

# Mycophenolate Mofetil vs Azathioprine for Remission Maintenance in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

## A Randomized Controlled Trial

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**A**NTINEUTROPHIL CYTOPLASMIC antibodies (ANCA) are frequently found in patients with Wegener granulomatosis and microscopic polyangiitis. Together, Wegener granulomatosis and microscopic polyangiitis are considered ANCA-associated vasculitis (AAV) due to their similarity in clinical and histological features, prognosis, and treatment. Standard therapy for patients with AAV consists of induction of remission with cyclophosphamide and glucocorticoids, followed by remission maintenance with azathioprine or methotrexate and a tapering course of glucocorticoids.<sup>1,2</sup> Relapses of

For editorial comment see p 2413.

**Context** Current remission maintenance therapies for antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) are limited by partial efficacy and toxicity.

**Objective** To compare the effects of mycophenolate mofetil with azathioprine on the prevention of relapses in patients with AAV.

**Design, Setting, and Participants** Open-label randomized controlled trial, International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitides (IMPROVE), to test the hypothesis that mycophenolate mofetil is more effective than azathioprine for preventing relapses in AAV. The trial was conducted at 42 centers in 11 European countries between April 2002 and January 2009 (42-month study). Eligible patients had newly diagnosed AAV (Wegener granulomatosis or microscopic polyangiitis) and were aged 18 to 75 years at diagnosis.

**Interventions** Patients were randomly assigned to azathioprine (starting at 2 mg/kg/d) or mycophenolate mofetil (starting at 2000 mg/d) after induction of remission with cyclophosphamide and prednisolone.

**Main Outcome Measures** The primary end point was relapse-free survival, which was assessed using a Cox proportional hazards model. The secondary end points were Vasculitis Damage Index, estimated glomerular filtration rate, and proteinuria.

**Results** A total of 156 patients were assigned to azathioprine (n=80) or mycophenolate mofetil (n=76) and were followed up for a median of 39 months (interquartile range, 0.66-53.6 months). All patients were retained in the analysis by intention to treat. Relapses were more common in the mycophenolate mofetil group (42/76 patients) compared with the azathioprine group (30/80 patients), with an unadjusted hazard ratio (HR) for mycophenolate mofetil of 1.69 (95% confidence interval [CI], 1.06-2.70; *P*=.03). Severe adverse events did not differ significantly between groups. There were 22 severe adverse events in 13 patients (16%) in the azathioprine group and there were 8 severe adverse events in 8 patients (7.5%) in the mycophenolate mofetil group (HR, 0.53 [95% CI, 0.23-1.18]; *P*=.12). The secondary outcomes of Vasculitis Damage Index, estimated glomerular filtration rate, and proteinuria did not differ significantly between groups.

**Conclusions** Among patients with AAV, mycophenolate mofetil was less effective than azathioprine for maintaining disease remission. Both treatments had similar adverse event rates.

**Trial Registration** clinicaltrials.gov Identifier: NCT00307645

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AAV occur in 50% of patients within 5 years of diagnosis, and treatment toxicity is common.<sup>3,4</sup> Safe and effective therapies to maintain remission of AAV are a priority.

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Abnormal lymphocyte function is a pathogenic factor in AAV.<sup>5</sup> Mycophenolate mofetil inhibits the inosine monophosphate dehydrogenase DNA synthesis pathway, and is a relatively lymphocyte-specific immunosuppressive therapy.<sup>6</sup> Mycophenolate mofetil is as effective or even more effective than azathioprine in the treatment of systemic lupus erythematosus<sup>7,8</sup> and for preventing organ rejection.<sup>9,10</sup> In AAV, small observational studies and randomized controlled trials reported successful remission induction<sup>11-13</sup> and remission maintenance with mycophenolate mofetil.<sup>14-16</sup> Whether mycophenolate mofetil is more effective than azathioprine for preventing relapses in AAV is uncertain.

