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Reduced dose methotrexate and mycophenolate mofetil in noninfectious uveitis: a sub-analysis from the First-Line Antimetabolites as Steroid Sparing Therapy (FAST) Trial

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Abstract

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Declaration of Interest Statement

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Purpose: Some patients taking methotrexate (MTX) or mycophenolate mofetil (MMF) experience intolerable side effects at full doses. We evaluated whether dose reduction affected treatment outcomes in uveitis patients.

Methods: Subanalysis of the First-line Antimetabolites as Steroid-sparing Treatment (FAST) uveitis trial. Patients were randomized to receive MTX (25 mg weekly) or MMF (3 g daily). A pre-specified dose reduction protocol could be employed for intolerable side effects. Primary analysis was performed at 6 months.

Results: 43/194 patients (22%) required dose reduction. 88/151 patients (58%) on maximum doses and 32/43 patients (74%) on reduced doses were deemed treatment successes at six months. The odds ratio point estimate (1.60, 95% CI 0.72–3.74)) favored dose-reduction but this was not significant. Following reduction, adverse events improved at the subsequent study visit (79 events reduced to 63 events).

Conclusion: Dose reduction of antimetabolites was not associated with worse outcomes in this subanalysis of a uveitis trial.

Keywords

Uveitis; methotrexate; mycophenolate mofetil; antimetabolite; dosing

Introduction

Noninfectious uveitis is a major cause of ocular morbidity. Antimetabolite therapy with methotrexate and mycophenolate mofetil are mainstay treatments for noninfectious uveitis, but some patients experience intolerable side effects at full therapeutic doses. Up to 16% of patients on methotrexate and 12% of patients on mycophenolate mofetil discontinue their medications due to intolerability, and many more experience a reduced quality of life from side effects.[1,2] Approximately 60% of patients on either medication experience fatigue.[3] Other common side effects include headache, muscle weakness, gastrointestinal distress, and laboratory abnormalities.

Different strategies to improve tolerability of antimetabolite therapy have been used. For methotrexate, patients can increase concurrent folic acid supplementation, add folinic acid (leucovorin), split dosing, or change the route of administration from oral to subcutaneous for gastrointestinal side effects (or vice-versa if the side effects are injection-related). Dose reduction is also an option. Antimetabolites demonstrate dose-dependence whereby higher doses increase efficacy and worsen side effects.[4] Thus, there is a theoretical risk of reduced effectiveness with dose reduction, but little data exists to guide optimal dosing in noninfectious uveitis.

The First-line Antimetabolites as Steroid-sparing Treatment (FAST) Trial was an international, randomized clinical trial that compared methotrexate to mycophenolate mofetil in the treatment of noninfectious uveitis.[3] All patients were randomized to receive standard dosing of antimetabolite therapy (oral methotrexate 25 mg weekly or oral mycophenolate mofetil 3 g daily). Dose reduction was allowed in patients who experienced intolerable side effects. The purpose of this study was to determine whether dose reduction

of antimetabolite therapy impacted efficacy or adverse effects in patients with noninfectious uveitis.

Material and methods

This study was a subanalysis from the First-line Antimetabolites as Steroid-sparing Treatment (FAST; ClinicalTrials.gov Identifier: NCT 01829295) uveitis trial, a National Eye Institute-funded, multicenter, international, observer-masked, randomized clinical trial that compared the efficacy of methotrexate and mycophenolate mofetil in adults with noninfectious intermediate, posterior, and panuveitis. Institutional review board approval was obtained at all centers. All patients provided informed consent. All research procedures adhered to the tenets of the Declaration of Helsinki. Patients were recruited from nine sites in five countries. Patients were randomized to either methotrexate or mycophenolate mofetil in a 1:1 ratio. After two-weeks on lower-dose therapy to assess tolerability (oral methotrexate 15 mg weekly + folic acid 1 mg daily or mycophenolate mofetil 500 mg twice daily), patients were placed on max dose antimetabolite therapy (oral methotrexate 25 mg weekly with split dosing on the day of administration + folic acid 1 mg daily or mycophenolate mofetil 1.5 g twice daily) for the entire treatment course. Patients were instructed to not eat 1 hour before or after taking each dose of mycophenolate mofetil. Treatment success was assessed at the primary endpoint of 6 months. Patients who met the primary endpoint at 6 months were eligible to participate in a second phase of the trial, during which patients who succeeded during the first phase were followed for an additional 6 months. Patients who were deemed treatment failures during the first six months were switched to the alternate medication and followed for an additional 6 months. Treatment success for the second phase of the trial was assessed at month 12. Treatment success was defined as having control of inflammation with less than or equal to 7.5 mg of prednisone daily and less than or equal to 2 drops of prednisolone acetate 1% daily.

