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Mycophenolate Mofetil for Ocular Inflammation

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Ocular inflammation is a common cause of ocular morbidity and vision loss, with uveitis alone accounting for approximately 10% of new cases of blindness in the US.[1] Because many of those affected are children or working age adults, the years of potential vision lost and economic impact of each case of vision loss is higher, on average, than with eye diseases of the elderly. Immunosuppressive drugs are used to treat many potentially blinding cases of ocular inflammation, primarily in three settings: as corticosteroid-sparing therapy when the disease can be controlled with oral corticosteroids, but substantial toxicity is expected at the dose required; for inflammation that is recalcitrant to corticosteroids; and for management of specific diseases expected to fare poorly with corticosteroids alone.[2]

Mycophenolate mofetil, an immunosuppressive drug that is increasingly popular for management of various types of non-infectious ocular inflammation,[2–6] suppresses the immune system by selectively inhibiting the purine biosynthesis enzyme inosine monophosphate dehydrogenase (IMPDH), thereby resulting in depletion of guanosine nucleotides that are essential for purine synthesis used in the proliferation of B and T

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lymphocytes.[7,8] Extraocular applications of mycophenolate mofetil therapy include prevention of renal allograft rejection, psoriasis, and various autoimmune diseases.[9,10]

Small to medium-sized studies evaluating mycophenolate mofetil for ocular inflammation suggest that it often is an effective corticosteroid-sparing agent in this setting, and may be faster acting than methotrexate and azathioprine.[11–15] In children, the drug is generally well-tolerated, typically without significant end organ toxicity.[16] However the precision of these studies have been limited by the relatively small number of patients studied, and estimates of success may be inflated in some instances where some patients used additional immunosuppressive agents simultaneously.

In order to better characterize the effectiveness of mycophenolate mofetil for ocular inflammation in a large population of patients, we report here the outcomes of 236 patients followed from the point of initiation of mycophenolate mofetil as the only non-corticosteroid immunosuppressive therapy for patients with ocular inflammatory diseases at four tertiary ocular inflammation centers in the United States.

Methods

Study population

All patients with non-infectious ocular inflammatory disease who had started receiving treatment with mycophenolate mofetil during the study as the sole non-corticosteroid immunosuppressive agent at three ocular immunology and uveitis clinics and an approximate 40% random sample of such patients from a fourth center were selected to be the study population. This group of patients was nested within a larger study, the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study, the methods of which have been reported previously.[17] Patients from a fifth center participating in the parent study were excluded, because the co-management approach used by the center—wherein many follow-up visits were conducted outside the center—markedly biased ascertainment of the time-to-treatment response.

Data collection

Trained, certified, expert reviewers reviewed the medical records of all patients, and entered information for each eye of every patient at every visit into a custom Microsoft Access database (Microsoft Corporation, Redmond, Washington). Demographic information obtained during the initial visit and details of all medications in use at every clinic visit were recorded. Details of ocular inflammation activity status—based on clinical evaluation using external, slit-lamp and dilated fundus examination—also were recorded. Sequelae of ocular inflammation were noted when present.

Follow-up and main outcome measures

Patients were followed until they stopped using mycophenolate mofetil or started using an additional non-corticosteroid immunosuppressive agent; had an event of interest; stopped attending a study clinic; or the end of data collection was reached—whichever occurred first. The primary outcome measures were: success in gaining control of inflammation; success in maintaining control of inflammation after tapering systemic corticosteroids to specified thresholds (“corticosteroid-sparing effects”); and discontinuation of treatment. Control of inflammation was categorized at each visit as “active,” “slightly active,” or “inactive” for every eye at every visit. Descriptors such as “active,” “uncontrolled,” “worsening inflammation,” or “disease progression” in the case notes were counted as indicating “active inflammation.” Inflammatory activity was scored as “slightly active” when inflammation was minimally present, described in the patient notes using descriptors such as “mild,” “few,” “trace cells,”

or “trace activity.” Inflammation was defined as “inactive” when descriptors such as “quiet,” “quiescent,” “no cells” and “no active inflammation” were used.[18, 19] When data regarding activity could not be ascertained from case notes, data regarding activity at the visit in question were entered as missing. Corticosteroid–sparing effects were evaluated based on the time-to-reduction of the prednisone dose to 10 mg, 5 mg, or 0 mg while maintaining inactivity of the ocular inflammation, among those not meeting each respective criterion for success at the outset. Prednisone-equivalent doses of alternative corticosteroids were included in these evaluations when required.20 When applicable, dates of discontinuation of mycophenolate mofetil and the reasons for the discontinuation documented in the charts were noted.

Statistical Methods

SAS version 9.1 (SAS Corporation, Cary, North Carolina) was used for all analyses. The frequencies of demographic and clinical characteristics at enrollment among patients treated with mycophenolate mofetil were tabulated. The benefits of therapy were evaluated based on time-to-success (control of inflammation and corticosteroid-sparing effects). A time-to-failure approach was used for time-to-discontinuation of mycophenolate mofetil. In the primary analyses, outcomes were accepted only when observed at 2 or more visits spanning at least 28 days, to avoid the error of including transient improvements and brief interruptions in therapy as successes or failures.

