BMJ Open Gastroenterology

What is the optimal first-line treatment of autoimmune hepatitis? A systematic review with meta-analysis of randomised trials and comparative cohort studies

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To cite: Gleeson D, Martyn-StJames M, Oo Y, *et al*. What is the optimal first-line treatment of autoimmune hepatitis? A systematic review with meta-analysis of randomised trials and comparative cohort studies. *BMJ Open Gastroenterol* 2025;**12**:e001549. doi:10.1136/bmjgast-2024-001549

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjgast-2024-001549).

Received 3 August 2024
Accepted 9 October 2024

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ABSTRACT

Objectives Uncertainty remains about many aspects of first-line treatment of autoimmune hepatitis (AIH).

Design Systemic review with meta-analysis (MA).

Data sources Bespoke AIH Endnote Library, updated to 30 June 2024.

Eligibility criteria Randomised controlled trials (RCTs) and comparative cohort studies including adult patients with AIH, reporting death/transplantation, biochemical response (BR) and/or adverse effects (AEs).

Data extraction and synthesis Data pooled in MA as relative risk (RR) under random effects. Risk of bias (ROB) assessed using Cochrane ROB-2 and ROBINS-1 tools.

Results From seven RCTs (five with low and two with some ROB) and 18 cohort studies (12 moderate ROB, six high for death/transplant), we found lower death/transplantation rates in (a) patients receiving pred+/−aza (vs no pred): overall (RR 0.38 (95% CI 0.20 to 0.74)), in patients without symptoms (0.38 (0.19–0.75)), without cirrhosis (0.30 (0.14–0.65)), and with decompensated cirrhosis (RR 0.38 (0.23–0.61)), and (b) patients receiving pred+aza (vs pred alone) (0.38 (0.22–0.65)). Patients receiving higher (vs lower) initial pred doses had similar BR rates (RR 1.07 (0.92–1.24)) and mortality (0.71 (0.25–2.05)) but more AEs (1.73 (1.17–2.55)). Patients receiving bud (vs pred) had similar BR rates (RR 0.99 (0.71–1.39)), with fewer cosmetic AEs (0.46 (0.34–0.62)). Patients receiving mycophenolate mofetil (MMF) (vs aza) had similar BR rates (RR 1.32 (0.73–2.38)) and fewer AEs requiring drug cessation (0.20 (0.09–0.43)).

Conclusions Mortality is lower in pred-treated (vs untreated) patients, overall and in several subgroups, and in those receiving pred+aza (vs pred). Higher initial pred doses confer no clear benefit and cause more AEs. Bud (vs pred) achieves similar BR rates, with fewer cosmetic AEs. MMF (vs aza) achieves similar BR rates, with fewer serious AEs.

WHAT IS ALREADY KNOWN ABOUT THIS TOPIC

⇒ Prednisolone (pred)+/−azathioprine (aza) is effective in achieving remission in patients with autoimmune hepatitis (AIH). However, survival benefit has not been conclusively demonstrated, and uncertainty remains about (a) efficacy in several subgroups, (b) value of adding aza (vs pred alone), (c) optimal initial pred dose, and (d) efficacy and frequency of adverse effects (AEs) of budesonide (bud) vs pred, and mycophenolate (MMF) vs aza.

WHAT THIS STUDY ADDS

⇒ In an updated systematic review with meta-analysis of first-line AIH treatment, we show that (a): transplant-free survival rates are higher in pred-treated (vs untreated) patients: overall, and in patients without symptoms, without cirrhosis, with decompensated cirrhosis and with acute severe AIH. Also, in those receiving pred+aza (vs pred), (b): higher (>40 mg/day or 0.5 mg/kg/day) initial pred doses (vs lower) confer no clear benefit and cause more AEs; (c): bud (vs pred) achieves similar biochemical response (BR) rates, with fewer cosmetic AEs; and (d) MMF (vs aza) achieves similar BR rates, with fewer serious AEs.

HOW THIS STUDY MIGHT AFFECT PUBLIC PRACTICE OR POLICY

⇒ It confirms that further placebo controlled randomised controlled trials in AIH would be unethical and suggests benefits in several patient subgroups. Also, that initial predniso(lo)ne doses exceeding 40 mg/day or 0.5 mg/kg/day are unlikely to confer additional benefits over lower doses and cause more AEs. Third, that a decision regarding budesonide use as a first-line agent should be informed by concern regarding about cosmetic AEs rather than considerations regarding maximum efficacy. Finally, it suggests a role for MMF as a potentially better-tolerated steroid-sparing agent in patients who cannot or who are taking steps not to conceive.

INTRODUCTION

First-line treatment of autoimmune hepatitis (AIH) is based on randomised controlled trials (RCTs) performed in the 1960s and 70s. In a meta-analysis,[1] prednisolone+/−azathioprine was more effective than placebo and more effective than azathioprine alone at achieving disease remission. Prednisolone plus azathioprine was as effective as higher-dose

prednisolone monotherapy, with fewer adverse effects (AEs).

However, evidence of survival benefit from steroid-based treatment was not demonstrated statistically. Also, it remains unclear whether all patients with AIH require steroids. Or whether there are subgroups who do not.

Acute severe (AS)-AIH comprises about 5% of presentations and about 30% of patients require early liver transplant for survival.[2 3] The efficacy of corticosteroids is not established.

In a RCT in patients without cirrhosis,[4] budesonide showed higher efficacy than prednisolone in achieving normal serum transaminases after 6 months, with fewer AEs. Its longer-term efficacy is unclear. A meta-analysis[5] of this trial and one observational study[6] informed the recommendation of prednisolone and budesonide as equivalent first-line treatments in the 2020 American Association for the Study of Liver Diseases guidelines.[7] However, more information on budesonide is now available.

Recommendations regarding initial dose of prednisolone have varied widely in guidelines[7–9] and from expert opinion.[10] Questions also remain regarding steroid-sparing agents (SSAs) in AIH. Azathioprine was shown in early RCTs to enable reduction of steroid dose without loss of efficacy but with fewer AEs.[11] However, it is unclear if SSAs improve survival. Mycophenolate is used as an alternative SSA in patients intolerant of azathioprine, and recently, as a first-line agent[12] and its efficacy has been compared with that of azathioprine in a recent RCT.[13]

We present a systemic review with meta-analysis of first-line treatment of AIH to support the (submitted) British Society of Gastroenterology (BSG) AIH Guidelines. We aimed to address the following questions:

1. Is use of corticosteroid (±steroid-sparing agent) associated with better transplant-free survival (compared with non-use), in patients with (a) AIH overall, (b) asymptomatic AIH, (c) without cirrhosis and (d) with decompensated cirrhosis?
2. Are these first-line treatment options associated with better outcomes and/or fewer AEs than their comparators: budesonide (vs prednisolone), mycophenolate (vs azathioprine) and 'high' (>35–40 mg/day or 0.5 mg/kg/day) dose prednisolone (vs lower dose)?