If a patient experienced intolerable side effects during the trial, physicians could employ a pre-specified dose reduction (oral methotrexate 20 mg weekly or mycophenolate mofetil 1 g twice daily). If tolerability remained an issue, there was an option for a second dose reduction (methotrexate 15 mg weekly or mycophenolate mofetil 500 g twice daily). If the patient still experienced intolerable side effects after two dose reductions, treatment failure could be declared, and the patient could be switched to an alternate medication. Study visits were conducted at baseline, two weeks after enrollment, four weeks after enrollment, and every four weeks thereafter. At each study visit, patients received a complete ophthalmic exam and were assessed for adverse events using a standardized questionnaire. Treating physicians were masked to the randomized study treatment and remained so when dose reductions were made. Study coordinators and patients were unmasked.

The main analysis included everyone (n = 194) who reached the 6-month primary endpoint. A subanalysis of patients enrolled in India (Coimbatore, Madurai, Pondicherry; n = 119) and non-Indian sites (n = 75) was conducted. Logistic regression was used to calculate the odds ratio of treatment success. Two logistic regression models were applied in the primary and subanalyses. The first model (covariate adjustment model) assessed the association between dose reduction and treatment success, adjusting for the randomized treatment, age, sex,

race, site, weight, and prior treatment with immunosuppressive therapy. Race and site were not adjusted for in the Indian and non-Indian subanalyses. A test for interaction between study medication and dose reduction was performed. The second model was an inverse probability-weighted logistic regression model. Inverse probability of treatment weights (IPTW) were calculated separately for each analysis, using logistic regression with dose reduction (reduced dose 1; max dose 0) as the outcome, with randomized treatment, age, sex, race, site, weight, and prior treatment with immunosuppressive therapy as covariates (race and site were not included in the Indian and non-Indian subanalyses). All inverse probability weights were truncated at the 99th percentile. Balance assessment of the characteristic covariates was performed by comparing the standardized mean differences (SMD) in the unweighted and weighted samples. The 95% confidence intervals from the IPTW model were computed using bootstrapping, with 1000 bootstrap samples.

Results

Table 1 shows baseline characteristics. 216 patients were enrolled in the trial, and 194 patients reached the primary endpoint at six months and were included in the analysis. 43 patients underwent dose reduction, of which 31 underwent a one-step dose reduction and 12 underwent a two-step dose reduction. Age and gender were similar between the two groups. Patients taking methotrexate were more likely to try a dose reduction (56%) compared with mycophenolate mofetil (44%). Compared to patients who remained on the full dose, patients who dose reduced were more often Indian (56% versus 79%, respectively), lower weight (69.1 kg versus 64.1 kg, respectively), and diagnosed with Vogt-Koyanagi-Harada disease (40% versus 56%, respectively).

Treatment success at six months was compared between max-dose patients and reduced-dose patients (Table 2; Figure 1). 58% of max-dose patients and 74% of reduced-dose patients achieved treatment success at 6 months. 23/31 (74%) patients who required 1-step dose reduction and 9/12 (75%) patients who required 2-step reduction succeeded. The odds ratio point estimate favored dose-reduction but was not statistically significant [1.60, 95% confidence interval (CI) 0.72 – 3.74, p=0.26]. In a subanalysis of Indian sites, the odds ratio point estimate favored dose reduction [2.51, 95% CI 0.97–7.43, p=0.07], and in non-Indian sites, the odds ratio point estimate favored maximum dose [0.92, 95% CI 0.22 – 3.75, p=0.91]. None of the subanalysis groups showed a difference at the 95% confidence level.

