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# Mycophenolate mofetil treatment in patients with autoimmune hepatitis failing standard therapy with prednisolone and azathioprine☆

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ABSTRACT

*Background:* Data on rescue treatment of autoimmune hepatitis in patients that fail standard treatment are sparse.
*Aims:* To report our long-term experience with mycophenolate mofetil.
*Methods:* Retrospective study in 22 patients with autoimmune hepatitis who failed azathioprine and prednisolone due to adverse events (n = 14, 64%), lack of remission (n = 5, 23%) or a combination (n = 3, 13%).
*Results:* Mycophenolate mofetil was started at a dose of 20 mg/kg/day and increased to a maximum of 3 g/day. Follow-up was 0–6 months in 7 patients; more than 12 months in 15 (68%) and more than 24 months in 10. Normal aminotransferase levels were obtained (n = 3) or maintained (n = 7) in 10 patients (45%) after three to 30 weeks. 12 patients (55%) were withdrawn during the first 6 months, due to adverse events. Three patients were switched to cyclosporine and one underwent liver transplantation. Successful treatment with mycophenolate mofetil continued in 10 patients (45%) for a median of 71 months (range 20–124). Of these, one stopped prednisolone, five have a prednisolone dose <5 mg daily and four patients 5–10 mg.
*Conclusion:* Approximately one of two patients with autoimmune hepatitis that fail standard treatment benefit from long-term maintenance with mycophenolate mofetil, especially those with previous intolerance to thiopurines, where mycophenolate mofetil is effective in two thirds.


## 1. Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory disease that untreated leads to cirrhosis and liver failure. Standard treatment involves immune suppression with prednisolone alone or in combination with azathioprine (AZA) [1–5]. With this treatment about 80% of patients achieve biochemical remission within three years. Approximately 20% of patients cannot tolerate prednisolone and/or AZA or have an insufficient response [6–8]. However, a meta-analysis based on eleven randomised controlled trials from 1950 to 2009 with altogether 578 patients, suggests that these remission rates represent an overestimation and that the true rate is 45% [9]. Therefore, even established first line therapy needs to be reassessed.

When standard therapy fails (≈20%) various second-line immunosuppressors including mycophenolate mofetil (MMF), cyclosporine, tacrolimus, budesonide, and mercaptopurine have been tried [10]. There are no randomized studies with these treatments, and, therefore no optimal therapeutic agent identified for these difficult-to-treat patients [11–19].

MMF is a prodrug hydrolyzed by liver esterases to produce the active metabolite mycophenolate acid which in turn acts as a non-competitive, reversible inhibitor of inosine monophosphate

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dehydrogenase (IMPDH), the rate-limiting enzyme for the de-novo synthesis of purines. MMF selectively prevents the proliferative responses of T- and B-cells to various stimuli. This immunosuppressive mode of action has promoted the use of MMF in clinical practice for the treatment of autoimmune disorders [20–22].

MMF exerts it's actions independent from the thiopurine methyl transferase pathway necessary for thiopurine metabolism and represents an attractive alternative to AZA [20–23]. Transplant centers incorporate MMF into the management of heart, kidney and liver recipients where MMF to a large extent has replaced AZA because of its' better ability to prevent graft rejection [24,25].

MMF thus present an alternative treatment option in AIH patients intolerant or unresponsive to standard therapy with prednisolone and thiopurines. The aim of this retrospective study was to report our experience of MMF in this patient group.

## 2. Patients and methods

We performed a retrospective multicenter observational study and included 22 patients (12 women) with AIH seen at 6 university hospitals in Sweden (Göteborg, Linköping, Lund, Malmö, Uppsala and Örebro) who had failed standard treatment and commenced MMF. The median age was 47 years (range 13–72) at diagnosis of AIH and 51 years (range 25–73) at the start of MMF.

Patients were diagnosed with AIH following the American Association for the study of Liver Diseases (AASLD) guidelines, which include the combination of elevated serum aminotransferase levels, presence of antinuclear antibody or anti-smooth muscle antibodies, hypergammaglobulinemia, and histologic evidence of chronic hepatitis [26]. Patients with overlap syndromes to primary biliary cholangitis or primary sclerosing scholangitis were not included. 20 of 22 patients had a liver biopsy at diagnosis of AIH of which 6 (30%) had already developed cirrhosis.