An open-label, multicenter, randomized controlled trial (International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitides [IMPROVE]) was conducted to assess whether mycophenolate mofetil reduces the risk of relapse compared with azathioprine in patients with AAV in remission. Our primary objective was to determine whether treatment with mycophenolate mofetil during maintenance of remission resulted in a different risk of relapse of AAV compared with azathioprine. The secondary objectives were to compare the risk of major relapse and serious adverse events between treatment groups.

## METHODS

The IMPROVE trial was conducted at 42 centers in 11 European countries between April 2002 and January 2009 in accordance with the Declaration of Helsinki. All participants provided written informed consent. The study protocol was reviewed and approved by every participating center. Patients with a new diagnosis of Wegener granulomatosis or microscopic polyangiitis seen as inpatients or outpatients at tertiary or academic centers across Europe were recruited for this trial. The diagnosis of Wegener granulomatosis or microscopic polyangiitis complied with definitions from the 1992 Chapel Hill Consensus Conference.<sup>17</sup> Other inclusion

criteria were age of 18 to 75 years at diagnosis and a positive indirect immunofluorescence or enzyme-linked immunosorbent assay test result for ANCA.

Exclusion criteria were previous exposure to cytotoxic drugs; coexistence of other autoimmune diseases; presence of hepatitis B or C or positive test results for human immunodeficiency virus; active mycobacterial disease; previous malignancy; and inability to provide informed consent. Patients were withdrawn for failure to control progressive disease with the induction protocol (1 patient) or for failure to achieve remission by 6 months (6 patients).

## Enrollment and Randomization

Patients were enrolled by the treating physician within 4 weeks of diagnosis of AAV by fax submission of a form, which included information on treatment center and patient demographics, to the central IMPROVE trial office. Patients were randomized to receive open-label mycophenolate mofetil or azathioprine maintenance therapy in a 1:1 ratio with the use of a minimized central-computerized randomization procedure.<sup>18</sup> Randomization was stratified for age, diagnosis (Wegener granulomatosis vs microscopic polyangiitis), and route of cyclophosphamide administration (daily oral vs intravenous pulse).

## Treatment Protocol

The full treatment protocol is available at <http://www.vasculitis.org>. All patients received cyclophosphamide and glucocorticoids for induction of remission. Plasma exchange and/or up to 3000 mg of methylprednisolone over 3 days was allowed for severe disease. Cyclophosphamide could be administered as daily oral or intermittent intravenous doses (based on regimens published by our group<sup>19</sup>) for a maximum of 6 months.

All patients initially received 1 mg/kg/d (maximum 80 mg) of oral prednisolone, which was reduced to 0.75 mg/kg/d after 1 week, 0.50 mg/kg/d after 2 weeks, 0.40 mg/kg/d after 4 weeks, 0.30 mg/kg/d after 7 weeks, 0.28 mg/kg/d after 10 weeks, and 0.25 mg/kg/d after 13

weeks; prednisolone was reduced to 15 mg/d at the start of the remission regimen, tapered to 5 mg/d after 12 months, and was withdrawn after 24 months.

Patients assigned to the azathioprine group were given 2 mg/kg/d of azathioprine (maximum 200 mg), rounded down to the nearest 25-mg increment. The dose was reduced to 1.5 mg/kg/d after 12 months, 1 mg/kg/d after 18 months, and withdrawn after 42 months. Complete blood cell count and transaminases were measured weekly for 1 month, bimonthly for the first year, and then every 3 months. Azathioprine use was stopped for presence of leukopenia ( $<4 \times 10^6/L$ ) until recovery, and then reintroduced with the dose reduced by 25 mg/d. Patients with leukopenia were monitored weekly for a minimum of 4 weeks.