Of the 120 patients who were declared a treatment success at six months, 114 were followed for an additional six months during a second phase of the trial (Table 2). At 12 months, 73% of patients on max-dose therapy and 90% of patients on reduced-dose therapy were treatment successes. Among 68 treatment failures at six months, 49 switched to the alternate medication and were followed for an additional six months. 51% of patients on max-dose therapy and 66% of patients on reduced-dose therapy were deemed treatment successes at 12 months.

The most common reason for dose reduction was intolerability (51.5%) followed by laboratory abnormalities (18.2%) (Table 3). To assess whether dose reduction improved tolerability, the number and type of self-reported adverse events at the visit when the dose

reduction occurred was compared to those at the subsequent visit (Table 4). The total number of adverse events decreased from 79 to 63. Events that are commonly attributed to antimetabolite therapy were lower on the subsequent visit, such as constitutional symptoms (44 versus 35) and gastrointestinal side effects (17 versus 13).

Discussion

In this subanalysis of the First-Line Antimetabolites as Steroid Sparing Therapy (FAST) Trial, we compared outcomes for patients on max-dose antimetabolite therapy to those who required dose reduction. When comparing the 43 patients who required dose reduction to the 151 patients who did not, we did not find a statistically significant association between dose reduction and treatment efficacy. This result suggests that modest dose reductions of methotrexate (MTX) or mycophenolate mofetil (MMF) may be an acceptable strategy in patients with noninfectious uveitis who have intolerable side effects.

We found a non-significant trend towards treatment success in patients who were on reduced-dose therapy (Figure 1). Improved efficacy with lower doses is contrary to the typical dose-response relationship of antimetabolite therapy, which demonstrates improved efficacy and more side effects with greater doses.[4] One explanation is that the dose-reduced group contained a disproportionate number of patients with Vogt-Koyanagi-Harada disease (VKH) (Table 1). It is possible that VKH responds better to antimetabolite therapy than other causes of noninfectious uveitis.[5,6] Another explanation may be lower weight or a disproportionate number of Indian patients in the dose-reduced group. Differences in genetics, weight, and renal function contribute to variable drug levels for methotrexate and mycophenolate mofetil.[7,8] Indian patients or low-weight patients may respond better to lower doses of antimetabolite therapy. Subanalysis of Indian sites favored dose reduction, and subanalysis of non-Indian sites favored max-dose therapy, though none of the point estimates achieved statistical significance. A final explanation is that patients who were doing well felt more comfortable reducing their dose, thereby introducing a bias (confounding by intention).

There is no consensus on the optimal dosing of antimetabolite therapy to balance efficacy and adverse events. There is little prospective data for noninfectious uveitis, so dosing for uveitis is largely based on dosing strategies for other rheumatologic conditions. In the FAST Trial, 25 mg weekly of MTX or 3 g daily of MMF were used as the standard maintenance dose. 15–20 mg weekly of MTX or 1–2 g daily of MMF were used as the reduced maintenance dose. In the rheumatoid arthritis literature, the four randomized controlled trials that compared different dosages of oral methotrexate showed dose-dependent efficacy and adverse events.[9–12] These findings, summarized in consensus opinion guidelines[13], found that the difference between 5–10 mg/week and 12.5– 20 mg/week resulted in higher efficacy without a statistically significant increase in adverse events. The transition from 12.5–20 mg to 25–30 mg/week resulted in higher efficacy with a significant increase in non-serious adverse events, particularly gastrointestinal side effects and transaminitis. The literature on psoriatic arthritis reports similar findings. A subanalysis of a multi-phase, randomized control trial found that non-responders to MTX 15 mg oral weekly benefited from a dose adjustment to 20 mg weekly but that there was little benefit to increasing the dose from 20

mg weekly to 25 mg weekly.[14] A randomized controlled trial for psoriatic arthritis found that a simplified up-titration strategy using 17.5 mg and 22.5 mg as starting- and high-dose therapies balanced efficacy and adverse events comparably to slower up-titration strategies starting at doses as low as 7.5 mg weekly.[15] The renal transplant literature suggests that even brief dose-reductions in MMF dosage from 3 g daily to 2 g daily improves adverse events but significantly increases the risk for organ rejection.[16, 17] These findings must be applied with caution to uveitis patients, however, since uveitis is a distinct disease entity that may require higher doses of immunosuppressive therapy than other conditions.

