Review

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Treatment options for autoimmune hepatitis: A systematic review of randomized controlled trials

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Background & Aims: Predniso(lo)ne with or without azathioprine is considered the mainstay in the treatment of autoimmune hepatitis (AIH), but many therapeutic options are available. The primary objective of this review was to explore the published literature on the optimal induction and subsequent maintenance therapy for AIH.

Methods: We performed a systematic search on electronic databases MEDLINE (1950-07.2009), Web of Science, Cochrane, and the website www.clinicaltrials.gov. Randomized controlled trials (RCTs) on apparent beneficial treatment regimens as induction or maintenance treatment in AIH were included. Pediatric studies were excluded. We calculated relative risks (RR) for comparison of treatment options on the primary outcome measure, which was defined as clinical, biochemical and histological remission.

Results: Eleven RCTs were included, of which 7 studies evaluated the induction therapy in AIH patients: 3 treatment naive (n = 253), 2 relapse (n = 53), 2 combination of naive and relapse (n = 110). The remaining 4 studies (n = 162) assessed maintenance therapy. All but one maintenance study (thymostimulin versus no therapy) studied predniso(lo)ne (PRED), azathioprine (AZA) or combination PRED + AZA. We found no differences in primary outcome between induction therapy with PRED and PRED + AZA in treatment naive patients (RR = 0.98; 95% CI 0.65–1.47). AZA monotherapy as induction was considered as not viable because of a high mortality rate (30%). This was similar in AIH patients who relapsed: RR for PRED versus PRED + AZA for inducing remission was not different: 0.71 (95% CI 0.37–1.39). PRED + AZA maintained remission more often than PRED (RR = 1.40; 95% CI 1.13–1.73). Also AZA maintained a higher remission rate than PRED (RR = 1.35; 95% CI 1.07–1.70). Maintenance of remission was not different between PRED + AZA and AZA (RR = 1.06; 95% CI 0.94–1.20).

Conclusions: Based on available RCTs, PRED monotherapy and PRED + AZA combination therapy are both viable induction therapies for AIH treatment naives and relapsers, while for maintenance therapy PRED + AZA and AZA therapy are superior to PRED monotherapy.

Background

Autoimmune hepatitis (AIH) is a rare chronic progressive liver disease of unknown etiology [1]. Clinical presentation may include fatigue, pain in the right upper quadrant of the abdomen, polymyalgia, and arthralgia involving small joints [1]. The disease predominantly affects women and occurs in children and adults of all ages. The estimated annual incidence of AIH among Northern Europeans is 1.9 cases per 100,000 persons per year [1,2]. The clinical picture is heterogeneous and in absence of a single clinical or biochemical test, diagnosis is made according to a set of clinical criteria developed in 1993, which were revised in 1999 and simplified in 2008 [3–5]. These diagnostic criteria include (1) hypergammaglobulinaemia; (2) the presence of particular autoantibodies, i.e., ANA, SMA or anti-LKM1; (3) liver histology features similar to chronic hepatitis of other etiology; (4) the absence of viral and toxic hepatitis or other conditions that may resemble AIH [5,6]. Based on this set of criteria, the sensitivity of the scoring system for AIH ranges from 97% to 100%, and its specificity for excluding AIH in patients with chronic hepatitis C ranges from 66% to 92% [6].

Three randomized controlled trials (RCTs) dating from the 1970s have established the effect of immunosuppressive drugs for AIH [7–9]. Predniso(lo)ne monotherapy (PRED) or a combination of predniso(lo)ne and azathioprine (PRED + AZA) was superior to other treatment options, including titrating PRED, in improving liver function and life expectancy [7–9]. The current recommendations for AIH therapy originate from this era, and PRED, usually in combination with AZA, is considered the mainstay of therapy. In some cases cirrhosis develops despite treatment; in other cases, treatment discontinuation or dose reduction is necessary because of intolerable adverse events. This has fueled the search for treatment alternatives.

Our primary objective was to explore the published literature on evidence of optimal induction and subsequent maintenance

Keywords: Autoimmune; Hepatitis; Systematic review.

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Abbreviations: AIH, autoimmune hepatitis; PRED, predniso(lo)ne; AZA, azathioprine; PRED+AZA, predniso(lo)ne + azathioprine; RCTs, randomized controlled trials.

therapy for AIH. We therefore performed a systematic review and examined all RCTs for treatment of AIH published from 1950 until present.