The Kaplan–Meier method was used to estimate the proportion of patients who achieved success or experienced failure at or before six and 12 months of therapy. Incidence rates, by-person and/or by-eye, were calculated as the number of events divided by the person- or eye-years of observation. Cox regression was used to calculate crude and adjusted hazard ratios (HRs) for occurrence of major outcome events, in relation to potentially explanatory covariates.

Results

During follow-up, 236 patients started mycophenolate mofetil as a single (non-corticosteroid) immunosuppressive treatment. Their characteristics at the time when mycophenolate mofetil was started are given in Table 1. The median age was 47.1 years (range 8.1 – 84.2 years); 64% were female and 67% were Caucasian. The mean duration of inflammation prior to starting mycophenolate mofetil was 3 years. Bilateral involvement was present in 68% of patients; 130 (32.7%) patients had a visual acuity of 20/50 or worse. The primary site of ocular inflammation was as follows: 48 (20%) had anterior uveitis, 28 (12%) intermediate uveitis, 94 (40%) posterior or panuveitis, 33 (14%) scleritis, 18 (8%) mucous membrane pemphigoid, and 15 (6%) had other forms of inflammation.

Patients were followed for a median of 259 days while taking mycophenolate mofetil as a single non-corticosteroid immunosuppressive agent (range, 91 – 555 days). Table 2 summarizes our observations regarding successful control of inflammation and the corticosteroid-sparing results achieved with mycophenolate mofetil therapy among the inflammatory site categories, from a by-patient perspective. The corresponding by-eye results are given in Supplemental Table 1 available online at www.ajo.com. Among patients with either active or slightly active inflammation at the start of follow-up, complete control of inflammation sustained over at least two visits spanning at least 28 days was achieved within six months for 53% of patients overall. The proportion with sustained, successful control of inflammation within six months, by site of inflammation was as follows: anterior uveitis (55%), intermediate uveitis (65%), posterior or panuveitis (51%), scleritis (49%) and ocular mucous membrane pemphigoid (41%). At one year (see Table 2), inflammation was controlled completely in 73% of patients overall (anterior uveitis (72%), intermediate uveitis (77%), posterior or panuveitis (71%), scleritis (86%) and ocular mucous membrane pemphigoid (71%). When the criterion for success was broadened to include an improvement from active to either inactive or slightly active inflammation, the

overall likelihood of sustained success by six months was 78%. Using this success criterion, the number of patients meeting success criteria continued to rise after 6 months of therapy, with 91% achieving success by 12 months of therapy.

Regarding corticosteroid-sparing success, sustained complete inactivity of inflammation over at least two visits spanning at least 28 days after discontinuing prednisone was observed in fewer than 5% of patients within six months of therapy (12% by 12 months). However, 27% of patients maintained complete control of inflammation on prednisone ≤5 mg/day (44% by 12 months), and 41% at ≤10mg/day (55% by 12 months). Broadening corticosteroid-sparing "success" to include patients maintaining either an inactive or slightly active status after tapering prednisone, 86% of patients maintained either inactive or slightly active inflammatory status on 10 mg/day or less of prednisone by 6 months. In achieving corticosteroid-sparing goals, patients with uveitis tended to fare better than patients with scleritis or pemphigoid (see Table 2), although a substantial proportion of patients in all categories achieved treatment goals. Removing the requirement that success be sustained for at least 28 days, to correspond to the approach used in previous publications,[11,12,14] complete inactivity after tapering prednisone to ≤10mg was observed at one or more visits within 6 months in 69% (95% CI 60%–77%) of patients; the difference between 41% and 69% proportions with corticosteroid-sparing success primarily arose from reactivation of inflammation by the second visit after a single visit where success criteria had been met. Discontinuation of mycophenolate mofetil due to clinician-defined remission of disease was seen in 14 patients (4.8%/person-year).

Among 21 patients whose mycophenolate mofetil dose was reduced after being maintained at a usual dose, sustained corticosteroid-sparing success (complete control of inflammation at a dose ≤10mg prednisone) was achieved for only 14%. Among 38 patients whose dosage was increased after an initial starting dose, 21% of achieved sustained corticosteroid-sparing success thereafter. A second immunosuppressive agent was added to mycophenolate mofetil for 41 patients (17.4%). One hundred fourteen (48.3%) patients were still receiving mycophenolate mofetil as a single, non-corticosteroid immunosuppressive agent at the end of follow-up.