Patients assigned to the mycophenolate mofetil group were given 2000 mg/d of mycophenolate mofetil, reduced to 1500 mg/d after 12 months, 1000 mg/d after 18 months, and withdrawn after 42 months. Complete blood cell count was taken weekly for the first month, biweekly for the second month, and then monthly for the first year, and then every 3 months. Mycophenolate mofetil use was stopped for presence of leukopenia until recovery and reintroduced with the dose reduced by 500 mg/d. Patients intolerant of the initial dose were reduced to 1000 mg/d and increased monthly by 500-mg/d increments to the 2000-mg/d target or the highest tolerated dose. Dose reduction to 1000 mg/d was recommended for a glomerular filtration rate of less than 25 mL/min/kg<sup>-1</sup>. Mycophenolic acid levels were not measured.

## Outcomes

The primary end point was relapse-free survival, defined as the time from remission to the first relapse (major or minor), withdrawal, death or loss to follow-up, or the end of the follow-up period. Disease activity was evaluated using the Birmingham Vasculitis Activity Score, which has 9 domains corresponding to major organ systems (summed scores range: 0-63).<sup>20</sup> Remission was defined as a Birmingham Vasculitis Activity Score of 0 indicating no new or worsened ac-

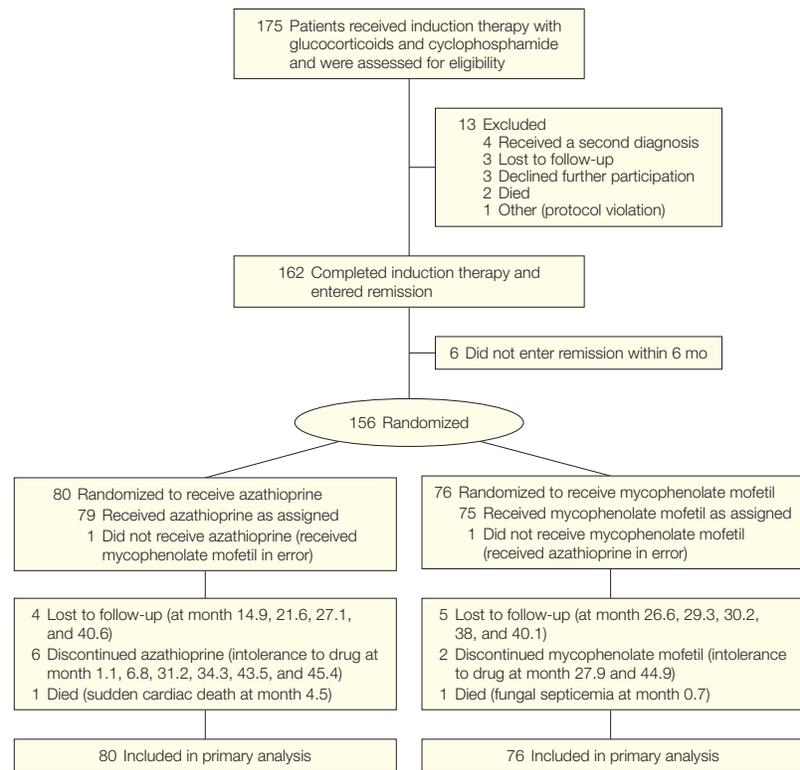
tivity or no persistently active disease manifestations within the previous 28 days. Major relapse was defined as the new appearance of major organ involvement attributable to active vasculitis. Minor relapse required recurrence or new occurrence of less severe disease attributable to active vasculitis (eBox at <http://www.jama.com>).

The main secondary end point was the adverse event rate, including leukopenia, infection, and treatment withdrawal due to drug intolerance. Other secondary outcomes included the assessment of accumulating organ damage using the Vasculitis Damage Index (index range: 0-64),<sup>21</sup> estimated glomerular filtration rate, and proteinuria. Patients were evaluated at 0, 1.5, 3, 6, 9, 12, 18, 24, 30, 36, 42, and 48 months after diagnosis and at relapse. If remission was not reached by 3 months, the induction period was extended to 6 months and the follow-up period was extended to 51 months.