Methods

Literature search

We performed a systematic literature search using a set of electronic databases: MEDLINE (1950-07.2009), Web of Science, Cochrane, and the website www.clinicaltrials.gov to identify all published articles and abstracts, and ongoing studies from 1950 until July 2009. The following terms were used: 'hepatitis', 'autoimmune' and 'clinical trial'. All papers published before August 2009 were eligible.

Selection of studies

We employed a 2-stage approach. First, we excluded all articles that were not written in English, German, French or Spanish. We subsequently removed all duplicates, and screened remaining articles on the basis of title and abstract. Only RCTs were included: case reports, case series, review articles, letters, and editorials were excluded. Studies not evaluating the efficacy of therapy for AIH in adult patients (age $\geqslant$18 years) were rejected. Subsequently, full text screening was applied to the remaining studies. Articles were systematically reviewed on the basis of their inclusion criteria and methodological aspects by two independent reviewers (ML, MP). Discrepancies were solved by discussion with a third party (JD). In order to check whether our search included all published papers that were possibly relevant for this review, we scrutinized reference lists of included articles. This strategy was adopted because of evolving definition of AIH prior to 1993.

Outcomes

Remission was considered as the primary outcome measure. We defined remission following recently published criteria: disappearance of symptoms; normal serum, bilirubin, and γ-globulin levels; serum aminotransferase level normal or less than twice normal; normal hepatic tissue or minimal inflammation and no interface hepatitis [10]. For each individual article, we evaluated all available outcomes that matched the criteria of our user definition of remission. For example, if liver biopsy was not an outcome described in a particular article, we applied all other presented outcomes, such as clinical and biochemical variables, in order to achieve the most appropriate definition of remission for that study.

The secondary outcome measures included mortality and occurrence of adverse events. All outcomes were extracted from the included trials and were assessed at maximum follow-up.

Clinical trials in the treatment of AIH can be divided in 2 categories (1) trials that assess the effect of induction therapy in newly identified or relapsed AIH patients (induction trials); (2) trials that have been performed during remission in order to compare the efficacy of two immunosuppressive regimens with maintenance of remission as the primary endpoint (maintenance trials).

Quality of the included studies was assessed, based on a well-established, validated scale developed by Jadad et al. [11]. The Jadad score gives a numerical score between 0 and 5 as a rough measure of clinical trial design/reporting quality (0 being weakest and 5 being strongest).

Extraction of data

After inclusion, we extracted data from each article and entered characteristics of trials, patients, and interventions, as well as the primary and secondary outcome measures. Trial characteristics included the first author's name, year and journal of publication, study design, type, dose and duration of applied therapy, and length of follow-up. Patient characteristics comprised inclusion and exclusion criteria, mean age, number of patients randomized, and number and reasons for dropouts and withdrawals.

Data on all patients, irrespective of compliance or follow-up were sought to allow intention-to-treat analyses. In this analysis the total number of patients randomized is the number of patients included in the efficacy analysis. We used data related to initial therapy and relevant to maintenance therapy. In case data were recorded immediately at the end of the evaluation period, this was preferred to follow-up data. In case of missing outcome values at the end of the evaluation period, due to premature withdrawal of therapy in patients with deterioration or drug intolerance, last measured values of outcome were substituted for missing values.

In order to evaluate adverse events related to therapy for AIH, data regarding adverse events in patients treated with the interventional drug(s) were extracted. In addition, data about deterioration in all patients reported in the included studies, were extracted.

Synthesis of data and analysis

In this review, a brief overview of the interventions and number of patients in the trials is given for each separate study. In addition, we pooled patient data from all studies and stratified them in different subgroups according to induction and maintenance therapy, applied intervention and obtaining remission, mortality or complications. This was done in order to determine the efficacy of the interventional drugs in terms of induction of favorable outcome in each of the different therapy groups.

