ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2017 September 7; 23(33): 6009-6196

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

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Weekly Volume 23 Number 33 September 7, 2017

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World Journal of Gastroenterology
Volume 23 Number 33 September 7, 2017

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AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 1375 experts in gastroenterology and hepatology from 68 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

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World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2017 edition of Journal Citation Reports® cites the 2016 impact factor for *WJG* as 3.365 (5-year impact factor: 3.176), ranking *WJG* as 29th among 79 journals in gastroenterology and hepatology (quartile in category Q2).

FLYLEAF **I-IX** Editorial Board

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORIAL OFFICE
Jin-Lei Wang, Director
Yuan Qi, Vice Director
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World Journal of Gastroenterology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
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http://www.wjgnet.com

PUBLICATION DATE
September 7, 2017

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Full instructions are available online at http://www.wjgnet.com/bpg/gerinfo/204

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World J Gastroenterol 2017 September 7; 23(33): 6030-6048

DOI: 10.3748/wjg.v23.i33.6030

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Autoimmune hepatitis: Standard treatment and systematic review of alternative treatments

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Author contributions: Terziroli Beretta-Piccoli B contributed to writing up the manuscript; Mieli-Vergani G and Vergani D contributed to critical revision and final approval of the report.

Conflict-of-interest statement: No potential conflicts of interest.

Manuscript source: Invited manuscript

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Received: June 6, 2017
Peer-review started: June 7, 2017
First decision: June 22, 2017
Revised: July 18, 2017
Accepted: August 2, 2017
Article in press: August 2, 2017
Published online: September 7, 2017

Abstract

Autoimmune hepatitis is a rare chronic inflammatory liver disease, affecting all ages, characterised by elevated transaminase and immunoglobulin G levels, positive autoantibodies, interface hepatitis at liver histology and good response to immunosuppressive treatment. If untreated, it has a poor prognosis. The aim of this review is to summarize the evidence for standard treatment and to provide a systematic review on alternative treatments for adults and children. Standard treatment is based on steroids and azathioprine, and leads to disease remission in 80%-90% of patients. Alternative first line treatment has been attempted with budesonide or cyclosporine, but their superiority compared to standard treatment remains to be demonstrated. Second-line treatments are needed for patients not responding or intolerant to standard treatment. No randomized controlled trials have been performed for second-line options. Mycophenolate mofetil is the most widely used second-line drug, and has good efficacy particularly for patients intolerant to azathioprine, but has the major disadvantage of being teratogenic. Only few and heterogeneous data on cyclosporine, tacrolimus, everolimus and sirolimus are available. More recently, experience with the anti-tumour necrosis factor-alpha infliximab and the anti-CD20 rituximab has been published, with ambivalent results; these agents may have severe side-effects and their use should be restricted to specialized centres. Clinical trials with new therapeutic options are ongoing.

Key words: Autoimmune hepatitis; Standard treatment; Second-line treatment; Adults; Children

Core tip: The first part of this review summarizes the standard therapeutic approach for autoimmune hepatitis (steroids and azathioprine) and the evidence on which it is based. The second part reviews systematically published data on first and second line alternative treatments. This information is summarized in two comprehensive tables, one for adult and one for paediatric patients.

Terziroli Beretta-Piccoli B, Mieli-Vergani G, Vergani D. Autoimmune hepatitis: Standard treatment and systematic review of alternative treatments. *World J Gastroenterol* 2017; 23(33): 6030-6048 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i33/6030.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i33.6030

INTRODUCTION

Autoimmune hepatitis (AIH) is a rare inflammatory liver disease of unknown origin characterised by high transaminase and immunoglobulin G (IgG) levels, positive autoantibodies, and, histologically, by interface hepatitis[1-4]. The condition affects all ages, and has a female preponderance[5]. There is no single diagnostic test[1,2]. The International Autoimmune Hepatitis Group (IAIHG) established comprehensive diagnostic criteria in 1993[6], based on expert opinion, intended to be used for research purposes. After their evaluation in a number of studies, the criteria were updated in 1999[7]. A simplified, clinical practice-friendly version was published in 2008[8]. These criteria are intended to help in guiding diagnosis and decision on therapy initiation in patients presenting with a clinical picture suggesting AIH, and have received extensive external validation since publication[9-11].

AIH is divided in type 1 and type 2, the latter being rare in adults and representing 30% of juvenile AIH. The distinction is made serologically: type 1 AIH is positive for anti-nuclear antibodies (ANA), and/or anti-smooth muscle antibodies (SMA), while type 2 AIH is positive for anti-liver kidney microsomal antibodies type 1 (anti-LKM1) and/or anti-liver cytosol type 1 (anti-LC1)[12].

AIH is the first liver disease for which pharmacologic treatment has been shown to improve survival. Indeed, it has an excellent response to steroid-based immunosuppressive therapy, with a reported response rate of 75%-90%[2]. Steroid-response is a crucial feature of AIH, and it is part of the IAIHG revised diagnostic criteria[7]. Lack of response to steroids should prompt a review of the diagnosis.

Treatment indications

If untreated, AIH has a severe prognosis. This knowledge derives from early clinical trials, when "HBsAg-negative hepatitis" (as AIH was called then) patients were treated with corticosteroids *vs* placebo. One placebo controlled study reported a 5-year survival rate of 32% in untreated patients *vs* 82% in patients treated with steroids[13]. According to the guidelines on the management of AIH by the American Association for the Study of Liver Diseases (AASLD)[2], the 6-mo survival rate in untreated patients is about 60%. Therefore, once diagnosed, AIH should be treated promptly. Elderly patients with mild pauci- or a-symptomatic disease, who have a high risk of developing steroid side effects, may be an exception, and in this clinical context treatment *vs* watchful waiting should be carefully evaluated case by case[14-16]. Untreated patients need a close follow-up. Treatment must be always initiated in the presence of clinical symptoms, severe biochemical and/or histological disease activity. Younger subjects, particularly children and adolescents, who have a more aggressive disease, should be treated without delay[17].

Treatment aims

The aim of treatment is disease remission, which is reached if the following criteria are met: (1) absence of clinical symptoms; (2) normal transaminase levels; and (3) normal IgG levels. In children/adolescents, negative or very low-titre autoantibodies (< 1:20 for ANA/SMA; < 1:10 for anti-LKM1) are an additional criterion of remission[3], which remains to be evaluated in adults by longitudinal studies.

In the past, transaminase levels below twice the upper limit of normal (ULN) have been considered proof of remission, but it is now clear that patients with abnormal transaminase levels have progressive disease[2,18]. Once remission is achieved, the lowest possible dose of immunosuppressive drugs should be used to maintain long-term remission with no or minimal side effects.

Disease relapse is defined as transaminase levels rising above the ULN after remission[12]. Relapse occurs mostly if the dose of the immunosuppressive drugs is reduced, or in case of non-adherence. Non-adherence is a frequent clinical problem, particularly in adolescents[19] and young adults, and is often due to real or perceived treatment side effects. It should always be suspected in case of relapse while on a stable dose of immunosuppressive drugs.

