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Comparison of CD4 counts with mycophenolate mofetil versus methotrexate from the First-line Antimetabolites as Steroid-sparing Treatment (FAST) Uveitis Trial

Christina L. Kong, BS[1], **Nicole K Kelly, MPH**[1], **Miel Sundararajan, MD**[2], **S.R Rathinam, MD, PhD**[3], **John A. Gonzales, MD**[1,2], **Radhika Thundikandy, MD**[3], **Rajesh Vedhanayaki, MD**[3], **Anuradha Kanakath, MD**[4], **Bala Murugan, MD**[5], **Thuy Doan, MD, PhD**[1,2], **Debra Goldstein, MD**[6], **Hassan A. Al-Dhibi, MD**[7], **Nisha R. Acharya, MD, MS**[1,2,8]

[1]F.I. Proctor Foundation, University of California, San Francisco, San Francisco, California, USA

[2]Department of Ophthalmology, University of California, San Francisco, San Francisco, California, USA

[3]Uvea Services, Aravind Eye Hospitals and Postgraduate Institute of Ophthalmology, Madurai, India

[4]Uvea Services, Aravind Eye Hospitals and Postgraduate Institute of Ophthalmology, Coimbatore, India

[5]Uvea Services, Aravind Eye Hospitals and Postgraduate Institute of Ophthalmology, Pondicherry, India

[6]Department of Ophthalmology, Northwestern University, Chicago, Illinois, USA

[7]Division of Vitreoretinal Surgery and Uveitis, King Khaled Eye Specialist Hospital, Riyadh, Kingdom of Saudi Arabia

[8]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California, USA

Abstract

Purpose: Sub-analysis of the FAST Trial comparing change in CD4 (ΔCD4) from baseline through 12 months in uveitis patients treated with mycophenolate mofetil (MMF) and methotrexate (MTX).

Methods: Patients were randomly allocated to 1.5g twice daily MMF or 25mg weekly MTX. Individuals with CD4 counts at baseline, 6-months (or treatment failure prior), and 12-months (or treatment failure between 6–12 months) were included. The association between treatment and ΔCD4 (cells/μL) was analyzed using multivariable linear regression.

Correspondence: Nisha R. Acharya, MD, MS, F.I. Proctor Foundation, University of California, San Francisco, 513 Parnassus Avenue, S309, San Francisco, CA 94143. Nisha.Acharya@ucsf.edu. .

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DECLARATION OF INTEREST

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Results: There was no significant difference in ΔCD4 between MMF and MTX at 6 months (−31.7 cells/μL for MMF compared to MTX; 95% CI: −358.2 to 294.8, P=0.85) and 12 months (−78.3 cells/μL for MMF compared to MTX; 95% CI: −468.0 to 311.3; P=0.69).

Conclusion: There was no significant difference in ΔCD4 between MMF and MTX from baseline to 12 months, suggesting that MMF does not confer additional risk of CD4 lymphopenia in uveitic patients.

Keywords

CD4; mycophenolate mofetil; methotrexate; antimetabolite; uveitis

INTRODUCTION

Antimetabolites are commonly used as corticosteroid-sparing immunosuppressive treatments for non-infectious uveitis and include mycophenolate mofetil (MMF) and methotrexate (MTX). MMF, which preferentially inhibits purine synthesis in B and T lymphocytes, is used for the prevention of transplant rejection as well as for autoimmune conditions such as lupus nephritis and sarcoidosis.[1,2] MTX, an inhibitor of dihydrofolate reductase that blocks purine and pyrimidine synthesis, is also used as first-line therapy for rheumatoid arthritis (RA) and other inflammatory conditions.[3,4]

