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REVIEW

Autoimmune hepatitis: Towards a personalized treatment

Alejandro Costaguta, Guillermo Costaguta, Fernando Álvarez

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Abstract

Autoimmune hepatitis is an uncommon condition that affects both adults and children and is characterized by chronic and recurrent inflammatory activity in the liver. This inflammation is accompanied by elevated IgG and autoantibody levels. Historically, treatment consists of steroids with the addition of azathioprine, which results in remission in approximately 80% of patients. Despite significant advancements in our understanding of the immune system over the past two decades, few modifications have been made to treatment algorithms, which have remained largely unchanged since they were first proposed more than 40 years ago. This review summarized the various treatment options currently available as well as our experiences using them. Although steroids are the standard treatment for induction therapy, other medications may be considered. Cyclosporin A, a calcineurin inhibitor that decreases T cell activation, has proven effective for induction of remission, but its long-term side effects limit its appeal for maintenance. Tacrolimus, a drug belonging to the same family, has been used in patients with refractory diseases with fewer side effects. Sirolimus and everolimus have interesting effects on regulatory T cell populations and may become viable options in the future. Mycophenolate mofetil is not effective for induction but is a valid alternative for patients who are intolerant to azathioprine. B cell-depleting drugs, such as rituximab and belimumab, have been successfully used in refractory cases and are useful in both the short and long term. Other promising treatments include anti-tumor necrosis factors, Janus kinases inhibitors, and chimeric antigen receptor T cell therapy. This growing armamentarium allows us to imagine a more tailored approach to the treatment of autoimmune hepatitis in the near future.

Key Words: Novel therapies; Immunosuppressors; Treatment tailoring; Personalization; Special populations

Core Tip: Autoimmune hepatitis is a serious condition that affects both adults and children and has a poor prognosis if left untreated. Historically, treatment has involved high-dose steroids to induce remission and maintenance therapy with azathioprine, which achieves remission in 80% of cases but requires alternative therapies for the remaining 20%. While there have been advancements in immunosuppressive therapies for other diseases, treatment protocols for autoimmune hepatitis have remained largely unchanged. In this article, we explored alternative treatment options for patients for whom the standard protocol is not suitable.

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INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic inflammatory disease of the liver with a fluctuating course that inevitably progresses to cirrhosis and liver failure if not treated promptly[1]. Up to half of the patients present with complications such as cirrhosis, portal hypertension, and decreased liver function[2-4]. AIH should be considered in the differential diagnosis of any liver disease regardless of severity. It was first described by Waldenström[5] in adult females with abnormal liver function tests, increased circulating IgG levels, and specific autoantibodies[6,7]. It can be classified into two types: AIH type 1 (AIH-1), with positive antinuclear antibodies and/or anti-smooth-muscle antibodies; and AIH type 2 (AIH-2), with anti-liver-kidney microsomal type 1 and/or anti-liver cytosol type 1 antibodies. While AIH-1 affects all ages, AIH-2 is predominantly diagnosed in female pediatric patients and often follows a more severe clinical course; thus, timely and appropriate treatment is critical for improving outcomes[8,9].

In 1999, the International AIH Group established diagnostic criteria[10-12], which were later validated for pediatric patients[13,14], encompassing clinical, biochemical, and histological features such as interface hepatitis, a hallmark of AIH, characterized by lymphoplasmacytic infiltration of the limiting plate of the liver[15,16]. To confirm the diagnosis, exclusion of viral or toxic hepatitis, alpha-1-antitrypsine deficiency, and Wilson's disease is necessary. When left untreated, AIH has a poor prognosis, with a 5-year survival rate of 30%, often leading to acute or chronic liver failure. Liver transplantation is the only treatment option for end-stage disease[17].

The primary goal of AIH treatment is to normalize transaminase levels, IgG levels, and autoantibody titers and achieve histological remission[11,17]. Treatment typically involves high-dose steroids during the induction phase followed by gradual tapering over several weeks. Azathioprine is subsequently introduced as a maintenance therapy, leading to remission rates of up to 80%[11,18]. For those patients who do not respond to or relapse during steroid tapering, alternative therapies should be considered[2,3]. Furthermore, steroids may not be suitable for individuals with comorbidities or those who develop side effects, such as diabetes, hypertension, growth stunting, and osteoporosis[17,19]. Recent advancements in immunology enable the use of new therapies in AIH, and targeted immunosuppression can be tailored to the individual patient's needs.

This article evaluated the current treatment options for AIH, including conventional and unconventional methods, and investigated promising therapies that have not yet been widely implemented in clinical practice as well as potential future treatments.

PATHOGENESIS

AIH is histologically characterized by a dense portal infiltrate, primarily composed of lymphocytes and plasma cells. Although autoantibodies are diagnostic markers, AIH is mainly considered a T cell-driven disease[20-22].

AIH is a complex disease influenced by both genetic predisposition and environmental triggers. Molecular mimicry and epitope spreading contribute to the activation of cluster of differentiation (CD) 4 + [T helper (Th) cells, mainly Th1] and CD8 + (cytotoxic T cells) cells within a proinflammatory microenvironment, leading to the breakdown of immunological tolerance against self-antigens[23,24]. Activated B cells acquire the necessary costimulatory signals to function as professional antigen-presenting cells (APCs), such as macrophages and dendritic cells, further stimulating T cell activation. Once activated, Th cells mature into different phenotypes that produce cytokines essential for orchestrating the immune response[25]. Regulatory T cells (Tregs) are important in the development of AIH. When activated within the liver microenvironment by specific cytokines such as transforming growth factor beta and low levels of interleukin (IL)-2, they secrete anti-inflammatory interleukins to dampen excessive immune responses. Tregs may be deficient in either the

number or function in patients with AIH, although findings can be contradictory across studies[21,26]. Nonetheless, prevailing evidence suggests that Tregs in patients with AIH fail to effectively control inflammation, allowing effector T cells, especially Th1 and Th17, to perpetuate the autoimmune attack on the liver tissue (Figure 1).