AIM AND METHODOLOGY OF THE SYSTEMATIC REVIEW

The aim of this review is, in its first part, to critically summarize the evidence on which standard AIH treatment (prednisone and azathioprine) is based, and, in its second part, to provide a systematic review of the published data on alternative treatments. For the purpose of the systematic review of the literature on alternative AIH treatment, publications cited in PubMed (http://www.ncbi.nlm.nih.gov/pubmed) were

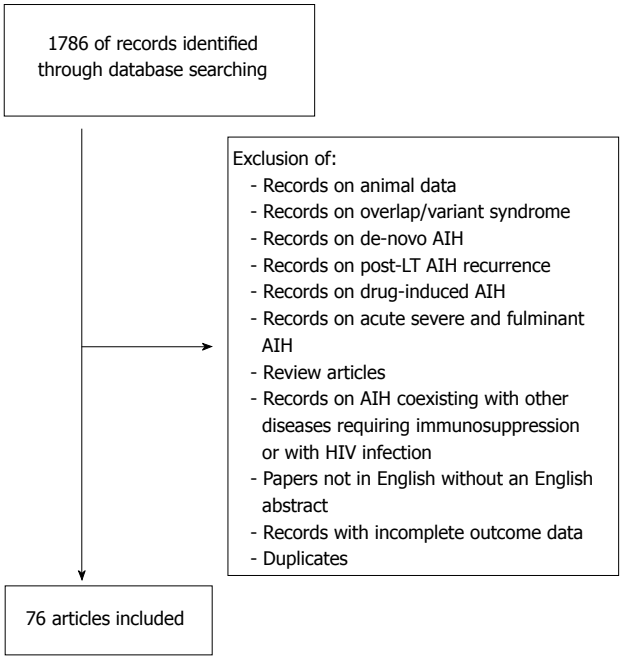

Figure 1 Selection of relevant articles for the systematic literature review on alternative AIH treatments. AIH: Autoimmune hepatitis; LT: Liver transplantation.

Table 1 Proposed schedule of prednisone tapering during remission-induction therapy in adults[25]

	Prednisone mg/d	Azathioprine
Week 1	60.0	Check transaminase levels every week before reducing the prednisone dose: if transaminase levels stop decreasing, add azathioprine 1-2 mg/kg per day, if jaundice is subsiding
Week 2	50.0	
Week 3	40.0	
Week 4	30.0	
Week 5	25.0	
Week 6	20.0	
Week 7	15.0	
Week 8-9	12.5	
Week 10-11	10.0	
If severe steroid side effects: consider reducing to 2.5 mg/d for 2 wk and then stopping prednisone		

Table 2 Proposed schedule of prednisone tapering during remission-induction therapy in children[2,12]

	Prednisone mg/kg/d	Azathioprine
Week 1	2.0	Check transaminase levels every week before reducing the prednisone dose: if transaminase levels stop decreasing, add azathioprine starting with 0.5 mg/kg per day, if jaundice is subsiding, at increasing doses up to 2-2.5 mg/kg/d until biochemical control
Week 2	1.75	
Week 3	1.50	
Week 4	1.25	
Week 5	1.00	
Week 6	0.75	
Week 7	0.50	
Week 8-9	0.25	
Week 10-11	0.10-0.20	
If severe steroid side effects: consider reducing to 2.5 mg/d for 2 wk and then stopping prednisone		

selected using the search words "autoimmune hepatitis" and "treatment". Citations were chosen on the basis of their relevance to the aim of this article (Figure 1). Fundamental characteristics of the abstracts judged pertinent to the review were noted, and full-length original articles were selected from the abstracts. Seventy-six articles were identified, 22 of them are not discussed in this review because of anedoctal reporting, the remaining 54 are included in Table 1 (adults) and Table 2 (children). Children/adolescents have a more aggressive disease, with a more frequent acute presentation[20] and therefore need a different management[17]. For this reason, the present review article discusses adult and pediatric treatment separately.

STANDARD TREATMENT

Why do we treat autoimmune hepatitis with steroids and azathioprine?

Standard treatment is based on steroids and azathioprine (Table 1). A systematic review of randomized controlled trials focused on these two drugs up to 2009 was published in 2010[21]. The exact azathioprine mechanism of action is unclear, but it is most probably linked to suppression of nucleic acid synthesis. The first evidence for steroid benefit in inducing remission and improving survival in treatment-naïve AIH stems from three trials performed in the 1970s, which demonstrated a significant better survival in patients with so called "HBsAg-negative chronic active liver disease" treated with steroids[22-24] in comparison to untreated patients. It should be noted that at that time the hepatitis C virus (HCV) had not been discovered and it is likely that some patients with HCV were included in the trials, although "HBsAg-negative chronic active hepatitis" was characterised by high globulin levels, female preponderance, and presence of autoantibodies, all features of AIH[13]. The benefit of steroid treatment would have probably been even greater if HCV-patients had been excluded[25]. In the Royal Free Hospital trial[22], 49 well characterised patients, including children, were randomised in a steroid-treated group (prednisolone 15 mg/d) and a placebo group. Mortality rate was 14% in the treated group, and 56% in the placebo group, with a follow-up ranging from 30 to 72 mo. The trial from the Mayo Clinic published one year later[23] included 63 patients, divided into four groups. Two groups were treated with protocols similar to current guidelines: the first group was treated with prednisone alone starting with 60 mg/d, tapered to a maintenance dose of 20 mg/d over 4 wk, the second group received prednisone 30 mg/d tapered to a maintenance dose of 10 mg/d combined with azathioprine at a fixed dose of 50 mg/d. The remaining groups were treated with azathioprine alone 100mg/d and placebo, respectively. The mortality rate in the first and second group was very low (6% and 7%), compared to a mortality rate of 36% and 41% in the groups treated with azathioprine

alone or placebo. The follow-up period ranged from 3 mo to 3.5 years. The side effect rate was lower in the azathioprine-prednisone group than in the prednisone alone group (10% *vs* 44%). A trial from King's College Hospital published in 1973[24] included 47 patients, divided into two groups, one treated with prednisone 15 mg/d, and the other with azathioprine alone, 75 mg/d, with a follow-up of two years. The mortality rate in the prednisone group was 5%, as compared to a mortality rate of 24% in the azathioprine group. From these early trials it is clear that prednisone is very effective in treating AIH, and that azathioprine alone is not able to obtain disease remission. Following these reports, strategies were sought to optimize the treatment schedule, *i.e.* to find the minimal doses of prednisone or prednisone/azathioprine able to control the disease with minimal side effects. A trial published in 1975[26] included 120 patients and compared four different schedules: (1) prednisone starting at 60 mg/d tapered to a maintenance dose of 20 mg/d; (2) prednisone starting at 30 mg/d tapered to 10 mg/d together with a 50 mg/d fixed dose of azathioprine; (3) prednisone at 60 mg/d tapered to a maintenance dose of 10 mg/d given on alternate days; and (4) placebo or azathioprine on a fixed dose of 100 mg/d without steroids, as control. Biochemical remission was achieved in 80% of patients in the first two groups, in 74% in the third group and in 34% in the control group. Histological remission was achieved in 57% and 60% of patients in the first two groups, but in only 19% and 24% in the third and in the control group. Side effects were less frequent in patients treated with prednisone/azathioprine from disease presentation, for which a lower dose of prednisone was used, leading to the conclusion that combined treatment is preferable. Of note, this trial enrolled "post-pubertal subjects", including patients from the age of 12 years. An additional trial published in 1982[27] compared a fixed low-dose prednisone alone (10 mg/d for body weight < 70 kg, 15 mg/d for body weight ⩾ 70 kg) in 37 patients with a fixed low-dose azathioprine alone (5 mg/kg per week for the first 2 wk, subsequently 10 mg/kg per week) in 47 patients. Mortality was very high in both groups at 1 year (27% and 28% respectively), indicating that a low prednisone dose and azathioprine alone are inadequate.

Despite the limitations of these early trials, prednisone ± azathioprine remains the mainstay of treatment for AIH, several reports showing high remission rates and favourable outcomes in both adult and juvenile AIH[20,28-38].

Of note, azathioprine monotherapy, though unsuccessful in the induction of remission, is effective in adults as maintenance therapy, at a dose of 2 mg/kg per day[39]. A 5-patient report suggests that it may be effective also in children[40]. In a recent retrospective series, 87% of 66 children with AIH were reported to maintain sustained biochemical remission (normal transaminase levels) in association with low 6-thioguanine nucleotides (TGN) levels (50-250 pmol 8 x 10 red blood cell cont) on an azathioprine dose of 1.2-1.6 mg/kg per day with or without associated steroids[41].

