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Mycophenolate mofetil : role in autoimmune hepatitis and overlap syndromes.

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List of abbreviations:
AIH= Autoimmune hepatitis
AZA = Azathioprine
IAHG = International Autoimmune Hepatitis Group
MMF = Mycophenolate Mofetil
PBC = Primary biliary cirrhosis
PRED = Prednisolone
PSC = Primary sclerosing cholangitis

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Abstract

Background and Aims: Treatment failure occurs in 20% of autoimmune hepatitis patients on prednisolone and azathioprine (AZA). There is no established second line treatment. This retrospective observational study was conducted to assess the efficacy of mycophenolate mofetil as second line treatment after AZA-intolerance or AZA-nonresponse in autoimmune hepatitis and overlap syndromes.

Methods: Consecutive patients from the Dutch Autoimmune Hepatitis Group cohort, consisting of 661 patients , with autoimmune hepatitis or overlap syndromes, AZA-intolerance or AZA-nonresponse, and past or present use of mycophenolate mofetil were included. Primary endpoint of mycophenolate mofetil treatment was biochemical remission. Secondary endpoints were biochemical response (without remission), treatment failure and prevention of disease progression.

Results: Forty-five patients treated with mycophenolate mofetil were included. In autoimmune hepatitis remission or response was achieved in 13% and 27% in the AZA-nonresponse group compared to 67% and 0% in the AZA-intolerance group (P = 0.008). In overlap-syndromes remission or response was reached in 57% and 14% in the AZA-nonresponse group and 63% and 25% of the AZA-intolerance group (NS). 33% had side-effects and 13% discontinued mycophenolate mofetil. Overall 38% had treatment failure; this was 60% in the autoimmune hepatitis AZA-nonresponse group. Decompensated liver cirrhosis, liver transplantations and death were only seen in the autoimmune hepatitis AZA-nonresponse group (P < 0.001).

Conclusion: Mycophenolate mofetil induced response or remission in a majority of patients with autoimmune hepatitis and azathioprine-intolerance and with overlap syndromes, irrespective of intolerance or nonresponse for azathioprine. In autoimmune hepatitis with azathioprine nonresponse mycophenolate mofetil is less often efective.

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Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease characterized by hypergammaglobulinemia, auto-antibodies and interface hepatitis. [1-3]. No single test exists to confirm AIH and a scoring system was devised by the International Autoimmune Hepatitis Group (IAHG) in 1993 which was revised in 1999 and simplified in 2008 [2, 4, 5]. The incidence of AIH among Caucasian Northern Europeans ranges from 0.1 to 1.9/100.000/years and its prevalence is 16.9/100.000/year [1, 6].

If left untreated as many as 35% of the patients with severe disease die within six months and of the remaining patients 40% develop cirrhosis [7, 8].

Randomized controlled trails published between 1973 and 1985 have established the role of prednisolone (PRED) alone and in combination with azathioprine (AZA) in the treatment of AIH [7, 9-14]. Although these trails have their limitations, as shown in a recently published review, current treatment is based upon these data and about 80% of the patients achieve remission within 3 years [14]. The immediate consequence is that about 20% of the patients cannot tolerate PRED and/or AZA or only have a partial response or treatment failure [15, 16]. There is no established second line treatment for these patients.

In the past 15 years several immunosuppressive drugs, including ciclosporin, tacrolimus, methothrexate, 6-mercaptopurine and 6-thioguanine have been investigated as possible second line treatment, mainly in small case series or single case-reports. The groups are too small to define the utility of these agents [17-23].

In the last decade ten case series describe the use of mycophenolate mofetil (MMF) in a total of 121 adult patients and 18 children with AIH. Eight studies conclude that MMF could be a good alternative for AZA, one disagreed and one is inconclusive. Two studies

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specifically focus on AZA-non-response versus AZA-intolerance. One concludes that MMF can be a good alternative for both groups. The largest of these two studies, describing 36 patients, concludes that MMF could be a good alternative but mainly in patients who do not tolerate AZA. Only one study included the AIH-overlap syndromes with primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) [24-33]. Because of the low prevalence of overlap syndromes little is known about the preferred treatment in this patient category. Usually the AIH-component in overlap syndromes is treated as AIH [34].