METHODS

We conducted a systemic review with meta-analysis of RCTs and comparative cohort studies including adult patients with AIH, reporting death/transplantation, biochemical response (BR) and/or AEs. We followed the PRISMA 2020 guidelines and registered the protocol in 2021 on the PROSPERO database (CRD42020182668).

Information sources

An EndNote AIH Library was generated by information specialists at the University of Sheffield to develop the BSG AIH Management Guidelines (in press).

Search methods and study inclusion

Systematic literature searches were undertaken in February 2020 by Information Specialists at the School of Medicine and Population Health, University of Sheffield, with an updated search in July 2022. We used thesaurus terms and free-text terms relating to patients with AIH (online supplemental table 1). Searches were from inception and limited to human studies. The searches were conducted on Ovid MEDLINE, EMBASE via Ovid, the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL). Search results were imported into Endnote, and duplicates removed.

This library was then searched independently by SF and DG for studies involving prednisolone, prednisone, budesonide, azathioprine and mycophenolate in initial treatment of AIH (and its historical synonyms) in adults: We used the search terms in online supplemental table 2, and manually selected studies published in full and compatible with the PICO (Patient, Intervention, Control, Outcome) framework inclusion criteria (online supplemental table 3).

We updated the search by applying this strategy first, to Medline publications between 1 July 2022 and 30 June 2024 containing the term autoimmune hepatitis plus each one of the search terms in online supplemental table 2. And second, EMBASE, the CDSR and the CENTRAL from 1 January 2022 to 30 June 2024, using only the term autoimmune hepatitis (assuming that other historical terms for AIH used in constructing the Library (online supplemental table 1) were no longer used). These searches yielded no additional studies meeting the criteria in online supplemental table 3.

Finally, we also searched for similar studies in the references cited in four previous meta-analysis of initial AIH treatment: two[1 14] addressing overall treatment, one comparison of budesonide and prednisolone,[5] and one high vs low initial prednisolone doses.[15]

Outcomes

Primary outcome

Number of patients dying (any cause) or undergoing liver transplantation, as a ratio of the total.

Secondary outcomes

1. Ratio of patients dying of or undergoing transplantation for liver disease. Not including gastrointestinal bleeding, unless explicitly from varices.
2. Ratio achieving BR after 6-month and after 12-month treatment (in one study[6] 'at least' 12 months). The denominator was the total cohort number; using instead the number of informative patients (at that time point) yielded essentially identical results. BR was compared between patients receiving high-dose vs low-dose prednisolone, prednisolone vs budesonide, and mycophenolate vs azathioprine. Primary definition of BR was: serum alanine (and where available, aspartate) transaminase levels: ALT (±AST) falling to within

the normal range; other definitions included (a) fall of ALT, AST and serum immunoglobulin G to within normal ranges (complete biochemical remission (CBR) if achieved within 6 months),[16] and (b) fall in serum ALT+/−AST to less than twice the upper limit of normal.[11 17] Within each study, definition of BR in the cohorts compared was identical.

3. Frequency of AEs:
   1. Steroid-related. Any of (a) cosmetic AEs: acne, Cushingoid appearance, striae, buffalo hump; (b) metabolic AEs: new-onset diabetes mellitus, hypertension and weight gain (defined as onset of obesity in one study;[18] (c) bone disease (either osteoporosis or a fracture); and (d) psychosis. AEs were binary, without regard to time. Other steroid-related AEs, including anxiety, depression, dyspepsia and myopathy, were not recorded consistently enough for analysis.
   2. Azathioprine and mycophenolate-related AEs (any, and those causing drug discontinuation).

When possible, we extracted information on the number of patients experiencing each AE. However, when aggregating cosmetic AEs, we summed the number of specific cosmetic AEs, which are thus expressed as total number of cosmetic AEs rather than number of patients with at least one cosmetic AE. For the variable 'all AEs', we included only studies which reported at least three of the above different categories of AEs.

Data extraction

Data were extracted by DG and checked by SF (online supplemental tables 4 and 5). We obtained additional results from a multicentre audit of AIH management[19] by DG (a coauthor) analysing raw data on file and provided by the first author. This included (i) data on BR in prednisolone and budesonide-treated patients without cirrhosis; (ii) AEs in patients receiving low-dose and high-dose prednisolone; (iii) per cent of patients receiving an SSA in those receiving high and low initial prednisolone doses; (iv) assessment of prednisolone dose in patients receiving and not receiving an SSA; and (v) comparison of death/transplant rates in patients presenting with decompensated cirrhosis. We also obtained additional data on mortality[20 21] and on AEs in patients without cirrhosis[18 22]; this was kindly provided by the authors on request.

Risk of bias assessment

Risk of bias (ROB) was independently assessed by SF and DG, using the Cochrane Risk of Bias (ROB-2) tool[23] for RCTs and the ROBINS-1 tool[24] for cohort studies. Discrepancies were resolved by discussion.

ROB in the cohort studies arose largely from inter-group differences regarding confounding baseline variables and follow-up times. For the outcome death/transplantation, we considered age, percentage with cirrhosis, serum bilirubin and serum ALT as confounding baseline variables.[19 25 26] For BR, we considered as baseline confounders: age, percentage with cirrhosis and serum and IgG, [19 20 27] (all variables which are predictive of BR, online supplemental table 5). Baseline serum transaminase levels do not predict their normalisation on treatment.[20] If inter-group differences for confounding variables did not reach a significance level of $p<0.05$ or were addressed by multivariate analysis, ROB due to cofounding was deemed moderate; otherwise, it was deemed high. In the absence of established variables predisposing to AEs, reporting of these was deemed at moderate ROB. Other potential sources of bias considered were (online supplemental table 5) imbalances in receiving comedications (ROBIN-1 domains 4.1–4.6: usually azathioprine), in follow-up time, and in missing data (domains 5.1–5.3).

Meta-analysis (MA)

We used R-Studio to aggregate outcome results (expressed as risk ratio (RR)). We performed no data conversions and considered only binary outcomes.

Forest plots were constructed using fixed and random effects models. A p value of <0.05 and RR values with CIs not overlapping unity were deemed significant. Heterogeneity was assessed using the I^2 statistic; values of 25%–49%, 50%–74% and ≥75% representing low, moderate and high heterogeneity. With three or more studies, we calculated the prediction interval.[28] As no analysis involved more than 10 studies, we did not assess publication bias. Reasons for heterogeneity were explored by sensitivity analysis, usually based on risk of bias.

Patient and public involvement

None. This meta-analysis was done specifically to support the (submitted) BSG AIH Guidelines, the development group of which included two patients. They were aware of the current work but were not involved in it.

