

Autoimmune Hepatitis: a Review of Established and Evolving Treatments

Sebastian Bischoff^{1*}, Kakharman Yesmembetov^{1,2*}, Christoph Antoni¹, Janina Sollors¹, Matthias Evert³, Matthias Ebert¹, Andreas Teufel¹

1) Department of Medicine II, University Medical Center Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim;

2) Department of Medicine III, University Medical Center Aachen, Aachen;

3) Department of Pathology, University of Regensburg, Regensburg, Germany

ABSTRACT

Autoimmune hepatitis (AIH) is a necroinflammatory liver disease commonly presenting with a fluctuating course of activity, presence of circulating autoantibodies, hyperglobulinemia of IgG, and/or response to immunosuppressive drugs. However, the disease displays a considerable heterogeneity. No single clinical or biochemical test may establish diagnosis of AIH. Thus, diagnosis still requires extensive clinical evaluation and experience. Prednisolone and azathioprine are considered standard treatment leading to remission in most patients. However, this standard treatment may not be effective in some patients or not be feasible due to one of these drugs. Over the past two decades additional immunosuppressant drugs for the treatment of AIH have been evaluated and have significantly extended the therapeutic spectrum. Among those novel drugs are mycophenolate mofetil, tacrolimus, everolimus, 6-mercaptopurine, infliximab, rituximab and several others. In this review we summarize the current standard of therapy but also efforts of providing novel therapeutic strategies to AIH patients.

Key words: autoimmune hepatitis – autoimmune liver disease – mycophenolate mofetil – budesonide – 6-mercaptopurine – tacrolimus – cyclosporine – infliximab – rituximab.

Address for correspondence:

Andreas Teufel, M.D., Ph.D.
Department of Medicine II,
Division of Hepatology,
Mannheim University Medical
Center,
University of Heidelberg
Theodor-Kutzer-Ufer 1-3
68167 Mannheim
Germany
andreas.teufel@medma.uni-heidelberg.de

Abbreviations: AASLD: American Association for the Study of Liver Diseases; AIH: autoimmune hepatitis; AMA: antimitochondrial antibodies; ANA: antinuclear antibodies; anti-LC1: antibodies to liver cytosol antigen type 1; AZA: azathioprine; DGVS: German Society for Digestive and Metabolic Diseases; EASL: European Association for the Study of the Liver; IAIHG International Autoimmune Hepatitis Group; LKM: liver-kidney microsome; MMF: mycophenolate mofetil; pANCA: perinuclear anti-neutrophil cytoplasmic antibodies; PBC: primary biliary cirrhosis; PSC: primary sclerosing cholangitis; RCT: randomized controlled trial; SMA: smooth-muscle antibody; SLA/LP: soluble liver antigen/liver-pancreas; TAC: tacrolimus; TPMT: thiopurine methyltransferase; TNF- α : tumor necrosis factor alpha; 6-MP: 6-mercaptopurine; 6-MMP: 6-methylmercaptopurine; 6-TG: 6-thioguanine; 6-TGN: thioguanine nucleotide.

EPIDEMIOLOGY

Autoimmune hepatitis (AIH) is a necroinflammatory liver disease of unknown aetiology that occurs in children and adults of all ages [1-3]. The majority of patients receive the diagnosis of AIH at age 40 to 70, a smaller peak occurs at early adolescence. However, many patients are diagnosed with AIH at very early childhood or close to age 80. Incidence of the disease is estimated to range between 1 and 2 per 100,000 persons per

year, while prevalence ranges between 10 and 30 per 100,000 persons [4-8]. Interestingly, long-term data show an increase of incidence over time, which cannot be attributed to a change in awareness [3, 7]. Autoimmune hepatitis was repeatedly reported to predominantly occur in females; the ratio of female to male patients is thought to be at least four to one [4-8].

CLINICAL PRESENTATION AND COURSE OF DISEASE

The presentation of AIH is very heterogeneous and may be characterized by an undulating course with periods of decreased or increased activity; thus, clinical manifestations are variable ranging from asymptomatic disease to severe icteric hepatitis and even fulminant hepatic failure requiring liver transplantation depending on the intensity of the autoimmune reaction [1].

Received: 12.03.2020

Accepted: 14.08.2020

* equal contribution

Patients may present with nonspecific symptoms of varying severity. Many patients report significant fatigue; other symptoms include lethargy, malaise, anorexia, nausea, abdominal pain, and itching. Arthralgia involving small joints is common. Physical examination may be inconspicuous in many cases. Common findings include hepatomegaly, splenomegaly, jaundice, or signs of chronic liver disease [1, 9]. It is suspected that many cases of AIH remain undetected and proceed subclinical for a long time. Many patients with an acute presentation already display histologic evidence of chronic disease in liver biopsy, further supporting this notion. At the same time, AIH may remain subclinical even after detection for a significant period of time.

On its natural course the disease ultimately leads to cirrhosis and around 30% of patients are diagnosed with already existing cirrhosis [7, 8]. The mortality of severe, untreated AIH is high with mortality rates exceeding 50% within five years after diagnosis [10-12]. Thus, therapeutic intervention is essential to the patient's survival.

Most patients are initially suspicious of chronic liver disease due to elevation of aminotransferases (AST, ALT). During initial work up, viral or toxic hepatitis are main differential diagnoses and must be excluded. Few cases may be characterized by cholestasis, requiring exclusion of extrahepatic obstruction and cholestatic forms of viral hepatitis, drug-induced disease, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) or variant syndromes. A characteristic feature of (but not exclusive to) AIH are circulating autoantibodies such as antinuclear antibodies (ANA), smooth-muscle antibody (SMA), soluble liver antigen/liver-pancreas autoantibodies (SLA/LP), and liver-kidney microsome autoantibodies (LKM). In addition, perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) and antibodies to liver cytosol antigen type 1 (anti-LC-1) are frequently encountered in patients with AIH. If antimitochondrial antibodies (AMA) are present in patients with AIH [13, 14] an overlap syndrome to PBC should be considered [15]. However, these autoantibodies are not specific to AIH and may be found in various liver diseases. It remains unclear whether they play a role in the pathogenesis of AIH. Currently, there is little evidence that autoantibodies play a crucial role in the development of the disease.

Depending on the antibody profile AIH may be differentiated into two types. Type 1, associated with HLA-DR3 and -DR4 is characterized by ANA and SMA and encompasses around 90% of all cases, while type 2, associated with HLA-DR3, -C4A-QO and -B14, displays LKM1 antibodies. While the distinction was originally made solely on the basis of antibodies, clinical differences have been proposed over time. Overall, AIH type 2 supposedly mostly affects juveniles and children, has a more severe and acute course of disease and frequent relapses [16]. The clinical relevance of these sub-classifications is, however, the subject of an ongoing debate [17], especially for adults [18].

Another characteristic feature of AIH is an elevation of serum globulins, particularly a selective IgG elevation of 1.2 to 3 times the normal level [19]. The reason for the elevation remains unclear.

Histology of AIH shares similarities with other chronic forms of hepatitis. Some histological features are more typical and common in AIH, but none of these are specific to AIH (Fig.

1). The disease is generally characterized by a mononuclear cell infiltrate invading the limiting plate (periportal infiltrate, also called piecemeal necrosis or interface hepatitis that progresses to lobular hepatitis). There may be an abundance of plasma cells, a finding that in the past led to the use of the term "plasma-cell hepatitis." Eosinophils are frequently present. The portal lesion generally spares the biliary tree. In advanced disease, increasing liver fibrosis can be recognized, and with the distortion of the hepatic lobule and the appearance of regenerative nodules, it may progress to liver cirrhosis [20].

Autoimmune hepatitis might be associated with other autoimmune diseases. Autoimmune thyroiditis might be present in approximately 10% of AIH patients [21]. Other autoimmune diseases more frequently found in AIH patients include ulcerative colitis, type 1 diabetes, rheumatoid arthritis and celiac disease [21].

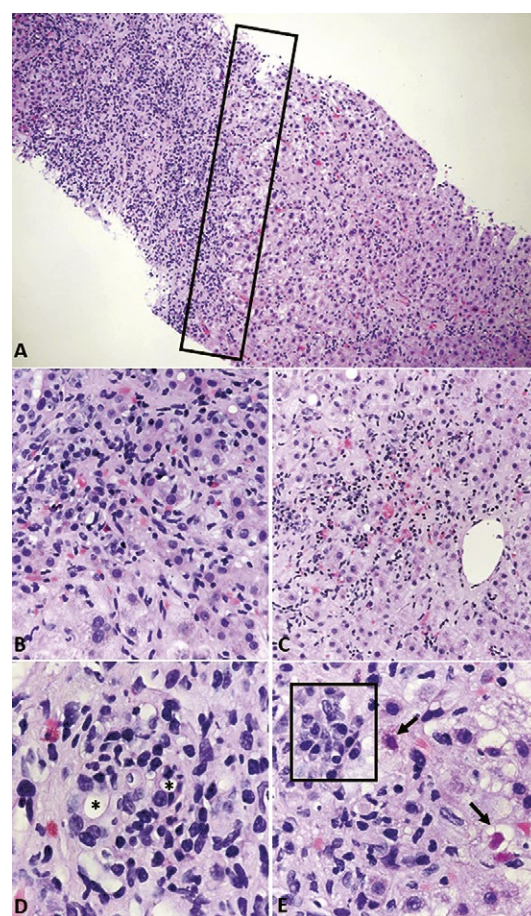


Fig. 1. Histology of a moderately active autoimmune hepatitis (AIH) H&E. (A, 100x) The inflammatory reaction is usually stronger within portal tracts (upper left) than in the liver acinus (bottom right) but seen in both areas. Interface hepatitis (boxed area): lymphocytes and plasma cells exit the portal tract and infiltrate into the liver parenchyma. (B, 400x) Interface hepatitis: infiltration of inflammatory cells from the portal tract (upper left) into the liver acinus. (C, 200x) Lobular (intracinar) hepatitis, close to a hepatic vein at the right. (D, 600x) Portal bile ducts (asterisks) involved in the inflammatory process of an AIH. However, if there is considerable cholangitis, the diagnosis of an overlap syndrome must be considered. (E, 600x) Apoptotic bodies and single cell apoptosis (arrow) are common features of viral, drug-induced and autoimmune hepatitis and do not help to distinguish these entities. Plasma cells (boxed area).

DIAGNOSIS

As AIH displays a considerable heterogeneity [1], no single clinical or biochemical test may securely diagnose it. An exception may be the presence of anti-SLA/LP autoantibodies.

In 1992, the International Autoimmune Hepatitis Group (IAIHG) recommended a scoring system for the diagnosis of AIH, which was further refined and updated in 1999 to its currently valid version [22]. Generally, the IAIHG scoring system offers high sensitivity ranging from 97.3 to 100%. Specificity remains lower with values ranging from 44 to 92%, depending on the most probable differential diagnosis. The revised scoring most notably improves specificity regarding differential diagnosis towards PSC from 65 to 90% [22].

However, as IAIHG scoring systems is time consuming in daily routine, shortened criteria consisting of only four relevant diagnostic parameters are used: IgG serum levels, autoantibody titers (ANA, SMA, SLA), histology and exclusion of viral hepatitis. The revised original scoring system performed better in patients with few or atypical features of AIH, and the simplified system (the Hennes criteria) was better at excluding the diagnosis in diseases with concurrent immune manifestations [23]. These findings were further validated in a large South American cohort reporting an AUROC for AIH simplified criteria of 0.976. Using a cutoff ≥ 6 and ≥ 7 points, the sensitivity was 86.4% and 54.6%; specificity 98.7% and 99.6%, respectively. Thus, overall the Hennes criteria certainly provide a valuable simplification for daily clinical practice [24].

OVERLAP SYNDROMES

Forms of AIH that share features with other putative autoimmune liver diseases such as PBC and PSC are common [15]. Overlap of AIH to PBC is observed in 4–14% [25], overlap to PSC in 2–8% [25–27]. These overlap syndromes are characterized by both elevated transaminases and cholestasis parameters and have histological features of both AIH and PBC or PSC. Standard diagnostic criteria for overlap syndromes of autoimmune liver disease are still lacking. Empiric treatment for patients with AIH-PBC overlap is immunosuppressive therapy plus ursodeoxycholic acid. Empiric treatment for patients with AIH-PSC overlap is immunosuppressive therapy with or without ursodeoxycholic acid. For patients suffering from AIH, the detection of overlap syndromes is important not only as they have a more progressive course towards cirrhosis and liver failure without adequate treatment but also as in some patients overlap-syndrome may be a reason for insufficient response to standard immunosuppression and in these cases addition of ursodeoxycholic acid may improve laboratory results, clinical symptoms and for AIH-PBC potentially also disease progression.