The aim of this retrospective multicentre observational study was to investigate whether MMF is a good second line treatment in patients with AIH or AIH-overlap syndromes who fail or do not tolerate AZA and whether this is true for all subgroups, namely AZA-intolerance versus AZA-non-response and AIH versus AIH-overlap syndromes.

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Patients and Methods

The Dutch AIH Group represents a cohort of identified AIH an AIH-overlap patients, including AIH-PBC and AIH-PSC, consisting of 661 patients from academic and non-academic centres. From this cohort those patients with AIH according to the IAHG criteria (definite and probable) [2] and all patients with AIH-overlap syndromes according to the Paris criteria [35, 36] with past and present use of MMF before May 2009 were included.

Intolerance was defined as stopping AZA because of AZA related side effects. Non-response was defined as failure to achieve or maintain remission, as determined by the treating physician. The response to MMF in identified AIH and AIH-overlap patients was determined by chart review. Treatment failure, response, remission and relapse were defined according to established criteria in the AASLD guideline [37]: Treatment failure: a rise in or stable AST and/or ALT three months after starting MMF or intolerance for MMF, defined as stopping MMF because of MMF related side effects. Response: a drop in AST and/or ALT below twice the upper limit of the reference range three months after starting MMF or a fifty percent fall in AST and/or ALT one month after starting MMF. Remission: a normalisation of AST and/or ALT after starting MMF. Relapse: a rise in AST and/or ALT of more than threefold the upper limit after a response or remission. A patient can fall into a category only once. So, if a patient has a treatment failure there cannot be a response or remission and vice versa. All the data was collected and processed by the same person (MACMP) and verified (BvH).

The primary endpoint was defined as biochemical remission while using MMF. Secondary endpoints were defined as biochemical response or treatment failure while using MMF and prevention of progression of the disease, defined as decompensated cirrhosis

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(presence of ascitis, hepatic encephalopathy or oesophageal varices), liver transplantation or death. To determine the progression of the disease at the time of data collection all modalities (radiology, pathology, endoscopy and letters, whatever gave the most recent information) were used. Follow up is from start of MMF treatment till may 2009 and differs per patient.

Fisher's exact test, Mann-Withney test, independent samples T-test and Log rank test were used with $p<0.05$ as the level of statistical significance.

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Results

Forty-nine patients with current or past use of MMF were selected from the 661 Dutch AIH Group cohort. One had to be excluded because the AIH score was too low, three because not all the information required for this study was available. The remaining 45 patients were divided into two main groups: AZA-non-responders (N = 22) and AZA-intolerance (N = 23). Subsequently both groups were divided into subgroups according to whether they had AIH or AIH-overlap syndrome (Figure 1). All patients with AIH-PBC overlap syndrome and one out of four patients with AIH-PSC overlap syndrome received ursodeoxycholic acid treatment in addition to immunosuppression.

Side effects of AZA before switching to MMF were gastro-intestinal complains (nine), rash (eight), fever (four), hepatitis (three), leucopenia (two), pancreatitis (two), arthralgia (one), myalgia (one), elevated amylase (one) and haemolytic anaemia (one). Some patients reported multiple side effects.

Table 1 shows the patient characteristics, including age at diagnosis. At the time of MMF treatment the youngest patient was 20 years of age. As shown in table 1, disease duration was equally distributed over the groups and not a confounding factor. Follow-up biopsies were scarce. Six patients had a liver biopsy before they were switched to MMF. Twenty-two patients (equally divided over the subgroups) ever had a second liver biopsy either during AZA/PRED or during MMF/PRED treatment. Though not significant, cirrhosis –as determined by liver biopsy, CTscan or presence of varices- was more prevalent in the AIH-AZA-non-response group.