RESULTS

Characteristics of included studies

Online supplemental figure 1 shows the PRISMA diagram. We found 24 studies meeting inclusion criteria (7 RCTs[4 11 13 17 29–31] and 17 observational studies).[2 3 12 18–22 32–40] We found one further observational study[6] cited in a prior meta-analysis,[41] making 25 included studies (online supplemental table 4).

All cohort studies and the two most recent RCTs[4 13] used the 1999[42] or 2008[43] International AIH Group diagnostic criteria (online supplemental table 4), although up to 10% of patients in the cohort studies did not meet these criteria. The remaining RCTs predated these criteria, and diagnosis of AIH was based on chronic liver disease (usually, abnormal liver tests for >3 months), compatible liver biopsy, serum autoantibodies and hyperglobulinaemia. In three RCTs,[11 29 31] serum was positive for hepatitis B markers in 14 (4%–16%) of patients, and all were performed before availability of hepatitis C testing.

All studies focused mainly on adults but two RCTs included some children.[4 30] One study included patients

initially diagnosed in childhood.[19] In eight studies (one RCT), information was not reported. The remaining studies explicitly excluded children.

We focused on first-line drug treatment following initial diagnosis. However, three RCTs[4 11 29] included previously treated patients in whom the episode reported represented treatment of a relapse. Since outcomes in these patients were not separately reported, they are included here.

Four RCTs used prednisone and three used prednisolone. Since these are clinically equivalent, the term predniso(lo)ne is used to refer to either drug.

Risk of bias (ROB)

Only three RCTs[4 11 17] were blinded to treatment allocation. However, for the outcome BR, all RCTs were deemed at low ROB (figure 1A). Four of the five RCTs reporting mortality were at low ROB; the fifth[11] was at some ROB because of shorter follow-up time in one of the steroid-receiving cohorts: (prednisolone and azathioprine combined). For AEs, blinded trials were deemed at low ROB and the others at some ROB.

Six cohort studies addressing mortality were deemed at high ROB (figure 1B) because potential baseline confounders were either unreported[32 34] or favoured one treatment group and uncorrected by multivariate analysis[2 20 33 36] (online supplemental table 5). Other observational studies were deemed at moderate ROB for remission and mortality. We evaluated imbalances regarding coreceipt of a steroid-sparing agent, follow-up time and missing data (Online supplemental table 5). We did not consider these ever sufficient in themselves to elevate ROB to severe. All 18 cohort studies were deemed at moderate ROB for AEs.

Survival benefit of steroid-based treatment

Unselected AIH

In meta-analysis (MA) of four RCTs and two observational studies, patients receiving corticosteroids (alone or with azathioprine) had (compared with patients receiving no treatment or azathioprine alone) lower rates of all-cause (figure 2A table 1) and liver-related (online supplemental table 6) mortality, with moderate and low heterogeneity respectively. Results were unchanged following exclusion of patients in the Mayo Clinic RCT[11] receiving combination therapy (shorter follow-up time, resulting in some ROB) (online supplemental table 7).

These differences remained when the four RCTs were considered separately (table 1, online supplemental table 7); significant for liver-related but not for all-cause mortality. Further subgroup comparisons (online supplemental table 7) also suggested lower rates in those receiving prednisolone monotherapy, compared with placebo (not significant for all-cause mortality). Differences between those receiving predniso(lo)ne alone and receiving azathioprine alone were not significant. The benefit of steroids was also seen (for all-cause and liver-related death/transplantation) in the two cohort

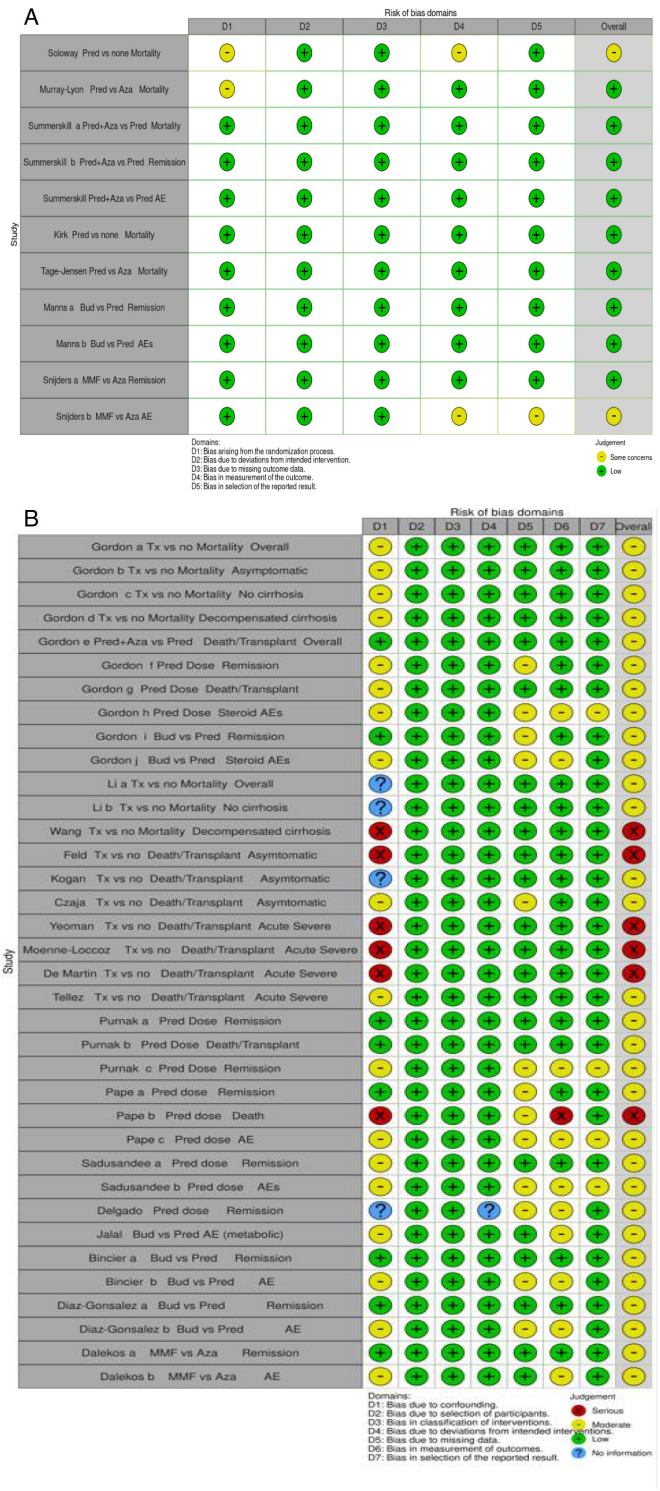
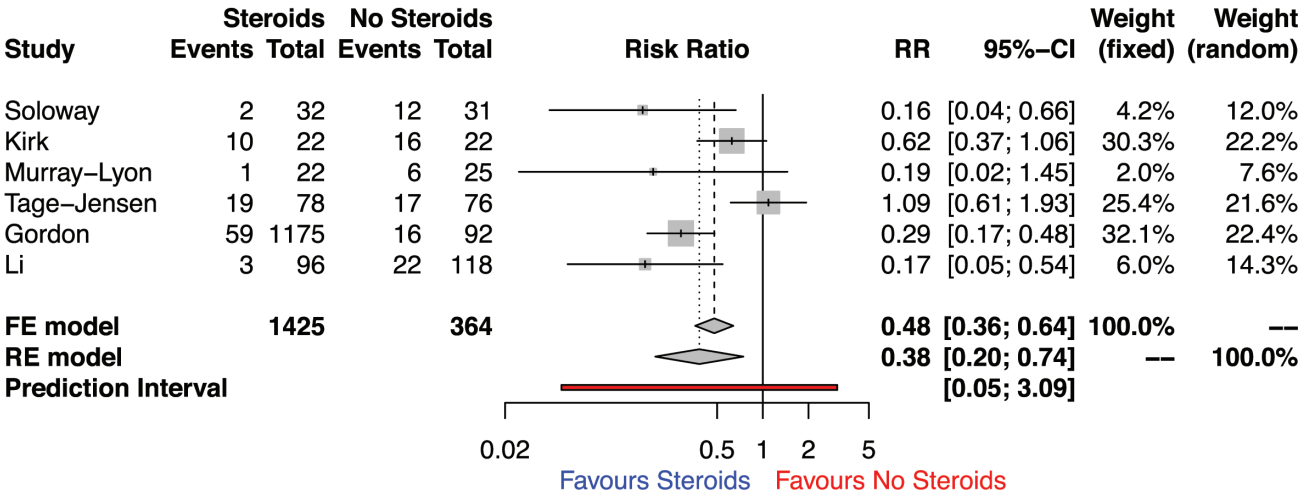