TREATMENTS

Treatment of AIH should focus on halting the necroinflammatory process, preventing progression, and ideally reversing fibrosis. A panel of experts proposed the definitions for response criteria in AIH including "complete biochemical response" as normalization of serum transaminases and IgG within 6 months of starting treatment, "insufficient response" as the lack of complete response by 6 months, and "non-response" as less than a 50% decrease in transaminase levels within the first 4 weeks[27] (Table 1).

Steroids

Since its first description by Waldenström[5] in 1951, prednisone has formed the backbone of treatment, making AIH the first liver disease for which effective medical therapy was available[28]. Doses are adapted throughout the treatment, being higher during induction at 2 mg/kg/day (maximum 60 mg/day), usually for the 1st month, and tapering according to biochemical response, aiming to stop them as soon as possible, usually within 6 months to 12 months. Occasionally, a low daily dose (3-5 mg) is required to maintain transaminase levels in the normal range[29]. Oral prednisone effectively achieves AIH remission, but this comes at the cost of myriad side effects, some of which are irreversible, including cataracts or cutaneous striae. Additionally, severe side effects, such as vertebral collapse in osteopenia, psychosis, and suicidal ideation may occur[30-32].

Budesonide: Budesonide, a synthetic steroid, has been demonstrated to be effective in several inflammatory conditions, particularly when used topically. Although it has been suggested as an alternative to prednisone in naïve patients[29], a recent publication indicated that in real-life scenarios it is typically considered a second-line option when the side effects of prednisone are to be avoided[33]. Furthermore, budesonide acts through the same glucocorticoid receptor and employs the same pathway as prednisone to suppress the inflammatory process[34]. Therefore, it is probably not useful for prednisone-refractory patients[35].

The appeal of budesonide comes from its safety profile derived from its high first-pass effect, which inactivates 90% of the drug, reaching the liver through portal circulation, resulting in high intrahepatic but low systemic levels. As expected, budesonide is associated with fewer and milder side effects than prednisone; however, its lower systemic levels may be insufficient to control activated T cells in secondary lymphoid organs, compromising the therapeutic effect[35]. Nevertheless, budesonide has been found to be an effective alternative to prednisone at doses of 6-9 mg/day, provided it is not used in patients with cirrhosis or acute liver failure[36].

Two recent randomized controlled trials favored budesonide over prednisone in both adults and children, suggesting budesonide as the first choice in the treatment of patients with AIH during induction and maintenance. However, the results should be interpreted with caution as they were criticized because of the unusually high rate of treatment failure observed in the prednisone group[37,38]. Considering all these factors, budesonide is a viable option for stable patients without cirrhosis experiencing unbearable side effects from systemic corticosteroids[35].

Antimetabolites

Azathioprine: Azathioprine is used to maintain remission, while steroids are tapered and withdrawn. It has demonstrated effectiveness as a monotherapy with a good safety profile. It can be initiated alongside prednisone at a dose of 1-2 mg/kg/day, although delaying its introduction during the first weeks to minimize potential hepatotoxicity is a common practice[29,36,39]. Azathioprine inhibits purine synthesis, hindering DNA duplication necessary for the proliferation of immune cells. Its most severe side effect is bone marrow toxicity. To prevent this, the American Association for the Study of Liver Diseases guidelines recommend screening for thiopurine S-methyltransferase activity before initiating azathioprine treatment, as enzyme-deficient individuals should not be treated with this medication[29]. Chronic high-dose azathioprine use is linked to hepatosplenic T cell lymphoma, an exceedingly rare but serious complication with a high mortality rate[40,41]. Azathioprine, in combination with prednisone, achieves remission in roughly 80% of patients with AIH. Non-responders, those with frequent relapses, cortico-dependents, or intolerable side effects, require alternative therapies. In recent years, the therapeutic armamentarium has expanded to include second-line and third-line options, offering different safety profiles and effectiveness, and stimulating the idea of "personalized" treatment for each individual patient as a goal to be reached in the near future[42].

Mofetil mycophenolate: Mofetil mycophenolate (MMF) is the prodrug of mycophenolic acid (MPA), which was the first application of human genetics to define a therapeutic target[43]. MPA functions by inhibiting the enzymes critical for guanosine monophosphate, guanosine triphosphate, and deoxyguanosine triphosphate synthesis, which are essential for lymphocyte proliferation[43,44]. MMF was developed to improve the oral bioavailability of MPA. Its effectiveness was first documented in the treatment of 15 adult patients who were either refractory or intolerant to standard therapy. These patients received 1 g of MMF twice daily for an average of 41 months, either alone or in combination with prednisone. Remarkably, all patients showed significant improvement, with 11 patients achieving remission. No hematological side effects were observed[45]. Subsequent studies corroborated these findings in 29 adult patients, where MMF was effective in inducing remission in 84% of the patients who tolerated the treatment. Although one-third of the patients experienced