All patients were treated with PRED and AZA before starting MMF (details in Table 2). Three patients (1 AIH-AZA-non-response, 1 AIH-AZA-intolerance and 1 Overlap-AZA

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intolerance) were treated with budesonide before switching to MMF. After switching to MMF two continued using budesonide. Most patients were subsequently treated with MMF and PRED (details in Table 3). Seven patients (1 Overlap-AZA-intolerance, 2 AIH-AZA-non-response and 4 AIH-AZA-intolerance) were treated with budesonide while on MMF. Two AIH-AZA-non-response patients had a treatment failure, the other five had a remission on MMF. In patients treated with MMF the AZA was discontinued in almost all cases, except in three AIH and three AIH-overlap syndrome patients, all non-responders. Of these six patients two AIH patients had a treatment failure, one AIH and one Overlap patient had a response and two Overlap patients had a remission.

At the time of data collection 29 out of 45 (64%) patients still used MMF (Table 3). Reasons for discontinuing MMF were non-response (seven (16%), five in the AZA-non-response group), intolerance (six (13%), four in the AZA-intolerance group), patients initiative (two) and unknown (one). Fifteen out of 45 (33%) patients had side-effects of MMF which were gastro-intestinal complaints (five), rashes or skin carcinomas (three), fatigue or concentration problems (three), alopecia (two), infections (two), leucopenia (one), palpitations (one) and ischemic colitis (one). Some patients reported multiple side effects.

Table 4 shows the number of patients and percentages of treatment failure, response, remission, relapses and disease progression with MMF treatment as defined after three months (A) and at the end of follow-up (B). Before starting MMF 78% of all patients had a response on AZA and PRED. Remissions on AZA and PRED before MMF were only seen in the intolerance group. After starting MMF 17 (38%) out of 45 patients had a treatment failure. Twelve of these patients stopped using MMF, six because of side-effects. Twenty-one out of 45 (47%) patients achieved a remission while using MMF. In 13 of these 21 patients IgG levels normalized, in four IgG levels stayed elevated and in four IgG levels were unknown.

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Two out of 45 (4%) patients (both AIH-AZA-intolerance) were on MMF monotherapy, they were both in remission.

Comparing the AZA-non-response versus the AZA-intolerance group remission rates (P = 0.0017) and relapse rates (P=0.028) are significantly higher in the AZA-intolerance group. Although not statistically significant, treatment failure was twice as high in de AZA-non-response group compared to the AZA intolerance group. In both groups, one patient progressed to cirrhosis while using MMF. Decompensated liver cirrhosis, liver transplantations and death were only seen in the AZA-non-response group (p<0.01).

Comparing the AIH-AZA-non-response versus de AIH-AZA-intolerance group remission rates are higher in de AIH-AZA-intolerance group (P = 0.008). Although not significant, treatment failure is twice as high in the AIH-AZA-non-response group compared to the AIH-AZA-intolerance group. Decompensated liver cirrhosis, liver transplantations and death were only seen in the AIH-AZA-non-response group. The AIH-AZA-non-response group has significantly less remissions compared to the other subgroups combined (P = 0.002) (Figure 2). The percentages of patients reaching remission, response or treatment failure with MMF in the four patient groups are shown in figure 3.

Fifteen AIH-overlap patients were included in this study, four PSC-AIH-overlap and 11 PBC-AIH-overlap (Figure 1). Three PBC-AIH-overlap patients (two AZA-non-response and one AZA-intolerance) had a treatment failure on MMF. Two PBC-AIH-overlap patients (one AZA-non-response and one AZA-intolerance) and one PSC-AIH- overlap patient (AZA-intolerance) had a response. Six PBC-AIH-overlap patients (three AZA-non-response and three AZA-intolerance) and three PSC-AIH- overlap patients (one AZA-non-response and two AZA-intolerance) had a remission. There were no significant differences between the overlap-AZA-intolerance and the overlap-AZA-non-response group.

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Discussion

Our data indicate that MMF is a valuable second line treatment in AIH-AZA-intolerant patients and in all AIH-overlap syndrome patients, irrespective if these patients were intolerant or non-responsive to AZA. However, in AIH-AZA-non-response patients treatment failure on MMF is frequent and in this group other therapies probably should be considered first.

Currently, most experience with the use of MMF is in the organ transplant setting. MMF has a more favorable side-effect profile than many other immunosuppressives [38, 39]. The last decade ten small case series described the use of MMF in AIH and the overall opinion was that it could be used as a second line treatment [24-33]. However, two series indicated that there was a difference between patients who were intolerant for AZA and those who were AZA-non-responders [30, 33]. This study is the largest on the use of MMF in AIH so far. It is the only study that compares both AZA-intolerance versus AZA-non-response and includes AIH-overlap syndromes.