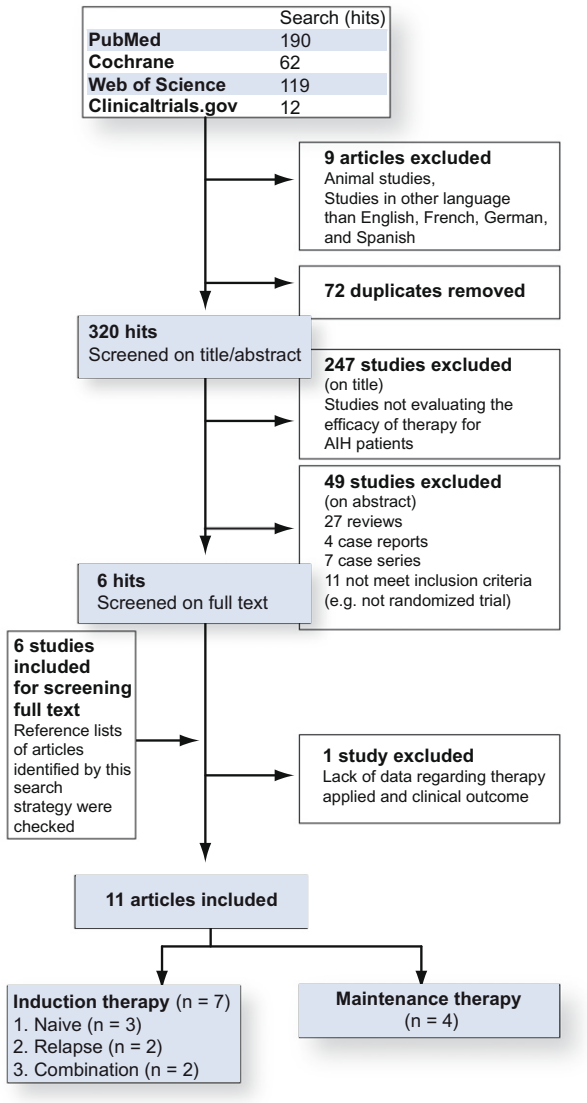

Fig. 1. Flowchart of included and excluded articles in the systematic literature search.

We calculated overall frequencies for the primary outcome measure expressed as percentages. Furthermore, frequencies and percentages for the secondary outcome measures, reported mortality and adverse events were calculated.

Data were stored in Reference Manager 11 and Excel database software for Windows XP. Due to heterogeneity of studies, we have focused on descriptive analysis and overall frequencies of favorable outcomes were determined by sample sized weighted pooled proportion. In order to quantify the differences between frequently studied treatment strategies we pooled the data and calculated relative risk with 95% confidence interval.

Results

Literature search and selection of studies

The results of our systematic literature search and subsequent selection of articles are summarized in a flow diagram (Fig. 1). The search identified 302 different studies, of which we excluded 247 studies due to study aims; 49 studies were rejected because of study design. Full text screening was applied for 6 articles, and all fulfilled the selection criteria. Of these articles, the reference lists were checked, and this strategy resulted in 5 additional articles that fulfilled the inclusion criteria. Thus, a total of 11 RCTs were included for further analyses [7–9,12–19] of which 7 studies evaluated the induction therapy in AIH patients: 3 treatment naive ($n = 253$), 2 relapse ($n = 53$), 2 combination of naive and relapse ($n = 110$). The remaining 4 studies ($n = 162$) assessed maintenance therapy.

Many drugs were studied, and we analyzed the most viable options: PRED, AZA or a combination of both. Outcome assessments in patients treated within the different treatment arms were made after an evaluation period of >3 months, the mean evaluation period was comparable for the different groups, and varied between 1 and 2 years.

Induction therapy in treatment naive AIH patients

We retrieved 5 studies, published between 1971 and 1982, that assessed the clinical outcome of AIH in drug naive patients (Table 1). These 5 studies included 363 patients in 6 different arms, 26% were male [7–9,17,18]. The calculated Jadad score for these studies ranged between 1 and 4. Two studies performed a head-to-head comparison between PRED and AZA [9,17]. One study evaluated the treatment with PRED, PRED + AZA, titrated PRED and placebo or AZA [18]. Another trial studied the same drugs but titrated PRED [8]. One study compared PRED with no intervention [7]. Applied dosages varied between 10 and 60 mg daily of PRED (maintenance dose 10–20 mg/day) [7–9,17,18] and between 50 and 100 mg daily of AZA [8,9,17,18].

Ninety-five patients were treated with PRED (not titrated), remission occurred in 42% [8,17,18]. We were not able to extract remission rates in two studies, as they contained only minimal information [7,9]. The mortality rate was 15% (21/139) (Fig. 2A) [7–9,17,18].

