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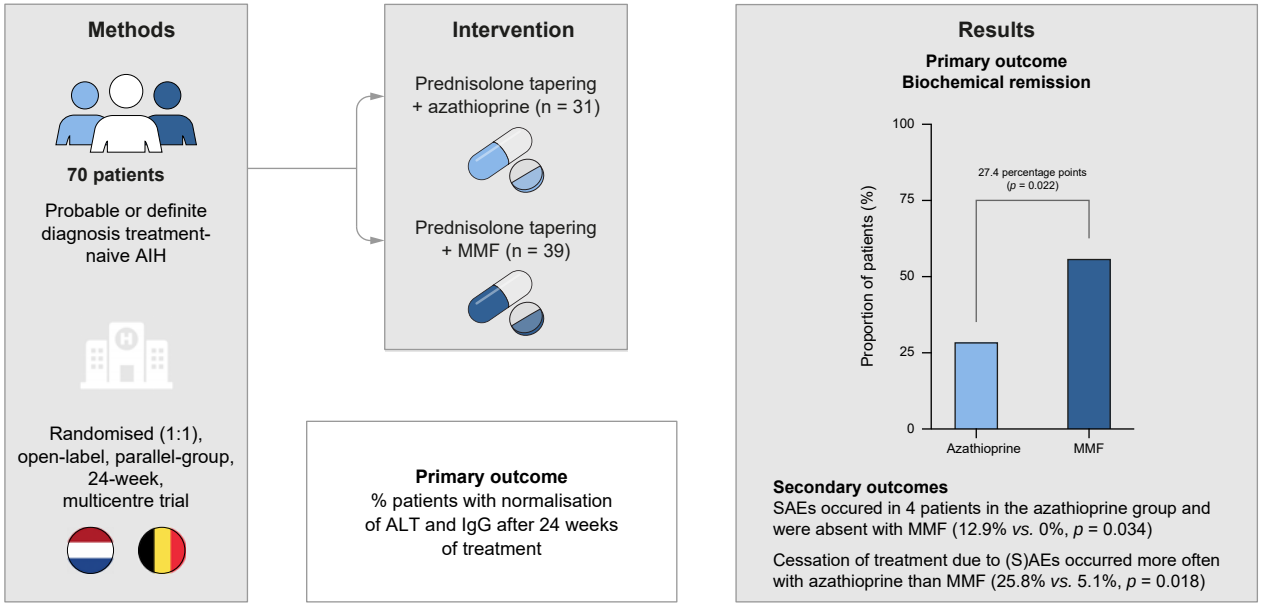
Graphical abstract



Highlights

- Limited efficacy and tolerability of standard prednisolone and azathioprine combination therapy in autoimmune hepatitis.
- Mycophenolate mofetil combined with prednisolone is effective as first-line therapy for achieving biochemical remission.
- Mycophenolate mofetil has a more favourable tolerability profile than azathioprine.

Impact and implications

This randomised-controlled trial directly compares azathioprine and mycophenolate mofetil, both in combination with prednisolone, for the induction of biochemical remission in treatment-naive patients with autoimmune hepatitis. Achieving complete remission is desirable to prevent disease progression. Patients assigned to the mycophenolate mofetil group reached biochemical remission more often and experienced fewer adverse events. The findings in this trial may contribute to the re-evaluation of international guidelines for the standard of care in treatment-naive patients with autoimmune hepatitis.

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An open-label randomised-controlled trial of azathioprine *vs.* mycophenolate mofetil for the induction of remission in treatment-naive autoimmune hepatitis

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Background & Aims: Patients with autoimmune hepatitis (AIH) almost invariably require lifelong immunosuppressive treatment. There is genuine concern about the efficacy and tolerability of the current standard combination therapy of prednisolone and azathioprine. Mycophenolate mofetil (MMF) has emerged as an alternative option. The aim of this study was to compare MMF to azathioprine as induction therapy for AIH.

Methods: In this 24-week, prospective, randomised, open-label, multicentre superiority trial, 70 patients with treatment-naive AIH received either MMF or azathioprine, both in combination with prednisolone. The primary endpoint was biochemical remission defined as normalisation of serum levels of alanine aminotransferase and IgG after 24 weeks of treatment. Secondary endpoints included safety and tolerability.

Results: Seventy patients (mean 57.9 years [SD 14.0]; 72.9% female) were randomly assigned to the MMF plus prednisolone (n = 39) or azathioprine plus prednisolone (n = 31) group. The primary endpoint was met in 56.4% and 29.0% of patients assigned to the MMF group and the azathioprine group, respectively (difference, 27.4 percentage points; 95% CI 4.0 to 46.7; $p = 0.022$). The MMF group exhibited higher complete biochemical response rates at 6 months (72.2% *vs*. 32.3%; $p = 0.004$). No serious adverse events occurred in patients who received MMF (0%) but serious adverse events were reported in four patients who received azathioprine (12.9%) ($p = 0.034$). Two patients in the MMF group (5.1%) and eight patients in the azathioprine group (25.8%) discontinued treatment owing to adverse events or serious adverse events ($p = 0.018$).

Conclusions: In patients with treatment-naive AIH, MMF with prednisolone led to a significantly higher rate of biochemical remission at 24 weeks compared to azathioprine combined with prednisolone. Azathioprine use was associated with more (serious) adverse events leading to cessation of treatment, suggesting superior tolerability of MMF.

Trial registration number: #NCT02900443.