SURVEILLANCE

Long-term immunosuppressive therapy in patients with AIH is associated with several preventable adverse effects, with most of them following long-term steroid and/or azathioprine (AZA) regimens. After 2 years up to 80% of patients on cortisone-based treatment and 10% of patients on

AZA reported side effects [28]. Thus, these patients require long-term surveillance for efficacy of treatment but also close monitoring for the development of side effects. Cirrhotic patients require additional surveillance. The latest guidelines of both EASL and AASLD recommend the following surveillance procedure [29, 30]: (1) ultrasound every 6 months in all cirrhotic patients with AIH for HCC screening; hepatitis A and B vaccination, yearly influenza vaccination; pre-emptive antiviral treatment with nucleos(t)ide analogues for HBsAg-positive AIH patients during and 12 months after the end of immunosuppressive treatment; bone density measurement before initiation of steroid therapy as well as vitamin D and calcium intake supplement in all patients receiving steroids.

CURRENT STANDARD TREATMENT WITH CORTICOSTEROIDS AND AZATHIOPRINE

Treatment Goals

The ultimate goal of AIH treatment is disease remission and prevention of progression of liver damage, especially cirrhosis, hepatocellular carcinoma and the need for liver transplantation (Fig. 2). Biochemical remission, in particular normalization of transaminases and IgG, is widely accepted as a sufficient surrogate parameter for effective disease control. Histological remission is not routinely monitored in clinical practice but may be considered before withdrawal of therapy [30]. Generally, a complete withdrawal of therapy is intended, but often results in the recurrence of disease over time.

Untreated, mortality of severe AIH is high with mortality rates exceeding 50% within five years after diagnosis [10–12].

Prednisolone with and without azathioprine

In a landmark publication Kirk et al. [11] demonstrated a 5-year survival of 63% of patients treated with prednisolone in contrast to only 27% of patients surviving on placebo, respectively. This study introduced corticosteroids for treatment of AIH, and up to date they remain the most effective immunosuppressive drug to induce remission. Soon further additional immunosuppressant drugs, particularly AZA, were investigated for treatment of AIH. Azathioprine is converted into 6-mercaptopurine subsequently blocking purine metabolism and DNA synthesis. Soloway et al. [10] and Summerskill et al. [31] both showed that prednisolone/AZA-combination is equally as effective as a prednisolone monotherapy. With its well documented efficacy and steroid-sparing properties AZA at a dose of 1–1.5 mg/kg body weight has become a corner stone in immunosuppressant therapy for AIH.

Based on these initial studies, the American Association for the Study of Liver Diseases (AASLD) 2019 guidelines recommend a fixed starting dose of 40–60 mg/day prednisolone as a monotherapy or 20–40 mg/day in combination with 50–150 mg/day azathioprine [29]. Across Europe, prednisolone is usually administered at a starting dose of 1mg/kg body weight and almost always in combination with AZA at a maximum dose of 1–1.5 mg/kg/day. Long-term prednisolone monotherapy is not primarily recommended by guidelines of the European Association for the Study of the Liver

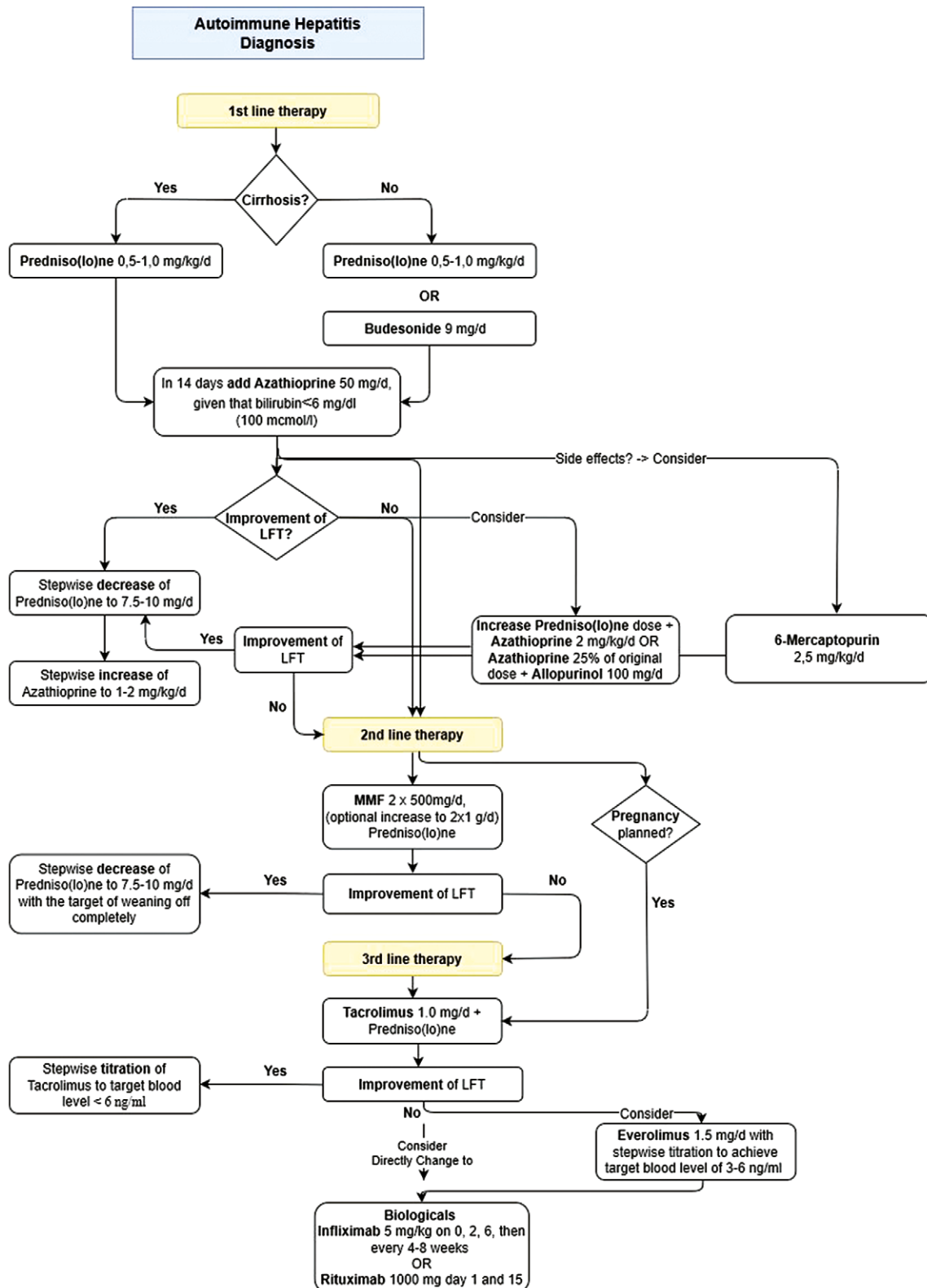


Fig. 2. Flowchart of AIH treatment.

(EASL) and the German Society for Digestive and Metabolic Diseases (DGVS) [30, 32]. However, AZA is added after two weeks of prednisolone to uncover possible hepatotoxicity of azathioprine [17] and separate this phenomenon from non-response to steroid based immunotherapy. In patients with high bilirubin or cholestasis, initiation of azathioprine should be delayed until bilirubin drops below 6 mg/dl [30].

Among specialized centers the optimal and necessary starting dose of prednisolone is still in debate. Recently, Purnak et al. [33] compared a starting dose of 40 mg/day to 30 mg/day, each in combination with azathioprine, and found earlier biochemical response and a lower mortality with comparable side effects in the group with the higher starting dose. However, with only 71 participants these results have to be treated with

precaution. In contrast Pape et al. [34] found in a retrospective study of 451 patients that a starting dose of more than 0.5 mg/kg/day prednisolone was not associated with a faster rate of normalization of transaminases, but a starting dose of less than 0.5 mg/kg/day substantially decreases unnecessary exposure to prednisolone. And while this data even affects current guidelines (e.g. 2019 AASLD guidelines recommend 40 to 60 mg of prednisolone for monotherapy in contrast to a fixed dose of 60 mg in the 2010 guidelines), a current metareview once again supported higher remission rates with higher starting doses of prednisolone [35].

Common practice and EASL guideline recommendation after initiation of prednisolone therapy is a quick and schematic tapering (e.g. reduction of 10 mg every week until 30mg/day, then reduction of 5 mg every week until 15mg/day, then 2.5 mg reduction every 2 weeks until 10 mg/day) of the initial prednisolone dose if transaminases remain decreasing [30]. In contrast, the AASLD guidelines recommend a slower tapering, with reductions of 2.5-5mg every 2-4 weeks between 20 mg/day and 10 mg/day and an overall tapering period of 6 months from start to 10 mg/day [29]. Reaching a dose of 7.5-10 mg/day, no controlled data exists on how fast prednisolone should be further reduced or completely weaned off. In our hands a rather slow reduction works better in terms of avoiding flairs-ups of the disease. The EASL guideline supports this notion by recommending a reduction of 2.5 mg every three to four months [30]. If steroids, even in marginal doses of 5 mg/day or below, are not favored, e.g. due to steroid-specific adverse events [36], several reports demonstrated that after successful induction, AZA alone may well be capable of maintaining remission [37].

An attempt of complete withdrawal of immunosuppressive therapy should, in our opinion, not be made before several years of therapy and complete normalization of liver enzymes. For most patients, reintroduction of immunosuppression is inevitable [38]. Some reports even state that patients should be in stable remission for at least four years before withdrawal of immunosuppressive therapy may be considered [38]. Since biochemical response and a clinical remission do not necessarily mean that there is histologic evidence of resolution of AIH, repeat liver biopsy should be considered.

Besides hepatotoxicity AZA has potential side effects, such as cytopenia, pancreatitis, nausea and increased risk for non-melanoma skin cancer. Thiopurine methyltransferase (TPMT) catalyzes conversion of metabolic active to inactive products within AZA metabolism and its deficiencies are linked to an increase in toxicity [39]. Current AASLD guidelines therefore recommend routine testing of TPMT status before therapy initiation, especially in a resource-rich setting [29]. However, routine testing is currently not implemented in many European centers.

Usually clinical and laboratory controls will suffice. Measurement of metabolites, such as 6-thioguanine nucleotide (6-TGN) or 6-methylmercaptopurine (6-MMP), may add further value. Their role in AIH therapy is however unclear. Neither AASLD or EASL do recommend routine testing of metabolites [29, 30].

Besides efficacy in treatment, early measures for management of steroid-associated adverse effects, such

as weight gain, Cushing's syndrome, diabetes mellitus, osteoporosis, high blood pressure, are highly important [40]. Osteoporosis prophylaxis should be performed with 800 to 1000 IU vitamin D3 per day accompanied by a daily calcium intake of at least 1000 mg.

Budesonide

Due to its high first pass metabolism, budesonide has been proposed to have favorable side effects in comparison to prednisolone. After several smaller studies had suggested an efficacy of budesonide in remission induction [41, 42], Manns et al. [43] published a large prospective and randomized cohort, comparing the efficacy of budesonide/azathioprine to standard prednisolone/azathioprine treatment. Budesonide treatment was initiated with 3x3 mg/day and subsequently reduced to 2x3 mg/day when patients reached clinical remission. Prednisolone was initiated with 40 mg/day and reduced to 10 mg/day in week nine by a fixed pattern. Azathioprine was administered in both groups at a dose of 1-2 mg/kg/day. Significantly more patients of the budesonide group reached the predefined primary endpoint of biochemical remission without steroid typical side effects (47% vs 18.4%, $p < 0.00001$). Furthermore, for secondary endpoints, especially overall biochemical remission after 6 months, budesonide was superior to prednisone (60% vs 38.8%, $p = 0.001$). Two main criticisms remain subject to controversial discussions since the publication of this data. Firstly, prednisolone starting dose was lower than commonly practiced in most European centers during that timeframe, and secondly, prednisolone was subject to a rigid reduction pattern, while budesonide was reduced depending on response to treatment. Both issues may explain a very low biochemical remission rate (38.8%) for prednisolone in this study, which seems unacceptably low compared to previous studies on prednisolone in AIH treatment.