We assessed adverse events for patients who underwent dose reduction (Table 3 and Table 4). We found that intolerability and laboratory abnormalities contributed to most dose reductions. To assess whether dose reduction improved adverse events, we assessed the total and type of self-reported adverse events at the visit when a dose reduction was undertaken and the subsequent visit. We found that the number of adverse events went down across categories. Notably, common antimetabolite-associated side effects of gastrointestinal distress reduced from 44 events to 35 events and constitutional side effects reduced from 17 events to 13 events. Improved adverse events with lower doses of antimetabolite therapy is consistent with others studies on antimetabolite dosing.[10, 14, 16] It is also possible that the placebo effect of a dose reduction, passage of time alone, or the tapering of steroids (when applicable) also contributed to improved adverse events from one visit to the next.

Strengths of our study include the standardized dose-reduction protocol, consistent results using different statistical methodologies, and the use of high-quality, government-funded international clinical trial data that included multiple sites, masking, and block randomization. Limitations include unbalanced numbers between the maximum dose and reduced dose groups which can reduce statistical power, disproportionate number of Indian patients, and an intervention that was done at the physician’s discretion, although the physician was masked to treatment.

In conclusion, in this subanalysis of a randomized clinical trial, we did not find an association between dose reduction of antimetabolite therapy and treatment outcome. We also found that adverse events improved in the visit after a dose reduction was undertaken. Thus, dose reduction may be a viable and safe strategy for patient who experience intolerable effects with methotrexate or mycophenolate mofetil.

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References

1. Gangaputra S, Newcomb CW, Liesegang TL, et al. Methotrexate for ocular inflammatory diseases. Ophthalmology 2009;116:2188–2198 e2181. [PubMed: 19748676]
2. Daniel E, Thorne JE, Newcomb CW, et al. Mycophenolate mofetil for ocular inflammation. Am J Ophthalmol 2010;149:423–432 e421–422. [PubMed: 20042178]
3. Rathinam SR, Gonzales JA, Thundikandy R, et al. Effect of Corticosteroid-Sparing Treatment With Mycophenolate Mofetil vs Methotrexate on Inflammation in Patients With Uveitis: A Randomized Clinical Trial. JAMA 2019;322:936–945. [PubMed: 31503307]
4. Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. Ann Rheum Dis 2009;68:1094–1099. [PubMed: 19033290]
5. Papasavvas I, Tugal-Tutkun I, Herbort CP Jr. Vogt-Koyanagi-Harada is a Curable Autoimmune Disease: Early Diagnosis and Immediate Dual Steroidal and Non-Steroidal Immunosuppression are Crucial Prerequisites. J Curr Ophthalmol 2020;32:310–314. [PubMed: 33553831]
6. Shen E, Rathinam SR, Babu M, et al. Outcomes of Vogt-Koyanagi-Harada Disease: A Subanalysis From a Randomized Clinical Trial of Antimetabolite Therapies. Am J Ophthalmol 2016;168:279–286. [PubMed: 27296490]
7. Dervieux T, Wessels JA, van der Straaten T, et al. Gene-gene interactions in folate and adenosine biosynthesis pathways affect methotrexate efficacy and tolerability in rheumatoid arthritis. Pharmacogenet Genomics 2009;19:935–944. [PubMed: 19858780]
8. Chladek J, Martinkova J, Simkova M, Vaneckova J, Koudelkova V, Nozickova M. Pharmacokinetics of low doses of methotrexate in patients with psoriasis over the early period of treatment. Eur J Clin Pharmacol 1998;53:437–444. [PubMed: 9551702]
9. Jain S, Dhir V, Aggarwal A, et al. Comparison of two dose escalation strategies of methotrexate in active rheumatoid arthritis: a multicentre, parallel group, randomised controlled trial. Ann Rheum Dis 2021.