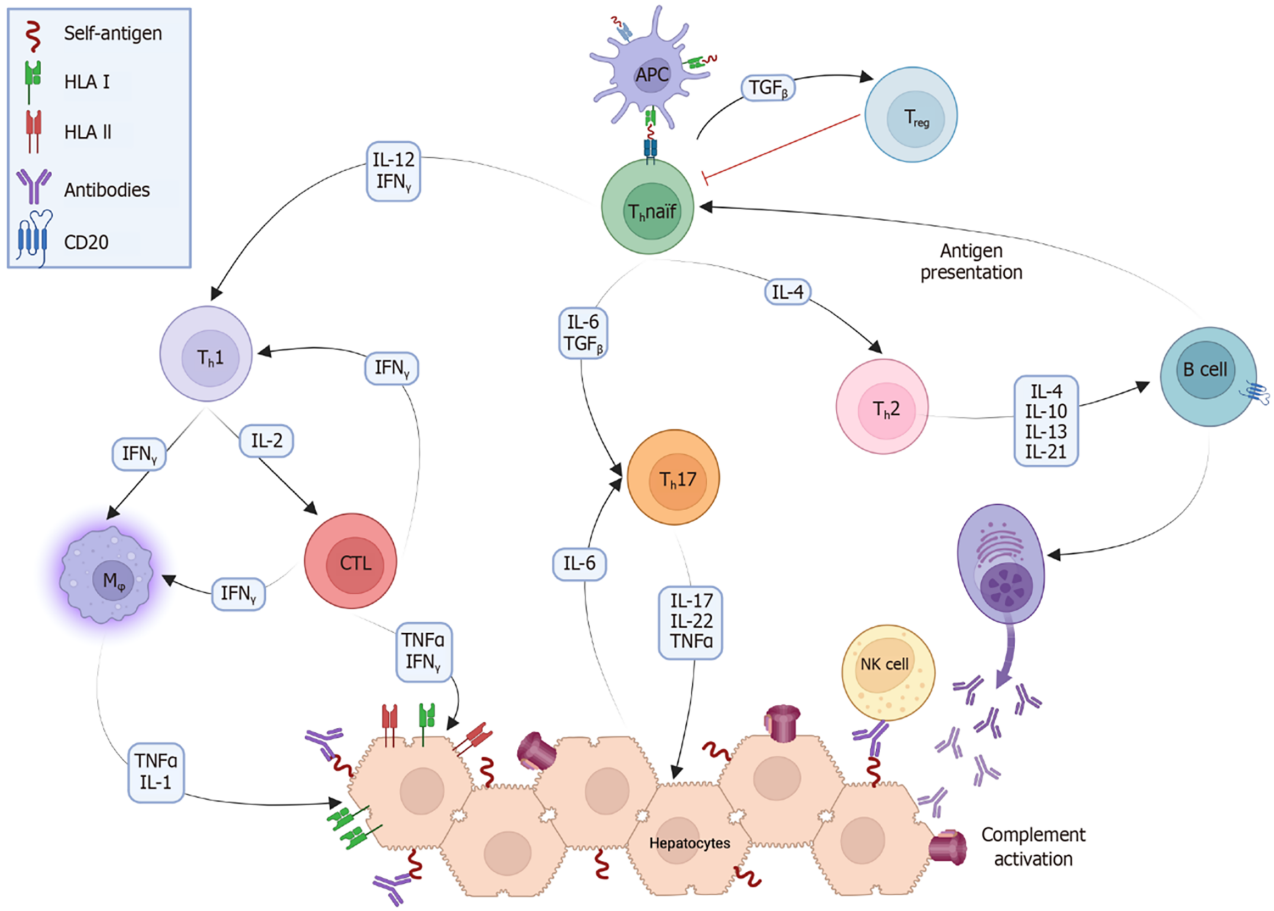

Figure 1 After a triggering event, peptides originating from healthy hepatocytes become self-antigens *via* a mechanism known as molecular mimicry. These antigens are processed by antigen-presenting cells (APCs), consisting primarily of dendritic cells, and presented through human leukocyte antigen (HLA) type II to naïve T cells. APCs produce certain cytokines that, along with those already present in the environment, stimulate the differentiation of T helper (Th) cells into their different phenotypes (Th1, Th2, and Th17). This triggers a cascade of immune reactions, where Th1 cells produce interleukin (IL)-2 and interferon (IFN) gamma, which in turn stimulate cytotoxic T cells and macrophages (Mφ), as well as enhance the expression of HLA type I and II in hepatocytes. Th2 cells produce IL-4, IL-10, IL-13, and IL-21, which stimulate B cells to become plasmacytes and to produce antibodies. Active B cells also act as APCs to further stimulate naïve Th0 cells. Th17 cells secrete the proinflammatory cytokines IL-17, IL-22, and tumor necrosis factor (TNF). Natural killer (NK) cells recognize the components of antibodies fixed to the surface of hepatocytes and begin to lyse them. The complement system becomes active mainly through the classical pathway, forming membrane attack complexes on the surface of hepatocytes. Finally, through the stimulation of transforming growth factor (TGF) beta, Th0 cells become regulatory T cells, which secrete anti-inflammatory cytokines. CD: Cluster of differentiation; CTL: Cytotoxic T lymphocyte; Thnaïf: T helper naïf.

side effects such as vomiting, pancreatitis, hair loss, and deep venous thrombosis, hematological complications were notably absent[46].

Pharmacokinetic studies are essential for monitoring the therapeutic threshold of MMF, as blood levels vary significantly in pediatric patients[47]. MMF continued to gain popularity as a second-line treatment, and experiences were published with a small case series[48,49]. A 2019 meta-analysis assessed the effectiveness of MMF in AIH, finding that patient profiles influenced response rates. Patients refractory to azathioprine showed a 32% response rate to MMF, whereas those initially responding to first-line antimetabolites but intolerant to them had an 82% response rate[50].

Other studies have consistently demonstrated that MMF is more tolerable than azathioprine in patients with AIH[51,52]. In a recent multicenter prospective trial, MMF and azathioprine were compared, associated to prednisolone for treating newly diagnosed adults with AIH. After 24 weeks, 56.4% of patients in the MMF group achieved remission, while only 29% in the azathioprine group achieved remission. MMF also showed significantly higher biochemical response than azathioprine (72.2%) to (32.3%). Notably, MMF had a good safety profile, with no serious adverse events reported, whereas four such events occurred in the azathioprine group. Drug tolerance was better for MMF, with only 2 patients discontinuing treatment due to side effects, compared to 8 patients in the azathioprine group[53]. These findings suggest that the combination of prednisolone and MMF could be a suitable alternative, considering the potential risks associated with azathioprine. However, further research and extensive clinical experience are needed to establish the role of MMF in AIH management.

Methotrexate: Methotrexate is commonly used in oncology and rheumatology because of its anti-inflammatory and immunosuppressive properties. It is a folate analog that inhibits dihydrofolate reductase, which is necessary for the production of purines and pyrimidines that are essential components of DNA synthesis and cellular proliferation[54].

