMID:37860535.
[48] Górski A, Międzybrodzki R, Jończyk-Matysiak E, Kniotek M, Letkiewicz S. Therapeutic Phages as Modulators of the Immune Response: Practical Implications. Clin Infect Dis 2023;77(Suppl 5):S433–S439. doi:10.1093/cid/ciad483, PMID:37932118.
[49] Rosenzwajg M, Lorenzon R, Cacoub P, Pham HP, Pitoiset F, El Soufi K, *et al*. Immunological and clinical effects of low-dose interleukin-2 across 11 autoimmune diseases in a single, open clinical trial. Ann Rheum Dis 2019;78(2):209–217. doi:10.1136/annrheumdis-2018-214229, PMID:30472651.
[50] Churlaud G, Abbara C, Vinot PA, Fourcade G, Ritvo PG, Lorenzon R, *et al*. Pharmacodynamics of regulatory T cells in mice and humans treated with low-dose IL-2. J Allergy Clin Immunol 2018;142(4):1344–1346.e3. doi:10.1016/j.jaci.2018.06.006, PMID:29920353.
[51] Tahvildari M, Dana R. Low-Dose IL-2 Therapy in Transplantation, Autoimmunity, and Inflammatory Diseases. J Immunol 2019;203(11):2749–2755. doi:10.4049/jimmunol.1900733, PMID:31740549.
[52] Graßhoff H, Comdühr S, Monne LR, Müller A, Lamprecht P, Riemekasten G, *et al*. Low-Dose IL-2 Therapy in Autoimmune and Rheumatic Diseases. Front Immunol 2021;12:648408. doi:10.3389/fimmu.2021.648408, PMID:33868284.
[53] Buitrago-Molina LE, Pietrek J, Noyan F, Schlue J, Manns MP, Wedemeyer H, *et al*. Treg-specific IL-2 therapy can reestablish intrahepatic immune regulation in autoimmune hepatitis. J Autoimmun 2021;117:102591. doi:10.1016/j.jaut.2020.102591, PMID:33387980.
[54] Josefowicz SZ, Lu LF, Rudensky AY. Regulatory T cells: mechanisms of differentiation and function. Annu Rev Immunol 2012;30:531–564. doi:10.1146/annurev.immunol.25.022106.141623, PMID:22224781.
[55] Huang Z, Nie S, Wang H, Yan W, Tian D, Liu M. The proportion of regulatory T cells in peripheral blood of patients with autoimmune hepatitis: A systematic review and meta-analysis. Int Immunopharmacol 2023;122:110576. doi:10.1016/j.intimp.2023.110576, PMID:37390643.
[56] Oo YH, Ackrill S, Cole R, Jenkins L, Anderson P, Jeffery HC, *et al*. Liver homing of clinical grade Tregs after therapeutic infusion in patients with autoimmune hepatitis. JHEP Rep 2019;1(4):286–296. doi:10.1016/j.jhepr.2019.08.001, PMID:32039380.
[57] McEachern E, Carroll AM, Fribourg M, Schiano TD, Hartzell S, Bin S, *et al*. Corrigendum to "Erythropoietin administration expands regulatory T cells in patients with autoimmune hepatitis" [J. Autoimmun. 119C (2021) 102629]. J Autoimmun 2021;121:102665. doi:10.1016/j.jaut.2021.102665, PMID:34058602.
[58] O'Brien CB, Barnea ER, Martin P, Levy C, Sharabi E, Bhamidimarri KR, *et al*. Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Trial of Synthetic Preimplantation Factor in Autoimmune Hepatitis. Hepatol Commun 2018;2(10):1235–1246. doi:10.1002/hep4.1239, PMID:30411073.
[59] Liu B, Yu T, Han X, Zhao C, Liu F, Chen N. Anti-inflammatory Effects of Ginsenosides: A Review of Its Purported Mechanisms of Action. Zhongguo Yao Xue Za Zhi 2019;54(4):253–258. doi:10.11669/cpj.2019.04.001.
[60] Wang W, Wang Q. Immunomodulatory Effects of Ginsenoside and Its Application. Zhonghua Zhong Yi Yao Za Zhi 2005;20(4):234–236. doi:10.3969/j.issn.1673-1727.2005.04.014.