Introduction

Autoimmune hepatitis (AIH) is a rare chronic liver disease characterised by progressive inflammation that can lead to cirrhosis and end-stage liver disease. Its prevalence is reported to be 10-17 per 100,000 in Europe.[1] When diagnosed and treated early, AIH can usually be managed with immunosuppressive drugs.[2,3] Patients with AIH almost invariably require lifelong immunosuppressive treatment.[4] The first aim of induction treatment is to reach a complete biochemical response, defined as normalisation of aminotransferases and IgG.[5] Clinical guidelines recommend combination therapy with glucocorticoid and azathioprine as first-line induction therapy in treatment-naive patients with AIH.[2,6] These recommendations are based on older clinical trials, as recently summarised in a systematic review and meta-analysis.[7] However, there is genuine concern about the limited efficacy and tolerability of the current standard combination therapy. With the combination of prednisolone and azathioprine, normalisation of aminotransferases is achieved in only 38.8-70.5% of patients

Keywords: autoimmune hepatitis; azathioprine; mycophenolate mofetil; first-line treatment; induction therapy; randomised-controlled trial; remission; biochemical remission; phase IV trial.
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after 6 months of treatment, independent of prednisolone dosage.[8–10] Patients with an insufficient response are at serious risk of disease progression.[8,11] In addition, complications such as intolerance to azathioprine due to gastrointestinal toxicity, cytopenia and arthralgias, necessitate cessation of treatment in approximately one-fifth of patients.[12,13]

Mycophenolate mofetil (MMF) has emerged as a second-line alternative to azathioprine in patients with AIH who are intolerant to azathioprine or who have an insufficient response.[14–25] MMF is a prodrug of mycophenolic acid that inhibits the activity of the type II isoform of inosine-5'-monophosphate dehydrogenase without affecting the type I isoform, leading to selective suppression of both T- and B-cell lymphocyte proliferation. MMF is labelled for use in preventing rejection after solid organ transplantation. Observational, uncontrolled studies have explored the efficacy of MMF in treatment-naive patients.[26–30] Reports from these studies document higher clinical response rates with MMF compared to azathioprine. Furthermore, MMF is generally well tolerated, with infrequent adverse effects.[29] In addition, the use of MMF facilitates rapid glucocorticoid withdrawal.[30] While these data are promising, randomised-controlled data are needed to inform clinical guidelines. Therefore, the aim of the current multicentre, randomised-controlled trial was to compare the biochemical efficacy and clinical tolerability of MMF and azathioprine, both in combination with prednisolone, as induction therapy in treatment-naive patients with AIH.

Patients and methods

Trial oversight and design

In this multicentre, randomised, open-label, two-arm trial, the efficacy and safety of MMF as first-line treatment compared to azathioprine, both in combination with prednisolone, was evaluated over a 24-week period in patients with treatment-naive AIH. The protocol was approved by the local ethics committee and registered in the ClinicalTrials.gov database (NCT02900443). All patients provided written informed consent before enrolment, and the study was conducted according to the ethical principles of the Declaration of Helsinki. Additional details of the trial design, eligibility criteria, assessments, endpoints, and statistical analysis are provided in our previously published protocol[31] and the supplementary methods.

Patients

Patients 18 years of age or older who had received a probable or definite diagnosis of AIH according to the simplified criteria for the diagnosis of AIH[32] were recruited (Table S1). Patients were eligible if they had a first presentation of AIH with at least compatible histology requiring treatment according to the current EASL guidelines.[2] Patients were excluded if they had any of the following 1) a variant syndrome with primary sclerosing cholangitis or primary biliary cholangitis;[33] 2) presentation with acute liver failure, defined as the presence of hepatic encephalopathy and coagulopathy (international normalised ratio >1.5); 3) current treatment with prednisolone and/or immunosuppressive medication for an indication other than AIH; 4) current systemic infection; and 5) other clinically important medical conditions that could interfere with the trial (including underlying diseases or medications that may interfere, such as malignancy or depression). Females of childbearing potential or men who wished to father a child were informed about the potential teratogenic effect of MMF and were counselled for effective contraception during the study period.

Randomisation

All patients received concomitant prednisolone. The prednisolone dosage started at 40 mg/day (patients with a weight of less than 80 kg) or 60 mg/day (patients with a weight of 80 kg or more) at week 0. The tapering schedule of prednisolone was identical between the MMF and azathioprine groups (Tables S2 and S3) and was based on the EASL Clinical Practice Guidelines.[2] Follow-up assessments were performed every 4 weeks for 24 weeks.

Patients were randomly assigned, with an allocation ratio of 1:1, to receive open-label MMF (CellCept® from F. Hoffmann-La Roche AG Pharmaceuticals) or azathioprine (Sandoz GmbH) 4 weeks after baseline. Centralised balanced-block randomisation was computer-generated (facilitated by Castor EDC), with stratification according to the centre and presence or absence of cirrhosis. MMF was dosed at 1,000 mg/day (2 × 500 mg daily) for the first 2 weeks and 2,000 mg/day (2 × 1000 mg daily) thereafter until the end of the study. Patients assigned to the azathioprine group received a dosage of 50 mg/day for the first 2 weeks and 100 mg/day subsequently. Dosing of the allocated add-on treatment was based on the available clinical practice guidelines.[2,6]

Endpoints

The primary endpoint was the proportion of patients in biochemical remission at 24 weeks of treatment, defined as normalisation of serum alanine aminotransferase (ALT) and IgG levels. The upper limits of normal for local laboratories were used to determine the normalisation of laboratory assessments. Secondary endpoints included the time to biochemical remission; the proportion of patients with non-response, defined as a <50% decrease in serum aminotransferases within 4 weeks after the initiation of treatment;[5] complete biochemical response, defined as normalisation of serum aminotransferases and IgG below the upper limit of normal (within 6 months after initiation of treatment);[5] the proportion of patients with an insufficient response, defined by lack of a complete biochemical response (at 6 months);[5] changes in pruritus intensity on a visual analogue scale; changes in quality of life assessed with the short form (SF)-36 and liver disease symptom index 2.0; and safety, which included assessment of (self-reported) adverse events, physical examination, and laboratory tests. Secondary endpoints also included differences in the cumulative prednisolone dose and changes in the model for end-stage liver disease (MELD) score.

Efficacy was assessed in all randomly assigned patients who had taken at least one dose of the study medication in accordance with the intention-to-treat principle. Safety was assessed in all patients who received one or more doses of the study medication.

Safety reports

Safety was assessed by the investigators at each patient visit during follow-up on the basis of clinical examination, blood tests, and patient-reported symptoms. The seriousness, intensity and cause-effect relationship of adverse events (AEs) were subjectively evaluated by the investigators. The National

Cancer Institute CTCAE version 5.0 was used to evaluate the severity of adverse events.[34] All serious adverse events (SAEs) were reported to the accredited Medical Ethics Committee within the first 24 h after onset through the web portal *ToetsingOnline* and were closely monitored.