All patients were initially given standard treatment for AIH. This included Prednisolone and AZA $\leq$ 2 mg/kg BW/day. Fourteen patients had tried AZA, eight AZA and mercaptopurine, and, in addition, ursodeoxycholic acid (n = 2), cyclosporine (n = 2) or tacrolimus (n = 1).

The indications for MMF were one of the following; (a) failure to achieve/maintain aminotransferase levels < 2 μkat/l on Prednisolone and AZA (non-responders), or, (b) significant side-effects associated with this treatment, or, (c) a combination of both. MMF was started at a dose of 20 mg/kg/day and gradually increased to a maximum of 3 g/day and AZA was stopped. 19 patients (86%) were on Prednisolone when MMF was commenced.

During follow-up, patients were monitored for symptoms, full blood count and liver biochemistry. Biochemical remission was defined as normalization of serum transaminases. Response was defined as achievement or maintenance of aminotransferase levels $\leq$ 2 μkat/l. Treatment failure was defined as worsening of symptoms, intolerable side effects and/or increase in serum aminotransferase levels above 2 μkat/l.

## 3. Ethics

The study was approved by the Intstitutional Review Board at Linköping University, Linköping.

## 4. Results

Patient characteristics at diagnosis and at commencement of MMF are shown in Table 1. Follow-up was 0–6 months in 7 patients and more than 12 months in 15 patients (68%). Altogether 10 patients (45%) were followed for more than 24 months.

**Table 1**
Characteristics of 22 patients with autoimmune hepatitis failing standard therapy with prednisolone and thiopurines and treated with mycophenolate mofetil. Values are median, IQR and range.

| | At diagnosis | At start of MMF |
|---|---|---|
| Gender (male/female) | 10/12 | |
| Age | 46,5, IQR 20,8 (13–72) | 50,5, IQR 20 (25–73) |
| ALAT (μkat/L) | 17,4, IQR 21,7 (1,5–61) | 2,6, IQR 3,4 (0,61–21) |
| IgG (g/L) | 21,6, IQR 18,6 (12,6–65) | 17, IQR 12,9 (7,6–41) |
| IgG elevated >ULN[a] | 14/19 (74%) | 10/14 (71%) |
| ANA positive | 9/21 (43%) | – |
| SMA positive | 15/22 (68%) | – |
| AMA positive | 3/20 (15%) | – |
| Liver biopsy | 20 | 6 |
| Cirrhosis | 6 (30%) | 2 (33%) |
| Prednisolone, mg/day | 40, IQR 22,5 (20–75) | 11,3, IQR 11,9 (0–40) (n = 19) |
| Azathioprine, mg/day | 100, IQR 75 (25–300) | |
| AZA intolerance | – | 14 (64%) |
| AZA non-response | – | 5 (23%) |
| Combination | – | 3 (13%) |

[a] ULN, Upper limit of normal.

Normal aminotransferase levels were obtained (n = 3) or maintained (n = 7) in 10 patients (45%) within three to 30 weeks. MMF treatment (median dose 2.0 g (range 1.0–2.5)) continued in altogether 10 patients for a median of 71 months (range 20–124): nine of 14 patients (64%) that had failed AZA due to adverse events, and one of 5 (20%) with insufficient response to AZA. One patient stopped prednisolone, five have a prednisolone dose <5 mg daily and four patients 5–10 mg (Fig. 1). None of three patients with a combination of adverse events and insufficient response to AZA tolerated MMF (Fig. 2).

Twelve patients (55%) were withdrawn from MMF; four during the first month and another eight during the first 6 months. The reasons were adverse events (n = 6), lack of biochemical response (n = 4), relapse of Hodgkin's lymphoma (n = 1) or wish to conceive (n = 1) (Fig. 3). Adverse events were nausea, headache, diarrhea, erythema and subcutaneous vasodilatation. At the end of MMF treatment, three of these withdrawn patients were switched to cyclosporine and one underwent liver transplantation.