All patients in the current cohort were treated with PRED and AZA before starting MMF. Here some expected differences between the AZA-intolerance and AZA-non-response

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group were seen (Table 2). Usually intolerance is seen within the first half year, which is why in the AZA-intolerance group it is not possible to increase the dose of AZA and lower the dose of PRED.

Six patients were treated with PRED, AZA and MMF. In all these patients MMF was added because they did not respond sufficiently to PRED and AZA despite long term treatment (minimum of 100 months). In our opinion the additional effect after adding MMF thus can be contributed to MMF en we therefore did not exclude these patients. Although four of these patients had a response or remission we do not recommend this triple therapy.

The number of relapses on MMF is higher in the AZA-intolerance group than in the AZA-non-response group (P =0.028). The explanation for this is that in order to have a relapse, first there must be a response or remission. In the AZA-non-response group there are fewer responses and remissions and more treatment failures on MMF. Apparently AZA-non-response predicts non-response to MMF in most patients. However, in AIH-overlap patients in both groups, AZA-intolerance and AZA-non-response, similar response and remission rates on MMF were seen, keeping in mind that both groups are very small, while the doses of PRED used in the overlap-AZA-non-response group were not significantly higher. Therefore in AIH-overlap syndrome patients AZA-non-response does not predict a non-response to MMF, while in AIH patients it does. The differences between AZA-non-response and AZA-intolerant patients were apparent when comparing the AIH-AZA-intolerance group to the AIH-AZA-non-response group (Table 4). The AIH-AZA-non-response group has the lowest remission rate (13%) and highest treatment failure (60%) on MMF treatment of all subgroups. There are no apparent differences in patient characteristics between the AIH-AZA-non-response group and the other subgroups, except possibly more cirrhosis at presentation than in the AIH-AZA-intolerance patients.

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Both the PSC-AIH-overlap (AIH remission rate 75%) and PBC-AIH-overlap (AIH remission rate 55%) patients often do very well on MMF but the individual groups are too small to look at differences between PSC and PBC overlap subgroups regarding the effect of MMF.

As in the other smaller case series a limitation of the current report is its retrospective nature. AZA-non-response is a conclusion of the treating physician. In some cases treatment with AZA and PRED may have been insufficient in dose or length according to current guidelines [37]. Also there were patients who did not achieve a response or remission on AZA and PRED who were already lowering the PRED dose and then were switched to MMF. Subsequently some of these patients did not achieve a response or remission on MMF with low dose PRED and were labeled as treatment failures. In some of these cases there was never a proper remission induction with sufficiently high PRED dose after switching to MMF. It was also quite difficult to compare the use of PRED before and after starting MMF. One of the main reasons for this was the increased use of budesonide as an alternative of PRED. As induction therapy budesonide appears superior to PRED in a recent study [40]. However, according to a meta-analysis of previous randomized controlled trials and the current AASLD guidelines PRED with or without AZA should be used to induce remission, while AZA with or without PRED currently is the standard in remission maintenance treatment in AIH and AIH-overlap syndrome patients [14, 37].

Out of the ten published MMF case series eight did not separate AZA-intolerance and AZA-non-response patients [24-29, 31]. Only one of these eight studies included AIH-overlap syndrome patients, but responses were not reported separately [31]. In two of these eight studies MMF is used to induce remission. One is a case series of five patients and concludes that MMF can be used to induce and maintain remission [25]. One is a study with eight patients receiving MMF who were compared to 17 patients receiving high dose corticosteroids. The

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conclusion of this study was that MMF cannot be used to induce remission [27]. Four of the eight studies describe the use of MMF in combination with corticosteroids and one describes the use of MMF with or without tacrolimus. These previous studies report a remission rate of 71-84%, which is high compared to our findings. The other studies reports side-effects in 6-34% of patients, which is comparable to our findings [24, 26, 29, 31].