Multiple regression analyses of time-to-treatment success (based on control of inflammation or corticosteroid-sparing success) are given in Table 3 and Supplemental Table 2 (available online at ajo.com). African-American patients were about 40% as likely to achieve corticosteroid-sparing success when compared to Caucasian patients ($p<0.05$ for all prednisone doses examined), and tended to be less likely to gain complete control of inflammation (adjusted hazard ratio (HR)=0.62, 95% confidence interval (CI): 0.32 – 1.19). However, for achievement of outcomes based on reduction of inflammation to either the slightly active or inactive levels, outcomes were similar for African-Americans and Caucasians. Adults ages 18–39 years tended to respond less well than other age groups, but most comparisons were not statistically significant. Patients with anterior uveitis tended to achieve success criteria more often than with other forms of inflammation, but few of the comparisons were statistically significant, even without adjusting for multiple comparisons.

As expected, prior use of alternative immunosuppressive agents tended to be associated with a lower likelihood of treatment success. Patients who had prior treatment with alkylating agents responded especially poorly to mycophenolate mofetil, with 70% lower likelihood of treatment success when compared with patients who had never been previously treated with non-corticosteroid immunosuppressive drugs. However, patients who previously had received different antimetabolites had a likelihood of success similar to that of patients who had not taken immunosuppressive drugs previously.

Mycophenolate mofetil was discontinued by 81 (34%) patients during follow-up (see Table 4). Among patients with known reasons for discontinuation, the two most common causes for discontinuation of the drug were failure to control ocular inflammation (23 patients, 13.1% of patients within the first year) and side effects (28 patients, 12% of patients within the first year). Gastrointestinal upsets and bone marrow suppression were the most frequently observed side effects, leading to discontinuation of therapy among 2.5% and 1.7% of patients respectively within 1 year of starting mycophenolate mofetil. In addition, 11.3% of patients discontinued mycophenolate mofetil for unknown reasons. None of the patients in this cohort were observed to develop an opportunistic infection while taking mycophenolate mofetil therapy.

Discussion

The effectiveness of mycophenolate mofetil for ocular inflammation has been reported in three prior medium-sized cohort reports,[11,12, 14] which differed from our methodology by including patients on combination immunosuppression in their series, and by not requiring that control of inflammation be sustained before counting a patient as achieving corticosteroid-sparing success. Among 73 patients who received mycophenolate mofetil as therapy for ocular inflammation, corticosteroid-sparing success was achieved by 82% and 70% of patients ≤10 mg and the ≤5 mg prednisone thresholds respectively, the majority within 6 months, and 40% were able to discontinue prednisone completely.10 In an overlapping group of 129 patients on mycophenolate mofetil therapy, 70% achieved corticosteroid-sparing success after 6 months at the ≤10 mg prednisone level, and 12% were able to completely discontinue prednisone within 6 months.[9] These reports were from one of the centers participating in the SITE Cohort Study; patients who started on mycophenolate mofetil during observation and were not on combination immunosuppressive therapy would be included in this report. At a different center, corticosteroid-sparing success (≤ 10 mg prednisone) among 100 patients treated with mycophenolate mofetil was achieved in 68% by 6 months and 85% by 1 year.[14] Our results appear less favorable than these reports because we used a more conservative definition of success, in which patients with transient improvement were not counted as successes. However, when success at any visit was studied in a sensitivity analysis, to mimic the success definitions used in the prior reports, our results were within the confidence intervals on the estimates of these reports. Because non-sustained control of inflammation is not truly a success, our results may be a more robust estimate of the benefits that can be expected with mycophenolate mofetil therapy than the estimates of the previous series. Even using our most conservative approach, successful control of inflammation was obtained in 53% of patients within six months. Success was achieved in over 90% within 12 months if sustained maintenance of suppression to a level of slight activity is counted as a success.

Galor, *et al*, previously have reported that scleritis and posterior/panuveitis were more likely to gain corticosteroid-sparing success with mycophenolate mofetil in comparison with other antimetabolite treatments.[11] As expected, the SITE Cohort patients from this center followed a similar (but not statistically significant) pattern. However, in the overall cohort, the beneficial effects of mycophenolate mofetil did not vary by the site of ocular inflammation consistently. The earlier, smaller report from the same center by Thorne, *et al*, also had found that the proportions of patients with corticosteroid-sparing success were relatively similar among a similar group of diagnoses studied, with the exception of those with orbital disease.[12]

Mucous membrane pemphigoid is a challenging disease with a guarded prognosis. Of the 18 (7%) ocular pemphigoid patients treated with mycophenolate mofetil in our cohort, complete control of inflammation was achieved in 70% by one year. During a similar period of observation, 83% of 94 patients with ocular pemphigoid achieved successful control of inflammation with a combination of immunosuppressive drugs that included mycophenolate mofetil.[21] In a larger series of 115 patients with ocular pemphigoid patients treated with various

immunosuppressive drugs, cyclophosphamide therapy was more successful (69% success) than mycophenolate (59% success)15. In both of these studies, mycophenolate had the least side-effects among the immunosuppressive drugs that were used. These results suggest that mycophenolate mofetil is reasonably effective for ocular pemphigoid, and may be a reasonable initial choice for management of cases that are not immediately vision-threatening, based on its relatively favorable side effect profile compared with cyclophosphamide.22,23 However, because cyclophosphamide likely was used preferentially for the most difficult cases, the difference in effectiveness between cyclophosphamide and mycophenolate mofetil for ocular pemphigoid may be greater than suggested by the numbers reported.