Six of 20 patients (30%) that had undergone liver biopsy were cirrhotic. Compared to the 16 non-cirrhotic patients, a similar proportion started MMF due to thiopurine intolerance (5/6, 83% vs 12/16, 75%). Despite that 4 (67%) compared to 6 (38%) patients normalized aminotransferase levels, 4 cirrhotics were withdrawn from MMF within 18 weeks due to adverse events compared to 8 (50%) of the non-cirrhotic patients. The remaining two cirrhotic patients continued MMF and were followed during 49 and 79 weeks, respectively.

Liver biopsy was not part of the follow-up protocol. However, six patients had a second liver biopsy at start of MMF, of which two had cirrhosis. Follow-up biopsy in one 57 year old man at 14 months of MMF treatment did not show persisting cirrhosis. At diagnosis, he had positive anti-small muscle antibodies and was negative for anti-nuclear antibodies; maximum value of ALAT was 38 μkat/l and of IgG 22,8 g/l. He had previously not responded to daily doses of prednisolone 30 mg, AZA 75 mg, budesonide 9 mg or cyclosporine. At the start of MMF, he was on prednisolone 15 mg daily. There was a prompt response to MMF within 4 weeks and he continued on 2 g MMF daily, discontinued prednisolone and has been followed for 79 weeks. ALAT-levels dropped from 16 to 0,65 μkat/l; IgG was not obtained during follow-up.

There were four deaths during MMF treatment; one each due to liver failure, combined liver plus heart failure, multi-organ failure after surgery for diverticulitis, and suicide.

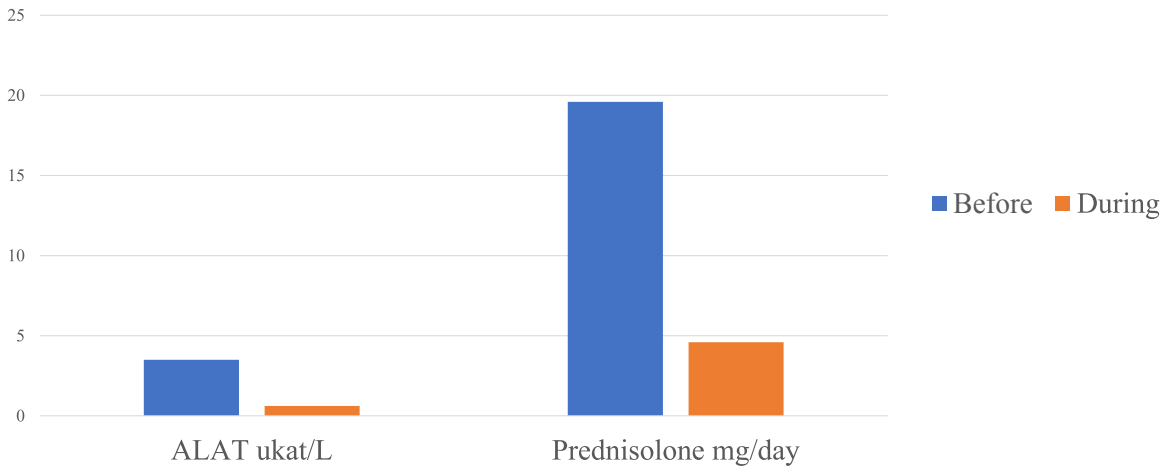


**Fig. 1.** Long-term follow-up of ten patients with autoimmune hepatitis treated with MMF for a median of 71 (range 20–124) months. Values are median.