A similar study by Woynarowski et al. [44], further supported equal treatment efficacy of budesonide in AIH, as the authors found no difference in either biochemical response, remission rates or side effects on budesonide in children. However, Peiseler et al. [45] recently reported 60 patients who were switched from prednisolone to budesonide for maintenance therapy due to steroid-associated side effects. Surprisingly long-term remission rates were lower than expected with 67% after 24 months. 25% of patients switched back to prednisolone due to insufficient response. Nevertheless, budesonide established itself as a first-line alternative to prednisolone in current guidelines, such as by the AASLD or DGVS [29, 32]. Budesonide was repeatedly associated with fewer steroid-specific side effects compared to prednisolone, namely osteopenia [45] and adrenal suppression [46].

On a final note, budesonide may not be administered to patients with cirrhosis. These patients have a higher rate of treatment failure and increase of systemic side effects potentially due to an altered metabolism and porto-systemic shunting as well as risk of hepatic vein thrombosis [46-48].

Evolving novel therapeutic options

Although standard treatment with prednisolone and AZA was implemented very successfully for treatment of AIH

over the past decades, some patients do not respond to these drugs or suffer from significant side effects. Those patients are in definite need for alternative, immunosuppressive treatment strategies. Over the past two decades many well-established immunosuppressive drugs were also evaluated in treatment of AIH, mainly in the form of small case series or case reports. However, together these data suggest high efficacy of these alternative treatments in AIH as well. Among these drugs are mycophenolate mofetil (MMF), tacrolimus (TAC) [49], everolimus (EVR), methotrexate (MTX) [50], 6-mercaptopurine (6-MP), infliximab, rituximab, cyclosporine, and many more (Table I).

Mycophenolate mofetil

A considerable number of patients with AIH and in need for immunosuppressant treatment tolerate AZA only poorly or do not respond efficiently or even fail to standard treatment [1]. Especially for patients intolerant to AZA, MMF may be a valuable alternative. It acts as an inhibitor of the inosine

monophosphate dehydrogenase, thereby inhibiting purine synthesis. It is widely used in several autoimmune diseases such as rheumatoid arthritis or Crohn's disease but also in solid organ transplantation.

Since an early case report publication of successful MMF treatment for AIH [51], several small cohorts particularly from Canada and the U.S. further supported a role of MMF in AIH treatment. Patients were reported to benefit from MMF with transaminases normalization, a steroid sparing effect and histological remission [52]. In addition, Inductivo-Yu et al. [53] also documented a decrease of Ishak fibrosis scores upon treatment with MMF.

Since then, larger cohorts further supported the use of MMF as second-line therapy of AIH. In 2008, Hennes et al. [2] provided data on 33 patients treated with MMF. In contrast to earlier studies, they observed a much lower frequency of response to MMF treatment as only 15 patients (45%) experienced biochemical remission. In subgroup analyses, they furthermore reported a high likelihood of non-response

Table I. Available drugs for treatment of AIH.

Drug	Dosing	Major/characteristic side effects*	Indication
Prednisolone	start 0.5-1 mg/kg/day	Adrenal suppression with iatrogenic Cushing's syndrome, weight gain, hyperglycemia, dyslipidemia, psychiatric symptoms, hypertonus, gastric ulcer, dermatitis, osteoporosis	first-line therapy mono or combination
Budesonide	start 9mg/day	Same as prednisolone, however reduced frequency due to increased first pass-metabolism, portal vein thrombosis in case of cirrhosis, do not use in patients with liver cirrhosis	alternative first-line therapy or in case of prednisolone-intolerance
Azathioprine	start 50mg/day, max. 1-2 mg/kg/day	Malignancy (lymphoproliferative, non-melanoma skin cancer), nausea, diarrhea, cytopenia, pancreatitis, hepatitis	first-line therapy (combination)
Mycophenolate mofetil	1,5-2g/day	Malignancy (lymphoproliferative, non-melanoma skin cancer), nausea, diarrhea, cytopenia, teratogenic	second-line therapy in case of azathioprine intolerance or first-line alternative to azathioprine
6-Mercaptopurine	1,5 mg/kg/day	Malignancy (lymphoproliferative, non-melanoma skin cancer), nausea, diarrhea, cytopenia, pancreatitis, hepatotoxicity, hyperuricemia	second-line alternative for azathioprine intolerance
6-Thioguanine	0,3 mg/kg/day	Portal vein hypertension, liver necrosis, nausea, diarrhea, cytopenia, pancreatitis, hyperuricemia	second-line alternative for azathioprine intolerance
Tacrolimus	2-6 mg/kg/day (target blood level around 6 ng/ml)	Malignancy (lymphoproliferative, non-melanoma skin cancer), nephrotoxicity, hirsutism, hepatotoxicity, nausea, cytopenia, hyperglycemia, cardiomyopathy	second-line therapy in case of azathioprine treatment failure
Sirolimus	2mg/day (target blood level > 10 ng/dl)	Malignancy (lymphoproliferative, non-melanoma skin cancer), nephrotoxicity, hepatotoxicity, nausea, cytopenia, hyperglycemia	alternative to tacrolimus in specialist center
Everolimus	0.75-1.5 mg/kg/day (target blood level around 3-6 ng/ml)	Malignancy (lymphoproliferative, non-melanoma skin cancer), nephrotoxicity, hirsutism, nausea, cytopenia, hyperglycemia, pneumonitis	alternative to tacrolimus in specialist center
Cyclosporin	2-5 mg/kg/day	Malignancy (lymphoproliferative, non-melanoma skin cancer), nephrotoxicity, hirsutism, hepatotoxicity, pancreatitis, nausea, cytopenia, hyperglycemia	alternative to tacrolimus in specialist center
Cyclophosphamide	1-1.5 mg/kg/day	Hemorrhagic cystitis, cytopenia, malignancy (bladder carcinoma, leukemia, myelodysplastic syndrome), neurotoxicity, cardiomyopathy, pneumonitis, nausea	third-line therapy in specialist center
Methotrexate	7.5mg/week	Malignancy (lymphoma), hepatotoxicity, cytopenia, pneumonitis	third-line therapy in specialist center
Rituximab	1000mg i.v. qw2	Infusion related reactions, cardiotoxicity, dermatitis	third-line therapy in specialist center
Infliximab	5mg/kg i.v. at day 0, week 2, week 6, then every 4-8 weeks	Infusion related reactions, cardiotoxicity, dermatitis, autoimmune-like syndromes (psoriasis, lupus, etc.)	third-line therapy in specialist center

*Increased risk of infections due to immunosuppression applies to all drugs mentioned and is not listed individually

to MMF treatment in patients with prior non-response to AZA. Jothamani et al. [53] found that 73.6% of patients (n=20) achieved biochemical remission over a median follow-up of 46 months, while two formerly AZA refractory patients were also non-responsive to MMF. More recently, Giannakopoulos et al. [55] reported a 45% long term remission rate for MMF in 22 patients failing AZA and prednisolone. Only 1 of 5 patients non-responsive to azathioprine responded to MMF. Finally, a recent meta-analysis performed by Santiago et al. [56] calculated response rates over 397 patients from twelve studies and found a pooled response rate of 0.82 (95%CI: 0.77-0.87) in patients, who received MMF second-line due to intolerance to standard therapy, versus 0.32 (95%CI: 0.24-0.39) among non-responders to standard therapy. Overall adverse events rate was only 0.14 (95%CI: 0.11-0.17) and discontinuation rate was even lower. In contrast, Roberts et al. [57] found no difference in rate of remission induction for 105 patients either non-responsive or intolerant to standard therapy in 17 major Australian liver centers. Side effects to MMF occurred in less than 10% of patients. Lower remission rates were noted in patients with cirrhosis. Subsequently, the same research group published a report stating 60% overall remission rate for second-line MMF usage and found age over 54 years and IgG-levels pre-treatment below 17 g/l to be positive predictors of successful therapy [58].

In conclusion, reported long term success rates of MMF as second-line treatment vary among studies, which may be due to small patient numbers. However, a majority of studies support MMF for second line treatment except for patients previously non-responsive to AZA (combination) treatment.

Of note, not all second-line therapies are similarly ineffective after non-response to standard therapy. Efe et al. [59] published a comparative study of MMF and TAC for second line therapy. They found no difference in remission rates between MMF and TAC for patients intolerant of AZA and prednisolone. A comparable study performed for pediatric patients showed similar results but failed to prove statistical significance for their findings [60].

Given the efficacy of MMF in at least the subgroup of patients experiencing side effects from AZA and given its favorable side effect profile compared to AZA in most patients the drug was repeatedly discussed to even be moved to first line treatment substituting AZA. This issue was explored by Zachou et al. in two studies published in 2016 and 2011 [61, 62]. These reports explored MMF as an alternative to AZA for first-line therapy in 109 patients; 71.6% achieved complete biochemical remission and 30 of 109 patients even maintained remission on a median two-year follow-up after complete therapy withdrawal. The numbers of initial biochemical remission are comparable to those of randomized controlled trials (RCTs) regarding AZA and prednisolone [31]. Relevant side effects were low (6.4%). Since these studies were observational, the use of MMF should be further evaluated in RCTs.

Purine analogues: 6-mercaptopurine and 6-thioguanine

Just as AZA, its metabolite 6-MP exhibits immunosuppressive activity by suppression of DNA and RNA synthesis via inhibition of purine nucleotide biosynthesis. Furthermore, 6-MP was suggested to down regulate B- and T-cell function.

While a small case series from 1996 shows response for three patients after a switch from AZA to 6-MP [63], Hübener et al. [64] evaluated whether 6-MP was an effective second-line therapy for patients with AIH on a larger cohort. Of 20 patients with AIH switched to 6-MP after treatment with standard therapy (AZA and prednisolone), 15 (75%) responded to 6-MP, the treatment being generally well tolerated. Eight patients had a complete biochemical response. Two patients with insufficient response to AZA did not benefit from 6-MP.

Similarly, 6-thioguanine (6-TG) offers an additional treatment options even more downstream in the metabolism of AZA and 6-MP, theoretically providing less possibilities for unwanted metabolites, partly responsible for adverse effects of purine analogue therapies. After a small case series consisting of three patients [65], van den Brand et al. [66] presented a cohort of 52 patients receiving 6-TG. Of 29 patients starting 6-TG due to intolerance to AZA or 6-MP, 24 (83%) achieved complete remission. In non-responders to AZA or 6-MP 7 out of 11 patients showed partial or complete response. Overall 79% of patients tolerated 6-TG. In addition, Legué et al. [67] reported maintained biological response in 11 of 17 patients (64%) and overall low rate of adverse events.

In summary, both 6-MP and 6-TG may be effective alternatives in patients intolerant to standard therapy (AZA and prednisolone). Both drugs however are not considered first choice in patients non-responsive to AZA.

Interestingly, modulation of AZA metabolism to reduce side effects through co-administration of allopurinol was suggested and reported in small case series [68-72]. As side effects by this co-medication may be rather mild, this combinatory therapy should be further evaluated in RCTs.

Cyclosporine

Cyclosporine inhibits intracellular calcineurin. Subsequently this results in a lack of ability to dephosphorylate nuclear factor of activated T cells, which then remains in the cytoplasm and is unable to transactivate nuclear genes involved in T-cell activation [73]. Since the 1990s several case reports and case series have been published regarding treatment of AIH with cyclosporine, at 2-5 mg/kg [74-76]. Most featuring single-digit patients as second-line therapy with variable dose, follow-up and treatment duration. Overall, the results were positive.

A recent report of second line and third-line usage of cyclosporine or TAC assessed a 55% biochemical response rate [77]. A RCT in adults [78], concluded that prednisolone and cyclosporine were equally effective for inducing remission in a 48-week observation period, while side effects were less common in the cyclosporine group. Unfortunately, the standard regime with prednisolone did not meet current standards of induction therapy with prednisolone and AZA (starting dose of 50 mg prednisolone, reduction of 10mg/day every 4 weeks on average, adding AZA at 20mg/day of prednisolone).

Larger studies exist on children and adolescents, though mostly observational. Alvarez et al. [79] and Cuarterolo et al. [80] observed remission induction rates well above 90%. Long-term results after the switch to prednisolone/azathioprine maintenance therapy were promising as well and adverse events

were rare. A recent long-term follow-up study from Nastasio et al. [81] with 20 patients on long-term cyclosporine treatment concluded overall effective and safe treatment within a median 8.6-year follow-up.