Figure 1 Estimations of risk of bias. (**A**) Randomised controlled trials (Cochrane ROB tool). (**B**) Observational studies (ROBINS-1 tool).

studies (table 1, online supplemental table 6); in one,[19] Cox regression analysis confirmed that the association with steroids was independent of baseline prognostic variables.

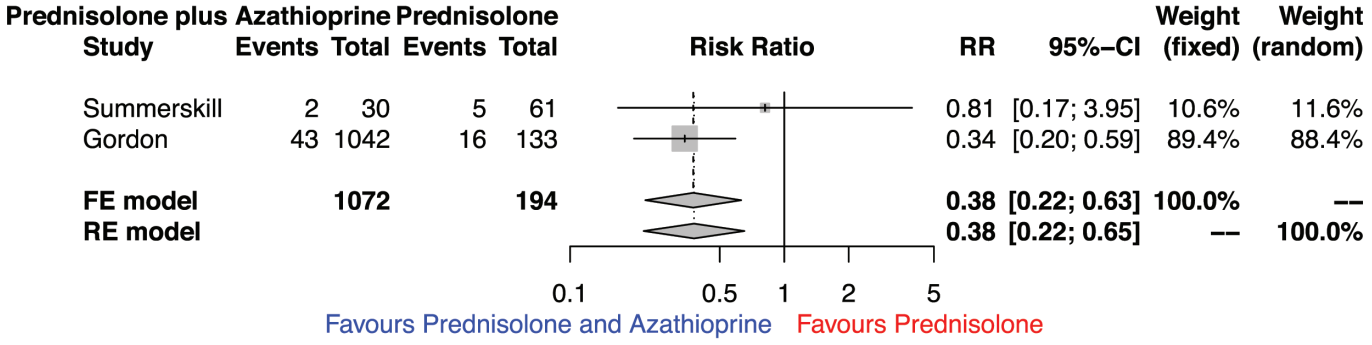
In one study, mortality was similar in those receiving azathioprine compared with placebo.[11] However, in MA of two studies (one RCT; one cohort), patients given

A



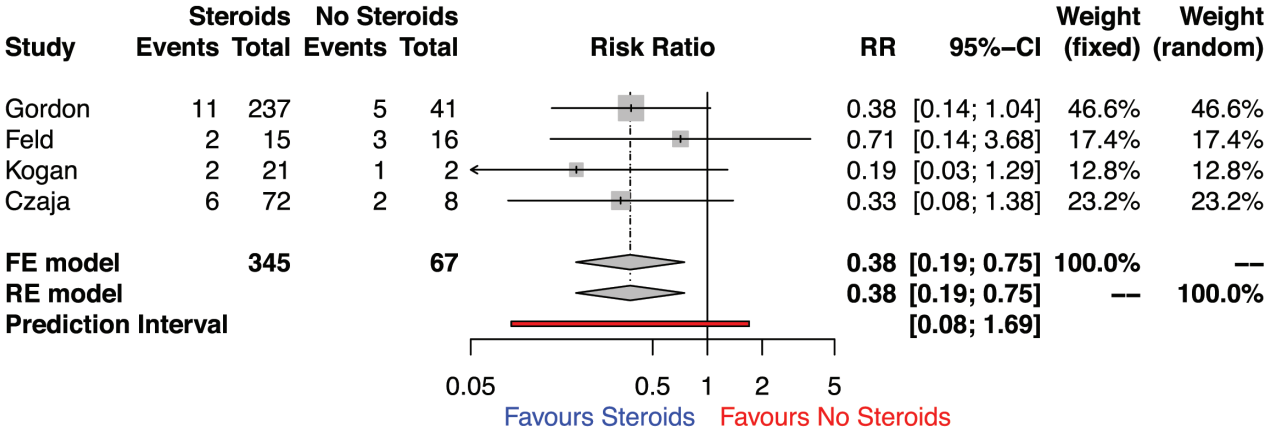
Heterogeneity: I^2 = 73% [39%; 88%], τ^2 = 0.4518, χ^2_5 = 18.80 (p < 0.01)

B



Heterogeneity: I^2 = 2%, τ^2 = 0.0089, χ^2_1 = 1.02 (p = 0.31)

C



Heterogeneity: I^2 = 0% [0%; 85%], τ^2 = 0, χ^2_3 = 1.09 (p = 0.78)

Figure 2 Comparison of all-cause deaths/transplants in patients receiving steroids vs no steroids. (**A**) All patients. Steroids±azathioprine vs placebo or azathioprine alone. (**B**) All patients. Steroids plus azathioprine vs steroid alone. (**C**) Asymptomatic patients—steroids±azathioprine vs placebo or azathioprine alone.