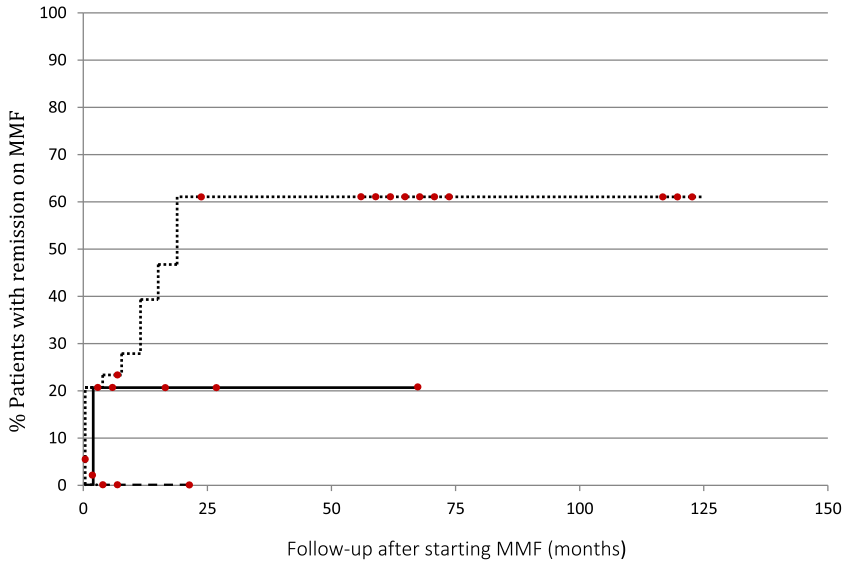


**Fig. 2.** Percentage of patients achieving remission and time to achieve remission with MMF in the three subgroups: ··· AZA intolerance, — AZA non-responders, — and AZA intolerance and non-response, • end of follow-up.

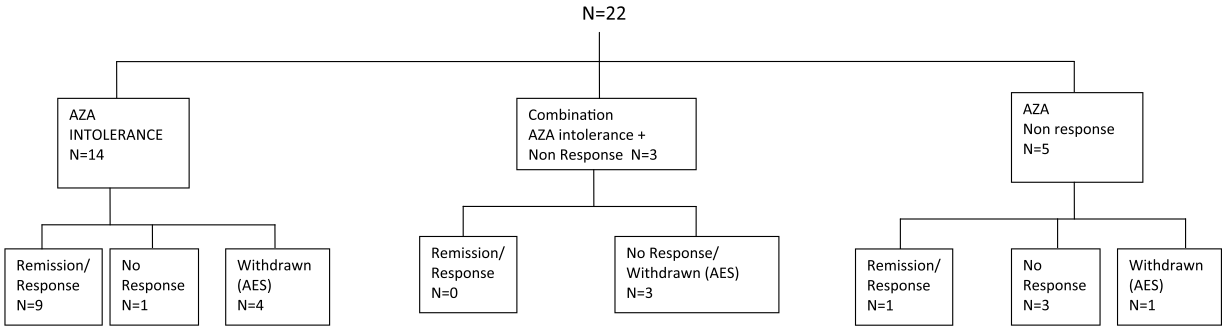


**Fig. 3.** Outcome of treatment with mycophenolate mofetil in 22 patients with AIH that had experienced intolerance or non-response or both to standard treatment with prednisolone and azathioprine.

## 5. Discussion

In this retrospective study, we found that approximately one of two AIH-patients (45%) that had failed standard treatment with prednisolone and AZA benefit from MMF maintenance treatment, especially those with previous intolerance to thiopurines (64%). The majority of a small group of cirrhotic patients (4/6, 67%), in whom amniotransferase levels normalized, were withdrawn during the first five months due to adverse drug events.

The application of MMF as a second-line therapy is supported by retrospective studies of altogether less than 450 patients [10,27,28]. These case series suggest that MMF is effective in at least 40% of patients intolerant or non-responsive to standard treatment. During the last decade nine case series (including ours) with between

16 and 121 patients have investigated the use of MMF as a second line treatment [27–34].

Four recent studies in adults [27,30,33,34] show a difference in clinical response rates between patients who have not respond to AZA/prednisolone (0–34%) compared to those who are intolerant (43–89%). However, one large study showed similar response rates in the two groups [28]. The compiled overall response rates in these five studies show that MMF treatment is effective in 74% (143/194) of intolerant patients and in 37% (50/134) of patients not responding to standard therapy. The corresponding figures in our cohort were 64% and 20%, respectively. None of three patients with combined intolerance and non-response to standard therapy benefited from MMF. It has been suggested that tacrolimus is a more effective second-line option than MMF in adults [27] as well as in children [35] who has not responded to standard treatment.