Statistical analysis

The primary objective was to compare the proportions of patients reaching biochemical remission at 24 weeks between the two groups. The power calculation for superiority was based on more recently published results from prospective studies for the treatment of new-onset AIH.[9,29] In the 'Budesonide Trial' by Manns *et al.*, normalisation of aspartate aminotransferase (AST) and ALT levels after 6 months of prednisolone and azathioprine treatment was achieved in 38.8% of patients.[9] Zachou *et al.* reported a 69.5% response rate at 3 months in the only available prospective induction study on the use of MMF.[29] Given the 69.5% response rate at 3 months, we hypothesised that 75% biochemical remission at 6 months with MMF would be feasible in the intervention group. With 32 patients per arm, the study was calculated to have 80% power to detect a difference in remission rate of -36.2% (75.0% *vs.* 38.8%) in favour of MMF, given the hypothesis of a difference in effect between MMF and azathioprine.[29] Accounting for a 10% drop-out rate, we determined that 35 patients were to be included per arm.

Analyses were performed at the end of the trial in the intention-to-treat (ITT) population (*i.e.*, all randomly assigned patients who had taken at least one dose of study medication). We used the Chi-square and fisher's exact test to compare the primary endpoint between groups (with the 95% CIs). Patients with missing data at a visit were counted as not having had a response or remission at that visit (non-response imputation). For the primary outcome, we used last observation carried forwards imputation. In cases in which ALT was elevated and the IgG level was unknown at 24 weeks, the patients were assessed as not having achieved biochemical remission. Sensitivity analyses were performed using different imputation methods. A per-protocol analysis was conducted in patients who received >80% of the study medication. We performed exploratory *post hoc* analyses using logistic regression to examine the possible impact of our randomisation stratum for the primary endpoint. This was also done with baseline values (ALT and IgG) as covariates. Additional *post hoc* exploratory analyses are described in the supplementary methods. Quantitative data are expressed as mean (SD) or median (IQR) when appropriate. A significant difference was defined as p <0.05. All statistical analyses were performed with SPSS, version 22.0 or higher. Additional details regarding the statistical analysis of the secondary endpoints are provided in the supplementary methods.

Results

Patients

From March 2017 through November 2022, a total of 72 patients were randomly assigned to the MMF (n = 40) and azathioprine (n = 32) treatment arms at 13 sites in the Netherlands and Belgium (Fig.1). Seventy patients received at least one dose of azathioprine (n = 31) or MMF (n = 39) (*i.e.*, ITT population). Baseline characteristics are presented in Table 1. The majority of the patients included in the trial were female (72.9%), with a mean age of 58 years. Additionally, 24.3% of the patients presented with cirrhosis at the time of diagnosis. One patient in the azathioprine group and one patient in the MMF group had decompensated cirrhosis (*i.e.*, hepatic encephalopathy and jaundice, respectively). Patients assigned to the azathioprine group had higher baseline levels of ALT.

A total of six patients were directly included from a liver transplant centre; two patients were assigned to the MMF group and four patients were assigned to the azathioprine group. None of these patients exhibited established cirrhosis at the baseline assessment.

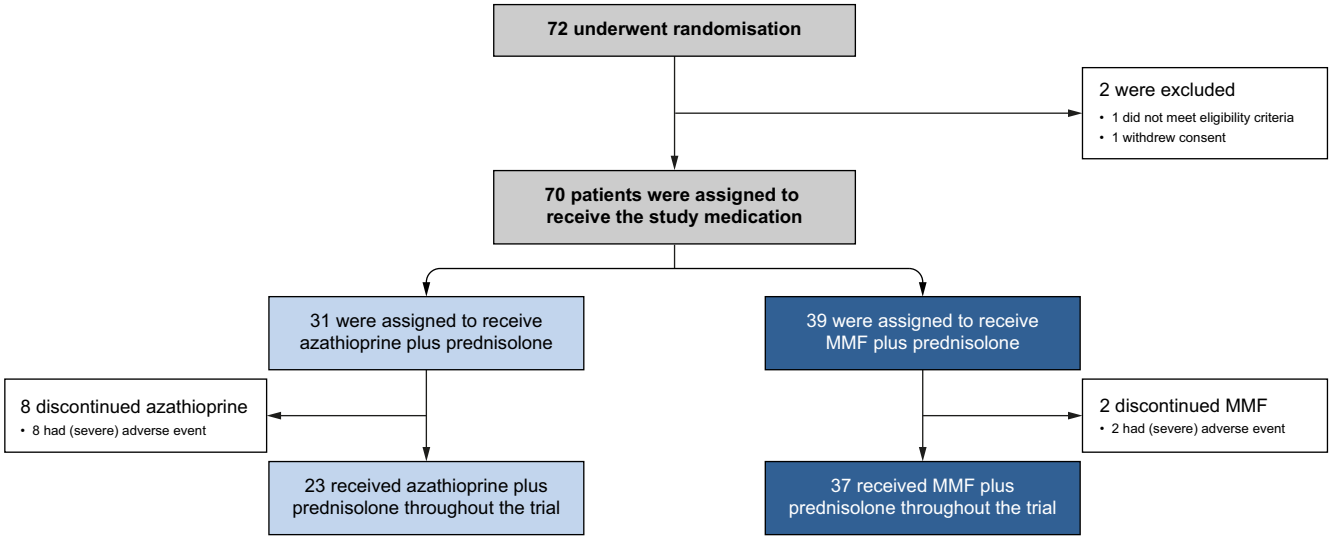

Fig. 1. Randomisation and treatment. Adult patients with AIH were assigned to receive azathioprine or MMF, both combined with prednisolone. AIH, autoimmune hepatitis; MMF, mycophenolate mofetil.

Table 1. Clinical characteristics and features of AIH at baseline (intention-to-treat population).