It has to be kept in mind, that cyclosporine itself may exhibit liver toxicity as reported by a case series on de-novo, cyclosporine-induced autoimmune hepatitis in paediatric patients after liver transplantation [82]. In the long term, tapering cyclosporin seems to have a low success rate, though a switch to prednisolone/AZA for maintenance was repeatedly and successfully reported in children [30, 80, 83].

Tacrolimus

Just as cyclosporine, TAC inhibits intracellular calcineurin activity, ultimately leading to a lack of T-cell activation [73]. Several smaller cohorts of up to 21 patients state a generally good response to TAC, between 69 and 100% of patients [49, 84-89]. Aql et al. [85] reported follow-up liver biopsies in 7 patients, demonstrating improvement of necroinflammatory activity score in all and fibrosis score in 3 patients. In addition, TAC treatment resulted not only in normalization of transaminases in all 11 patients, but also in a weight reduction of 9% ($p=0.02$), most likely due to prednisolone reduction. On the downside, Van Thiel et al. [49] reported reduction of kidney function after one year on TAC. Although others did not confirm those data in a small cohort [85], kidney failure on TAC is a well-documented side effect after solid organ transplantation [90].

Having proven itself as a potent immunosuppressive agent in AIH patients, TAC does not prevent post transplantation AIH. Tacrolimus in liver transplant recipients was associated with histologically proven AIH recurrence in 42% of patients ($n=12$), all of whom received TAC as the primary immunosuppressive drug [84].

Efe et al. [59] published a large cohort of patients treated with either MMF or TAC as second-line treatment in patients with AIH and either non-response or intolerance to standard therapy with prednisolone and AZA. Among 80 patients who had initially responded to standard treatment, 72.5% of those switched to TAC underwent complete biochemical response and 94.1% maintained a biochemical remission. If treatment was changed due to insufficient response to standard therapy, 56.5% of patients still had a complete response, significantly more compared to patients treated with MMF (34%) [59].

Dosing and therapeutic range varied in between the above-mentioned studies with doses ranging mostly from 2-6 mg/day and target blood levels hovering around 6 ng/ml.

Today, MMF must still be considered the most frequently applied second-line treatment for AIH [91]. However, the recent data by Efe et al. certainly support a broader use of TAC in AIH [60].

Everolimus

Everolimus was developed as a rapamycin analogue. Binding the FK binding protein complex (FKBP-12), the drug forms a complex binding to mammalian target of rapamycin (mTOR), thereby altering further downstream signaling, with a significant impact on cellular metabolism, growth, and proliferation.

In a small cohort of seven patients [92] treated with EVR, all patients had a successful induction of remission and after one year, three patients had normal alanine transaminases levels, while two additional patients had at least improved liver enzymes (partial remission). Re-biopsy after three years showed regredient fibrosis in two and stable histology in additional two patients. One patient was excluded for non-adherence; one died due to cholangiocarcinoma. Side effects were myalgias and minor bacterial infections yet not leading to discontinuation of the drug. Everolimus was started with 0.75-1.5 mg/day, the target blood levels were between 3 and 6 ng/ml. Notably, all patients had been non-responsive to standard therapy as well as at least MMF or a calcineurin inhibitor or both for 5 patients, making EVR a credible candidate for rescue therapy in case of second-line therapy failure [92].

Sirolimus

Sirolimus shares high similarities in action with cyclosporine and TAC by inhibiting intracellular calcineurin [73]. Regarding adult AIH patients only one case series was published, including five steroid-refractory patients [93]. Two patients achieved complete and two achieved partial biochemical remission. However, histological control was not performed. The authors note that liver tests did not tend to improve until the blood levels of sirolimus exceeded 10 ng/dL. Side-effect profile was acceptable with one patient displaying high cholesterol and triglyceridemic levels. In addition, Kerkar et al. [94] published a first report of rapamycin (sirolimus) treatment in pediatric patients with post-transplant AIH. Out of 22 patients, 13 (59%) had developed de novo AIH and 9 (41%) recurrent disease, confirmed histologically. Six AZA/MMF non-responder patients were treated with sirolimus. All patients achieved reduction of liver tests, and 4 were able to normalize alanine aminotransferases. Out of a total of 6 patients, 3 developed adverse events (cellulitis, adenoviral illness, high cholesterol and triglyceridemic levels). Sirolimus was discontinued in one patient, suspected of post-transplant lymphoproliferative disease, in whom, however, the diagnosis was not confirmed during the one-year follow-up.

Methotrexate

Methotrexate has been widely used for the treatment of diverse autoimmune disease, but particularly rheumatoid arthritis. The mechanisms of action of MTX are not fully understood. Among potential mechanisms of action are inhibition of purine and pyrimidine synthesis but also suppression of transmethylation, reduction of antigen-dependent T-cell proliferation, and promotion of adenosine release with adenosine-mediated suppression of inflammation. It has recently been suggested that a combination of these mechanisms may be the key to its full immunosuppressant efficacy [95]. A successful use of MTX in treatment of AIH has been repeatedly reported since the late 1990s [50, 96, 97]. However, all of these reports only described successful treatment of single patients, including two pediatric cases [98]. Of note, single case reports documented that MTX itself may induce AIH after long-term therapy for other indications [99, 100]. Recently, a small cohort of 11 patients [101] with a response rate of only 54.5% was reported; 5 out of 11 patients discontinued MTX within 12 months due

to deterioration of liver enzymes, 2 out of these were suspected to have drug-induced liver injury. Therefore, in comparison to other second line options described above, efficacy of MTX in AIH seems rather low and this treatment option may not be pursued in larger studies. However, in difficulty to treat AIH and failure of alternative treatment options MTX may still be considered [101].

Cyclophosphamide

Cyclophosphamide is metabolized to phosphor amide mustard and acrolein, its active metabolites, through the cytochrome P-450 oxidase system in the liver. Phosphor amide mustard gets cross-linked to DNA, thereby interfering with regular cell division. The drug is thought to exhibit its immunosuppressive effects by deterioration of normal lymphocytes development and proliferation. Kanzler et al. [102] reported successful long-term management of AIH (cumulative observation period more than 12 years) in 3 patients, who received cyclophosphamide 1-1.5 mg/kg/d and prednisolone at a starting dose of 1 mg/kg/day. Prednisolone dose was tapered to 2.5-10 mg/day, which combined with 50 mg of cyclophosphamide on every other day permitted histologic remission. No severe adverse events or on-treatment flare of AIH was noticed [102].

Infliximab

Infliximab is a chimeric monoclonal antibody directed against tumor necrosis factor alpha (TNF- α). By forming stable complexes with both soluble or membrane bound TNF and the antibody may terminate the biological activity and signals of TNF, a key regulator in immune cell activation and migration via gene expression of chemokines, cytokines, and toxic molecules including reactive oxygen species. Developed in Crohn's disease and rheumatoid arthritis, the antibody has shown effectiveness and promising clinical results in diverse autoimmune diseases such as psoriasis, sarcoidosis, graft versus host disease and many others. In autoimmune liver disease, infliximab and other TNF- α inhibitors may have been used with caution in early years as infliximab itself was repeatedly documented to possess hepatotoxic potential. Indeed, there are many case reports of anti-TNF- α associated AIH with characteristic features (as well as toxic hepatitis [103]) in patients treated with infliximab [104-116], adalimumab [117-121] or etanercept [122, 123] for different indications. The underlying mechanism is not yet fully understood [124, 125]; however, cessation of therapy usually leads to improvement of liver function. Additionally, AIH and drug-induced liver injury may often be very similar in clinical and serological presentation and hard to differentiate [126, 127].

However, first case reports demonstrated feasibility and efficacy of this therapeutic option as a rescue-therapy in AIH.

Single case reports with and without comorbidities demonstrate improving liver enzymes under infliximab treatment in adult [128, 129] and pediatric patients [130] (as well as one report regarding etanercept [131]).

Recently, Weiler-Normann et al. [132] reported successful rescue treatment with infliximab in 11 difficult-to-treat AIH patients, of whom the majority failed to respond to MMF,

cyclophosphamide, cyclosporine, TAC and adalimumab [132]. In 3 patients infliximab was stopped, due to a flare-up under therapy, pneumonia and allergic reaction with incomplete response. Considering the severe course of the disease in these patients, previously treated with several consecutive immunosuppressive regimens, infliximab has shown a good response rate with an acceptable safety profile. In 2 patients long-term infliximab treatment for 3-10 years permitted sustained remission without losing drug efficacy or causing infectious complications. Furthermore, Nedelkopoulou et al. [133] reported improvement in liver function in 5 out of 8 children treated with infliximab for inflammatory bowel disease and concurrent AIH or AIH/PSC-overlap and no deterioration in the remaining 3. One study on etanercept in patients with both, rheumatic arthritis and AIH, reported biochemical and histological response in all 7 patients [134].

Considering the above mentioned, reports of anti-TNF- α -induced AIH, therapy should only be initiated with caution. Nevertheless, given the eligible patients are selected carefully and infliximab treatment is monitored closely, safety of anti-TNF agents seems acceptable to be considered as a rescue therapy for severe AIH cases.

Rituximab

Rituximab binds to CD20, a cell-surface antigen expressed on B cells. Upon binding, CD20 induces cytotoxicity in these cells the mechanism of which is not entirely known. It likely includes diverse mechanisms such as induction of apoptosis, complement-dependent cytotoxicity, or antibody-dependent cellular cytotoxicity. As a result, CD20 treatment leads to a depletion of B-cells and impairment of immune response making it a candidate drug for the treatment of diverse autoimmune diseases [135, 136].

In 2013, Burak et al. [137] reported a small case series of six patients who were either refractory to prednisolone plus AZA/MMF based therapy or did not tolerate either prednisolone or AZA and MMF combination therapy. After 24 weeks of anti-CD20 therapy transaminases and immunoglobulin G levels had significantly improved, indicating effectiveness of rituximab in these patients. Four patients underwent follow-up biopsy after 48 weeks and in all four histologic signs of inflammation grade was improved as well. Finally, the prednisolone dose was weaned in three of four subjects. However, one patient suffered from flaring disease after steroid withdrawal.

In addition, several single patient case reports exist. Two on adult AIH patients and two on pediatric patients, all of whom achieved biochemical remission by additional treatment with rituximab [138-140]. Furthermore, case reports of (adult) patients with concurrent AIH and primary disease of cryoglobulinemic glomerulonephritis, idiopathic thrombocytopenic purpura, Evans syndrome and B-cell-lymphoma exist, all of whom have been treated with rituximab for their primary disease, but reported a biochemical response of AIH as a positive side effect [141-145].

Overall, these very few patients (14 in total) do indicate a strong biochemical and histological effect of rituximab in AIH and certainly warrant a further case series and small clinical studies.

Chloroquine

The 2019 Terrabuio et al. [146] evaluated the use of chloroquine for remission maintenance after discontinuation of immunosuppressive therapy in a randomized, double-blind study against placebo. Once used for malaria treatment, it is now established in the treatment of rheumatic arthritis due to its immunomodulatory properties. Chloroquine in a dose of 250 mg/day led to a relapse-free survival in 59.3% of patients after weaning off prednisolone and AZA versus 19.9% in the placebo group. This research builds on a single pilot study from 2005 [147]. However, up to now there is no data comparing chloroquine to immunosuppressive therapy for maintenance of remission and side effects were frequent for chloroquine use. Regardless, chloroquine could be used as a substitute for immunosuppressants in long-term maintenance therapy in case of side effects due to the immunosuppressive attributes of standard therapeutics.

Other substances evaluated in AIH treatment

Many more therapies have successful treatment or remission maintenance published as single patient case reports, including intravenous immunoglobulin treatment [148], leukocytapheresis [149], sareito (a Japanese herbal medicine product) [150], fenofibrate [151] and dextroamphetamine [152]. Two studies, one case report and one small retrospective study, evaluated the use of deflazacort instead of prednisolone [153, 154]. Glycyrrhizin, an ingredient of licorice root inhibiting inactivation of corticosteroids, was evaluated in acute onset AIH and reported better recovery rates for glycyrrhizin in comparison to glycyrrhizin in combination with prednisolone [155].

A recent phase one study tested the safety of the synthetic preimplantation factor, an embryonic peptide promoting immunotolerance, but reported no data yet regarding therapeutic effects in AIH patients [156].