Table 1 Current available treatments and mechanisms of action

Drug family	Medication	Remission rates	Mechanism of action	Advantages	Disadvantages	Ref.
Steroids	Prednisone	80%	CD4 + T cell sequestration in reticuloendothelial system; Inhibition of IL-1 and IL-6 synthesis; Inhibition of cell-cell adhesion molecules	Inexpensive; Widely available; Extensive experience in its use	Weight-gain; Growth stunting; Hyperglycemia; Psychosis; Osteoporosis; Arterial hypertension	Mieli-Vergani *et al* [17]; Mack *et al*[29]
	Budesonide	70%-80%		Theoretically less side-effects than prednisone	Expensive; Contrain-dicated in cirrhosis and liver failure; May not control autoreactive cells in peripheric lymphoid tissue	Mack *et al*[29]; Olivas *et al*[36]; Manns *et al*[37]; Woynarowski *et al* [38]
Antimetabolites	Azathioprine	80%	Purine synthesis inhibition	Extensive experience in its use	Not for induction; Bone marrow toxicity; Vomiting and gastrointestinal symptoms; Hepato-splenic T cell lymphoma	Mack *et al*[29]; Olivas *et al*[36]; Muratori *et al*[39]
	Mycophenolate mofetil	72%-84%	GMP, GTP, dGTP synthesis inhibition halting lymphocyte proliferation	Excellent alternative in azathioprine intolerance; Better tolerated than azathioprine; Less side effects	Not for induction; Diarrhea; Abdominal pain; Dizziness	Inductivo-Yu *et al* [45]; Santiago *et al* [50]; Snijders *et al* [53]
	Methotrexate	55%	Purine and pyrimidines through folate depletion	May be an alternative in azathioprine intolerance	Not for induction; Hepatotoxicity; Limited experience; Low tolerability	Haridy *et al*[56]
Calcineurin inhibitors	Cyclosporin A	80%-94%	Binding of immunophilins; Proinflammatory cytokine synthesis inhibition	Useful as an alternative to steroids for induction; Useful for steroid-sparing (liver failure)	Monitoring of trough levels; Nephro-toxicity; Gingival hyperplasia; Hypertrichosis; Not ideal for chronic use	Alvarez *et al*[67]; Malekzadeh *et al* [68]; Cuarterolo *et al* [72]
	Tacrolimus	69%-75%		Good alternative in anti-metabolite refractory patients	Same as cyclosporin A; Diabetes	Abdollahi *et al*[78]; Hanouneh *et al*[79]; Efe *et al*[80]; Efe *et al* [81]
mTOR inhibitors	Sirolimus	0% (response in 50%)	Impair dendritic cells and T cell proliferation and differen-tiation	Alternatives in difficult-to-treat patients; Sparing of Tregs	Anecdotical experience; Not effective in monotherapy	Kurowski *et al*[90]; Chatrath *et al*[91]
	Everolimus	0% (response in 83%)				Jannone *et al*[92]
B cell depletion	Anti-CD 20 (rituximab)	75%-100%	Direct decrease in antigen-presenting cells; Indirect decrease in autoreactive plasmacytes; Decrease of B cell-mediated T cell activation; Direct decrease in autoreactive T cells (belimumab only)	Useful for induction and maintenance; Ensures compliance; Steroid-sparing	Expensive; Lack of long-term safety data	D'Agostino *et al* [102]; Than *et al* [108]; Costaguta *et al* [110]
	Anti-BAFF (belimumab)	Unknown		Better response in other diseases than with rituximab	Ongoing trial for AIH	ClinicalTrials.gov [124]; Wise and Stohl[125]
Biologics	Anti-TNF (infliximab)	61%	Inhibits dendritic cell activation; Inhibits T helper differentiation; Inhibits cytotoxic T cells	Useful for induction and/or maintenance; Extensive experience in other diseases; Good safety profile	Anti-TNF may trigger AIH; Hepato-toxicity	Weiler-Normann *et al*[129]; Rajanayagam and Lewindon[130]; Weiler-Normann *et al*[131]
	Anti-IL1 (anakinra)	Unknown	Inhibits monocyte/macrophage activation; Inhibits fibroblast proliferation; Inhibits ROS synthesis	Experimental benefits in other forms of hepatitis; Theoretical benefits on fibrosis	Unknown efficacy in AIH; Possible hepatotoxicity	Iracheta-Vellve *et al* [137]; Petrasek *et al* [138]

	Anti-IL17 (secukinumab)	Unknown	Inhibits macrophage cytokine secretion; Inhibit endothelial cell expression of integrins and selectins; Inhibit neutrophil recruitment and decrease survival	Effective in murine models; Experimental benefits since IL-17 is central in many autoimmune disorders	Unknown efficacy in human AIH; Th17/Treg disbalance may paradoxically be detrimental in some autoimmune disorders	Zhao *et al*[144]; Yu *et al*[145]
JAK inhibitors	Tofacitinib	Unknown	Inhibition of proinflammatory cytokine synthesis	Effective in murine models; Effective in STAT gain-of-function-related AIH	Unknown efficacy in human AIH; Relatively new medications	Hadžić *et al*[157]; Kaneko *et al*[158]
Cell therapy	Chimeric antigen receptor-T cell therapy	Unknown	Selective targeting of autoreactive CD19 + cells; Cell therapy-mediated B cell depletion	Effective in B cell malignancies; Excellent safety profile; Targeted immunosuppression	Expensive therapy; Not easily available	Schett *et al*[169]
	Treg cell transfer	Unknown	Induction of peripherical tolerance to self-antigens; Dampening of the inflammatory response	Effective in murine models; Theoretical possibility of tolerance "resetting"; Excellent safety profile	Lack of specific self-antigens in AIH-1; Expensive therapy; Not easily available	Lapierre *et al*[172]; Sánchez-Fueyo *et al*[173]

AIH: Autoimmune hepatitis; BAFF: B-cell activating factor; CD: Cluster of differentiation; dGTP: Deoxyguanosine triphosphate; GMP: Guanosine monophosphate; GTP: Guanosine triphosphate; IL: Interleukin; JAK: Janus kinase; mTOR: Mammalian target of rapamycin; ROS: Reactive oxygen species; STAT: Signal transducer and activator of transcription; Th: T helper cell; TNF: Tumor necrosis factor; Treg: Regulatory T cell.

Despite its broad application in other conditions, its use in AIH is limited and generally discouraged due to several factors, such as low tolerability, possible hepatotoxicity, and contraindication in patients with cirrhosis[55]. A 2018 case series revealed that only 54.5% of 11 adult patients with AIH achieved remission within 12 months on methotrexate. However, liver biochemical deterioration led to discontinuation, and 2 patients experienced drug-induced liver injury [56]. Experience with methotrexate in pediatric AIH cases is even more limited and primarily consists of sporadic case reports[57].