In our opinion the study of Hennes et al is best comparable to our study in terms of size and design. The remission rate in the AZA-non-response group, percentage of treatment failure, side effects and patients who had to stop MMF because of side effects were comparable. Compared to our data (67% remission rate) this other study reached a remission rate of 43% in the AZA-intolerance group. The difference is mainly explained by differences in definition, since the other study did not use the definitions of the AASLD-guideline but stated its own, more strict definitions [37]. In contrast to that study the current study also looked at MMF in AIH-overlap syndromes and 86% of these patients had a response and/or remission with MMF [30]. In our opinion the similarity of the results of this study and the study of Hennes et al suggests that the findings are an accurate reflection of the use of MMF as a second line treatment in the real world. Both studies are retrospective but describe relatively large numbers of patients being treated with MMF.

In conclusion, this study shows that MMF with PRED is an excellent alternative treatment in patient with AIH who do not tolerate AZA (remission rate 67%). In addition our data show that MMF can induce remission in 60% of patients with AIH-overlap syndromes, irrespective if they were intolerant or non-responsive to AZA. However, the majority of patients with AIH and a non-response on AZA fail treatment with MMF. Since twothirds of these AIH patients with non-respsonse to AZA progressed to decompensated liver disease,

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liver transplantation or death, in AIH-non-response patients other therapies than MMF, including calcineurin inhibitors or liver transplantation, should be considered instead.

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Legends to figures

Figure 1. Patient distribution according to reasons for starting MMF and underlying disease in the patients derived from the 661 AIH and AIH-overlap patients in the Dutch AIH cohort.

Figure 2. Percentage of patients achieving remission and time to achieve remission with MMF in the four subgroups:

·····	AIH-AZA-intolerance
– – – –	Overlap-AZA-intolerance
———	Overlap-AZA-non-response
– · – · ·	AIH-AZA-non-response
+	End of follow up

Figure 3. Percentage of patients reaching remission (light), response (gray) or treatment failure (dark) with MMF.

AIH-INT: AIH with intolerance for AZA; AIH-NR: AIH with non-response to AZA; Overlap-INT: Overlap syndrome with intolerance for AZA; Overlap-NR: Overlap syndrome with non-response to AZA. Decompensated cirrhosis, liver transplantation and death only occurred in the AIH-NR group (in 60%)($p<0.01$). Remission in AIH-NR vs AIH-NT: $p=0.008$; Remission AIH-NR vs other groups: $p=0.002$; Remission NR vs INT: $p=0.002$; Relapse NR vs INT: $p=0.03$.

Legends to tables

Table 1. General characteristics of the study population.

Table 2. Data on initial treatment with PRED and AZA per group.

Table 3. Data on treatment with MMF per group.

Table 4. Overview of treatment failure, response, remission and disease progression with MMF treatment as defined after three months (A) and at the end of follow-up (B). .

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Table 1. General characteristics of the study population

	AZA-intolerance N = 23		AZA-non-responders N = 22	
	AIH	Overlap syndrome	AIH	Overlap syndrome
	N = 15	N = 8	N = 15	N = 7
Gender (male/female)	2/13	2/6	4/11	0/7
AIH Score	16 (12-21)	12 (9-20)	16 (12-21)	13 (6-17)
Age at diagnosis (year)	38 (10-71)	36 (16-72)	35 (11-61)	46 (25-59)
Disease duration (year)	8 (1-22)	10 (2-20)	9 (3-21)	10 (3-23)
IgG/gamma globuline elevated at diagnosis	10/15 (67%)	6/7 (86%)	12/13 (92%)	6/7 (86%)
ANA	10/15 (67%)	4/8 (50%)	10/14 (71%)	6/7 (86%)
ASMA	11/13 (85%)	5/7 (71%)	11/14 (79%)	4/6 (67%)
SLA	1/1 (100%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
LKM	0/4 (0%)	0/1 (0%)	0/2 (0%)	0/2 (0%)
AMA	0/10 (0%)	3/7 (43%)	1/10 (10%)	4/7 (57%)
Liver biopsy at diagnosis	14 (93%)	8 (100%)	15 (100%)	7 (100%)
Interface hepatitis	14/14 (100%)	6/8 (75%)	13/14 (93%)	6/7 (86%)
Plasma cell infiltrate	10/14 (71%)	7/8 (88%)	13/14 (93%)	7/7 (100%)
Biliary changes	3/14 (21%)	4/8 (50%)	3/14 (21%)	7/7 (100%)
Cirrhosis at diagnosis	2/15 (13%)	4/8 (50%)	9/15 (60%)	2/7 (29%)
IgG/gamma globuline elevated at start MMF	5/10 (50%)	4/5 (80%)	5/8 (63%)	4/6 (67%)
Liver biopsy at start MMF	1/15 (7%)	2/8 (25%)	1/15 (7%)	2/7 (29%)
Cirrhosis before MMF	3/15 (20%)	5/8 (63%)	11/15 (73%)	5 (71%)