Only 14% of 51 AZA treated patients achieved remission [8,17], and 30% deceased (27/89) [8,9,17,18]. The therapy of PRED + AZA in 44 patients yielded a remission rate of 43% and a mortality rate of 7% [8,18]. Remission rates of PRED treated patients versus PRED + AZA treated patients yielded a comparable rate (RR = 0.98; 95% CI 0.65–1.47). Neither of 33 patients randomized for placebo achieved remission, and 13 patients (39%) died [8,18]. One study assessed 27 patients with no intervention, the remission rate could not be extracted and the mortality rate was

Table 1. Induction therapy in naive patients with autoimmune hepatitis.

First author, journal, year	Intervention	Treatment duration	Patients (n)	Remission (%)	Mortality (%)	Jadad score
Cook, Quarterly, Journal of Medicine, 1971	Prednisolone 15 mg/day No intervention	30–72 months	22 27	– –	14 56	2
Soloway, Gastroenterology, 1972	Prednisone 60 mg/day 1 week, 40 mg/day 1 week, 30 mg/day 2 weeks, 20 mg/day maintenance	3 months–3.5 years	18	44	6	4
	Azathioprine 100 mg/day		14	7	36	
	Prednisone 30 mg/day 1 week, 20 mg/day 1 week, 15 mg/day 2 weeks, 10 mg/day maintenance + azathioprine 50 mg/day		14	21	7	
	Placebo		17	0	41	
Murray-Lyon, Lancet, 1973	Prednisone 5 mg 3dd Azathioprine 75 mg 1dd	2 years	22 25	– –	5 24	3
Summerskill, Gut, 1975	Prednisone 60 mg/day 1 week, 40 mg/day 1 week, 30 mg/day 2 weeks, 20 mg/day maintenance	36 months	30	37	10	1
	Prednisone 30 mg/day 1 week, 20 mg/day 1 week, 15 mg/day 2 weeks, 10 mg/day maintenance + azathioprine 50 mg/day		30	53	7	
	Prednisone in titrated doses given on alternate days		31	10	7	
	Placebo/azathioprine 100 mg/day		29 (16/13)	–	41 (38/46)	
Tage-Jensen, Liver, 1982	Azathioprine 10 mg/kg/week, first 2 weeks 5 mg/kg/week	38 (12–83) months	37*	16	27	2
	Prednisone <70 kg 10 mg/day, ⩾70 kg 15 mg/day		47*	45	28	

* Ninety-nine autoimmune patients, information provided for 84 patients only. 34 patients prednisone for 1 year, 27 patients azathioprine for 1 year. 13 patients who were treated with prednisone died before 1 year of treatment, while 10 patients died in the azathioprine group.