Calcineurin inhibitors

Calcineurin inhibitors (CNI) such as cyclosporine A (CsA) and tacrolimus have revolutionized immunosuppression in post-transplant settings, as first described by Calne *et al*[58] and Starzl *et al*[59]. These drugs inhibit calcineurin, an enzyme critical for activating nuclear factor of activated T cells, which is crucial for the synthesis of the cytokines necessary for the development and survival of activated T cells[60-62]. CNI binds to cytoplasmic receptors known as immunophilins, cyclophilin (for CsA), and FK-binding protein (for tacrolimus), which inhibits the function of calcineurin, leading to reduced cytokine transcription[63]. While CNI are widely used in transplant medicine and other autoimmune conditions[64], their role in AIH has been limited and is typically reserved as a second-line or third-line option[4,17].

The use of CsA in the treatment of AIH has shown promising results, particularly in cases resistant to steroids, as initially reported in the treatment of a 14-year-old patient[65]. This early success made CsA an option for treating steroid-refractory AIH, with a success rate of approximately 80%[66]. In 1999, a study investigating the use of CsA as first-line treatment for pediatric AIH was conducted. This study included 32 children diagnosed with AIH who were administered CsA with a target trough concentration of 250 ng/mL for the first 3 months. Responders then reduced their CsA doses to maintain a trough level of 200 ng/mL. After 6 months of treatment, the patients transitioned to a low dose of prednisone combined with azathioprine for 3 months, followed by prednisone tapering. The results showed that 25 of 30 patients who completed the study (83%) achieved normal liver function tests after CsA induction, and this improvement was sustained in all patients after 12 months. The protocol was well tolerated, with gingival hyperplasia being the main side effect, which resolved after discontinuation of CsA. Importantly, none of the patients developed renal dysfunction or arterial hypertension, likely because of careful CsA dosing and monitoring. Furthermore, patients with extrahepatic immune diseases, such as atopic dermatitis, psoriasis, and ulcerative colitis, showed resolution of their conditions[67].

Despite other promising results with CsA in AIH treatment[68], its use has been limited by adverse side effects. In one series, 15 children received CsA for 6 years, and significant side effects were reported, with drug withdrawal in 3 patients and dose reductions in another 3 patients due to hypertension, tremors, or glomerulopathy[69]. CsA is associated with a high incidence of adverse events, but most cases are mild and temporary, such as gingival hyperplasia and hypertrichosis [70]. A study of 84 pediatric patients showed a more favorable outcome, with 94% achieving remission over a mean follow-up period of 29 months, many within the first 12 months, and 72% within the first 6 months. Adverse effects were mostly mild, sporadic, and transient, with hypertrichosis affecting 55% and gingival hyperplasia affecting 39% of patients. Additionally, 8 patients had a single instance of abnormal serum creatinine levels, and 3 patients experienced one episode of arterial hypertension. All adverse events resolved quickly[71].

CsA was also effective in treating patients with liver failure, as determining the optimal timing is challenging due to the uncertainty of patient response and the possible need for liver transplantation. High-dose steroids are associated with poor postoperative outcomes and high complication rates. In a retrospective study of 237 pediatric patients with AIH, 37

children with liver failure and no prior treatment received 1 mg/kg prednisone with CsA targeting a trough level of 200 ng/mL, while 13 received standard of care. After a median of 24 days, 45 patients normalized their internation normalized ratio, with no significant difference between the groups. Forty patients achieved remission within a median of 3 months. Infection episodes were similar between the two treatments[72]. Current evidence supports the use of a short course of CsA as first-line treatment for inducing remission in AIH, particularly in patients for whom long-term steroid use poses significant risks. However, patient compliance and the need for regular trough-level monitoring can limit their broader application.

Since its introduction in the early 1990s, tacrolimus has become a nearly universal immunosuppressor for post-liver transplantation because of its higher affinity for immunophilins[73]. In 1995, the use of tacrolimus in 21 treatment-naïve patients with AIH resulted in a mean transaminase level decrease of 80% after 3 months and only a mild increase in serum creatinine[74]. Similar outcomes have been reported previously[75-77]. A recent systematic review analyzed the use of tacrolimus *vs* MMF as second-line treatment. The study found biochemical remission rates of 68.9% and 73.5% for tacrolimus and MMF, respectively. Notably, most studies have focused on patients who were intolerant to first-line treatments, with remission rates of 25%-32% for first-line non-responders. The rates of side effects were similar for tacrolimus (25.5%) and MMF (24.2%)[78].

Another meta-analysis reviewed seven studies involving 162 adult patients who were either refractory or intolerant to standard treatment. The analysis found a biochemical response rate of 74.7%, with an 85% histological remission rate in patients who underwent a control biopsy[79]. Two additional systematic reviews compared tacrolimus and MMF as second-line therapies in adults[80] and children[81]. The remission rates for MMF and tacrolimus were 69.4% and 72.5%, respectively, with side effects of 8.3% and 12.5%, respectively. In the pediatric cohort, tacrolimus appeared to be more effective than MMF in patients refractory to treatment, although the difference was not statistically significant. These findings have been corroborated by other authors[82], and an open trial is currently underway to further clarify the role of tacrolimus in AIH treatment[83].

Mammalian target of rapamycin inhibitors

Mammalian target of rapamycin (mTOR) is a protein kinase that activates anabolic cellular pathways that increase protein, nucleotide, and lipid synthesis and inhibits catabolic pathways associated with autophagy[84-86]. Targeted immunosuppression by blocking mTOR with sirolimus or everolimus impairs dendritic cell maturation and inhibits T cell proliferation and differentiation[87]. Evidence suggests that mTOR inhibition does not affect CD4 + T cells with *FOXP3* upregulation in the thymus, indicating that these drugs do not affect natural Tregs[88,89]. Unfortunately, practical evidence has largely failed to demonstrate significant benefits with mTOR inhibitors.

