

Management of autoimmune hepatitis: Focus on pharmacologic treatments beyond corticosteroids

Marta Casal Moura, Rodrigo Liberal, Hélder Cardoso, Ana Maria Horta e Vale, Guilherme Macedo

Marta Casal Moura, Serviço de Medicina Interna, Centro Hospitalar de São João, E.P.E., Porto 4200-319, Portugal
Marta Casal Moura, Rodrigo Liberal, Hélder Cardoso, Ana Maria Horta e Vale, Guilherme Macedo, Faculdade de Medicina da Universidade do Porto, Hernâni Monteiro, Porto 4200-319, Portugal

Rodrigo Liberal, Paediatric Liver Centre and Institute of Liver Studies, King's College London School of Medicine at King's College Hospital, London SE5 9RS, United Kingdom

Hélder Cardoso, Ana Maria Horta e Vale, Guilherme Macedo, Serviço de Gastrenterologia, Centro Hospitalar de São João, E.P.E., Porto 4202-451, Portugal

Author contributions: Casal Moura M and Liberal R design and performed the research; Casal Moura M and Liberal R wrote the paper; Cardoso H, Horta e Vale AM and Macedo G reviewed the paper.

Correspondence to: Marta Casal Moura, MD, Alameda Professor, Faculdade de Medicina da Universidade do Porto, Hernâni Monteiro, Porto 4200-319, Portugal. martacasalmoura@gmail.com

Telephone: +3-51-225512100 Fax: +3-51-22502576

Received: November 5, 2013 Revised: April 19, 2014

Accepted: May 8, 2014

Published online: June 27, 2014

Abstract

In autoimmune hepatitis, patients who are intolerant or with toxicity experience, non-responders, relapsers or refractory are challenging. Non-standard drugs are being tried to preemptively avoid corticosteroid-related side effects. Prognosis and quality of life of life rely on treatment optimization. Recently, emergence of powerful immunosuppressive agents, mainly from liver transplantation, challenged the supremacy of the corticosteroid regime and promise greater immunosuppression than conventional medications, offer site-specific actions and satisfactory patient tolerance. Successes in experimental models of related diseases have primed these molecular interventions. We performed a literature review on alternative treatments. Azathioprine intolerance is the principal indication for mycophenolate use but

it can be used as a front-line therapy. Cyclosporine A and tacrolimus have been tested for non-responders or relapsers. Rituximab may be used as salvage therapy. Anti-tumor necrosis factor-alpha agents may be used for incomplete responses or non-responders. Methotrexate is possibly an alternative for induction of remission and maintenance in refractory patients. Cyclophosphamide has been included in the induction regimen with corticosteroids. Ursodeoxycholic acid action is mainly immunomodulatory. Non-standard treatments are coming slowly to the attention, but its use should be cautious performed by experienced centers.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

Key words: Autoimmune hepatitis; Pharmacologic non-standard treatment; Immunosuppression; Azathioprine intolerance; Difficult-to-treat patients; Salvage therapy

Core tip: With our review we pretend to describe the non-standard pharmacologic treatments available for autoimmune hepatitis, the indications for its use and the main applications. Also, we pretend to enhance that those alternatives are only available guided by the experience in liver transplant patients and should be only used by experienced centers. The difficult-to-treat patients lead to the application of those therapies mainly as salvage treatments.

Casal Moura M, Liberal R, Cardoso H, Horta e Vale AM, Macedo G. Management of autoimmune hepatitis: Focus on pharmacologic treatments beyond corticosteroids. *World J Hepatol* 2014; 6(6): 410-418 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v6/i6/410.htm> DOI: <http://dx.doi.org/10.4254/wjh.v6.i6.410>

INTRODUCTION

Liver chronic inflammation, interface hepatitis (on histol-

ogy), hypergammaglobulinemia, and autoantibodies presence are landmarks of autoimmune hepatitis (AIH)^[1,2]. AIH is an immune-mediated liver disease, its etiology is unknown^[3]. A loss of tolerance seems to be the principal immunologic explanation^[3,4]. Women are more affected than men and it occurs across all ages. Men are diagnosed at 40 years of age and women at 50 years of age in median^[5]. Prevalence and incidence data on AIH are still limited. In Western Europe and North America Caucasian people the estimated prevalence ranges from 50 to 200 cases per million^[6]; the annual incidence in Northern Europeans is 1.9 cases per 100000 persons per year^[1,2,7]. An acute presentation occurs in 25% of patients, fulminant presentation is rare but AIH should be considered as etiology in the study of acute liver failure^[4]. In addition, the prognosis of disease is influenced by age (young patients having an increased risk), presence of cirrhosis, treatment response (as opposed to activity) and relapses.

The clinical manifestations are heterogeneous. Unspecific symptoms like fatigue, lethargy, jaundice and right upper quadrant pain, are the most frequent clinical presentation. The complications of portal hypertension, *i.e.*, ascites, esophageal varices, hypersplenism and encephalopathy, may ensue on the natural course of the disease. About 25% of patients present extrahepatic immune-mediated symptoms and diseases, arthralgia is the most frequent^[4]. Clinical criteria were developed in 1993 and they help to establish the diagnosis when there isn't a single clinical or biochemical test to affirm it^[8,9]. These diagnostic criteria include hypergammaglobulinaemia; positivity for autoantibodies: anti-nuclear antibody (ANA), smooth muscle antibody (SMA) or anti-LKM1; typical histology; other causes of hepatitis (viral or toxic) should be excluded as well as other diseases with similar presentation of AIH^[8,10]. The autoantibody profile helps to classify AIH: in type 1, SMA and ANA are present; on type 2 anti-LKM1 antibodies are present. Type 1 AIH affects adults and children, while type 2 AIH is mainly a disease of children and adolescents^[11]. The scoring system for AIH has a sensitivity of 97% to 100%. In the presence of chronic hepatitis C, the specificity for excluding AIH relies between 66% to 92%^[7,10].

Inflammatory activity at the onset of disease and cirrhosis are the main determinants of natural history and prognosis of AIH. Without treatment, mortality of 90% in 10 years is expected when a 5- to 10-times elevation of aspartate aminotransferase and a twofold increase of γ -globulins are present. Cirrhosis occurs in 17% within 5 years of the diagnosis in patients periportal hepatitis and in 82% of patients with bridging necrosis or necrosis of multiple lobules^[2]. At diagnosis, 58% of mortality is expected within 5 years of diagnosis^[2,4].

The diagnostic criteria may be too strict when applied to diverse ethnic groups because heterogeneous clinical phenotypes and outcomes may be present^[12-14] which may be determined by antigenic exposure, variations in immune response, genetic predisposition and cultural, social and economic factors^[14]. The diagnosis may be delayed as the institution of corticosteroid treatment^[14].