How to use prednisone and azathioprine

There is no treatment schedule applicable to all AIH patients. The suggested algorithms and treatment schedules must be tailored to the single patient, taking into account the severity of the disease, age and co-morbidities[1].

The AASLD guidelines published in 2010[2] recommend two alternative schedules: either prednisone alone at a dose of 60 mg/d or a combination of prednisone 30 mg/d and azathioprine 50 mg/d as initial treatment, favouring the latter because of fewer steroid side-effects[26]. However, as azathioprine can be hepatotoxic, particularly in cirrhotic and jaundiced patients[25], the more recent guidelines by the European Association for the Study of the Liver (EASL) recommend that it is added after two weeks of steroid monotherapy [predniso(lo)ne 1 mg/kg per day in adults], when partial disease control has been achieved[1]. In addition, this approach avoids the problem of distinguishing between azathioprine-induced hepatotoxicity and non-response, this distinction being an important issue in clinical practice. A retrospective series of 133 adult patients reports better results with a combination of steroids and another immunosuppressant (azathioprine in 96%, other unspecified drugs in 4%) from disease presentation compared to steroids alone or steroids followed by the addition of azathioprine/other immunosuppressants. Of note, only 2% of the patients included in this study were jaundiced at presentation[42], possibly explaining the high remission rate on azathioprine, without hepatotoxicity.

Prednisone should be rapidly tapered (Table 1) to minimise steroid side effects. This rapid decrease of the prednisone dose requires weekly checks of the transaminase levels to monitor response. Azathioprine should be added if the transaminase levels stop decreasing on steroid treatment alone (Table 1). Ultimately 85% of the patients will need azathioprine in addition to low-dose prednisone[12]. This protocol was originally used for children[25], but it is suitable to treat adult patients as well, because it allows to avoid azathioprine in a small proportion of patients and especially because it limits steroid side effects, which are often the reason for non-adherence. The initial recommended dose of azathioprine in adults is 50 mg/d or 1 mg/kg per day[2]. If steroid side effects are severe and require steroid discontinuation, the azathioprine dose is increased to 2 mg/kg per day.[39,43]

In children, the recommended treatment schedule is similar to that of adults, but a higher steroid dose is required due to the more aggressive disease course in this age group (Table 2). Children were included in early clinical trials[22,26], but a sub-analysis of paediatric patients was not performed, and the numbers were small. Current recommendations are based on series

from large centres, which report a remission rate of about 90% using predniso(lo)ne ± azathioprine[20,35,36]. Conventional treatment of juvenile AIH consists of prednisolone (or prednisone) 2 mg/kg per day (maximum 60 mg/d), decreased over a period of 4 to 8 wk in parallel to the decline of transaminase levels, to a maintenance dose of 2.5-5 mg/d (Table 2). Long-term low daily doses are not associated with impaired adult height[44]. The timing for the addition of azathioprine as a steroid-sparing agent varies according to the protocols used in different centres. In some, azathioprine is added only in the presence of steroid adverse effects, or if the transaminase levels stop decreasing on steroid treatment alone. In other centres azathioprine is added after a few weeks of steroid treatment in all patients, when the serum aminotransferase levels begin to decrease. Some centres use a combination of steroids and azathioprine from the beginning, but caution is recommended because of the azathioprine hepatotoxicity mentioned above[1,2,34]. The initial recommended azathioprine dose is 0.5 mg/kg per day[12], which can be increased to 1-2 mg/kg per day until normalization of the transaminase levels is reached. As in adults, azathioprine alone has been shown to be able to control the disease as long-term maintenance therapy, although only in retrospective series[40,41,45].

As AIH is very sensitive to prednisone, a maintenance dose of 5 mg/d is effective in controlling the disease, usually with, but sometimes without, azathioprine. Steroid reduction below 5 mg/d (or 2.5 mg/d in children) requires careful monitoring of transaminase levels, even if implemented after long-term disease remission. The dose should be reduced very slowly, *e.g.,* by 1 mg per month if 1 mg prednisone tablets are available, or, if not available, by reducing to 5-2.5 mg on alternate days for 1-2 mo, and then to 2.5 mg/d.

Side effects of steroids and azathioprine

Steroid side effects are dose and time dependent, and arise if a dose exceeding 7.5-10 mg/d is administered over several months[25]. The most common side effect is the development of cushingoid features. In a retrospective monocentric study of 103 adult AIH patients[46], mostly treated according to a standard protocol with a steroid starting dose of 1 mg/kg per day and a mean follow-up period of 95 mo, 15.5% developed cushingoid features. Although not severe, these changes are often a great concern for the patients, and may lead to non-adherence, with the dangerous consequence of poor disease control. Almost half of AIH patients discontinue steroids because of cosmetic changes (including acne) or obesity[47]. Severe, but less frequent steroid side effects include osteoporosis, brittle diabetes, cataract, psychosis and hypertension[2]. They are mainly related to the initial high dose, and are reversible[43,46]. Monitoring of these complications is advisable, including ophthalmologic controls and bone density scans on a regular basis.

Azathioprine side effects affect 10%-20% of patients and include hepatotoxicity, acute cholestatic hepatitis, pancreatitis, nausea and vomiting, rash, bone marrow suppression, veno-occlusive disease, opportunistic infections, and malignancy[2]. The most common side effect is bone marrow suppression, which is unpredictable, and can be aggravated by concomitant cytopaenia due to liver disease and hypersplenism. Haematological monitoring is necessary, particularly at the beginning of treatment. Measurement of erythrocyte concentrations of thiopurine methyltransferase (TPMT) activity may be advisable before institution of azathioprine therapy, but does not invariably predict response to the drug or toxicity[48,49]. TPMT genotyping predicts azathioprine haematological toxicity in those rare individuals with variant homozygosity, while heteroxygotes do not experience more toxicity than wild-type patients[50]. Five percent of patients develop early intolerance, most frequently with nausea and vomiting.

A possible complication of long-term treatment with azathioprine is the development of malignancies. In one study aiming at investigating disease control by azathioprine monotherapy at a dose of 2 mg/kg per day, 5 of 72 patients (7%) developed malignancies over a median follow up of 12 years[39]. Recently, two cases of T-cell lymphoma in adolescents treated with azathioprine for AIH were reported[51]. Thus, a lower azathioprine dose in association with low-dose steroids may be preferable for long-term maintenance therapy. Azathioprine is considered to be safe in pregnancy[52-54].

Measurement of the azathioprine metabolites 6-TGN and 6-methylmercaptopurine can be helpful in identifying drug toxicity and non-adherence, and in distinguishing azathioprine hepatotoxicity from disease non-response, as shown by a retrospective study in adults[55], and a small prospective study in children[56], but an ideal therapeutic level of the 6-thioguanine metabolites has not been established for AIH, unlike for inflammatory bowel diseases (IBD).

Treatment withdrawal

The AASLD[2] and the EASL guidelines[1] recommend a treatment duration of at least 2 and 3 years respectively, and both advise against a trial of treatment withdrawal before 2 years of complete biochemical remission. They recommend performing a liver biopsy before attempting treatment discontinuation, because histological inflammatory activity can still be present despite biochemical remission, predicting relapse. A recent report on 28 patients in whom treatment was withdrawn without histological evaluation, shows that the 54% of patients who did not relapse had transaminase levels less than half the ULN and IgG levels below 12 g/L on low-dose monotherapy (azathioprine/mercaptopurine or steroids) for at

least 2 years, suggesting that patients meeting these parameters may avoid pre-withdrawal liver biopsy[57]. This suggestion, however, requires confirmation by other centres.