	Azathioprine (n = 31)	MMF (n = 39)
Clinical features		
Female, n (%)	21 (68%)	30 (77%)
Age (years), mean ± SD	56 ± 14.4	60 ± 14
Diagnosis simplified criteria		
Probable, n (%)	10 (32%)	13 (33%)
Definite, n (%)	21 (68%)	26 (67%)
Antibodies*, n (%)		
ANA	22 (76%)	28 (78%)
SMA	17 (63%)	18 (49%)
Anti-SLA/LP	3 (23%)	4 (22%)
Anti-LKM	0 (0%)	1 (4%)
Histology**		
Compatible with AIH, n (%)	15 (48.4%)	19 (48.7%)
Typical of AIH, n (%)	14 (45.2%)	20 (51.3%)
Cirrhosis (yes/no), n (%)	7 (23%)	10 (26%)
Acute/acute severe AIH[∞]		
A-AIH, n (%)	7 (23.3%)	6 (17.1%)
AS-AIH, n (%)	3 (10.0%)	5 (14.3%)
BMI (kg/m^2)[†], median (IQR)	26 (23–29)	25 (23–28)
Laboratory values, median (IQR)		
ALT (U/L)[‡]	541 (175–936)	333 (173–689)
AST (U/L)[§]	332 (130–801)	239 (128–621)
IgG (g/L)[¶]	25.1 (17.8–31.8)	23.3 (17.6–31.7)
ALP (U/L)***	170 (143–253)	157 (105–221)
GGT (U/L)[††]	212 (89–333)	176 (99–372)
Total bilirubin (mg/dl)[‡‡]	32 (15–114)	28 (15–63)
Albumin (g/dl)[§§]	32 (27–39)	34 (30–38)
INR[¶¶]	1.2 (1.1–1.4)	1.1 (1.1–1.5)
MELD score (original pre-2016)****	11.0 (8.0–14.5)	9.0 (7.0–15.5)

Values with (%) are frequencies. Plus-minus values are means ±SD. Other values are median with IQR.

A-AIH, acute AIH; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibodies; Anti-LKM, liver/kidney microsomal antibodies; Anti-SLA/LP, soluble liver antigen/liver pancreas antibodies; AS-AIH, acute severe AIH; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; INR, international normalised ratio; MMF, mycophenolate mofetil; SMA, smooth muscle antibodies.

*ANA data were missing for two patients in the azathioprine group and three patients in the MMF group; SMA data were missing for four patients in the azathioprine group and two patients in the MMF group; anti-SLA/LP data were missing for 18 patients in the azathioprine group and 21 patients in the MMF group; LKM data were missing for 14 patients in both groups.

**For one patient in the azathioprine group, a liver biopsy was not performed at baseline. For one patient in the azathioprine group, liver histology was deemed atypical after revision.

[∞]Acute AIH (A-AIH) was defined as bilirubin >45 μmol and INR <1.5 but no evidence of hepatic encephalopathy. Acute severe AIH (AS-AIH) was defined as bilirubin level >45 μmol/L and INR ≥1.5 but no evidence of hepatic encephalopathy.[49] Data were missing in one patient for the azathioprine group and four patients in the MMF group.

[†]BMI is the weight in kilograms divided by the square of the height in meters. Data were missing in one patient in the MMF group.

[‡]Data were missing in one patient in the MMF group.

[§]Data were missing in one patient for the azathioprine group and two patients in the MMF group.

[¶]Data were missing in three patients in the MMF group.

***Data were missing in two patients for the azathioprine group and four patients in the MMF group.

[††]Data were missing in one patient for the azathioprine group and two patients in the MMF group.

[‡‡]Data were missing in one patient for the azathioprine group and two patients in the MMF group.

[§§]Data were missing in six patients for the azathioprine group and thirteen patients in the MMF group.

[¶¶]Data were missing in three patients for the azathioprine group and twelve patients in the MMF group.

****Data were missing in seven patients for the azathioprine group and eighteen patients in the MMF group.

Two patients in the MMF group and eight patients in the azathioprine group discontinued treatment owing to AEs or SAEs. Overall, 37 (94.9%) patients in the MMF group and 23 patients (74.2%) in the azathioprine group completed treatment (*i.e.*, received the study treatment until week 24).

Primary efficacy endpoint

At week 24, the proportion of patients in the ITT population with biochemical remission was 56.4% in the MMF group (22 of 39 patients) *vs*. 29.0% in the azathioprine group (9 of 31 patients) — a difference of 27.4 percentage points (95% CI, 4.0 to 46.7; $p = 0.022$ [χ^2], $p = 0.030$ [Fisher's exact]) (Fig. 2). These significant effects were confirmed in the sensitivity analyses. The disparity between the groups in relation to the primary outcome continued to exhibit statistical significance in the analysis, even when assuming nonachievement of the outcome for missing data ($p = 0.031$). This difference was also observed in the analysis utilizing only the data available at the 24-week timepoint ($p = 0.031$). At week 24, the proportion of patients in the per-protocol population with biochemical remission was 59.5% in the MMF group (22 of 37 patients) *vs*. 39.1% in the azathioprine group (9 of 23 patients) — a difference of 20.4 percentage points. Additional details are provided in Table S4.

In the subset of patients who presented with established cirrhosis at baseline, no significant difference in the biochemical remission rate was observed. The proportion of patients with cirrhosis achieving biochemical remission was 20.0% in

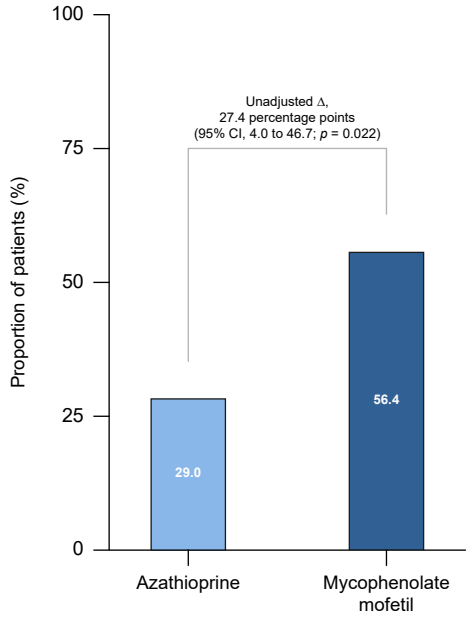

Fig. 2. Biochemical remission at 24 weeks (intention-to-treat population). Biochemical remission was defined as normalisation of serum alanine aminotransferase and IgG levels at 24 weeks. The risk difference, 95% CIs, and *p* values for the unadjusted analysis were calculated. The Δ symbol refers to difference between the azathioprine and mycophenolate mofetil group (with the exact 95% CI).

the MMF group (2 out of 10 patients) and 28.6% in the azathioprine group (2 out of 7 patients), a difference of 8.6 percentage points (95% CI -28.5 to 46.9; $p = 0.69$).