### Statistical Analysis

Data from each patient were analyzed according to their allocated treatment (ie, intention-to-treat analysis). Patients were censored when they reached the primary end point, died, or were lost to follow-up. Patients lost to follow-up were censored at the last visit. Repeated-measures analyses used all available follow-up times with outcome data without imputation of missing data at follow-up times. The primary outcome was assessed using a Cox proportional hazards model with the allocated treatment as the predictor variable. The risk of adverse events was assessed as recurrent failure time in an extended proportional hazards model.<sup>22</sup> The proportional hazards assumption was assessed with scaled Schoenfeld residuals. We used an ordered logistic regression model in which the Vasculitis Damage Index was the outcome and allocated treatment was the sole predictor variable to compare the Vasculitis Damage Index between treatment groups. We compared estimated glomerular filtration rate and proteinuria using multilevel mixed-effects models for repeated measures in which the allocated treatment was a fixed effect.<sup>23</sup>

**Figure 1.** Enrollment, Randomization, and Inclusion in Primary Analysis in IMPROVE Trial



IMPROVE indicates International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitides.

Adherence with allocated treatment was assessed by comparing the proportion of patients that discontinued the allocated treatment using the Fisher exact test and by comparing the percentage of time that patients took at least 85% of the protocol-specified dose. The percentage of the protocol dose received across time points was also calculated with a repeated-measures, mixed-effects model with treatment as the fixed effect. Use of prednisolone was assessed by comparing the cumulative doses with the Wilcoxon rank sum test.

All primary analyses using regression models were conducted with the allocated treatment as the only predictor variable. Prespecified, exploratory, secondary analyses were conducted using age, sex, diagnostic subtype (Wegener granulomatosis or microscopic polyangiitis), route of cyclophosphamide administration during induction, and baseline serum creatinine level as additional predictor

variables. For each effect estimate, 95% confidence intervals (CIs) and 2-sided *P* values were calculated. No adjustments were made to *P* values for multiple comparisons. All analyses were performed using Stata MP version 11 (StataCorp, College Station, Texas).

The sample size estimation was based on an overall relapse rate of 0.105 per patient-year (median time to first relapse: 5 years; associated hazard ratio [HR]: 0.139) in the control group.<sup>4</sup> Under these assumptions, to detect an HR of 0.5 with 80% power and a 2-sided  $\alpha$  level of .05, 150 patients were required, in whom 67 events would occur. Assuming a 10% loss to follow-up, we aimed to recruit 165 patients.

## RESULTS

A total of 175 patients were recruited between April 2002 and July 2004 (FIGURE 1). Thirteen were excluded because they did not complete induction therapy and 6 were excluded be-

cause they did not achieve remission by 6 months. Of the remaining 156 patients, 80 were randomized to azathioprine and 76 to mycophenolate mofetil at study entry. All 156 patients were retained for the analyses. Patient characteristics were similar between treatment groups at diagnosis and at remission (TABLE 1).

The remission induction phase was extended from 3 to 6 months in 72 patients (36 in each group). Median follow-up for both treatment groups from start of maintenance therapy was 39 months (interquartile range [IQR], 0.66-53.6 months), and cumulative exposure to cyclophosphamide and prednisolone during induction was similar between groups. Eight patients crossed over between treatment groups due to drug intolerance before reaching the primary end point; 6 patients from the azathioprine group to mycophenolate mofetil (1 of whom subsequently relapsed) and 2 patients from the mycophenolate mofetil group to azathio-

prine (1 of whom subsequently relapsed).

### Outcomes

Relapses were more common in the mycophenolate mofetil group (42/76 patients; 18 with major and 24 with minor relapses) compared with the azathioprine group (30/80 patients; 10 with major and 20 with minor relapses), with an unadjusted HR for mycophenolate mofetil use of 1.69 (95% CI, 1.06-2.70;  $P = .03$ ; FIGURE 2). After adjustment for the prespecified factors of age, sex, diagnostic subtype, route of cyclophosphamide administration, and baseline creatinine level, the HR for relapses associated with mycophenolate mofetil use was 1.80 (95% CI, 1.10-2.93;  $P = .02$ ). In the mycophenolate mofetil group, 18 major relapses occurred compared with 10 major relapses in the azathioprine group. The unadjusted HR for major relapses associated with mycophenolate mofetil use was 2.14 (95% CI, 0.99-4.64;  $P = .054$ ). The organ systems involved at relapse were not different

between the groups (eFigure at <http://www.jama.com>).