Patients who were treated with either alkylating agents or T-cell inhibitors were found to respond to mycophenolate mofetil substantially less often than patients not previously treated with immunosuppressive drugs. Disease which could not controlled by these agents may have been more severe and therefore less likely to respond to mycophenolate mofetil. However, prior use of other anti-metabolite immunosuppressive drugs was not associated with a difference in the subsequent effectiveness of mycophenolate mofetil in controlling ocular inflammation. A previous report from one of the centers participating in the SITE Cohort Study has confirmed that patients previously treated with methotrexate often respond to subsequent mycophenolate mofetil therapy,[24] suggesting that mycophenolate mofetil is a reasonable next step for patients failing methotrexate.

Mycophenolate mofetil was well tolerated by most patients, with approximately 12% of patients stopping treatment because of side effects within the first year of treatment, and few thereafter. These numbers are probably slightly underestimated, given that some of the 8.5% of patients who stopped mycophenolate mofetil within one year for unknown reasons may have had toxicity. Gastrointestinal upset, the foremost cause for discontinuation of therapy, resulted in discontinuation among fewer than 3% of patients within a year of therapy. The toxicities observed typically were reversible with discontinuation of mycophenolate mofetil. Toeh *et al* also reported a low incidence of intolerance resulting in dose reduction or discontinuation of mycophenolate mofetil (0.09/PY).[14] The pattern of side effects in their cohort was similar to the pattern in ours, except that one of their patients developed cytomegalovirus retinitis and another developed lower limb sepsis while taking mycophenolate mofetil. Each of these occurred in patients receiving combination immunosuppression, not mycophenolate mofetil monotherapy (AD Dick, personal communication to JH Kempen, April 30, 2009). No opportunistic infections requiring discontinuation of therapy occurred in our series. The United States Food and Drug Administration recently has required that a warning be distributed with prescriptions of mycophenolate mofetil, in part because of reports of cases of progressive multifocal leukoencephalopathy (PML) in renal transplant patients receiving the drug. However, no cases of PML have been reported among ocular inflammation patients to the best of our knowledge.

Our comprehensive review of the risk of cancer with immunosuppressive therapy concluded it is unlikely (based on a limited available evidence base) that mycophenolate mofetil increases the risk of cancer in ocular inflammation patients, and that some aspects of the mechanism of mycophenolate could be protective against cancer.[22] Our study evaluating mortality risk following immunosuppressive therapy in patients with ocular inflammation did not find an increased risk of either overall (HR=0.90, 95% CI: 0.48 – 1.68) or cancer mortality (HR=0.83, 95% CI: 0.20 – 3.52) following use of mycophenolate mofetil.23 The former is based on a limited number of reports, and the latter has wider confidence intervals than would be desired, because mycophenolate mofetil is a newer drug than alternative immunosuppressive agents, and less experience is available. Nevertheless, it is encouraging that the best estimates of the hazards of overall and of cancer mortality following use of mycophenolate mofetil are no greater than the hazards of these events among ocular inflammation patients who never used

immunosuppressive therapy. Thus, the available data suggest that serious morbidity is rare when systemic mycophenolate mofetil monotherapy for ocular inflammation is used following published guidelines2, and that the risk of morbidity is probably much lower than the morbidity associated with long-term, high dose systemic corticosteroids. Unlike corticosteroids, recent publications have reported that mycophenolate mofetil does carry a risk for congenital anomalies,25,26 so withdrawal of mycophenolate mofetil before planned pregnancy and use of birth control during therapy is mandatory.

The major limitations of this study arise from its retrospective, observational design. Because the indications for choosing mycophenolate mofetil rather than an alternative immunosuppressive drug are unknown, we cannot be certain whether the clinicians tended to use mycophenolate mofetil for more severe, less severe, or average cases, making it difficult to compare results directly with those for other agents. Cases referred to the participating tertiary centers are expected to be more severe on average than those expected to be encountered in a primary ophthalmology setting, so our results are most generalizable to tertiary uveitis practices—results may have been better had we been able to study a non-tertiary population. The survival analysis also assumes that patients stopping treatment would have the same outcome as those continuing treatment, whereas those stopping for failure likely did not have as good of an outcome subsequently, suggesting that our estimates are slightly better than the reality. These limitations are applicable to prior reports as well. The more conservative definition of treatment success used in this report reduces the apparent success of mycophenolate therapy with respect to prior reports, but is probably a more realistic estimate of the likelihood of treatment success in a tertiary setting. However, “success” is substantially higher if patients with minimal residual inflammation are considered successes. While the SUN consensus panel[27] has defined “inactive” inflammation with respect to anterior chamber cells, “inactive” has yet to be defined by a consensus group with respect to vitreous, scleral or other sites of inflammation. We have used for our primary analyses an approach similar to the conservative approach suggested by the SUN group for anterior chamber inflammation, and extended it to involve other sites of inflammation. “Slightly active” inflammation also has been addressed as a separate category so that results can be compared to reports which include cases with minimal signs of inflammation as a treatment success.