10. Furst DE, Koehnke R, Burmeister LF, Kohler J, Cargill I. Increasing methotrexate effect with increasing dose in the treatment of resistant rheumatoid arthritis. J Rheumatol 1989;16:313–320. [PubMed: 2724250]
11. Schnabel A, Reinhold-Keller E, Willmann V, Gross WL. Tolerability of methotrexate starting with 15 or 25 mg/week for rheumatoid arthritis. Rheumatol Int 1994;14:33–38. [PubMed: 7939138]
12. Verstappen SM, Jacobs JW, van der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis 2007;66:1443–1449. [PubMed: 17519278]
13. Visser K, Katchamart W, Loza E, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis 2009;68:1086–1093. [PubMed: 19033291]
14. Saurat JH, Langley RG, Reich K, Unnebrink K, Sasso EH, Kampman W. Relationship between methotrexate dosing and clinical response in patients with moderate to severe psoriasis: subanalysis of the CHAMPION study. Br J Dermatol 2011;165:399–406. [PubMed: 21564071]
15. Warren RB, Mrowietz U, von Kiedrowski R, et al. An intensified dosing schedule of subcutaneous methotrexate in patients with moderate to severe plaque-type psoriasis (METOP): a 52 week, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;389:528–537. [PubMed: 28012564]
16. Knoll GA, MacDonald I, Khan A, Van Walraven C. Mycophenolate mofetil dose reduction and the risk of acute rejection after renal transplantation. J Am Soc Nephrol 2003;14:2381–2386. [PubMed: 12937317]
17. Bunnapradist S, Lentine KL, Burroughs TE, et al. Mycophenolate mofetil dose reductions and discontinuations after gastrointestinal complications are associated with renal transplant graft failure. Transplantation 2006;82:102–107. [PubMed: 16861948]