In 2014, a study of 127 children with AIH found that only two of the four children treated with sirolimus showed a biochemical response after 6 months albeit with continued low-dose prednisone[90]. Simultaneously, 5 adult patients with steroid-refractory AIH were treated with sirolimus for 4-72 months. Four of these patients had a biochemical response, but only two achieved remission. All patients reduced their steroid doses, and sirolimus was well tolerated, with only two experiencing increased cholesterol and triglyceride levels[91]. A study on 6 difficult-to-treat patients who received everolimus reported reduced transaminase levels in 5 patients, although none achieved complete remission. No negative side effects were observed when therapeutic trough levels were maintained[92]. Recently, researchers have compared lymphocyte populations in patients with AIH under standard and non-standard therapy. They found a proportional increase in Treg infiltration in partial responders under non-standard therapy, but overall lymphocytic infiltration decreased. Treg infiltration did not differ significantly between patients in biochemical remission and was similar among those treated with various medications[93].

B cell-depleting agents

AIH is primarily a T cell-mediated disease, but B cell activation and stimulation are necessary to maintain the immune response. The two main mechanisms that contribute to this process are B cell expression of specific antigen receptors that act as APCs for T cells and B cell costimulation of T cells[94]. AIH is thought to be triggered by the presentation of self-antigens by professional APCs to unstimulated Th0 cells, which then mature into various Th subtypes (Figure 1). Activated B cells differentiate into plasma cells, which produce antibodies, and into APCs, which stimulate Th0 cells to sustain the immune response[95-97]. B cell and T cell interactions are essential for adapting and directing immune responses and involve membrane proteins such as CD40/CD40 L and CD28/cytotoxic T-lymphocyte-associated protein 4. These interactions not only contribute to the production of autoantibodies but also play a critical role in Th1 activation observed in AIH[98-101].

B cells play a crucial role in the development of AIH, as initially demonstrated in a murine model of AIH-2, in which B cell depletion *via* anti-CD-20 antibodies resulted in significant improvement in liver inflammation and reduction in the number of memory B cells[24]. The successful treatment of the first pediatric patient with refractory AIH using rituximab, an anti-CD20 antibody, provided evidence of B cell depletion efficacy and demonstrated a direct link between B cell activation and inflammatory activity in AIH[102]. Remarkably, this patient was able to discontinue all immunosuppressive medications, maintained normal liver function and histology for 14 years, and recently gave birth to a healthy child (personal communication).

Since then, numerous case reports have documented the efficacy of rituximab in the treatment of AIH[103-107]. A study from 2019 by the International AIH Group involving 22 adults with refractory AIH found that 71% achieved flare-free remission after 2 years, with only 5 patients experiencing flares over an 11-year follow-up. Furthermore, a 61% reduction in the prednisolone dose in the first 12 months of treatment and no serious adverse events related to rituximab were reported[108].

The first pediatric series successfully treated with rituximab was published in 2021[109]. Recently, we reported 6 patients treated with rituximab, all of whom normalized liver enzymes and IgG levels and achieved negative autoantibody status, with no flares recorded over an average follow-up of 22 months. One patient developed hypogammaglobulinemia and another developed mild lymphopenia, but no serious adverse events occurred. Rituximab was initiated in 5 patients due to concerns about steroid side effects, such as severe metabolic syndrome, stunted growth, severe acne, or concomitant autoimmune conditions[110]. Since then, 3 more patients have received rituximab as first-line treatment due to similar concerns, including two with severe refractory acne and one with anorexia nervosa. All patients showed a rapid and sustained response, with no observed side effects (unpublished data).

Rituximab is not yet a standard treatment for AIH despite successful reports of B cell depletion and is only considered a potential rescue therapy without formal recommendations in guidelines[17]. Moreover, no governmental health authorities have approved rituximab for the treatment of AIH[111]. Concerns about long-term safety, including B cell depletion and infection risk, may account for this hesitation. However, information on rituximab comes mostly from hematologic malignancies, which may differ from AIH risk[112,113].

Recently, alternative methods for reducing B cell survival have been suggested, such as inhibition of B-cell activating factor (BAFF), a protein belonging to the tumor necrosis factor (TNF) family[114]. BAFF can be either a membrane-bound or soluble protein that binds to B cell receptors to extend survival and promote maturation, and elevated BAFF levels are found in the sera of patients with autoimmune disease[115-118]. Belimumab, a humanized monoclonal antibody targeting BAFF, is effective in treating various autoimmune diseases, including systemic lupus erythematosus in both adults and children[119] and rheumatoid arthritis[120] and is currently being studied in clinical trials for multiple sclerosis[121].

The rationale for using BAFF inhibitors in AIH is to reduce B cell activity and thereby dampen the autoimmune response. However, its efficacy in AIH remains to be established[122,123]. An ongoing clinical trial is expected to provide more insights and is projected to be completed between 2028 and 2029[124]. The efficacy of depleting B cells using monoclonal antibodies targeting the high-affinity BAFF receptor has not been established in AIH, although it has already been proven superior in other B cell-mediated diseases[125].

Other biologics agents and future therapies

Antibody-mediated cytokine neutralization has become the primary therapy for various autoimmune diseases including rheumatoid arthritis, ulcerative colitis, Crohn's disease, and psoriasis[126,127]. Despite these successes, its use in AIH has been limited, partly due to the complex pathogenesis of AIH involving a multitude of cytokines and mechanisms. Anti-TNF therapy for AIH remains controversial despite its potential benefits due to sporadic cases of anti-TNF-triggered AIH [128]. Nevertheless, infliximab, an antibody against TNF, has been used to treat refractory AIH with some success[129], including some pediatric cases[130]. To date, a case series involving 11 patients with refractory AIH is the largest to date. Researchers have used infliximab to induce remission, with the aim of discontinuing the drug after enzyme normalization. After the induction phase, 8 of the 11 patients exhibited significant improvement in liver function tests. Three of these patients were able to discontinue infliximab within the first 12 months of therapy, while two maintained remission on antimetabolite monotherapy. One patient experienced recurrent flares during treatment, leading to discontinuation, and another required intermittent infusions to control the flares. Two patients were unable to discontinue infliximab, and one remained on treatment for over 12 years[131]. Seven patients experienced adverse effects, with five developing infliximab-related infections. These included hepatic abscesses, urinary tract infections, recurrent shingles, and pneumonia. The causality of these infections with infliximab use is unclear due to comorbidities such as diabetes and cirrhosis at the time of diagnosis[132].

