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Mycophenolate mofetil (MMF) does not slow the progression of subclinical atherosclerosis in SLE over 2 years

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Abstract

Accelerated atherosclerosis is a major cause of mortality in SLE. Mycophenolate mofetil (MMF) has been shown to suppress growth factor-induced proliferation of vascular smooth muscle and endothelial cells in animal models. We hypothesized that MMF might modify the inflammatory component of atherosclerosis in SLE. We examined the effect of MMF on atherosclerosis as measured by changes in carotid intima-media thickness (IMT) or coronary artery calcium (CAC) over 2 years. CAC and carotid IMT were measured at baseline and 2 years later in a cohort of 187 patients with SLE. The cohort was 91% women, 59% Caucasian, and 35% African-American, with a mean age of 45 ± 11 years. Of these, 12.5% ($n = 25$) received MMF during follow-up. The daily dose ranged from 500 to 3,000 mg/day, and duration ranged from 84 days to the entire 2 years. We divided MMF users into three groups: low exposure ($<1,500$ mg average daily dose), high exposure ($>1,500$ average daily dose), and any exposure of MMF ($<1,500$ or $>1,500$ average daily dose) for 2 years. The mean CAC increased in all four groups: no MMF: 1.17–1.28, low MMF: 1.02–1.13, high MMF: 1.44–1.61, and any MMF: 1.21–1.34 log-Agatston units. Compared to no MMF, there was no statistically different change between the three groups ($p = 0.99$, 0.87 , and 0.91). Similarly, mean carotid IMT increased in all four groups: no MMF: 0.58–0.66, low MMF: 0.55–0.60, high MMF: 0.56–0.71, and any MMF: 0.56–0.66. We then adjusted for statin use, lupus nephritis, body mass index, systolic blood pressure, cholesterol, and age during the 2-year follow-up. The association between MMF exposure and change in CAC or carotid IMT was not statistically significant ($p = 0.63$ for CAC, and $p = 0.085$ for carotid IMT). There was no evidence that MMF slowed or decreased the progression of atherosclerosis as measured by carotid IMT or CAC. Because the number of patients taking MMF was only twenty-five, larger studies for longer time periods are needed to explore any effect of MMF on subclinical atherosclerosis in SLE.

Keywords

Systemic lupus erythematosus; Mycophenolate mofetil; Atherosclerosis

Introduction

Mycophenolate mofetil (MMF) is an immunosuppressant used in various autoimmune conditions, including systemic lupus erythematosus [1]. Mycophenolate mofetil selectively blocks de novo purine synthesis, a pathway crucial for both B and T lymphocytes [2]. It reduces the infiltration of lymphocytes into inflammatory sites such as atherosclerotic plaque [3, 4]. It also inhibits the transfer of fucose and mannose to adhesion molecules, thereby reducing leukocyte attachment to endothelial cells [5]. It has been effectively used for lupus nephritis in randomized clinical trials [6–8].

Animal studies in mice have shown that atheroma progression and formation rely on monocytes and macrophages, including their adherence to the vascular wall [9, 10]. Mycophenolate mofetil reduces the attachment of monocytes to endothelial cells in humans [11]. Animal and human studies have shown that mycophenolate mofetil may reduce transplant arteriosclerosis by direct inhibition of vascular smooth muscle cell proliferation [12, 13].

In a clinical trial of 578 cardiac transplant patients, randomized to mycophenolate mofetil or azathioprine, patients on mycophenolate mofetil had a smaller increase in maximal coronary intimal thickness as well as lower levels of coronary stenosis than those on azathioprine [14]. In another study of 30 cardiac transplant patients, markers of inflammation such as C-reactive protein were lower in patients treated with mycophenolate mofetil [15].

Cardiovascular disease remains a major cause of both morbidity and mortality in SLE [16, 17]. The risk of myocardial infarction among SLE patients aged 35–44 years is 50 times higher compared to Framingham controls [18]. Immune-mediated damage, traditional cardiovascular risk factors, and prothrombotic factors all play crucial roles in atherosclerosis in SLE [19].

Coronary artery calcium (CAC) is now widely recognized as a surrogate measure of coronary atherosclerosis [20, 21]. Measurement of coronary artery calcium has been suggested as a potential means for noninvasive assessment of subclinical atherosclerosis in the general population to determine aggressiveness of preventive strategies [22, 23]. Von Feldt and colleagues found that 38% of SLE patients had significant (70 AU or greater) coronary artery calcification [24]. We have shown that age, obesity, and diabetes mellitus were independently associated with coronary artery calcium in our study of 200 SLE patients [25].