Strengths of the study include the large number of observations compared with previous reports, improving the precision of estimates regarding the outcomes studied. Data collection was highly standardized, using an extensive array of quality control mechanisms, in order to optimize data quality within the constraints of a retrospective design. We also evaluated the effect of mycophenolate mofetil therapy without the potential confounding effects of additional immunosuppressive agents.

To summarize, these results suggest that mycophenolate mofetil given as a single non-corticosteroid immunosuppressive agent is likely to result in complete, sustained control of inflammation in an estimated 53% of patients with ocular inflammation within 6 months after initiating therapy, and 73% by one year. Within six months and one year respectively, approximately 40% and 55% of patients were able to lower their corticosteroid treatment to acceptable levels while maintaining sustained, complete control of inflammation. As with other immunosuppressive drugs, the time until treatment success is gained can be several months.[11,19,25] The drug was well-tolerated by most patients, with 12% stopping treatment because of side effects in a year’s time, side effects which typically were reversible. Evidence that suggests a low risk of severe side effects with mycophenolate mofetil given for ocular inflammatory diseases is accumulating. Because the indications for selection of one immunosuppressive agent versus another are unknown, a randomized controlled trial evaluating the incremental cost-effectiveness of mycophenolate mofetil relative to alternative, less expensive immunosuppressive treatments would provide valuable guidance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Patient and Eye specific Characteristics at the Time of Starting Mycophenolate Mofetil

Characteristic	Anterior Uveitis	Intermediate Uveitis	Posterior /Panuveitis	Scleritis	MMP[a]	Other	Total
Person Specific Characteristics							
Patient Number	**48**	**28**	**94**	**33**	**18**	**15**	**236**
Median age, years (range)	34.1 (8.1 71.4)	44.3 (19.8 – 75.4)	48.0 (8.5 – 80.3)	56.2 (19.3 – 72.7)	70.6 (45.9 – 84.2)	39.4 (13.2 – 69.1)	47.1 (8.1 – 84.2)
Gender, % Female	38 (79.2%)	16 (57.1%)	56 (59.6%)	22 (66.7%)	9 (50.0%)	9 (60.0%)	150 (63.6%)
Race, % Caucasian	29 (60.4%)	20 (71.4%)	60 (63.8%)	22 (66.7%)	16 (88.9%)	11 (73.3%)	158 (66.9%)
Race, % Black	12 (25.0%)	5 (17.9%)	22 (23.4%)	9 (27.3%)	0 (0.0%)	2 (13.3%)	50 (21.2%)
Race, % Other	7 (14.6%)	3 (10.7%)	12 (12.8%)	2 (6.1%)	2 (11.1%)	2 (13.3%)	28 (11.9%)
Duration of Inflammation	4.1 (0.0 – 18.9)	5.9 (0.1 – 22.4)	3.0 (0.0 – 35.1)	1.8 (0.1 – 21.3)	1.3 (0.0 – 17.4)	3.0 (0.3 – 17.1)	3.0 (0.0 – 35.1)
Bilateral Inflammation	34 (70.8%)	19 (67.9%)	67 (71.3%)	18 (54.5%)	13 (72.2%)	10 (66.7%)	161 (68.2%)
Corticosteroid Dose Less or equal to 10mg	34 (70.8%)	15 (53.6%)	53 (56.4%)	8 (24.2%)	12 (66.7%)	5 (33.3%)	127 (53.8%)
Prior Mycophenolate	8 (16.7%)	6 (21.4%)	9 (9.6%)	2 (6.1%)	1 (5.6%)	0 (0.0%)	26 (11.0%)
Prior Antimetabolites (Other than Mycophenolate)	23 (47.9%)	6 (21.4%)	21 (22.3%)	10 (30.3%)	3 (16.7%)	3 (20.0%)	66 (28.0%)
Prior Alkylating Agents	2 (4.2%)	1 (3.6%)	5 (5.3%)	3 (9.1%)	4 (22.2%)	2 (13.3%)	17 (7.2%)
Prior T-cell Inhibitors	9 (18.8%)	11 (39.3%)	13 (13.8%)	3 (9.1%)	0 (0.0%)	0 (0.0%)	36 (15.3%)
Prior Biologics	5 (10.4%)	3 (10.7%)	4 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (5.1%)
Any Prior Immunosupressive Treatment	30 (62.5%)	15 (53.6%)	37 (39.4%)	14 (42.4%)	8 (44.4%)	5 (33.3%)	109 (46.2%)
Eye Specific Characteristics							
Number of affected eyes	**82**	**47**	**161**	**51**	**31**	**25**	**397**
20/50 or Worse	23 (28.0%)	20 (42.6%)	67 (41.6%)	10 (19.6%)	10 (32.3%)	0 (0.0%)	130 (32.7%)
20/200 or Worse	12 (14.6%)	8 (17.0%)	28 (17.4%)	5 (9.8%)	4 (12.9%)	0 (0.0%)	57 (14.4%)
Any ocular complication, affected eyes[b]	36 (43.9%)	37 (78.7%)	95 (59.0%)	14 (27.5%)	7 (22.6%)	1 (4.0%)	190 (47.9%)