The human leukocyte antigen (HLA) profile also determines the clinical outcome of AIH: HLA DR3 is associated with more severe disease; HLA DR4 is associated with onset at a later age and a more benign outcome of AIH^[4]. The HLA-DRB1 locus, specially the alleles HLA-DR3 (DRB1*0301) and DR4 (DRB1*0401) are related to AIH type 1 susceptibility in European populations and North Americans and the strongest genetic associations contributing to the diagnosis of AIH and are included in the IAIHG revised diagnostic scoring system^[15]. Genetic profile determines the response to treatment: those who do not respond to corticosteroid treatment have usually DRB1*0301 alleles^[15]. Also, clinical manifestations and prognosis may be determined by genetic profile.

AIH, if left untreated, may lead to cirrhosis, liver failure and even death^[16]. Survival is increased when immunosuppressive therapy is used. Initially, induction of remission is the main goal^[4]. Corticosteroid regimens are effective^[2,17]. Prednisolone, alone or in association to azathioprine leads to symptom improvement, laboratory and histologic manifestations of liver inflammation within 6-12 mo in the majority of patients^[4,18]. Standard therapy leads to complete biochemical response in 77% in 6 mo^[19], improves hepatic fibrosis^[18] and 20-year life expectancy is increased in 80%^[20].

Early recognition and treatment of the disease, treatment until complete resolution of inflammation, prevention of complications of treatment and early identification and treatment of problematic patients may improve the outcomes of current therapy^[21]. Main prognostic determinant is the response to corticosteroid therapy: rapid disease progression is expected when the treatment is delayed or deferred^[17].

Between those 23% that do not respond, 5% are intolerant or present toxicity, 7% are non-responders or have refractory disease and the remain 10% have incomplete responses^[2]. The relapses after drug withdrawal are frequent (50%-86%)^[2,22]. Other efficient treatments are needed. Complete biochemical remission determines the outcome^[23] and, therefore, optimization of treatment has implications on prognosis and quality of life^[2]. Liver transplantation supersedes empirical drug therapy in decompensated patients^[21].

PHARMACOLOGIC TREATMENT OF AIH

The recognition of the response of AIH to immunosuppression changed its prognosis^[24,25]. Immunosuppressive treatments should be established immediately, especially in the presence of severe disease^[24].

The goal of AIH treatment includes: induction of remission; maintenance of remission; prevention of the establishment of cirrhosis and complications using the lowest possible dose of medication^[11,15]. AIH has a good response to immunosuppressive treatment with 80% of remission rate^[15,26].

According to the American Association for Study of Liver Diseases guidelines treatment is indicated for patients with established diagnosis of AIH, elevation

of aminotransferase activities [≥ 5 times upper normal limit-(ULN)], rises of immunoglobulin G (≥ 2 times upper normal value) and presence of interface hepatitis or necroinflammatory activity (Ishak score 4-6)^[2,16]. If untreated, high mortality of 60% at 6 mo is expected when serum aspartate aminotransferase (AST) levels of 10 times the ULN or more than 5 times the ULN especially if associated with serum γ -globulin level more than twice the ULN. Also, in 82% there is progression from bridging necrosis or multilobular necrosis at presentation to cirrhosis, associated with 45% mortality within 5 years^[2,16]. Corticosteroid treatment is indicated in the presence of these findings^[2,16]. Treatment should also be started in the presence of incapacitating, such as fatigue and arthralgia^[2].

Standard therapy may be not an option if corticosteroids, azathioprine or other immunosuppressive therapies are contraindicated by itself or by patient risk factors. The treatment doesn't alter the outcome in patients with decompensated liver cirrhosis on waiting list for liver transplantation or in those with cirrhosis without inflammatory activity^[6].

The outcomes of therapy include: remission, relapse, treatment failure, and stabilization^[11]. Normal inflammatory parameters and histology is necessary to assume remission. Histological remission should be differentiated from biochemical remission (complete normalization of aminotransferase levels including IgG). Treatment should definitely be considered in any patient with proven AIH, histological activity and a more than marginal elevation of aminotransferase levels, not only in patients with levels greater $5 \times$ ULN. In 65% to 75% of patients after 24 mo on standard therapy remission is achieved^[11,27]. Relapse is defined as a flare in aminotransferase levels with symptoms under treatment, following the minimum dose of maintenance therapy, or after withdrawal. Relapse occurs in about 50%; loss of remission in 42% within 6 mo of treatment withdrawal and in 80% after 3 years; progression to cirrhosis occurs in 38% and liver failure in 14%^[11,17]. Retrospective analysis indicates that loss of remission or relapse occurs in virtually all patients with AIH in long-term remission when immunosuppressive therapy is discontinued^[28]. Treatment failure should be assumed when there is progression of symptoms, non-improvement of histological parameters and deterioration of serologic features during standard therapy. In case of treatment failure, diagnosis should be reconsidered to exclude an overlap syndrome with primary sclerosing colangitis or primary biliar cirrhosis or different etiologies^[11]. Partial remission corresponds to stabilization of the disease^[11].

STANDARD PHARMACOLOGIC TREATMENT

The standard initial treatment of AIH includes the corticosteroids only or combined with azathioprine. Combination therapy is the first choice and low-dose of prednisolone (30 mg/d) with 1 mg/kg azathioprine are used in the induction phase^[11]. In the United States, 50 mg is

used for azathioprine, but in Europe a dose of 1-2 mg/kg bodyweight is used^[2]. Alternatively, monotherapy may be used, with 60 mg of steroid and reductions of 10 mg/wk to maintenance dose of 20 mg for at least 6 mo, and further reduction until lowest dose in 2.5 mg decrements. Maybe the initial prednisolone dose in combination therapy should be considered since the percentage of response is higher. There are no differences in the remission induction. Combined treatment is preferred because it allows to decrease the dose of the prednisone dose to below 10 mg and reduces the steroid side effects^[6].

Standard therapy is the best option unless contraindicated and may be especially useful by reducing corticosteroids side-effects in older patients, in patients with osteoporosis, metabolic syndrome or psychiatric lability^[6]. Monotherapy with steroids is the best treatment option in patients with hematological abnormalities or a proven homozygous deficiency of thiopurine methyltransferase because azathioprine causes hematological side effects such as leukopenia or anemia^[6]. Thiopurine methyltransferase (TPMT) is an enzyme responsible for the conversion in one of azathioprine to 6-mercaptopurine (active metabolite) and in 6-methyl mercaptopurine or 6-thiouric acid (inactive metabolites)^[12]. In patients with azathioprine intolerance, lower TPMT activity is documented but measurements of TPMT activity cannot be used to identify those patients^[29]. Pre-treatment TPMT testing provides some certain of the presence of risk for azathioprine toxicity and strengthens physician confidence in the treatment regimens^[12]. Allopurinol may safely and effectively optimize thiopurine therapy in patients with intolerance and/or nonresponse due to an unfavourable thiopurine metabolism and this is another option in order to maintain the standard treatment^[30].