[61] Fan S, Zhang Z, Su H, Xu P, Qi H, Zhao D, *et al*. Panax ginseng clinical trials: Current status and future perspectives. Biomed Pharmacother 2020;132:110832. doi:10.1016/j.biopha.2020.110832, PMID:33059260.
[62] Danielsson Borssén Å, Wallerstedt S, Nyhlin N, Bergquist A, Lindgren S, Almer S, *et al*. Pregnancy and childbirth in women with autoimmune hepatitis is safe, even in compensated cirrhosis. Scand J Gastroenterol 2016;51(4):479–485. doi:10.3109/00365521.2015.1115893, PMID:26631429.
[63] Chung YY, Heneghan MA. Autoimmune hepatitis in pregnancy: Pearls and pitfalls. Hepatology 2022;76(2):502–517. doi:10.1002/hep.32410, PMID:35182079.
[64] Llovet LP, Horta D, Eliz MG, Berenguer M, Fábrega E, Sáez-Royuela F, *et al*. Presentation and Outcomes of Pregnancy in Patients With Autoimmune Hepatitis. Clin Gastroenterol Hepatol 2019;17(13):2819–2821. doi:10.1016/j.cgh.2018.12.030, PMID:30616023.
[65] Si T, Huang Z, Hegarty R, Ma Y, Heneghan MA. Systematic review with meta-analysis: outcomes of pregnancy in patients with autoimmune hepatitis. Aliment Pharmacol Ther 2022;55(11):1368–1378. doi:10.1111/apt.16924, PMID:35393675.
[66] Olsen K, Hodson J, Ronca V, Bozward AG, Hayden J, Wootton G, *et al*. Type 2 Autoimmune Hepatitis and Nonadherence to Medication Correlate With Premature Birth and Risk of Postpartum Flare. Hepatol Commun 2021;5(7):1252–1264. doi:10.1002/hep4.1714, PMID:34278173.
[67] Peng M, Li Y, Zhang M, Jiang Y, Xu Y, Tian Y, *et al*. Clinical features in different age groups of patients with autoimmune hepatitis. Exp Ther Med 2014;7(1):145–148. doi:10.3892/etm.2013.1363, PMID:24348780.
[68] Baven-Pronk MAMC, Biewenga M, van Silfhout JJ, van den Berg AP, van Buuren HR, Verwer BJ, *et al*. Role of age in presentation, response to therapy and outcome of autoimmune hepatitis. Clin Transl Gastroenterol 2018;9(6):165. doi:10.1038/s41424-018-0028-1, PMID:29961755.
[69] Dalekos GN, Azariadis K, Lygoura V, Arvaniti P, Gampeta S, Gatselis NK. Autoimmune hepatitis in patients aged 70 years or older: Disease characteristics, treatment response and outcome. Liver Int 2021;41(7):1592–1599. doi:10.1111/liv.14900, PMID:33896089.
[70] Rizvi S, Gawrieh S. Autoimmune Hepatitis in the Elderly: Diagnosis and Pharmacologic Management. Drugs Aging 2018;35(7):589–602. doi:10.1007/s40266-018-0556-0, PMID:29971609.
[71] Hadžić N, Deheragoda M, Worth A, Bansal S, Samyn M, Kusters M. JAK Inhibition in STAT1 Gain-of-Function-Mediated Treatment-Resistant Autoimmune Hepatitis. N Engl J Med 2024;390(3):284–286. doi:10.1056/NEJMc2311867, PMID:38231631.
[72] Hegarty R, Hadžić N. Genomic testing for inborn errors of immunity in seronegative autoimmune hepatitis of childhood. J Hepatol 2024:S0168–8278(24)00289-7. doi:10.1016/j.jhep.2024.04.021, PMID:38679070.
[73] Pandurangi S, Malik A, Owens J, Valencia CA, Miethke AG, Center for Autoimmune Liver Disease Research Group. Deleterious variants in TNFAIP3 are associated with type II and seronegative pediatric autoimmune hepatitis. J Hepatol 2024;80(1):e26–e28. doi:10.1016/j.jhep.2023.09.028, PMID:37821019.