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BENEFICIAL RESPONSE TO MYCOPHENOLATE MOFETIL BY PATIENTS WITH AUTOIMMUNE HEPATITIS, WHO HAVE FAILED STANDARD THERAPY, IS PREDICTED BY OLDER AGE AND LOWER IMMUNOGLOBULIN G AND INR LEVELS

Short running title:

Age, IgG and INR predict response to MMF in AIH

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Abbreviations:

AIH: Autoimmune hepatitis

~~AIHG: Autoimmune hepatitis group~~

~~ALA CRN: Australian Liver Association Clinical Research Network~~

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

~~CP: Child Pugh~~

IgG: Immunoglobulin G

IQR: Interquartile range

MMF: Mycophenolate mofetil

Key words: Autoimmune hepatitis, immunotherapy, mycophenolate mofetil

Abstract:

Background: Mycophenolate mofetil is a commonly used salvage therapy for patients with autoimmune hepatitis.

Aim: The aim of this study was to evaluate the predictors of response to mycophenolate rescue therapy to facilitate clinical decision making.

Methods: We performed a retrospective observational cohort study of autoimmune hepatitis patients managed in 17 major Australian liver centres who received mycophenolate after an inadequate response or intolerance to corticosteroids with/without thiopurine(s). Baseline demographic, clinical and laboratory variables were compared between responders and non-responders. A multivariable logistic regression model was developed using forward selection to identify independent predictors of treatment response.

Results: A total of 105 patients received mycophenolate rescue therapy of whom 63 (60%) achieved biochemical remission. On univariable analysis, older age ($p=0.003$), INR <1.1 ($p=0.02$), ethnicity ($p=0.01$) and lower immunoglobulin gamma ($p<0.002$) levels were associated with treatment response, while no association was found with cirrhosis status ($p=0.07$) or treatment indication ($p=0.63$). On multivariable analysis, lower pre-treatment serum immunoglobulin gamma level ($p=0.01$), higher age at commencing mycophenolate ($p=0.01$) and higher INR ($p=0.03$) were the only significant independent predictors. An immunoglobulin gamma level <17 g/L had a positive and negative predictive value for response of 71% and 60% respectively, while age ≥ 54 years when commencing mycophenolate had a positive and negative predictive value for response of 80% and 59%, respectively.

Conclusion: Mycophenolate remains an excellent treatment option for patients with autoimmune hepatitis refractory to or intolerant of standard therapy with those most likely to benefit being older and/or having lower pre-treatment immunoglobulin gamma levels. **Introduction**

Autoimmune hepatitis (AIH) is an incompletely understood inflammatory liver disease that occurs due to loss of tolerance to self-antigens^{1,2}. It is characterised by its female predominance, raised transaminases, and association with other autoimmune diseases³. Usually AIH responds well to corticosteroids either as monotherapy or in combination with thiopurine(s), with the elevated transaminases and gamma globulins returning to within the normal range over weeks to months and between 75-80% of patients achieving remission within 2 years^{4,5}. A recent review of all randomised controlled trials of AIH therapies, concluded that both corticosteroid monotherapy and corticosteroids in combination with azathioprine were equally effective in inducing remission⁶. However, all 11 studies included in this systematic review were performed before the introduction in 2010 of more stringent criteria to define remission⁴. Subsequently, it has been shown that when

the 2010 response criteria are applied as opposed to the previous 2002 criteria⁷, the remission rate on standard therapy may be as low as 26%⁸. Moreover, two-thirds of patients receiving corticosteroid therapy experience significant side-effects including diabetes, hypertension, cataracts, osteoporosis, vertebral compression fractures and psychoses that warrant premature discontinuation of treatment in up to 13% of patients⁹. In addition, as many as 25% of patients on azathioprine develop side-effects including skin rash, fever, arthralgias, nausea, vomiting, pancreatitis and marrow suppression that leads to discontinuation of treatment in about 10% of patients¹⁰. Further, maintenance therapy is required in the majority of patients to control inflammation and/or prevent relapse and in the long term, complications of liver disease¹¹; this is usually with a thiopurine, with or without a low dose of corticosteroid^{4,12-14}. Life expectancy of patients who respond well to therapy is similar to the general population¹⁵, and response to treatment is the best guide to prognosis⁸.