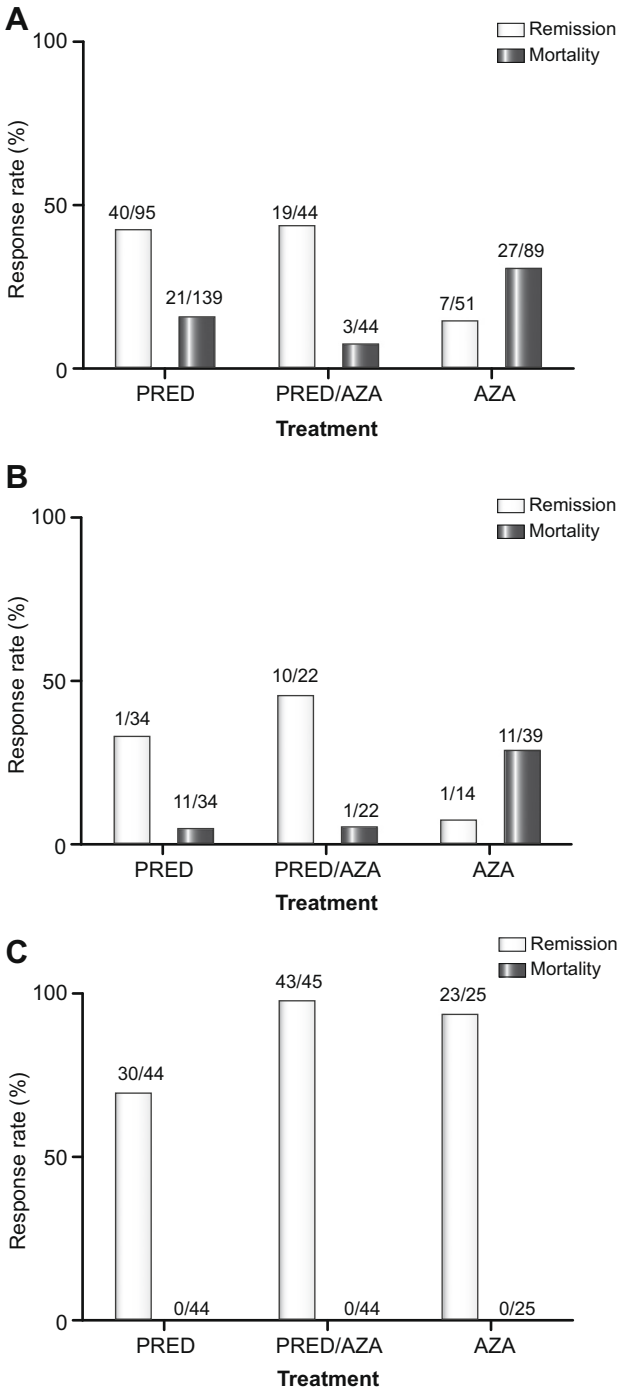

Fig. 2. Effect of prednisone and azathioprine in autoimmune hepatitis treatment. (A) Induction therapy naive AIH patients. (B) Induction therapy relapse AIH patients. (C) Maintenance therapy AIH patients.

56% [7]. One study evaluating the effect of titrated PRED showed no benefit [18].

Induction therapy in AIH patients who relapsed

Four studies, with a Jadad score between 2 and 4, assessed the clinical outcome of induction therapy in AIH patients who relapsed (Table 2) [8,9,14,15]. In total, these 4 studies included 163 patients (22% males) in 7 different arms. The most important comparators were similar to the studies in naive patients: PRED (15–60 mg/day) versus AZA (75–100 mg/day) or a combination of these two (PRED 10–30 mg/day, AZA 50 mg/day) versus monotherapy [8,9,15]. One study compared ursodeoxycholic acid (UDCA 13–15 mg/kg/day) with placebo in PRED treated patients, and UDCA showed no additional value [14]. A total of 32% from 34 PRED treated patients obtained remission [8,14], 4% died (Fig. 2B) [8,9,14]. Twenty-two patients treated with PRED + AZA achieved remission in 45% and had a corresponding mortality of 5% [8,15]. Treatment with PRED or with PRED + AZA was not different (RR = 0.71; 95% CI 0.37–1.39). Two studies focused on AZA treatment [8,9]. Only 7% reached remission [8], and 28% died [8,9]. For comparison, none of the patients who received placebo came into remission, and there was an associated mortality of 41% [8].

Maintenance therapy in AIH patients

We identified 4 clinical trials that focused on AIH patients in remission on maintenance therapy (Table 3) [12,13,16,19]. These studies included 162 patients in 6 different arms, of which 22% were male. Three studies scored 3 on the Jadad scale [12,13,19], one study scored 1 [16]. One study compared AZA (2 mg/kg/day) with PRED (5–12.5 mg/kg/day) + AZA (1 mg/kg/day) [13], another study compared this combination ((PRED 5–10 mg/kg/day) + (AZA 50–100 mg/day)) with PRED (5–12.5 mg/day) [12]. Two trials compared either thymostimulin with no intervention or PRED (15 mg/day) with D-penicillamine [16,19]. Thymostimulin and D-penicillamine had no relevant clinical value. PRED + AZA yielded a higher rate of maintaining remission (96%) [12,13] than PRED (68% [12,19], RR = 1.40; 95% CI 1.13–1.73). A total of 92% of AZA treated patients maintained remission (Fig. 2C) [13]. Maintenance treatment with PRED + AZA is not better than with AZA (RR = 1.06; 95% CI 0.94–1.20). AZA also maintained a higher remission rate than PRED (RR = 1.35; 95% CI 1.07–1.70). In all studied treatment groups none deceased [12,13,19].

Adverse events

Frequencies and percentages of reported adverse events were not adequately mentioned in most studies. Patients receiving PRED had a number of well known steroid related adverse events such as cushingoid appearance, diabetes mellitus, hypertension, and cataracts (Table 4). Adverse events associated with AZA treatment were gastrointestinal bleeding, leucopenia, trombopenia, and arthralgia. Cushingoid appearance and diabetes mellitus were adverse events associated with the combination therapy PRED + AZA, but in a lower reported frequency than PRED monotherapy. We found no differences in adverse event incidence between treatment indications (naive, relapse or remission).

Discussion

This systematic review evaluates the evidence that is available for the induction and maintenance therapy in AIH.