Table 1 Main results of meta-analyses (see also figures 2–4 and online supplemental tables 6 and 7)

AIH population	Intervention	Studies selected	Outcome	Number of studies	Ref	Number of patients	Risk ratio		I2	τ	Prediction interval
							Fixed effects	Random effects			
General	Steroids±aza vs no steroids±aza	RCTs only	All-cause death/ transplant	4	11 29–31	154 vs 154	0.69 (0.48–0.99)	0.50 (0.2–1.18)	63	0.48	0.02–16.86
General	Steroids±aza vs no steroids±aza	Cohorts only	All-cause death/ transplant	2	19 32	1271 vs 210	0.26 (0.17–0.42)	0.26 (0.17–0.42)	0	0	na
No cirrhosis	Steroids±aza vs no steroids±aza	Cohorts	All-cause death/ transplant	2	19 32	940 vs 138	0.30 (0.14–0.65)	0.30 (0.14–0.65)	0	0	na
Cirrhosis	Steroids±aza vs no steroids±aza	Cohorts	All-cause death/ transplant	2	19 32	331 vs 72	0.26 (0.15–0.43)	0.26 (0.15–0.43)	0	0.31	na
Decompensated cirrhosis	Steroids±aza vs no steroids±aza	Cohorts	All-cause death/ transplant	2	19 38	169 vs 32	0.38 (0.23–0.61)	0.38 (0.23–0.61)	0	0	na
General	High vs low-dose pred	RCT, cohorts	Remission 12 months	5	17 19–21 39	854 vs 929	1.00 (0.93–1.09)	1.05 (0.91–1.22)	58	0.01	0.68–1.64
General	High vs low-dose pred	Cohorts	Complete biochemical remission	2	20 21	221 vs 118	1.13 (0.95–1.34)	1.15 (0.92–1.43)	32	0.009	na
General	High vs low-dose pred	RCT, cohorts	All AEs	5	17 19–21 39	811 vs 915	1.54 (1.26–1.89)	1.73 (1.17–2.55)	63	0.12	0.48–6.19
General	Bud vs pred	RCT, cohorts	Remission 12 months*	3	6 19 22	161 vs 1126	0.98 (0.84–1.14)	0.99 (0.71–1.39)	88	0.15	0–281
No cirrhosis	Bud vs pred	RCT, cohorts	Remission 6 months	3	4 22 40	263 vs 1027	0.96 (0.83–1.12)	0.97 (0.69–1.36)	81	0.089	0.21–4.50
No cirrhosis	Bud vs pred	RCT cohorts	All AEs	3	4 22 40	230 vs 404	0.61 (0.46–0.80)	0.61 (0.43–0.87)	14	0.03	0.03–14
No cirrhosis	Bud vs pred	RCT cohorts	Cosmetic AEs	3	4 22 40	230 vs 404	0.49 (0.37–0.66)	0.70 (0.25–1.96)	74	0.66	0–150 290
General	MMF vs aza	RCT cohort	Remission 6 months	2	12 13	221 vs 78	1.08 (0.94–1.24)	1.32 (0.73–2.38)	72	0.14	na
General	MMF vs aza	RCT cohort	All AEs	2		222 vs 95	0.96 (0.83–1.10)	0.80 (0.47–1.37)	85	0.126	na
General	MMF vs aza	RCT cohort	AEs requiring drug cessation	2		222 vs 95	0.20 (0.09–0.43)	0.20 (0.09–0.43)	0	0	na

*Delgado: time unspecified; assumed to be after 12 months.
AEs, adverse effects; AIH, autoimmune hepatitis; MMF, mycophenolate mofetil; na, not applicable; RCTs, randomised controlled trials.

prednis(ol)one plus azathioprine had lower all cause (figure 2B) and liver-related mortality (online supplemental table 6) than those taking prednis(ol)one monotherapy. In the RCT, those receiving predniso(lo)ne alone received higher doses,[17] but in the cohort study,[19] they received lower doses, and the survival benefit of adding an SSA was independent of baseline covariates and of initial prednisolone dose.

Cirrhosis

In meta-analysis (two cohort studies) of patients both with and without cirrhosis at diagnosis, steroid-based treatment was associated with a 3–4-fold reduction in (all-cause) death/transplant rate (table 1). An almost threefold reduction was also seen in two cohort studies of decompensated cirrhosis; one[38] was at high ROB because of uncorrected baseline confounding, but the association with treatment persisted on multivariate analysis (unpublished data on file) in the other.[19]

Asymptomatic AIH

In MA of four cohort studies in patients without symptoms at diagnosis, steroid-based treatment was (compared with no treatment) associated with a reduced all-cause (figure 2C) and liver related (online supplemental table 6) death/transplantation rate. Removing the study at high ROB[36] yielded identical results (online supplemental table 7), which were confirmed on multivariate analysis in another study.[19]

Acute severe AIH

In MA of four cohort studies, corticosteroids were associated with reduced death/transplantation rate (all liver-related), compared with no treatment, with low heterogeneity (online supplemental table 6).[3] However ROB was high because in three studies,[2 3 33] baseline model for end-stage liver disease (MELD) score was lower in those receiving steroids (online supplemental table 5); data were unreported in the fourth.[34] This suggests systemic bias, although in the largest study,[3] multivariate analysis confirmed an association of steroid therapy with survival, independent of MELD score.

Initial prednis(ol)one dose

We found five studies (online supplemental table 4, one RCT, four cohorts), in which results regarding at least one outcome were compared between patients receiving 'high' and 'low' initial doses of prednis(ol)one. The cut-off value between high and low dose was usually 35–40 mg/day or 1 mg/kg/day.

In MA, patients receiving high and low initial prednis(ol)one doses were not different, regarding percentage achieving BR after 6 months (figure 3A) or 12 months (table 1); nor were rates of CBR (normal serum transaminases and IgG within 6 months) in two studies (table 1).

Rates of all-cause (figure 3B) and of liver-related (online supplemental table 6) death/transplant in four studies were also similar in patients receiving high vs low doses of predniso(lo)ne. However, there was high heterogeneity and a wide prediction interval. Of the two largest cohort studies, one[20] found lower mortality in patients receiving higher doses. This study was at high ROB: it included deaths only (no data on transplants) and patients receiving high-dose predniso(lo)ne had favourable baseline variables (online supplemental table 5) which were uncorrected for. However, excluding this study did not alter the result (online supplemental table 7). In the other large cohort,[19] those receiving high-dose prednisio(lo)ne had higher mortality, which persisted in multivariate analysis.

Patients receiving high-dose prednis(ol)one had higher rates of any AE (table 1) but with moderate heterogeneity and a wide prediction interval (PI). They also had higher rates of cosmetic AEs (figure 3C) and of new-onset diabetes (figure 3d). Differences in bone disease (four studies), weight gain and psychosis (three studies each) and hypertension (two studies) were not significant (online supplemental table 7).