Median (Range), Number positive/Number measured or known (Percentage)

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Table 2. Data on initial treatment with PRED and AZA per group

	AZA-intolerance N = 22		AZA-non-responders N = 21	
	AIH N = 14	Overlap syndrome N = 8	AIH N = 14	Overlap syndrome N = 7
AZA treatment duration (months) *	2 (1-225)	3 (1-8)	30 (1-146)	113 (3-260)

Median (Range)

	AZA-intolerance N = 20		AZA-non-responders N = 20	
	AIH N = 13	Overlap syndrome N = 7	AIH N = 14	Overlap syndrome N = 6
Maximum dose AZA (mg/day) **	50 (50-150)	75 (50-125)	137.5 (50-200)	100 (50-150)
Maximum dose PRED on AZA (mg/day)	30 (2.5-40)	30 (15-50)	30 (15-40)	30 (20-60)
Minimum dose PRED on AZA (mg/day) ***	15 (0-40)	15 (7.5-40)	7.5 (0-25)	8.75 (0-12.5)

Median (Range)

Of six patients details on dose (five) or length (two) of the initial treatment were missing

** Significant difference between AZA-intolerance and AZA-non-response (P<0.001), AIH-AZA-intolerance and AIH-AZA-non-response (P=0.001) and Overlap-AZA-intolerance and Overlap-AZA-non-response (P=0.019)*

***Significant difference between AZA-intolerance and AZA-non-response (P=0.002) and AIH-AZA-intolerance and AIH-AZA-non-response (P=0.005)*

****Significant difference between AZA-intolerance and AZA-non-response (P=0.006) and AIH-AZA-intolerance and AIH-AZA-non-response (P=0.039)*

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Table 3. Data on treatment with MMF per group

	AZA-intolerance N = 23		AZA-non-responders N = 22	
	AIH N = 15	Overlap syndrome N = 8	AIH N = 15	Overlap syndrome N = 7
MMF treatment duration (months)	34 (1-133)	28.5 (3-112)	13 (2-62)	26 (2-87)
Maximum dose MMF (mg/day)	1500 (500-2000)	2000 (1000-3000)	2000 (1000-2000)	2000 (1000-2000)
Maximum dose PRED on MMF (mg/dag)*	15 (0-60)	20 (0-40)	20 (10-60)	40 (5-60)
Minimum dose PRED on MMF (mg/dag)*	10 (0-15)	5 (0-15)	10 (0-12.5)	10 (0-15)
MMF stopped (number)	4 (28%)	3 (38%)	8 (53%)	1 (14%)
Follow up (months)	39 (3-133)	52.5 (5-133)	35 (11-109)	26 (5-87)

Median (Range), Number (percentage)

**Patients on budesonide excluded. No significant differences*

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Table 4. Overview of treatment failure, response, remission and disease progression during MMF, A) Three months after starting MMF (according to definition), B) At the end of follow-up.

A

	AZA-intolerance N = 23		AZA-non-responders N = 22	
	AIH N = 15	Overlap syndrome N = 8	AIH N = 15	Overlap syndrome N = 7
Response before MMF	7 (47%)	3 (38%)	12 (80%)	4 (57%)
Remission before MMF*	5 (33%)	4 (50%)	0 (0%)	0 (0%)
Treatment failure on MMF	5 (33%)	1 (13%)	9 (60%)	2 (29%)
Response on MMF **	0 (0%)	2 (25%)	4 (27%)	1 (14%)
Remission on MMF***	10 (67%)	5 (63%)	2 (13%)	4 (57%)
Relapses on MMF per patient****	0 (0-5)	0.5 (0-3)	0 (0-2)	0 (0-2)