For patients who fail to achieve a satisfactory response and/or who are intolerant of standard therapy with steroids with/without thiopurine(s), MMF is the most widely used second-line agent in the real-world setting^{12,16}. We and others^{9,17-21} have previously shown that treatment with MMF as rescue therapy for AIH appears to be well tolerated and is moderately effective in achieving an overall remission rate of 60%. However, response rates appear to be lower in those with cirrhosis¹⁷, and those receiving MMF for lack of efficacy rather than intolerance to standard therapy^{9,20,21}. The aim of this study was therefore to evaluate the predictors of response to MMF in AIH to facilitate clinical decision making when considering MMF as second line therapy.

Methods:

The Australian Liver Association Clinical Research Network performed a retrospective, multicentre, observational cohort study of patients with AIH refractory to or intolerant of standard therapy who received MMF as salvage therapy. The study design has been published in detail previously¹⁷. Seventeen major liver centres across Australia contributed cases, and records were reviewed for demographics, clinical and laboratory characteristics, initial therapy, and treatment outcome. All except one of the 17 liver centres involved in the study were affiliated with a large metropolitan hospital and University, while one site was based in a large regional hospital affiliated with a University. Sites were selected to participate in the study based on an affirmative response by site principal investigators to an expression of interest questionnaire and protocol circulated via email

to 21 major centres across mainland Australia. Inclusion criteria were age greater than 18 years, a definite or probable diagnosis of AIH²², and having received at least one MMF dose, as shown in Figure 1. Patients with overlap syndromes were excluded, as were those with other concomitant chronic liver disease, human immunodeficiency virus infection, co-existing immunological disorders requiring systemic therapy, active malignancy (except non-melanoma skin cancer) or prior liver transplantation¹⁷.

The definition of complete response to MMF was alanine transaminase (ALT), aspartate transaminase, and immunoglobulin gamma (IgG) levels returning to the normal reference range, with or without normal liver histology, within the first two years of treatment as previously detailed⁴. Baseline was taken as the results closest to the time of failure of standard therapy and institution of MMF therapy.

The predictors of response in the patients' baseline demographic, clinical and laboratory characteristics were determined by comparing patients who achieved a complete response to MMF to those with no or incomplete response to MMF second-line therapy.

Ethics:

Cases were de-identified using a unique code including institution, patient's initials, and date of birth. A password-protected electronic database was used to store data. Ethics approval for the study was granted at all sites by the relevant institution's Human Research Ethics Committee.

Statistics:

Descriptive statistics of the cohort were performed with continuous variables assessed for normality and expressed as mean $\pm$ standard deviation (SD) or median inter-quartile range (IQR) depending on the underlying data distribution. Independent student t-test and Wilcoxon rank-sum test were used where appropriate. Categorical variables were expressed as numbers with percentages. Pearson chi-squared test was used for independent categorical variables. Odds ratios were calculated as effect size, with 95% confidence intervals (95%CI). Univariable and multivariable logistic regression analyses were performed to determine associations with treatment response and baseline characteristics. Multiple logistic regression was performed using purposeful forward selection methodology as described²³ using a criterion for inclusion of $p < 0.20$ of co-variables on univariable analysis. Where there was high co-linearity between variables, only the variable with the strongest association with treatment response was selected in the model. All

reported p values are two-tailed and $p < 0.05$ indicated statistical significance. Analyses were performed with Stata software version 14.1 (StataCorp®, College Station, TX, USA).

Results:

Study Population:

One hundred and five patients met the inclusion and exclusion criteria. The baseline characteristics of the overall cohort are shown in Table 1. The median age at diagnosis of AIH was 50 years (IQR 38-57), and age at starting MMF was 53 years (IQR 43-61), 88% were female, 86% were Caucasian, and 97% were Type 1 AIH. Thirty-seven percent of the cohort had cirrhosis, which was established in patients either by liver biopsy and/or on the basis of results of clinical, laboratory and imaging studies²⁴. The vast majority (82%) of these had compensated Child-Pugh A cirrhosis. Previous standard therapy was the combination of corticosteroids (prednisolone and/or budesonide) plus a thiopurine(s) (azathioprine or 6-mercaptopurine) in 98% of patients. Forty-two (40%) patients required MMF second-line therapy for refractory disease while 63 (60%) received MMF for treatment intolerance. The main causes of treatment intolerance to azathioprine/6-mercaptopurine included: nausea and/or vomiting (n=20) and other gastrointestinal symptoms (n=4), hepatotoxicity (n=13), joint, muscle and/or body pain (n=7), pancreatitis (n=3), fever (n=3), headache (n=3), hair loss (n=3), rash (n=3), bone marrow suppression (n=2), allergic reaction (n=1) and vasculitis (n=1). Two patients were intolerant to prednisolone due to insomnia. Five patients had received treatment with a calcineurin inhibitor (cyclosporin A, n=2; tacrolimus, n=3) a median of 62 months (range: 6.0-177 months) prior to the addition to MMF for reasons of lack of efficacy (n=3) or intolerance to standard therapy (n=2). The median starting and maximum dose of cyclosporin A was 325 mg/day (range 50-600 mg/day) and 350 mg/d (range: 100-600 mg/day) respectively, and for tacrolimus was 2 mg/day (range: 1-2 mg/day) and 2 mg/day (range: 2-8 mg/day) respectively. In addition, six patients commenced a calcineurin inhibitor a median of 6.4 months (range: 2.0 to 25.3 months) after commencing MMF due to lack of efficacy (n=5) or intolerance (n=1) to MMF. The median and maximum dose of MMF administered was 1 g/day (IQR 0.88-1.0 g/d) and 2.0 g/day (IQR 1.0-2.0 g/day) respectively, while the median duration of therapy was 25 months (IQR 13-60 months).