Recently, anti-TNF-related AIH cases have emerged, likely resulting from the widespread use of anti-TNF therapies for other conditions[133-135]. Although liver injury in these cases resembles drug-induced liver injury, further research and experience are necessary to provide formal recommendations on using anti-TNF agents in AIH.

Figure 1 shows the various theoretical targets for cytokine inhibition. Recently, the IL-1 superfamily has attracted the attention of researchers owing to its involvement in other autoimmune diseases and its potential role in liver diseases [136]. Two studies have shown that IL-1 inhibitors, such as anakinra or canakinumab, can significantly reduce inflammation in animal models of ethanol-induced hepatitis[137,138]. However, there is currently no real-life experience with the use of these inhibitors in AIH, and reports of anakinra-related hepatotoxicity complicate their potential application [139,140]. Consequently, the use of IL-1 inhibitors in AIH remains theoretical at this time.

Another cytokine, IL-17, is important in many autoimmune diseases and merits a mention[141-143]. Over the past decade, evidence has suggested that Th17 cells and IL-17 are central to AIH pathogenesis. Patients with AIH have significantly higher circulating levels of IL-17 than patients with other chronic liver diseases, and downstream IL-17-related cytokines are also elevated. Anti-IL-17 administration in murine AIH models improves liver inflammation[144, 145]. However, it must be noted that while IL-17 is necessary for the development of inflammatory bowel disease (IBD), the use of anti-IL-17 has led to paradoxical intestinal inflammation in some cases, and the pathogenesis of this effect remains unclear[146-148]. Therefore, more evidence is needed before anti-IL-17 can be considered a viable treatment option for AIH.

Janus kinases inhibitors

Janus kinases (JAK), including JAK1, JAK2, JAK3, and tyrosine kinase 2, are a group of intracellular enzymes that play an essential role in the production of numerous cytokines. When a cytokine binds to its specific receptor, JAK kinases become active, leading to signal transduction through signal transducer and activator of transcription (STAT) transcription factors[149]. Recently, JAK inhibitors have gained popularity in the treatment of various diseases, such as rheumatoid arthritis, IBD, and graft-*vs*-host disease[150-153]. A study in a murine model of AIH used tofacitinib, a pan-JAK inhibitor. The JAK1/STAT signaling pathway is activated following liver injury. Tofacitinib-treated mice showed

improvement, with a decrease in proinflammatory cytokines and an increase in anti-inflammatory cytokines. This study also reported a higher Treg/Th17 ratio and reduced liver fibrosis[154].

A second study found that ruxolitinib, a JAK1/2 inhibitor, reduced serum and liver cytokines, liver fibrosis, hepatocyte apoptosis, and neutrophil infiltration in a similar animal model[155]. Other authors have confirmed similar impacts on most proinflammatory cytokines and a decrease in T cell liver infiltration, along with an increase in the Treg population in murine models[156]. Although there is currently limited research on the use of JAK inhibitors for human AIH, recent cases of STAT1 and STAT3 gain-of-function-related AIH were successfully treated with baricitinib and tofacitinib, respectively[157,158].

Cellular therapy

Cellular therapy has experienced a resurgence thanks to advancements in stem cell therapy and applied genetics[159-161], including chimeric antigen receptor (CAR)-T cells for treating autoimmune conditions. This approach involves genetically modifying a patient's cells to target specific antigens, thereby offering a versatile and effective solution[162]. CAR-T cells targeting CD19 have successfully eliminated neoplastic cells in lymphomas, leukemia, and myelomas[163,164]. Additionally, this therapy can be applied to Tregs or dendritic cells to harness their immunomodulatory capabilities in certain autoimmune-related or immune-related diseases[165,166]. The process involves extracting, isolating, expanding, and modifying the patient's immune cells, then reinfusing them in larger numbers to suppress the autoreactive immune response. However, Tregs alone have not been proven to be sufficient in clinical settings[167,168]. A clinical trial examining the efficiency of CAR-T cells for B cell-mediated autoimmune illnesses, including pemphigus vulgaris and systemic lupus erythematosus, is anticipated to conclude by 2026[169]. The results of this trial, considering the critical role of B cells in AIH, suggest the potential of CAR-T cells for treating AIH[170].

Another approach is to use Tregs isolated from patients with autoimmune disease. These Tregs can be naturally isolated from peripheral blood, expanded before reinfusion, or induced from conventional T cells by stimulating them with transforming growth factor beta or low-dose IL-2. Induced Tregs have shown promise in the treatment of autoimmune diseases in murine models[171,172]. While the exact role of Tregs in the development of AIH is still debated, an experimental study provided major insights. Using a murine model of AIH-2, the study revealed the following: (1) Ectopic expression of the autoantigen formiminotransferase cyclodeaminase in the thymus led to a decreased number of autoreactive T cells, halting the development of AIH; (2) In the absence of central tolerance to formiminotransferase cyclodeaminase, the adoptive transfer of *ex vivo* expanded Tregs inhibited the proliferation of liver-specific autoreactive T cells; and (3) Once inflammation was resolved, high numbers of Tregs were no longer needed to maintain tolerance, suggesting that although a break in immunotolerance triggers AIH, it can be restored under certain circumstances[173]. The main issue with these therapies is that AIH-1, which accounts for most AIH cases, lacks liver-specific autoantigens. This could limit the effectiveness of the transferred T cells in targeting the liver. However, Treg infusion has shown promise in inducing tolerance after liver transplantation, suggesting that these cells can remain home to the liver during active inflammation[174].

TAILORING OF TREATMENT FOR SPECIFIC PATIENTS

Given the current armamentarium of different immunosuppressive treatments available, tailoring therapy to individual patient needs should become the mainstay (Table 2). Although most patients respond to standard treatments, special considerations may be given to certain subpopulations.

The incidence of obesity and metabolic syndrome is increasing worldwide across all ages, posing significant challenges to patient care[175,176]. High-dose steroids are associated with several side effects, including weight gain, fluid and sodium retention, hypertension, lipid anabolism, and peripheral insulin resistance[177,178]. For patients with obesity, it is challenging to determine the appropriate steroid dosage owing to inconclusive pharmacokinetics[179]. In our experience, these patients benefit from alternate induction protocols using either CsA or rituximab, both of which help avoid steroid-related adverse effects. In some cases, CsA can be combined with low-dose steroids to minimize the side effects while achieving remission[67,72,110].