B

	AZA-intolerance N = 23		AZA-non-responders N = 21[&]	
	AIH[$] N = 15	Overlap syndrome N = 8	AIH[$] N = 15	Overlap syndrome N = 6
Response/remission on MMF *****	11 (73%)	5 (63%)	3 (20%)	5 (83%)
Response/remission on other therapies******	4 (27%)	2 (25%)	2 (13%)	1 (16%)
Progression to cirrhosis[#]	0 (0%)	1 (13%)	1 (7%)	0 (0%)
Decompensated cirrhosis[#]	0 (0%)	0 (0%)	5 (33%)	0 (0%)
Liver transplantation[#]	0 (0%)	0 (0%)	3 (20%)	0 (0%)
Death[#]	0 (0%)	0 (0%)	1 (7%)	0 (0%)

Number (percentage), Median (range)

** Significant difference between AZA-intolerance and AZA-non-response (P=0.001)*

*** Response but no remission*

**** Significant difference between AZA-intolerance and AZA-non-response (P=0.017) and AIH-AZA-intolerance and AIH-AZA-non-response (P=0.008)*

*****Significant difference between AZA-intolerance and AZA-non-response (P=0.028)*

[&]*One patient was excluded because she had treatment failure on MMF, continued it and still had*

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stable disease, but follow up was only 5 months.

[$]In both groups one patient had a treatment failure according to definition, continued using MMF and had a response. They were counted as a remission/response on MMF.

******Significant difference between AZA-intolerance and AZA-non-response (P=0.038) and AIH-AZA-intolerance and AIH-AZA-non-response (P=0.009)*

*******Other therapies were corticosteroids, either monotherapy or combined with AZA and one patient using no medication anymore.*

[#]Progression of liver disease defined as to progression to cirrhosis, decompensated cirrhosis, liver transplantation and death was significantly more prevalent in the AZA-non-response group versus the AZA-intolerance group (P=0.001) and in the AIH-AZA-non-response versus de AIH-AZA-intolerance group (P<0.001)

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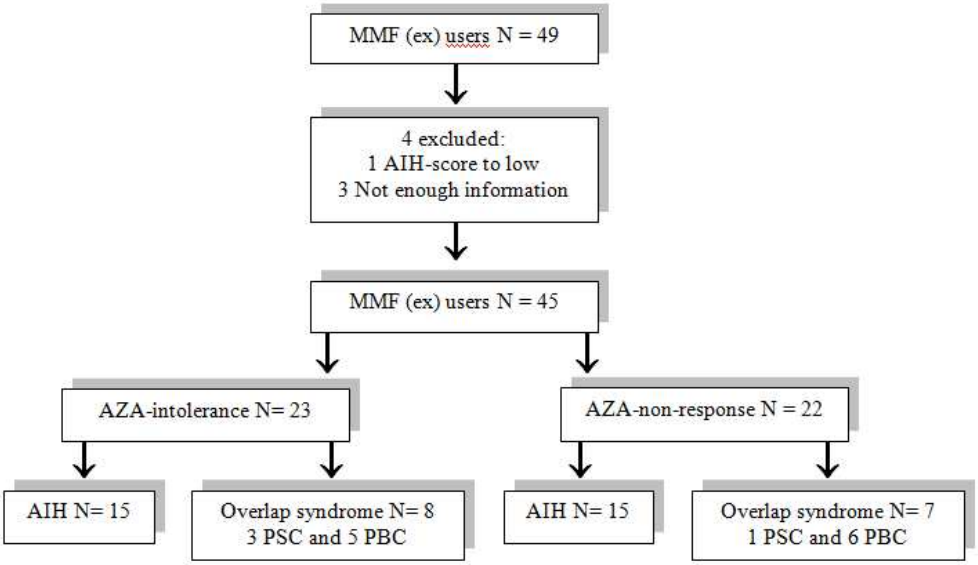

Patient distribution according to reasons for starting MMF and underlying disease in the patients derived from the 661 AIH and AIH-overlap patients in the Dutch AIH cohort.
191x111mm (96 x 96 DPI)