Most of these therapeutic strategies have no immunosuppressive effect, and some are even either very expensive or not available for standardized medical use. As many novel therapeutic options with growing and genuine underlying research show promising results in difficult-to-treat AIH, it is unlikely that these options will be further evaluated in near future. Regarding current evidence level, the therapeutic agents mentioned in this section cannot be recommended.

CONCLUSIONS

The overall prognosis of AIH is mostly determined by the response to immunosuppressive therapy. Overall, long-term survival and average life expectancy of patients with well treated AIH are excellent and estimated to be comparable to the normal population [157]. Thus, consistent therapy is critical. Several second line treatment options, MMF, TAC, but also biologicals have proven to be potent options if prednisolone and AZA fail to improve liver inflammation.

Unwanted side effects of medication are important with respect to compliance. Given the efficacy of numerous evolving therapeutic options, treatment selection based on expected side effect profiles may become more important and increase the patients' compliance with treatment. As most available studies

contain limited patient numbers, the challenge remains to merge worldwide efforts on small case series into large RCTs on second line treatment but also on treatment sequences.

Conflicts of interest: None to declare.

Authors' contribution: S.B., K.Y. and A.T.: conceived of the manuscript; S.B., K.Y., C.A., J.A., M.Evert. data/publications research; S.B., A.T., M.Evert, M.Ebert. data interpretation; S.B., K.Y., A.T. reviewed the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

REFERENCES

1. Krawitt EL. Autoimmune hepatitis. *N Engl J Med* 2006;354:54-66. doi:[10.1056/NEJMra050408](https://doi.org/10.1056/NEJMra050408)
2. Hennes EM, Oo YH, Schramm C, et al. Mycophenolate mofetil as second line therapy in autoimmune hepatitis? *Am J Gastroenterol* 2008;103:3063-3070.
3. Czaja AJ. Global Disparities and Their Implications in the Occurrence and Outcome of Autoimmune Hepatitis. *Dig Dis Sci* 2017;62:2277-2292. doi:[10.1007/s10620-017-4675-y](https://doi.org/10.1007/s10620-017-4675-y)
4. Ngu JH, Bechly K, Chapman BA, et al. Population-based epidemiology study of autoimmune hepatitis: a disease of older women? *J Gastroenterol Hepatol* 2010;25:1681-1686. doi:[10.1111/j.1440-1746.2010.06384.x](https://doi.org/10.1111/j.1440-1746.2010.06384.x)
5. van Gerven NM, Verwer BJ, Witte BI, et al. Epidemiology and clinical characteristics of autoimmune hepatitis in the Netherlands. *Scand J Gastroenterol* 2014;49:1245-1254. doi:[10.3109/00365521.2014.946083](https://doi.org/10.3109/00365521.2014.946083)
6. Boberg KM, Aadland E, Jahnsen J, Raknerud N, Stiris M, Bell H. Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. *Scand J Gastroenterol* 1998;33:99-103. doi:[10.1080/00365529850166284](https://doi.org/10.1080/00365529850166284)
7. Gronbaek L, Vilstrup H, Jepsen P. Autoimmune hepatitis in Denmark: incidence, prevalence, prognosis, and causes of death. A nationwide registry-based cohort study. *J Hepatol* 2014;60:612-617. doi:[10.1016/j.jhep.2013.10.020](https://doi.org/10.1016/j.jhep.2013.10.020)
8. Werner M, Prytz H, Ohlsson B, et al. Epidemiology and the initial presentation of autoimmune hepatitis in Sweden: a nationwide study. *Scand J Gastroenterol* 2008;43:1232-1240. doi:[10.1080/00365520802130183](https://doi.org/10.1080/00365520802130183)
9. Czaja AJ. Variant forms of autoimmune hepatitis. *Curr Gastroenterol Rep* 1999;1:63-70. doi:[10.1007/s11894-999-0089-0](https://doi.org/10.1007/s11894-999-0089-0)
10. Soloway RD, Summerskill WH, Baggenstoss AH, et al. Clinical, biochemical, and histological remission of severe chronic active liver disease: a controlled study of treatments and early prognosis. *Gastroenterology* 1972;63:820-833.
11. Kirk AP, Jain S, Pocock S, Thomas HC, Sherlock S. Late results of the Royal Free Hospital prospective controlled trial of prednisolone therapy in hepatitis B surface antigen negative chronic active hepatitis. *Gut* 1980;21:78-83. doi:[10.1136/gut.21.1.78](https://doi.org/10.1136/gut.21.1.78)
12. Cook GC, Mulligan R, Sherlock S. Controlled prospective trial of corticosteroid therapy in active chronic hepatitis. *Q J Med* 1971;40:159-85. doi:[10.1093/oxfordjournals.qjmed.a067264](https://doi.org/10.1093/oxfordjournals.qjmed.a067264)
13. Kanzler S, Weidemann C, Gerken G, et al. Clinical significance of autoantibodies to soluble liver antigen in autoimmune hepatitis. *J Hepatol* 1999;31:635-640. doi:[10.1016/s0168-8278\(99\)80342-0](https://doi.org/10.1016/s0168-8278(99)80342-0)

14. Herkel J, Lohse AW. Significance of autoantibodies. *Hepatology* 2008;47:786-788. doi:[10.1002/hep.22271](https://doi.org/10.1002/hep.22271)
15. Lohse AW, zum Buschenfelde KH, Franz B, Kanzler S, Gerken G, Dienes HP. Characterization of the overlap syndrome of primary biliary cirrhosis (PBC) and autoimmune hepatitis: evidence for it being a hepatic form of PBC in genetically susceptible individuals. *Hepatology* 1999;29:1078-1084. doi:[10.1002/hep.510290409](https://doi.org/10.1002/hep.510290409)
16. Czaja AJ, Manns MP. The validity and importance of subtypes in autoimmune hepatitis: a point of view. *Am J Gastroenterol* 1995;90:1206-1211.
17. Lohse AW, Mieli-Vergani G. Autoimmune hepatitis. *J Hepatol* 2011;55:171-182. doi:[10.1016/j.jhep.2010.12.012](https://doi.org/10.1016/j.jhep.2010.12.012)
18. Muratori P, Lalanne C, Fabbri A, Cassani F, Lenzi M, Muratori L. Type 1 and type 2 autoimmune hepatitis in adults share the same clinical phenotype. *Aliment Pharmacol Ther* 2015;41:1281-1287. doi:[10.1111/apt.13210](https://doi.org/10.1111/apt.13210)
19. Fallatah HI, Akbar HO. Elevated serum immunoglobulin G levels in patients with chronic liver disease in comparison to patients with autoimmune hepatitis. *Libyan J Med* 2010 Jan 25;5. doi:[10.3402/ljm.v5i0.4857](https://doi.org/10.3402/ljm.v5i0.4857)
20. Pratt DS, Fawaz KA, Rabson A, Dellelis R, Kaplan MM. A novel histological lesion in glucocorticoid-responsive chronic hepatitis. *Gastroenterology* 1997;113:664-668. doi:[10.1053/gast.1997.v113.pm9247489](https://doi.org/10.1053/gast.1997.v113.pm9247489)
21. Teufel A, Weinmann A, Kahaly GJ, et al. Concurrent autoimmune diseases in patients with autoimmune hepatitis. *J Clin Gastroenterol* 2010;44:208-213. doi:[10.1097/MCG.0b013e3181c74e0d](https://doi.org/10.1097/MCG.0b013e3181c74e0d)
22. Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol* 1999;31:929-938. doi:[10.1016/s0168-8278\(99\)80297-9](https://doi.org/10.1016/s0168-8278(99)80297-9)
23. Czaja AJ. Performance parameters of the diagnostic scoring systems for autoimmune hepatitis. *Hepatology* 2008;48:1540-1548. doi:[10.1002/hep.22513](https://doi.org/10.1002/hep.22513)
24. Candia R, Norero B, Aguero C, et al. Validation of the Simplified Criteria for the Diagnosis of Autoimmune Hepatitis in Chilean-Hispanic Patients. *Ann Hepatol* 2017;16:772-779. doi:[10.5604/01.3001.0010.2787](https://doi.org/10.5604/01.3001.0010.2787)
25. Boberg KM, Chapman RW, Hirschfield GM, et al. Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. *J Hepatol* 2011;54:374-385. doi:[10.1016/j.jhep.2010.09.002](https://doi.org/10.1016/j.jhep.2010.09.002)
26. Abdalian R, Dhar P, Jhaveri K, Haider M, Guindi M, Heathcote EJ. Prevalence of sclerosing cholangitis in adults with autoimmune hepatitis: evaluating the role of routine magnetic resonance imaging. *Hepatology* 2008;47:949-957. doi:[10.1002/hep.22073](https://doi.org/10.1002/hep.22073)
27. Lewin M, Vilgrain V, Ozenne V, et al. Prevalence of sclerosing cholangitis in adults with autoimmune hepatitis: a prospective magnetic resonance imaging and histological study. *Hepatology* 2009;50:528-537. doi:[10.1002/hep.23024](https://doi.org/10.1002/hep.23024)
28. Czaja AJ. Safety issues in the management of autoimmune hepatitis. *Expert Opin Drug Saf* 2008;7:319-333. doi:[10.1517/14740338.7.3.319](https://doi.org/10.1517/14740338.7.3.319)
29. Mack CL, Adams D, Assis DN, 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* 2019 Dec 21. doi:[10.1002/hep.31065](https://doi.org/10.1002/hep.31065)
30. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. *J Hepatol* 2015;63:971-1004. doi:[10.1016/j.jhep.2015.06.030](https://doi.org/10.1016/j.jhep.2015.06.030)
31. Summerskill WH, Korman MG, Ammon HV, Baggenstoss AH. Prednisone for chronic active liver disease: dose titration, standard dose, and combination with azathioprine compared. *Gut* 1975;16:876-883. doi:[10.1136/gut.16.11.876](https://doi.org/10.1136/gut.16.11.876)
32. Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) (federführend); Deutsche Gesellschaft für Innere Medizin (DGIM); et al. Practice guideline autoimmune liver diseases - AWMF-Reg. No. 021-27. *Z Gastroenterol* 2017;55:1135-1226. doi:[10.1055/s-0043-120199](https://doi.org/10.1055/s-0043-120199)
33. Purnak T, Efe C, Kav T, Wahlin S, Ozaslan E. Treatment Response and Outcome with Two Different Prednisolone Regimens in Autoimmune Hepatitis. *Dig Dis Sci* 2017;62:2900-2907. doi:[10.1007/s10620-017-4728-2](https://doi.org/10.1007/s10620-017-4728-2)
34. Pape S, Gevers TJG, Belias M, et al. Prednisolone Dosage and Chance of Remission in Patients With Autoimmune Hepatitis. *Clin Gastroenterol Hepatol* 2019;17:2068-2075 e2. doi:[10.1016/j.cgh.2018.12.035](https://doi.org/10.1016/j.cgh.2018.12.035)
35. Zhang C, Wu SS, Dong XQ, Wu Z, Zhao H, Wang GQ. The efficacy and safety of different doses of glucocorticoid for autoimmune hepatitis: A systematic review and meta-analysis. *Medicine (Baltimore)* 2019;98:e18313. doi:[10.1097/MD.00000000000018313](https://doi.org/10.1097/MD.00000000000018313)
36. van den Brand FF, van der Veen KS, Lissenberg-Witte BI, et al. Adverse events related to low dose corticosteroids in autoimmune hepatitis. *Aliment Pharmacol Ther* 2019;50:1120-1126. doi:[10.1111/apt.15528](https://doi.org/10.1111/apt.15528)
37. Stellon AJ, Keating JJ, Johnson PJ, McFarlane IG, Williams R. Maintenance of remission in autoimmune chronic active hepatitis with azathioprine after corticosteroid withdrawal. *Hepatol* 1988;8:781-784. doi:[10.1002/hep.1840080414](https://doi.org/10.1002/hep.1840080414)
38. Kanzler S, Gerken G, Lohr H, Galle PR, Meyer zum Buschenfelde KH, Lohse AW. Duration of immunosuppressive therapy in autoimmune hepatitis. *J Hepatol* 2001;34:354-355. doi:[10.1016/s0168-8278\(00\)00095-7](https://doi.org/10.1016/s0168-8278(00)00095-7)
39. Langley PG, Underhill J, Tredger JM, Norris S, McFarlane IG. Thiopurine methyltransferase phenotype and genotype in relation to azathioprine therapy in autoimmune hepatitis. *J Hepatol* 2002;37:441-447. doi:[10.1016/s0168-8278\(02\)00214-3](https://doi.org/10.1016/s0168-8278(02)00214-3)
40. Hartl J, Ehlken H, Weiler-Normann C, et al. Patient selection based on treatment duration and liver biochemistry increases success rates after treatment withdrawal in autoimmune hepatitis. *J Hepatol* 2015;62:642-646. doi:[10.1016/j.jhep.2014.10.018](https://doi.org/10.1016/j.jhep.2014.10.018)
41. Wiegand J, Schuler A, Kanzler S, et al. Budesonide in previously untreated autoimmune hepatitis. *Liver Int* 2005;25:927-934. doi:[10.1111/j.1478-3231.2005.01122.x](https://doi.org/10.1111/j.1478-3231.2005.01122.x)
42. Danielsson A, Prytz H. Oral budesonide for treatment of autoimmune chronic active hepatitis. *Aliment Pharmacol Ther* 1994;8:585-590. doi:[10.1111/j.1365-2036.1994.tb00334.x](https://doi.org/10.1111/j.1365-2036.1994.tb00334.x)
43. Manns MP, Woynarowski M, Kreisel W, et al. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. *Gastroenterology* 2010;139:1198-1206. doi:[10.1053/j.gastro.2010.06.046](https://doi.org/10.1053/j.gastro.2010.06.046)
44. Woynarowski M, Nemeth A, Baruch Y, et al. Budesonide versus prednisone with azathioprine for the treatment of autoimmune hepatitis in children and adolescents. *J Pediatr* 2013;163:1347-1353. e1. doi:[10.1016/j.jpeds.2013.05.042](https://doi.org/10.1016/j.jpeds.2013.05.042)
45. Peiseler M, Liebscher T, Sebode M, et al. Efficacy and Limitations of Budesonide as a Second-Line Treatment for Patients With Autoimmune Hepatitis. *Clin Gastroenterol Hepatol* 2018;16:260-267. e1. doi:[10.1016/j.cgh.2016.12.040](https://doi.org/10.1016/j.cgh.2016.12.040)
46. Miehle S, Acosta MB, Bouma G, et al. Oral budesonide in gastrointestinal and liver disease: A practical guide for the clinician. *J Gastroenterol Hepatol* 2018;33:1574-1581. doi:[10.1111/jgh.14151](https://doi.org/10.1111/jgh.14151)
47. Geier A, Gartung C, Dietrich CG, Wasmuth HE, Reinartz P, Matern S. Side effects of budesonide in liver cirrhosis due to chronic autoimmune