Comparison of responders and non-responders to MMF:

Overall, 63 (60%) patients achieved biochemical remission on MMF after a median treatment duration of 12 weeks. This included 3 (60%) of the 5 patients commenced on MMF after prior calcineurin inhibitor treatment including 2 of 3 (67%) patients receiving calcineurin inhibitor

therapy for lack of efficacy and 1 of 2 (50%) patients treated for intolerance to standard therapy (Table 1). Of note, none of the six patients commenced on a calcineurin inhibitor after MMF non-response or intolerance achieved remission. The baseline characteristics of responders and non-responders are shown in Table 1. Patients who responded to MMF were significantly older at the time of diagnosis of AIH and at commencing MMF and had a higher frequency of being Caucasian. In addition, responders to MMF had significantly lower serum aminotransferase (i.e. aspartate transaminase, ALT), total bilirubin, immunoglobulin G (IgG) and INR levels than non-responders. The dosing details and indication for treatment with MMF were similar between responders and non-responders, while there was a trend towards a higher frequency of cirrhosis in non-responders ($p=0.07$).

Predictors of response in overall cohort

On univariable analysis, the baseline characteristics that predicted response to MMF included lower IgG levels (<17 g/L) ($p=0.002$), older age (≥ 54 years) at commencing MMF ($p=0.001$), and lower international normalised ratio (≤ 1.1) (INR) ($p=0.02$) (Table 2). Cirrhosis was weakly associated with a poorer response to MMF ($p=0.07$). There was no association between response to MMF and gender, treatment indication for MMF, and baseline ALT, aspartate transaminase, bilirubin, albumin, creatinine, haemoglobin or platelet levels.

On multivariable analysis, higher age at commencing MMF, lower pre-treatment serum IgG level and lower INR were the only significant independent predictors of a beneficial response to MMF (Table 2). A higher age ≥ 54 years at the time of commencing MMF had a good positive predictive value of response of 80% and modest negative predictive value of 59%, while the sensitivity and specificity were 65% and 76% respectively. Similarly, serum IgG <17 g/L prior to commencement of MMF had a good positive predictive value for response of 71% and modest negative predictive value of 60%, while the sensitivity and specificity were 66% and 72%, respectively. A lower INR of ≤ 1.1 was also a predictor of good response to MMF however, the clinical significance of the lower INR is unclear as the majority of readings were within normal range in this cohort. Importantly, results of univariable and multivariable analyses were similar after the five patients who received calcineurin inhibitor treatment in combination with standard therapy were excluded. In particular, lower baseline IgG (<17 g/L) levels ($p=0.015$) and older age (≥ 54 years) ($p=0.015$) at the time of commencing MMF remained independent predictors of response while a lower INR (≤ 1.1) ($p=0.08$) showed a trend towards having predictive value.

Predictors of response according to treatment indication

Table 3 shows the results of univariable analysis of the predictors of response to MMF according to MMF treatment indication. In patients who commenced MMF for refractoriness to standard therapy (n=42), only older age at commencing MMF ($p=0.005$) predicted good response to second-line therapy. In those intolerant to standard therapy (n=63), lower baseline total IgG < 17 g/L ($p=0.008$), lower INR ($p=0.03$), and older age at commencing MMF ($p=0.007$) were associated with complete treatment response.