Secondary endpoints

Biochemical efficacy measures

In the ITT population, the proportion of patients with normalisation of serum ALT levels at 24 weeks in the MMF group and in the azathioprine group was 56.4% and 38.7%, respectively ($p = 0.141$). The proportion of patients with normalisation of serum IgG levels at 24 weeks was higher in the MMF group than in the azathioprine group (74.4% *vs.* 45.2%, respectively $p = 0.013$). Fig. 3A,B show the time course of ALT and IgG levels (mean ± 95% CI) during the study period.

Additionally, in the log rank analysis, the cumulative proportion of patients with biochemical remission was significantly higher over the study period in the MMF group than in the azathioprine group ($X^2 = 6.752$, $p = 0.009$) (Fig. 4).

Other prespecified biochemical responses

Non-response at 4 weeks (prior to the initiation of either azathioprine or MMF), as defined according to the recently established criteria proposed by the International Autoimmune Hepatitis Group,[5] was similar between the groups (15.4% [6 of 39 patients] in the MMF group and 19.4% [6 of 31 patients] in the azathioprine group, $p = 1.000$). As the patients initiated the intervention after being on prednisolone monotherapy for 4 weeks (Tables S2 and S3), we also compared the non-response rate within 8 weeks after the initiation of the intervention; again, the non-response rates were similar between the two groups (15.4% [6 of 39 patients] in the MMF group and 12.9% [4 of 31 patients] in the azathioprine group, $p = 1.000$).

The rates of a complete biochemical response, defined as normalisation of ALT, AST, and IgG within 6 months, as defined recently in a Delphi consensus,[5] were significantly higher in the MMF group than in the azathioprine group (72.2% [26 of 39 patients] *vs.* 32.3% [10 of 31 patients] — a difference of 39.9 percentage points (95% CI 16.4 to 57.8; $p = 0.004$). This shows that only a small proportion of patients had a complete biochemical response at a certain time within 6 months but were not in biochemical remission at 24 weeks (the primary endpoint in this trial).

Laboratory values at T4 and T24 can be found in Tables S5 and S6.

Prednisolone dose

The mean cumulative, daily and weekly prednisolone doses are described in Table 2, with no significant differences between the two groups ($p = 0.369$, 0.100 and 0.100, respectively). The

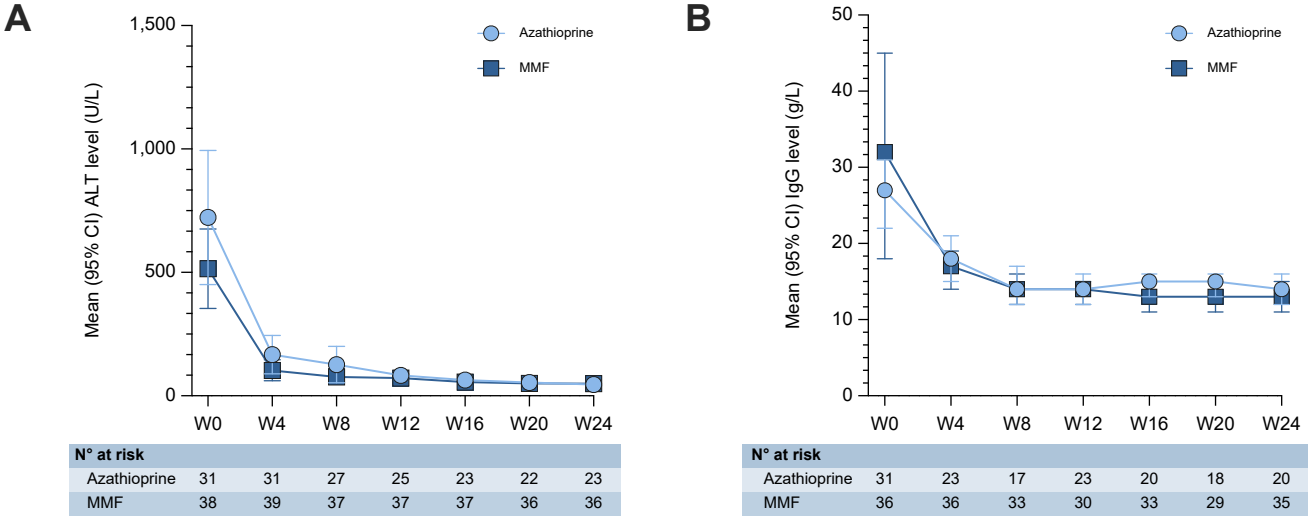

Fig. 3. Biochemical efficacy variables during the study according to time and trial group (intention-to-treat population). (A) Time course of ALT levels (mean ± 95% CI); (B) Time course of IgG levels (mean ± 95% CI). ALT, alanine aminotransferase; MMF, mycophenolate mofetil.