Corticosteroids are the first option of treatment in all populations, but its use should be individualized in the presence of cholestatic features^[14].

However, as the combination treatment fails, other drugs have been tried although its use requires further validation^[24].

In fulminant hepatic failure and in en-stage liver disease, transplantation is the treatment of choice. Post-transplantation AIH recurrence may occur^[24].

ALTERNATIVE CORTICOSTEROID REGIMEN-BUDESONIDE

Budesonide is glucocorticoid from the next-generation, more than 90% has first pass hepatic clearance and metabolites don't have glucocorticoid activity^[31]. These pharmacological properties seem to predict less secondary effects. In non-cirrhotic patients, treatment combination between budesonide and azathioprine may be an alternative in uncomplicated AIH with mild disease^[32,33] or with conditions that may be worsened by prednisone treatment like hypertension, osteopenia, diabetes and obesity^[34].

In corticosteroids refractory or dependent AIH patients may not be used as a rescue treatment. The budesonide

regimen normalized serum AST and alanine aminotransferase (ALT). Budesonide histological resolution and persistent response is unknown^[34].

NON-STANDARD PHARMACOLOGIC TREATMENT

There are some difficult-to-treat patients for whom newer immunosuppressive agents, usually employed as anti-rejection drugs, have been tried with variable success. Immunosuppression with non-standard drugs is being tried to avoid corticosteroid side effects (13%) but are being used specially as superior regimens to corticosteroid treatment^[21]. The use of such regimens has to be weighed and data available comes only from few small studies or case reports^[15]. Other treatments considered are: mycophenolate mofetil (MMF)^[35-43], cyclosporine A (CyA)^[44,45], tacrolimus (FK506)^[46-49], rituximab^[50], anti-tumor necrosis factor- α (TNF- α) agents^[51], methotrexate^[52], cyclophosphamide and ursodeoxycholic acid (UDCA)^[53] (Table 1). These non-standard treatments application is not widespread and they are not included into any standard management algorithm^[15].

Only recently has the emergence of powerful immunosuppressive agents, mainly from liver transplantation, challenged the supremacy of the corticosteroid regimens^[22,54]. Drugs outside of the standard repertoire now promise greater immune suppression than conventional medications, offer site-specific actions and satisfactory patient tolerance^[22,54]. Site-specific molecular treatments are also possible because of improved understanding of the central pathogenic disease pathways and technological advances that now enable modulation of these pathways^[22,54]. Furthermore, successes in experimental models and in other autoimmune diseases have primed these molecular interventions for study in AIH^[22,54].

Importantly, publication bias may be considered since there is, probably, underreport of studies with negative results. Also, target populations, dosing schedules, safety profiles and monitoring strategies are not yet clear; adjunctive therapy with corticosteroids is still required; the standard algorithms do not include already the risks and expense of these drugs^[55]. Newer agents are much more expensive than the standard treatment irrespectively of the generic use (as recently available generic MMF may attenuate this problem) and this may be a limitation to the accessibility to these treatments.

MMF

MMF, is most frequently used in patients with refractory AIH or azathioprine intolerance but it may be used as a first choice treatment^[16,22,35,38,40,41]. It acts as a purine antagonist.

MMF is hydrolyzed by to mycophenolic acid by liver esterases and acts as reversible noncompetitive inhibitor of inosine monophosphate dehydrogenase: it selectively impairs the synthesis of nucleotides based on purines, inhibits the new synthesis of DNA, impairing proliferation

of activated lymphocytes. The thiopurine methyltransferase pathway does not interfere on the activation or elimination of lymphocytes^[16,22].

De novo synthesis of purines, in contrast with other cells, is essential for B and T cell proliferation: this is why MMF exerts its cytotoxicity specially on these cell populations^[4].

According to eleven small single-centre experiences, MMF is effective in difficult-to-treat patients in doses ranging from 0.5 g/d to 3 g/d^[22,35]; 2 g/d in divided doses was the most used regimen, initially with corticosteroids^[16].

Recent studies^[43,56-58] showed that 47% of the patients had positive response and 53% showed no response or drug intolerance^[22]. From 11 studies, 40% of the patients included achieved complete corticosteroid withdrawal and 15% experimented treatment-ending side effects^[22]. MMF treatment was more efficient in patients where it was used because of azathioprine intolerance than in patients who were treated for refractory liver disease (58% *vs* 12%)^[57,58]. Nonresponders were mainly children with AIH and sclerosing cholangitis^[56].

MMF has been used as first choice therapy in naive patients. MMF was used in 59 previously untreated AIH patients for up to 92 mo: 88% showed normal aminotransferase and gamma-globulin serum levels (within three months) and 12% showed partial response^[59]. Corticosteroids withdrawn occurred within eight months in 58% and 3% presented serious side effects. MMF can be administered effectively and safely as a front-line treatment, but the reasons for preferring this treatment as a front-line strategy are unclear^[22].

The most common side effects of treatment with MMF in AIH patients have been gastrointestinal discomfort (nausea, diarrhea and abdominal pain) (11%), rash (including skin cancers) (7%), fatigue (7%) and leukopenia (1%)^[57]. The frequency of side effects has ranged from 3% to 33%^[57,59] and the frequency of treatment-ending complications has been as high as 13%^[57].

The differences between the costs of MMF and azathioprine may be important^[60]; treatment ending side effects occur in 3% to 13%^[57,59]; most patients require continuous corticosteroid therapy; the duration of treatment is indefinite; and is more efficient as a salvage therapy in patients with azathioprine intolerance than in patients with steroid-refractory liver disease^[57,59]. MMF has a limited and evolving off-label role in AIH, and its use as a salvage therapy for azathioprine intolerance is currently its most effective application^[22].

Data about histological remission are poor and further studies are needed before recommend MMF as a first-line treatment for AIH^[16]. MMF is contraindicated in pregnancy^[16,22].

Calcineurin inhibitors

CyA and FK506 are calcineurin inhibitors that alter phosphatase activity, interfere with lymphocyte T proliferation blunting cell-mediated immune responses. Cyclosporine and FK506 have each been used in AIH patients, primarily as salvage therapies for steroid-refractory disease^[22,54].