Patients in the azathioprine group spent a median of 327 days (IQR, 0-881 days) below the target dose by 15% or more while patients in the mycophenolate mofetil group spent a median of 174 days (IQR, 0-709 days) below the target dose by 15% or more ( $P = .35$ ; FIGURE 3). The proportion of the target dose received was similar in each group across all time points with patients in the azathioprine group receiving 4% (95% CI, 3%-10%) more relative to the target dose compared with patients in the mycophenolate mofetil group ( $P = .28$ ). Prednisolone exposure was similar in each group at all time points. Patients in the azathioprine group received a mean (SD) cumulative prednisolone dose of 8411 (2457) mg and patients in the mycophenolate mofetil group received 8524 (3299) mg ( $P = .44$ ).

There was no evidence of difference between groups for any secondary out-

**Table 1.** Demographic and Clinical Characteristics of Patients

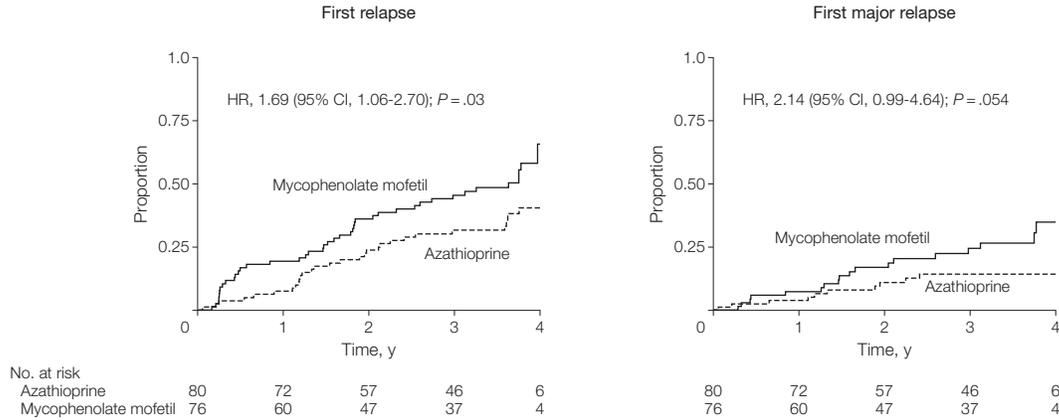
Characteristic	Azathioprine (n = 80)	Mycophenolate Mofetil (n = 76)	P Value
	<b>At Diagnosis</b>		
Age, mean (SD), y	55.1 (15.2)	54.2 (12.8)	
Male sex, No. (%)	58 (72.5)	46 (60.5)	
Diagnosis, No. (%)			
Microscopic polyangiitis	25 (31.3)	31 (40.8)	
Wegener granulomatosis	55 (68.7)	45 (59.2)	
Positive for ANCA, No. (%) <sup>a</sup>			
Myeloperoxidase	23 (28.8)	28 (36.8)	
Proteinase 3	49 (61.3)	41 (53.9)	
BVAS, mean (SD)	16 (11)	14 (11)	
Serum creatinine, median (IQR), mg/dL	2.9 (1.1-3.5)	2.7 (1.2-3.6)	
C-reactive protein, median (IQR), mg/L	68 (13-136)	64 (12-118)	
Cyclophosphamide intravenously, No. (%)	45 (56)	38 (50)	
	<b>At Remission</b>		
Positive for ANCA, No. (%)			
Myeloperoxidase	12 (15.2)	18 (23.7)	.22
Proteinase 3	29 (36.3)	31 (40.7)	.62
C-reactive protein, median (IQR), mg/L	1.8 (0-5.2)	3 (0.88-9.25)	.04
ESR, median (IQR), mm/h	16 (8-27)	23 (9.8-34.3)	.09
Time to start of maintenance, median (IQR), d	97 (90-123)	102 (90-149)	.51
Cumulative cyclophosphamide, median (IQR), mg			
Oral	13 168 (8913-14 063)	13 335 (8800-13 800)	.97
Intravenous	6932 (3200-6651)	6894 (3063-6463)	.42
Cumulative prednisolone, mean (SD), mg	3497 (1107)	3621 (1986)	.63
Plasma exchanges, median (IQR)	(n = 14) 5.5 (5-7)	(n = 11) 5.1 (5-10)	.62