Studies show that MMF and MTX are capable of affecting CD4+ T-cell expression; however, there is little data on the extent of their effect on total levels of CD4.[5,6] Understanding the risk of CD4 lymphopenia associated with these antimetabolites is crucial given that low CD4 counts place patients at higher risk of opportunistic infections such as cytolomegalovirus infection and *Pneumocystis* pneumonia.[7–9] There is particular concern that MMF lowers CD4 counts, which is especially evident in the transplant literature.[6,10,11] However, when examining the effect of MMF and MTX on CD4 levels in patients with autoimmune disease, it is unclear if low CD4 counts are attributable to these medications or to the underlying immune dysfunction. For example, CD4+ T-cell lymphopenia has been reported in patients with sarcoidosis in whom MMF is a common treatment option.[12,13]

While several studies have explored the potential effect of MMF and MTX on CD4 counts in systemic autoimmune diseases, little information exists on the effect of these antimetabolites on CD4 counts in patients with uveitis.[12,14] Understanding the relationship between antimetabolite use and CD4 counts is crucial for maintaining patient safety and informing clinician practice. In the First-line Antimetabolites for Corticosteroid-sparing Treatment (FAST) trial, MMF and MTX were compared as treatments for non-infectious uveitis.[15] To better understand the potential effects of antimetabolite use on CD4+ T-cell counts, we conducted a sub-analysis of the FAST trial by comparing the change in CD4 counts among uveitis patients on MMF to those on MTX for a period of up to 12 months.

MATERIALS AND METHODS

The FAST Trial (ClinicalTrials.gov Identifier: NCT01829295) was an individually randomized, observer-masked comparative effectiveness trial comparing MMF and MTX

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as treatment for non-infectious intermediate, posterior, and panuveitis.[15] All patients were 16 years of age or older with a history of active non-infectious uveitis in at least one eye requiring corticosteroid-sparing treatment. From August 2013 to August 2017, 216 patients were recruited from 9 eye care centers in India, the United States, Australia, Saudi Arabia and Mexico. Patients were block randomized in a 1:1 ratio to receive either 1.5 g twice daily oral MMF or 25 mg weekly oral MTX and were followed up at 2 weeks and then every 4 weeks up to the primary endpoint (6-month visit or treatment failure before 6 months) and secondary endpoint (12-month visit or treatment failure between 6 to 12 months). The trial was approved by the local institutional review board of each site and all patients provided written informed consent. The FAST Trial was conducted in accordance with the tenets of the Declaration of Helsinki. Details about the FAST Trial protocol and the primary study outcome have been previously reported.[15]

A subset of clinical sites (Aravind Eye Hospitals in Coimbatore, Madurai, and Pondicherry, India; Proctor Foundation at University of California, San Francisco; Northwestern University in Chicago, Illinois; and King Khaled Eye Specialist Hospital in Riyadh, Saudi Arabia) obtained CD4+ T-cell counts in the FAST Trial. CD4+ T-cell count monitoring was part of the study protocol for sites that had the capacity to conduct this testing. Patients with documented CD4 counts at baseline, the primary endpoint, and secondary endpoint who did not change treatment during the trial were included in this analysis. Patients who did not have CD4 counts at both baseline and the primary endpoint were excluded. Only patients who were a treatment success at the primary endpoint and who remained on the initial randomized treatment through 12 months were included in the secondary endpoint analysis. Change in CD4 count was measured from baseline to the primary and secondary endpoints and reported in cells/μL.

Patient sex, age, country, study site, history of sarcoidosis, baseline CD4 count, final CD4 count, and raw change in CD4 count were reported by treatment group. Comparisons of mean CD4 counts at baseline, the primary endpoint, and secondary endpoint between MMF and MTX were conducted using 2-sample t-tests. Differences in the mean CD4 count at baseline, the primary endpoint, and the secondary endpoint within each treatment group were measured using paired t-tests. The effect of treatment on change in CD4 count was analyzed using multivariable linear regression, adjusting for country, age, and sex. An additional sensitivity analysis was performed looking at change in CD4 levels from baseline to the primary endpoint after adjusting for a confirmed diagnosis of sarcoidosis (biopsy-proven or bilateral hilar lymphadenopathy as seen on chest X-ray). All analyses were conducted using R (R Project for Statistical Computing, version 3.6.1).