[a] MMP=Mucous membrane pemphigoid

[b] Any ocular complications included ocular hypertension, ocular hypotony, band keratopathy, macular edema, epiretinal membrane, exudative retinal detachment, retinal neovascularization, choroidal neovascularization, glaucoma surgery, cataract surgery, inflammatory cells in the anterior chamber, inflammatory cells in the posterior chamber and vitreous haze..

Table 2

Control of Ocular Inflammation with Mycophenolate Mofetil in Patients Within 6 months and 1 year

Outcomes	Anterior	Intermediate	Posterior/Panuveitis	Scleritis	Mucous Membrane Pemphigoid	Other	Total
Used as only immunosuppressive drug therapy	48	28	94	33	18	15	236
Controlled Inflammation - No Activity at 6 months	55.2 (38.0– 74.1)	65 (39.3 – 89)	50.6 (38.2 – 64.4)	48.7 (27.7 – 74.7)	41 (19.2 – 73)	77.8 (49.2 – 96.5)	53.1 (44.9 – 61.8)
Controlled Inflammation - No Activity or Slightly Active at 6 months	84.9 (63 – 97.3)	83.1 (48.5 – 99.2)	86.5 (72 – 95.7)	62.5 (38.8 – 86)	63.6 (38.2 – 88.1)	68.9 (37.6 – 94.5)	77.5 (68.0 – 85.7)
Controlled Inflammation and Steroid Sparing - ≤ 10 mg at 6 months	47.2 (31.4 – 66.1)	39.0 (20.6 – 65.3)	41.2 (30.7 – 53.7)	25.5 (12.1 – 49.0)	37.8 (17.5 – 69)	58.5 (31.5 – 87)	40.7 (33.5 – 48.7)
Controlled Inflammation and Steroid Sparing - ≤5 mg at 6 months	46.4 (31.3 – 64.5)	26 (11.6 – 51.9)	21.3 (13.6 – 32.5)	20.5 (9 – 43.0)	30.7 (12.7 – 63.0)	23.9 (8.4 – 57.3)	27.3 (21.3 – 34.5)
Controlled Inflammation and Steroid Sparing - 0 mg at 6 months	5.8 (1.5 – 21.3)	0.0	2.6 (0.7 – 10.1)	7.1 (1.8 – 25.4)	7.7 (1.1 – 43.4)	9.1 (1.3 – 49.2)	4.4 (2.2 – 8.7)
Controlled Inflammation - No Activity at 12 months	72.4(52.4 – 89.2)	76.7 (49.1 – 95.6)	70.9 (57.1 – 83.5)	85.7 (55.5 – 99.1)	70.5 (30.8 – 98.3)	88.9 (61.5 – 99.4)	73.1 (63.9 – 81.6)
Controlled Inflammation - No Activity or Slightly Active at 12 months*	100.0	100.0	93.2 (80.6 – 98.8)	100.0	75.8 (47.9 – 95.4)	84.4 (51.7 – 99.1)	91.2 (82.5 – 96.6)
Controlled Inflammation and Steroid Sparing - ≤10 mg at 12 months	53.1 (35.6 – 72.7)	49.2 (26.9 – 76.7)	60.3 (48.1 – 72.9)	49.4 (27.2 – 76.8)	37.8 (17.5 – 69)	68.8 (40.8 – 92.5)	55 (46.7 – 63.5)
Controlled Inflammation and Steroid Sparing - ≤ 5 mg at 12 months	51.3 (35.0 – 69.9)	43.6 (22.5 – 72.5)	41.7 (30.7 – 54.8)	44.7 (23.4 – 73.2)	48.1 (20.9 – 84.0)	42.9 (16.2 – 83.0)	43.7 (36 – 52.4)
Controlled Inflammation and Steroid Sparing - 0 mg at 12 months	18.4 (8.7 – 36.6)	13.8 (3.6 – 45.0)	9.1 (4.2 – 19.1)	7.1 (1.8 – 25.4)	7.7 (1.1 – 43.4)	20.4 (5.5 – 60.7)	12.1 (7.9 – 18.4)

* 95% confidence intervals are not available for estimates of 100%.

Table 3

Treatment Success with Mycophenolate Mofetil Among Patients with Ocular Inflammation.