Relapse after treatment withdrawal is frequent, having been reported in some 80% of patients[1,2,58]. Repeated relapses are associated with a poorer prognosis and a higher rate of drug side effects[2]. For this reason, patients experiencing a first relapse episode after appropriate evaluation of disease remission, should undergo life-long low-dose immunosuppressive therapy[1].

For AIH type 2, relapse is almost universal if treatment is completely withdrawn[20], and long-term low-dose maintenance therapy should be planned from the diagnosis. Since this condition mostly affects children, adolescents and young adults, life-long duration of the therapy should be discussed and carefully explained to the patients and their family.

ALTERNATIVE TREATMENTS

For patients who experience azathioprine side effects, ranging from the relatively frequent early gastrointestinal intolerance to the rarer and more serious bone marrow suppression, and for poor responders to standard treatment, alternative regimens are needed, primarily to avoid high-dose steroid side-effects. A systematic review of the published clinical data on pharmacological treatments different from prednisone and azathioprine is provided in this section. Treatments for whom there are only anecdotal data are not discussed cyclophosphamide[59], methotrexate[60-62], ursodeoxycholic acid[63-69], etanercept[70], plasma exchange[71], intravenous immunoglobulin[72], leukapheresis[73], chloroquine[74], thymostimulin[75], deflazacort[76,77], saireito[78], sympathomimetic amines[79], glycyrrhizin[80], fenofibrate[81].

Budesonide

Budesonide is a glucocorticosteroid with a potent topical effect and a high first-pass uptake (> 90%) in the healthy liver, thus appearing ideal for treating AIH. The first reports on its use included small numbers of patients at different stages of disease and gave controversial results[79-83] (Table 3). Subsequently, a large randomized controlled trial in 203 AIH patients (including 46 children/adolescents) was carried out, involving several European centres[82] (Table 3). Cirrhotic patients were excluded, because the first pass hepatic extraction of budesonide may be reduced in cirrhosis due to portosystemic shunting. In fact, severe complications have been reported in cirrhotic patients on budesonide[83,84], including portal vein thrombosis and Budd-Chiari syndrome, indicating that AIH patients with cirrhosis at diagnosis (at least one third) should not be treated with budesonide. The trial primary end-point was biochemical remission (defined as normalization of transaminase levels) in absence of steroid side effects. The overall results of the trial showed better response to budesonide/azathioprine than to prednisone/azathioprine treatment, the primary end-point being achieved in 60% of patients given budesonide *vs* 38.8% of those given prednisone[82]. These response rates, however, are below the remission rates achieved with standard treatment, and this has raised concerns. In the control arm, the prednisone dose was reduced as per-protocol, irrespective of the course of the clinical and biochemical response, an approach not recommended in AIH treatment[1], which should be tailored to individual patient response. The initial prednisone dose (40 mg/d) was low at least for children/adolescents[1,12], who should be treated with 2 mg/kg per day (up to 60 mg/d). All patients were prescribed azathioprine from the beginning, irrespective of the presence of jaundice, raising the possibility that the low response rate might be partly due to azathioprine hepatotoxicity[85]. The trial included treatment naïve patients and patients experiencing disease relapse, who are likely to represent a subgroup of poor responders[85]. Moreover, only transaminase levels were used to define biochemical remission, while the combination of normal transaminase and IgG/gammaglobulin levels best predicts absence of histological activity[46,86,87].

Though budesonide is still not recommended as first line therapy for AIH[1], it may be a valid alternative for the maintenance of remission long-time, particularly for patients experiencing steroid side effects. In a retrospective study 60 patients with either prednisolone side effects or dependence on a relative high dose of prednisolone were switched to budesonide[88]: the biochemical remission rate at 6 mo was 55%, and 25% of the patients needed to be switched back to prednisone due to budesonide side-effects or insufficient response. However, all patients who were in remission at the time of switching remained in remission. These findings indicate that budesonide is effective in maintaining remission in patients who have achieved it with prednisone, but also that it is not free of side effects, and that, not surprisingly, it is not effective in patients resistant to prednisone, as prednisone and budesonide share the same receptor.

A sub-analysis of the paediatric population (46 patients aged 9 to 17) enrolled in the budesonide trial[89] reported no significant difference in biochemical remission rate at 6 and 12 mo between the budesonide and the prednisone groups (32% and 33% at 6 mo and 50% and 42% at 12 mo, respectively) (Table 4). The frequency of steroid side effects was also not different, being 47% in the budesonide group and 63% in the prednisone group, apart from a lower mean weight gain in the budesonide group. The remission rate was well below that achieved with standard treatment, therefore, budesonide cannot be recommended for the treatment of children/

Table 3 Published data on autoimmune hepatitis treatment different from steroids and azathioprine in adults (from age 16)

Reference, yr	Country	Number and type of patients	Design	Outcome	Follow-up	Dose	Safety
Budesonide							
Danielsson *et al*[79], 1994	Sweden	13 naïve	Prospective	Significant decrase of mean transaminase levels	9 mo	6-8 mg/d	Plasma cortisol reduction in cirrhotic patients
Czaja *et al*[80], 2000	United States	10 AZA-NR	Prospective	3/10 BR	2-12 mo	9 mg/d	All patients had side-effects
Wiegand *et al*[81], 2005	Germany	12 naïve	Prospective	10/12 BR	3 mo	9 mg/d	3 discontinued due to side effects
Csepregi *et al*[82], 2006	Germany	10 naïve 8 AZA-NR	Prospective	7/10 naïve BR 8/8 AZA-NR BR	24 wk	9 mg/d	Steroids side-effects in cirrhotic patients
Zandieh *et al*[83], 2008	Canada	6 AZA-INT 3 PDN-INT	Retrospective	4/6 AZA-INT CBR 3/3 PDN-INT CBR	24 wk-8 yr	1.5-9 mg/d	Not reported
Manns *et al*[84], 2010[1]	Europe	208 naïve or relapsing	Prospective, randomized,	60% BR in budesonide 39% BR in PDN	6 mo	9 mg/d	Steroids side effects: 28% in budesonide arm, 53% in PDN arm
Mycophenolate mofetil							
Richardson *et al*[177], 2000	United Kingdom	3 AZA-INT 4 AZA-NR	Retrospective	5/7 BR	46 mo	2 g/d	Leukopaenia in 1
Zolfino *et al*[93], 2002	United Kingdom	3 second line	Retrospective	1/3 BR	Not reported	2 g/d	Not reported
Devlin *et al*[94], 2004	Canada	5 second-line	Retrospective	5/5 BR	Not reported	Not reported	1 pyelonephritis
Chatur *et al*[95], 2005	Canada	11 second-line	Retrospective	7/11 BR	10-54 mo	0.5-2 g/d	Leukopaenia in 1, diarrhoea in 1
Czaja *et al*[96],2005	United States	8 first- and second line	Retrospective	0/8 CBR	12-26 mo	0.5-3 g/ d	None reported
Inductivo-Yu *et al*[97], 2007	United States	15 second-line	Retrospective	Significant decrease of mean transaminase levels and of histological fibrosis and inflammation	41 mo	2 g/d	None significant
Hlivko *et al*[98], 2008	United States	17 naïve 12 second-line	Retrospective	16/19 BR	Not reported	0.5-2 g/d	10 discontinued for side-effects
Hennes *et al*[99], 2008[2]	Germany	27 AZA-INT 9 AZA-NR	Retrospective	57% AZA-INT BR 25% AZA-NR BR	16 mo	1-2 g/d	11 GI side effects
Wolf *et al*[178], 2009	United States	16 second-line	Retrospective	5/16 BR	Not reported	1-2 g/d	1 discontinued due to paresthesias
Sharzehi *et al*[100], 2010	United States	9 AZA-INT 12 AZA-NR	Retrospective	21/21 BR	12 mo	0.5-2 g/d	1 discontinued for GI side-effects
Baven-Pronk *et al*[101], 2011	The Netherlands	23 AZA-INT 22 AZA-NR	Retrospective	67% AZA-INT BR 13% AZA-NR BR	3-133 mo	0.5-3 g/d	6 discontinued for side-effects
Jothinami *et al*[102], 2014	India- United Kingdom	18 AZA-INT 2 AZA-NR	Retrospective	14 BR	5-83 mo	1-2 g/d	3 discontinued due to side-effects
Zachou *et al*[103], 2016	Greece	109 naïve	Prospective	83/102 BR at 3 mo	72 mo	1.5-2 g/d	2 discontinued for septicaemia; 5 dose reduction for leukopaenia or infections
Gazzola *et al*[179], 2016	Australia	51 AZA-INT 45 AZA-NR	Retrospective	27/49 AZA-INT BR 17/40 AZA-NR BR	Median: 31.9 mo	1-2 g/d	1 death, 2 hospitalisations, 8 GI side effects, 5 infections, 3 cytopoenia, 3 neuropsychiatric, 2 skin cancer, 1 lymphoproliferative disorder
Park *et al*[180], 2016	South Korea	1 AZA-INT	Retrospective	1/1 CBR	1 yr	1 g/d	None
Cyclosporine A							
Mistilis *et al*[121], 1985	Australia	1 AZA-INT	Retrospective	1/1 BR	1 yr	Not reported	None
Paroli *et al*[116], 1992	Italy	3 naïve	Prospective	3/3 BR	1 yr	5 mg/kg/d	Not reported
Person *et al*[118], 1993	United States	1 second-line	Retrospective	BR	Not reported	Not reported	Not reported
Sherman *et al*[114], 1994	United States	6 AZA-NR (1 paediatric)	Retrospective	5/6 BR at 10 wk	Not reported	Not reported	1 increased serum creatinine
Senturk *et al*[119], 1995	India	1 second-line	Retrospective	BR	1 yr	Not reported	None