Carotid duplex ultrasonography can ascertain the degree of plaque both in the carotid arteries and the intimal–medial wall thickness (IMT) and is also predictive of cardiovascular events [26]. Several cardiovascular trials in the general population have used carotid ultrasound as a surrogate for cardiovascular events [27, 28]. Carotid atherosclerosis has been widely studied in SLE [29, 30]. Carotid intima–media thickness associates in SLE have included older age, higher SLICC damage scores, and cumulative prednisone dosage [31, 32]. In our 605 SLE patients who underwent carotid duplex testing, other significant associations included male gender, hypertension, diabetes mellitus, and serum creatinine [29].

Given the high burden of atherosclerotic disease in SLE and the potential anti-atherosclerotic effects of mycophenolate mofetil, we sought to determine whether mycophenolate mofetil could reduce progression of subclinical atherosclerosis in SLE, as measured by coronary artery calcium and carotid intima–media thickness, over a 2-year period of time.

Methods

Two hundred patients with SLE were followed for 2 years as part of a randomized trial on the effect of atorvastatin on subclinical markers of atherosclerosis. Of the 200 patients who participated, 187 had measures of subclinical atherosclerosis at baseline and at follow-up, and of these patients, 13% ($n = 25$) received mycophenolate mofetil at some point during the 2 years. Mycophenolate mofetil was prescribed for lupus nephritis. The dose ranged from 500 to 3,000 mg/day, and the duration ranged from 84 days to the entire follow-up period. We divided the mycophenolate mofetil users into 3 groups, low ($n = 12$, <1,500 mg/day average daily dose), high ($n = 13$, 1,500 mg/day average daily dose), and any dose of mycophenolate mofetil (<1,500 or 1,500 average daily dose) for 2 years. The study was approved by the Johns Hopkins University School of Medicine Institutional Review Board. All patients gave informed consent.

As part of the Hopkins Lupus Cohort Study, all patients had been seen quarterly since cohort entry, for assessment of disease activity (by the Physician's Global Assessment, on a 0–3 visual analog, and the SELENA SLEDAI) [33, 34], laboratory tests (complete blood count, erythrocyte sedimentation rate, serum creatinine, cholesterol, urinalysis, urine protein/creatinine ratio, C3, C4, anti-dsDNA, anticardiolipin, lupus anticoagulant by dRVVT), and cardiovascular risk factors, including total cholesterol, homocysteine, lipoprotein(a), and fibrinogen.

Coronary artery calcium was assessed by multidetector computerized tomography with a Siemens Volume Zoom Scanner (Siemens Medical Solutions Malvern, Pa) using a 2.5-mm collimation and a slice width of 3 mm at baseline and 2 years. Data were reloaded into Siemens Leonardo workstation, using the Siemens calcium scoring software. Coronary artery calcification was quantified using a standard scoring system, available as part of the scanner software package [35]. Coronary artery calcification scores were calculated using Agatston scoring.

Carotid duplex was assessed at baseline and at approximately 2 years. High-resolution B-mode ultrasound was performed to image the right and left common carotid arteries using a single ultrasound machine (Philips Medical Systems Sonos 5500) with a linear array 8-MHz scan head with standardized image settings, including resolution mode, depth of field, gain, and transmit focus. Digital imaging and communications in medicine (DICOM) images from a diastolic frame of the cine-loop recording were electronically stored and transferred via optical disk to an off-line work station for analysis. Carotid intima–media thickness was measured between the lumen intima and media–adventitia interfaces of the far wall of the common carotid artery (the 1-cm segment proximal to the bifurcation) by a single reader using an automated edge detection system. The mean intima–media thickness of this 1-cm segment was measured on two separate images of the left and the right common carotid arteries at the peak of the R wave on a simultaneous electrocardiogram tracing. The mean of these four measurements was used as the intima–media thickness. This location was chosen because of its demonstrated reproducibility compared with measurements of carotid intima–media thickness at other sites [36, 37].

Statistical analysis

Cumulative exposure to mycophenolate mofetil was calculated as the product of the dose times the number of days on that dose, summed over the 2-year period. This was then converted to an average daily dose by dividing by the number of days between baseline and follow-up. Coronary artery calcium scores were transformed by the “Log ($x + 1$)” transformation prior to computing the difference from baseline to follow-up. Paired t tests were used to assess whether there was a significant change in CAC or IMT over time in each

group. The significance of differences between the groups with respect to changes was assessed using ANOVA. Multiple linear regression was used to assess the association between any exposure to mycophenolate mofetil and changes in CAC or IMT controlling for potential confounding variables.

Results

Of the 187 patients in the study, 171 (91%) were women, 111 (59%) were Caucasian, 66 (35%) were African-American, and 10 (5%) were Asian, Hispanic, or other race. Their mean age was 45 years (SD = 11).