On multivariable analysis (Table 4) using a cut-off of $p=0.10$ for variable inclusion, in patients commenced on MMF for non-efficacy of standard therapy, the only significant independent predictor of response to MMF was older age at commencing MMF ($p=0.006$). In contrast, in those intolerant to standard therapy the only significant independent predictor of response to MMF was a lower baseline IgG level ($p=0.03$).

Discussion:

To our knowledge this is the largest study to examine predictors of treatment response in AIH patients receiving MMF as rescue therapy because of intolerance or inefficacy to standard therapy. The main findings were that among the 105 AIH patients receiving MMF, 60% of whom achieved remission, younger age and higher pre-treatment IgG levels and higher INR were independently associated with a significantly lower likelihood of treatment response. In addition, we found that the relationship between pre-treatment IgG levels and treatment response was most marked among those receiving MMF for intolerance to standard therapy rather than those who had failed previous treatment, whilst age at commencing MMF, was most relevant in predicting response among those treated for inefficacy of standard therapy. Furthermore, we found that those with cirrhosis had similar responses to MMF compared to those without cirrhosis, and that pre-treatment transaminase levels did not predict the response to second line therapy.

The only other large series of AIH patients receiving MMF rescue therapy found a similar response rate of 69%¹⁸, and of interest this result was only marginally lower than the 72% complete response rate reported by Zachou et al²⁵ in their study of MMF as first-line therapy. The study by Efe et al of 121 patients on MMF rescue therapy had a large number of patients with cirrhosis or pre-cirrhosis (75% prior to starting MMF). Despite this, pre-MMF IgG levels and biochemistry were quite low in their cohort and INR data was not reported in the context of our observation that

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lower IgG and INR values are associated with a more responsive phenotype¹⁸. Data was not provided in this study on the predictors of response to MMF rescue therapy to validate our results.

Our finding that patients with higher IgG levels had a poorer response to MMF rescue therapy may reflect a more aggressive disease and/or immunoreactivity in these patients. One of the largest studies of the natural history of AIH²⁶ showed that predictors of remission on standard first-line therapies included HLA haplotype DRB1*04:01, older age, absence of cirrhosis, and absence of soluble liver pancreas antigen. They also found that younger patients were more likely to relapse. However, their study did not examine baseline IgG levels or INR. There is also evidence to show that long term prognosis is associated with histological activity, and it is interesting to speculate that this may correlate with IgG levels as both reflect the severity of liver inflammation²⁷. Certainly, untreated AIH with high IgG levels (greater than twice upper limit of normal), confluent necrosis on liver biopsy, and high transaminase levels, has been shown to have a very poor prognosis²⁸⁻³¹. Similarly, lower IgG levels appear to be predictive of histological resolution³², a lower frequency of relapse³³⁻³⁷, and were predictive of successful treatment withdrawal³⁸. Other studies have shown that older patients are often less symptomatic at presentation, and often biochemically responsive to therapy^{14,39-42}, consistent with our finding of better responses in older patients. However, our results need to be interpreted with some caution as the high IgG correlation with good response to MMF was not demonstrated in those with a poor response to standard therapy, only in those intolerant of corticosteroids and/or thiopurines.

Ours is a real-world cohort of AIH patients that includes patients who have a poor response to standard therapy, as well as those intolerant to the side effects. We pooled these two groups as their overall response rate to MMF was the same¹⁷. However, when we analysed the data separately, there were differences in the factors predictive of response to MMF, with patients intolerant to standard therapy more likely to respond if they had lower IgG levels, and refractory patients more likely to respond if they were older at diagnosis and/or when starting MMF.

Histologic cirrhosis is associated with reduced long-term survival of AIH patients in some^{26,40,43} but not all^{44,45} studies; however, in this large study cirrhosis status did not confer a negative prognosis to treatment response once other potentially confounding factors were taken into account. This result is similar to that of Zachou et al who failed to show any association between the response to MMF as *first-line* therapy and the presence or absence of cirrhosis²⁵, and that of Ngu et al who found biochemical response rates to conventional therapy were similar between those with and

without cirrhosis⁴⁵. Our finding is not surprising given that bilirubin and aminotransferase levels were not predictive of response; however, a lower baseline INR did predict better response even in patients with previously suboptimal treatment efficacy. The clinical implications are that the INR should be taken into consideration when assessing likelihood of treatment response in patients requiring second line therapy^{46,47}.