- hepatitis: influence of hepatic metabolism versus portosystemic shunts on a patient complicated with HCC. *World J Gastroenterol* 2003;9:2681-2685. doi:[10.3748/wjg.v9.i12.2681](https://doi.org/10.3748/wjg.v9.i12.2681)
48. Efe C, Ozaslan E, Kav T, et al. Liver fibrosis may reduce the efficacy of budesonide in the treatment of autoimmune hepatitis and overlap syndrome. *Autoimmun Rev* 2012;11:330-334. doi:[10.1016/j.autrev.2011.09.006](https://doi.org/10.1016/j.autrev.2011.09.006)
 49. Van Thiel DH, Wright H, Carroll P, et al. Tacrolimus: a potential new treatment for autoimmune chronic active hepatitis: results of an open-label preliminary trial. *Am J Gastroenterol* 1995;90:771-776.
 50. Burak KW, Urbanski SJ, Swain MG. Successful treatment of refractory type I autoimmune hepatitis with methotrexate. *J Hepatol* 1998;29:990-993. doi:[10.1016/s0168-8278\(98\)80128-1](https://doi.org/10.1016/s0168-8278(98)80128-1)
 51. Schuppan D, Herold C, Strobel D, Schneider HT, Hahn EG. Successful treatment of therapy-refractory autoimmune hepatitis with mycophenolate mofetil. *Hepatology* 1998;28:A1960.
 52. Devlin SM, Swain MG, Urbanski SJ, Burak KW. Mycophenolate mofetil for the treatment of autoimmune hepatitis in patients refractory to standard therapy. *Can J Gastroenterol* 2004;18:321-326. doi:[10.1155/2004/504591](https://doi.org/10.1155/2004/504591)
 53. Inductivo-Yu I, Adams A, Gish RG, et al. Mycophenolate mofetil in autoimmune hepatitis patients not responsive or intolerant to standard immunosuppressive therapy. *Clin Gastroenterol Hepatol* 2007;5:799-802. doi:[10.1016/j.cgh.2007.02.030](https://doi.org/10.1016/j.cgh.2007.02.030)
 54. Jothimani D, Cramp ME, Cross TJ. Role of mycophenolate mofetil for the treatment of autoimmune hepatitis-an observational study. *J Clin Exp Hepatol* 2014;4:221-25. doi:[10.1016/j.jceh.2014.05.003](https://doi.org/10.1016/j.jceh.2014.05.003)
 55. Giannakopoulos G, Verbaan H, Friis-Liby IL, et al. Mycophenolate mofetil treatment in patients with autoimmune hepatitis failing standard therapy with prednisolone and azathioprine. *Dig Liver Dis* 2019;51:253-257. doi:[10.1016/j.dld.2018.10.004](https://doi.org/10.1016/j.dld.2018.10.004)
 56. 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;49:830-839. doi:[10.1111/apt.15157](https://doi.org/10.1111/apt.15157)
 57. Roberts SK, Lim R, Strasser S, et al. Efficacy and Safety of Mycophenolate Mofetil in Patients With Autoimmune Hepatitis and Suboptimal Outcomes After Standard Therapy. *Clin Gastroenterol Hepatol* 2018;16:268-277. doi:[10.1016/j.cgh.2017.09.063](https://doi.org/10.1016/j.cgh.2017.09.063)
 58. Nicoll AJ, Roberts SK, Lim R, et al. Beneficial response to mycophenolate mofetil by patients with autoimmune hepatitis who have failed standard therapy, is predicted by older age and lower immunoglobulin G and INR levels. *Aliment Pharmacol Ther* 2019;49:1314-1322. doi:[10.1111/apt.15248](https://doi.org/10.1111/apt.15248)
 59. Efe C, Hagstrom H, Ytting H, et al. Efficacy and Safety of Mycophenolate Mofetil and Tacrolimus as Second-line Therapy for Patients With Autoimmune Hepatitis. *Clin Gastroenterol Hepatol* 2017;15:1950-1956. e1. doi:[10.1016/j.cgh.2017.06.001](https://doi.org/10.1016/j.cgh.2017.06.001)
 60. Efe C, Taii HA, Ytting H, et al. Tacrolimus and Mycophenolate Mofetil as Second-Line Therapies for Pediatric Patients with Autoimmune Hepatitis. *Dig Dis Sci* 2018;63:1348-1354. doi:[10.1007/s10620-018-5011-x](https://doi.org/10.1007/s10620-018-5011-x)
 61. Zachou K, Gatselis NK, Arvaniti P, et al. A real-world study focused on the long-term efficacy of mycophenolate mofetil as first-line treatment of autoimmune hepatitis. *Aliment Pharmacol Ther* 2016;43:1035-1047. doi:[10.1111/apt.13584](https://doi.org/10.1111/apt.13584)
 62. Zachou K, Gatselis N, Papadamou G, Rigopoulou EI, Dalekos GN. Mycophenolate for the treatment of autoimmune hepatitis: prospective assessment of its efficacy and safety for induction and maintenance of remission in a large cohort of treatment-naïve patients. *J Hepatol* 2011;55:636-646. doi:[10.1016/j.jhep.2010.12.032](https://doi.org/10.1016/j.jhep.2010.12.032)
 63. Pratt DS, Flavin DP, Kaplan MM. The successful treatment of autoimmune hepatitis with 6-mercaptopurine after failure with azathioprine. *Gastroenterology* 1996;110:271-274. doi:[10.1053/gast.1996.v110.pm8536867](https://doi.org/10.1053/gast.1996.v110.pm8536867)
 64. Hubener S, Oo YH, Than NN, et al. Efficacy of 6-Mercaptopurine as Second-Line Treatment for Patients With Autoimmune Hepatitis and Azathioprine Intolerance. *Clin Gastroenterol Hepatol* 2016;14:445-453. doi:[10.1016/j.cgh.2015.09.037](https://doi.org/10.1016/j.cgh.2015.09.037)
 65. de Boer NK, van Nieuwkerk CM, Aparicio Pages MN, de Boer SY, Derijks LJ, Mulder CJ. Promising treatment of autoimmune hepatitis with 6-thioguanine after adverse events on azathioprine. *Eur J Gastroenterol Hepatol* 2005;17:457-461. doi:[10.1097/00042737-200504000-00012](https://doi.org/10.1097/00042737-200504000-00012)
 66. van den Brand FE, van Nieuwkerk CMJ, Verwer BJ, et al. Biochemical efficacy of tioguanine in autoimmune hepatitis: a retrospective review of practice in the Netherlands. *Aliment Pharmacol Ther* 2018;48:761-767. doi:[10.1111/apt.14939](https://doi.org/10.1111/apt.14939)
 67. Legue C, Legros L, Kammerer-Jacquet S, et al. Safety and Efficacy of 6-thioguanine as a Second-line Treatment for Autoimmune Hepatitis. *Clin Gastroenterol Hepatol* 2018;16:290-291. doi:[10.1016/j.cgh.2017.07.032](https://doi.org/10.1016/j.cgh.2017.07.032)
 68. Bolia R, Rajanayagam J, Hardikar W. Lower 6-MMP/6-TG Ratio May Be a Therapeutic Target in Pediatric Autoimmune Hepatitis. *J Pediatr Gastroenterol Nutr* 2018;67:695-700. doi:[10.1097/MPG.0000000000002146](https://doi.org/10.1097/MPG.0000000000002146)
 69. Al-Shamma S, Eross B, McLaughlin S. Use of a xanthine oxidase inhibitor in autoimmune hepatitis. *Hepatology* 2013;57:1281-1282. doi:[10.1002/hep.26198](https://doi.org/10.1002/hep.26198)
 70. Guedes ALV, Andrade AR, Nunes VS, et al. Histological remission of autoimmune hepatitis after the addition of allopurinol and azathioprine dose reduction. *Autops Case Rep* 2017;7:35-42. doi:[10.4322/acr.2017.021](https://doi.org/10.4322/acr.2017.021)
 71. Deswal S, Srivastava A. Role of Allopurinol in Optimizing Thiopurine Therapy in Patients with Autoimmune Hepatitis: A Review. *J Clin Exp Hepatol* 2017;7:55-62. doi:[10.1016/j.jceh.2017.01.115](https://doi.org/10.1016/j.jceh.2017.01.115)
 72. de Boer YS, van Gerven NMF, de Boer NKH, Mulder CJJ, Bouma G, van Nieuwkerk CMJ. Allopurinol safely and effectively optimises thiopurine metabolites in patients with autoimmune hepatitis. *Aliment Pharmacol Ther* 2013;37:640-646. doi:[10.1111/apt.12223](https://doi.org/10.1111/apt.12223)
 73. Reynolds NJ, Al-Daraji WI. Calcineurin inhibitors and sirolimus: mechanisms of action and applications in dermatology. *Clin Exp Dermatol* 2002;27:555-561. doi:[10.1046/j.1365-2230.2002.01148.x](https://doi.org/10.1046/j.1365-2230.2002.01148.x)
 74. Sherman KE, Narkewicz M, Pinto PC. Cyclosporine in the management of corticosteroid-resistant type I autoimmune chronic active hepatitis. *J Hepatol* 1994;21:1040-1047. doi:[10.1016/s0168-8278\(05\)80615-4](https://doi.org/10.1016/s0168-8278(05)80615-4)
 75. Fernandes NF, Redeker AG, Vierling JM, Villamil FG, Fong TL. Cyclosporine therapy in patients with steroid resistant autoimmune hepatitis. *Am J Gastroenterol* 1999;94:241-248.
 76. Malekzadeh R, Nasser-Moghaddam S, Kaviani MJ, Taheri H, Kamalian N, Sotoudeh M. Cyclosporin A is a promising alternative to corticosteroids in autoimmune hepatitis. *Dig Dis Sc* 2001;46:1321-1327. doi:[10.1023/a:1010683817344](https://doi.org/10.1023/a:1010683817344)
 77. Pape S, Nevens F, Verslype C, Mertens C, Drenth JPH, Tjwa ETT. Profiling the patient with autoimmune hepatitis on calcineurin inhibitors: a real-world-experience. *Eur J Gastroenterol Hepatol* 2020;32:727-732. doi:[10.1097/MEG.0000000000001580](https://doi.org/10.1097/MEG.0000000000001580)