RESULTS

Patient Characteristics

A total of 124 patients were included in the sub-analysis for the primary outcome, with 62 patients on MTX and 62 patients on MMF. For the analysis for the secondary outcome, there were a total of 73 patients, with 36 on MTX and 37 on MMF. Patient demographic characteristics were comparable between treatment groups (Table 1). The mean age of patients taking MMF was 42.1 years old (standard deviation (SD): 14.0) and 37.5 years old

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(SD: 14.4) for patients taking MTX. The majority of patients were female, with 66.1% and 72.6% receiving MMF and MTX, respectively. Most patients were from the Aravind Eye Hospital in Madurai, India.

Change in CD4+ T-cell Levels within Treatment Groups

The mean CD4+ T-cell count increased from baseline to the primary endpoint for both MMF and MTX (Table 2). For MMF, the mean CD4 count at baseline was 1018 cells/μL (95% confidence interval (CI): 785 to 1250) and increased by a mean of 19 cells/μL (95% CI: −250 to 288) at the primary endpoint. For MTX, the mean CD4 count at baseline was 960 cells/μL (95% CI: 796 to 1124) and increased by a mean of 43 cells/μL (95% CI: −129 to 214) at the primary endpoint. The distribution of the change in CD4 from baseline to the primary endpoint is further depicted in Figure 1. There was no statistically significant difference in the mean change in CD4 count from baseline to the primary endpoint when comparing within treatment groups for both MMF (P=0.89) and MTX (P=0.62). The mean CD4 count decreased from baseline to the secondary endpoint by 173 cells/μL (95% CI: −474 to 129) for MMF and 74 cells/μL (95% CI: −327 to 179) for MTX, but this was not statistically significant for both MMF (P=0.25) and MTX (P=0.56).

Change in CD4+ T-cell Levels between Treatment Groups

There was no significant difference in the mean CD4+ T-cell counts between treatment groups at baseline (P=0.69), the primary endpoint (P=0.74), and the secondary endpoint (P=0.85). Multivariable linear regression adjusting for age, sex, and country did not reveal a statistically significant difference in the change in CD4 when comparing between treatment groups at the primary endpoint (−31.7 cells/μL for MMF compared to MTX; 95% CI: −358.2 to 294.8, P=0.85) and at the secondary endpoint (−78.3 cells/μL for MMF compared to MTX; 95% CI: −468.0 to 311.3; P=0.69) (Table 2).

Change in CD4+ T-cell Levels in Patients with Sarcoidosis

A total of 5 patients had a diagnosis of sarcoidosis, 3 patients on MMF and 2 patients on MTX. The mean CD4+ T-cell count at baseline was 532 cells/μL (95% CI: 79 to 985) in patients with sarcoidosis compared to 1008 cells/μL (95% CI: 863 to 1153) among the 119 patients without a history of sarcoidosis. At the primary endpoint, the mean CD4 count was 829 cells/μL (95% CI: 776 to 882) for sarcoidosis patients compared to 1028 cells/μL (95% CI: 922 to 1134) for non-sarcoidosis patients. The mean CD4 count was significantly lower at baseline (P=0.039) and at the primary endpoint (P=0.001) in patients with sarcoidosis. Although the CD4 count increased from baseline to the primary endpoint, the increase in CD4 was not statistically significant (P=0.16). A sensitivity analysis adjusting for a diagnosis of sarcoidosis in the linear model did not reveal a statistically significant difference in the change in CD4 count from baseline to the primary endpoint by treatment group (−34.7 cells/μL for MMF compared to MTX; 95% CI: −362.03 to 292.66; P=0.83).