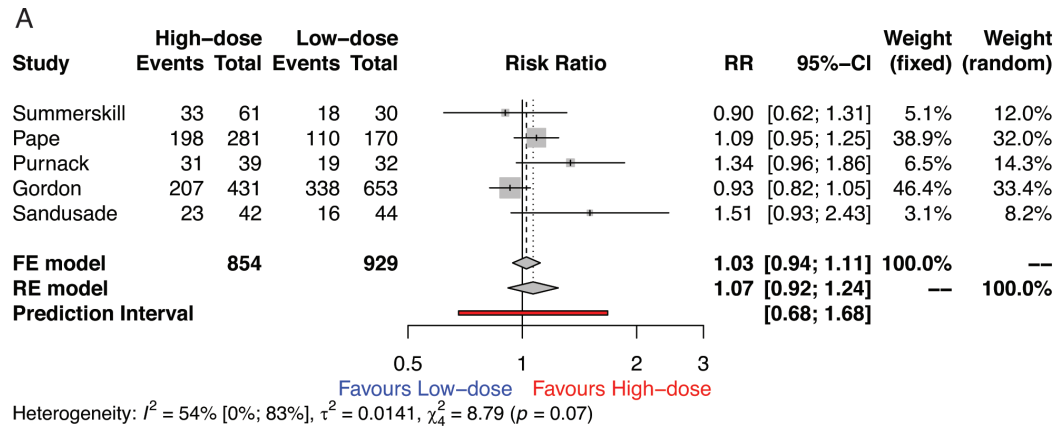
Budesonide versus prednisolone

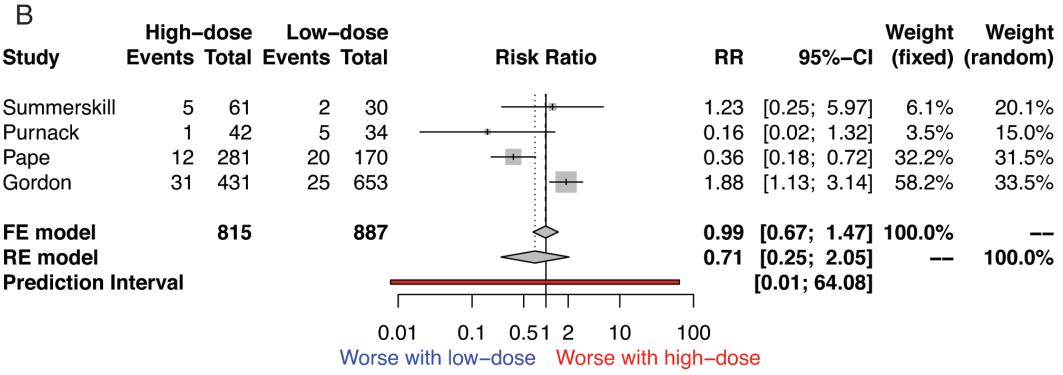
In MA of four studies, biochemical remission rates in patients initially receiving budesonide and prednisolone were not different after 6 months (figure 4a) or after 12 months (table 1). There was high heterogeneity and wide prediction intervals. Considering only patients without cirrhosis (table 1), remission rates were similar after 6 months (three studies) but in one study,[22] were lower after 12 months in patients receiving budesonide. The single RCT[4] showed a higher remission rate after 6 months in budesonide-treated patients, but the rate was unusually low (39%) in the prednisolone group. In one cohort study,[22] CBR rate (after 6 months) was lower in patients receiving budesonide than receiving predniso(lo)ne. In another cohort study,[19] 5-year survival in patients receiving prednisolone and budesonide (overall and in those without cirrhosis) was not significantly different.

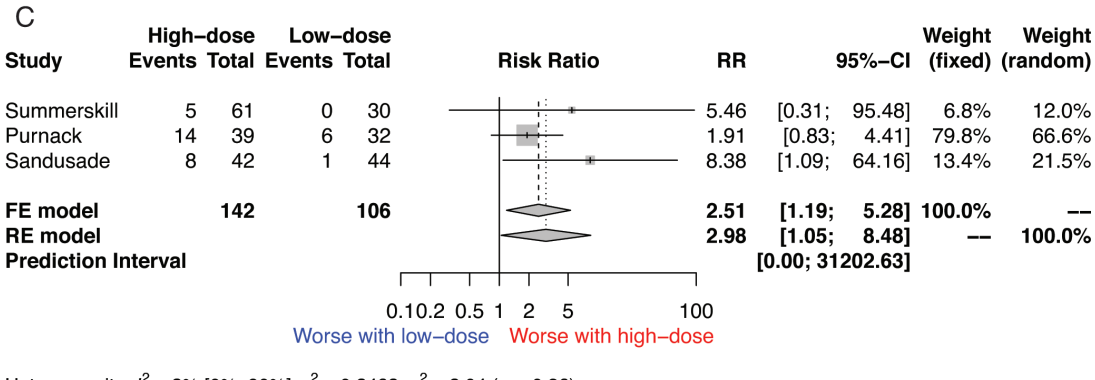
Patients receiving budesonide had (compared with receiving prednisolone) lower rates of any (figure 4B) and of cosmetic AEs (figure 4C); Considering only patients without cirrhosis (three informative studies), these differences remained significant (table 1). However, incidence of new onset diabetes (figure 4D), or of hypertension, weight gain, psychosis and bone disease (online supplemental table 7) was not significantly different in budesonide vs prednisolone-treated patients, either overall, or in patients without cirrhosis (not shown). Apart from with hypertension, heterogeneity was high.

Mycophenolate versus azathioprine

In MA of two studies (one RCT; one cohort), 6-month BR rate was similar in patients receiving mycophenolate and those receiving azathioprine (both with prednisolone). BR rate at 12 months (available only in the cohort study) was higher in patients receiving mycophenolate (p=0.04). Rate of any AE was similar in the two groups; however, patients receiving mycophenolate had fewer







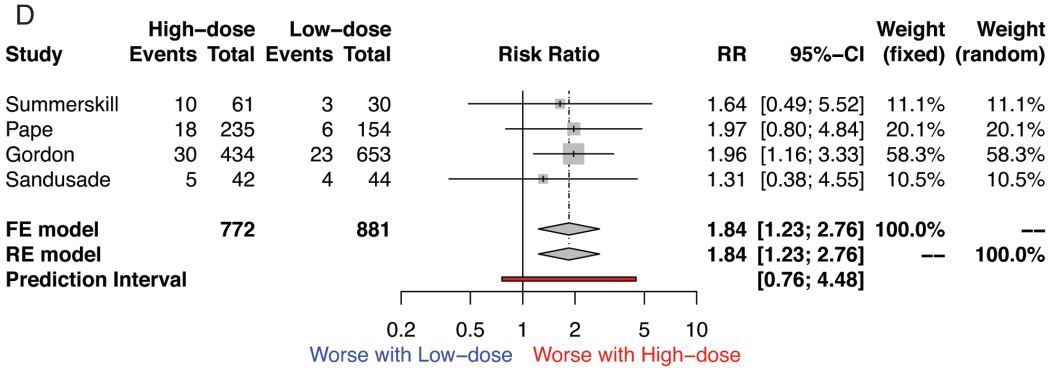


Figure 3 Comparison of high and low initial predniso(lo)ne doses. (**A**) Biochemical remission after 6 months. (**B**) All-cause death or transplant. (**C**) Cosmetic adverse effects. (**D**) Diabetes.