Fernandes *et al*[113], 1999	United States	5 AZA-NR	Retrospective	4/5 BR at 3 mo	27 mo	3-5 mg/kg/d	Minimal
Malekzadeh *et al*[117], 2001	Iran	9 naïve 10 second-line	Prospective	79% BR and HI	26 mo	2-5 mg/kg/d	4 discontinued due to side effects
Zolfino *et al*[93], 2002	United Kingdom	1 second-line	Retrospective	NR	Not reported	Serum level 100-200 μg/L	Not reported
Malekzadeh *et al*[181], 2012	Iran	22 steroid-intolerant or NR	Retrospective	9 BR	60 mo	Not reported	Hirsutism (frequency not reported)
Tacrolimus							
Van Thiel *et al*[134], 1995	United States	21 naïve	Prospective	Mean 80% ALT drop at 3 months	3 mo	6.6-8 mg/d; blood levels 0.6-1.0 ng/mL	Mild mean creatinine elevation after 1 yr
Heneghan *et al*[137], 1999	United Kingdom	7 naïve	Prospective	BR in 86%		Not reported	Not reported
Zolfino *et al*[93], 2002	United Kingdom	5 AZA-NR	Retrospective	2/5 BR	Not reported	2-4 mg/d	Not reported
Aqel *et al*[130], 2004	United States	11 second-line	Retrospective	Normalization of mean ALT value	16 mo	0.5-1 mg/d(blood level < 6 ng/mL)	Minimal
Chatur *et al*[95], 2005	Canada	3 second-line	Retrospective	3/3 NR	10-54 mo	2-4 mg/d	1 discontinued for abdominal pain
Larsen *et al*[131], 2007	Denmark	9 AZA- or MMF-NR (1 pediatric)	Retrospective	9/9 BR	12-37 mo	2 mg/d (target blood level < 6 ng/mL)	1 mild tremor
Tannous *et al*[133], 2011	United States	13 second-line	Retrospective	12/13 BR	1-65 mo	2-6 mg/d (mean blood level 6 ng/mL)	1 HUS; 1 oral carcinoma
Than *et al*[135], 2016	German, United Kingdom	16 AZA-NR 1 AZA-INT	Retrospective	BR in most	60 mo	0.5-5 mg/d	1 LT; 4 PSC overlap
Al Taii *et al*[136], 2017[3]	United States	23 second-line	Retrospective	27% CBR 41% BR		5 mg/d (mean) serum level: 6.7 ng/mL (mean)	Significant increase of serum creatinine; 1 discontinued for GI hemorrhage
Sirolimus							
Chatrath *et al*[139], 2014	United States	5 AZA-NR	Prospective	4/5 BR	4-72 mo	2 mg/d	2 hyperlipidemia
Rubin *et al*[141], 2016	United States	2 second-line	Retrospective	1/2 BR	Not reported	3-6 mg/d	1 discontinued due to leg ulcer
Everolimus							
Ytting *et al*[143], 2015	Denmark	7 second-line	Retrospective	3/7 CBR 4/7 BR	1-3 yr	0.75-1.5 mg/d (target blood levels: 3-6 ng/mL)	Minimal
Rituximab							
Burak *et al*[144], 2013	Canada	3 AZA-NR 3 AZA-INT	Prospective	6/6 BR at 24 wk	72 wk	1000 mg on day 0 and 15	1 mild infection
Al-Busafi *et al*[182], 2013	Oman	1 steroid-resisitant	Retrospective	BR	Not reported	Not reported	None reported
Rubin *et al*[141], 2016	United States	1 second-line	Retrospective	1/1 BR	14 mo	475 mg/m^2 per week	None reported
Infliximab							
Weiler-Normann *et al*[154], 2013	Germany	11 second-line	Retrospective	8/11 BR	6 to > 40 infusions	5 mg/kg on 0, 2, 6, then every 4-8 wk	7/11 infections, 3 discontinued for side effects
Vallejo *et al*[156], 2014	Spain	1 AZA-NR	Retrospective	1/1 BR	3 mo	5 mg/kg given 3 times	Mild respiratory infection
6-mercaptopurine							
Pratt *et al*[167], 1996	United States	2 AZA-INT	Retrospective	2/2 CBR, 1/2 HI	24 mo in one not reported in the other	100 mg/d	None reported
Hübener *et al*[168], 2016	Germany/ United Kingdom	20 AZA-INT 2 AZA-NR	Retrospective	8/20 CBR 7/20 BR	18.5 mo	25-100 mg/d	4 discontinued for GI side-effects, 1 for leucopaenia
Elnegouly *et al*[183], 2017	Germany/ Austria	17 AZA-INT	Retrospective	11/12 CBR	1 yr	25-50 mg/d	2 discontinued for side-effects
Allopurinol							
Al-Shamma *et al*[170], 2013	United Kingdom	1 AZA-NR	Retrospective	1/1 BR	12 mo	100 mg/d	None reported

De Boer *et al*[171], 2013	The Netherlands	3 AZA-INT 5 AZA-NR	Retrospective	7/8 BR	13 mo	100 mg/d	1 discontinued for neuropathy
Al-Shamma *et al*[172], 2013	United Kingdom	1 AZA-NR	Retrospective	1/1 CBR	Not reported	100 mg/d	None reported
6-thioguanine							
De Boer *et al*[174], 2005	The Netherlands	3 AZA-INT	Retrospective	3/3 BR	Not reported	0.3 mg/kg/d	None reported
Van den Brand *et al*[175], 2017	The Netherlands	6 AZA-NR 6 AZA-INT	Retrospective	Significant median ALT decrease	12-75 mo	0.3 mg/kg/d	1 nodular regenerative hyperplasia

[1]The series includes 46 children (Woynarowski *et al*[91] 2013); [2]The series includes 4 adolescents, but only overall results are reported, and youngest age at diagnosis was 13 yr; [3]The series includes 6 adolescents, but only overall results are reported, and youngest age at diagnosis was 15 yr. BR: Biochemical response; AZA-NR: Azathioprine non-responder; AZA-INT: Azathioprine intolerant; CBR: Complete biochemical response; PDN: Prednisone; GI: Gastrointestinal; HI: Histological improvement; LT: Liver transplant; NR: Non-responder; ALT: Alanine aminotransferase; HUS: Haemolytic-uremic syndrome; PSC: Primary sclerosing cholangitis.