Table 1 Non-standard immunosuppressive drugs used in autoimmune hepatitis

Non-standard pharmacologic treatments	Studies	Indications	Contra-indications	Outcomes
Mycophenolate mofetil, 0.5 to 3.0 g/d Purine antagonist (inhibits inosine monophosphate dehydrogenase, limits purine nucleotides, impairs lymphocyte proliferation)	¹ 46 mo, 7 patients ^[35] ¹ 19 mo, 8 patients ^[39] ¹ 41 mo, 15 patients ^[40] ¹ 61.5 mo, 26 patients ^[56] ¹ 26 mo, 59 naïve-patients ^[59]	Azathioprine Intolerance Refractory AIH Front-line therapy	Pregnancy Hypersensitivity to mycophenolate mofetil, mycophenolic acid or mycophenolate sodium	Salvage ^[22,35-43,56] : 47% overall improvement 58% azathioprine intolerance 12% refractory disease 53% failure or side effects 40% steroid withdrawal 3%-33% Serious side effects Front-line ^[59] : 88% complete response 12% partial response 58% steroid withdrawal 3% serious side effects
Cyclosporin, 2 to 5 mg/kg per day Calcineurin inhibitor (impairs NF-κB, reduces IL-2 and lymphocyte proliferation)	6 mo, 19 patients ^[44] 3 mo, 5 patients ^[45]	Refractory AIH Relapsing AIH Non-responding AIH	Rheumatoid arthritis and psoriasis: abnormal renal function, uncontrolled hypertension, malignancies Psoriasis: under PUVA, UVB therapy, methotrexate Hypersensitivity to cyclosporin or to polyoxyethylated castor oil Pregnancy	Composite results ^[22,44,45] : 93% improvement 7% failure/side effects
Tacrolimus, 0.075 to 4 mg/kg twice a day Calcineurin inhibitor (impairs NF-κB, reduces IL-2 and lymphocyte proliferation)	12 mo, 21 patients ^[46] 25 mo, 11 patients ^[48] 18 mo, 9 patients ^[49]	Refractory AIH Relapsing AIH Non-responding AIH	Hypersensitivity to tacrolimus Pregnancy	Composite results ^[22,46,49] : 98% improvement 2% failure/side effects
Rituximab, 1.0 g, two doses 15 d apart ¹ Anti-CD20 (B-cell depletion, impairs type 2 cytokine pathway, interferes with antibody-dependent cell-mediated cytotoxicities)	5 mo, 6 patients ^[66] case reports; data from studies for hematological malignancies, rheumatoid arthritis	Refractory AIH Relapsing AIH Non-responding AIH	Type 1 hypersensitivity or anaphylatic reaction to murine proteins Progressive multifocal leukoencephalopathy	Biochemical improvement
Infliximab, dose of 5 mg/kg at weeks 0, 2 and 6, and then every 4 to 8 wk ¹ Anti-TNF-α (neutralizing soluble transmembrane forms of TNF-α impairing cytotoxic type 1 cytokine pathway)	Case reports	Refractory AIH Relapsing AIH Non-responding AIH	Heart failure NYHA class III/IV Hypersensitivity to infliximab or murine proteins	Biochemical improvement
Cyclophosphamide, 1 to 1.5 mg/kg per day Alkylating agents (covalent binding and crosslinking to deoxyribonucleic acid-DNA, ribonucleic acid-RNA and proteins)	95 mo, 94 patients with long-term auto-immune hepatitis ^[71]	Refractory AIH Relapsing AIH Non-responding AIH	Hypersensitivity to cyclophosphamide, urinary outflow obstructions, severe myelosuppression, severe renal or hepatic impairment, severe immunosuppression Pregnancy	91% complete remission
Methotrexate, 7.5 mg/wk Purine antagonist (inhibits the binding of dihydrofolic acid)	Case reports ^[52]	Refractory AIH	Hypersensitivity Breast-feeding Pregnancy	Biochemical and histologic improvement
Ursodeoxycholic acid, 13 to 15 mg/kg per day Immunomodulation (epimer of chenodeoxycholic acid)	6 mo, 37 patients ^[53]	In addition to other immunosuppressive strategies	Hypersensitivity Unremitting acute cholecystitis, cholangitis, biliary obstruction, gallstone pancreatitis, biliary-gastrointestinal fistula, allergy to bile acids	Biochemical improvement Corticosteroid dose reduction

¹Careful is needed in women of childbearing age since those treatments have uncertain effects on reproduction and are presumable teratogenic. AIH: Auto-immune hepatitis; NF-κB: Nuclear factor kappa B; TNF-α: Tumor necrosis factor-alpha; IL-2: Interleukin-2; UVB: Ultra-violet B; PUVA: Psoralen and ultra-violet A.

Calcineurin activates nuclear factor- κ B *via* a pathway dependent on phosphatase activity. The activated nuclear factor binds to promoter regions of interleukin-2 (*IL-2*) gene increasing transcription of *IL-2*. In turn, *IL-2* stimulates the cell cycle by binding to *IL-2* receptor, and lymphocytes proliferate by a type 1 cytokine pathway^[22,54]. In difficult-to-treat AIH patients calcineurin inhibitors have been used as a rescue treatment^[15].

CyA: CyA is a calcineurin inhibitor extracted from the *tobypocladium inflatum* and *cylindrocarpum lucidum*^[11]. It has been used, since 1985, mainly as a rescue therapy but also in relapsing or non-responsive AIH^[22]. There are no long-term reports on safety but results in these situations seem promising^[16]. Ten studies^[22,44,61] showed that 93% of the 133 patients included within 26 years had a positive response, and 7% showed no response or drug intolerance^[22].

Serum aminotransferases and histological activity index scores decreased over 6 mo in an open label trial of 19 patients^[16,44].

In a multicenter study, 32 children were included and CyA was administered as monotherapy for 6 mo (200-250 ng/mL levels). Then, prednisolone and azathioprine were given in low doses for 1 mo and stopped after^[62]. Alanine aminotransferase activity levels normalized in 25 patients by 6 mo and in all patients by 1 year of treatment. There was a trend to improvement of Z-scores for height during treatment^[62].

Between 1994 and 2000, 84 children were recruited from five centers, CyA was administered during 6 mo in doses similar to that previously described; after 6 mo, patients with AST/ALT levels lower than 2-ULN started standard therapy. Aminotransferase levels were normal in 94% of patients, 72% within the first 6 mo of treatment^[16].

In all studies, CyA adverse effects seem to be mild and transient and standard therapy is not related with relapse during follow-up^[16,44,62].

The data are encouraging and CyA might be considered an alternative therapy to steroids in patients who do not achieve a complete remission. However, side effects are a serious problem and include: dyslipidemia, hypertension, renal failure, infection, hirsutism and malignancy^[16].

FK506: FK506, macrolide lactone antibiotic, acts as a potent immunosuppressive agent on CD4+ T-helper cells^[11]. FK506 and CyA have similar mechanisms of action however, FK506 binds to a different immunophilin (FK-binding protein) leading to the inhibition of lymphokine synthesis (*IL-2*, *IL-3* and *IFN- α*), *IL-2* receptor expression and the generation of cytotoxic T cells^[6]. FK506 has been used as a rescue therapy since 1995^[22]. Experience with this drug is reported in three studies, 41 patients were included within 16 years: 98% presented a positive response; 2% presented no response or treatment-ending drug intolerance^[22,46,49]. There are no controlled trials on the use of FK506 in AIH^[11]. In a preliminary trial, 21 patients were treated with FK506 (drug

levels of 0.6-1.0 ng/mL): biochemical improvement was documented after 3 mo^[46]. Although the reported results are encouraging, more extensive studies are warranted before FK506 can be recommended as a safe and useful agent in AIH^[11]. Remission can be achieved with FK506 for most patients, only or combined with corticosteroids. All series are limited by a short time of follow-up^[16].