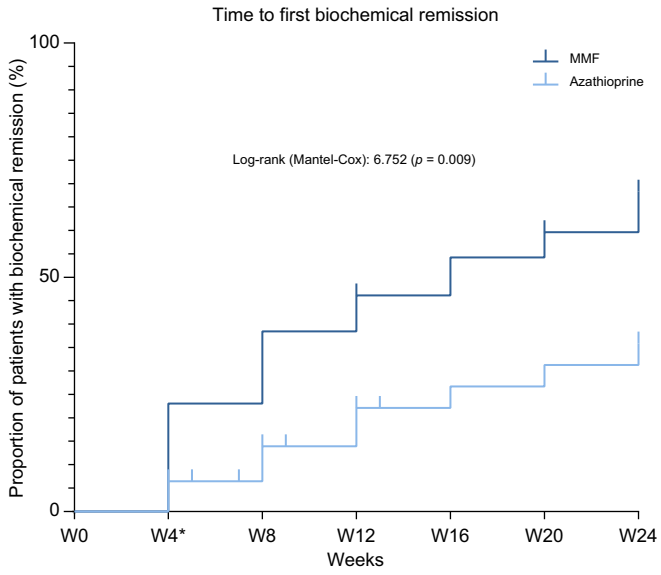

Fig. 4. Time to first biochemical remission (intention-to-treat population). MMF, mycophenolate mofetil.

mean cumulative prednisolone dose in the first 4 weeks did not differ significantly (p = 0.897) (Table 2). The mean daily azathioprine (mg/kg) and MMF (mg/day) doses are presented in Table 2. Six patients on azathioprine (19.4%) and five patients on MMF (12.8%) received more than 5 mg prednisolone at week 24.

Patient-reported outcomes

No significant differences between the groups were found in pruritus intensity. The change in quality of life scores from the start of intervention did not differ between the groups. Data are provided in Tables S7 and S8 and Fig. S1.

Changes in liver function

At baseline, the median MELD score was 11.0 (8.0–14.5) in the azathioprine group and 9.0 (7.0-15.5) in the MMF group. At the end of the study, compared to baseline the median MELD score in the azathioprine group decreased to 6.5 (6.0–8.0) (p = 0.002) and to 7.0 (6.0–8.0) (p = 0.023) in the MMF group. The MELD score did not differ between the groups after 24 weeks of treatment (p = 0.992). Additional data regarding the MELD score are provided in Figs S2 and S3.

Clinical outcomes

No patients in either group underwent liver transplantation or were placed on a waiting list for transplantation. One patient in the azathioprine group died during the study. Additional data are provided in Table S9.

Safety

A total of 181 and 109 AEs of any cause in the MMF and azathioprine groups, respectively, were reported after commencements of add-on treatment. AEs were reported in 64 patients: 92.3% (36 patients) in the MMF group and 90.3% (28 patients) in the azathioprine group (Table 3). Most reported AEs were graded mild to moderate in severity. A total of four SAEs were reported after commencement of the add-on study treatment: in 0% (0 of 39 patients) of the patients in the MMF group and 12.9% (4 of 31 patients) in the azathioprine group (p = 0.034, Fisher's exact) (Table 3, Fig. S4A, and Table S9). Two patients who experienced an SAE had pre-existing cirrhosis at baseline.

The most common AEs that were reported during the treatment period in both the MMF and azathioprine groups were fatigue and infections (28.2% *vs.* 29.0% and 23.1% *vs.* 22.6%, respectively). The proportion of (drug-related) AEs was numerically higher in the azathioprine group, particularly regarding nausea and vomiting (32.3% *vs.* 7.7% p = 0.09 and 12.9% *vs.* 2.6% p = 0.095, respectively). Changes in laboratory safety parameters (*i.e.*, decrease in leukocytes, neutrophils, and platelets or increase in serum creatinine) occurred 9 times in seven patients assigned to the MMF group and 14 times in ten patients assigned to the azathioprine group (Table 4). Severe changes (grade 3 or above) only occurred in one patient assigned to the MMF group. This concerned a grade 4 decrease in neutrophil count (Table 4). From the laboratory parameters, only severe neutropenia led to discontinuation of the study treatment.

AEs of any cause that led to discontinuation of the trial regimen were reported in 5.1% (2 of 39 patients) of the patients assigned to the MMF group and 25.8% (8 of 31 patients) of the patients assigned to the azathioprine group (p = 0.018, Fisher's exact). By group, the events were related to treatment in 5.1% and 22.6% of patients in the MMF and azathioprine groups, respectively (p = 0.068). One patient who discontinued MMF treatment during the study had severe peripheral oedema, and the other had marked neutropenia, which was reversed after discontinuation of the study medication. The first mentioned patient switched to azathioprine and later 6-thioguaine, while

Table 2. Treatment evaluation (intention-to-treat population).

Treatment evaluation	Azathioprine (n = 31)	MMF (n = 39)	p value
Biochemical remission	8 (25.8%)	22 (56.4%)	0.010
Mean starting dose prednisolone (mg/kg/day)	0.56 ± 0.1	0.58 ± 0.1	0.479
Cumulative prednisolone dose (mg)	1,834.11 ± 543.67	1,944.29 ± 475.13	0.369
Daily prednisolone dose (mg/day)	14.15 ± 6.14	12.10 ± 3.32	0.100
Weekly prednisolone dose (mg/week)*	99.07 ± 42.97	84.68 ± 23.26	0.100
Cumulative prednisolone dose T_0-T_4	889.68 ± 22.42	885.32 ± 24.15	0.897
Mean daily azathioprine dose (mg/kg)	1.16 ± 0.22	—	—
Mean daily MMF dose (mg/day)	—	1,853 ± 169	—

Values with (%) are frequencies. Plus-minus values are means ±SD.
MMF, mycophenolate mofetil.
*Three patients were tapered to 0 mg prednisolone before the end of study, upon discretion of the treating physician. One patient received less than 1 mg/kg/day, specifically 0.90 mg/kg/day.

Table 3. (Severe) adverse events.