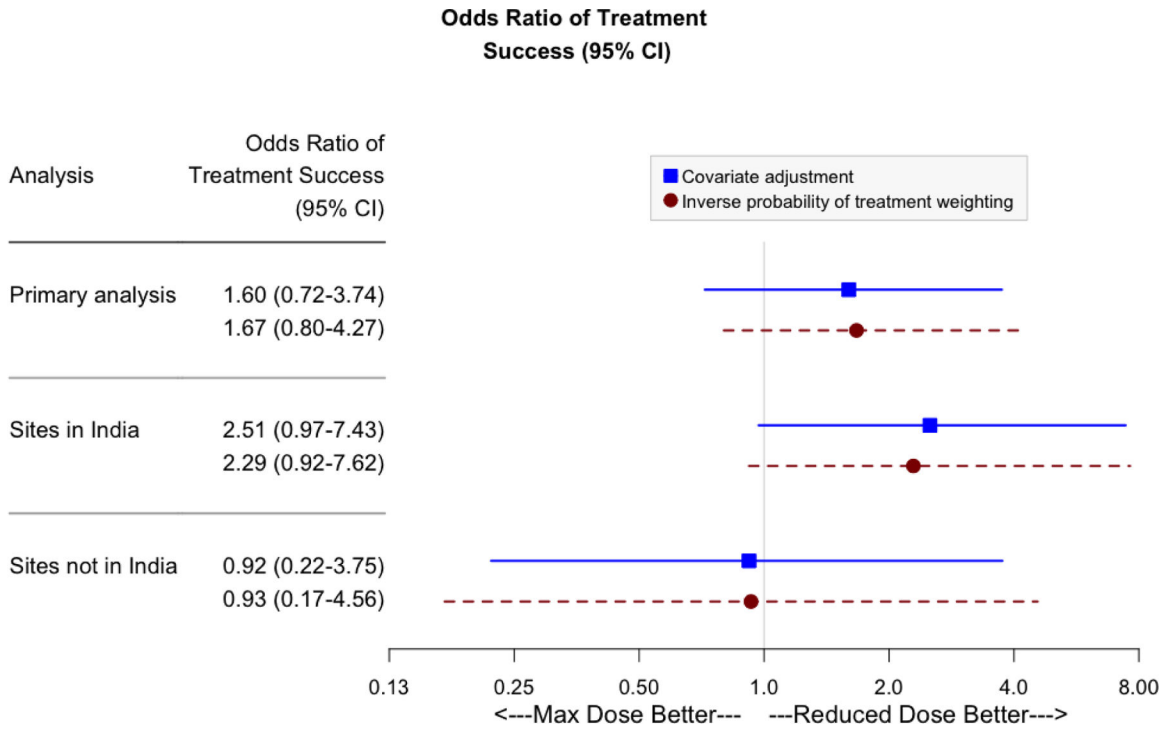

Figure 1: Dose reduction of antimetabolite therapy is not associated with treatment outcome.

If patients experienced intolerable side effects during the trial, physicians could employ a pre-specified dose reduction. Treatment success at six months was compared between those on maximum-dose antimetabolite therapy (n = 151) and those who on reduced-doses (n = 43). Dose reduction was not associated with treatment success or failure. There was a non-significant trend towards treatment success in dose-reduced patients, and sub-analysis revealed that this trend was driven by patients from Indian sites. Two different statistical models (covariate adjustment and inverse probability of treatment weighting) showed consistent results.

Table 1:

Baseline Characteristics by dose reduction status

	Patients on Maximum Dose (n = 151 patients)	Patients on Dose Reduction (n=43 patients)	All Patients (n = 194)
Patient-Level Characteristics			
Age, median (IQR) years	40 (27–52)	36 (30–50)	38 (28–51)
Female Sex	100 (66%)	29 (67%)	129 (66%)
Weight (kg), mean (SD)	69.5 (19.8)	64.1 (18.7)	68.3 (19.6)
Medication			
Methotrexate	72 (48%)	24 (56%)	96 (49%)
Mycophenolate mofetil	79 (52%)	19 (44%)	98 (51%)
Race			
Indian	84 (56%)	34 (79%)	118 (61%)
White	37 (25%)	5 (12%)	42 (22%)
Asian	7 (4.6%)	0 (0%)	7 (4%)
Middle Eastern	9 (6.0%)	0 (0%)	9 (5%)
Black	8 (5.3%)	0 (0%)	8 (4%)
Native American	1 (0.7%)	0 (0%)	1 (0.5%)
Pacific Islander	1 (0.7%)	1 (2.3%)	2 (1%)
Multiracial	4 (2.6%)	3 (6.9%)	7 (4%)
Uveitis Diagnosis			
Vogt-Koyanagi-Harada disease	61 (40%)	24 (56%)	85 (44%)
Undifferentiated	29 (19%)	7 (16%)	36 (19%)
Retinal vasculitis	14 (9.2%)	3 (7.0%)	17 (9%)
Sarcoidosis	13 (8.6%)	2 (4.6%)	15 (8%)
Sympathetic ophthalmia	7 (4.6%)	1 (2.3%)	8 (4%)
Behcet disease	6 (4.0%)	2 (4.6%)	8 (4%)
Pars planitis	6 (4.0%)	0 (0%)	6 (3%)
Birdshot chorioretinopathy	3 (2.0%)	1 (2.3%)	4 (2%)
Multifocal choroiditis and panuveitis	3 (2.0%)	1 (2.3%)	4 (2%)
Serpiginous	2 (1.3%)	0 (0%)	2 (1%)
Other	6 (PIC, Takayasu, possible sarcoid, choroiditis, ampiginous, multifocal choroiditis)	2 (possible sarcoid)	8 (4%)
Bilateral uveitis	135 (89.4%)	41 (95.3%)	176 (90.7%)
Duration of uveitis, median (IQR), days	143 (26–811)	83 (19–524)	122 (21–783)
Anatomic Location			
Panuveitis	85 (55%)	25 (58%)	110 (57%)
Posterior uveitis	32 (21%)	13 (30.2%)	45 (23%)
Anterior uveitis and intermediate uveitis	21 (14%)	4 (9.3%)	25 (13%)
Intermediate	16 (10%)	1 (2.3%)	17 (9%)