Abbreviations: ANCA, antineutrophil cytoplasmic antibodies; BVAS, Birmingham Vasculitis Activity Score; ESR, erythrocyte sedimentation rate; IQR, interquartile range.

SI conversion factors: To convert C-reactive protein to nmol/L, multiply by 9.524; creatinine to  $\mu\text{mol/L}$ , multiply by 88.4.

<sup>a</sup>Fifteen patients did not have an ANCA value recorded at entry (8 in the azathioprine group and 7 in the mycophenolate mofetil group).

**Figure 2.** Time to First Relapse and First Major Relapse



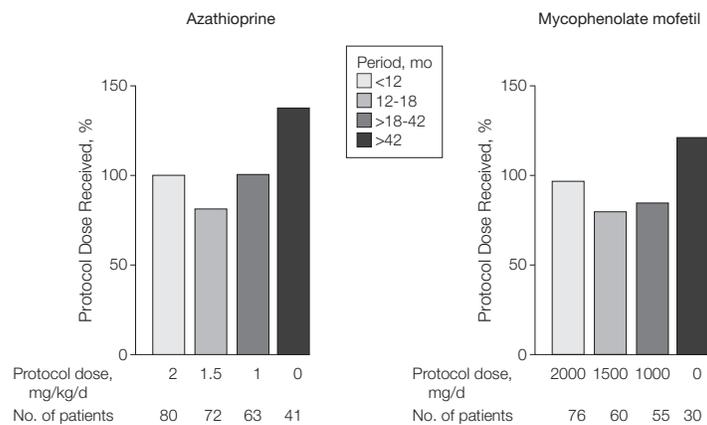
Patients were censored at first relapse or death. CI indicates confidence interval; HR, hazard ratio.

come. The Vasculitis Damage Index increased in both groups from a median of 0 (IQR, 0-0) to a median of 2 (IQR, 0-3) for the azathioprine group and 2 (IQR, 1-3) for the mycophenolate mofetil group at the end of follow-up ( $P=.96$ ). At study end, the median estimated glomerular filtration rate was 52.8 mL/min/1.73 m<sup>2</sup> (IQR, 38.5-70.1 mL/min/1.73 m<sup>2</sup>) for patients in the mycophenolate mofetil group compared with 59.2 mL/min/1.73 m<sup>2</sup> (IQR, 45.2-71.7 mL/min/1.73 m<sup>2</sup>) in the azathioprine group ( $P=.35$ ). The proteinuria of the mycophenolate mofetil group was reduced by a median of 0.82 g/d (IQR, 0.06-1.78 g/d) over the study compared with 0.53 g/d (IQR, 1.13-0.15 g/d) in the azathioprine group ( $P=.26$ ).

**Severe Adverse Events**

The risk of severe adverse events was not significantly different between groups (TABLE 2). There were 22 severe adverse events in 13 patients in the azathioprine group and 8 events in 8 patients in the mycophenolate mofetil group (HR, 0.53 [95% CI, 0.23-1.18];  $P=.12$ ). There were 8 severe infections in 8 patients in the azathioprine group and 3 severe infections in 3 patients in the mycophenolate mofetil group (HR, 0.52 [95% CI, 0.11-2.36];  $P=.40$ ). There were 11 episodes of leukopenia in 7 patients in the azathioprine group and 5 leukopenia episodes in 4 patients in the