The success of the calcineurin inhibitors as a salvage therapy for AIH has been impressive, but the overall reported clinical experience with these agents has been lacking. Calcineurin inhibitors still lack a uniform dosing schedule, an acceptable safety profile and an established monitoring protocol for AIH despite their longstanding empirical use in this disease. Efforts to launch large, multicentre, clinical trials have been frustrated by low patient recruitment. Calcineurin inhibitors remain empirical, off-label treatments reserved for steroid-refractory disease and even in these cases should be used with caution and only in experienced centres^[22].

Rituximab

Rituximab is an anti-CD20 chimeric monoclonal antibody, a surface marker expressed on B cells, from early pre-B to memory B lymphocytes. Treatment with rituximab leads to B cell depletion through both complement- and antibody-dependent cellular cytotoxicity^[63]. Initially developed for the treatment of B-cell lymphoma, rituximab has since proven effective for the treatment of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus or autoimmune haemolytic anemia^[64], suggesting it might also be effective in patients with AIH.

Treatment with rituximab has been reported as effective in patients with Epstein Barr virus infection associated with lymphoproliferative disease secondary to azathioprine^[64], in a patient with concurrent diagnoses of B cell lymphoma^[65] and steroid resistant AIH/primary biliary cirrhosis overlap syndrome, in patients with concomitant idiopathic thrombocytopenic purpura, cryoglobulinemic glomerulonephritis, or Evans syndrome. Isolated AIH refractory to standard treatment in 6 patients was studied in a phase 1 study: they were treated with rituximab (1000 mg at days 1 and 15)^[66]. All patients were maintained on stable doses of prednisolone plus azathioprine for at least 1 mo before and 3 mo after rituximab infusions, after which steroids were tapered. Biochemical remission was achieved by all patients by week 12, with good tolerance to treatment with no serious adverse event being reported during the 72-wk follow-up^[66]. Although these results are promising and the toxicity profile is favourable, controlled clinical trials are needed before rituximab can be recommended as an alternative treatment in AIH^[11].

Anti-TNF- α agents

TNF- α is a pro-inflammatory cytokine known to be implicated in the pathogenesis of AIH^[67]. Additionally, genetic polymorphisms in the TNF promoter region have been identified in patients with AIH type 1, associated with a poorer response to corticosteroid therapy

and higher incidence of cirrhosis^[68,69]. Infliximab, etanercept and adalimumab are anti-TNF- α agents commonly used for treatment of immunemediated diseases such as rheumatoid arthritis, psoriasis and inflammatory bowel disease^[11]. Soluble and transmembrane forms of TNF- α are neutralized by anti-TNF- α agents. It also seems to have pro-apoptotic effect on activated lymphocytes. Its effect in AIH is explained by the impairment of activated lymphocytes activity^[51].

Weiler-Normann *et al*^[51] reported the first series of AIH patients treated with infliximab in a single centre. This retrospective study included 11 AIH patients who did not achieve remission with a standard immunosuppressive regimen upon diagnosis, and who also failed to respond to other alternative treatments, including cyclosporine, FK506 and cyclophosphamide. Patients were given infusions of infliximab at a dose of 5 mg/kg at weeks 0, 2 and 6, and then every 4 to 8 wk depending on response. After 3 infusions of infliximab, all patients showed a decrease in the levels of transaminases and of IgG; normalisation of transaminases and IgG levels was observed in 8 and 6 patients respectively. Of the 5 patients in whom a liver biopsy was performed after treatment, all showed reduction of inflammation, as expressed by a modified histological activity index. Some cautions in the use of this agents in AIH must be present since treatment with infliximab has been associated with the induction of severe de novo AIH in some patients treated for other diseases^[51,70].

For all the above reasons, while more studies are warranted to evaluate the efficacy and tolerability of infliximab in AIH, this type of treatment should be considered in defined cases and administered only in specialised centres^[11,70].

Cyclophosphamide

For the induction of remission in combination with steroids cyclophosphamide was used in the dose of 1-1.5 mg/kg per day^[71]. Cyclophosphamide use is highly experimental because of the potential severe hematological side effects^[6].

Methotrexate

Methotrexate is an antagonist of folate metabolism, it has anti-inflammatory and immunomodulating properties. Bone marrow suppression and mucosal ulceration at higher doses are the principal side-effects but it is generally well tolerated^[52].

A once-weekly dose is reported as induction and maintenance regimen in two case reports. Fibrogenic effect might enable its long-term use^[72].

UDCA

UDCA may have immunomodulatory functions. It is a hydrophilic bile acid that changes HLA-1 antigen expression on cellular surfaces and suppresses the production of immunoglobulin. Non-controlled studies show improvement in histology features, in clinical presentation and biochemical parameters. A reduction of fibrosis

wasn't established in four AIH type 1 patients. Its role in AIH treatment is not yet established^[6,53]. UDCA monotherapy is effective for some Japanese AIH patients, may have a role during the taper of corticosteroids for prevention of early relapse but is not recommended on patients with high-grade inflammatory activity or poor residual capacity of liver^[73].

CONCLUSION

In AIH, identification of efficient salvage treatment options is urgently needed for the difficult-to-treat patients: those who experience intolerance or toxicity, non-responders, relapsers or with refractory disease. Also, non-standard drugs are being tried as superior drugs to corticosteroid regimens and to minimize its side effects. Optimization of treatment plays a major role in long-term prognosis and quality of life for patients with AIH. Recently, the emergence of powerful immunosuppressive agents, mainly from liver transplantation, challenged the supremacy of the corticosteroid regime and promise greater immunosuppression than conventional medications, offer site-specific actions and satisfactory patient tolerance. Successes in experimental models and in other autoimmune diseases have pointed these molecular interventions for study in AIH. Some encouraging results were described, but the establishment of these non-standard drugs as alternative treatments has evolved slowly and they weren't already included into a standard management algorithm. Therefore, those treatments should be used with caution and only in experienced centers.