The strengths of this study are its multicentre, real-world design and cohort size, as it is the second largest study to date to report on the outcomes of second line therapies in AIH patients. Real-world studies such as this and the recent study by Dyson and colleagues from the United Kingdom⁴⁸, provide important insights into the management of AIH across a wide spectrum of hospitals, and in particular the treatment options and results when standard therapy fails; a point highlighted in a recent editorial by Hupa-Breier et al⁴⁹. While most AIH subjects tolerate first-line treatment well, and achieve remission, for the 20% who do not, it is important to better understand the factors that influence the effectiveness of second line therapies in order to optimise treatment choice and facilitate patient counselling and expectations. Our study has shown that only 60% of patients receiving MMF as second line therapy achieve complete remission¹⁷, highlighting the importance of identifying the best candidates and looking at possible other agents such as calcineurin inhibitors where necessary. This point was emphasised in a recent article by Janmohamed et al who stressed the importance of intensifying efforts towards identifying patients at greatest risk of treatment failure in order to provide rational personalised management for AIH patients at greatest risk of a poor outcome⁵⁰.

We acknowledge that this study has its limitations, as the data have been collected retrospectively, and as a consequence there are missing data in some fields. For example, whilst liver biopsy data were available on more than 80% of patients at the time of diagnosis, limited histologic data was available for analysis at the time of starting MMF or to document remission. Moreover, this study does not have longer-term outcome data such as changes in liver histology, transient elastography, or serological markers of fibrosis on MMF therapy. Additionally, we did not collect data on the corticosteroid dose or the number of patients who ceased corticosteroids completely while receiving MMF as part of this work. The sub-analysis of intolerant versus refractory patients has limitations in interpretation due to smaller numbers, and we recommend cautious interpretation about the observed differences. In spite of these limitations, this is the first study to elucidate the characteristics of patients most likely to respond to second line MMF therapy.

Conclusions

In conclusion, the best predictors of poor response to second line therapy with MMF in AIH are a higher total IgG level and higher INR value. MMF remains an excellent treatment option for AIH patients refractory to or intolerant of standard therapy; however, future studies looking at the long term outcomes of these patients are required. Effective treatment alternatives for patients who fail second line therapy remains a high priority.

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MMF treatment outcome

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Characteristics	Responders (n=63)	Non-responders (n=42)	P#	Table 1. Demographic, clinical, and laboratory characteristics of patients with autoimmune hepatitis receiving mycophenolate mofetil rescue therapy according to treatment outcome
Clinical features*				
Female gender, n (%)	55 (87)	37 (88)	0.90	
Age at diagnosis of AIH, years	56 (48-63)	41 (27-53)	<0.0001	
Age at starting MMF, years	57 (49-64)	46 (34-53)	<0.0001	
Ethnicity: Caucasian/other, n (%)	58/5 (92/8)	34/8 (81/19)	0.09	
Cirrhosis [‡] Y/N, n (%)	18/42 (30/70)	20/22 (48/52)	0.07	
Baseline laboratory results [†]				
Aspartate transaminase, IU/L	61 (39-113)	97 (66-235)	0.009	
Alanine transaminase, IU/ml	97 (52-311)	177 (100-294)	0.046	
Total bilirubin, μmol/L	13 (9-25)	27 (15-52)	0.003	
Albumin, g/dl	39 (34-42)	37 (31-42)	0.32	
INR	1.0 (1.0-1.2)	1.2 (1.1-1.4)	0.018	
Creatinine, μmol/L	70 (61-80)	66 (60-71)	0.24	
Immunoglobulin G, g/L	12 (9.9-19)	21 (16-29)	0.0001	
Hemoglobin, g/L	137 (130-142)	137 (126-147)	0.85	
Platelet count, x10 ⁹ /L	233 (193-265)	211 (154-305)	0.28	
Prior treatment details, n (%)				
Combination therapy	61 (97)	42 (100)	NS	
Calcineurin inhibitor	3 (5)	2 (5)	NS	
Indication for MMF, n (%)			0.63	
Inefficacy of standard therapy	24 (38)	18 (43)		
Intolerance to standard therapy	39 (62)	24 (57)		
Dosing of MMF				
Median starting dose (IQR), g/d	1.0 (0.5-1.0)	1.0 (1.0-1.0)	0.81	
Median maximal dose (IQR), g/d	2.0 (1.25-2.0)	2.0 (1.0-2.0)	0.35	
Median follow up (IQR), months	34 (19-76)	30 (11-69)	0.24	