Characteristic		Crude HR Control of Inflammation (inactive)	Adjusted HR Control of Inflammation (inactive)	Crude HR Control of Inflammation (inactive or slightly active)	Adjusted HR Control of Inflammation (inactive or slightly active)	Crude HR Corticosteroid-sparing Success (≤10 mg prednisone)	Adjusted HR Corticosteroid-sparing Success (≤10 mg prednisone)
Gender	Male	0.93 (0.63 – 1.37, 0.71)	1.20 (0.75 – 1.90, 0.45)	1.00 (0.66 – 1.53, 0.10)	1.00 (0.55 – 1.81, 0.10)	1.07 (0.72 – 1.60, 0.74)	1.37 (0.88 – 2.14, 0.16)
Race	White	1.00	1.00	1.00	1.00	1.00	1.00
	Black	0.64 (0.38 – 1.08, 0.10)	0.62 (0.32 – 1.19, 0.15)	0.97 (0.62 – 1.52, 0.91)	1.17 (0.65 – 2.09, 0.60)	0.50 (0.29 – 0.86, 0.01)	0.43 (0.22 – 0.82, 0.01)
	Other	0.92 (0.49 – 1.73, 0.80)	0.78 (0.38 – 1.61, 0.51)	1.22 (0.66 – 2.23, 0.53)	1.00 (0.48 – 2.09, 0.10)	0.97 (0.51 – 1.83, 0.92)	0.70 (0.33 – 1.48, 0.35)
Age	<18 years	1.42 (0.43 – 4.73, 0.57)	1.21 (0.32 – 4.60, 0.78)	0.99 (0.30 – 3.26, 0.99)	1.20 (0.24 – 6.10, 0.83)	2.29 (0.69 – 7.57, 0.18)	1.55 (0.42 – 5.76, 0.51)
	18–39 years	1.00	1.00	1.00	1.00	1.00	1.00
	40–54 years	1.68 (1.03 – 2.75, 0.04)	2.05 (1.14 – 3.66, 0.016)	1.12 (0.73 – 1.72, 0.61)	1.33 (0.78 – 2.27, 0.30)	1.98 (1.18 – 3.29, 0.0091)	1.99 (1.08 – 3.65, 0.027)
	55–64 years	1.71 (0.94 – 3.12, 0.082)	2.09 (1.07 – 4.08, 0.03)	0.92 (0.52 – 1.62, 0.77)	1.37 (0.70 – 2.71, 0.36)	1.86 (0.97 – 3.56, 0.06)	1.79 (0.85 – 3.74, 0.12)
	65 years or more	1.47 (0.75 – 2.88, 0.27)	1.70 (0.72 – 4.02, 0.22)	0.82 (0.40 – 1.67, 0.59)	1.21 (0.51 – 2.85, 0.66)	1.92 (0.99 – 3.72, 0.055)	1.35 (0.58 – 3.17, 0.49)
Type of inflammation	Anterior	1.00	1.00	1.00	1.00	1.00	1.00
	Intermediate	0.97 (0.51 – 1.83, 0.91)	0.61 (0.25 – 1.47, 0.27)	0.94 (0.48 – 1.83, 0.85)	0.58 (0.22 – 1.51, 0.27)	0.54 (0.24 – 1.23, 0.14)	0.45 (0.18 – 1.13, 0.088)
	Posterior/Panuveitis	1.08 (0.59 – 1.95, 0.81)	0.87 (0.43 – 1.73, 0.69)	1.21 (0.69 – 2.12, 0.50)	0.92 (0.55 – 1.55, 0.77)	0.95 (0.53 – 1.72, 0.87)	0.69 (0.33 – 1.47, 0.34)
	Scleritis	0.78 (0.41 – 1.49, 0.45)	0.47 (0.21 – 1.06, 0.068)	0.64 (0.32 – 1.28, 0.21)	0.49 (0.25 – 0.96, 0.037)	0.78 (0.39 – 1.54, 0.47)	0.59 (0.25 – 1.41, 0.24)
Type of inflammation	Mucous Membrane Pemphigoid	1.01 (0.39 – 2.58, 0.98)	0.80 (0.25 – 2.56, 0.71)	0.87 (0.34 – 2.22, 0.77)	0.78 (0.23 – 2.70, 0.70)	1.14 (0.47 – 2.73, 0.77)	0.83 (0.26 – 2.63, 0.75)
	Other	2.22 (1.00 – 4.92, 0.049)	1.58 (0.56 – 4.41, 0.39)	1.25 (0.52 – 2.99, 0.61)	1.18 (0.46 – 2.99, 0.73)	1.51 (0.70 – 3.24, 0.29)	1.32 (0.50 – 3.51, 0.58)
Previous mycophenolate	Yes	0.44 (0.19 – 1.02, 0.057)	0.38 (0.11 – 1.25, 0.11)	0.31 (0.10 – 1.02, 0.053)	0.30 (0.07 – 1.31, 0.11)	0.35 (0.13 – 0.98, 0.046)	0.38 (0.12 – 1.15, 0.086)
Other antimetabolite(s) prior to treatment	Yes	1.05 (0.68 – 1.63, 0.83)	1.26 (0.75 – 2.09, 0.38)	0.91 (0.60 – 1.39, 0.67)	0.87 (0.54 – 1.39, 0.56)	0.86 (0.54 – 1.38, 0.54)	0.95 (0.55 – 1.64, 0.85)