REFERENCES

- 1 **Czaja AJ**. Diagnosis, pathogenesis, and treatment of autoimmune hepatitis after liver transplantation. *Dig Dis Sci* 2012; **57**: 2248-2266 [PMID: 22562533 DOI: 10.1007/s10620-012-2179-3]
- 2 **Manns MP**, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, Vierling JM. Diagnosis and management of autoimmune hepatitis. *Hepatology* 2010; **51**: 2193-2213 [PMID: 20513004 DOI: 10.1002/hep.23584]
- 3 **Liberal R**, Longhi MS, Mieli-Vergani G, Vergani D. Pathogenesis of autoimmune hepatitis. *Best Pract Res Clin Gastroenterol* 2011; **25**: 653-664 [PMID: 22117632 DOI: 10.1016/j.bpg.2011.09.009]
- 4 **Manns MP**, Strassburg CP. Therapeutic strategies for autoimmune hepatitis. *Dig Dis* 2011; **29**: 411-415 [PMID: 21894012 DOI: 10.1159/000329805]
- 5 **Al-Chalabi T**, Underhill JA, Portmann BC, McFarlane IG, Heneghan MA. Impact of gender on the long-term outcome and survival of patients with autoimmune hepatitis. *J Hepatol* 2008; **48**: 140-147 [PMID: 18023911 DOI: 10.1016/j.jhep.2007.08.013]
- 6 **Strassburg CP**, Manns MP. Therapy of autoimmune hepatitis. *Best Pract Res Clin Gastroenterol* 2011; **25**: 673-687 [PMID: 22117634 DOI: 10.1016/j.bpg.2011.08.003]
- 7 **Lamers MM**, van Oijen MG, Pronk M, Drenth JP. Treatment options for autoimmune hepatitis: a systematic review of randomized controlled trials. *J Hepatol* 2010; **53**: 191-198 [PMID: 20400196 DOI: 10.1016/j.jhep.2010.01.037]
- 8 **Hennes EM**, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL, Bittencourt PL, Porta G, Boberg KM, Hofer H, Bianchi FB, Shibata M, Schramm C, Eisenmann de Torres B, Galle PR, McFarlane I, Dienes HP, Lohse AW. Simplified cri-

- teria for the diagnosis of autoimmune hepatitis. *Hepatology* 2008; **48**: 169-176 [PMID: 18537184 DOI: 10.1002/hep.22322]
- 9 **Krawitt EL.** Clinical features and management of autoimmune hepatitis. *World J Gastroenterol* 2008; **14**: 3301-3305 [PMID: 18528927 DOI: 10.3748/wjg.14.3301]
 - 10 **Teufel A, Galle PR, Kanzler S.** Update on autoimmune hepatitis. *World J Gastroenterol* 2009; **15**: 1035-1041 [PMID: 19266594 DOI: 10.3748/wjg.15.1035]
 - 11 **Floreani A, Liberal R, Vergani D, Mieli-Vergani G.** Autoimmune hepatitis: Contrasts and comparisons in children and adults - a comprehensive review. *J Autoimmun* 2013; **46**: 7-16 [PMID: 24035197 DOI: 10.1016/j.jaut.2013.08.004]
 - 12 **Czaja AJ.** Review article: the management of autoimmune hepatitis beyond consensus guidelines. *Aliment Pharmacol Ther* 2013; **38**: 343-364 [PMID: 23808490 DOI: 10.1111/apt.12381]
 - 13 **Abe M, Mashiba T, Zeniya M, Yamamoto K, Onji M, Tsubouchi H.** Present status of autoimmune hepatitis in Japan: a nationwide survey. *J Gastroenterol* 2011; **46**: 1136-1141 [PMID: 21597932 DOI: 10.1007/s00535-011-0421-y]
 - 14 **Czaja AJ.** Autoimmune hepatitis in diverse ethnic populations and geographical regions. *Expert Rev Gastroenterol Hepatol* 2013; **7**: 365-385 [PMID: 23639095 DOI: 10.1586/egh.13.21]
 - 15 **Liberal R, Grant CR, Mieli-Vergani G, Vergani D.** Autoimmune hepatitis: a comprehensive review. *J Autoimmun* 2013; **41**: 126-139 [PMID: 23218932 DOI: 10.1016/j.jaut.2012.11.002]
 - 16 **Gleeson D, Heneghan MA.** British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. *Gut* 2011; **60**: 1611-1629 [PMID: 21757447 DOI: 10.1136/gut.2010.235259]
 - 17 **Czaja AJ, Manns MP.** Advances in the diagnosis, pathogenesis, and management of autoimmune hepatitis. *Gastroenterology* 2010; **139**: 58-72.e4 [PMID: 20451521 DOI: 10.1053/j.gastro.2010.04.053]
 - 18 **Czaja AJ, Carpenter HA.** Decreased fibrosis during corticosteroid therapy of autoimmune hepatitis. *J Hepatol* 2004; **40**: 646-652 [PMID: 15030981 DOI: 10.1016/j.jhep.2004.01.009]
 - 19 **Schramm C, Weiler-Normann C, Wiegand C, Hellweg S, Müller S, Lohse AW.** Treatment response in patients with autoimmune hepatitis. *Hepatology* 2010; **52**: 2247-2248 [PMID: 20815018 DOI: 10.1002/hep.23840]
 - 20 **Roberts SK, Therneau TM, Czaja AJ.** Prognosis of histological cirrhosis in type 1 autoimmune hepatitis. *Gastroenterology* 1996; **110**: 848-857 [PMID: 8608895 DOI: 10.1053/gast.1996.v110.pm8608895]
 - 21 **Czaja AJ.** Difficult treatment decisions in autoimmune hepatitis. *World J Gastroenterol* 2010; **16**: 934-947 [PMID: 20180231 DOI: 10.3748/wjg.v16.i8.934]
 - 22 **Czaja AJ.** Autoimmune hepatitis: focusing on treatments other than steroids. *Can J Gastroenterol* 2012; **26**: 615-620 [PMID: 22993733]