Event	Azathioprine (n = 31)		Mycophenolate mofetil (n = 39)		*p* values (any grades)
Any event	109		181		n.s.
Any serious adverse event	5 (16.1%)		1 (2.6%)		n.s.
Any serious adverse event after commencing add-on treatment	4 (12.9%)		0 (0%)		0.034
Any event leading to discontinuation of treatment	8(25.8%)		2 (5.1%)		0.018
Events reported in ≥10% of patients in any group	**Any grade**	**Grade 3 or 4**	**Any grade**	**Grade 3 or 4**	
Skin abnormalities	4 (12.9%)	—	9 (23.1%)	—	0.277
Alopecia	5 (16.1%)	—	4 (10.3%)	—	0.466
Nausea	10 (32.3%)	—	3 (7.7%)	—	0.009*
Abdominal pain	4 (12.9%)	—	8 (20.5%)	—	0.401
Vomiting	4 (12.9%)	—	1 (2.6%)	—	0.095
Other gastrointestinal complaints	1 (3.2%)	—	4 (10.3%)	—	0.257
Muscle spasms	1 (3.2%)	—	4 (10.3%)	—	0.257
Vertigo	1 (3.2%)	—	4 (10.3%)	—	0.257
Headache	2 (6.5%)	—	4 (10.3%)	—	0.572
Palpitations	1 (3.2%)	—	4 (10.3%)	—	0.257
Fluctuating mood	0 (0%)	—	6 (15.4%)	—	0.022*
Insomnia	2 (6.5%)	—	5 (12.8%)	1 (2.6%)	0.378
Fatigue	9 (29.0%)	—	11 (28.2%)	—	0.939
Infections	7 (22.6%)	—	9 (23.1%)	—	0.961
Malaise	4 (12.9%)	—	4 (10.3%)	—	0.730
Miscellaneous	5 (16.1%)	—	8 (20.5%)	—	0.558
Steroid-induced side effects					
Cushing face	1 (3.2%)	—	1 (2.6%)	—	0.869
Diabetes	3 (9.7%)	—	3 (7.7%)	—	0.768
Weight gain/increase	1 (3.2%)	—	2 (5.1%)	—	0.696
Striae	0 (0%)	—	0 (0%)	—	—

Shown are adverse events of any cause that occurred in at least 10% of the patients during the treatment period; data are included for all the patients in the intention-to-treat population. Values with (%) are frequencies.

the other patient resumed MMF without encountering AEs. SAEs that led to discontinuation in the azathioprine group consisted of hospitalizations due to malaise (n = 1), drug-induced liver injury, fever and thrombocytopenia (n = 1), influenza B pneumonia (n = 1), and mortality (n = 1). Other AEs that led to discontinuation in the azathioprine group were severe gastrointestinal symptoms (n = 4), in particular nausea and vomiting. Among these patients, one successfully underwent re-exposure, another patient commenced 6-mercaptopurine, and five patients were switched to MMF therapy. Dose reduction was required in three patients receiving MMF (7.7%) and in one patient receiving azathioprine (3.2%) (Table S11). According to the protocol, dose reductions for both azathioprine and MMF were implemented by reducing the prescribed doses by 50% when AEs occurred. All dose reductions and discontinuation of treatment were left at the discretion of the treating physician, frequently without consulting the coordinating investigator. Additional details about AEs are provided in Tables 3 and S10, and Fig. S4B.

Post hoc analyses

The aforementioned primary and selected secondary outcomes were adjusted *post hoc* for cirrhosis as a randomisation stratum. In addition, after adjusting for both baseline ALT and IgG levels, logistic regression analysis also demonstrated significant results for the primary outcome. Details and results can be found in Table S12.

Discussion

In this randomised, open-label, multicentre superiority trial, the proportion of patients with treatment-naive AIH achieving normalisation of both serum ALT and IgG levels at 24 weeks of treatment was significantly higher in patients treated with MMF plus prednisolone than in those treated with azathioprine plus prednisolone. There was a 27% difference in the proportion of patients who met the primary endpoint of biochemical remission at 24 weeks. In the per-protocol analysis, consistent outcomes favouring MMF were also observed, showing a

Table 4. Changes in laboratory safety assessments.

	Azathioprine (n = 31)		Mycophenolate mofetil (n = 39)		
Event	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	*p* values
WBC count decreased	2 (6.5%)	0 (0.0%)	3 (7.7%)	0 (0.0%)	0.841
Neutrophil count decreased	3 (9.7%)	0 (0.0%)	1 (2.6%)	1 (2.6%)	0.203
Platelet count decreased	8 (25.8%)	0 (0.0%)	5 (12.8%)	0 (0.0%)	0.165
Creatinine increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	—

Shown are all changes in laboratory safety assessments after starting intervention (*i.e.*, mycophenolate mofetil or azathioprine); data are included for all patients in the intention-to-treat population. Values with (%) are frequencies. WBC, white blood cell.

numerical difference in biochemical remission rates exceeding 20 percentage points. However, this per-protocol analysis lacks the statistical power to formulate a representative conclusion.

The results of this trial are noteworthy for several reasons. First, the evidence for the current standard induction therapy in AIH with azathioprine and prednisolone is limited and stems from the early seventies of the last century.[7,9] The current trial comes more than 13 years after the last randomised-controlled trial that probed alternatives for induction therapy in AIH and investigated the role of budesonide *vs*. prednisolone in inducing remission.[9] Second, while observational studies of patients treated in specialised centres suggest that biochemical remission can be achieved in up to 80% of patients treated with the classical prednisolone/azathioprine regimen,[9,10,30] such percentages are only reached after 3 or more years of treatment.[35] The trial conducted in 2010 reported a remission rate of 38% at 6 months.[9] In a systematic review, including all randomised trials published since 1950, a response rate of approximately 43% was documented.[7] This finding aligns with the relatively low cumulative remission rate of 29% at 24 weeks of treatment observed in the present trial with azathioprine. This puts patients at risk for progression to cirrhosis, liver failure, and the need for liver transplantation. Third, patients assigned to azathioprine were significantly more prone to discontinuing treatment because of intolerance or SAEs, with nausea and vomiting as the main reasons for cessation of treatment. In contrast, only two MMF-treated patients discontinued treatment in our study.