DISCUSSION

This subanalysis of a randomized clinical trial did not find a statistically significant difference in the change in CD4+ T-cell levels from baseline through 12 months in patients

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with non-infectious uveitis treated with MMF or MTX. Comparing CD4 counts at baseline to the primary endpoint showed that CD4 levels increased in both treatment groups, but there was no significant difference in the change in CD4 when comparing within and between treatment groups. At the secondary endpoint, the mean CD4 count decreased from baseline for both MMF and MTX, but there was again no significant difference in the change in CD4 counts between and within the groups.

Existing literature suggests that a decrease in CD4+ T cells is primarily a concern in patients on MMF. This medication is a reversible inhibitor of inosine-5'-monophosphate dehydrogenase (IMD), an enzyme crucial for the synthesis of the purine guanosine and its downstream product, guanosine triphosphate (GTP).[16] MMF preferentially inhibits the isoform of IMD found in B and T lymphocytes, thus decreasing lymphocyte proliferation and suppressing both antibody and cell-mediated responses.[16] Earlier studies on lymphocyte counts showed that MMF treatment was associated with a decrease in CD4 and the CD4/CD8 ratio when used in combination with other immunosuppressants in renal transplant patients.[6,10] These results differ from a more recent study in cardiac transplant patients, which demonstrated no change in CD4+ T lymphocytes but a significant decline in B lymphocytes in patients that were treated with MMF alone.[11] The conflicting evidence may be due to differences in study methodology, such as patient population, drug dosage and combination, and time to follow-up. In this study, the CD4 levels decreased by 6 months and increased by 12 months in patients on MMF; however, these fluctuations in CD4 counts were not statistically significant and were most likely due to chance. These findings suggest that MMF is not associated with a significant reduction in CD4 levels in patients with uveitis.

Previous research has shown that MTX can modulate the subset expression of CD4+ T cells but there is little data on the potential effect of MTX on total CD4 counts.[5,14,17] Studies from the last two decades demonstrated that MTX doses of 7.5 mg to 15 mg per week were not associated with a change in CD4 counts in patients with RA.[14,18,19] However, more recent studies have shown that MTX may decrease the CD4+ T-cell levels in particular subsets.[17,20,21] In many of these studies, it remains difficult to separate the effect of MTX from that of RA itself on total CD4 levels. In our study, the change in CD4 counts decreased and then increased by 6 and 12 months, respectively, but these results were not found to be statistically significant and should not be interpreted as meaningful changes. This suggests that MTX did not have a significant effect on CD4 counts in patients with non-infectious uveitis.

In addition, we did not observe a significant difference in the change in CD4 counts from baseline to the primary endpoint by treatment when adjusting for a diagnosis of sarcoidosis, one of the autoimmune conditions in which CD4+ T-cell lymphopenia has been reported. However, the mean CD4 counts at baseline and at the primary endpoint were significantly lower compared to CD4 levels for patients without sarcoidosis. Our findings suggest that sarcoidosis alone may be responsible for CD4 lymphopenia. On the contrary, the increase in CD4 up to the primary endpoint, though not statistically significant, may be due to antimetabolite treatment. Given that the sample size for the sarcoidosis subgroup was small, the results of the analysis should be interpreted cautiously, and warrant further

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investigation. In another study on patients with sarcoidosis, disease severity was associated with a low CD4 count, which the researchers concluded was independent of the use of immunosuppressants.[12] CD4 lymphopenia has also been found to be a potential predictor of sarcoidosis in patients presenting with new-onset uveitis.[13] Both MMF and MTX are common treatments for sarcoidosis and may be used alone, in combination, or following other immunosuppressants. Though our sample size was small, our results suggest that CD4 lymphopenia may be due to the underlying autoimmune condition in patients with sarcoidosis-associated uveitis.