 - 23 **Muratori L, Muratori P, Lanzoni G, Ferri S, Lenzi M.** Application of the 2010 American Association for the study of liver diseases criteria of remission to a cohort of Italian patients with autoimmune hepatitis. *Hepatology* 2010; **52**: 1857; author reply 1857-1858 [PMID: 20931560 DOI: 10.1002/hep.23924]
 - 24 **Vergani D, Longhi MS, Bogdanos DP, Ma Y, Mieli-Vergani G.** Autoimmune hepatitis. *Semin Immunopathol* 2009; **31**: 421-435 [PMID: 19533129 DOI: 10.1007/s00281-009-0170-7]
 - 25 **Johnson PJ.** Treatment of autoimmune hepatitis. *Gut* 1997; **41**: 3-4 [PMID: 9274462 DOI: 10.1136/gut.41.1.3]
 - 26 **Krawitt EL.** Autoimmune hepatitis. *N Engl J Med* 2006; **354**: 54-66 [PMID: 16394302 DOI: 10.1056/NEJMra050408]
 - 27 **Czaja AJ.** Special reports: autoimmune hepatitis. *Curr Treat Options Gastroenterol* 1999; **2**: 423-436
 - 28 **van Gerven NM, Verwer BJ, Witte BI, van Hoek B, Coenraad MJ, van Erpecum KJ, Beuers U, van Buuren HR, de Man RA, Drenth JP, den Ouden JW, Verdonschot RC, Koek GH, Brouwer JT, Guichelaar MM, Mulder CJ, van Nieuwkerk KM, Bouma G.** Relapse is almost universal after withdrawal of immunosuppressive medication in patients with autoimmune hepatitis in remission. *J Hepatol* 2013; **58**: 141-147 [PMID: 22989569 DOI: 10.1016/j.jhep.2012.09.009]
 - 29 **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 [PMID: 12217596 DOI: 10.1016/S0168-8278(02)00214-3]
 - 30 **de Boer YS, van Gerven NM, de Boer NK, Mulder CJ, Bouma G, van Nieuwkerk CM.** Allopurinol safely and effectively optimises thiopurine metabolites in patients with autoimmune hepatitis. *Aliment Pharmacol Ther* 2013; **37**: 640-646 [PMID: 23347359 DOI: 10.1111/apt.12223]
 - 31 **Danielsson A, Prytz H.** Oral budesonide for treatment of autoimmune chronic active hepatitis. *Aliment Pharmacol Ther* 1994; **8**: 585-590 [PMID: 7696446]
 - 32 **Czaja AJ.** Autoimmune hepatitis in special patient populations. *Best Pract Res Clin Gastroenterol* 2011; **25**: 689-700 [PMID: 22117635 DOI: 10.1016/j.bpg.2011.09.011]
 - 33 **Czaja AJ.** Features and consequences of untreated type 1 autoimmune hepatitis. *Liver Int* 2009; **29**: 816-823 [PMID: 19018980 DOI: 10.1111/j.1478-3231.2008.01904.x]
 - 34 **Czaja AJ.** Advances in the current treatment of autoimmune hepatitis. *Dig Dis Sci* 2012; **57**: 1996-2010 [PMID: 22476586 DOI: 10.1007/s10620-012-2151-2]
 - 35 **Richardson PD, James PD, Ryder SD.** Mycophenolate mofetil for maintenance of remission in autoimmune hepatitis in patients resistant to or intolerant of azathioprine. *J Hepatol* 2000; **33**: 371-375 [PMID: 11019991 DOI: 10.1016/S0168-8278(00)80271-8]
 - 36 **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 [PMID: 15152283]
 - 37 **Brunt EM, Di Bisceglie AM.** Histological changes after the use of mycophenolate mofetil in autoimmune hepatitis. *Hum Pathol* 2004; **35**: 509-512 [PMID: 15116334 DOI: 10.1016/j.humpath.2003.10.017]
 - 38 **Chatur N, Ramji A, Bain VG, Ma MM, Marotta PJ, Ghent CN, Lilly LB, Heathcote EJ, Deschenes M, Lee SS, Steinbrecher UP, Yoshida EM.** 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 [PMID: 15998421 DOI: 10.1111/j.1478-3231.2005.01107.x]
 - 39 **Czaja AJ, Carpenter HA.** Empiric therapy of autoimmune hepatitis with mycophenolate mofetil: comparison with conventional treatment for refractory disease. *J Clin Gastroenterol* 2005; **39**: 819-825 [PMID: 16145346]
 - 40 **Inductivo-Yu I, Adams A, Gish RG, Wakil A, Bzowej NH, Frederick RT, Bonacini M.** Mycophenolate mofetil in autoimmune hepatitis patients not responsive or intolerant to standard immunosuppressive therapy. *Clin Gastroenterol Hepatol* 2007; **5**: 799-802 [PMID: 17509945 DOI: 10.1016/j.cgh.2007.02.030]
 - 41 **Hlivko JT, Shiffman ML, Stravitz RT, Luketic VA, Sanyal AJ, Fuchs M, Sterling RK.** A single center review of the use of mycophenolate mofetil in the treatment of autoimmune hepatitis. *Clin Gastroenterol Hepatol* 2008; **6**: 1036-1040 [PMID: 18586559 DOI: 10.1016/j.cgh.2008.04.006]
 - 42 **Hennes EM, Oo YH, Schramm C, Denzer U, Buggisch P, Wiegand C, Kanzler S, Schuchmann M, Boecker W, Galle PR, Adams DH, Lohse AW.** Mycophenolate mofetil as second line therapy in autoimmune hepatitis? *Am J Gastroenterol* 2008; **103**: 3063-3070 [PMID: 18853972 DOI: 10.1111/j.1572-0241.2008.02180.x]
 - 43 **Wolf DC, Bojito L, Facciuto M, Lebovics E.** Mycophenolate mofetil for autoimmune hepatitis: a single practice experience. *Dig Dis Sci* 2009; **54**: 2519-2522 [PMID: 19082888 DOI: 10.1007/s10620-008-0632-0]
 - 44 **Malekzadeh R, Nasseri-Moghaddam S, Kaviani MJ, Taheri**