Patients with diabetes often cannot tolerate steroids owing to their glucocorticoid effects and risk of decompensation [180-182]. High doses of steroids can even induce diabetic ketoacidosis, especially in poorly controlled diabetes[183,184]. Thus, steroids should be avoided, and tacrolimus is not ideal for maintenance therapy due to its impact on carbohydrate metabolism[185,186]. As in the previous subgroup of patients, an induction protocol using either rituximab or CsA can be used to avoid the use of steroids. Thereafter, azathioprine, MMF, and rituximab were all suitable for maintenance therapy.

Adolescent patients with AIH present additional challenges owing to the significant role of body image and self-perception during this developmental stage[187]. Steroid-induced physical changes (weight gain, stretch marks, and acne) can lead to bullying and social exclusion, profoundly impacting mental health, especially in female patients[188,189]. The asymptomatic nature of AIH, coupled with these adverse effects, often leads to poor compliance with long steroid courses, resulting in treatment failure and potential liver decompensation[190,191]. The use of rituximab may be considered in this subgroup of patients when expressing serious concern about the steroid-related side effects. Budesonide may also be a valuable treatment option for mild cases. Induction with a combination of CsA followed by low-dose prednisone may also be effective, as it generally avoids undesired side effects.

Patients with eating disorders and body dysmorphia face similar challenges as the psychological aspects of body composition changes are critical[192,193]. Unexpected weight gain can reduce treatment compliance and complicate the

Table 2 Special considerations when choosing a treatment for specific populations

Population	Less-desirable options	Reasons	Available options
Obesity and metabolic syndrome	Steroids	Weight gain; Arterial hypertension; Steroid-induced hyperglycemia	Induction with cyclosporin A: Trough target of 250 ng/mL for 3 months and decrease to 200 ng/mL for the next 3 months. Tapering of cyclosporin with addition of 0.3-0.5 mg/kg daily prednisone for 3 months, and then every other day for another 3 months. Azathioprine at usual dose from the 6th month onwards; Induction with rituximab at 375 mg/m^2 once a week for 4 weeks. Maintenance with the same dose every 6 months. Adapt according to lymphocyte (CD20 +) count and IgG levels
Adolescents; Eating disorders; Body dysmorphia	Steroids; CsA	Weight gain; Stretch marks; Acne; Growth stunting; Psychosis and suicidal ideation; Hypertrichosis; Gingival hyperplasia	Budesonide at doses of 9 mg for induction, with progressive tapering to 6 mg and then 3 mg. Maintenance with azathioprine: Rituximab induction as previously mentioned. Maintenance with rituximab or azathioprine; Prednisone at 0.5-1 mg/kg daily + CsA targeting 200 ng/mL for 3-6 months as induction
Concomitant autoimmune disorders	NA	Treatment should be aimed at controlling all the conditions simultaneously with the smaller number of medications possible	In antibody-mediated diseases: Rituximab at 375 mg/m^2 for induction and maintenance
Inflammatory bowel disease	NA		Infliximab at 5-10 mg/kg at week 0, 2, and 6 for induction. Maintenance with a dose every 4 weeks to 8 weeks. Doses and frequencies are adapted according to IBD activity; Although not yet proven, in this scenario the use of JAK inhibitors may become useful, although no evidence exists presently
Non-compliance	Steroids; CsA; Tacrolimus	Medications with significant side effects, requiring multiple daily doses, and with a set therapeutic range are less desirable	Rituximab ensures the compliance of patients as doses are administered a few times a year and under healthcare personnel surveillance

CD: Cluster of differentiation; CsA: Cyclosporin A; IBD: Inflammatory bowel disease; JAK: Janus kinases; NA: Not applicable.

management of eating disorders. In these cases, CsA induction protocols may be less desirable because of transient side effects, such as hypertrichosis and gingival hyperplasia. Therefore, rituximab was successfully used for both induction and maintenance in these patients.

Some patients with AIH may have other immune dysregulation syndromes[194] and may be associated with other immune-mediated diseases[195]. In these cases, close collaboration with an immunology team is warranted. We successfully treated such patients with rituximab, achieving remission in both hepatic and extrahepatic autoimmune diseases [110]. Patients with IBD deserve special attention because of its increasing global incidence[196]. These patients are often treated with long-term biologics, primarily anti-TNF agents, which can also manage AIH, although they may worsen liver disease. We used anti-TNFs, with or without steroids, depending on the overall inflammation, to induce remission in both conditions. Given the frequent liver function test abnormalities in patients newly diagnosed with IBD, we closely monitored them. If liver enzymes remain elevated after achieving IBD remission, we investigated drug-induced liver injury or active AIH and may discontinue anti-TNFs.

Patients diagnosed with renal disease warrant mention. Glomerulonephritis, which is sometimes associated with AIH, precludes the use of CNIs. Additionally, although not inherently nephrotoxic, high-dose steroids should be avoided because of their detrimental effects in patients who may already have hypertension. Considering that several cases of glomerulonephritis are secondary to circulating immunocomplexes, rituximab may be the preferred treatment option.

Patients who do not comply with treatment also pose a challenge, as detection is difficult owing to fluctuating liver enzyme levels, which may be only slightly abnormal. Other causes of liver enzyme abnormalities must be investigated until nonadherence to the therapeutic strategy is confirmed. Psychological disorders that affect patient autonomy and reliability can exacerbate these issues. We successfully used rituximab as a second-line treatment in these situations, as it allowed us to ensure adherence through biannual administration in a controlled setting.

CONCLUSION

AIH is a complex disease that involves various aspects of the immune system. Steroids have been pivotal for the effective management of these patients, yielding excellent results. Nevertheless, not every patient responds adequately, necessitating alternative treatment. Recent advancements in immunology have provided us with the ability to personalize treatment strategies to better adapt to our patient's specific needs. This tailored approach allows for the selection of treatments that optimize outcomes while minimizing adverse effects, thereby significantly advancing the management of this complex autoimmune condition.

FOOTNOTES

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