Results from our analysis show that both PRED monotherapy and PRED + AZA are better in achieving remission and limiting mortality in treatment naive AIH patients than any other treat-

Table 2. Induction therapy in patients with autoimmune hepatitis who relapsed.

First author, journal, year	Intervention	Treatment duration	Patients (*n*)	Remission (%)	Mortality (%)	Jadad score
Soloway, Gastroenterology, 1972	Prednisone 60 mg/day 1 week, 40 mg/day 1 week, 30 mg/day 2 weeks, 20 mg/day maintenance	3 months –3.5 years	18	44	6	4
	Azathioprine 100 mg/day		14	7	36	
	Prednisone 30 mg/day 1 week, 20 mg/day 1 week, 15 mg/day 2 weeks, 10 mg/day/week maintenance + azathioprine 50 mg/day		14	21	7	
	Placebo		17	0	41	
Murray-Lyon, Lancet, 1973	Prednisone 5 mg 3dd	2 years	22	–	5	3
	Azathioprine 75 mg 1dd		25	–	24	
Czaja, Hepatology, 1993	Oral pulse prednisone 90 mg/day for 5 consecutive days, every 28 days	Indefinite	8	0	0	3
	Prednisone 30 mg/day 1 week, 20 mg/day 1 week, 15 mg/day 2 weeks, 10 mg/day/week + azathioprine 50 mg/day		8	88	0	
Czaja, Hepatology, 1999	UDCA 13–15 mg/kg/day + usual corticosteroid schedule	6 months	21	14	5	2
	Placebo + usual corticosteroid schedule		16	19	0	

ment option evaluated in the literature between 1950 and July 2009. The efficacy of both strategies seems similar, and the lower mortality rate with PRED or PRED + AZA is an important additional argument to favor this therapy over AZA monotherapy for the initial treatment of both naive and relapsing patients.

For patients who require maintenance therapy, the combination PRED + AZA and AZA monotherapy provides higher maintenance rates of persistent remission compared to PRED monotherapy. Testament to this is that mortality was absent with either choice. Although AIH is much more prevalent in females, we could not discern a gender difference in efficacy for either naives, relapsers or patients in remission.

Surprisingly, the number of RCTs describing the clinical efficacy of different treatment strategies in AIH patients is low. We only found 11 RCTs published between 1950 and July 2009. For comparison, between July 2008 and July 2009 alone, already around 150 clinical trials in hepatitis C were reported in the literature. Moreover, studies were heterogeneous, performed decades apart with an evolving set of diagnostic criteria and no proper evidence based definition for remission until 1999. In order to offer recommendations for optimal induction and maintenance treatment in AIH, we performed a descriptive analysis of the published RCTs.

The question is whether we need future RCTs with currently available treatment options in AIH. We believe that there is a large unmet need. The trials that established the current standard PRED + AZA stem from an era with different, and currently considered suboptimal, laboratory diagnostics. In addition, the epidemiology of AIH probably has shifted. Due to improved diagnostics AIH is probably diagnosed in a much earlier phase, and patients that were considered to have AIH at the time of the earlier trials will currently receive an alternative diagnosis. Thus, there is a need for trials that reflects and benefits the current AIH patient. This brings us to the design of these future trials. Inclusion of a placebo arm for induction treatment of either naive or relapsing AIH is probably unethical. The remission rates with placebo are poor (<12%), and earlier trials have shown that this strategy is associated with significant mortality [7,8,16,18]. We concur that the therapy of AIH with PRED with or without AZA is far from ideal, and the search for drugs with a favorable risk–benefit ratio is ongoing [20]. For most of the alternative approaches in the past, the results have been disappointing and the adverse effects severe

Table 3. Maintenance therapy for autoimmune hepatitis patients in remission.

First author, journal, year	Intervention	Treatment duration	Patients (*n*)	Remission (%)	Mortality (%)	Jadad score
Stern, Gut, 1977	D-Penicillamine 1.2 g/day	1 year	18	50	0	3
	Prednisone 15 mg/day		17	65	0	
Hegarty, Gut, 1984	Thymostimulin 1 mg/kg/day i.m. for 7 days; 1 mg/kg/weekly thereafter	Indefinite	13	16	0	1
	No therapy		17	12	0	
Stellon, Lancet, 1985	Prednisolone 5–10 mg/day + Azathioprine 50–100 mg/day	3 years	23	96	0[1]	3
	Prednisolone 5–12.5 mg/day		27	70	0[1]	
Stellon, Hepatology, 1988	Azathioprine 2 mg/kg/day	1 year	25	92	0	3
	Azathioprine 1 mg/kg/day + Prednisolone 5–12.5 mg/day		22	100	0	

[1] One patient died in a road accident, inclusion group unknown.