**Figure 3.** Percentage of Allocated Treatment Actually Taken



Withdrawal of the allocated treatment later than the protocol-specified time point will result in more than 100% of the protocol dose received.

mycophenolate mofetil group (HR, 0.57 [95% CI, 0.21-1.55];  $P=.27$ ). The mycophenolate mofetil and azathioprine groups were not statistically different with respect to cardiovascular adverse events (HR, 1.17 [95% CI, 0.27-5.04];  $P=.83$ ). Two bladder malignancies and 3 skin cancers (basal or squamous cell carcinomas) occurred in the azathioprine group compared with 1 skin malignancy in the mycophenolate mofetil group (HR, 0.25 [95% CI, 0.02-2.62];  $P=.25$ ).

Drug intolerance led to withdrawal in 6 patients receiving azathioprine (1 diarrhea, 1 vomiting and abdominal

pain, 2 hepatotoxicity, 1 persistent severe leukopenia, 1 rash), and 2 patients receiving mycophenolate mofetil (1 diarrhea and abdominal pain, 1 asthenia and edema) (HR, 2.59 [95% CI, 0.55-12.08];  $P=.25$ ).

There were 2 deaths during the remission maintenance phase. One patient died from fungal septicemia after receiving mycophenolate mofetil for 21 days; another had sudden cardiac death after receiving azathioprine for 136 days.

**COMMENT**

We conducted a randomized controlled trial with long-term follow-up

**Table 2.** Summary of Adverse Events

	Azathioprine <sup>a</sup>		Mycophenolate Mofetil <sup>b</sup>		HR (95% CI)	P Value
	No. of Events	No. of Patients	No. of Events	No. of Patients		
Severe adverse events	22	13	8	8	0.53 (0.23-1.18)	.12
Severe infection	8	8	3	3	0.52 (0.11-2.36)	.40
Any adverse events	97	28	75	22	0.94 (0.61-1.43)	.77
Any infection	37	17	29	12	0.92 (0.42-2.02)	.84
Cardiovascular	4	3	4	3	1.17 (0.27-5.04)	.83
Neoplasia	5	3	1	1	0.25 (0.02-2.62)	.25
Gastrointestinal tract	10	8	10	8	1.27 (0.52-3.08)	.60
Drug intolerance	6	6	2	2	2.59 (0.55-12.08)	.25
Hepatic dysfunction	3	3	0	0	NA	.16 <sup>c</sup>
Leukopenia	11	7	5	4	0.57 (0.21-1.55)	.27
Other	21	8	24	6	1.10 (0.54-2.22)	.79

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, data not available because the model failed to converge.

<sup>a</sup>The number of person-years for this group is 217.

<sup>b</sup>The number of person-years for this group is 187.

<sup>c</sup>Calculated using the Fisher exact test for the incidence rate comparison.

comparing mycophenolate mofetil with azathioprine for the prevention of relapses in patients with AAV. We found that mycophenolate mofetil was less effective at preventing relapses. The effect of mycophenolate mofetil with respect to the risk of relapse was consistent across major and minor relapses and in sensitivity analyses. Furthermore, we found no significant advantages to the use of mycophenolate mofetil in terms of safety or tolerability. Although mycophenolate mofetil is frequently regarded as a potent alternative to azathioprine, we found no evidence to support its use as the initial remission maintenance therapy for patients with AAV.

Our results contradict our hypothesis that mycophenolate mofetil would be more effective than azathioprine for the prevention of relapses. One explanation is that our mycophenolate mofetil regimen provided an inadequate dose. However, our starting dose of mycophenolate mofetil was the same as that found effective in both autoimmune disease<sup>24,25</sup> and solid organ transplantation rejection prophylaxis,<sup>26</sup> and is similar to or greater than doses previously reported for remission maintenance in AAV.<sup>14,16,27-29</sup> Furthermore, in pharmacokinetic studies of mycophenolate mofetil in autoimmune disease, 2000 mg/d (the dose our patients were taking when the majority of relapses oc-

curred) provided adequate trough levels of mycophenolic acid in the majority of patients.<sup>25</sup>