Of note, the majority of patients in this study were of Indian ethnicity. Previous studies have looked at the potential effect of genetic polymorphisms on the pharmacology of MMF in renal transplant patients and of MTX in RA patients; however, it remains unclear if genetic variation has a significant effect on treatment response or drug toxicity. In addition, studies on genetic variation by race in RA patients have been inconclusive.[22–25] While research in patients with human immunodeficiency virus (HIV) suggests that affected Asians may have lower baseline CD4 counts than their non-Asian counterparts, there appears to be no significant racial difference in the change in CD4 count during antiretroviral therapy.[26–29] There is little data on genetic differences in response to MMF or MTX in South Asian patients compared to other races or on genetic differences in the risk of CD4+ T cell lymphopenia.

This study has several limitations. In addition to the antimetabolites, patients received an oral corticosteroid taper, and we did not adjust for steroid use in this sub-analysis. However, the baseline corticosteroid dose was the same in both treatment groups, and the steroid taper followed a prescribed guideline.[15] Randomization likely minimized confounding due to measured and unmeasured factors. In addition, only 64% of patients from the FAST Trial that were followed up to the primary outcome had CD4+ T cells measured, but the decision to measure CD4 counts was based on feasibility at sites rather than patient or disease characteristics. Since investigators were masked to the randomized treatment through the trial, this limitation would be unlikely to bias the comparisons between treatment groups. Lastly, this study was limited by a relatively small sample size, which can lead to a lack of precision in the estimates for subgroups such as in the patients with sarcoidosis. Although we analyzed total CD4+ T-cell counts, we could not assess for CD4 subset expression, which has been found to be dysregulated with MTX use and in other autoimmune conditions such as Behçet’s and Vogt-Koyanagi-Harada disease.[12,30,31]

In summary, this sub-analysis of the FAST trial did not find a significant difference in the change in CD4+ T cells from baseline to the primary and secondary endpoints for patients with uveitis treated with 1.5 g twice a day of oral MMF compared to patients on 25 mg weekly of oral MTX. These findings suggest that specific monitoring of CD4 counts may not be necessary in uveitis patients receiving these medications.

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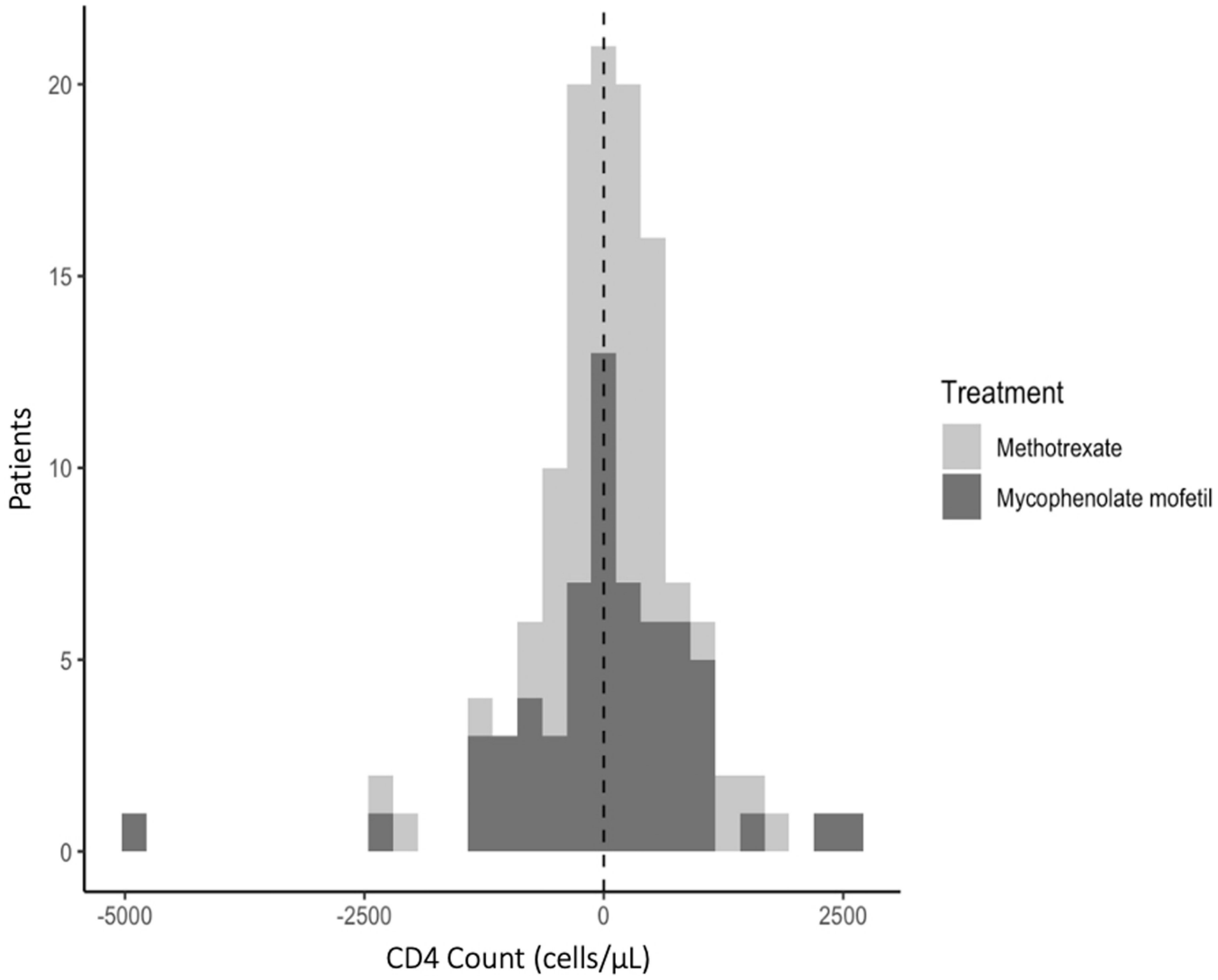