Characteristic		Crude HR Control of Inflammation (inactive)	Adjusted HR Control of Inflammation (inactive)	Crude HR Control of Inflammation (inactive or slightly active)	Adjusted HR Control of Inflammation (inactive or slightly active)	Crude HR Corticosteroid-sparing Success (≤10 mg prednisone)	Adjusted HR Corticosteroid-sparing Success (≤10 mg prednisone)
T-cell inhibitor(s) prior to treatment	Yes	0.71 (0.39 – 1.32, 0.28)	0.98 (0.45 – 2.13, 0.96)	1.13 (0.64 – 1.99, 0.68)	1.61 (0.69 – 3.75, 0.27)	0.52 (0.27 – 1.01, 0.053)	0.59 (0.29 – 1.20, 0.15)
Biologic(s) prior to treatment	Yes	0.54 (0.10 – 3.00, 0.48)	1.43 (0.21 – 9.55, 0.71)	0.50 (0.16 – 1.51, 0.22)	1.15 (0.23 – 5.86, 0.86)	0.37 (0.08 – 1.74, 0.21)	0.76 (0.28 – 2.05, 0.59)
Alkylating agent(s) prior to treatment	Yes	0.49 (0.22 – 1.12, 0.092)	0.33 (0.14 – 0.82, 0.017)	0.39 (0.22 – 0.69, 0.0014)	0.31 (0.15 – 0.63, 0.0014)	0.42 (0.26 – 0.69, 0.0006)	0.28 (0.12 – 0.64, 0.0029)
Dosage	< 2000 mg/day	1.00	1.00	1.00	1.00	1.00	1.00
	Equal to 2000 mg/day	1.00 (0.54 – 1.83, 0.99)	0.86 (0.45 – 1.63, 0.64)	1.34 (0.69 – 2.60, 0.39)	1.29 (0.59 – 2.82, 0.53)	1.00 (0.58 – 1.71, 0.99)	0.83 (0.47 – 1.47, 0.53)
	> 2000 mg/day	1.63 (0.83 – 3.19, 0.16)	1.47 (0.70 – 3.09, 0.31)	1.31 (0.56 – 3.04, 0.53)	1.57 (0.59 – 4.20, 0.37)	0.74 (0.35 – 1.58, 0.44)	0.57 (0.24 – 1.38, 0.22)
Systemic (extraocular) autoimmune disease	Yes	0.78 (0.49 – 1.24, 0.30)	0.73 (0.39 – 1.35, 0.31)	0.68 (0.39 – 1.16, 0.15)	0.82 (0.45 – 1.51, 0.53)	1.01 (0.65 – 1.57, 0.98)	1.03 (0.56 – 1.90, 0.92)

Table 4

Reasons for Stopping Mycophenolate Mofetil Among Patients with Ocular Inflammation

Reason	No. of affected patients	Rate (number stopping per person year) (95% Confidence Interval)	KM estimate for 1 year, %, 95% CI
Favorable Reasons			
Remission	14 (5.9%)	0.049 (0.026, 0.081)	3.3 (1.2 – 8.6)
Unfavorable Reasons			
Discontinuation for side effects	28 (12%)	0.097 (0.064, 0.14)	14.5(10.0 – 20.8)
Gastrointestinal upset	6 (2.5%)	0.021 (0.0076, 0.045)	3.1 (1.3 – 7.5)
Bone Marrow suppression	4 (1.7%)	0.014 (0.0038, 0.036)	2.1 (0.8 – 5.5)
Elevated liver enzymes	3 (1.3%)	0.0104 (0.0021, 0.030)	1.5 (0.5 – 4.8)
Allergy	2 (0.8%)	0.0069 (0.0008, 0.025)	1.1 (0.3 – 4.5)
Malaise	2 (0.8%)	0.0069 (0.0008, 0.025)	1.4 (0.3 – 5.4)
Other Lab Abnormalities[a]	1 (0.4%)	0.0035 (0.0001, 0.019)	0.9 (0.1 – 6.0)
Other Side Effects[b]	9 (3.8%)	0.0312 (0.014, 0.059)	4.2 (2.1 – 8.3)
Ineffectiveness	23 (9.7%)	0.0796 (0.05, 0.12)	13.1 (8.6 – 19.7)
Unknown Reasons	20 (8.5%)	0.069 (0.042, 0.11)	7.9 (4.8 – 12.9)
Total Stopping[c]	81 (34%)	0.28 (0.22, 0.35)	32.2 (25.9 – 39.5)

[a] Abnormal renal function tests

[b] Hypertension, palpitation, epistaxis, fever, sore throat

[c] Some patients may have stopped for more than one reason.