- H, Kamalian N, Sotoudeh M. Cyclosporin A is a promising alternative to corticosteroids in autoimmune hepatitis. *Dig Dis Sci* 2001; **46**: 1321-1327 [PMID: 11414311]
- 45 **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 [PMID: 9934764]
- 46 **Van Thiel DH**, Wright H, Carroll P, Abu-Elmagd K, Rodriguez-Rilo H, McMichael J, Irish W, Starzl TE. Tacrolimus: a potential new treatment for autoimmune chronic active hepatitis: results of an open-label preliminary trial. *Am J Gastroenterol* 1995; **90**: 771-776 [PMID: 7537444]
- 47 **Heneghan MA**, Rizzi P, McFarlane IG, Portmann B, Harrison PM. Low dose tacrolimus as treatment of severe autoimmune hepatitis: potential role in remission induction. *Gut* 1999; **44**: A61
- 48 **Aqel 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 [PMID: 15365410]
- 49 **Larsen FS**, Vainer B, Eefsen M, Bjerring PN, Adel Hansen B. Low-dose tacrolimus ameliorates liver inflammation and fibrosis in steroid refractory autoimmune hepatitis. *World J Gastroenterol* 2007; **13**: 3232-3236 [PMID: 17589903]
- 50 **Barth E**, Clawson J. A Case of Autoimmune Hepatitis Treated with Rituximab. *Case Rep Gastroenterol* 2010; **4**: 502-509 [PMID: 21151634 DOI: 10.1159/000322693]
- 51 **Weiler-Normann C**, Schramm C, Quaas A, Wiegard C, Glaubke C, Pannicke N, Möller S, Lohse AW. Infliximab as a rescue treatment in difficult-to-treat autoimmune hepatitis. *J Hepatol* 2013; **58**: 529-534 [PMID: 23178709 DOI: 10.1016/j.jhep.2012.11.010]
- 52 **Burak KW**, Urbanski SJ, Swain MG. Successful treatment of refractory type 1 autoimmune hepatitis with methotrexate. *J Hepatol* 1998; **29**: 990-993 [PMID: 9875647 DOI: 10.1016/S0168-8278(98)80128-1]
- 53 **Czaja AJ**, Carpenter HA, Lindor KD. Ursodeoxycholic acid as adjunctive therapy for problematic type 1 autoimmune hepatitis: a randomized placebo-controlled treatment trial. *Hepatology* 1999; **30**: 1381-1386 [PMID: 10573515 DOI: 10.1002/hep.510300603]
- 54 **Czaja AJ**. Emerging opportunities for site-specific molecular and cellular interventions in autoimmune hepatitis. *Dig Dis Sci* 2010; **55**: 2712-2726 [PMID: 20108036 DOI: 10.1007/s10620-009-1122-8]
- 55 **Czaja AJ**. Drug choices in autoimmune hepatitis: part B--Nonsteroids. *Expert Rev Gastroenterol Hepatol* 2012; **6**: 617-635 [PMID: 23061712 DOI: 10.1586/egh.12.38]
- 56 **Aw MM**, Dhawan A, Samyn M, Bargiota A, Mieli-Vergani G. Mycophenolate mofetil as rescue treatment for autoimmune liver disease in children: a 5-year follow-up. *J Hepatol* 2009; **51**: 156-160 [PMID: 19446911 DOI: 10.1016/j.jhep.2009.02.024]
- 57 **Baven-Prong AM**, Coenraad MJ, van Buuren HR, de Man RA, van Erpecum KJ, Lamers MM, Drenth JP, van den Berg AP, Beuers UH, den Ouden J, Koek GH, van Nieuwkerk CM, Bouma G, Brouwer JT, van Hoek B. The role of mycophenolate mofetil in the management of autoimmune hepatitis and overlap syndromes. *Aliment Pharmacol Ther* 2011; **34**: 335-343 [PMID: 21668459 DOI: 10.1111/j.1365-2036.2011.04727.x]
- 58 **Sharzehi K**, Huang MA, Schreiberman IR, Brown KA. Mycophenolate mofetil for the treatment of autoimmune hepatitis in patients refractory or intolerant to conventional therapy. *Can J Gastroenterol* 2010; **24**: 588-592 [PMID: 21037986]
- 59 **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 [PMID: 21238519 DOI: 10.1016/j.jhep.2010.12.032]
- 60 **Seikaly MG**. Mycophenolate mofetil--is it worth the cost? The in-favor opinion. *Pediatr Transplant* 1999; **3**: 79-82 [PMID: 10359036 DOI: 10.1034/j.1399-3046.1999.00015.x]
- 61 **Jackson LD**, Song E. Cyclosporin in the treatment of corticosteroid resistant autoimmune chronic active hepatitis. *Gut* 1995; **36**: 459-461 [PMID: 7698710 DOI: 10.1136/gut.36.3.459]
- 62 **Alvarez F**, Ciocca M, Cañero-Velasco R, Ramonet M, de Davila MT, Cuarterolo M, Gonzalez T, Jara-Vega P, Camarena C, Brochu P, Drut R, Alvarez E. Short-term cyclosporine induces a remission of autoimmune hepatitis in children. *J Hepatol* 1999; **30**: 222-227 [PMID: 10068099]
- 63 **Reff ME**, Carner K, Chambers KS, Chinn PC, Leonard JE, Raab R, Newman RA, Hanna N, Anderson DR. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. *Blood* 1994; **83**: 435-445 [PMID: 7506951]
- 64 **Dörner T**, Isenberg D, Jayne D, Wiendl H, Zillikens D, Burmester G. Current status on B-cell depletion therapy in autoimmune diseases other than rheumatoid arthritis. *Autoimmun Rev* 2009; **9**: 82-89 [PMID: 19716441 DOI: 10.1016/j.autrev.2009.08.007]
- 65 **Tranchida P**, Bayerl M, Voelpel MJ, Palutke M. Testicular ischemia due to intravascular large B-cell lymphoma: a novel presentation in an immunosuppressed individual. *Int J Surg Pathol* 2003; **11**: 319-324 [PMID: 14615832 DOI: 10.1177/106689690301100414]
- 66 **Burak KW**, Swain MG, Santodomingo-Garzon T, Lee SS, Urbanski SJ, Aspinall AI, Coffin CS, Myers RP. Rituximab for the treatment of patients with autoimmune hepatitis who are refractory or intolerant to standard therapy. *Can J Gastroenterol* 2013; **27**: 273-280 [PMID: 23712302]
- 67 **Kolmos HJ**. The bactericidal action of benzoic acid and sodium acetate on the gram-negative flora of dialysis fluid. *Acta Pathol Microbiol Scand B* 1976; **84B**: 259-264 [PMID: 788461 DOI: 10.1097/00005176-199501000-00005]
- 68 **Czaja AJ**, Cookson S, Constantini PK, Clare M, Underhill JA, Donaldson PT. Cytokine polymorphisms associated with clinical features and treatment outcome in type 1 autoimmune hepatitis. *Gastroenterology* 1999; **117**: 645-652 [PMID: 10464141]
- 69 **Cookson S**, Constantini PK, Clare M, Underhill JA, Bernal W, Czaja AJ, Donaldson PT. Frequency and nature of cytokine gene polymorphisms in type 1 autoimmune hepatitis. *Hepatology* 1999; **30**: 851-856 [PMID: 10498633]
- 70 **Weiler-Normann C**, Wiegard C, Schramm C, Lohse AW. A case of difficult-to-treat autoimmune hepatitis successfully managed by TNF-alpha blockade. *Am J Gastroenterol* 2009; **104**: 2877-2878 [PMID: 19888264 DOI: 10.1038/ajg.2009.433]
- 71 **O'Steen WK**, Shear CR, Anderson KV. Extraocular muscle degeneration and regeneration after exposure of rats to incandescent radiant energy. *J Cell Sci* 1975; **18**: 157-177 [PMID: 1141391]
- 72 **Jothimani D**, Cramp ME, Mitchell JD, Cross TJ. Treatment of autoimmune hepatitis: a review of current and evolving therapies. *J Gastroenterol Hepatol* 2011; **26**: 619-627 [PMID: 21073674 DOI: 10.1111/j.1440-1746.2010.06579.x]
- 73 **Miyake Y**, Iwasaki Y, Kobashi H, Yasunaka T, Ikeda F, Takaki A, Okamoto R, Takaguchi K, Ikeda H, Makino Y, Ando M, Sakaguchi K, Yamamoto K. Efficacy of ursodeoxycholic acid for Japanese patients with autoimmune hepatitis. *Hepatol Int* 2009; **3**: 556-562 [PMID: 19847577 DOI: 10.1007/s12072-009-9155-9]

P- Reviewers: Al-Shamma S, Schramm C, Yoshizawa K
S- Editor: Song XX **L- Editor:** A **E- Editor:** Liu SQ





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