Figure 1.
Distribution of the change in CD4+ T-cell count from baseline to the primary endpoint by treatment group

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Table 1.

Patient demographic characteristics stratified by treatment group

	Methotrexate (N=62)	Mycophenolate Mofetil (N=62)
Sex		
Female	45 (72.6%)	41 (66.1%)
Male	17 (27.4%)	21 (33.9%)
Age		
Mean (SD)	37.5 (14.4)	42.1 (14.0)
Country		
India		
Coimbatore	17 (27.4%)	12 (19.4%)
Madurai	27 (43.5%)	26 (41.9%)
Pondicherry	9 (14.5%)	14 (22.6%)
USA		
San Francisco	7 (11.3%)	10 (16.1%)
Chicago	1 (1.6%)	0 (0%)
Saudi Arabia		
Riyadh	1 (1.6%)	0 (0%)
Diagnosis of Sarcoidosis		
Presumed diagnosis	2 (3.2%)	3 (4.8%)

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Table 2.

CD4+ T-cell count by treatment group

CD4+ T-cell Count (cells/μL)	Methotrexate	Mycophenolate Mofetil	P-value
At Baseline	N = 62	N = 62	
Mean CD4 Count (95% CI)	960 (796, 1124)	1018 (785, 1250)	0.69
At Primary Endpoint *	N = 62	N = 62	
Mean CD4 Count (95% CI)	1003 (881, 1125)	1037 (870, 1204)	0.74
Mean Change in CD4 from Baseline (95% CI)	43 (−129, 214)	19 (−250, 288)	0.85***
At Secondary Endpoint **	N = 37	N = 36	
Mean CD4 Count (95% CI)	936 (785, 1087)	912 (705, 1119)	0.85
Mean Change in CD4 from Baseline (95% CI)	−74 (−327, 179)	−173 (−474, 129)	0.69***

* Primary endpoint = 6 months or treatment failure prior to 6 months

** Secondary endpoint = 12 months or treatment failure between 6 to 12 months

*** Differences in the mean change in CD4+ T-cell count between treatment groups were analyzed using multivariable linear regression, adjusting for age, sex, and country