Our findings were not explained by differences between groups in terms of treatment with glucocorticoids or cyclophosphamide during remission induction. Sensitivity analyses that adjusted for potential group imbalances also did not explain the increased risk associated with mycophenolate mofetil. In fact, the adjusted analyses estimated even higher risk with mycophenolate mofetil treatment. Furthermore, the relative dose reductions in immunosuppression were similar between groups and the period in which the greatest number of relapses was seen was during a period when the dose of both immunosuppressive agents was highest (ie, first year after remission was induced) and protocol compliance was similar in both groups. It seems unlikely that these factors were the cause of the increased risk of relapse in the mycophenolate mofetil group.

We did not demonstrate a difference between the mycophenolate mofetil and azathioprine groups with respect to severe adverse events, although there were fewer adverse events in the mycophenolate mofetil group. The azathioprine adverse event rate in our study (42.5%) was comparable with that reported with azathioprine previously.<sup>2</sup> Our trial was not powered to

demonstrate a difference in adverse events so we cannot exclude the presence of lower toxicity with mycophenolate mofetil. However, if mycophenolate mofetil causes fewer adverse events, this would come at a price of inferior efficacy.

Our study has several strengths. It is among the largest trials in AAV maintenance therapy, to our knowledge, and has the longest follow-up and broad eligibility criteria, suggesting the results may be generalized to a broad population of patients with AAV. Our results appear robust because they are consistent across secondary outcomes and sensitivity analyses and the observed number of events was consistent with the assumptions of our sample size estimate. Furthermore, we are confident that mycophenolate mofetil is not a justified first-choice maintenance therapy over azathioprine because we not only failed to demonstrate that mycophenolate mofetil reduced the risk of relapses but actually increased the risk of relapse.

Higher mycophenolate mofetil dosing or the addition of trough level monitoring may improve the efficacy of mycophenolate mofetil.<sup>25,30</sup> However, to reverse the observed qualitative treatment effect (ie, to show mycophenolate mofetil was superior), an improved mycophenolate mofetil regimen would have had to prevent 26 relapses

in the mycophenolate mofetil group (ie, a reduction from 55% with relapse to 21% with relapse). Such an improvement with an increase in dose or tailored monitoring may render mycophenolate mofetil equally efficacious to azathioprine but is unlikely to render it superior and would increase the costs and/or adverse events associated with mycophenolate mofetil treatment substantially.

The results of our study must be considered within the context of several limitations. Our trial was conducted as an open-label study. However, the purpose of blinding is to prevent contamination of the allocated treatments, bias in the application of co-treatments, or bias in outcome assessment. In our trial, there was no evidence of difference between groups in the number of patients that crossed over (ie, received the treatment they were not randomized to) or the receipt of adjuvant treatments (such as glucocorticoids). Similarly, bias in the assessment of outcomes is unlikely because the outcomes were all adjudicated by an expert panel that had access to all disease activity assessments for all patients. Our trial, although among the largest in AAV, still had a relatively small sample size. However, as discussed, it is unlikely that a larger trial would reverse the direction of the effect we demonstrated. Although we did not record ethnicity, patients with AAV at the participating centers are almost exclusively white, potentially reducing generalizability to other ethnicities. However, evidence that the efficacy of fixed doses of mycophenolate might vary significantly by ethnicity in autoimmune diseases is limited.<sup>7</sup>

Contrary to the hypothesis that mycophenolate mofetil is more efficacious than azathioprine without compromising patient safety, we have shown that mycophenolate mofetil is less effective than azathioprine for the prevention of relapses in AAV. Although mycophenolate mofetil may be considered in refractory cases, it should not be considered the first-line remission maintenance therapy in AAV.<sup>2,31</sup>

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**Author Contributions:** Drs Hiemstra and Walsh had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. These 2 authors contributed equally to the manuscript.

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**Online-Only Material:** The eBox and eFigure are available at <http://www.jama.com>.

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