[20]. Recently, a German study group compared combined budesonide and AZA treatment to PRED + AZA in 208 AIH patients. Remarkably this trial alone includes ~25% of all AIH patients included in a RCT to date. The primary endpoint of the study was complete remission in absence of typical steroid-induced adverse effects [21,22]. Preliminary results indicate that budesonide is an efficacious alternative to PRED, with a more favorable side effect profile. Less adverse events were experienced compared to the data that we presented here. However, results have only been published in abstract-form and long-term results of budesonide are awaited.

In general, the results from our systematic analysis accord with the current guidelines, which advise PRED or PRED + AZA for naive AIH patients [1,6,10,20]. The combination regimen is the preferred treatment because it is associated with a lower occurrence of corticosteroid-related adverse events than the higher dose PRED regimen (10% versus 44%) [18,20]. However, in individual patients, therapy is best tailored to the patient's presentation [20]. For

Table 4. Adverse events.

First author, journal, year	Intervention	Treatment duration	Patients (*n*)	Adverse events (*n*)
Cook, Quarterly J. of Medicine, 1971	Prednisolone 15 mg	Indefinite	22	Severe: osteoporosis + vertebral collapse (2), perforated duodenal ulcer (1), acute steroid psychosis (1), terminal bronchopneumoniae (1). Mild: obesity (5), facial "mooning" (5), acne (4), myositis (1)
Soloway, Gastroenterology, 1972	Prednisone 60 mg/day 1 week, 40 mg/day 1 week, 30 mg/day 2 weeks, 20 mg/day maintenance	3 months–3.5 years	18	Cushingoid appearance (13), diabetes requiring insulin (1), GI-bleeding (1), spinal collapse, aseptic necrosis of hip, or cataracts (3)
Murray-Lyon Lancet, 1973	Prednisone 5 mg 3dd	2 years	22	–
Summerskill, Gut, 1975	Prednisone 60 mg/day 1 week, 40 mg/day 1 week, 30 mg/day 2 weeks, 20 mg/day maintenance	36 months	30	Severe cosmetic changes, diabetic mellitus cataracts, hypertension
Summerskill, Gut, 1975	Prednisone in doses titrated given on alternated days	36 months	31	Diabetes mellitus, diabetes mellitus and hypertension, haematemesis/melaena
Tage-Jensen, Liver 1982	Prednisone <70 kg, 10 mg/day, >70 kg, 15 mg/day	38 (12–83) months	47	–
Stellon, Lancet, 1985	Prednisolone 5–12.5 mg/day	3 years	27	-
Czaja, Hepatology, 1993	Oral pulse prednisone 90 mg/day for 5 consecutive days, every 28 days	Indefinite	8	None
Soloway, Gastroenterology, 1972	Prednisone 30 mg/day 1 wk, 20 mg/day 1 wk, 15 mg/day 2 wks, 10 mg/day/wk + AZT 50 mg/day	3 months–3.5 years	14	Cushingoid appearance (10)
Summerskill, Gut, 1975	Prednisone 30 mg/day 1 wk, 20 mg/day 1 wk, 15 mg/day 2 wks, 10 mg/day/wk + AZT 50 mg/day	36 months	30	Diabetes mellitus, haematemesis
Stellon, Lancet, 1985	Prednisolone 5–10 mg/day + azathioprine 50–100 mg/day	3 years	23	None
Stellon, Hepatology, 1988	Prednisolone 5–12.5 mg/day + azathioprine 1 mg/kg/day	1 year	22	Arthralgias (1)
Czaja, Hepatology, 1993	Prednisone 60 mg/day 1 week, 40 mg/day 1 week, 30 mg/day 2 weeks, 20 mg/day maintenance	Indefinite	8	Severe adverse events of azathioprine not observed
Soloway, Gastroenterology, 1972	Azathioprine 100 mg/day	3 months–3.5 years	14	Cushingoid appearance (2), GI – bleeding (3), spinal collapse, aseptic necrosis of hip, or cataracts (1), leucopenia/thrombocyto (2), ascites + 2× increase in bilirubin (>6 mg/100 ml) (2)
Murray-Lyon, Lancet 1973	Azathioprine 75 mg 1dd	2 years	25	–
Summerskill, Gut, 1975	Azat hioprine 100 mg/day	36 months	13	–
Tage-Jensen, Liver 1982	Azathioprine 10 mg/day/week, first 2 weeks 5 mg/kg/week	38 (12–83) months	37	–
Stellon, Hepatology, 1988	Azathioprine 2 mg/kg/day	1 year	25	Arthralgia most hinged joints (14), myalgias (7), transient leucopenia (1), pancytopenia (2)