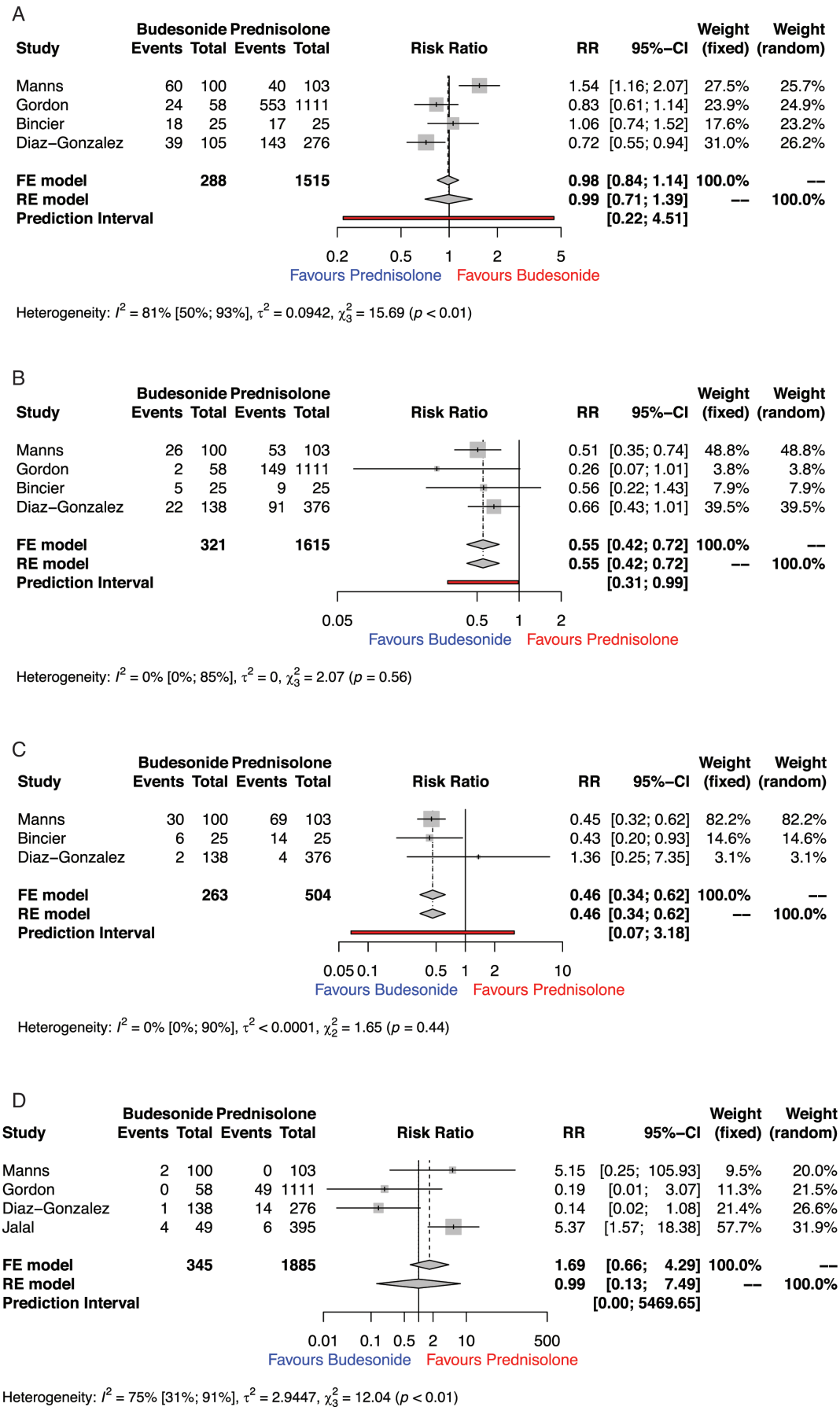


Figure 4 Comparison of budesonide and prednis(ol)one (both with azathioprine). (**A**) Biochemical remission after 6 months. (**B**) Any adverse effect. (**C**) Cosmetic adverse effects. (**D**) Diabetes.

AEs requiring drug discontinuation (low heterogeneity) (table 1). In one study,[12] survival rates were not different between patients receiving mycophenolate and receiving azathioprine.

DISCUSSION

In this updated systemic review and MA of first-line treatment of AIH, we make several novel observations. First, we provide more robust evidence for the overall mortality benefits of steroid-based treatment. Efficacy of steroids in achieving remission and a suggestive survival benefit were demonstrated by Lamers.[1] In a network analysis of six RCTs, Lu also demonstrated superiority of prednis(ol)one over azathioprine and over placebo in achieving remission but included no data on survival.[14] By incorporating two more recent cohort studies, we observe a significant survival benefit of steroid-based therapy, although we acknowledge the caveats of combining studies of different designs.

The initial meta-analysis[1] also suggested fewer AEs on predniso(lo)ne plus azathioprine than on prednisolone monotherapy, probably because of higher doses in the latter regime. Here, we show that this combination therapy may also have a survival benefit; however, this is based on only two studies and needs confirmation.

Third, we demonstrate likely survival benefits of steroid-based therapy in several AIH subgroups: including asymptomatic patients, patients with and without cirrhosis, and with decompensated cirrhosis. Also, in patients with acute severe AIH, although the results are biased by the treated groups having less severe liver dysfunction. A trial of steroids may however be justified in acute AIH of moderate severity.

Thus, steroid treatment is beneficial in most patients with AIH. However, in one cohort study,[19] no association was found (on multivariate analysis) between steroids and transplant-free survival in patients with 'mild' AIH (by several criteria). In such patients, deferring treatment might occasionally be justified.

Fourth, we provide clarification on initial prednisolone dose, regarding which guideline recommendations[7–9] and expert opinion[10] have varied. Usually predniso(lo)ne is tapered as serum transaminases improve. In assessing dose effects, ideally, cumulative dose would be considered but is rarely reported. However, in one study,[20] cumulative predniso(lo)ne dose was 47% higher in patients initially receiving high (vs low) dose, suggesting that initial dose is a reasonable marker of cumulative dose.