78. Nasseri-Moghaddam S, Nikfam S, Karimian S, Khashayar P, Malekzadeh R. Cyclosporine-A Versus Prednisolone for Induction of Remission in Auto-immune Hepatitis: Interim Analysis Report of a Randomized Controlled Trial. *Middle East J Dig Dis* 2013;5:193-200.
79. Alvarez F, Ciocca M, Canero-Velasco C, et al. Short-term cyclosporine induces a remission of autoimmune hepatitis in children. *J Hepatol* 1999;30:222-227. doi:[10.1016/s0168-8278\(99\)80065-8](https://doi.org/10.1016/s0168-8278(99)80065-8)
80. Cuarterolo M, Ciocca M, Velasco CC, et al. Follow-up of children with autoimmune hepatitis treated with cyclosporine. *J Pediatr Gastroenterol Nutr* 2006;43:635-639. doi:[10.1097/01.mpg.0000235975.75120.38](https://doi.org/10.1097/01.mpg.0000235975.75120.38)
81. Nastasio S, Sciveres M, Matarazzo L, et al. Long-term follow-up of children and young adults with autoimmune hepatitis treated with cyclosporine. *Dig Liver Dis* 2019;51:712-718. doi:[10.1016/j.dld.2018.10.018](https://doi.org/10.1016/j.dld.2018.10.018)
82. Damoiseaux JG, van Breda Vriesman PJ. Cyclosporin A-induced autoimmunity: the result of defective de novo T-cell development. *Folia Biol (Praha)* 1998;44:1-9.
83. Franulovic OZ, Rajacic N, Lesar T, Kuna AT, Moric BV. Cyclosporine induced biochemical remission in childhood autoimmune hepatitis. *Coll Antropol* 2012;36:973-979.
84. Ayata G, Gordon FD, Lewis WD, et al. Liver transplantation for autoimmune hepatitis: A long-term pathologic study. *Hepatology* 2000;32:185-192. doi:[10.1053/jhep.2000.9077](https://doi.org/10.1053/jhep.2000.9077)
85. Aql BA, Machicao V, Rosser B, Satyanarayana R, Harnois DM, Dickson RC. Efficacy of tacrolimus in the treatment of steroid refractory autoimmune hepatitis. *J Clin Gastroenterol* 2004;38:805-809. doi:[10.1097/01.mcg.0000139050.67178.be](https://doi.org/10.1097/01.mcg.0000139050.67178.be)
86. Chatur N, Ramji A, Bain VG, et al. Transplant immunosuppressive agents in non-transplant chronic autoimmune hepatitis: the Canadian association for the study of liver (CASL) experience with mycophenolate mofetil and tacrolimus. *Liver Int* 2005;25:723-727. doi:[10.1111/j.1478-3231.2005.01107.x](https://doi.org/10.1111/j.1478-3231.2005.01107.x)
87. Tannous MM, Cheng J, Muniyappa K, et al. Use of tacrolimus in the treatment of autoimmune hepatitis: a single centre experience. *Aliment Pharmacol Ther* 2011;34:405-407. doi:[10.1111/j.1365-2036.2011.04749.x](https://doi.org/10.1111/j.1365-2036.2011.04749.x)
88. Than NN, Wiegand C, Weiler-Normann C, et al. Long-term follow-up of patients with difficult to treat type 1 autoimmune hepatitis on Tacrolimus therapy. *Scand J Gastroenterol* 2016;51:329-336. doi:[10.3109/00365521.2015.1095351](https://doi.org/10.3109/00365521.2015.1095351)
89. Al Taii H, Hanouneh MA, Hanouneh I, Lopez R, Zein N, Alkhouri N. The use of tacrolimus in refractory autoimmune hepatitis in children and adults: a single center experience. *Scand J Gastroenterol* 2017;52:157-158. doi:[10.1080/00365521.2016.1236398](https://doi.org/10.1080/00365521.2016.1236398)
90. Shrestha BM. Two Decades of Tacrolimus in Renal Transplant: Basic Science and Clinical Evidences. *Exp Clin Transplant* 2017;15:1-9. doi:[10.6002/ect.2016.0157](https://doi.org/10.6002/ect.2016.0157)
91. Liberal R, de Boer YS, Andrade RJ, et al. Expert clinical management of autoimmune hepatitis in the real world. *Aliment Pharmacol Ther* 2017;45:723-732. doi:[10.1111/apt.13907](https://doi.org/10.1111/apt.13907)
92. Ytting H, Larsen FS. Everolimus treatment for patients with autoimmune hepatitis and poor response to standard therapy and drug alternatives in use. *Scand J Gastroenterol* 2015;50:1025-1031. doi:[10.3109/00365521.2014.998271](https://doi.org/10.3109/00365521.2014.998271)
93. Chatrath H, Allen L, Boyer TD. Use of sirolimus in the treatment of refractory autoimmune hepatitis. *Am J Med* 2014;127:1128-1131. doi:[10.1016/j.amjmed.2014.06.016](https://doi.org/10.1016/j.amjmed.2014.06.016)
94. Kerker N, Dugan C, Rumbo C, et al. Rapamycin successfully treats post-transplant autoimmune hepatitis. *Am J Transplant* 2005;5:1085-1089. doi:[10.1111/j.1600-6143.2005.00801.x](https://doi.org/10.1111/j.1600-6143.2005.00801.x)
95. Tian H, Cronstein BN. Understanding the mechanisms of action of methotrexate: implications for the treatment of rheumatoid arthritis. *Bull NYU Hosp Jt Dis* 2007;65:168-173.
96. Venkataramani A, Jones MB, Sorrell MF. Methotrexate therapy for refractory chronic active autoimmune hepatitis. *Am J Gastroenterol* 2001;96:3432-3434.
97. Efe C, Ozaslan E, Purnak T. Methotrexate in the Treatment of Autoimmune Hepatitis. *Clin Gastroenterol Hepatol* 2018;16:149. doi:[10.1016/j.cgh.2017.08.029](https://doi.org/10.1016/j.cgh.2017.08.029)
98. Sultan MI, Biank VF, Telega GW. Successful treatment of autoimmune hepatitis with methotrexate. *J Pediatr Gastroenterol Nutr* 2011;52:492-494. doi:[10.1097/MPG.0b013e3181f3d9c0](https://doi.org/10.1097/MPG.0b013e3181f3d9c0)
99. Ksouda K, Affes H, Atheymen R, Ezzeddine M, Zeghal K, Hammami S. Autoimmune hepatitis as an adverse effect of long-term methotrexate therapy. *Indian J Pharmacol* 2014;46:649-650. doi:[10.4103/0253-7613.144940](https://doi.org/10.4103/0253-7613.144940)
100. Moreno-Otero R, Garcia-Buey L, Garcia-Sanchez A, Trapero-Marugan M. Autoimmune hepatitis after long-term methotrexate therapy for rheumatoid arthritis. *Curr Drug Saf* 2011;6:197-200. doi:[10.2174/157488611797579221](https://doi.org/10.2174/157488611797579221)
101. Haridy J, Nicoll A, Sood S. Methotrexate Therapy for Autoimmune Hepatitis. *Clin Gastroenterol Hepatol* 2018;16:288-289. doi:[10.1016/j.cgh.2017.07.003](https://doi.org/10.1016/j.cgh.2017.07.003)
102. Kanzler S, Gerken G, Dienes HP, Meyer zum Buschenfelde KH, Lohse AW. Cyclophosphamide as alternative immunosuppressive therapy for autoimmune hepatitis--report of three cases. *Z Gastroenterol* 1997;35:571-578.
103. Carlsen KM, Riis L, Madsen OR. Toxic hepatitis induced by infliximab in a patient with rheumatoid arthritis with no relapse after switching to etanercept. *Clin Rheumatol* 2009;28:1001-1003. doi:[10.1007/s10067-009-1179-y](https://doi.org/10.1007/s10067-009-1179-y)
104. Goldfeld DA, Verna EC, Lefkowitz J, Swaminath A. Infliximab-induced autoimmune hepatitis with successful switch to adalimumab in a patient with Crohn's disease: the index case. *Dig Dis Sci* 2011;56:3386-3388. doi:[10.1007/s10620-011-1748-1](https://doi.org/10.1007/s10620-011-1748-1)
105. Doyle A, Forbes G, Kontorinis N. Autoimmune hepatitis during infliximab therapy for Crohn's disease: a case report. *J Crohns Colitis* 2011;5:253-5. doi:[10.1016/j.crohns.2010.12.007](https://doi.org/10.1016/j.crohns.2010.12.007)
106. Ricciuto A, Kamath BM, Walters TD, et al. New Onset Autoimmune Hepatitis during Anti-Tumor Necrosis Factor-Alpha Treatment in Children. *J Pediatr* 2018;194:128-135.e1. doi:[10.1016/j.jpeds.2017.10.071](https://doi.org/10.1016/j.jpeds.2017.10.071)
107. Germano V, Picchianti Diamanti A, Baccano G, et al. Autoimmune hepatitis associated with infliximab in a patient with psoriatic arthritis. *Ann Rheum Dis* 2005;64:1515-1520. doi:[10.1136/ard.2004.032821](https://doi.org/10.1136/ard.2004.032821)
108. Fairhurst DA, Sheehan-Dare R. Autoimmune hepatitis associated with infliximab in a patient with palmoplantar pustular psoriasis. *Clin Exp Dermatol* 2009;34:421-422. doi:[10.1111/j.1365-2230.2008.03088.x](https://doi.org/10.1111/j.1365-2230.2008.03088.x)
109. Mancini S, Amorotti E, Vecchio S, Ponz de Leon M, Roncucci L. Infliximab-related hepatitis: discussion of a case and review of the literature. *Intern Emerg Med* 2010;5:193-200. doi:[10.1007/s11739-009-0342-4](https://doi.org/10.1007/s11739-009-0342-4)
110. Cravo M, Silva R, Serrano M. Autoimmune hepatitis induced by infliximab in a patient with Crohn's disease with no relapse after switching to adalimumab. *BioDrugs* 2010;24 Suppl 1:25-27. doi:[10.2165/11586210-000000000-00000](https://doi.org/10.2165/11586210-000000000-00000)
111. Ozorio G, McGarity B, Bak H, Jordan AS, Lau H, Marshall C. Autoimmune hepatitis following infliximab therapy for ankylosing spondylitis. *Med J Aust* 2007;187:524-526. doi:[10.5694/j.1326-5377.2007.tb01396.x](https://doi.org/10.5694/j.1326-5377.2007.tb01396.x)