Our results are in accordance with those of Dalekos *et al.*[27,30] Based on these results, the Hellenic Association for the Study of the Liver (HASL[36]) recommends that MMF may be considered as a first-line therapy option, particularly within specialised AIH centres. Notably, one of these studies[30] did not demonstrate a significant difference in response rates at 6 months. Additionally, a recent meta-analysis found significantly higher response rates when MMF was combined with prednisolone compared to standard treatment.[26]

The AE profile as well as the relatively high discontinuation rate with azathioprine is a recurrent theme in the literature.[30,37] Most gastrointestinal AEs occurred in the first weeks of treatment, as captured by the design of our study. The literature suggests that at least 15% of patients discontinue azathioprine,[37] which is much higher than the 3.8% reported for MMF. This discrepancy suggests that MMF may possess a more favourable tolerability profile than azathioprine.[30] Implementation of therapeutic drug monitoring for azathioprine or MMF may potentially yield beneficial outcomes.[38,39] However, treatment-related AEs such as nausea and vomiting, which are related to cessation of treatment, are unlikely to be affected by drug monitoring. Thiopurine methyltransferase (TPMT) genotyping or activity measurement was not conducted in this study. Notably, azathioprine toxicity often occurs in the absence of TPMT deficiency, and the predictive value of TPMT genotyping has demonstrated inconsistent results in previous research.[39–42] In addition, the mean daily dose of azathioprine administered was 1.16 mg/day (SD 0.22), which falls within the recommended range specified in both the EASL (1-2 mg/kg/day)[2] and AASLD (100-150 mg/day) guidelines.[6]

In the current study, a numerically higher baseline ALT level was observed in the azathioprine group than in the MMF group. In the absence of stratification for baseline ALT levels, one could speculate that this observed imbalance could potentially have influenced the primary endpoint measure at 24 weeks. It is worth considering that patients with higher aminotransferase levels are more prone to achieve a rapid response and subsequent normalisation of aminotransferases within a 6-month timeframe.[43] In addition, according to the CONSORT statement,[44] significance testing of baseline imbalances in randomised-controlled trials should not be performed because trials are not powered for this purpose. Overall, the non-response rates[5] within 4 and 8 weeks were comparable between the two groups.

Our trial has limitations. First, it is not possible to determine whether better efficacy of MMF is also associated with higher rates of sustained biochemical remission after longer follow-up or after immunosuppression cessation, and differences in histological remission were not assessed. In the CAMARO trial, we deliberately chose to investigate the induction phase rather than maintenance of remission, as we knew that patients with AIH who experienced a rapid response to induction treatment have a better survival rate.[5,43] Data regarding sustained remission at 12 months are currently being gathered. The endpoint biochemical remission, defined as normalisation of ALT and IgG at 24 weeks, was deemed the most suitable for this trial based on the current guidelines. To compare trials, we incorporated the recently adopted 'complete biochemical response,' defined as the normalisation of ALT, AST, and IgG levels, as a secondary endpoint.[5] This analysis revealed even more favourable outcomes for MMF, with rates of 72.2% compared to 32.3% (p = 0.004). Interestingly, when assessing the normalisation of ALT as a separate outcome, we did not observe a significant difference. Therefore, the relevance of the current findings to long-term outcomes require further assessment.[45] Another limitation is that this randomised-controlled trial was open-label due to limited financial resources, thus patient-reported outcomes and reported AEs may have been subject to bias. Last, there is a slight difference in the group sizes. This is due to use of centralised balanced-block randomisation with stratification based on centre and on cirrhosis, which resulted in an imbalance. Although beyond our control, this imbalance may have introduced a degree of sampling bias.

The outcome of this study has practical implications. The improved efficacy signal and lower adverse event rate favour MMF as part of the standard of care for treating patients with treatment-naive AIH. It should be emphasised that MMF exhibits high teratogenicity. MMF should not be used during pregnancy and may only be used with strict contraceptive measures in women of childbearing age and men planning to father a child, as its use is absolutely contraindicated during pregnancy. In contrast, azathioprine can be used safely during pregnancy. It is worth considering creating a two-tier treatment algorithm specifically for patients at a fertile age (*i.e*. azathioprine only in case of active pregnancy [wish]). In addition, MMF must be administered twice daily, while azathioprine is given as a single dose daily. This is relevant for a disease that requires lifelong treatment, and a bis-in-die regimen may compromise adherence. MMF is registered for use after transplantation, and extensive experience and the current study show that it is safe. Notably, follow-up data on the tolerability of both treatment regimens are required to evaluate the occurrence of late-onset side effects, which have been described after solid organ transplantation and MMF use.[46–48] A cost-effectiveness

analysis could not be performed due to insufficient data on additional incidental and structural healthcare costs.

In conclusion, in patients with treatment-naive AIH, the combination of MMF with prednisolone demonstrated a significantly higher rate of biochemical remission at 24 weeks compared to the use of azathioprine combined with prednisolone. The frequent treatment discontinuation due to (S)AEs with azathioprine supports the superior tolerability profile for MMF in the management of AIH. These outcomes provide a potential basis to inform international guidelines regarding the standard of care in patients with treatment-naive AIH. It remains essential to undertake further research involving novel immunomodulatory or immunosuppressive agents to enhance treatment strategies in AIH.

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Abbreviations

AEs, adverse events; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ITT, intention-to-treat; MMF, mycophenolate mofetil; SAEs, serious adverse events.

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Conflict of interest

The authors declare that they have no competing interests.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

R.J.A.L.M.S. (study coordinator): data acquisition, data analysis and interpretation, writing – original draft preparation. A.E.C.S. (study coordinator): data acquisition, data analysis and interpretation, writing – original draft preparation. S.P. (former study coordinator): data acquisition, critical revision of manuscript. M.B. (former study coordinator): data acquisition, critical revision of manuscript. J.P.H.D. (initiating and coordinating investigator): co-designer of the trial, supervision, critical revision of the manuscript. B. van H. (initiating and coordinating investigator), co-designer of the trial, supervision, critical revision of the manuscript. All remaining authors: critical revision of the manuscript. All authors have given approval to the final version of the manuscript.

Data availability statement

The data that support the findings of this study are available from the corresponding author, J.P.H.D., upon reasonable request.

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Declaration of use of AI-assisted technologies in the writing process

During the preparation of this work the author(s) used Chat GPT to assist in ensuring adherence to British English standards and the guidelines of the journal. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Supplementary data

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