Here, we show that initial predniso(lo)ne doses exceeding 35–40 mg/day or 0.5 mg/kg/day are no more effective than lower doses in achieving BR or in improving survival (A recent study[44] confirms lack of association between initial prednisolone dose and biochemical remission or event-free survival. Not included here as different dose 'cut-off' (30 mg/day), and dose-group numbers were not reported). Comparison of death/transplant rates for patients receiving high vs low initial doses showed high heterogeneity. The larger study[20] of two suggesting lower mortality was at high ROB: however, excluding this did not change the results. Clearly conclusions are tentative, but at the very least, there is no clear evidence for a survival benefit from higher doses.

We focused on comparing high vs low-dose cohorts within single studies. The meta-analysis of Zhang[15] did not include some older, or more recent studies, and also, compared 'average' doses across studies, inevitably with much overlap. We could not confirm their finding of higher doses associated with higher rates of BR or death/transplant.

Regarding steroid-related AES, we confirmed the qualitative associations with higher predniso(lo)ne dose suggested by others.[1 15] We had access to more studies and our results suggest dose-relationships with cosmetic and overall AEs, and with diabetes. Although we could not confirm a dose relationship with weight gain, psychosis or bone disease (osteoporosis or fracture), a dose relationship with bone disease is suggested in another cohort study.[45]

Regarding comparisons between budesonide and prednisolone, we could access more studies than the one RCT[4] considered by Lu,[14] and the two studies[4 6] considered in the quantitative MA of Vierling.[5] We could not confirm their observation of superior BR rates with budesonide. Indeed, budesonide may be inferior (although based on one study)[22] in achieving CBR. In one cohort study,[19] 5-year death/transplant rates were not different in budesonide and prednisolone-tested patients; however, more data are needed on longer-term outcome.

We found that budesonide was associated with fewer overall AEs, and fewer cosmetic AEs than predniso(lo)ne, although this remains largely based on the single RCT, in which AEs were monitored prospectively. However, we fail to show associations of budesonide with reduced diabetes, hypertension, weight gain, psychosis or bone disease, although this might also reflect a bias favouring use of budesonide in patients at high risk of such AEs.

Our comparisons of AEs on budesonide vs prednisolone are tentative. Some cohort studies reported very low (or zero) rates of cosmetic AEs[22] or of diabetes,[40] which (given that these studies are retrospective) may result from inadvertent under-reporting.

Finally, analysis of two studies suggests that mycophenolate achieves similar rates of biochemical remission after 6 months, and perhaps, higher rates after 12 months; it is also associated with fewer AEs requiring drug discontinuation.

Our study has limitations. Despite a detailed search, we found only 25 informative studies. Only three of the seven RCTs were blinded, and in five (performed during the 1960s and 70s), about 15% had hepatitis B virus and an unknown number hepatitis C virus. However, the biopsy and immunological features and the response to predniso(lo)ne suggested that most patients did have AIH.

We used established methods for assessing ROB. Many end points (death/transplantation), biochemical

remission and some side effects (diabetes) we considered as objective endpoints, assessment of which should be relatively bias-free, even in unblinded studies. The biggest sources of bias were confounding of outcomes in the cohort studies by imbalance between prognostic baseline variables. Assessment of such confounding was usually possible and was sometimes addressed using multivariate analysis. When this was not done and imbalances were clear, we deemed such studies at high ROB; however, excluding them did not change the results. Other potential sources of bias were imbalances in comedications (usually azathioprine) and missing data (see online supplemental table 5). We considered these insufficient in themselves to elevate the ROB to serious in any study. Nevertheless, we could not address all sources of bias.

We calculated pooled relative risk (RR), using the fixed and random (RE) effects models. We base our conclusions on the RE model, which makes no assumption that patients in individual studies are randomly selected from the same overall AIH pool. We also calculated the PI, which estimates the range of RR values expected in a hypothetical additional study or the likelihood of a future hypothetical patient benefiting from treatment.[28] For many analyses, PI range overlapped with unity, suggesting that benefit (while more likely than not) is not guaranteed. Thus, the evidence for benefit of steroid treatment of AIH is suggestive rather than conclusive.

Our results may have implications for practice. First, that steroid treatment of AIH improves transplant-free survival—overall and in several subgroups. Second, that higher initial predniso(lo)ne doses cause more AEs but achieve no clear benefit. Third, that budesonide is not more effective than predniso(lo)ne but has fewer cosmetic AEs; its first-line use should be informed by concerns regarding the latter rather than by the need to maximise efficacy. Finally, that mycophenolate is as effective as azathioprine in achieving BR and is better tolerated; it can thus be considered as a first-line steroid-sparing agent in patients who (because of its teratogenicity) cannot or who are taking active steps not to conceive.

Finally, our meta-analysis points to the need for further RCTs and prospective cohort studies of first-line treatments. In these, comparison of AEs will be particularly important. Lamers in the initial MA of AIH treatment[1] noted that AEs were 'not adequately mentioned'. Unfortunately, this remains the case, especially for cosmetic and mental health AEs, weight gain and even diabetes. Incorporation into clinical practice of a standard proforma for prospectively recording steroid AEs is long overdue in AIH.

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Acknowledgements Doctors Victoria Gordon, Simon Pape, Craig Lammert, Therese Bittermann, Cumali Efe, Maria Londono and Alvaro Diaz-Gonzalez for generously sharing additional unpublished data in regard to their cited studies. Anthea Sutton and Angie Rees, School of Medicine and Population Health, University of Sheffield for help with development of the EndNote Library and updated searches. Members of the British Society of Gastroenterology AIH management guideline development Group for additions to the EndNote Library and for helpful discussions.

Contributors DG. Conceived study and designed methods. Extracted data, performed meta-analyses and wrote draft manuscript and is the guarantor. MMS. Helped design protocol. Advised on methodology, including assessing risk of bias and performing the meta-analysis. Commented on manuscript. YO. Discussed planning of the study and commented on the protocol. Commented on manuscript. SF. Commented on the protocol. Replicated the library search. Independently calculated risk of bias. Checked the accuracy of the extracted data.

Funding The British Society of Gastroenterology funded the Endnote Library generation (£2500; award/grant number not applicable) but had no input into the conduct of the study.

Competing interests DG: Invited speaker (on PSC) Dr Falk sponsored symposium 2023; hospitality, no honorarium. Other authors: no interests declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All studies used in the meta-analysis are cited in the references. Extracted data are stored in an Excel file; applications to access this may be directed to the authors. As described in Methods, we have used some unpublished additional data, kindly shared with us by the authors.

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