112. 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;6:630-631. doi:[10.1016/j.crohns.2012.01.017](https://doi.org/10.1016/j.crohns.2012.01.017)
113. Dang LJ, Lubel JS, Gunatheesan S, Hosking P, Su J. Drug-induced lupus and autoimmune hepatitis secondary to infliximab for psoriasis. *Australas J Dermatol* 2014;55:75-79. doi:[10.1111/ajd.12054](https://doi.org/10.1111/ajd.12054)
114. Subramaniam K, Chitturi S, Brown M, Pavli P. Infliximab-induced autoimmune hepatitis in Crohn's disease treated with budesonide and mycophenolate. *Inflamm Bowel Dis* 2011;17:E149-E150. doi:[10.1002/ibd.21880](https://doi.org/10.1002/ibd.21880)
115. Goujon C, Dahel K, Berard F, Guillot I, Gunera-Saad N, Nicolas JF. Autoimmune hepatitis in two psoriasis patients treated with infliximab. *J Am Acad Dermatol* 2010;63:e43-e44. doi:[10.1016/j.jaad.2009.02.029](https://doi.org/10.1016/j.jaad.2009.02.029)
116. Rodrigues S, Lopes S, Magro F, et al. Autoimmune hepatitis and anti-tumor necrosis factor alpha therapy: A single center report of 8 cases. *World J Gastroenterol* 2015;21:7584-7588. doi:[10.3748/wjg.v21.i24.7584](https://doi.org/10.3748/wjg.v21.i24.7584)
117. Petrikova J, Jarcuska P, Svajdlar M, Pella D, Macejova Z. Autoimmune hepatitis triggered by adalimumab and allergic reactions after various anti-TNFalpha therapy agents in a patient with rheumatoid arthritis. *Isr Med Assoc J* 2015;17:256-258.
118. Adar T, Mizrahi M, Pappo O, Scheiman-Elazary A, Shibolet O. Adalimumab-induced autoimmune hepatitis. *J Clin Gastroenterol* 2010;44:e20-e22. doi:[10.1097/MCG.0b013e3181a745e7](https://doi.org/10.1097/MCG.0b013e3181a745e7)
119. Grasland A, Sterpu R, Boussoukaya S, Mahe I. Autoimmune hepatitis induced by adalimumab with successful switch to abatacept. *Eur J Clin Pharmacol* 2012;68:895-898. doi:[10.1007/s00228-011-1191-4](https://doi.org/10.1007/s00228-011-1191-4)
120. Miranda-Bautista J, Menchen L. Adalimumab-induced autoimmune hepatitis in a patient with Crohn's disease. *Gastroenterol Hepatol* 2019;42:306-307. doi:[10.1016/j.gastrohep.2018.06.006](https://doi.org/10.1016/j.gastrohep.2018.06.006)
121. Nakayama S. Autoimmune Hepatitis Triggered by Anti-TNF-alpha Therapy. *Case Rep Med* 2013;2013:561748. doi:[10.1155/2013/561748](https://doi.org/10.1155/2013/561748)
122. Harada K, Akai Y, Koyama S, Ikenaka Y, Saito Y. A case of autoimmune hepatitis exacerbated by the administration of etanercept in the patient with rheumatoid arthritis. *Clin Rheumatol* 2008;27:1063-1066. doi:[10.1007/s10067-008-0885-1](https://doi.org/10.1007/s10067-008-0885-1)
123. Fathalla BM, Goldsmith DP, Pascasio JM, Baldrige A. Development of autoimmune hepatitis in a child with systemic-onset juvenile idiopathic arthritis during therapy with etanercept. *J Clin Rheumatol* 2008;14:297-298. doi:[10.1097/RHU.0b013e318188b1df](https://doi.org/10.1097/RHU.0b013e318188b1df)
124. French JB, Bonacini M, Ghabril M, Foureau D, Bonkovsky HL. Hepatotoxicity Associated with the Use of Anti-TNF-alpha Agents. *Drug Saf* 2016;39:199-208. doi:[10.1007/s40264-015-0366-9](https://doi.org/10.1007/s40264-015-0366-9)
125. Efe C. Drug induced autoimmune hepatitis and TNF-alpha blocking agents: is there a real relationship? *Autoimmun Rev* 2013;12:337-339. doi:[10.1016/j.autrev.2012.03.010](https://doi.org/10.1016/j.autrev.2012.03.010)
126. Weiler-Normann C, Schramm C. Drug induced liver injury and its relationship to autoimmune hepatitis. *J Hepatol* 2011;55:747-749. doi:[10.1016/j.jhep.2011.02.024](https://doi.org/10.1016/j.jhep.2011.02.024)
127. Lucena MI, Kaplowitz N, Hallal H, et al. Recurrent drug-induced liver injury (DILI) with different drugs in the Spanish Registry: the dilemma of the relationship to autoimmune hepatitis. *J Hepatol* 2011;55:820-827. doi:[10.1016/j.jhep.2010.12.041](https://doi.org/10.1016/j.jhep.2010.12.041)
128. Vallejo Senra N, Fernandez Castroagudin J, Molina Perez E, Dominguez-Munoz JE. Onset of severe acute autoimmune hepatitis refractory to conventional treatment, rescued with infliximab. *Gastroenterol Hepatol* 2014;37:524-546. doi:[10.1016/j.gastrohep.2014.02.012](https://doi.org/10.1016/j.gastrohep.2014.02.012)
129. Fujii K, Rokutanda R, Osugi Y, Koyama Y, Ota T. Adult-onset Still's disease complicated by autoimmune hepatitis: successful treatment with infliximab. *Intern Med* 2012;51:1125-1128. doi:[10.2169/internalmedicine.51.6824](https://doi.org/10.2169/internalmedicine.51.6824)
130. Rajanayagam J, Lewindon PJ. Infliximab as rescue therapy in paediatric autoimmune hepatitis. *J Hepatol* 2013;59:908-909. doi:[10.1016/j.jhep.2013.05.046](https://doi.org/10.1016/j.jhep.2013.05.046)
131. Umekita K, Miyauchi S, Ueno S, et al. Improvement of rheumatoid arthritis and autoimmune hepatitis in a patient treated with the tumor necrosis factor inhibitor, etanercept. *Intern Med* 2011;50:1245-1249. doi:[10.2169/internalmedicine.50.4879](https://doi.org/10.2169/internalmedicine.50.4879)
132. Weiler-Normann C, Schramm C, Quaas A, et al. Infliximab as a rescue treatment in difficult-to-treat autoimmune hepatitis. *J Hepatol* 2013;58:529-534. doi:[10.1016/j.jhep.2012.11.010](https://doi.org/10.1016/j.jhep.2012.11.010)
133. Nedelkopoulou N, Vadamalayan B, Vergani D, Mieli-Vergani G. Anti-TNFalpha Treatment in Children and Adolescents With Combined Inflammatory Bowel Disease and Autoimmune Liver Disease. *J Pediatr Gastroenterol Nutr* 2018;66:100-105. doi:[10.1097/MPG.0000000000001759](https://doi.org/10.1097/MPG.0000000000001759)
134. Toulemonde G, Scoazec JY, Miossec P. Treatment with etanercept of autoimmune hepatitis associated with rheumatoid arthritis: an open label proof of concept study. *Ann Rheum Dis* 2012;71:1423-1424. doi:[10.1136/annrheumdis-2011-200830](https://doi.org/10.1136/annrheumdis-2011-200830)
135. Smith MR. Rituximab (monoclonal anti-CD20 antibody): mechanisms of action and resistance. *Oncogene* 2003;22:7359-7368. doi:[10.1038/sj.onc.1206939](https://doi.org/10.1038/sj.onc.1206939)
136. Taylor RP, Lindorfer MA. Drug insight: the mechanism of action of rituximab in autoimmune disease--the immune complex decoy hypothesis. *Nat Clin Pract Rheumatol* 2007;3:86-95. doi:[10.1038/ncprheum0424](https://doi.org/10.1038/ncprheum0424)
137. Burak KW, Swain MG, Santodomingo-Garzon T, et al. Rituximab for the treatment of patients with autoimmune hepatitis who are refractory or intolerant to standard therapy. *Can J Gastroenterol* 2013;27:273-280. doi:[10.1155/2013/512624](https://doi.org/10.1155/2013/512624)
138. Rubin JN, Te HS. Refractory Autoimmune Hepatitis: Beyond Standard Therapy. *Dig Dis Sci* 2016;61:1757-1762. doi:[10.1007/s10620-015-4022-0](https://doi.org/10.1007/s10620-015-4022-0)
139. Al-Busafi SA, Michel RP, Deschenes M. Rituximab for refractory autoimmune hepatitis: a case report. *Arab J Gastroenterol* 2013;14:135-138. doi:[10.1016/j.ajg.2013.08.009](https://doi.org/10.1016/j.ajg.2013.08.009)
140. D'Agostino D, Costaguta A, Alvarez F. Successful treatment of refractory autoimmune hepatitis with rituximab. *Pediatrics* 2013;132:e526-e530. doi:[10.1542/peds.2011-1900](https://doi.org/10.1542/peds.2011-1900)
141. Evans JT, Shepard MM, Oates JC, Self SE, Reuben A. Rituximab-responsive cryoglobulinemic glomerulonephritis in a patient with autoimmune hepatitis. *J Clin Gastroenterol* 2008;42:862-863. doi:[10.1097/MCG.0b013e3180f60b7a](https://doi.org/10.1097/MCG.0b013e3180f60b7a)
142. Santos ES, Arosemena LR, Raez LE, O'Brien C, Reggev A. Successful treatment of autoimmune hepatitis and idiopathic thrombocytopenic purpura with the monoclonal antibody, rituximab: case report and review of literature. *Liver Int* 2006;26:625-629. doi:[10.1111/j.1478-3231.2006.01262.x](https://doi.org/10.1111/j.1478-3231.2006.01262.x)
143. Carey EJ, Somaratne K, Rakela J. Successful rituximab therapy in refractory autoimmune hepatitis and Evans syndrome. *Rev Med Chil* 2011;139:1484-1487. doi:[10.4067/S0034-98872011001100015](https://doi.org/10.4067/S0034-98872011001100015)
144. Jarasvaraparn C, Imran H, Siddiqui A, Wilson F, Gremse DA. Association of autoimmune hepatitis type 1 in a child with Evans syndrome. *World J Hepatol* 2017;9:1008-1012. doi:[10.4254/wjth.v9.i23.1008](https://doi.org/10.4254/wjth.v9.i23.1008)
145. Barth E, Clawson J. A Case of Autoimmune Hepatitis Treated with Rituximab. *Case Rep Gastroenterol* 2010;4:502-509. doi:[10.1159/000322693](https://doi.org/10.1159/000322693)

146. Terrabuio DRB, Diniz MA, de Moraes Falcão LT, et al. Chloroquine Is Effective for Maintenance of Remission in Autoimmune Hepatitis: Controlled, Double-Blind, Randomized Trial. *Hepatology* 2018;3:116-128. doi:[10.1002/hep4.1275](https://doi.org/10.1002/hep4.1275)
147. Mucenic M, de Mello ES, Cancado ELR. Chloroquine for the maintenance of remission of autoimmune hepatitis: results of a pilot study. *Arq Gastroenterol* 2005;42:249-255. doi:[10.1590/s0004-28032005000400011](https://doi.org/10.1590/s0004-28032005000400011)
148. Carmassi F, Morale M, Puccetti R, et al. Efficacy of intravenous immunoglobulin therapy in a case of autoimmune-mediated chronic active hepatitis. *Clin Exp Rheumatol* 1992;10:13-17.
149. Sawada K, Ohnishi K, Kosaka T, et al. Exacerbated autoimmune hepatitis successfully treated with leukocytapheresis and bilirubin adsorption therapy. *J Gastroenterol* 1997;32:689-695. doi:[10.1007/bf02934123](https://doi.org/10.1007/bf02934123)
150. Fukunishi S, Nishida S, Nakamura K, et al. Co-Administration of Saireito Enabled the Withdrawal of Corticosteroids in an Elderly Woman with Autoimmune Hepatitis. *Intern Med* 2016;55:43-47. doi:[10.2169/internalmedicine.55.5128](https://doi.org/10.2169/internalmedicine.55.5128)
151. Okamoto H, Kamatani N. Successful treatment with fenofibrate of autoimmune hepatitis in a patient with rheumatoid arthritis. *Scand J Rheumatol* 2007;36:235-236. doi:[10.1080/03009740600991828](https://doi.org/10.1080/03009740600991828)
152. Weidner J, Check JH. Marked improvement of the autoimmune syndrome associated with autoimmune hepatitis by treatment with sympathomimetic amines. *Clin Exp Obstet Gynecol* 2014;41:460-461.
153. Rebollo Bernardez J, Cifuentes Mimoso C, Pinar Moreno A, et al. Deflazacort for long-term maintenance of remission in type I autoimmune hepatitis. *Rev Esp Enferm Dig* 1999;91:630-638.
154. Bae SH, Kim JS, Kim DH. Deflazacort for type-I autoimmune hepatitis in a Korean girl. *J Korean Med Sci* 2006;21:758-760. doi:[10.3346/jkms.2006.21.4.758](https://doi.org/10.3346/jkms.2006.21.4.758)
155. Yasui S, Fujiwara K, Tawada A, Fukuda Y, Nakano M, Yokosuka O. Efficacy of intravenous glycyrrhizin in the early stage of acute onset autoimmune hepatitis. *Dig Dis Sci* 2011;56:3638-3647. doi:[10.1007/s10620-011-1789-5](https://doi.org/10.1007/s10620-011-1789-5)
156. O'Brien CB, Barnea ER, Martin P, et al. Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Trial of Synthetic Preimplantation Factor in Autoimmune Hepatitis. *Hepatology* 2018;2:1235-1246. doi:[10.1002/hep4.1239](https://doi.org/10.1002/hep4.1239)
157. Kanzler S, Lohr H, Gerken G, Galle PR, Lohse AW. Long-term management and prognosis of autoimmune hepatitis (AIH): a single center experience. *Z Gastroenterol* 2001;39:339-348. doi:[10.1055/s-2001-13708](https://doi.org/10.1055/s-2001-13708)