* Results given as median (IQR); IQR=interquartile range

¶ Baseline values are those immediately prior to starting MMF

‡ in 3 patients cirrhosis status was not determined

Refers to comparison between responders and non-responders

Table 2. Univariable and multivariable analyses of predictors of response to MMF rescue therapy

Parameter	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Gender: Male	1.07	[0.33-3.55]	0.90			

Age at diagnosis, years	1.06	[1.03-1.09]	0.0001			
Age at starting MMF, years	1.07	[1.03-1.11]	0.0001			
Age at starting MMF ≥54 years	5.96	[2.5-14.4]	0.0001	25.3	[2.0-318]	0.01
Ethnicity: Non-Caucasian	0.37	[0.11-1.21]	0.10	0.16	[0.01-1.82]	0.12
Cirrhosis status: Yes	0.47	[0.21-1.07]	0.07	0.35	[0.07-1.65]	0.14
Indication for MMF: Intolerance	1.22	[0.55-2.7]	0.63			
Aspartate transaminase, IU/L	0.999	[0.997-1.00]	0.16	1.00	[0.996-1.01]	0.77
Total bilirubin, µmol/L	0.99	[0.99-1.00]	0.16	1.00	[0.97-1.03]	0.98
Albumin, g/dl	1.04	[0.98-1.11]	0.23			
INR level	0.05	[0.004-0.72]	0.03			
INR >1.1	0.27	[0.09-0.79]	0.02	0.8	[0.01-0.73]	0.03
Immunoglobulin, g/L	0.91	[0.85-0.97]	0.004			
Immunoglobulin G ≥ 17 g/L	0.20	[0.07-0.56]	0.002	0.05	[0.01-0.48]	<0.01
Creatinine, µmol/L	1.01	[0.98-1.04]	0.45			
Haemoglobin, g/L	1.01	[0.97-1.04]	0.63			
Platelet count, x10 ⁹ /L	1.00	[1.00-1.00]	0.84			

NB. All laboratory parameters represent baseline readings just prior to commencing MMF

Table 3. Univariable analysis of predictors to response to MMF according to treatment indication

Parameter	Indication for MMF					
	Treatment inefficacy			Treatment intolerance		
	HR	95% CI	P	HR	95% CI	P
Gender: Male	2.11	[0.33-3.55]	0.90	0.53	[0.11-3.16]	0.53
Age at starting MMF ≥54 years	11.2	[2.1-60]	0.005	4.5	[1.5-13.4]	0.007
Ethnicity: Non-Caucasian	0.70	[0.15-3.28]	0.65	0.13	[0.01-1.26]	0.08
Cirrhosis status: Yes	0.47	[0.13-1.69]	0.25	0.48	[0.17-1.40]	0.18
Aspartate transaminase, IU/L	0.998	[0.995-1.00]	0.18	0.999	[0.998-1.00]	0.42

Total bilirubin, $\mu\text{mol/L}$	0.99	[0.985-1.00]	0.30	0.995	[0.97-1.03]	0.41
Albumin, g/dl	1.04	[0.94-1.15]	0.43	1.04	[0.95-1.13]	0.40
INR >1.1	0.37	[0.07-1.97]	0.24	0.19	[0.04-0.87]	0.03
Immunoglobulin G ≥ 17 g/L	0.32	[0.06-1.60]	0.17	0.14	[0.03-0.60]	0.008
Creatinine, $\mu\text{mol/L}$	1.00	[0.96-1.04]	0.95	1.02	[0.98-1.07]	0.32
Haemoglobin, g/L	1.04	[0.99-1.10]	0.10	0.98	[0.93-1.03]	0.36
Platelet count, $\times 10^9/\text{L}$	1.00	[0.997-1.01]	0.25	0.996	[0.989-1.00]	0.24

Table 4. Multivariable analysis of predictors to response to MMF according to treatment indication

Parameter	Indication for MMF					
	Treatment inefficacy			Treatment intolerance		
	HR	95% CI	P	HR	95% CI	P
Age at starting MMF ≥ 54 years	11.6	[2.0-68]	0.006	12.1	[0.71-205]	0.09
Ethnicity: Non-Caucasian				0.02	[0.00-1.38]	0.07
INR >1.1				0.06	[0.003-1.20]	0.07
Immunoglobulin G ≥ 17 g/L				0.04	[0.002-0.71]	0.03
Haemoglobin, g/L	1.05	[0.99-1.11]	0.10			

Figure 1: Flow chart showing the patient cohort, exclusions and subgroups.

APPENDIX:

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In alphabetical order

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