adults who have relapsed more than once the AASLD advises to be treated with PRED + AZA therapy, low dose PRED, or AZA only [10]. Current maintenance regimens include PRED + AZA or AZA [4,10]. Many AIH patients who have been in complete remission for at least one year with PRED + AZA can remain in remission with a higher dose of AZA alone [23]. Altogether, we can conclude that our results in all three categories match with the current guidelines.

This review has some limitations. A standardized, universally accepted definition of remission in AIH patients exists since 1999. All articles that are part of this review were published in or prior to 1999, and could consequently not match the overall definition.

Apart from differences in definition of remission, the trials described in the included articles used various doses of PRED and AZA. Therefore, we were not able to abstract the best dose for the highest remission rates using a systematic review.

Moreover, variations in medication schemes, outcome measures, and validity of trials introduced heterogeneity between included studies. Another limitation is that only 11 RCTs have been published since 1950. The current literature is replete with reviews reflecting personal opinion, but lacks well executed RCTs. In addition, most studies include a small number of patients. Indeed, current therapy guidelines are based on 11 trials with only 578 patients reflecting the perpetual lack of evidence. In the same vein we note that there is also a paucity of structured and systematic recording of adverse events with AIH therapy.

Current literature indicates remission rates of 65–80% [24], but we found much lower percentages. The early RCTs in the 1970s that established the efficacy of corticosteroids in the treatment of AIH included severe cases of AIH with severe, rapidly progressive disease. Consequently, these studies contained more patients with cirrhosis, which led to worse treatment outcomes and a higher mortality rate. Patients with less severe disease probably have not been included in the controlled clinical trials [25]. Data on mild AIH are missing from the literature, and this introduces a potential source of bias. Furthermore, the hepatitis C virus was identified in 1989 [21]. Thus, AIH patients diagnosed prior to 1989 could have hepatitis C, and probably some patients were inadvertently included in the initial trials. This could translate in a lower remission rate. In addition, we did not take into account the lead time bias, which also may affect the achievement of remission and mortality.

In conclusion, PRED monotherapy and PRED + AZA combination therapy are equivalent in efficacy for induction treatment in naive and relapsing AIH patients. For maintenance therapy PRED + AZA combination and AZA monotherapy are superior to PRED monotherapy. Alternative proposed strategies, in patients who have failed to achieve remission on standard therapy or patients with drug toxicity, are very welcome to optimize treatment.

Conflicts of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding conflict of interset with respect to this manuscript.

Acknowledgements

This systematic review has been discussed within the Dutch Autoimmune Hepatitis Working Party. Apart from the first (M.L.), third (M.P.) and last author (J.D.) the Dutch Autoimmune Hepatitis Working Party has the following members: G. Koek MD PhD, Department of Gastroenterology and Hepatology, University Medical Center Maastricht, Maastricht, The Netherlands; H.R. van Buuren MD PhD and R. de Man MD PhD, Department of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands; K.J. van Erpecum MD PhD, J.F. Monkelbaan, MF, Ph.D, Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands; A.P. van den Berg MD PhD, Department of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; K.M.J. van Nieuwkerk MD PhD, B. Verwer MD, N. van Gerven MD and G. Bouma MD PhD, Department of Gastroenterology and Hepatology, Vrije University Medical Center, Amsterdam, The Netherlands; U.H. Beuers, MD, PhD, Department of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands; B. van Hoek MD PhD and M. Coenraad MD PhD, Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands; J. den Ouden MD PhD, Department of Gastroenterology and Hepatology, Sint Franciscus Hospital Rotterdam, Rotterdam, The Netherlands; J.T. Brouwer MD PhD, Reinier de Graaf Medical Center Delft, Delft, The Netherlands. Further we are indebted to S. Gordinou de Gouberville for his help at the initial stage of this project.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jhep.2010.01.037.

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