	Patients on Maximum Dose (n = 151 patients)	**Patients on Dose Reduction (n=43 patients)**	**All Patients (n = 194)**
Prior treatment with immunosuppressive therapy	11 (7.3%)	3 (7.0%)	14 (7%)
Eye level characteristics	N=302	N=85	387
Inflammation at baseline			
Anterior chamber cells			
0+	119 (39%)	53 (62%)	172 (45%)
0.5+	78 (25%)	8 (9.5%)	86 (23%)
1+	81 (26%)	16 (19%)	86 (23%)
>2+	30 (10%)	7 (8.2%)	37 (9.7%)
Macular edema	73 (32%)	18 (33%)	91 (32%)
LogMAR visual acuity, median (IQR)	0.3 (0.1–0.6)	0.3 (0.2–0.6)	0.3 (0.1–0.6)

Abbreviations: IQR, interquartile range; SD, standard deviation; PIC, punctate inner choroidopathy

Table 2:

Treatment success of maximum-dose and reduced-dose antimetabolite therapy at 6 months and 12 months

Phase 1 (month 0–6; primary endpoint)		
	Max dose	Reduced Dose
Patients	151	43
Treatment successes	88 (58%)	32 (74%)
MTX (N) -Successes:	72 45 (62.5%)	24 19 (79%)
MMF (N) -Successes:	79 43 (54%)	19 13 (68%)
Phase 2 (month 6–12; those who succeeded month 0–6 and continued the same medication)		
	Max dose	Reduced Dose
N	84	30
Treatment successes	61 (73%)	27 (90%)
MTX (N) -Successes:	44 34 (77.2%)	16 14 (87.5%)
MMF (N) -Successes:	40 27 (67.5%)	14 13 (93%)
Phase 2 (month 6–12; those who failed month 0–6, requiring a switch to the alternate medication)		
	Max dose	Reduced Dose
N	37	12
Treatment successes	19 (51%)	8 (66%)
MTX (N) -Successes:	20 14 (70%)	3 2 (66%)
MMF (N) -Successes:	17 5 (29%)	9 6 (66%)

Abbreviations: MTX, methotrexate; MMF, mycophenolate mofetil

Table 3:

Reason for dose reduction

Reason for dose reduction	N (%)
Intolerability	17 (51.5%)
Lab abnormality	6 (18.2%)
Systemic infection	2 (6.1%)
Other reason[a]	8 (24.2%)

[a]Restarting drug (4), restarting at lower doses after discontinuing (1), refusal to take higher doses (1), oral ulcers (1), worried about side effects (1)

Table 4

: Changes in lab abnormalities following dose reduction

		Before	After
Patient 1	WBC (cells/μL)	5.7	5.5
	Creatinine (μmol/L)	0.66	0.61
*	AST (U/L)	90	25
*	ALT (U/L)	48	32
Patient 2	WBC	11	10.9
*	Lymphocyte (%)	6.1	5.4
	Creatinine	0.7	0.7
	AST	16	18
	ALT	39	24
Patient 3	WBC	10.7	11.1
*	Creatinine	1.1	0.9
	AST	30	33
*	ALT	107	71
Patient 4	WBC	11.1	9.8
*	Creatinine	1.1	1
	AST	21	22
	ALT	33	22
Patient 5	WBC	12.4	14.1
*	Creatinine	1	1.1
	AST	14	26
*	ALT	42	36
Patient 6	WBC	9	9
	Creatinine	0.8	0.8
	AST	22	39
*	ALT	70	59

*Abnormal lab value prompting dose reduction

Abbreviations: WBC, white blood cells; AST, aspartate aminotransferase; ALT, alanine aminotransferase; U, units

Table 5:

The impact of dose reduction on adverse events.

Adverse event	No. reported at dose reduction visit	No. reported at subsequent visit
Constitutional (fatigue, headache, mood changes, muscle weakness, dyspnea)	44	35
Gastrointestinal (nausea, vomiting, diarrhea)	17	13
Neurologic	3	3
Systemic infection	2	1
Other systemic	11	10
Total	77	62