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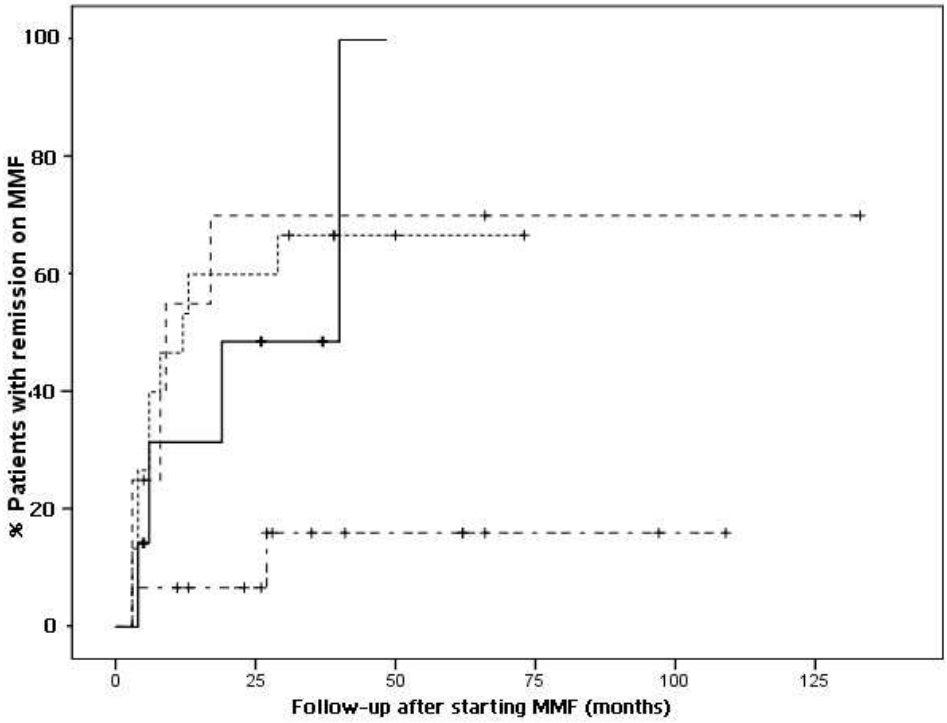
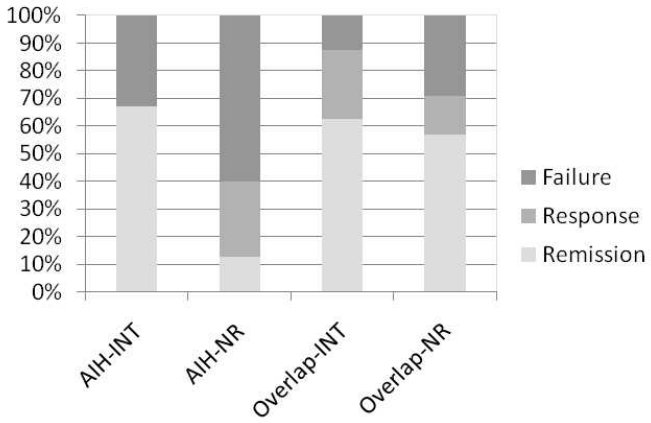


Percentage of patients achieving remission and time to achive remission on MMF in the four subgroups:
.....AIH-AZAintolerance;
--- overlap-AZAintolerance;
___overlap-AZAnonresponse;
-.-. AIH-AZAnonresponse
166x133mm (96 x 96 DPI)



Percentage of patients achieving remission (light), response (gray) or with treatment failure (dark) on MMF.
AIH-INT: AIH with intolerance for AZA; AIH-NR: AIH with non-response to AZA; Overlap-INT: Overlap syndrome with intolerance for AZA; Overlap-NR: Overlap syndrome with non-response to AZA. Decompensated cirrhosis, liver transplantation and death only occurred in the AIH-NR group (in 60%)($p<0.01$). Remission in AIH-NR vs AIH-NT: $p=0.008$; Remission AIH-NR vs other groups: $p=0.002$; Remission NR vs INT: $p=0.002$; Relapse NR vs INT: $p=0.03$.

254x190mm (96 x 96 DPI)