Table 4 Published data on autoimmune hepatitis treatment different from steroids and azathioprine in children

Ref.	Country	Number and type of patients (*n*)	Design	Outcome	Follow-up	Dose	Side effects
Budesonide							
Woynarowski *et al*[91], 2013	Europe	46 including naïve and second-line	Prospective	16% BR AZA+BUD 15% BR AZA+PDN at 6 mo	1 yr	6-9 mg/d	More weight gain in PDN group
Mycophenolate mofetil							
Lee *et al*[107], 2007	Malaysia	2 second-line	Retrospective	0/2 BR at 6 mo	6-18 mo	20-40 mg/kg/d	Not reported
Aw *et al*[106], 2009	United Kingdom	20 AZA-NR 6 AZA-INT	Retrospective	18/26 CBR	0.75-12 mo	20-40 mg/kg/d	7 Leukopaenia
Jiménez-Rivera *et al*[108], 2012	Canada	12 second-line	Retrospective	Not reported	Not reported	1000-1500 mg/d	Not reported
Dehghani *et al*[109], 2013	Iran	5 second-line	Retrospective	5/5 BR	None reported	Not reported	Not reported
Cyclosporine A							
Jackson *et al*[120], 1995	South Africa	1 AZA-INT	Retrospective	1/1 BR at 2 wk	19 mo	5 mg/kg/d	None
Debray *et al*[111], 1999	France	8 naïve 7 second-line (all type 2 AIH)	Retrospective	8/8 naïve BR 7/7 second-line (including 3 with ALF)	1-6 yr	4.7-5.6 mg/kg/d	Minimal
Ben Halima *et al*[122], 2002	Tunisia	1 first-line	Retrospective	1/1 BR	Not reported	Not reported	None
Sciveres *et al*[184], 2004	Italy	4 naïve 4 steroid/AZA-intolerant	Retrospective	8/8 BR at 2-8 wk	1.5-15 yr	4-10 mg/kg per day	2 gingival hypertrophy, 1 creatinine elevation
Cuarterolo *et al*[124], 2006	Agentina	86 naïve, type 1 AIH	Prospective	BR 94%	2 yr	4 mg/kg per day	8/84 creatinine elevation 3/84 hypertension
Nastasio *et al*[115], 2011	Italy	19 naïve[1] 10 second-line1	Retrospective	19/19 naïve BR at 4-18 wk 9/10 second-line BR	6.5 yr	Not reported	11 hyperthricosis, 13 gingival hypertrophy
Dehghani *et al*[109], 2013	Iran	3 second-line	Retrospective	3/3 BR	Not reported	Not reported	Not reported
Lee *et al*[107], 2015	Malaysia	2 second-line	Retrospective	1 /2 BR	6-18 mo	5 mg/kg per day, serum level 250-350 ng/mL	
Zaya *et al*[112], 2012	Croatia	9 naïve (1 type 2 AIH)	Retrospective	7/9 BR after 1 yr	24 mo	3-5 mg/kg per day	Minor
Jiménez-Rivera *et al*[108], 2012	Canada	9 naïve 15 second-line	Retrospective	Not reported	4 ± 2 yr	4 ± 0.8 mg/kg per day intially 4.9 ± 1.8 mg/kg per day in follow-up	Not reported
Tacrolimus							
Zolfino *et al*[93], 2002	United Kingdom	1 second-line	Retrospective	NR	Not reported	2 mg/d	Not reported
Marlaka *et al*[138], 2012	Sweden	20 naïve	Prospective	3/20 BR in monotherapy	1 yr	Target blood levels: 2.5-5 ng/ml	1 discontinued for side-effects; 2 developed IBD
Dehghani *et al*[109], 2013	Iran	2 second-line	Retrospective	2/2 BR	Not reported	Not reported	Not reported

Jiménez-Rivera *et al*[108], 2015	Canada	6 second-line	Retrospective	Not reported	Not reported	Not reported	Not reported
Sirolimus							
Kurowski *et al*[140], 2014	United States	4 second-line	Retrospective	2/4 BR	Not reported	Not reported	2 mo ulcers
Rituximab							
D'Agostino *et al*[150], 2013	Canada/ Argentina	2 second-line	Retrospective	2/2 CBR at 3/8 mo	26-38 mo	375 mg/m^2 weekly for 4 wk	None reported
Infliximab							
Rajanayagam *et al*[158], 2013	Australia	1 second-line	Retrospective	1/1 BR	19 mo	5 mg/kg 4 infusions at 4 wk interval	LT was not prevented
6-mercaptopurine							
Pratt *et al*[167], 1996	United States	1 AZA-NR	Retrospective	1/1 CBR and HR	36 mo	1.5 mg/kg	None reported

[1]Twelve patients had additional concomintant immunosuppressive drugs. BR: Biochemical response; AZA: Azathioprine; BUD: Budesonide; PDN: Prednisone; INT: Intolerant; NR: Non-responder; AIH: Autoimmune hepatitis; ALF: Acute liver failure; IBD: Inflammatory bowel disease; LT: Liver transplant; CRB: Complete biochemical response.

adolescents with AIH until a trial including strict diagnostic criteria and drug schedules appropriate for the juvenile disease is performed[85].

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is the prodrug of mycophenolic acid. It is an inhibitor of inosine monophosphate dehydrogenase, the rate-limiting enzyme in de novo purine synthesis on which, in contrast to other cells, B and T lymphocyte proliferation relies. MMF is widely used as second line AIH treatment, mostly combined with prednisone, both for patients intolerant to azathioprine and for patients with unsatisfactory response to standard azathioprine/prednisone treatment. Its use in AIH is based on retrospective series[90-103] (Table 3) with a total number of 313 patients treated, suggesting that MMF is partially effective in patients intolerant to azathioprine, but may not be effective in case of azathioprine poor response. However, a recent paper from Australia including 96 patients[104] reported a similar remission rate both in patients intolerant and poor responders to azathioprine (Table 3). One single prospective uncontrolled trial from Greece tested the use of MMF as first-line treatment[102,105] (Table 3). MMF was reported to be safe and effective in inducing and maintaining remission in treatment-naïve patients (83/102 patients achieved biochemical remission at 3 mo) and to have a rapid steroid sparing effect. However, it is not clear whether it offers an advantage over azathioprine, as a head-to-head comparison with azathioprine was not performed. A trial comparing azathioprine to MMF is currently ongoing (NCT02900443). MMF has the major disadvantages of being about 15 times more expensive than azathioprine, and, most importantly, of being teratogenic, which is highly relevant, since AIH affects mainly young females. The most frequent side effects are gastro-intestinal symptoms.

In juvenile AIH patients in whom standard immunosuppression is unable to induce stable remission, or who are intolerant to azathioprine, MMF at a dose of 20 mg/kg twice daily, together with prednisolone, has been used successfully used[90,106–108] (Table 4). A recent meta-analysis, including data from several small studies of second line treatments in children refractory to standard therapy shows that MMF is efficacious with a low side effect profile (in contrast to calcineurin inhibitors), supporting the notion that MMF should be the primary choice for second-line therapy in juvenile AIH[109].