In our patients with biopsy-proven cirrhosis (n = 6, 30%) efficacy was lower than in the non-cirrhotic patients. Even if normalization of aminotransferases occurred, early withdrawal of MMF was necessary in four of them due to drug intolerance. An overall lower efficacy in cirrhotic patients is in line with data from the large study of 105 patients by Roberts et al. [28] where 37% had cirrhosis. However, the reason for a lower treatment response in their study was mainly incomplete biochemical response and not drug intolerance. In contrast, neither one study of standard therapy for AIH [36] nor a study of MMF as first line therapy [37] showed a difference in response rates between patients with and without cirrhosis. This indicates that cirrhotic AIH-patients in need of second-line therapy represent a phenotypically more treatment-resistant population compared to treatment naïve or non-cirrhotic patients.

Few studies have included liver biopsy results [27,37–40]. Improvement of necroinflammatory activity is seen in the majority of patients (71–89%) [37,38,40] as early as three months [38]. Progression of fibrosis has been demonstrated in 14–25% of patients at follow-up biopsies after 16–28 months [27,38,39]. Conversely, regression of fibrosis stage, including cirrhosis – similar to that in one of our patients – is possible [37,40]. In the study by Inductivo-Yu et al. [40], five of seven patients with cirrhosis (Ishak stage 5–6) had no longer cirrhosis at follow-up biopsy after a median of 23 months. Similarly, after five years treatment with MMF as first-line therapy, cirrhosis was no longer present in two patients with cirrhosis at baseline [37].

Even if our study was retrospective and multi-centric in nature, advantages were a longer follow-up period (median 71 months) after initiation of treatment with MMF than the 22–45 months in previous series [27,28,41]. Despite patient management was physician-directed, a fairly uniform evaluation was undertaken in the participating expert centers. However, our study does not allow us to draw reliable conclusions on the exact dose of MMF that is effective, on the optimal duration of treatment with MMF or how long one can wait until treatment is considered to be ineffective. The majority of patients required concomitant Prednisolone therapy at low doses. Furthermore, it would have been of value to obtain data on serological biomarkers at baseline and on blood concentrations of MMF at fixed time points in order to relate them to therapeutic response. However, none of the hitherto published studies have provided such information. Despite these limitations, our real-life experience indicates that MMF is a valid treatment option mainly in AIH patients intolerant to standard therapy.

Withdrawal due to adverse drug events was necessary in a rather high proportion of patients (27%). Withdrawal rates in previous studies have ranged from 3% to 33%, and the frequency of withdrawals due to liver-related complications, between 3% and 13% [24–33,38–40,42,43]. The most common side effects have been gastrointestinal discomfort (nausea, diarrhea, abdominal pain, 3–11%), rash, including skin cancers (3–7%), fatigue (3–7%), infections (4%) and leukopenia (1–5%).

In all, there were four deaths (18%) during MMF treatment. Two of these were liver-related and one further patient underwent liver transplantation, i.e 3 of 22 patients (13.6%) suffered terminal liver failure, a proportion similar to the 7.2–13.2% in previous reports [27,34,41].

Other available second-line therapies for AIH have been less studied than MMF [10,27,41]. Cyclosporine has been used since 1985 and tacrolimus since 1995 primarily as salvage therapy for steroid-refractory disease. Ten reports of cyclosporine in AIH patients with altogether 133 patients and six reports of tacrolimus with 150 patients have been published. All were retrospective series and indicated a response of variable degree in 73%–98% of patients [10,27,35,41]. A recent meta-analysis [41] which, however, did not include the two largest studies [27,28], found decreased aminotransferase levels in 94% of patients treated with tacrolimus, in 91% in patients treated with cyclosporine, and in 78% of MMF patients; all had combination treatment with prednisolone. The corresponding figure for budesonide was 86%. What still is lacking is randomized head-to-head comparions between these second-line drugs in patients resistant and/or intolerant to standard therapy with prednisolone plus thiopurines.

In conclusion, our study shows that one of two AIH-patients that failed thiopurines benefit from MMF maintenance treatment, especially those with previous drug intolerance to standard treatment, where MMF is tolerated and effective in two thirds.

## Conflict of interest

None declared.

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