Of the twenty-five SLE subjects who were taking mycophenolate mofetil, 13 had high exposure (1,500 mg average daily exposure) and 12 had low exposure (<1,500 mg average daily exposure). They were 92% women. The patients were 74% Caucasian, 22% African-American, and 4% Asian. The mean age was 44 years (SD = 13). Cumulative SLE clinical manifestations included malar rash 60%, discoid rash 32%, photosensitivity 56%, oral ulcers 56%, arthritis 84%, serositis 72%, renal disorder 84%, neurological disorder 12%, immunologic disorder 96%, and ANA positivity 100%.

Tables 1 and 2 show mean changes in coronary artery calcium and carotid intima-media thickness by mycophenolate mofetil exposure over 2 years. *p* values reflect the comparison of each exposure group to those with no exposure. With reference to coronary artery calcium and taking "no MMF" as the reference group, there was no statistically different change between the three groups. The increase in carotid intima-media thickness was somewhat greater among those with high exposure to mycophenolate mofetil than the other groups (*p* = 0.055).

After controlling for lupus nephritis, body mass index (BMI), systolic blood pressure, statin use, cholesterol, and age, there was no significant difference between those ever exposed to mycophenolate mofetil and those not, with respect to mean change in carotid intima-media thickness and coronary artery calcium. In fact, there was very little correlation between mycophenolate mofetil exposure and these potentially confounding variables. Table 3 shows the estimated crude and adjusted effects of mycophenolate mofetil on changes in outcomes.

Discussion

In our study, mycophenolate mofetil failed to reduce progression in carotid intima-media thickness scores during the 2-year period of the trial. Studies of mycophenolate mofetil in cardiac transplant patients have given conflicting results. In a randomized trial with 289 patients per group, cardiac transplant patients on mycophenolate mofetil (3,000 mg/days) had a significantly smaller increase in IMT over a 3-year period than patients taking azathioprine [14]. However, one of the limitations of this cardiac transplant study was that only 54% of transplant recipients were able to take the recommended mycophenolate mofetil dose for the 36-month time period. In a second study of 30 transplant patients, there was actually an increase in coronary intimal-medial proliferation seen in cardiac transplant patients taking mycophenolate mofetil after 1 year of follow-up [15].

In addition, we found no reduction in progression of coronary artery calcification with mycophenolate mofetil. In a study of 281 renal transplant patients, independent predictors of aortic calcification included shorter time taking mycophenolate mofetil and higher pulse pressure [38]. Other than our study, there has been no study of mycophenolate use and coronary artery calcium.

We also looked at crude and adjusted effects of mycophenolate mofetil and changes in the measures of subclinical atherosclerosis, after adjusting for lupus nephritis, cumulative body mass index, statin use, systolic blood pressure, and cholesterol during follow-up. These adjusted analyses failed to show any benefit of mycophenolate mofetil on subclinical atherosclerosis.

Limitations of our study include the small sample size and 2-year follow-up period. Further SLE studies will need a larger study population and a longer follow-up period. However, our initial study is disappointing and suggests that mycophenolate mofetil may not retard progression of subclinical atherosclerosis over time in SLE.

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Table 1

Mean changes in log (coronary artery calcium +1) by mycophenolate mofetil exposure

Group	Mean at baseline	Mean at follow-up	Mean change	<i>p</i> value comparing those with exposure to MMF to those with no exposure to MMF with respect to mean change
No MMF (<i>n</i> = 162)	1.17	1.28	0.11	Reference group
Low MMF (<i>n</i> = 14)	1.02	1.13	0.11	0.99
High MMF (<i>n</i> = 11)	1.44	1.61	0.17	0.87
Any MMF (<i>n</i> = 25)	1.21	1.34	0.14	0.91

Table 2

Mean changes in carotid intima-media thickness by mycophenolate mofetil exposure

Group	Mean at baseline	Mean at follow-up	Mean change	<i>p</i> value comparing those with exposure to MMF to those with no exposure to MMF with respect to mean change
No MMF (<i>n</i> = 162)	0.58	0.66	0.08	Reference group
Low MMF (<i>n</i> = 14)	0.55	0.60	0.05	0.27
High MMF (<i>n</i> = 11)	0.56	0.71	0.15	0.055
Any MMF (<i>n</i> = 25)	0.56	0.66	0.08	0.66

Table 3

Crude and adjusted effect of having been exposed to mycophenolate mofetil during the follow-up period on changes in atherosclerosis outcomes

Marker	<u>Estimated effect of MMF exposure on the mean change in various cardiovascular markers</u>			
	Crude estimate	<i>p</i> value	Adjusted ^a estimate	<i>p</i> value
Change in coronary artery calcium score	0.03	0.91	0.13	0.63
Change in carotid intima–media thickness	0.01	0.66	0.04	0.085

^a Adjusted for lupus nephritis, cumulative BMI, systolic blood pressure, statin use, and cholesterol exposure during follow-up