Calcineurin inhibitors

Cyclosporine A: Cyclosporine A is a calcineurin inhibitor extensively used in the setting of transplant medicine. Important side effects are renal toxicity and cosmetic changes, particularly in association to high doses. In small retrospective series[90,108,110–115], small prospective open and uncontrolled trials[115,116] and single case studies[91,107,117-121] cyclosporine A has been reported to be effective - using variable doses, duration of treatment and follow-up - either as first-line option or in patients not responding to azathioprine and prednisone, both in children and in adults (Tables 3 and 4). Though the results of these reports appear to be encouraging, the quality and quantity of the data are insufficient to recommend its use. In paediatrics, cyclosporine A has been used as first line treatment for type 1 AIH in an attempt to reduce steroid side effects in a prospective multicentre study in 84 treatment-naïve children[122,123] (Table 4). Cyclosporine alone was administered for 6 mo, and the patients were subsequently switched to azathioprine and prednisone. Transaminase levels normalization was obtained in 72% of the subjects after six months of cyclosporine monotherapy, but IgG levels were not included in the remission criteria. Cyclosporine side effects included hypertrichosis (55%), gingival hyperplasia (39%), elevation of creatinine (9%) and hypertension (3%). The main limitation of this study is lack of direct comparison with standard treatment.

Animal data suggest that cyclosporine A may promote autoimmunity[124-127], and the first reports of de novo autoimmune hepatitis arising after liver transplantation were in children treated with

cyclosporine[128]. These observations call for caution in the use of cyclosporine in AIH.

Tacrolimus: Tacrolimus is a more potent calcineurin inhibitor than cyclosporine, has less cosmetic side effects, but similar drug class toxicity. In AIH, it has been used both for refractory cases and for patients intolerant to other immunosuppressive regimens. A few retrospective small case series in adults have been published, with variable remission criteria, sometimes including only transaminase levels[91,93,129-135]. The reported efficacy was good in a total number of 80 patients (Table 3). Two prospective open-label trials from the '90s are available, both in naïve patients[133,136] (Table 3). The oldest one included 21 adult patients[133], with a follow up of 1 year, after which a liver biopsy was repeated, but histological results are not reported. Half of the patients were anti-LKM1 positive; tacrolimus was used as monotherapy. Of note, the serum target level of tacrolimus was low (0.6-1 ng/mL). The mean decrease of transaminase and bilirubin levels was satisfactory, but the remission rate is not reported. In terms of side effects, the mean creatinine value increased significantly after 1 year of treatment. The second prospective trial in naïve patients included seven adult subjects and used lower tacrolimus doses combined with 20 mg/d of prednisolone. Transaminase levels, albumin, bilirubin and prothrombin time significantly improved in 6/7 patients[136].

In children, one prospective, single centre, open label trial including 20 treatment naïve patients is available: none was anti-LKM1 positive, follow up was 1 year, after which a liver biopsy was repeated[137] (Table 4). Target tacrolimus blood levels were 2.5-5 ng/mL. 14/20 patients needed azathioprine and prednisone in addition to tacrolimus to achieve remission. Histological improvement of inflammation was seen in 12/14 cases. No effect on the renal function was observed. This trial suggests that tacrolimus as monotherapy is not effective in juvenile AIH, but could be considered as steroid/azathioprine sparing agent.

More high-quality data are needed, both in adults and children, to assess tacrolimus efficacy in AIH.

m-TOR inhibitors

Sirolimus: Sirolimus is a macrolide molecule acting by inhibiting the mammalian target of rapamycin (mTOR), a protein that modulates the proliferation and survival of activated lymphocytes. It is produced by the bacterium Streptomyces hygroscopicus and was isolated in 1972 on Easter Island (Rapa Nui). Sirolimus is used to prevent rejection in solid organ transplantion.

There is very limited experience in the use of this drug for poor responders to standard AIH treatment. Retrospective data on 5 adult patients with AIH refractory to prednisone, azathioprine and mycophenolate are available[138] (Table 3). Only transaminase levels were used to define remission, median follow up was 24 mo, the target serum level was low, 10-20 ng/dL. Complete remission was achieved in 2/5 patients. Side effects were limited to hyperlipidaemia occurring in 2/5 patients. In paediatrics, a small retrospective series reports the use of rapamycin in 5 cases refractory to standard treatment (3/4 also to MMF)[139], including 1 case of non-adherence (Table 4). Two of the four patients showed an improvement in transaminase levels; tolerability was good, though 2/4 had mouth ulcerations not requiring drug discontinuation. The target sirolimus blood levels reported in the paper are 4-8 ng/mL. A report of two additional adult cases of difficult-to-treat AIH patients managed with sirolimus is even less encouraging: in one case sirolimus was discontinued due to legs ulcers, and in the other it was ineffective[140]. No drug serum levels were reported.

In conclusion, data on sirolimus in difficult-to-treat AIH patients are scanty and rather disappointing.

In the transplant setting, sirolimus has been reported to be effective in difficult-to-treat de novo AIH or AIH recurrence[141] in a small series of 6 paediatric patients. Three of them experienced infections while on sirolimus, including one case of colitis and fever leading to drug discontinuation.

Everolimus: Everolimus has a mechanism of action similar to sirolimus, and is used to prevent solid organ rejection, or at higher doses, as an anti-cancer drug. Only one report is available on the use of everolimus for the treatment of AIH. It is a retrospective series of 7 adult patients with insufficient response to standard or alternative treatments (budesonide, MMF, calcineurin inhibitors), or with severe treatment side-effects[142] (Table 3). Everolimus target blood concentration was 3-6 ng/mL. Complete biochemical response was obtained in 3/7 patients after 5 mo, but all patients, except one who was non-adherent, had significant decrease in serum transaminase levels, allowing reduction of the steroid dose. Histology did not show disease progression in four patients treated for 3-5 years. No severe side effects were reported, but one patient died from cholangiocarcinoma diagnosed 6 mo after starting everolimus, though cancer was not considered to be associated with the drug. In conclusion, in view of the very few data available, the role of everolimus in the treatment of AIH remains to be explored.

Biologicals

Rituximab: Rituximab is a monoclonal chimaeric (murine/human) antibody that specifically binds the CD-20 antigen, a phosphoprotein expressed on the surface of B-lymphocytes, leading to B-cell depletion. It is approved for the treatment of non-Hodgkin lymphoma, rheumatoid arthritis and ANCA-

associated vasculitis. It has also been used recently as rescue treatment in refractory AIH. In a single-centre open-label pilot study in Canada, 6 AIH adult patients who had failed treatment with prednisone and/or azathioprine[143] for intolerable side-effects (3/6) or refractory disease (3/6) were treated with two doses of 1000 mg rituximab administered two weeks apart (Table 3). Tolerance was good, only one patient developing minor infections. In all patients, transaminase and IgG levels decreased; a liver biopsy performed after 1 year in 4 of the 6 patients showed improvement of the inflammatory activity. Though a recent survey shows that rituximab is used for difficult-to-treat AIH patients in several centres[144], this experience has not been published. A few case reports of patients with AIH coexisting with other autoimmune diseases have been published[145-149], all demonstrating a positive effect of rituximab also on AIH.

In children, two cases of refractory AIH have been successfully treated with rituximab[149] (Table 4). In addition, the recently published preliminary results of a real-world expert management of paediatric AIH also reported the use of rituximab as rescue therapy[150].

In summary, rituximab has shown good efficacy in a small number of difficult-to-treat AIH patients, but its safety profile needs to be evaluated carefully, as the drug may have severe long term side-effects, including B-cell depletion[151].

Infliximab: Infliximab is a recombinant humanized chimaeric antibody used for the treatment of ulcerative colitis, Crohn disease, rheumatoid arthritis, psoriatic arthritis/plaque psoriasis, and ankylosing spondylitis. It acts mainly by direct neutralization of soluble tumour necrosis factor-alpha, but it has also pro-apoptotic and anti-proliferative effects on lymphocytes[152].

One small retrospective series from Germany on the use of infliximab as salvage therapy in 11 adult AIH patients reports[153] (Table 3) normalisation of transaminase levels in 8 and of IgG levels in 6. However, 7 patients developed infectious complications, and treatment had to be stopped because of side effects in three cases. Recently, preliminary results of an extension of this cohort of difficult-to-treat AIH patients was published: the cohort now includes 18 cases, 15 reaching biochemical remission[154]. Two case reports have also been published: one describing a difficult-to-treat AIH patient who achieved normalization of transaminases levels after 3 mo of infliximab treatment[155], and one reporting good disease control on infliximab in a young patient with AIH and adult onset Still disease[156].

In children, a 10-year old girl with aggressive disease, unresponsive to standard treatment, MMF and tacrolimus, has been reported to have a good response to infliximab, though liver transplantation was deferred but not avoided[157] (Table 4).

As for rituximab, specialized centres have unreported experience[144,150]. It is important to note that anti-tumour necrosis factor-alpha can induce hepatotoxicity resembling AIH[158-162], as well as other immune-mediated disorders, such as lupus erythematosus[163]. This should raise caution in using this agent, which should be reserved for treatement–resistant AIH cases in specialised centres.

Thiopurines

6-mercaptopurine: Azathioprine is the prodrug of 6-mercaptopurine (6-MP), and is non-enzymatically converted into 6-MP, which represents the biologically active form of the drug. 6-MP is used for the treatment of IBD, where it has been shown that 6-MP is better tolerated than azathioprine[164,165], despite the close biochemical relationship and shared metabolic pathways (Figure 2). In AIH, 6-MP was used successfully in 3 patients intolerant or unresponsive to azathioprine, including one paediatric patient[166], representing the only published experience in children (Tables 3 and 4). The largest series of AIH patients intolerant or unresponsive to standard treatment switched to 6-MP is a retrospective study on 22 adult cases[167] (Table 3). The two patients with insufficient response to standard treatment did not respond to 6-MP, whereas 15/20 patients intolerant to azathioprine showed either partial (7/15) or complete (8/15) biochemical remission. Five patients discontinued 6-MP, four for gastrointestinal side effects, and one for leukopaenia. Recently, preliminary data from an additional multicentre retrospective series of 17 patients, all azathioprine-intolerant, reported complete biochemical response in 11 of the 12 patients followed-up for at least 12 mo[168]. These data suggest that 6-MP can be an alternative for patients intolerant to azathioprine, but the available data are insufficient to formulate recommendations.

Allopurinol: Azathioprine hepatotoxicity can be due to a skewed metabolism of the drug, leading to a preferential generation of the hepatotoxic metabolite 6-methylmercaptopurine (6-MMP) instead of the metabolic active 6-thioguanine nucleotides (6-TGN). Allopurinol co-administration redirects the thiopurine metabolism towards 6-TGN. This strategy is used in the treatment of IBD. A case report suggests that allopurinol can be helpful also in AIH[169] (Table 3). A retrospective case-series of 8 AIH adult patients intolerant or with insufficient response either to azathioprine/prednisone (4/8) or 6-MP/prednisone (4/8), one patient in each group being also on budesonide, reported complete biochemical remission in 3/3 intolerant patients and in 4/5 unresponsive patients[170] (Table 3). All patients had skewed thiopurine metabolism. In one further case report of a patient with insufficient response to prednisone/

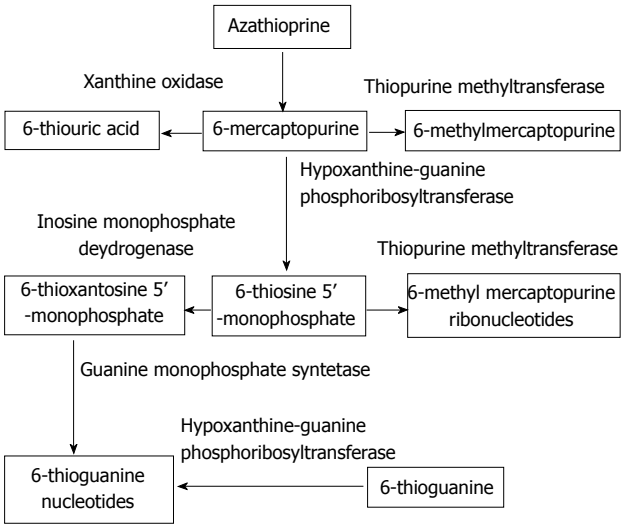

Figure 2 Simplified representation of the thiopurine metabolism. Azathioprine is non-enzymatically converted to 6-mercaptopurine, which is competitively converted into 6-methymercaptopurine, 6-thiouric acid and 6-thiosine 5'-monophosphate by different enzymes. The latter metabolite is further transformed into the metabolic active 6-thioguanine nucleotides.

azathioprine and shunted metabolism, allopurinol (100 mg/d) allowed rapid normalisation of transaminase levels and steroid reduction[171] (Table 3).

6-thioguanine: 6-thioguanine (6-TG) is enzymatically converted into 6-TGN, which are the active metabolites of azathioprine, bypassing the metabolic steps leading to the formation of the hepatotoxic metabolite 6-MMP (Figure 2). 6-TG is approved for the treatment of acute and chronic myeloid leukaemia, and chronic lymphatic leukaemia. It is used in IBD patients with insufficient response or intolerant to azathioprine or 6-MP[172]. Safety issues have been raised, particularly in respect to the development of nodular regenerative hyperplasia and sinusoidal obstruction syndrome[172]. In AIH, after an early preliminary report[173], a retrospective series of 12 adult patients switched from azathioprine or 6-MP to 6-TG for intolerance or insufficient response reported a median alanine aminotransferase levels drop from 81 IU/L to 30 IU/L (Table 3). Nodular regenerative hyperplasia developed in one case after 8 years of 6-TG treatment[174].

Due to the paucity of data and its potential hepatotoxicity, 6-TG cannot be recommended in AIH.

TREATMENTS UNDER INVESTIGATION

New compounds are currently under investigation in AIH. Preliminary results of a phase 1, first-in-human trial of preimplantation factor in AIH demonstrated good safety and tolerability, but a non-significant decrease in mean transaminase levels[175]. Other investigational drugs in AIH include VAY736, which leads to B-cell depletion and B-cell activating factor receptor blockade (NCT03217422), JKB-122, which is a toll-like receptor 4 antagonist (NCT02556372) and low dose interleukin 2 (NCT01988506).

CONCLUSION

The pharmacological treatment of AIH should be personalized, because of the heterogeneity of the disease. Treatment schedules in children differ, because of the more aggressive disease course in this age group. Standard treatment, based on steroids and azathioprine, is effective in the vast majority of patients, and side-effects can be minimised by rapid prednisone tapering. Budesonide was tried as first-line treatment in an attempt to reduce steroids side-effects, but the results of a randomized controlled trial do not allow to universally recommending it as first-line treatment instead of prednisone. A minority of patients prove difficult-to-treat, either because of severe side effects from standard treatment, or resistant disease. Mycophenolate mofetil is the most widely used second-line drug, and also the drug with the highest amount of available data. Calcineurin inhibitors are alternative options, but data on their efficacy are scanty. Infliximab and rituximab may represent an additional treatment option for selected difficult-to treat cases, but their use should be restricted to specialised centres because of potentially severe side effects. New pharmaceutical treatments are currently under investigation.

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P- Reviewer: Dehghani S, Drenth JPH, Lee HC, Rodrigues AT, Watanabe T, Wirth S **S- Editor**: Ma YJ **L- Editor**: A **E- Editor**: Xu XR

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ISSN 1007-9327